08 - PART 1 The Profession of Medicine

01 - 1 The Practice of Medicine

1 The Practice of Medicine

The Editors

The Practice of Medicine ENDURING VALUES OF THE MEDICAL PROFESSION No greater opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering, [the physician] needs technical skill, scientific knowledge, and human under standing. Tact, sympathy, and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered func tions, damaged organs, and disturbed emotions. [The patient] is human, fearful, and hopeful, seeking relief, help, and reassurance. —Harrison’s Principles of Internal Medicine, 1950 The practice of medicine has changed in significant ways since the first edition of this book was published in 1950. The advent of molecular genetics, sophisticated new imaging techniques, robotics, and advances in bioinformatics and information technology have contributed to an explosion of scientific information that has changed fundamentally the way physicians define, diagnose, treat, and attempt to prevent disease. This growth of scientific knowledge continues to evolve at an acceler ated pace. The widespread use of electronic medical records and the Internet have altered the way physicians and other health care providers access and exchange information as a routine part of medical education and practice (Fig. 1-1). As today’s physicians strive to integrate an everexpanding body of scientific knowledge into everyday practice, it is critically important to remember two key principles: first, the ultimate goal of medicine is to prevent disease and, when it occurs, to diagnose it early and provide effective treatment; and second, despite 70 years of scientific advances since the first edition of this text, a trusting rela tionship between physician and patient still lies at the heart of effective patient care. ■ ■THE SCIENCE AND ART OF MEDICINE Deductive reasoning and applied technology form the foundation for the approach and solution to many clinical problems. Extraordinary advances in biochemistry, cell biology, immunology, and genomics, FIGURE 1-1 The Doctor by Luke Fildes depicts the caring relationship between this Victorian physician and a very ill child. Painted in 1891, the painting reflects the death of the painter’s young son from typhoid fever and was intended to reflect the compassionate care provided by the physician even when his tools were not able to influence the course of disease. (Source: History and Art Collection/Alamy Stock Photo.)

The Profession of Medicine PART 1 coupled with newly developed imaging techniques, provide a window into the most remote recesses of the body and allow access to the innermost parts of the cell. Revelations about the nature of genes and single cells have opened a portal for understanding physiology and unraveling the causes of disease. Researchers are deciphering the complex

mechanisms by which genes are regulated, and increasingly, physicians are learning how subtle changes in many different genes, acting in an integrative contextual way, can affect the function of cells and organisms. Clinicians have developed a new appreciation of the role of stem cells in the renewal and repair of normal tissues, in the development of cancer and other disorders, and in the treatment of certain diseases. Entirely new areas of research, including studies of the human microbiome, epigenetics, and noncoding RNAs as regula tory features of the genome, have become important for understanding both health and disease. Extraordinary advances in vaccine platform technology and the use of cryo-electron microscopy for the structurebased design of vaccine immunogens have transformed the field of vaccinology, resulting in the unprecedented speed and success with which COVID-19 vaccines were developed. Information technology enables the interrogation of medical records from millions of individu als, yielding new insights into the etiology, characteristics, prognosis, and stratification of many diseases. With the increasing availability of very large data sets (“big data”) from omic analyses and the electronic medical record, there is now a growing interest in machine learning and artificial intelligence for unbiased analyses that enhance clinical predictive accuracy. The field of artificial intelligence in particular is expanding rapidly, perhaps more rapidly than our understanding of how to use it optimally. In the coming years, it will be essential to learn the value and limitations of artificial intelligence methods and not abdicate decision-making entirely to a computer algorithm. The knowledge gleaned from the science of medicine continues to enhance the under standing by physicians of complex pathologic processes and to provide new approaches to disease prevention, diagnosis, and treatment. With continued refinement of unique omic signatures coupled with nuanced clinical pathophenotypes, the profession moves ever closer to practical precision medicine. Yet, skill in the most sophisticated applications of laboratory technology and in the use of the latest therapeutic modality alone does not make a good physician. When a patient poses challenging clinical problems, an effective physician must be able to identify the crucial elements in a complex history and physical examination; order the appropriate laboratory, imaging, and diagnostic tests; and extract the key results from densely populated computer screens to determine whether to treat or to “watch.” As the number of tests increases, so does the likelihood that some incidental finding, completely unrelated to the clinical problem at hand, will be uncovered. Deciding whether a clinical clue is worth pursuing or should be dismissed as a “red herring” and weighing whether a proposed test, preventive measure, or treatment entails a greater risk than the disease itself are essential judgments that a skilled clinician must make many times each day. This combination of medi cal knowledge, intuition, experience, and judgment defines the art of medicine, which is as necessary to the practice of medicine and the pre cision medicine of the future as is a sound scientific base, and as impor tant for contemporary medical practice as it has been in earlier eras. ■ ■CLINICAL SKILLS History-Taking The recorded history of an illness should include all the facts of medical significance in the life of the patient. Recent events should be given the most attention. Patients should, at some early point, be given the opportunity to tell their own story of the illness without frequent interruption and, when appropriate, should receive expressions of interest, encouragement, and empathy from the physician. Any event related by a patient, however trivial or seem ingly irrelevant, may provide the key to solving the medical problem. A methodical review of systems is important to elicit features of an

underlying disease that might not be mentioned in the patient’s nar rative. In general, patients who feel comfortable with the physician will offer more complete information; thus, putting the patient at ease contributes substantially to obtaining an adequate history.

An informative history involves more than eliciting an orderly list ing of symptoms. By listening to patients and noting the ways in which they describe their symptoms, physicians can gain valuable insight. Inflections of voice, facial expression, gestures, and attitude (i.e., “body language”) may offer important clues to patients’ perception of and reaction to their symptoms. Because patients vary considerably in their medical sophistication and ability to recall facts, the reported medical history should be corroborated whenever possible. The social history also can provide important insights into the types of diseases that should be considered and can identify practical considerations for subsequent management. The family history not only identifies rare genetic disorders or common exposures, but often reveals risk factors for common disorders, such as coronary heart disease, hypertension, autoimmunity, certain cancers, and asthma. A thorough family history may require input from multiple relatives to ensure completeness and accuracy. An experienced clinician can usually formulate a relevant differential diagnosis from the history alone, using the physical exami nation and diagnostic tests to narrow the list or reveal unexpected findings that lead to more focused inquiry. PART 1 The Profession of Medicine The very act of eliciting the history provides the physician with an opportunity to establish or enhance a unique bond that can form the basis for a good patient–physician relationship. This process helps the physician develop an appreciation of the patient’s view of the illness, the patient’s expectations of the physician and the health care system, and the financial and social implications of the illness for the patient. Although current health care settings may impose time constraints on patient visits, it is important not to rush the encounter. A hurried approach may lead patients to believe that what they are relating is not of importance to the physician, and, as a result, they may withhold relevant information. The confidentiality of the patient–physician rela tionship cannot be overemphasized. Physical Examination The purpose of the physical examination is to identify physical signs of disease. The significance of these objective indications of disease is enhanced when they confirm a functional or structural change already suggested by the patient’s history. At times, however, physical signs may be the only evidence of disease and may not have been suggested by the history. The physical examination should be methodical and thorough, with consideration given to the patient’s comfort and modesty. Although attention is often directed by the history to the diseased organ or part of the body, the examination of a new patient must extend from head to toe in an objective search for abnormalities or other diagnostic clues. The results of the examination, like the details of the history, should be recorded at the time they are elicited—not hours later, when they are subject to the distortions of memory. Physical examination skills should be learned under direct observation of experienced clinicians. Even highly experienced clinicians can benefit from ongoing coaching and feedback. Simulation laboratories and standardized patients play an increasingly important role in the development of clinical skills. Although the skills of physical diagnosis are acquired with experience, it is not merely technique that determines success in identifying signs of disease. The detection of a few scattered petechiae, a faint diastolic murmur, or a small mass in the abdomen is not only a question of keen eyes and ears or more sensitive fingers but also of a mind alert to those findings. Because physical findings can change with time, the physical examination should be repeated as frequently as the clinical situation warrants. Given the many highly sensitive diagnostic tests now available (particularly imaging techniques), it may be tempting to place less emphasis on the physical examination. Some are critical of physical diagnosis based on perceived low levels of specificity and sensitiv ity. Indeed, many patients are seen by consultants only after a series of diagnostic tests have been performed and the results are known. This fact should not deter the physician from performing a thorough

physical examination since important clinical findings may have escaped detection by diagnostic tests. Especially important, a thorough and thoughtful physical examination may render a laboratory finding unimportant (i.e., certain echocardiographic regurgitant lesions). The act of a hands-on examination of the patient also offers an opportunity for communication and may have reassuring effects that foster the patient–physician relationship. Diagnostic Studies Physicians rely increasingly on a wide array of laboratory and imaging tests to make diagnoses and ultimately to solve clinical problems; however, such information does not relieve the physician from the responsibility of carefully observing and examining the patient. It is also essential to appreciate the limitations of diagnos tic tests. By virtue of their apparent precision, these tests often gain an aura of certainty regardless of the fallibility of the tests themselves, the instruments used in the tests, and the individuals performing or interpreting the tests. Physicians must weigh the expense involved in laboratory procedures against the value of the information these pro cedures are likely to provide. Single laboratory tests are rarely ordered. Instead, physicians gener ally request “batteries” of multiple tests, which often prove useful and can be performed with a single specimen at relatively low cost. For example, abnormalities of hepatic function may provide the clue to nonspecific symptoms such as generalized weakness and increased fatigability, suggesting a diagnosis of chronic liver disease. Sometimes a single abnormality, such as an elevated serum calcium level, points to a particular disease, such as hyperparathyroidism. The thoughtful use of screening tests (e.g., measurement of low-density lipoprotein cholesterol) may allow early intervention to prevent disease (Chap. 6). Screening tests are most informative when they are directed toward common diseases and when their results indicate whether other potentially useful—but often costly—tests or interventions are needed. On the one hand, biochemical measurements, together with simple laboratory determinations such as routine serum chemistries, blood counts, and urinalysis, often provide a major clue to the presence of a pathologic process. On the other hand, the physician must learn to evaluate occasional screening-test abnormalities that do not necessar ily connote significant disease. An in-depth workup after the report of an isolated laboratory abnormality in a person who is otherwise well is often wasteful and unproductive. Because so many tests are performed routinely for screening purposes, it is not unusual for one or two values to be slightly outside the normal range or to reflect physiologic varia tion. Nevertheless, even if there is no reason to suspect an underlying illness, tests yielding abnormal results ordinarily are repeated to rule out laboratory error. If an abnormality is confirmed, it is important to consider its potential significance in the context of the patient’s condi tion and other test results. There is almost continual development of technically improved imaging studies with greater sensitivity and specificity. These tests provide remarkably detailed anatomic information that can be pivotal in informing medical decision-making. MRI, CT, ultrasonography, a variety of isotopic scans, and positron emission tomography (PET) have supplanted older, more invasive approaches and opened new diagnostic vistas. In light of their capabilities and the rapidity with which they can lead to a diagnosis, it is tempting to order a battery of imaging studies. All physicians have had experiences in which imaging studies revealed findings that led to an unexpected diagnosis. None theless, patients must endure each of these tests, and the added cost of unnecessary testing is substantial. Furthermore, investigation of an unexpected abnormal finding may lead to an iatrogenic complication or to the diagnosis of an irrelevant or incidental problem. A skilled physician must learn to use these powerful diagnostic tools judiciously, always considering whether the results will alter management and benefit the patient. ■ ■MANAGEMENT OF PATIENT CARE Team-Based Care Medical practice has long involved teams, particularly physicians working with nurses and, more recently, with physician assistants and nurse practitioners. Advances in medicine

have increased our ability to manage very complex clinical situations (e.g., intensive care units [ICUs], bone marrow transplantation) and have shifted the burden of disease toward chronic illnesses. Because an individual patient may have multiple chronic diseases, they may be cared for by several specialists as well as a primary care physician. In the inpatient setting, care may involve multiple consultants along with the primary admitting physician. Communication through the medical record is necessary but not sufficient, particularly when patients have complex medical problems or when difficult decisions need to be made about the optimal management plan. Physicians should optimally meet face-to-face or by phone to ensure clear communication and thought ful planning. It is important to note that patients often receive or perceive different messages from various care providers; thus, attempts should be made to provide consistency among these messages to the patient. Management plans and treatment options should be outlined succinctly and clearly for the patient. Another dimension of team-based care involves allied health profes sions. It is not unusual for a hospitalized patient to encounter physical therapists, pharmacists, respiratory therapists, radiology technicians, social workers, dieticians, and transport personnel (among others) in addition to physicians and nurses. Each of these individuals contrib utes to clinical care as well as to the patient's experience with the health care system. In the outpatient setting, disease screening and chronic disease management are often carried out by nurses, physician assis tants, or other allied health professionals. The roles and responsibilities of various team members can be confusing for patients. Within reason, different providers should introduce themselves, explain their role, and wear nametags or other identifying information. The growth of team-based care has important implications for medical culture, student and resident training, and the organization of health care systems. Despite diversity in training, skills, and respon sibilities among health care professionals, common values need to be espoused and reinforced. Many medical schools have incorporated interprofessional teamwork into their curricula. Effective communica tion is inevitably the most challenging aspect of implementing teambased care. While communication can be aided by electronic devices, including medical records, apps, or text messages, it is vitally important to balance efficiency with taking the necessary time to speak directly with colleagues. The Dichotomy of Inpatient and Outpatient Internal Medicine The hospital environment has undergone sweeping changes over the past few decades. Emergency departments and critical care units have evolved to manage critically ill patients, allowing them to survive formerly fatal conditions. In parallel, there is increasing pres sure to reduce the length of stay in the hospital and to manage complex disorders in the outpatient setting. This transition has been driven not only by efforts to reduce costs but also by the availability of new outpatient technologies, such as imaging and percutaneous infusion catheters for long-term antibiotics or nutrition, minimally invasive surgical procedures, and evidence that outcomes often are improved by reducing inpatient hospitalization. Telehealth and remote monitoring tools can also enhance connectivity with patients and reduce visits to the clinic or hospital. In addition to traditional medical beds, hospitals now encompass multiple distinct levels of care, such as the emergency department, procedure rooms, overnight observation units, critical care units, and palliative care units. A consequence of this differentiation has been the emergence of new specialties (e.g., emergency medicine and end-of-life care) and the provision of in-hospital care by hospitalists and intensiv ists. Most hospitalists are board-certified internists who bear primary responsibility for the care of hospitalized patients and whose work is limited entirely to the hospital setting. The shortened length of hospital stay means that most patients receive only acute care while hospital ized; the increased complexities of inpatient medicine make the pres ence of an internist with specific training, skills, and experience in the hospital environment extremely

beneficial. Intensivists are boardcertified physicians who are further certified in critical care medicine and who direct and provide care for very ill patients in critical care

units. Clearly, an important challenge in internal medicine today is to ensure the continuity of communication and information flow between a patient's primary care physician and those who are in charge of the patient's hospital care. Maintaining these channels of communication is frequently complicated by patient "handoffs"—i.e., transitions from the outpatient to the inpatient environment, from the critical care unit to a general medicine floor, from a medical to a surgical service and vice versa, from the hospital environment to the recently developed "home hospital" setting (for select patients with adequate home support), and from the hospital or home hospital to the outpatient environment.

CHAPTER 1 The Practice of Medicine The involvement of many care providers in conjunction with these transitions can threaten the traditional one-to-one relationship between patient and primary care physician. Of course, patients can benefit greatly from effective collaboration among a number of health care professionals; however, it is the duty of the patient's principal or primary physician to coordinate these collaborations and provide cohe sive guidance through an illness. To meet this challenge, primary care physicians must be familiar with the techniques, skills, and objectives of specialist physicians and allied health professionals who care for their patients in the hospital. In addition, primary care physicians must ensure that their patients benefit from scientific advances and the expertise of specialists, both in and out of the hospital. Primary care physicians should explain the role of these specialists to reassure patients that they are in the hands of physicians best trained to man age their current illness. However, the primary care physician should assure patients and their families that decisions are being made in con sultation with these specialists. The evolving concept of the "medical home" incorporates team-based primary care with subspecialty care in a cohesive environment that ensures smooth transitions of care. Mitigating the Stress of Acute Illness Few people are prepared for a new diagnosis of cancer or anticipate the occurrence of a myocar dial infarction, stroke, or major accident. The care of a frightened or distraught patient is confounded by these understandable responses to life-threatening events. The physician and other health providers can reduce the shock of life-changing events by providing information in a clear, calm, consistent, and reassuring manner. Often, information and reassurance need to be repeated. Caregivers should also recognize that, for the typical patient, hospital emergency rooms, operating rooms, ICUs, and general medical floors represent an intimidating and often frightening environment. Hospitalized patients find themselves sur rounded by air jets, buttons, and glaring lights; invaded by tubes and wires; and beset by the numerous members of the health care team— hospitalists, specialists, nurses, nurses' aides, physician assistants, social workers, technologists, physical therapists, medical students, house officers, attending and consulting physicians, and many others. They may be transported to special laboratories and imaging facilities replete with blinking lights, strange sounds, and unfamiliar personnel; they may be left unattended at times; and they may be obligated to share a room with other patients who have their own health problems. It is little wonder that patients may find this environment bewilder ing and stressful. The additive effects of an acute illness, unfamiliar environment, multiple medications, and sleep deprivation can lead to confusion or delirium, especially in older hospitalized patients. Physicians who appreciate the hospital experience from the patient's perspective and who make an effort to guide and comfort the patient through this experience may make a stressful situation more tolerable and enhance the patient's chances for an

optimal recovery. The advent of home-hospital care represents an attempt to improve the patient experience during uncomplicated acute illness by providing care in the familiar surroundings of the home environment, mitigating the stress of conventional hospitalization and shortening recovery times. Medical Decision-Making Medical decision-making is a fun damental responsibility of the physician and occurs at each stage of the diagnostic and therapeutic process. The decision-making process involves the ordering of additional tests, requests for consultations, decisions about treatment, and predictions concerning prognosis. This process requires an in-depth understanding of the pathophysiology and natural history of disease. Formulating a differential diagnosis

PART 1 The Profession of Medicine requires not only a broad knowledge base but also the ability to assess the relative probabilities of various diseases for a given patient. Appli cation of the scientific method, including hypothesis formulation and data collection, is essential to the process of accepting or ruling out a particular diagnosis. Analysis of the differential diagnosis is an itera tive process. As new information or test results are acquired, the group of disease processes being considered can be contracted or expanded appropriately. Whenever possible, decisions should be evidence-based, taking advantage of data from rigorously designed clinical trials or objective comparisons of different diagnostic tests. Evidence-based medicine stands in sharp contrast to anecdotal experience, which is often biased. Unless attuned to the importance of using larger, objec tive studies for making decisions, even the most experienced physi cians can be influenced to an undue extent by recent encounters with selected patients. Evidence-based medicine has become an increasingly important part of routine medical practice and has led to the publica tion of many useful practice guidelines. It is important to remember, however, that only a fraction of the many decisions made in clinical practice are based on rigorous clinical trial evidence; other guideline recommendations are, therefore, predicated on expert consensus and weaker evidentiary support. Thus, the importance of evidence-based medicine notwithstanding, much medical decision-making still relies on good clinical judgment, an attribute that is difficult to quantify or even to assess qualitatively. Physicians must use their knowledge and experience as a basis for weighing known factors, along with the inevitable uncertainties, and then making a sound judgment; this synthesis of information is partic ularly important when a relevant evidence base is not available. Several quantitative tools may be invaluable in synthesizing the available infor mation, including diagnostic tests, Bayes' theorem (the probability of an event predicated on prior knowledge of conditions possibly related to the event), and multivariate statistical models (Chap. 4). Diagnos tic tests serve to reduce uncertainty about an individual's diagnosis or prognosis and help the physician decide how best to manage that individual's condition. The battery of diagnostic tests complements the history and physical examination. The accuracy of a particular test is ascertained by determining its sensitivity (true-positive rate) and speci ficity (true-negative rate), as well as the predictive value of a positive and a negative result. See Chap. 4 for a more thorough discussion of decision-making in clinical medicine. Practice Guidelines Many professional organizations and govern ment agencies have developed formal clinical-practice guidelines to aid physicians and other caregivers in making diagnostic and therapeutic decisions that are evidence-based, cost-effective, and most appropri ate to a particular patient and clinical situation. As the evidence base of medicine increases, guidelines can provide a useful framework for managing patients with particular diagnoses or symptoms. Clinical guidelines can protect patients—particularly those with inadequate health care benefits—from receiving substandard care. These guide lines also can protect conscientious caregivers from inappropriate charges of malpractice and society from the excessive costs associated with the overuse of medical resources.

There are, however, caveats associated with clinical-practice guidelines since they tend to oversim plify the complexities of medicine. Furthermore, groups with differ ent perspectives may develop divergent recommendations regarding issues as basic as the need for screening of women by mammography or of men with serum prostate-specific antigen (PSA) measure ments. Finally, guidelines, as the term implies, do not—and cannot be expected to—account for the uniqueness of each individual and their illness. The physician's challenge is to integrate into clinical practice the useful recommendations offered by experts without accepting them blindly or being inappropriately constrained by them. Precision Medicine The concept of precision or personalized medi cine reflects the growing recognition that diseases once lumped together can be further stratified based on genetic, biomarker, phenotypic, and/ or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations. Inherent in this con cept is the goal of targeting therapies in a more specific way to improve clinical outcomes for the individual patient and minimize unnecessary side effects for those less likely to respond to a particular treatment. In some respects, precision medicine represents the evolution of clinical practice guidelines, which are usually developed for populations of patients or a particular diagnosis (e.g., hypertension, thyroid nodule). As the pathobiology, prognosis, and treatment responses of subgroups within these diagnoses become better understood (i.e., through refined genomic analysis or enhanced deep phenotyping), the relevant clinical guidelines incorporate progressively more refined recommendations for individuals within these subgroups. The role of precision medicine is best illustrated for cancers in which genetic testing is able to predict responses (or the lack thereof) to targeted therapies (Chap. 78). Increas ingly, biomarkers, including assessment of specific genetic alterations, are being used to define more precisely subsets of disease and identify therapeutic approaches tailored to the cellular pathobiology. Effective management often relies on the detection of biomarker expression. The validity of such tests is certified by the U.S. Food and Drug administra tion based on the collection of data from clinical trials. One can antici pate similar applications of precision medicine in pharmacogenomics, immunologic disorders, and diseases in which biomarkers can predict treatment responses. See Chap. 5 for a more thorough discussion of precision medicine. Evaluation of Outcomes Clinicians generally use objective and readily measurable parameters to judge the outcome of a therapeutic intervention. These measures may oversimplify the complexity of a clinical condition as patients often present with a major clinical prob lem in the context of multiple complicating background illnesses. For example, a patient may present with chest pain and cardiac ischemia, but with a background of chronic obstructive pulmonary disease and renal insufficiency. For this reason, outcome measures, such as mor tality, length of hospital stay, or readmission rates, are typically riskadjusted. An important point to remember is that patients usually seek medical attention for subjective reasons; they wish to obtain relief from pain, to preserve or regain function, and to enjoy life. The components of a patient's health status or quality of life can include bodily com fort, capacity for physical activity, personal and professional function, sexual function, cognitive function, and overall perception of health. Each of these important domains can be assessed through structured interviews or specially designed questionnaires. Such assessments pro vide useful parameters by which a physician can judge patients' subjec tive views of their disabilities and responses to treatment, particularly in chronic illness. The practice of medicine requires consideration and integration of both objective and subjective outcomes. Many health systems use survey and patient feedback data to assess qualitative features such as patient satisfaction, access to care, and com munication with nurses and physicians. In the United States, HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) surveys are used by many systems

and are publicly reported. Social media is also being used to assess feedback in real time as well as to share patient experiences with health care systems, potentially enrich ing the information available for use in medical decisions. Errors in the Delivery of Health Care A series of reports from the Institute of Medicine (now the National Academy of Medicine [NAM]) called for an ambitious agenda to reduce medical error rates and improve patient safety by designing and implementing fundamen tal changes in health care systems (Chap. 7). It is the responsibility of hospitals and health care organizations to develop systems to reduce risk and ensure patient safety. Medication errors can be reduced through the use of ordering systems that rely on electronic processes or, when electronic options are not available, that eliminate misread ing of handwriting, or that highlight important drug interactions. Whatever the clinical situation, it is the physician's responsibility to use powerful therapeutic measures wisely, with due regard for their beneficial actions, potential dangers, and cost. Implementation of infection control systems, enforcement of hand-washing protocols, and careful oversight of antibiotic use can minimize the complications of nosocomial infections. Central-line infection rates and catheterassociated urinary tract infections have been dramatically reduced at

many centers by careful adherence of trained personnel to standard ized protocols for introducing, maintaining, and removing central lines and urinary catheters, respectively. Rates of surgical infection and wrong-site surgery can likewise be reduced by the use of standardized protocols and checklists. Falls by patients can be minimized by judi cious use of sedatives and appropriate assistance with bed-to-chair and bed-to-bathroom transitions. Taken together, these and other measures are saving thousands of lives each year. Electronic Medical Records Both the growing reliance on computers and the strength of information technology now play central roles in medicine, including efforts to reduce medical errors. Laboratory data are accessed almost universally through computers. Many medical centers now have electronic medical records (EMRs), computerized order entry, and bar-coded tracking of medications. Some of these systems are interactive, sending reminders or warning of potential medical errors. EMRs offer rapid access to information that is invaluable in enhanc ing health care quality and patient safety, including relevant data, historical and clinical information, imaging studies, laboratory results, and medication records. These data can be used to monitor and reduce unnecessary variations in care and to provide real-time information about processes of care and clinical outcomes. Ideally, patient records are easily transferred across the health care system; however, techno logical limitations and concerns about privacy and cost continue to limit broad-based use of EMRs in many clinical settings. For all of the advantages of EMRs, they can create distance between the physician and patient if care is not taken to preserve face-to-face contact. EMRs also require training and time for data entry. Many providers spend significant time entering information to generate structured data and to meet billing requirements. They may feel pres sured to take short cuts, such as "cutting and pasting" parts of earlier notes into the daily record, thereby increasing the risk of errors. EMRs also structure information in a manner that disrupts the traditional narrative flow across time and among providers. These features, which may be frustrating for some providers, must be weighed against the advantages of ready access to past medical history, imaging, laboratory data, and consultant notes. Furthermore, the effort, time, and attention needed to maintain and utilize the EMR have led to a growing sense of dissatisfaction among physicians, lessening professional and personal well-being as a result. Clearly, this is an area of daily practice that requires improvement both for the delivery of safe and optimal care and physician wellness. It is important to emphasize that information technology is merely a tool and can never replace the clinical decisions that are

best made by the physician. Clinical knowledge and an understanding of a patient's needs, supplemented by quantitative tools, still represent the best approach to decision-making in the practice of medicine. THE PATIENT–PHYSICIAN RELATIONSHIP The significance of the intimate personal relationship between physician and patient cannot be too strongly emphasized, for in an extraordinarily large number of cases both the diagnosis and treatment are directly dependent on it. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient. —Francis W. Peabody, October 21, 1925,

Lecture at Harvard Medical School Physicians must never forget that patients are individuals with prob lems that all too often transcend their physical complaints. They are not "cases" or "admissions" or "diseases." Patients do not fail treat ments; treatments fail to benefit patients. This point is particularly important in this era of high technology in clinical medicine. Most patients are anxious and fearful. Physicians should instill confidence and offer reassurance, but they must never come across as arrogant, patronizing, impatient, or hurried. A professional attitude, coupled with warmth and openness, can do much to alleviate anxiety and to encourage patients to share all aspects of their medical history. Empa thy and compassion are the essential features of a caring physician. The

physician needs to consider the setting in which an illness occurs—in terms not only of patients themselves but also of their familial, social, and cultural backgrounds. The ideal patient–physician relationship is based on thorough knowledge of the patient, mutual trust, and the ability to communicate. Informed Consent The fundamental principles of medical ethics require physicians to act in the patient's best interest and to respect the patient's autonomy. Both principles are reflected in the process of informed consent. Patients are required to sign consent forms for most diagnostic or therapeutic procedures. Many patients possess limited medical knowledge and must rely on their physicians for advice. Com municating in a clear and understandable manner, physicians must fully discuss the alternatives for care and explain the risks, benefits, and likely consequences of each alternative. The physician is responsible for ensuring that the patient thoroughly understands these risks and benefits; encouraging questions is an important part of this process. It may be necessary to go over certain issues with the patient more than once. This is the very definition of informed consent. Complete, clear explanation and discussion of the proposed procedures and treatment can greatly mitigate the fear of the unknown that commonly accom panies hospitalization. Often the patient's understanding is enhanced by repeatedly discussing the issues in an unthreatening and supportive way and answering new questions that occur to the patient as they arise. Continuing efforts to educate the patient are essential. Patients are frequently inhibited from understanding by the fear of an uncer tain future and potential impact of the illness on themselves and their families. Clear communication can also help alleviate misunderstand ings in situations where complications of intervention occur. Special care should also be taken to ensure that a physician seeking a patient's informed consent has no real or apparent conflict of interest. Approach to Grave Prognoses and Death No circumstance is more distressing than the diagnosis of an incurable disease, particularly when premature death is inevitable. What should the patient and fam ily be told? What measures should be taken to maintain life? What can be done to optimize quality of life?

 Transparency of information, delivered in an appropriate manner, is essential in the face of a terminal illness. Even patients who seem unaware of their

medical circumstances, or whose family members have protected them from diagnoses or prognoses, often have keen insights into their condition. They may also have misunderstand ings that can lead to additional anxiety. The patient must be given an opportunity to speak with the physician and ask questions. A wise and insightful physician uses such open communication as the basis for assessing what the patient wants to know and when they want to know it. On the basis of the patient's responses, the physician can assess the most appropriate time and pace for sharing information. Ultimately, the patient must understand the expected course of the disease so that appropriate plans and preparations can be made. The patient should participate in decision-making with an understanding of the goal of treatment (palliation) and its likely effects. The patient's religious beliefs should be taken into consideration. Some patients may find it easier to share their feelings about death with their physician, nurses, or members of the clergy than with family members or friends. The physician should provide or arrange for emotional, physical, and spiritual support, and must be compassionate, unhurried, and open. In many instances, there is much to be gained by the laying on of hands. Pain should be controlled adequately, human dignity main tained, and isolation from family and close friends avoided. These aspects of care tend to be overlooked in hospitals, where the intrusion of life-sustaining equipment can detract from attention to the individ ual person and encourage concentration instead on the life-threatening disease, against which the battle ultimately will be lost in any case. In the face of terminal illness, the goal of medicine must shift from cure to care in the broadest sense of the term. Primum succurrere, first to help, is a guiding principle. In offering care to a dying patient, a physician should be prepared to provide information to family members and deal with their grief and sometimes their feelings of guilt or even anger. It is important for the physician to assure the family that everything

reasonable is being done. A substantial challenge in these discussions is that the physician often does not know exactly how to gauge the prognosis. In addition, various members of the health care team may offer different opinions. Good communication among providers is essential so that consistent information is provided to patients. This is especially important when the best path forward is uncertain. Advice from experts in palliative and terminal care should be sought whenever appropriate to ensure that clinicians are not providing patients with unrealistic expectations. For a more complete discussion of end-oflife care, see Chap. 13.

PART 1 The Profession of Medicine Maintaining Humanism and Professionalism Many trends in the delivery of health care tend to make medical care feel impersonal. These trends, some of which have been mentioned already, include (1) vigorous efforts to reduce the escalating costs of health care; (2) the growing number of managed-care programs, which are intended to reduce costs but where the patient may have little choice in selecting a physician; (3) increasing reliance on technological advances and com puterization; (4) the need for numerous physicians and other health professionals to be involved in the care of most patients who are seri ously ill; and (5) the growth of telemedicine and virtual encounters that place physical limitations on patient interactions. In light of these changes in the medical care system, it is a major challenge for physicians to maintain the humane aspects of medical care. The American Board of Internal Medicine, working together with the American College of Physicians–American Society of Inter nal Medicine and the European Federation of Internal Medicine, has published a Charter on Medical Professionalism that underscores three main principles in physicians' contract with society: (1) the primacy of patient welfare, (2) patient autonomy, and (3) social justice. While medical schools appropriately place substantial emphasis on profes sionalism, a physician's personal attributes,

including integrity, respect, and compassion, also are extremely important. Availability to the patient, expression of sincere concern, willingness to take the time to explain all aspects of the illness, and a nonjudgmen tal attitude when dealing with patients whose cultures, lifestyles, atti tudes, and values differ from those of the physician are just a few of the characteristics of a humane physician. Every physician will, at times, be challenged by patients who evoke strongly negative or positive emotional responses. Physicians should be alert to their own reactions to such situations and should consciously monitor and control their behavior so that the patient's best interest remains the principal moti vation for their actions at all times. Many organizations use implicit bias training to assist with these skills. Another important aspect of patient care involves an appreciation of the patient's "quality of life," a subjective assessment of what each patient values most. This assessment requires detailed, sometimes intimate knowledge of the patient, which usually can be obtained only through candid, unhurried, and often repeated conversations. Time pressures will always threaten these interactions, but they should not diminish the importance of understanding and seeking to fulfill the priorities of the patient. The patient encounter should be focused on the patient and not on distractions such as data available in the EMR displayed on the office or bedside computer. ■ ■EXPANDING FRONTIERS IN MEDICAL PRACTICE The Era of "Omics" In the spring of 2003, announcement of the complete sequencing of the human genome officially ushered in the genomic era. However, even before that landmark accomplishment, the practice of medicine had been evolving as a result of insights into both the human genome and the genomes of a wide variety of microbes. The clinical implications of these insights are illustrated by the complete genome sequencing of H1N1 influenza virus in 2009 and even faster sequencing of COVID-19 in early 2020, leading to the swift development and dissemination of safe and effective vaccines. Today, gene expression profiles are being used to guide therapy and inform prognosis for a number of diseases, and genotyping is providing a new means to assess the risk of certain diseases as well as variations in response to a number of drugs. Despite these advances, the use of

complex genomics in the diagnosis, prevention, and treatment of dis ease is still in its early stages. The task of physicians is complicated by the fact that phenotypes generally are determined not by genes alone but by the complex interactions among genes and gene products and by the interplay of genetic and environmental factors. Rapid progress is also being made in other areas of molecular medi cine. Epigenetics is the study of alterations in chromatin and histone proteins and methylation of DNA sequences (often caused by envi ronmental factors) that influence gene expression (Chap. 497). Every cell of the body has identical DNA sequences; the diverse phenotypes a person's cells manifest are, in part, the result of epigenetic regulation of gene expression. Epigenetic alterations are associated with a number of cancers and other diseases. Proteomics is the study of the entire library of proteins made in a cell or organ and the complex relationship of these proteins to disease. This huge repertoire of proteins is gener ated through alternate splicing of genes, posttranslational processing, and posttranslational modifications that often have unique functional consequences. The presence or absence of particular proteins in the circulation or in cells is being explored for many diagnostic and dis ease-screening applications. Microbiomics is the study of the resident microbes in humans and other mammals, which together compose the microbiome. The human haploid genome has ~23,000 genes, whereas the microbes residing on and in the human body encompass more than 3–4 million genes; these resident microbes are likely to be of great significance with regard to health status of the host. Ongoing research is demonstrating that the microbes inhabiting human mucosal and skin surfaces play a critical role in maturation of the immune system, in metabolic balance, in brain function, and in

disease susceptibility. A variety of environmental factors, including the use and overuse of antibiotics, have been tied experimentally to substantial increases in disorders such as obesity, metabolic syndrome, atherosclerosis, and immune-mediated diseases in both adults and children. Metagenomics, of which microbiomics is a part, is the genomic study of environmental species that have the potential to influence human biology directly or indirectly. An example is the study of exposures to microorganisms in farm environments that may be responsible for the lower incidence of asthma among children raised on farms. Metabolomics is the study of the range of metabolites in cells or organs and the ways they are altered in disease states. The aging process itself may leave telltale metabolic footprints that allow the prediction (and possibly the prevention) of organ dysfunction and disease. It seems likely that disease-associated patterns will be found in lipids, carbohydrates, membranes, mitochon dria and mitochondrial function, and other vital components of cells and tissues. Exposomics is the study of the exposome—i.e., the envi ronmental exposures such as smoking, sunlight, diet, exercise, educa tion, and violence that together have an enormous impact on health. All of this new information represents a challenge to the traditional reductionist approach to medical thinking. The variability of results in different patients, together with the large number of variables that can be assessed, creates challenges in identifying preclinical disease and defining disease states unequivocally. Accordingly, the tools of systems biology and network medicine are being applied to the enormous body of information (“big data”) now obtainable for every patient and may eventually provide new approaches to classifying, diagnosing, treating, and preventing disease. For a more complete discussion of a complex systems and network science approach to human disease, see Chap. 499. The rapidity of these advances may seem overwhelming to practic ing physicians; however, physicians have an important role to play in ensuring that these powerful technologies and sources of new informa tion are applied judiciously to patient care. Since omics are evolving so rapidly, physicians and other health care professionals must engage in continuous learning so that they can apply this new knowledge to the benefit of their patients’ health and well-being. Genetic testing requires wise counsel based on an understanding of the value and limitations of the tests as well as the implications of their results for specific individu als. For a more complete discussion of genetic testing, see Chap. 480. The Globalization of Medicine Physicians should be cognizant of diseases and health care services beyond local boundaries. Global

travel has critical implications for disease spread, and it is not uncom mon for diseases endemic to certain regions to be seen in other regions after a patient has traveled to and returned from those regions. The outbreak of Zika virus infections in the Americas is a cogent example of this phenomenon. In addition, factors such as wars, the migration of refugees, travel patterns, and the impact of increasing climate extremes are contributing to changing disease profiles worldwide. Patients have broader access to unique expertise or clinical trials at distant medi cal centers, even those in other countries, and the cost of travel may be offset by the quality of care at those distant locations. As much as any other factor influencing global aspects of medicine, the Internet has transformed the transfer of medical information throughout the world. This change has been accompanied by the transfer of techno logical skills through telemedicine and international consultation—for example, interpretation of radiologic images and pathologic specimens. For a complete discussion of global issues, see Chap. 485. Medicine on the Internet On the whole, the Internet has had a positive effect on the practice of medicine; through personal computers, a wide range of information is available to physicians and patients almost instantaneously at any time and from anywhere in the world. This medium holds enormous potential for the delivery of current

informa tion, practice guidelines, state-of-the-art conferences, journal content, textbooks (including this text), and direct communications with other physicians and specialists, expanding the depth and breadth of infor mation available to the physician regarding the diagnosis and care of patients. Medical journals are now accessible online, providing rapid sources of new information. By bringing them into direct and timely contact with the latest developments in medical care, this medium also serves to lessen the information gap that has hampered physicians and health care providers in remote areas. Patients, too, are turning to the Internet in increasing numbers to acquire information about their illnesses and therapies and to join Internet-based support groups. Patients often arrive at a clinic visit with sophisticated information about their illnesses. In this regard, physicians are challenged in a positive way to keep abreast of the lat est relevant information while serving as an information "editor" as patients navigate this seemingly endless source of information, the accuracy and validity of which are not uniform. A critically important caveat is that virtually anything can be pub lished on the Internet, with easy circumvention of the peer-review process that is an essential feature of academic publications. Both physicians and patients who search the Internet for medical informa tion must be aware of this danger. We have recently seen the adverse consequences of misinformation and disinformation (often in service of some political agenda) in social media. It is difficult to calculate the harm done by the widespread deceptions that prevented perhaps millions of people from accepting life-saving preventions like the COVID-19 vaccine. Notwithstanding this limitation, appropriate use of the Internet is revolutionizing information access for physicians and patients, and in this regard, the Internet represents a remarkable resource that was not available to practitioners a generation ago. Public Expectations and Accountability The general public's level of knowledge and sophistication regarding health issues has grown rapidly over the past few decades. As a result, expectations of the health care system in general and of physicians in particular have risen. Physicians are expected to master rapidly advancing fields (the science of medicine) while considering their patients' unique needs (the art of medicine). Thus, physicians are held accountable not only for the technical aspects of the care they provide but also for their patients' satisfaction with the delivery and costs of care. In many parts of the world, physicians increasingly are expected to account for the way in which they practice medicine by meeting certain standards prescribed by federal and local governments. The hospi talization of patients whose health care costs are reimbursed by the government and other third parties is subjected to utilization review. Thus, a physician must defend the cause for and duration of a patient's hospitalization if it falls outside certain "average" standards. Authoriza tion for reimbursement increasingly is based on documentation of the

nature and complexity of an illness, as reflected by recorded elements of the history and physical examination. A growing "pay-forperformance" movement seeks to link reimbursement to quality of care. The goal of this movement is to improve standards of health care and contain spiraling health care costs. In many parts of the United States, managed (capitated) care contracts with insurers have replaced traditional fee-for-service care, placing the onus of managing the cost of all care directly on the providers and increasing the emphasis on pre ventive strategies. In addition, physicians are expected to give evidence of their current competence through mandatory continuing education, patient record audits, maintenance of certification, and relicensing.

CHAPTER 1 The Practice of Medicine Medical Ethics and New Technologies The rapid pace of tech nological advances has profound implications for medical applications that go far beyond the traditional goals of disease prevention, treat ment, and cure. Cloning, gene therapy, gene editing,

human–computer interfaces, nanotechnology, and use of targeted therapies have the potential to modify inherited predispositions to disease, select desired characteristics in embryos, augment “normal” human performance, replace failing tissues, and substantially prolong life span. Given their unique training, physicians have a responsibility to help shape the debate on the appropriate uses of and limits placed on these new technologies and to consider carefully the ethical issues associated with the implementation of such interventions. As medicine becomes more complex, shared decision-making is increasingly important, not only in areas such as genetic counseling and end-of-life care but also in diagnostic and treatment options. Learning Medicine More than a century has passed since the publication of the Flexner Report, a seminal study that transformed medical education and emphasized the scientific foundations of medi cine as well as the acquisition of clinical skills. In an era of burgeoning information and access to medical simulation and informatics, many schools are implementing new curricula that emphasize lifelong learn ing and the acquisition of competencies in teamwork, communication skills, system-based practice, and professionalism. The tools of medi cine also change continuously, necessitating formal training in the use of EMRs, large datasets, ultrasound, robotics, and new imaging tech niques. These and other features of the medical school curriculum pro vide the foundation for many of the themes highlighted in this chapter and are expected to allow physicians to progress, with experience and learning over time, from competency to proficiency to mastery. At a time when the amount of information that must be mastered to practice medicine continues to expand, increasing pressures both within and outside of medicine have led to the implementation of restrictions on the amount of time a physician-in-training can spend in the hospital and in clinics. Because the benefits associated with continuity of medical care and observation of a patient’s progress over time were thought to be outstripped by the stresses imposed on trainees by long hours and by fatigue-related errors, strict training parameters were introduced by the Accreditation Council for Graduate Medical Education (ACGME) to reduce fatigue and enhance learning. The impact of these changes is still being assessed, and there are con tinual efforts to optimize training and move toward competency-based endpoints. An unavoidable by-product of fewer hours at the bedside is an increase in the number of “handoffs” of patient responsibility from one physician to another. It is imperative that these transitions of responsibility be handled with care and thoroughness, with all relevant information exchanged and acknowledged. These issues highlight the challenge our profession has in establishing a reliable measure of physi cian effectiveness. The Physician as Perpetual Student From the time physi cians graduate from medical school, it becomes all too apparent that this milestone is symbolic and that they must embrace the role of a “perpetual student.” This realization is at the same time exhilarating and anxiety-provoking. It is exhilarating because physicians can apply constantly expanding knowledge to the treatment of their patients; it is anxiety-provoking because physicians realize that they will never know as much as they want or need to know. Ideally, physicians will

02 - 2 Promoting Good Health

2 Promoting Good Health

translate the latter feeling into energy through which they can continue to improve and reach their potential. It is the physician’s responsibility to pursue new knowledge continually by reading, attending confer ences and courses, and consulting colleagues and the Internet. This is often a difficult task for a busy practitioner; however, a commitment to continued learning is an integral part of being a physician and must be given the highest priority.

PART 1 The Profession of Medicine The Physician as Citizen Being a physician is a privilege. The capacity to apply one’s skills for the benefit of fellow human beings is a noble calling. The physician–patient relationship is inherently unbalanced in the distribution of power. In light of their influence, physicians must always be aware of the potential impact of what they do and say and must always strive to strip away individual biases and preferences to find what is best for their patients. To the extent possible, physicians should also act within their communities to promote health and alleviate suffering. Meeting these goals begins by setting a healthy example and continues in taking action to deliver needed care even when personal financial compensation may not be available. Research, Teaching, and the Practice of Medicine The word doctor is derived from the Latin docere, “to teach.” As teachers, physicians should share information and medical knowledge with colleagues, students of medicine and related professions, and their patients. The practice of medicine is dependent on the sum total of medical knowledge, which in turn is based on an unending chain of scientific discovery, clinical observation, analysis, and interpretation. Advances in medicine depend on the acquisition of new information through research, and improved medical care requires the transmission of that information. As part of their broader societal responsibilities, physicians should encourage patients to participate in ethical and properly approved clinical investigations if these studies do not impose undue hazard, discomfort, or inconvenience. Physicians engaged in clinical research must be alert to potential conflicts of interest between their research goals and their obligations to individual patients. The best interests of the patient must always take priority. To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions. —William Osler, 1849–1919 ■ ■FURTHER READING Cheston CC et al: Social media use in medical education: A systematic review. Acad Med 88:893, 2013. Cooke M et al: American medical education 100 years after the Flexner report. N Engl J Med 355:1339, 2006. Excel JL et al: Vaccine development for emerging infectious diseases. Nat Med 27:591, 2021. Institute of Medicine: Dying in America: Improving Quality and Honoring Individual Preferences Near the End of

Life. Washington, DC, National Academies Press, 2015. Institute of Medicine: Improving Diagnosis in Health Care. Washington, DC, National Academies of Sciences, Engineering, and Medicine, 2015. Kohane IS: Injecting artificial intelligence into medicine. NEJM AI 1, 2023. Levine DM et al: Hospital-level care at home for acutely ill adults: A qualitative evaluation of a randomized controlled trial. J Gen Intern Med 36:1965, 2021. Romanella M et al: The 2022 report of the Lancet Countdown on health and climate change: Health at the mercy of fossil fuels. Lancet 400:1619, 2022. Stern DT, Papadakis M: The developing physician—becoming a professional. N Engl J Med 355:1794, 2006. West P et al: Intervention to promote physician well-being, job satisfaction, and professionalism. A randomized clinical trial. JAMA Intern Med 174:527, 2014.

Donald M. Lloyd-Jones,

Kathleen M. McKibbin

Promoting Good Health ■ ■GOALS AND APPROACHES TO PREVENTION Prevention of acute and chronic diseases before their onset has been recognized as one of the hallmarks of excellent medical practice for centuries and is now used as a metric for highly functioning health care systems. The ultimate goal of preventive strategies is to avoid premature death. However, as longevity has increased dramatically worldwide over the last century (largely as a result of public health practices), increasing emphasis is placed on prevention for the purpose of preserving quality of life and extending the health span, not just the life span. Given that all patients will eventually die, the goal of preven tion ultimately becomes compression of morbidity toward the end of the life span; that is, reduction of the amount of burden and time spent with disease prior to dying. As shown in Fig. 2-1, normative aging tends to involve a steady decline in the stock of health, with accelerat ing decline over time. Successful prevention offers the opportunity both to extend life and to extend healthy life, thus “squaring the curve” of health loss during aging. Prevention strategies have been characterized as tertiary, secondary, primary, and primordial. Tertiary prevention requires rapid action to prevent imminent death and preserve organ function in the setting of acute illness, such as through thrombolysis or thrombectomy in acute ischemic stroke. Secondary prevention strategies focus on avoiding the recurrence of disease and death in an individual who is already affected. For example, tamoxifen is recommended for women with surgically treated early-stage, estrogen receptor–positive breast cancer, because it reduces the risk of recurrent breast cancer (including in the contralateral breast) and death. Primary prevention attempts to reduce the risk of incident disease among individuals with one or more risk factors. Treatment of elevated blood pressure in individuals who have not yet experienced cardiovascular disease represents one example of primary prevention that has proven effective in reducing the incidence of stroke, heart failure, and coronary heart disease. Primordial prevention is a more recent concept (first introduced in 1979) that focuses on prevention of the development of risk factors for disease, not just prevention of disease. Primordial prevention strate gies emphasize upstream determinants of risk for chronic diseases, such as eating patterns, physical activity, and environmental and social determinants of health. It therefore encompasses medical treatment strategies for some individuals as well as a strong reliance on public health and social policy. It is increasingly clear that primordial preven tion represents the ultimate means for reducing the burden of chronic

Squaring the curve with compression of morbidity 0.8 Stock of health 0.6 Normative aging with gradual loss of stock of health 0.4 0.2

Age

FIGURE 2-1 Loss of health with aging. Representation of normative aging with loss of the full stock of health with which individuals are born (indicating gain of morbidity), contrasted with a squared curve with greater longevity and fuller stock of health (less morbidity) until shortly before death. The “squared curve” represents the likely ideal situation for most patients.

diseases of aging. Once risk factors develop, it is difficult to restore risk to the low level of someone who never developed the risk fac tor. The time spent with adverse levels of the risk factor often causes irreversible damage that precludes complete restoration of low risk. For example, individuals with hypertension who are treated back to optimal levels (<120/<80 mmHg) do have a lower risk compared with untreated patients with hypertension, but they still have twice the risk of cardiovascular events as those who maintained optimal blood pres sure without medications. Patients with elevated blood pressure that is subsequently treated have greater left ventricular mass index, worse renal function, and more evidence of atherosclerosis and other target organ damage as a result of the time spent with elevated blood pres sure; such damage cannot be fully reversed despite efficacious therapy with antihypertensive medications. Conversely, as described below in greater detail, individuals who maintain optimal levels of all major cardiovascular risk factors into middle age through primordial preven tion essentially abolish their lifetime risk of developing cardiovascular disease while also living substantially longer and having a lower burden and later onset of other chronic comorbid illnesses (compression of morbidity). Prevention strategies should be distinguished from disease-screening strategies. Screening attempts to detect evidence of disease at its ear liest stages, when treatment is likely to be more efficacious than for advanced disease (Chap. 6). Screening can be performed in service of prevention, especially if it aids in identifying preclinical mark ers, such as dyslipidemia or hyperglycemia, associated with elevated disease risk. ■ ■HEALTH PROMOTION In recent decades, medical practice has increasingly focused on clinical and public health approaches to promote health and not just prevent disease. Prevention of disease is a worthy individual and societal goal in and of itself, but it does not necessarily guarantee health. Health is a broader construct encompassing more than just absence of disease. It includes biologic, physiologic, and psychological domains (among others) in a continuum, rather than occurring as a dichotomous trait. Health is therefore somewhat subjective, but attempts have been made to use more objective criteria to define health in order to raise aware ness, prevent disease, and promote healthy longevity. For example, in 2010, the American Heart Association (AHA) formally defined a new construct of “cardiovascular health” based on evidence of associations with longevity, disease avoidance, healthy longevity, and quality of life. The concept was updated and expanded in 2022 to encompass eight metrics that help define an individual’s or population’s current health status. The eight metrics (termed Life’s Essential 8TM) include diet, physical activity, sleep, nicotine exposure, body mass index, blood lipids, glycemia, and blood pressure. Each met ric is scored on a scale of 0 to 100 points (higher is better), and overall health is measured as the average of the scores (also from 0 to 100). Higher cardiovascular health scores at all ages have been associated with greater longevity, lower incidence of cardiovascular disease, lower incidence of other chronic diseases of aging (including dementia, can cer, diabetes, and more), compression of morbidity, greater quality of life, and lower

health care costs, achieving both individual and societal goals for healthy aging and further establishing the critical importance of primordial prevention and health promotion. Focusing on health promotion, rather than just disease prevention, may also provide greater motivation for patients to pursue lifestyle changes or adhere to clinician recommendations. Extensive literature suggests that providing patients solely with information regarding disease risk, or risk reduction with treatment, is unlikely to motivate desired behavior change. Empowering patients with strategies to achieve positive health goals after discussing risks can provide more effective adherence and better long-term outcomes. In the case of smoking cessation, enumerating only the risks of smoking can lead to patient inertia and therapeutic nihilism and has proven to be an inef fective approach, whereas strategies that incorporate positive health messaging, support, and feedback, with appropriate use of evidence-based therapies, have proven far more effective.

■ ■PRIORITIZING PREVENTION STRATEGIES In secondary prevention, the patient already has manifest clinical dis ease and is therefore at high risk for progression. The approach should be to work with the patient to implement all evidence-based strategies that will help to prevent recurrence or progression. This will typically include drug therapy as well as therapeutic lifestyle changes to control ongoing risk factors that may have caused disease in the first place. Juggling priorities can be difficult, and barriers to implementation are many, including costs, time, patient health literacy, and patient and caregiver capacity to organize the regimen. Addressing these potential barriers with the patient can help to forge a therapeutic bond and may improve adherence; ignoring them will likely lead to therapeutic failure. Numerous studies demonstrate that, even in high-functioning health systems, only ~50% of patients are taking recommended, evidence-based secondary prevention medications, such as statins, by 1 year after a myocardial infarction.

CHAPTER 2 Promoting Good Health In patients who are eligible for primary prevention strategies, it is important to frame the discussion around the overall evidence base as well as an individual patient’s likelihood of benefit from a given preventive intervention. A first step is to understand the patient’s estimated absolute risk for disease in the foreseeable future or during their remaining life span. However, absolute risk estimation and pre sentation of those risks are generally insufficient to motivate behavior change. It is critical to assess the patient’s understanding and tolerance of the risk, their readiness to implement lifestyle changes or adhere to drug therapy, and their overall preferences regarding use of drug therapy to prevent an event (e.g., cancer, myocardial infarction, stroke). The clinician can help the patient by informing them of the risks for disease and potential for absolute benefits (and harms) from the avail able evidence-based choices. This may take more than one conversa tion, but given that diseases, such as cancer and cardiovascular disease, are the leading causes of premature death and disability, the time is well spent. Partnering with the patient through motivational interviewing may assist in the process of selecting initial approaches to prevention. Selecting an area that the patient feels they are ready to change can lead to better adherence and greater achievement of success in the short and longer term. If the patient is uncertain what course to choose, prudence would dictate focusing on control of risk factors that may lead to the most rapid reduction in risk for acute events. For example, blood pres sure is both a chronic risk factor and an acute trigger for cardiovascular events. Thus, if a patient has both significant elevations in blood pres sure and dyslipidemia, it would be appropriate to focus initial efforts on blood pressure control. Likewise, a focus on smoking cessation can lead to more rapid reductions in risk for acute events than some other lifestyle interventions. ■ ■PREVENTION AND

ACROSS THE LIFE COURSE Periodic Health Evaluations The “routine annual physical” has in many ways become an expected part of the patient-physician rela tionship in primary care practice. However, evidence for the efficacy of the periodic health evaluation in asymptomatic adults unselected for risk factors or disease is mixed and depends on the study design and outcome. Systematic reviews and meta-analyses of published random ized trials have consistently observed lack of benefit (and also lack of harm) in terms of total mortality in association with periodic health evaluations. Data are more heterogeneous but overall suggest no ben efit for cancer- or cardiovascular-specific mortality, with the potential for either benefit or harm depending on number of evaluations and patient-level factors. Well-designed studies on nonfatal clinical events and morbidity have been sparsely reported, but there appear to be no large effects. Periodic health evaluations do appear to lead to greater diagnosis of certain conditions such as hypertension and dyslipidemia, as expected. Likewise, periodic health examinations also improve the delivery of recommended preventive services, such as gynecologic examinations and Papanicolaou smears, fecal occult blood testing, and cholesterol

screening. The benefits and risks associated with screening tests are discussed in detail in Chap. 6. Risks of routine evaluations include inappropriate testing or overtesting, or false-positive findings that require follow-up and induce patients to worry. Periodic health exami nations appear to be associated with less patient worry. On balance, given the lack of convincing evidence of harm and the potential for better delivery of appropriate screening, counseling, and preventive services, periodic health evaluations appear reasonable for general populations at average risk for chronic conditions.

PART 1 The Profession of Medicine It is important to note that routine annual comprehensive physical examinations of asymptomatic adult patients have very low yield and may take an inordinate amount of time in a wellness visit. Such time may be better spent on assessing and counseling the patient on other aspects of their health, as discussed below. Evidence-based components that should be included in periodic evaluations focused on health and prevention include a number of age-appropriate screening tests for chronic disease and risk factors, preventive interventions including immunizations and chemoprevention for at-risk individuals, and pre ventive counseling. The U.S. Preventive Services Task Force publishes its Guide to Clinical Preventive Services, which contains evidence-based recommendations from the Task Force on preventive services for which there is a high degree of certainty that the service provides at least moderate net clinical benefit (i.e., benefits outweigh harms sig nificantly and to a reasonable magnitude). Healthy Behaviors and Lifestyles Owing to the heterogeneity of study designs and the diverse nature of lifestyle interventions studied, many clinicians are uncertain as to how to deliver advice regarding healthy behaviors and lifestyles. Nevertheless, adverse behaviors and lifestyles contribute to >75% of premature, preventable deaths and disability. Estimates from the U.S. National Health and Nutrition Examination Survey indicate that fewer than 1% of Americans achieve an optimal heart-healthy eating pattern. Thus, whereas there are many TABLE 2-1 Guidelines and Key Recommendations from the Dietary Guidelines for Americans, 2020–2025 GUIDELINES KEY RECOMMENDATIONS

1. Follow a healthy dietary pattern at every life The Dietary Guidelines' Key Recommendations for healthy eating patterns should be applied in their entirety, given the interconnected relationship that each dietary component can have with others. They are also intended as a framework to accommodate personal preferences, cultural traditions, and budgetary considerations. Focus on meeting food group needs with nutrient-dense foods and beverages, and stay within calorie limits to achieve a healthy weight and reduce the risk of chronic disease. The core elements that make up a healthy dietary pattern include: • Vegetables of all types—dark green; red and orange; beans, peas, and lentils; starchy; and other stage. For the first 6 months of life, infants should exclusively be fed human milk, or iron-fortified formula if human milk is unavailable. From 6 to 12 months, infants should be introduced to a variety of complementary nutrient-dense foods. From 12 months to older adulthood, the dietary pattern should meet nutrient needs, help achieve a healthy body weight, and reduce the risk of chronic disease.
2. Customize and enjoy nutrient-dense food and vegetables • Fruits, especially whole fruit • Grains, at least half of which are whole grain • Dairy, including fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations. The Dietary Guidelines provide a framework of several dietary patterns intended to be customized to individual needs and preferences, as well as the foodways of the diverse cultures in the United States.
3. Focus on meeting food group needs with nutrientbeverages and yogurt as alternatives • Protein foods, including lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products • Oils, including vegetable oils and oils in food, such as seafood and nuts A healthy eating pattern limits: • Added sugars—Less than 10% of calories per day starting at age 2. Avoid foods and beverages with added dense foods and beverages and stay within calorie limits. Nutrient-dense foods provide vitamins, minerals, and other health-promoting components and have no or little added sugars, saturated fat, and sodium. A healthy dietary pattern consists of nutrient-dense forms of foods and beverages across all food groups, in recommended amounts, and within calorie limits.
4. Limit foods and beverages higher in added sugars, sugars for those younger than age 2. • Saturated fat—Less than 10% of calories per day starting at age 2. • Sodium—Less than 2300 mg/d—and even less for children younger than age 14. • Alcoholic beverages—Adults of legal drinking age can choose not to drink or to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women, when alcohol is consumed. Drinking less is better for health than drinking more. There are some adults who should not drink alcohol, such as women who are pregnant. Meet the U.S. Department of Health and Human Services' Physical Activity Guidelines for Americans In tandem with the recommendations above, Americans of all ages—children, adolescents, adults, and older adults—should meet the Physical Activity Guidelines for Americans to help promote health and reduce the risk of chronic disease. Americans should aim to achieve and maintain a healthy body weight. The relationship between diet and physical activity contributes to calorie balance and managing body weight. saturated fat, and sodium, and limit alcoholic beverages. At every life stage, meeting food group recommendations, even with nutrient-dense choices, fulfills most of a person's daily calorie needs and sodium limits, with little room for extra added sugars, saturated fat, or sodium, or for alcoholic beverages. Source: Adapted from the Dietary Guidelines for

Americans, 2020-2025. Washington, DC: U.S. Department of Agriculture and U.S. Department of Health and Human Services;
5. Available at https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf.

demands on time during a typical patient-clinician encounter, few things may have more impact on longevity, health, and quality of life for asymptomatic patients than an efficient approach to assessing, doc umenting, and improving patients' health behaviors. Indeed, the mere act of assessing health behaviors has been shown to affect patients' health behaviors. Facility with tools for assessment of lifestyle and with strategies for counseling are therefore of paramount importance. Healthy Eating Patterns (see Chap. 343) Despite the existence of numerous "fad" diets and seemingly inconsistent recommendations on dietary composition, there is remarkable agreement about what should constitute a healthy eating pattern for the broad population to avoid nutritional deficits (i.e., vitamin deficiency) and excesses (i.e., excessive caloric intake) and to maximize potential health (Table 2-1). Optimal eating patterns consist of whole fruits and vegetables, whole grains, lean proteins, and healthy oils, and allow for nonfat or low-fat dairy intake. They tend to exclude frequent ingestion of foods high in refined sugars and starches, saturated fat, and sodium. Since sodium and refined sugars and starches are the hallmark of much of the pro cessed/packaged food supply, a simple rule of thumb is to provide or cook the majority of one's own meals starting from whole foods and emphasizing fruits and vegetables. Likewise, foods prepared outside of the home tend to have higher fat and sodium content, so special atten tion to menu choices focused on fruits, vegetables, lean proteins, and whole grains, while minimizing sauces and dressings, can help most individuals follow healthier eating patterns when eating food prepared outside the home. In all cases, sugar-sweetened beverages and non nutritious snack foods should be minimized. If snacks are included, small amounts of healthy nuts and seeds or more fruits and vegetables should be encouraged. Specific conditions and diseases, such as diabetes or hypertension, other metabolic disorders, allergies, and gastrointestinal disorders, may require tailored approaches to diet. In counseling most patients,

the general approach should focus on whole foods, eating patterns, and appropriate calorie balance, rather than on specific micronutrients such as electrolytes or selected vitamins. It should be remembered that most patients have difficulty understanding nutritional labels on packaged foods, with the attendant demands on numeracy and health literacy. Dietary guidelines are published by the U.S. Department of Agri culture (USDA) and U.S. Department of Health and Human Services every 5 years, and these guidelines have undergone substantial evolu tion over time. The current U.S. Dietary Guidelines and Key Recom mendations for 2020–2025 are summarized in Table 2-1 and emphasize the importance of healthy eating patterns for every stage of life, to avoid chronic diseases including obesity, diabetes, cancer, and cardiovascular disease. The core elements include eating patterns with nutrient-dense (rather than calorie-dense) whole foods and appropriate caloric intake to achieve and maintain healthy weight. The USDA guidelines focus on the concept of a healthy plate (rather than the prior food pyramid) for ease of counseling and adoption. Fifty percent of the plate should con sist of vegetables and whole fruits, with remaining portions for whole grains and lean protein foods. When using fat for cooking, it should be done by sauteing in healthier oils (e.g., canola oil), and addition of judicious amounts of healthy raw oils (e.g., olive oil, nuts) to dishes is appropriate. Recommendations also focus on limitation of foods and beverages higher in added sugars, saturated fat, and sodium, and mod eration or

avoidance of alcohol intake. The USDA guidelines focus on specific healthy eating patterns that adhere to these broad recommendations and are appropriate for ~97% of the general population. They identify a “Healthy U.S.-Style Dietary Pattern” that adheres closely to the evidence-based Dietary Approaches to Stop Hypertension (DASH) eating pattern but is customizable for different cultural or personal preferences. Alternative patterns, which vary more in emphasis than in content, include a “Healthy Mediterra nean-Style Dietary Pattern” and a “Healthy Vegetarian Dietary Pattern.” AGE- AND SEX-SPECIFIC RECOMMENDATIONS Current dietary frame work recommendations are generally similar for all life stages from ages ≥12 months, but recommended levels of caloric intake (and hence amounts of foods) differ by age, sex, and physical activity level. For example, recommended caloric intake ranges from 1000 calories/d for sedentary 2-year-old children to as high as 3200 calories/d for active 16- to 18-year-old young men. Recommended caloric intakes peak in late adolescence or early adulthood for men and women and gradually decrease over ensuing decades. As with all lifestyle counseling aimed at behavior change, dietary approaches that partner with the patient and utilize motivational inter viewing strategies and shared goals and commitments tend to work best, as described below (see “Approach to the Patient”). Physical Activity Similar to the approach to counseling regarding healthy eating patterns, recommendations on participation in physical activity emphasize the point that any physical activity is better than none. A simple rule of thumb for patients is: “If you are doing nothing, do something; and if you are doing something, do more, every day.” The evidence base for physical activity indicates that the marginal ben efits from physical activity are greatest in advancing from no activity to low levels of moderate activity. With increasing duration and intensity of activity, there is a continued curvilinear increase in health benefits, but the marginal gains for each additional minute of moderate-to-

vigorous activity slowly diminish. Thus, for adults, the recommended amount of physical activity is 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity per week, performed in episodes of at least 5 min, and preferably spread throughout the week, plus participation in muscle-strengthening activity at least 2 days per week. Additional health benefits can be realized by engaging in physical activity beyond this amount. In counseling patients regarding physical activity, it is important to note that sedentary time (e.g., seated at work or at home in front of electronic screens) has adverse health consequences independent of the lack of physical activity during these episodes. Therefore, even modest

efforts like standing at the desk and doing gentle stretching for periods during the day may be beneficial. It is also important to emphasize that participating in a variety of aerobic activities (biking, swimming, walking, jogging, rowing, elliptical training, stair-climbing, etc.) can be beneficial and may help to avoid overuse injuries and boredom with the exercise regimen. Addition of resistance (muscle-strengthening) activities is also beneficial for health improvement. Emphasis should be placed on body-weight resistance or weights that allow more repeti tions (e.g., 3 sets of 15–20 repetitions that can be performed comfort ably, with a rest period in between) and on avoiding breath-holding and straining against a closed glottis.

CHAPTER 2 Promoting Good Health SUDDEN CARDIAC DEATH RISK Patients may express concerns regard ing the risk of sudden cardiac death during exercise. Whereas the risk of sudden death during exercise does increase directly with the amount of time spent exercising, this association is substantially mitigated by training effects. Thus, patients embarking on an exercise program

should be encouraged to increase the duration of aerobic exercise gradually as tolerated, aiming for episodes of at least 30 min 5 times a week as an ideal. Once a comfortable duration is reached, incorporat ing interval training periods of more intensive activity interspersed during the exercise can provide greater fitness gains. EXTREME ENDURANCE ACTIVITIES As with other forms of exercise, extreme endurance activities such as triathlons and marathons should be undertaken only with appropriate and graded training. Such activi ties tend to take a greater toll on the musculoskeletal system over time than less extreme activities, and they are also associated with measur able damage to the myocardium and greater risks for other organ damage. Athletes participating in endurance activities routinely have elevations in cardiac troponin (a specific circulating marker of myocar dial cell damage and death) at the end of the race, although elevations are lower in those who are well trained. Patients and clinicians should consider the patient's overall health, specific limitations, potential for injury, and ability to train in decision-making regarding participation in endurance events. AGE-SPECIFIC RECOMMENDATIONS The U.S. Department of Health and Human Services' Physical Activity Guidelines for Americans, second edition (2018) (Table 2-2), recommend that preschool-aged children (aged 3–5 years) should be physically active throughout the day in a variety of activity types to enhance growth and development. Children and adolescents aged 6–17 years should participate in ≥60 min of physical activity daily, most of which should be moderate- or vigorous-

intensity aerobic activity, including vigorous, muscle-strengthening, and bone-strengthening activities at least 3 days a week each. As noted above, adults aged 18–64 years are recommended to pursue at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity per week (or equivalent combinations), with at least

2 days of muscle-strengthening activities. Adults aged ≥65 years should follow the adult guidelines or be as active as possible as abilities and conditions allow. For older adults, special emphasis is also placed on multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities. Sleep Hygiene Sleeping between 7 and 9 h per night appears to be optimal for health in adults aged ≥18 years. Sleeping <7 h is associated with adverse outcomes, including obesity, diabetes, elevated blood pressure, cardiovascular disease, depression, and all-cause mortality, as well as physiologic disturbances such as impaired immune function, increased pain sensitivity, and impaired cognitive performance. Con versely, achieving appropriate levels of sleep is associated with more success in weight loss, better blood pressure control among patients with hypertension, and improved mental health and performance. Regular sleep more than 9 h per night is appropriate for children and adolescents or individuals recovering from sleep deprivation or illness, but for most individuals, the effects on health are uncertain. Patients often express concerns about the quantity and quality of their sleep. With aging, both aspects of sleep tend to decline, even with out overt sleep disorders. Documentation of sleep using a sleep log may assist in understanding different types of insomnia and sleep disorders.

PART 1 The Profession of Medicine TABLE 2-2 Recommendations from Physical Activity Guidelines for Americans, 2nd Edition (2018) AGE RECOMMENDATIONS 3–5 years • Preschool-aged children (ages 3 through 5 years) should be physically active throughout the day to enhance growth and development. • Adult caregivers of preschool-aged children should encourage active play that includes a variety of activity types. 6–17 years • It is important to provide young people opportunities and encouragement to participate in physical activities that are appropriate for their

age, that are enjoyable, and that offer variety. • Children and adolescents ages 6 through 17 years should do 60 min (1 h) or more of moderate-to-vigorous physical activity daily: • Aerobic: Most of the 60 min or more per day should be either moderate- or vigorous-intensity aerobic physical activity and should include vigorous-intensity physical activity on at least 3 days a week. • Muscle-strengthening: As part of their 60 min or more of daily physical activity, children and adolescents should include muscle-strengthening physical activity on at least 3 days a week. • Bone-strengthening: As part of their 60 min or more of daily physical activity, children and adolescents should include bone-strengthening physical activity on at least 3 days a week. 18–64 years • Adults should move more and sit less throughout the day. Some physical activity is better than none. Adults who sit less and do any amount of moderate-to-vigorous physical activity gain some health benefits. • For substantial health benefits, adults should do at least 150 min (2 h and 30 min) to 300 min (5 h) a week of moderate-intensity or 75 min (1 h and 15 min) to 150 min (2 h and 30 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorousintensity aerobic activity. Preferably, aerobic activity should be spread throughout the week. • Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 min (5 h) of moderate-intensity physical activity a week. • Adults should also do muscle-strengthening activities of moderate or greater intensity and that involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits. ≥65 years • The key guidelines for adults also apply to older adults. In addition, the following key guidelines are just for older adults: • As part of their weekly physical activity, older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities. • Older adults should determine their level of effort for physical activity relative to their level of fitness. • Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely. • When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow. Moderate-intensity physical activity: Aerobic activity that increases a person’s heart rate and breathing to some extent. On a scale relative to a person’s capacity, moderate-intensity activity is usually a 5 or 6 on a 0 to 10 scale. Brisk walking, dancing, swimming, or bicycling on a level terrain are examples. Vigorous-intensity physical activity: Aerobic activity that greatly increases a person’s heart rate and breathing. On a scale relative to a person’s capacity, vigorous-intensity activity is usually a 7 or 8 on a 0 to 10 scale. Jogging, singles tennis, swimming continuous laps, or bicycling uphill are examples. Muscle-strengthening activity: Physical activity, including exercise that increases skeletal muscle strength, power, endurance, and mass. It includes strength training, resistance training, and muscular strength and endurance exercises. Bone-strengthening activity: Physical activity that produces an impact or tension force on bones, which promotes bone growth and strength. Running, jumping rope, and lifting weights are examples. Source: Adapted from U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S. Department of Health and Human Services; 2018. Available at https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf. Encouraging daily activity to promote fatigue, avoidance of eating and drinking alcohol too close to bedtime, and regular daily sleep habits may help patients achieve better sleep. Regular use of sedative medi cations should generally be discouraged given the high potential for dependence, addiction, and altered sleep quality. DISORDERS OF SLEEP The prevalence of sleep-related breathing disor ders, including obstructive sleep apnea (OSA), is high and increasing in our aging and increasingly overweight population. A recent systematic review suggested that that the

prevalence of clinically important OSA in the general adult population may be between 9 and 38%, with higher rates in men versus women, older versus younger adults, and those with higher versus lower body mass index (BMI). In the United States, ~40 million adults, and worldwide, nearly a billion adults, are affected by OSA. Patients with persistent complaints of poor sleep quality or excessive daytime somnolence or with witnessed apneic spells may ben efit from screening for sleep disorders prior to consideration of a formal sleep study. A number of clinical tools have been developed to screen for sleep apnea, including the Epworth Sleepiness Scale, the STOP (snoring, tiredness, observed apnea, high blood pressure) Questionnaire, and the STOP-Bang Questionnaire (STOP plus assessment of BMI, age, neck circumference, and gender), among others. The U.S. Preventive Services Task Force found that current evidence is insufficient to assess the bal ance of benefits and harms of screening for OSA in asymptomatic adults owing to a lack of validation data in primary care settings. Nonetheless, the high prevalence and significant health consequences of sleep apnea suggest that clinicians should be alert for its potential presence, par ticularly in patients who are obese with symptoms of excessive daytime somnolence or witnessed apnea episodes. Other sleep disorders, such as restless leg syndrome, may be identified with simple history. Weight Management Overweight and obesity are prevalent in epidemic proportions in the United States and other industrialized nations (Chaps. 413 and 414). Since 1985, the prevalence of obesity in the United States has increased from ~10 to ~35%, and the prevalence of overweight is now ~40%. Overweight and obesity disproportion ately affect individuals in lower socioeconomic strata and in many underrepresented populations, including individuals who identify as Black, Latino, and American Indian. In all race/ethnic groups, both overweight and obesity are associated with adverse health conse quences, including diabetes, certain cancers, cardiovascular diseases, and degenerative joint disease. Eating disorders such as anorexia and bulimia are much less common but pose major health consequences for affected patients and should be suspected particularly in younger women with history of rapid weight shifts, electrolyte disturbances, or underweight status. Weight loss is one of the most difficult preventive interventions to achieve and sustain over time. However, several key factors can assist the patient and clinician, and early referral to a dietician can be very helpful. The first therapeutic goal is to aim for weight stabilization. Many of the risks of overweight and obesity are driven more strongly by continued weight gain, rather than overweight/obese status per se. Working with the patient to find initial strategies for weight mainte nance can be a successful initial step with success for many patients. For those who can progress to considering weight loss, it is critical to help the patient understand that there is no standard solution. Experimentation and documentation are key. Tools to assist patients can include food and weight logs, activity logs, and smart phone apps. Some patients respond best to structured approaches such as intermit tent fasting regimens or commercial dietary programs where meals are

provided. Any of these approaches can be tried with or without social group supports. The key construct for weight loss is, of course, negative calorie bal ance. This is achieved through a combination of reduced caloric intake and increased physical activity. Patients may already understand, from prior weight loss attempts, what combination works best for them to achieve this. Some patients find that they cannot lose weight without increasing their exercise. For many, reduction of caloric intake is most efficient. Encouraging the patient to find what works for them is most important. The same principle holds for dietary content. Well-done feeding studies indicate that weight loss is dependent far more on the reduction of caloric intake than on the relative composition of fat, protein, and carbohydrate in the diet. There may be other medical reasons to

choose one approach over another, but if not, encouraging the patient to pick one approach and document the results is an impor tant start. Newer pharmacologic agents (e.g., GLP1 receptor agonists) appear to be remarkably successful in helping patients achieve substan tial weight loss (up to 20% of baseline body weight), with proven shortterm benefits in cardiovascular risk reduction, but issues of access, cost, and long-term safety remain. Once weight loss is achieved, increase in activity is often required for its successful maintenance. Tobacco Cessation (see Chap. 465) Escaping nicotine depen dence is another major, but critical, challenge to prevention and wellness efforts. The addictive effects of nicotine have been well documented, with effects that can last for years after successful ces sation. Assessing a patient's past history of cessation attempts and current readiness for change are key first steps in forging a successful approach. Frequent follow-up and reinforcement, as well as use of nicotine replacement therapy and other cessation-promoting medi cations, are additional critical elements. Recidivism is the rule, and patients should expect to resume smoking and attempt again as they journey to tobacco cessation. Electronic cigarettes have some evidence for benefit in adult cessation of combustible tobacco, but this approach may transfer and worsen nicotine addiction, and the potential for use by adolescents and young adults who are not smokers represents a major public health threat for a new generation of nicotine addiction, with unknown health consequences as a result of the high doses of nicotine delivered to developing organs, including the brain. Vaping of other substances, often in association with flavoring compounds, has also been associated with pulmonary and cardiovascular damage and should be actively discouraged. ■ ■VACCINATION (CHAP. 129) One of the major advances in public health that has contributed to increases in health and longevity worldwide is the development of safe and effective vaccinations against endemic and epidemic infectious diseases. Patients should be counseled regarding age-appropriate vac cinations for their children and for themselves. Some individuals may be reluctant to receive a vaccination; in these cases, listening to the patient's concerns is important, followed by explanation of the benefits to the indi vidual, their family, and their community and review of the low risk for potential harms. It is true to say that no current vaccines are ever worse than the disease they prevent, although side effects may occur rarely. Thorough knowledge of the data on side effect rates and of efficacy will aid the clinician in helping the patient make a fully informed decision. ■ ■MENTAL HEALTH AND ADDICTION Assessment for depression and cognitive impairment is important to address when patients exhibit symptoms or they or their family members express concerns. Both of these common conditions play a major role in reducing quality of life and are high on patients' lists of concerns, even if not clearly expressed. Screening tools for depression are reviewed in Chap. 463. Cognitive function decline with aging or comorbid illness, including depression, should be anticipated. Assessment tools such as the General Practitioner Assessment of Cognition or the Mini-Cog test are widely available and effective rapid assessment tools. Alcohol and Opioids (see Chaps. 464 and 467) Alcohol dependence and abuse are common and underdiagnosed. Rapid

screening tools have proven efficacy for identifying patients with alcohol problems. In a systematic review, the CAGE (cut down, annoyed, guilty, eye opener) questionnaire was most effective at identifying alcohol abuse and dependence, with reasonable sensitivity and high specificity. The present opioid epidemic in the United States presents a new and substantial public health challenge given the high potential for depen dency and abuse of these drugs. Rapid screening tools are available to assist clinicians in screening for opioid dependence.

CHAPTER 2 ■ ■ACCIDENTS AND SUICIDE Regular assessment of patient safety through simple questions about seat belt use, domestic violence, and gun safety in the home continues to be an important part of health promotion and wellness. Longstand ing recommendations for assessment of suicidal ideation among patients with depression or a history of suicide attempts also continue to be relevant. Promoting Good Health APPROACH TO THE PATIENT In the context of a clinical visit focused on health assessment, health promotion, and prevention, the basic skills of history-taking are of paramount importance. Much of the evaluation, counsel ing, and management that focus on health promotion and prevention also require engagement and buy-in from the patient in order to assist with recognition of contributing behaviors and to promote adherence to therapeutic plans. Therefore, in addition to standard history-taking, additional skills such as motivational interviewing and eliciting patient commitments and contracting may prove of significant value. The availability of additional tools to assist with screening, monitoring, and chronic management, both online and through wearable devices and mobile health technologies, is rap idly expanding, with uncertain implications for the future. Major research gaps exist in our understanding of how best to employ these newer technologies to improve health outcomes. Concepts of behavioral economics are being explored to better understand the psychology of decision-making and incentives as a means to improve lifestyle choices and adherence to treatment plans (Chap. 494). The limited time available to clinicians and patients during a wellness visit or periodic health examination (not driven by spe cific patient issues) makes it important to prioritize assessment and counseling for factors that affect longevity, health span, and quality of life over approaches that may have low yield, such as the annual comprehensive physical examination in an asymptomatic patient. Setting clear expectations for the content of a wellness visit may be a first step, and scheduling follow-up visits for findings or to con tinue indicated counseling are important steps to achieving better health outcomes. ■ ■FURTHER READING Boulware LE et al: Systematic review: The value of the periodic health evaluation. Ann Intern Med 146:289, 2007. Dietary Guidelines for Americans, 2020–2025. Washington, DC: U.S. Department of Agriculture and U.S. Department of Health and Human Services; 2020. Available at https://www.dietaryguidelines.gov/sites/default/ files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf. Krogsboll LT et al: General health checks in adults for reducing morbidity and mortality from disease. Cochrane Database Syst Rev 1:CD009009, 2019. Lloyd-Jones DM et al: Life’s Essential 8: Updating and enhancing the American Heart Association’s Construct of Cardiovascular Health: A presidential advisory from the American Heart Association. Circula tion 146:e18, 2022. U.S. Department of Health and Human Services: Physical Activity Guidelines for Americans, 2nd ed. Washington, DC: U.S. Department of Health and Human Services; 2018. Available at https://health.gov/ sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf. U.S. Preventive Services Task Force webpage. Available at https:// www.uspreventiveservicestaskforce.org/uspstf/.

03 - 3 Vaccine Opposition and Hesitancy

3 Vaccine Opposition and Hesitancy

Julie A. Bettinger, Hana Mitchell

Vaccine Opposition and Hesitancy PART 1 The Profession of Medicine Vaccines have been recognized as one of the top public health achieve ments of the twentieth century. Dramatic declines in the morbidity and mortality of vaccine-preventable diseases have been observed, and the contribution of vaccines to the elimination, control, and prevention of infectious disease cannot be overstated. However, opposition and hesi tancy to vaccines occurred, even prior to the COVID-19 pandemic, and are not new. Vaccine hesitancy has existed since Edward Jenner intro duced the first vaccine against smallpox in the eighteenth century and the World Health Organization (WHO) ranked these attitudes as one of the ten greatest threats to public health in 2019. Are current opposition and hesitancy any different from what has been seen before? Many soci ologists, public health experts, and health care providers (HCPs) argue yes. Recent social and cultural trends, combined with new communica tion formats and further amplified by the COVID-19 pandemic, have converged to create a particularly potent form of hesitancy and what some have labeled a crisis of confidence. This crisis manifests as a lack of trust in specific vaccines, vaccine programs, researchers, HCPs, the health care system, pharmaceutical companies, academics, policymakers, governments, and authority in general. The roots of modern vaccine hesitancy and opposition—defined as delay or rejection of vaccines despite availability—vary depending on the place and the population. For some individuals and communities, pseudoscience and false claims about the safety of existing vaccines (e.g., an unsupported link between measles vaccine and autism) have driven fears, increased hesitancy, and decreased acceptance. For others, real safety events, such as the association of narcolepsy with a specific pandemic influenza vaccine (Pandemrix), have justified concerns. In a few locations, vaccine hesitancy is the result of failed health systems or even state failures. Finally, for some groups, including some funda mentalist religious groups and alternative-culture communities, vac cine hesitancy and opposition reflect exclusion from and rejection of mainstream society and allopathic health care and manifest as a deep distrust of these institutions and their HCPs. Although the genesis of modern vaccine hesitancy is multifactorial, its outcomes are uniform: a decrease in vaccine demand and uptake, a decrease in coverage by childhood and adult vaccines, and an increase in vaccine-preventable diseases, outbreaks, and epidemics of disease. Addressing this crisis and moving people from

vaccine hesitancy and refusal to acceptance and active demand require intervention at multiple levels: the indi vidual, the health system (including public health), and the state. This chapter will define vaccine hesitancy and briefly describe its determinants and effects in North America (the United States and Canada). Physicians and other HCPs are well positioned to address the crisis of confidence many patients feel toward HCPs and the health care system. Studies demonstrate that an unambiguous, strong recommenda tion by trusted HCPs is most often the reason that patients, including those who are vaccine hesitant, choose to vaccinate. Strategies for coun seling vaccine-hesitant and vaccine-resistant patients will be presented and examples of strong vaccine recommendations provided. Presenting strategies to increase vaccine demand at a system and policy level is beyond the scope of this chapter. While some physicians may have roles that allow them to act at this level, all physicians can act and influence their individual patients. Strategies to create active vaccine demand at the individual level alone will not solve vaccine hesitancy, but vaccine hesi tancy cannot be addressed without these efforts. For further discussion of immunization principles and vaccine use, see Chap. 129. ■ ■VACCINE COVERAGE AND OUTBREAKS The epidemiologic data from measles outbreaks over the past 15 years provide an interesting illustration of the effects of vaccine opposition and hesitancy. For further discussion of measles, see Chap. 211.

North America Herd immunity occurs when enough individu als in a population become immune to an infectious disease, usually through vaccination, that transmission of the infection stops. The level of immunity (or level of vaccine coverage) required to confer herd immunity varies with the specific infectious disease. Because measles is a highly contagious virus, a coverage rate of 93–95% must be achieved for vaccination to confer herd immunity and interrupt measles trans mission. National coverage estimates place one-dose measles vaccine coverage rates in 2-year-old children at 92% in the United States and 92% in Canada. Despite these relatively high levels of coverage in young children, numerous measles outbreaks have occurred in both countries since 2010 (Table 3-1). The vast majority (>80%) of measles cases described in Table 3-1 occurred in under- or completely unvaccinated individuals. Of note, many of these outbreaks highlight pockets of significantly under- or unvaccinated individuals that are not apparent in national vaccine coverage statistics. Moreover, many of the outbreaks listed in Table 3-1 were ignited by unvaccinated returned travelers from areas with exist ing outbreaks or epidemics, who spread disease into an unvaccinated or undervaccinated community. Many of the outbreaks were contained within the nonvaccinating community, but several spread to other undervaccinated communities geographically contiguous with the outbreak community. More concerning still are the cases and outbreaks originating in communities that had not previously been identified as nonvaccinating. These cases likely highlight pockets of unvaccinated individuals who object for cultural rather than religious reasons. In the past, these nonvaccinating individuals did not exist in large enough clusters to sustain the spread of measles. Of further concern is the number of individuals included in outbreak statistics who have had one or sometimes even two doses of vaccine and who were thought to be protected but who still end up with the disease. The assumption is that one or two doses provide full disease immunity, but this is not always true. Often, individual-level characteristics (e.g., age, immunocompro mise) affect the individual’s response to the vaccine and their level of protection. In other instances, vaccine protection can wane over time, thus leaving fully immunized individuals susceptible to infection. In fact, when herd immunity breaks (i.e., the level of immunity in a com munity becomes too low to prevent transmission of disease), the occur rence of cases even in fully immunized persons is seen, as

reflected in outbreak statistics. As a result of decreased vaccination rates and the resulting disruption of herd immunity, these individuals may become more identifiable as nonimmune. Outside North America Although overall coverage rates may still be high in North America, they are lower in other parts of the world and further decreased during the COVID-19 pandemic. In 2022, for example, only 34% of countries met the WHO goal of pro viding one dose of measles vaccine to at least 95% of their 1-year-old children, a decrease of 10% from prepandemic levels. Twenty years ago, vaccine coverage was sufficiently high in some parts of the world, including Europe, that an unvaccinated traveler from a nonvaccinat ing community to most regions would have been protected by herd immunity at their destinations. Today that is not the case: such trav elers are likely to become infected in a country with active measles transmission and return home to spread the infection into their communities and possibly beyond. Thus, active measles transmis sion, whether at home or abroad, places individuals who rely on herd immunity (e.g., immunocompromised persons and young infants) at increased risk. ■ ■FACTORS IN VACCINE HESITANCY Vaccination coverage rates provide an estimate of the proportion of children or adults in the population who have been vaccinated, but they do not indicate the proportion of individuals who are vaccine hesitant. An individual may be fully vaccinated but still be hesitant about the safety and effectiveness of vaccines, or an individual may be unvaccinated as a result of access issues but may not be hesitant. Therefore, in attempts to understand a patient’s lack of vaccination, it is important to distinguish persons who are hesitant and refuse vaccines

TABLE 3-1 Measles Outbreaks in North America YEAR/PLACE NO. OF CASES REASON 2010/Canada

An infected traveler to the 2010 Winter Olympics transmitted infection to an under- and unvaccinated local population in British Columbia. 2011/Canada

Disease was imported from France by an unvaccinated returned traveler to Quebec. The outbreak spread in a nonvaccinating religious community and outside that community. A majority of cases occurred in under- and unvaccinated persons. 2011/United States

Of 118 cases, 46 were in returned travelers from Europe and Asia/Pacific regions; 105 cases (89%) occurred in unvaccinated persons. 2013/United States

Disease was imported by a returned unvaccinated traveler from Europe. The outbreak spread in a nonvaccinating religious community in New York. 2014/Canada

Disease was imported from the Netherlands. The outbreak spread in a nonvaccinating religious community in

British Columbia. 2014/United States

The outbreak occurred in nonvaccinating religious communities in Ohio. 2015/United States

A multistate/multicountry outbreak was linked to Disneyland amusement park. More than 80% of cases occurred in unvaccinated persons. 2015/Canada

Disease was imported from the United States (part of the Disneyland outbreak) by an unvaccinated traveler. The outbreak spread in a nonvaccinating religious community in Quebec. 2017/United

States

The outbreak occurred in an undervaccinated community in Minnesota; 95% of patients were unvaccinated. 2018/United States

Disease was imported by returned unvaccinated travelers from Israel. The outbreak spread in nonvaccinating religious communities in New York and New Jersey. 2019/Canada

Disease was imported from Vietnam by a returned traveler to British Columbia. The outbreak spread throughout local area schools in under- and unvaccinated persons and resulted in a province-wide measles mass immunization campaign for schoolchildren. 2019/United States

Outbreaks occurred in 10 states; 73% of cases (~935) were linked to outbreaks in nonvaccinating religious communities in New York. Source: Centers for Disease Control and Prevention and Public Health Agency of Canada. from those who need assistance to access the health care system and successfully complete vaccination. To this end, an understanding of vaccine hesitancy and its determinants is needed. Vaccine hesitancy and opposition are defined by the WHO's SAGE Working Group on Vaccine Hesitancy as a "delay in acceptance or refusal of vaccines despite availability of vaccination services." The SAGE group describes vaccine hesitancy as "complex and context spe cific, varying across time, place, and vaccines." Characteristics • Strong distrust of health system/pharmaceutical industry/government • Strong-willed and committed against vaccines • Negative or traumatic experiences with HCPs and health system • May use natural approach to health/alternative HCPs • May have strong religious/moral considerations for refusal • May cluster in communities (geographic and online) • Vaccination is very unlikely; alternative strategies to protect individual and community must be discussed. • Questions safety and necessity of vaccines • Actively seeks information from many sources • Has conflicting feelings on whom to trust • Social norm is not vaccinating. • May have had negative or traumatic experience with health system • Vaccination may not occur; a strong trust relationship with HCP and many visits and conversations are required. • Focused on vaccine risks • Conversation with trusted HCP strongly influential • Trusts HCPs • Actively seeking information and wants to verify it • Wants advice specific for their child • Confused by conflicting information • Social norm is vaccinating, but individual may feel conflicted by this norm. • Vaccination requires longer conversation and may require multiple visits. • Focused toward vaccine risk • Complacency: low perceived benefits of vaccination • Can move up or down continuum as a result of various influences (HCP recommendation, vaccine scare, outbreak) • Trusts HCPs and health system • Convenience: need few barriers to vaccination • Vaccination requires longer conversation but likely can be performed at same visit; potential exists to move to active demand. • Confidence • Considers vaccines important • Considers vaccines safe • Trusts HCP/vaccines/health system • Social norm is vaccinating • Very short conversation with HCP about vaccination, in which HCP should address any questions to maintain active-demand status FIGURE 3-1 Vaccine acceptance continuum. HCPs, health care providers. (Adapted from J Leask et al: BMC Pediatrics 12:154, 2012; AL Benin et al: Pediatrics 117:1532, 2006; and E Dubé, NE MacDonald: The Vaccine Book, 2016, pp. 507-528.)

CHAPTER 3 Vaccine Opposition and Hesitancy It is useful to frame vaccine acceptance as a continuum pyramid, with active demand for all vaccines representing the largest group at the bot tom of the pyramid and outright refusal of all vaccines depicted in the smallest group at the top. In

the middle lies vaccine hesitancy, in which the degree of vaccine demand and acceptance varies. Fortunately, for disease control efforts, most individuals fall within the active-demand category or, if they are hesitant, still accept all vaccines. Hesitancy can be influenced by complacency, convenience, and confidence (Fig. 3-1). Rejects vaccines Refuses Participatory Communication Approach Late and selective Hesitant – many doubts and concerns Accepts vaccines Hesitant – minor doubts and concerns Presumptive Communication Approach Active demand – no doubts or concerns

Complacency is self-satisfaction when accompanied by a lack of awareness for real dangers or deficiencies. Complacency exists in communities and individuals when the perceived risks of vaccine-

preventable diseases are low and vaccination is not deemed a necessary preventive action. This attitude can apply to vaccination in general or to specific vaccines, such as influenza vaccines. Actual or perceived vaccine efficacy and effectiveness contribute to complacency. Patients who are complacent about vaccine-preventable diseases prioritize other lifestyle or health factors over vaccination. These individuals can be influenced toward vaccination by a strong recommendation from a trusted HCP or a local influenza outbreak. They can be influenced away from vaccination by a vaccine scare or misinformation on social media. Finally, the real or perceived ability of patients to take the action required for vaccination (i.e., self-efficacy) influences the role compla cency plays in hesitancy and willingness to seek vaccination.

PART 1 The Profession of Medicine Convenience is determined by the degree to which conversations about vaccination and other services can be provided in culturally safe contexts that are convenient and comfortable for the individual. Clearly, convenience varies by community, health clinic, and even patient. Persons who are criticized or scolded for not vaccinating themselves or their children may not feel comfortable or safe accessing health services. Factors such as affordability, geographic accessibil ity, language, and health literacy are important considerations when evaluating the convenience of existing clinical care. Any of these factors can affect vaccine acceptance and can push a patient who has some hesitancy toward vaccinating or not vaccinating. Confidence is based on trust in the safety and efficacy of vaccines, in the health care system that delivers vaccines (including HCPs), and in the policymakers or governments who decide which vaccines are needed and used. A continual erosion of confidence around vaccina tion, health systems, and governments drives today’s hesitancy and has been amplified by larger social and cultural trends in medicine, parent ing, and information availability. ■ ■SOCIAL AND CULTURAL TRENDS Individualized Health Care Over the past 30 years, the focus of medicine and health care has shifted to patient-oriented, individual ized care, with an increasing emphasis on treatment and prevention options tailored to the individual patient. In vaccination programs, this shift has manifested as requests for individualized vaccine recom mendations and customized immunization schedules. The increasing personalization of medicine, while positive overall, has forced public health away from a focus on the community and its common good and has created tension between individual rights and community health, which was further exacerbated during the COVID-19 pandemic. Parenting Trends The desire for an individualized approach to medicine and vaccination reflects broader cultural trends concerning individual risk management: accordingly, the individual is to blame for bad outcomes, and public institutions cannot be trusted to manage technological (i.e., vaccine-related) risks. This viewpoint is directly linked with cultural shifts in

parenting and social norms defining what it means to be a “good parent.” The image of a good parent has been reframed to refer to someone whom several investigators have described as “a critical consumer of health services and products, accounting for their own individual situation as they see it with little regard for the implications of their decision on other children.” The archetypical good parent no longer unquestioningly trusts HCPs and other authorities and experts. According to this social norm, “good parents” should seek individual medical advice that is tailored for their child and specific to that child’s needs. While in essence not a bad thing, this norm can conflict directly with public health vaccine recom mendations and schedules that are organized to maximize community health and to facilitate efficient provision of care at a community level. Traditional Media Newspapers, radio, and television have been criticized for their coverage of vaccines and in particular their cover age of the alleged link between the measles-mumps-rubella (MMR) vaccine and autism. By offering equal coverage throughout the early

to mid-2000s for both the scientific evidence and unproven claims of MMR vaccine harms, traditional media outlets provided a forum and a megaphone for the spread of pseudoscience. Equal coverage leads to false equivalencies. Celebrity advocates further amplified the message via this channel. The boost that traditional media provided to active vaccine resistance and, less directly, to vaccine hesitancy has not been adequately measured but must be considered in any discussion of vac cine hesitancy. After headlines about multiple outbreaks of measles and other vaccine-preventable diseases and continued direct criticism of the equal-coverage approach, some traditional media began rejecting this approach and attempted to discredit pseudoscience. During the COVID-19 pandemic, the approach of traditional media toward sci entific evidence further diversified based on the political orientation of the news source or organization. At the patient level, the political ori entation of their news source can affect their risk perceptions toward disease as well as their acceptance of vaccines. The Internet and Social Media Approximately 92% of Americans and 95% of Canadians use the Internet, and 90% of Americans and 86% of Canadians have an active social network profile. Widespread access to social media can be empowering, but it is also problematic. The Internet and social media require users to select their informa tion sources, creating an environment described as an “echo cham ber” in which individuals choose information sources harboring beliefs or opinions similar to their own and thereby reinforcing their existing views. This situation has created a new platform for further spread of vaccine misinformation (inaccuracies due to error) and disinformation (deliberate lies) and has provided a forum for vaccine-

resistant individuals, including celebrities, to organize and raise funds to support their efforts. The harmful effects of Internet and social media use on vaccine hesitancy have been well documented. Vaccine hesitancy increases for parents who seek their information from the Internet. In this medium, personal stories and anecdotes are now viewed as data and disproportionately influence vaccine decision-making, while traditional, more authoritative, fact-based information sources are deemphasized. As with traditional media, the social media landscape appears to be shifting. In 2019, the proliferation of antivaccination information com bined with measles outbreaks in North America and increasing pres sure from health leaders led large social media companies (Facebook, Instagram, Pinterest) to deemphasize antivaccination information by removing relevant advertisements and recommendations and decreas ing their prominence in search results. While this resulted in an initial decrease in both pro- and antivaccine content, misleading content was unfortunately still widely available. Moreover, antivaccination users switched to alternate platforms

without restrictions, and the level of engagement with antivaccine content remained unchanged. The COVID-19 pandemic further accelerated the spread of mis information and disinformation circulating on social media to the point that it was termed an “infodemic” and forced public health and health care institutions to respond. Centralized monitoring by jurisdiction of vaccine misinformation and disinformation, with summaries of the relevant discourses and rebuttals provided to HCPs, is a potential way to counter the influence of social media on vac cine hesitancy. Some early work is occurring with this through the WHO Early AI-Supported Response with Social Listening Platform (WHO EARS), which was used in 30 countries during the pandemic to provide centralized monitoring of the COVID-19 discourses on social media and the WHO/Centers for Disease Control and Preven tion (CDC) infodemic management training (see “Further Reading” below). While such strategies have been applied in single jurisdic tions and appear to have had some success, their applicability beyond a pandemic context is unknown. Moreover, while the resources for a coordinated response were available in some jurisdictions during the pandemic, it is unclear if they will continue to be provided. Most individual HCPs have been left to counter popular, shifting, viral communications on their own, patient by patient, or to adapt the general materials provided by the WHO/CDC to their local context using their own resources.

Given these social and cultural trends, no one should be surprised when individuals now question vaccination, express confusion about conflicting information and information sources, and feel unsure about whom to trust. Their broader social context is telling them they should question everything and trust no one. This message is rein forced via misinformation and disinformation on social media and a politicized traditional media and public. Recent vaccine-preventable disease outbreaks illustrate that effective engagement with individu als cannot be accomplished through one-way, top-down informa tion provision (which still is often the de facto choice for health system communication), but rather requires a dialogue that takes into account the social processes surrounding individual vaccination decisions. It is at the interface between the individual and the health system in which conversations between HCPs and their patients can have the greatest impact. It is critical for all HCPs to discuss vaccines and provide strong vaccine recommendations—including HCPs who do not administer vaccines but who have established trust with their patients. APPROACH TO THE PATIENT An ideal vaccine-hesitancy intervention would result in full compli ance with vaccination, the patient’s satisfaction with the health care encounter, and sustained trust in the HCP’s recommendations. On a programmatic level, vaccine-hesitancy interventions should be multicomponent, dialogue based, and tailored to specific undervac cinated populations. Communicating with vaccine-hesitant individuals can be chal lenging and time-consuming. HCPs may feel that vaccine-hesitant patients cast doubt on their personal and professional integrity, their authority as medical experts, and their competence as com municators. Some HCPs may be reluctant to initiate conversations about vaccination because of concerns that discussing a sensitive topic may compromise their clinical rapport with their patients. Other HCPs may believe that they have not received sufficient training to confidently recommend vaccines and answer questions. Discussing vaccines with hesitant patients, while not always easy, provides an opportunity to honor the principles of patient-centered care by demonstrating an interest in patients’ opinions, engaging in dialogue, and ideally increasing patients’ confidence in vaccine recommendations. FACTORS IN EFFECTIVE VACCINE RECOMMENDATIONS Vaccine recommendations ideally should be made within an estab lished, trusting patient–provider relationship in which patients are comfortable asking questions and voicing concerns, even if their views on vaccines contradict the HCP’s recommendations. Rec ommending vaccines requires both

provision of information and effective communication. There is no single “best practice” for how providers should approach recommending vaccines to vaccinehesitant individuals. In general, all vaccine recommendations should be (1) strong, making it clear that the provider supports and recom mends vaccination; (2) tailored, acknowledging the vaccine attitudes and potential concerns of individual patients; (3) transparent and accurate, highlighting the benefits of vaccines while also communi cating the risks; (4) supported by trustworthy information resources that patients can access and review after the clinical encounter; and (5) revisited, with repetition and reinforcement during follow-up health care encounters. Strength of the Recommendation HCPs should make it explicit (in the absence of medical contraindications) that vaccination based on the recommended schedule is the best option. While HCPs should take time to elicit patients’ questions and address concerns, the recommendation for vaccination should be made in clear and unambiguous terms. Tailored Communication Vaccine hesitancy occurs on a con tinuum (Fig. 3-1). Therefore, it is helpful for HCPs to have some understanding of their patients’ attitudes toward vaccination

at the start of the health care appointment. Unfortunately, vaccine-

hesitancy surveys for use as part of vaccine consultation visits have not been validated on a large scale. However, the following are some examples of questions that can be asked, depending on the setting. (1) Did you have a chance to review the vaccine leaflet/ online resource we provided? Did you have any questions about it? (2) Have you ever been reluctant or hesitant about getting a vac cination for yourself or your child? If so, what were the reasons? (3) Are there other pressures in your life that prevent you from getting yourself or your child immunized on time? (4) Whom/what resources do you trust the most for information about vaccines? Whom/what resources do you trust the least? CHAPTER 3 Vaccine Opposition and Hesitancy Communication style and content for patients in the active-

demand category for vaccination will be different from those for individuals who are hesitant, late and selective, or strongly inclined to refuse vaccines. Two communication styles have been proposed for vaccine recommendations. Evidence shows that a presumptive/ directive approach (“Your child is due for MMR vaccination.”) results in higher rates of vaccine uptake than a participatory/guid ing approach (“What are your thoughts about the MMR vaccine?”). However, adopting a strictly presumptive/directive approach may alienate some patients, especially those who are higher up on the hesitancy pyramid and who may feel that they are being pres sured into vaccination before their concerns have been heard and addressed. Adopting a participatory/guiding approach and clarifying receptivity to vaccines may be more suitable for hesitant individuals with many doubts and concerns, persons with a late or selective attitude, and those who are strongly inclined to refuse vaccines. In addition, a participatory/guiding approach provides an opportunity for ongoing clinical rapport and dialogue between unvaccinated or undervaccinated patients and their HCPs, even when it does not result in immediate vaccine uptake. Regardless of which approach is used, a strong vaccine recommendation should be made at each encounter. Transparency and Accuracy Vaccine recommendations should be transparent, should include accurate information about both the benefits and the risks of the vaccine, and should emphasize why the benefits outweigh the risks. For example, when evidence supports an association between a vaccine and an adverse event, the occurrence of the adverse event is often very rare and the event quickly resolves (Chap. 129). U.S. Federal law (under the National Childhood Vaccine Injury Act) requires HCPs to provide a copy of the current Vaccine Information Statement from the CDC,

which describes both benefits and risks of vaccines to an adult patient or to a child's parent/legal representative before vaccination. CDC Vaccine Information Statements should not replace a dis cussion with the HCP. Depending on the provider and the patient, a description of benefits and risks may include words and numbers, graphics, and personal anecdotes (e.g., why the provider vaccinates their own children). Personal anecdotes are powerful, and many hesitant patients seek and are influenced by them. A discussion of benefits and risks provides an opportunity to address specific misconceptions about a particular vaccine or about vaccines overall. For example, patients may be concerned about adverse events following vaccination that are not supported by evi dence, such as autism following MMR vaccination or myocardial infarction following influenza vaccination in the elderly. Most adults—even those whose children are fully immunized— still have questions, misconceptions, or concerns about vaccines that should be addressed. A risk/benefit discussion allows HCPs to describe the vaccine safety monitoring systems in place. Provid ers should emphasize that vaccines are developed and approved through a highly regulated process that includes prelicensure clini cal trials, review and approval by designated regulatory authorities (e.g., the U.S. Food and Drug Administration, Health Canada), strict manufacturing regulations, and ongoing postmarketing safety surveillance.

Support from Accessible Information Sources All vaccine recom mendations should be supported by additional information sources patients can assess after the health care encounter. HCPs play an important role as information intermediaries for their patients. They can navigate information (and misinformation) about vaccines and direct patients toward reliable, appropriate resources. HCPs should consider what resources will be suitable for a patient or patient population. Vaccine information resources are available in different media formats and use a combination of images and text to communicate the information to various audiences. See "Further Reading," below, for suggestions or refer to resources provided by local health authorities. PART 1 The Profession of Medicine Revisiting and Reinforcement of Vaccine Recommendations All health care encounters offer an opportunity to revisit and reinforce vaccine recommendations. Vaccine-hesitant individuals who do not accept vaccines but are willing to review information should be offered a follow-up appointment to reinforce previously made recommendations and address further questions. Vaccine-hesitant patients who accept vaccines should be seen at a follow-up appoint ment to confirm and document vaccine receipt (if vaccine is not TABLE 3-2 Sample Vaccine Conversations STRONG VACCINE RECOMMENDATION "We are headed into the respiratory virus season. Getting flu, RSV, and COVID vaccines not only protects you, but it helps protect other people around you who can get very sick from flu, RSV, or COVID. I strongly recommend you get shots. Do you know where to get them?" "You will be turning 50 next year. This means you will be eligible for a vaccine that prevents shingles, and I strongly recommend you receive it. Have you heard about this vaccine before? Can I answer your questions about it?" "I know you are not comfortable getting vaccinated today. I do want to make it clear that I recommend vaccines because I am convinced they are the best way to protect you from some serious diseases. Is there something that would lead you to think about getting vaccinated in the future?" TAILORED COMMUNICATION "I recommend that children and adults stay up to date on recommended vaccines. I see from your vaccine record that you've had your childhood vaccines, but you haven't gotten any adult vaccines. I wanted to clarify whether this is because you decided not to get vaccines or something else prevented you from getting vaccinated." "I understand that you are here for your pneumococcal vaccine. This is the best way to protect yourself and those around you from pneumonia. Do you have any questions before I give you the vaccine?" "There is strong evidence

that COVID-19 vaccines work well for all people, regardless of their ethnic or genetic background. What particular concerns did you have about the vaccine?" "Thank you for telling me about your fear of needles. This is quite common in children and in adults. Would you like to talk about some potential strategies to help you with getting vaccinated?" TRANSPARENCY AND ACCURACY "Serious side effects can develop after MMR vaccination but are very rare. On average, 3 out of 10,000 children who get MMR vaccine will have a febrile seizure/ convulsion in the days after vaccination. Febrile seizures can be frightening, but nearly all children who have a febrile seizure recover very quickly and without any long-term consequences. On the other hand, 1 out of 1000 children who get measles will develop encephalitis (brain inflammation) that not only causes seizures but can also lead to permanent damage." "About 10 out of every 10,000 Americans who do not get vaccinated against flu die because of influenza every year, and many more are hospitalized. While flu vaccine does not prevent all cases of influenza, it is the most effective vaccine we have. By getting the vaccine, you also help protect people around you from getting sick." "You are correct, aluminum is used in some vaccines to help the body's immune system respond. However, aluminum is also present in food and drinking water. In fact, the amount of aluminum present in vaccines is similar to or less than what is present in breast milk or infant formulas." SUPPORT FROM ACCESSIBLE INFORMATION SOURCES "Your child and other boys and girls his age will be eligible for the human papillomavirus vaccine this coming school year. Have you heard about this vaccine before? What questions do you have about it? Here's a list of websites for parents and teenagers that explain what it is about." "There's a lot of information about vaccines on the Internet, and a lot of that information is not based on facts. Here is a list of websites that have been reviewed by health care professionals and accurately describe benefits and risks of each vaccine, including information resources written by the LGBTQ community that many of my patients have found useful." REVISITING AND REINFORCEMENT OF THE RECOMMENDATION "During our last visit, we talked about why COVID vaccine is recommended for your son and some of the concerns you had about potential side effects, especially myocarditis. It is important to weigh the risks of side effects against the risks of infection. Have you had a chance to look at the take-home information I gave you? Was there anything else you or your partner would like to ask about?" "When you were here last month, we talked about receiving a pertussis booster during pregnancy and where you can get vaccinated. Have you had a chance to get your pertussis vaccine?" "I see that you got your vaccines at the public health clinic last week. How did it go? Did you have any questions?" "It's possible that the symptoms you experienced after receiving the vaccine were an adverse reaction to the vaccine. I will report this to the health authority. Let's discuss what we can do next time to prevent symptoms from occurring again." Note: Specific vaccine recommendations, vaccine eligibility guidelines, and statistics used to communicate benefits and risks will vary with the health jurisdiction and the country. Several sample statements here are adapted from the Australian National Centre for Immunisation Research and Surveillance website (www.skai.org.au/ healthcare-professionals). For patient vaccine information resources, see also the Immunization Action Coalition website for the public developed in partnership with the Centers for Disease Control and Prevention (vaccineinformation.org).

given at the point of care), ascertain whether the vaccine was well tolerated, and reinforce the message about vaccine safety and effectiveness. Patients who actively demand vaccines usually do not require much follow-up other than to confirm and document the receipt of vaccine (if it is not given at the point of care) and to address additional questions or concerns arising subsequent to vaccination. Often this follow-up can be covered without an office visit. WHAT TO SAY TO

VACCINE-HESITANT PATIENTS Engaging vaccine-hesitant individuals requires confidence, knowl edge, skills, time, and creativity to tailor the approach to each individual patient. Examples for each part of the vaccine recom mendation are listed in Table 3-2. ■ ■OTHER CONSIDERATIONS DURING

CLINICAL ENCOUNTERS Missed Opportunities The WHO defines a missed opportu nity for vaccination as “any contact with health services by an indi vidual (child or person of any age) who is eligible for vaccination

(e.g., unvaccinated or partially vaccinated and free of contraindications to vaccination), which does not result in the person receiving one or more of the vaccine doses for which he or she is eligible.” HCPs who do not offer point-of-care vaccination frequently miss the opportunity to recommend vaccines to their patients. Missed opportunities for recommending and providing vaccines during routine health care encounters contribute to undervaccination. Studies show that up to 45% of undervaccinated children could be up to date with all ageappropriate vaccines and up to 90% of female adolescents could be up to date with human papillomavirus (HPV) vaccination if all opportuni ties to vaccinate were taken. Vaccine counseling and vaccination should be incorporated into clinical care for individuals of all ages, not just young children. Clinical encounters should be used as an opportunity to remind patients about seasonal vaccines (influenza, COVID-19) as well as new vaccines as they become available, such as respiratory syncytial virus for older individuals. Because many adolescents and adults do not have regular health care follow-up, providers should take advantage of every health care encounter to recommend and provide vaccines. For example, a visit to an emergency department, a routine follow-up visit at a dia betes clinic, or a visit planning for elective orthopedic surgery offer opportunities to inquire about the patient’s vaccination status and to recommend vaccines. Depending on the jurisdiction, adolescents may or may not have the legal ability to consent to or decline vaccines. Ado lescents’ views, questions, and concerns related to vaccines may differ from those of their caregivers and should ideally be explored as part of adolescent health care. HCPs should make preemptive vaccine recommendations (e.g., initi ating discussions about infant vaccines during pregnancy, informing parents about HPV vaccine before their child becomes eligible). Such advance discussions may be especially helpful in identifying vaccinehesitant patients and ensuring that they have enough time to ask ques tions and make decisions before vaccines are due. HCPs should ensure that a vaccine recommendation is followed by vaccination. Providers who recommend vaccines but do not vaccinate at the point of care should inform patients where they can be vaccinated. This discussion may include information about public health clinics, travel clinics, and pharmacies or a referral to another provider. HCPs should follow up with their patients at subsequent appointments to confirm that they were vaccinated. HCPs should be prepared to discuss newer vaccines. While safety concerns about new vaccines can be anticipated on the basis of past experience with other new vaccines, the COVID-19 pandemic high lighted the need for HCPs to understand and be able to explain the newer vaccine platforms (mRNA, DNA, and viral vector vaccines) and to provide examples of other, older vaccines that have been developed by similar techniques. HCPs also need to be able to explain and provide information resources around how vaccines are evaluated before being approved for use and how vaccine safety is monitored after vaccines are used in the population. It is important to be honest, to describe known, rare side effects (e.g., myocarditis in young males following COVID-19 vaccine) and the positive outcomes in these cases. Placing potential vaccine risks in the context of known disease risks is helpful for some patients. Depending on the context, HCPs should explain why

specific high-risk groups may have been prioritized to receive the vaccine. Adverse Events Following Vaccination Although rare, adverse events (Chap. 129) may influence vaccine acceptance and willingness to be vaccinated in the future. Frequent, acute adverse effects can be captured in clinical trial data, whereas worries about rare and longterm side effects can be addressed only by direct evidence after the initiation of a new vaccination program. Providing patients with infor mation on the incidence of common or expected health events in an unvaccinated population (i.e., background rates) over a 4-week period is helpful in distinguishing what is normal and expected from a point of concern. It is important to ensure that more specific background-rate information is available to HCPs with regard to the individual groups being vaccinated (e.g., pregnant individuals, children, immunocom promised people) whenever possible. HCPs, public health programs,

and vaccine manufacturers can anticipate these questions and should develop answers and information to respond to them.

It is also essential for providers to identify and follow up with all patients who experience an adverse event, regardless of the patients' vaccine attitudes prior to the event. Adverse events following vaccina tion should be reported to the relevant vaccine monitoring system: the U.S. Vaccine Adverse Event Reporting System or the Canadian Adverse Event Following Immunization Surveillance System. CHAPTER 3 Addressing Inequities in Vaccine Access Discrepancies in access to health care services create inequitable access to vaccines for children and adults and contribute to undervaccination, dispropor tionally affecting black people, indigenous populations, and people of color. HCPs must recognize that socially disadvantaged individuals and populations are often at greater risk of vaccine-preventable diseases (e.g., as a result of crowded living conditions, limited access to sanita tion, poor nutrition, or substance abuse). They are also at greater risk of being undervaccinated because they have limited access to health care services and continue to face pervasive discrimination within the health care system. Vaccine Opposition and Hesitancy Depending on the setting and the patient, some recommended vac cines may not be covered through public funding or private insurance coverage. HCPs should be aware of alternative funding models, such as the Vaccines for Children Program, which provides free vaccines for U.S. children (<19 years of age) with financial barriers to vaccine access. When vaccines are not publicly funded or covered by private insurance and patients perceive that they cannot afford a vaccine, HCPs should not withhold a vaccine recommendation. The risks and benefits of vaccination still need to be communicated, with a strong recommendation, and the patient should be provided the opportunity to decide whether they can afford the vaccine. Providing Culturally Safe Care Cultural safety in health care is defined as an outcome based on respectful engagement between the patient and the HCP that recognizes and strives to address power imbalances inherent in the health care system. It results in an envi ronment free of racism and discrimination, where people feel safe when receiving health care. HCPs need to be aware of the legacy of discrimination, racism, and medical experimentation and the distrust in vaccines this has fostered for many individuals and communities1 and strive to approach clinical practice with cultural humility and selfreflection. While SARS-CoV-2 has critically highlighted fractures in our health care system for minority and marginalized communities, addressing these underlying issues goes beyond addressing vaccine hesitancy and is clearly needed for all types of medical care in these communities. Further Communication With Patients Who Refuse Vaccines

Fortunately, the proportion of people who completely refuse all vac cines and are not willing to talk to their HCP is small. Nevertheless, in some cases, attempts to initiate discussion and address vaccine refusal may be futile. When possible, HCPs should focus on the com mon goals of care and preserve the therapeutic relationship. Vaccine refusal should be well documented in the patient’s chart. The HCP should continue with tailored communication and be open to future discussions. Vaccine demand and vaccine refusal are rarely static over time. ■ ■CONCLUSION In summary, vaccine hesitancy is complex and context specific. It var ies with time, place, patient, and vaccine. HCPs are well positioned to address vaccine hesitancy and should develop the skills, knowledge, and confidence to make strong vaccine recommendations to their patients. 1The Tuskegee Syphilis Study is the most infamous example of medical experimentation in black communities in the United States. (See Brandt [1978] for details.)

04 - 4 Decision-Making in Clinical Medicine

4 Decision-Making in Clinical Medicine

■ ■FURTHER READING American Academy of Pediatrics: Talking with vaccine hesitant

parents. Available at www.aap.org/en/patient-care/immunizations/ communicating-with-families-and-promoting-vaccine-confidence/talking-

with-vaccine-hesitant-parents/. Accessed December 15, 2023. Brandt AM: Racism and research: The case of the Tuskegee Syphilis PART 1 The Profession of Medicine Study. Hastings Cent Rep 8:21, 1978. Centers for Disease Control and Prevention: How to address COVID-19 vaccine misinformation. Available at www.cdc.gov/vaccines/ covid-19/health-departments/addressing-vaccine-misinformation. html. Accessed January 15, 2024. Centers for Disease Control and Prevention: Vaccinate with confidence: Strategy to reinforce confidence in Covid-19 vaccines. Available at www.cdc.gov/vaccines/covid-19/vaccinate-with-confidence. html. Accessed January 15, 2024. DeStefano F et al: Principal controversies in vaccine safety in the United States. Clin Infect Dis 69:726, 2019. Dudley MZ et al: The state of vaccine safety science: Systematic reviews of the evidence. Lancet Infect Dis 20:e80, 2020. Immunization Action Coalition: For healthcare professionals. Available at www.immunize.org. Accessed December 15, 2023. Immunization Action Coalition: For the public: Vaccine information you need. Available at vaccineinformation.org. Accessed December 15, 2023. Leask J et al: Communicating with parents about vaccination: A framework for health professionals. BMC Pediatr 12:154, 2012. Lurie N et al: Developing Covid-19 vaccines at pandemic speed. N Engl J Med 382:21, 2020. MacDonald N et al: Vaccine hesitancy: Definition, scope and determi nants. Vaccine 33:4161, 2015. Quinn S et al: Addressing vaccine hesitancy in BIPOC communities: Toward trustworthiness, partnership, and reciprocity. N Engl J Med 385:8, 2021. World Health Organization: Infodemic. Available at www.who. int/health-topics/infodemic#tab=tab_1. Accessed January 15, 2024. World Health Organization: Reducing missed opportunities for vaccination (MOV). Available at www.who.int/teams/immunization-

vaccines-and-biologicals/essential-programme-on-immunization/ implementation/reducing-missed-opportunities-for-vaccination. Accessed December 15, 2023. Daniel B. Mark, John B. Wong

Decision-Making in

Clinical Medicine Practicing medicine at its core requires making decisions. What makes medical practice so difficult is not only the specialized technical knowledge required but also the intrinsic uncertainty that surrounds each decision. Mastering the technical aspects of medicine alone, unfortunately, does not ensure a mastery of the practice of medicine.

Sir William Osler's familiar quote "Medicine is a science of uncer tainty and an art of probability" captures well this complex duality. Although the science of medicine is often taught as if the mechanisms of the human body operate with Newtonian predictability, every aspect of medical practice is infused with an element of irreducible uncertainty that the clinician ignores at their peril. Although deeply rooted in science, more than 100 years after the practice of medicine took its modern form, it remains at its core a craft, to which individual doctors bring varying levels of skill, knowledge, and understanding. With the exponential growth in medical literature and other technical

information and an ever-increasing number of testing and treatment options, twenty-first century physicians who seek excellence in their craft must master a more diverse and complex set of skills than any of the generations that preceded them. This chapter introduces three of the pillars upon which the craft of modern medicine rests: (1) expertise in clinical reasoning (what it is and how it can be developed); (2) rational diagnostic test use and interpretation; and (3) integration of the best available research evidence with clinical judgment in the care of indi vidual patients (evidence-based medicine [EBM]). ■ ■BRIEF INTRODUCTION TO CLINICAL REASONING Clinical Expertise Defining "clinical expertise" remains surpris ingly difficult. Chess has an objective ranking system based on skill and performance criteria. Athletics, similarly, have ranking systems to distinguish novices from Olympians. But in medicine, after physicians complete training and pass the boards (or get recertified), no tests or benchmarks are used to identify those who have attained the highest levels of clinical performance. At each institution, there are often a few "elite" clinicians who are known for their "special problem-solving prowess" when particularly difficult or obscure cases have baffled everyone else. Yet despite their skill, even such master clinicians typi cally cannot explain their exact processes and methods, thereby limit ing the acquisition and dissemination of the expertise used to achieve their impressive results. Furthermore, clinical virtuosity appears not to be generalizable, e.g., an expert on hypertrophic cardiomyopathy may be no better (and possibly worse) than a first-year medical resident at diagnosing and managing a patient with neutropenia, fever, and hypotension. Broadly construed, clinical expertise encompasses not only cognitive dimensions involving the integration of disease knowledge with verbal and visual cues and test interpretation but also potentially the complex fine-motor skills necessary for invasive procedures and tests. In addi tion, "the complete package" of expertise in medicine requires effective communication and care coordination with patients and members of the medical team. Research on medical expertise remains sparse over all and mostly centered on diagnostic reasoning, so this chapter focuses primarily on the cognitive elements of clinical reasoning. Objective study of the clinical reasoning process is difficult as it occurs in the heads of clinicians. One research approach asks clinicians to "think out loud" as they receive increments of clinical information in a manner meant to simulate a clinical encounter. Another research approach focuses on how doctors should reason diagnostically, to identify remediable "errors," rather than on how they actually do reason. Much of what is known about clinical reasoning comes from empirical studies of nonmedical problem-solving behavior. Because of the diverse perspectives contributing to this area, with important con tributions from cognitive psychology, medical

education, behavioral economics, sociology, informatics, and decision sciences, no single integrated model of clinical reasoning exists, and not infrequently, dif ferent terms and reasoning models describe similar phenomena. Intuitive Versus Analytic Reasoning A useful contemporary model of reasoning, the dual-process theory distinguishes two gen eral conceptual modes of thinking as fast or slow. Intuition (System 1)

provides rapid effortless judgments from memorized associations using pattern recognition and other simplifying “rules of thumb” (i.e., heuristics). For example, a very simple pattern that could be useful in certain situations is “black woman plus hilar adenopathy equals sarcoid.” Because no effort is involved in recalling the pattern, the clinician is often unable to say how those judgments were formulated. In contrast, analysis (System 2), the other form of reasoning in the dual-process model, is slow, methodical, deliberative, and effortful. A student might read about causes of hilar adenopathy and from that list (e.g., Chap. 70), identify diseases more common in black women or examine the patient for skin or eye findings that occur with sarcoid. These dual processes, of course, represent two exemplars taken from the cognitive continuum. They provide helpful descriptive insights but very little guidance in how to develop expertise in clinical reasoning. How these idealized systems interact in different decision problems,

how experts use them differently from novices, and when their usage can lead to errors in judgment remain the subject of study and consid erable debate. Pattern recognition, an important part of System 1 reasoning, is a complex cognitive process that appears largely effortless. One can recognize people’s faces, the breed of a dog, an automobile model, or a piece of music from just a few notes within milliseconds without necessarily being able to articulate the specific features that prompted the recognition. Analogously, experienced clinicians often recognize familiar diagnostic patterns very quickly. The key here is having a large library of stored patterns that can be rapidly accessed. In the absence of an extensive stored repertoire of diagnostic patterns, students (as well as experienced clinicians operating outside their area of expertise and familiarity) often must use the more laborious System 2 analytic approach along with more intensive and comprehensive data collection to reach the diagnosis. The following brief patient scenarios illustrate three distinct pat terns associated with hemoptysis that experienced clinicians recognize without effort: • A 46-year-old man presents to his internist with a chief complaint of hemoptysis. An otherwise healthy, nonsmoker, he is recovering from an apparent viral bronchitis. This presentation pattern sug gests that the small amount of blood-streaked sputum is due to acute bronchitis, so that a chest x-ray provides sufficient reassurance that a more serious disorder is absent. • In the second scenario, a 46-year-old patient who has the same chief complaint but with a 100-pack-year smoking history, a productive morning cough with blood-streaked sputum, and weight loss fits the pattern of carcinoma of the lung. Consequently, along with the chest x-ray, the clinician obtains a sputum cytology examination and refers this patient for a chest computed tomography (CT) scan. • In the third scenario, the clinician hears a soft diastolic rumbling murmur at the apex on cardiac auscultation in a 46-year-old patient with hemoptysis who immigrated from a developing country and orders an echocardiogram as well, because of possible pulmonary hypertension from suspected rheumatic mitral stenosis. Pattern recognition by itself is not, however, sufficient for secure diagnosis. Without deliberative systematic reflection, undisciplined pattern recognition can result in premature closure: mistakenly jump ing to the conclusion that one has the correct diagnosis before all the relevant data are in. A critical second step, therefore, even when the diagnosis seems obvious, is diagnostic verification: considering whether the diagnosis adequately

accounts for all of the presenting symptoms and signs and can explain all the ancillary findings. The following case based on a real clinical encounter provides an example of premature closure. A 45-year-old man presents with a 3-week history of a “flulike” upper respiratory infection (URI) including dyspnea and a productive cough. The emergency department (ED) clinician pulled out a “URI assessment form,” which defines and standardizes the information gathered. After quickly acquiring the requisite structured examination components and noting in particular the absence of fever and a clear chest examination, the physician prescribed a cough suppressant for acute bronchitis and reassured the patient that his illness was not seri ous. Following a sleepless night at home with significant dyspnea, the patient developed nausea and vomiting and collapsed. He was brought back to the ED in cardiac arrest and was unable to be resuscitated. His autopsy showed a posterior wall myocardial infarction (MI) and a fresh thrombus in an atherosclerotic right coronary artery. What went wrong? Presumably, the ED clinician felt that the patient was basically healthy (one can be misled by the way the patient appears on examination—a patient that does not appear “sick” may be incorrectly assumed to have an innocuous illness). So, in this case, the physician, upon hearing the overview of the patient from the triage nurse, elected to use the URI assessment protocol even before starting the history, closing consideration of the broader range of possibilities and associ ated tests required to confirm or refute these possibilities. Specifically, by concentrating on the abbreviated and focused URI protocol, the clinician failed to elicit the full dyspnea history, which was precipitated

by exertion and accompanied by chest heaviness and relieved by rest, suggesting a far more serious disorder.

Heuristics or rules of thumb are a part of the intuitive system. These cognitive shortcuts provide a quick and easy path to reaching conclu sions and making choices, but when used improperly, they can lead to errors. Two major research programs have studied heuristics in a mostly nonmedical context and have reached different conclusions about the value of these cognitive tools. The “heuristics and biases” program focuses on how these mental shortcuts can lead to incorrect judgments. So far, however, little evidence exists that educating physi cians and other decision makers to watch for the >100 cognitive biases identified to date has had any effect on the rate of diagnostic errors. In contrast, the “fast and frugal heuristics” research program explores how and when relying on simple heuristics can produce good decisions. Although many heuristics have relevance to clinical reasoning, only four will be mentioned here. CHAPTER 4 Decision-Making in Clinical Medicine When diagnosing patients, clinicians usually develop diagnostic hypotheses based on the similarity of that patient’s symptoms, signs, and other data to their mental representations (memorized patterns) of the disease possibilities. In other words, clinicians pattern match to identify the diagnoses that share the most similar findings to the patient at hand. This cognitive shortcut is called the representativeness heuristic. Consider a patient with hypertension who has headache, palpitations, and diaphoresis. Given this classic presenting symptom triad suggesting pheochromocytoma, clinicians might judge pheochro mocytoma to be quite likely based on the representativeness heuristic. Doing so, however, would be incorrect given that other causes of hypertension are much more common than pheochromocytoma and this triad of symptoms can occur in patients who do not have it. Thus, clinicians using the representativeness heuristic may overestimate the likelihood of a particular disease based on the presence of represen tative symptoms and signs, failing to account for its low underlying prevalence (i.e., the prior, or pretest, probabilities). Conversely, atypi cal presentations of common diseases may lead to

underestimating the likelihood of a particular disease. Thus, inexperience with a specific disease and with the breadth of its presentations may also lead to diag nostic delays or errors, e.g., diseases that affect multiple organ systems, such as sarcoid or tuberculosis, may be particularly challenging to diagnose because of the many different patterns they may manifest. A second commonly used cognitive shortcut, the availability heu ristic, involves judgments based on how easily prior similar cases or outcomes can be brought to mind. For example, a clinician may recall a case from a morbidity and mortality conference in which an elderly patient presented with painless dyspnea of acute onset and was evalu ated for a pulmonary cause but was eventually found to have acute MI, with the diagnostic delay likely contributing to the development of ischemic cardiomyopathy. If the case was associated with a malpractice accusation, such examples may be even more memorable. Errors with the availability heuristic arise from several sources of recall bias. Rare catastrophic outcomes become memorable cases with a clarity and force disproportionate to their likelihood for future diagnosis—for example, a patient with a sore throat eventually found to have leu kemia or a young athlete with leg pain subsequently found to have an osteosarcoma—and those publicized in the media or recently experi enced are, of course, easier to recall and therefore more influential on clinical judgments. The third commonly used cognitive shortcut, the anchoring heu ristic (also called conservatism or stickiness), involves insufficiently adjusting the initial probability of disease up (or down) following a positive (or negative test) when compared with Bayes' theorem, i.e., sticking to the initial diagnosis. For example, a clinician may still judge the probability of coronary artery disease (CAD) to be high despite a negative exercise perfusion test and go on to cardiac catheterization (see "Measures of Disease Probability and Bayes' Rule," below). The fourth heuristic states that clinicians should use the simplest explanation possible that will adequately account for the patient's symptoms and findings (Occam's razor or, alternatively, the simplic ity heuristic). Although this is an attractive and often used principle, it is important to remember that no biologic basis for it exists. Errors

from the simplicity heuristic include premature closure leading to the neglect of unexplained significant symptoms or findings.

For complex or unfamiliar diagnostic problems, clinicians typi cally resort to analytic reasoning processes (System 2) and proceed methodically using the hypothetico-deductive model of reasoning. Based on the patient's stated reasons for seeking medical attention, clinicians develop an initial list of diagnostic possibilities in hypothesis generation. During the history of the present illness, the initial hypotheses evolve in diagnostic refinement as emerging information is tested against the mental models of the diseases being considered with diagnoses increas ing and decreasing in likelihood or even being dropped from or added to consideration as the working hypotheses of the moment. These mental models often generate additional questions that distinguish the diagnostic possibilities from one another. The focused physical exami nation contributes to further distinguishing the working hypotheses. Is the spleen enlarged? How big is the liver? Is it tender? Are there any palpable masses or nodules? Diagnostic verification involves testing the adequacy (whether the diagnosis accounts for all symptoms and signs) and coherency (whether the signs and symptoms are consistent with the underlying pathophysiologic causal mechanism) of the working diagnosis. For example, if the enlarged and quite tender liver felt on physical examination is due to acute hepatitis (the hypothesis), then certain specific liver function tests will be markedly elevated (the pre diction). Should the tests come back normal, the hypothesis may have to be discarded and others reconsidered.

Although often neglected, negative findings are as important as positive ones because they reduce the likelihood of the diagnostic hypotheses under consideration. Chest discomfort that is not provoked or worsened by exertion and not relieved by rest in an active patient lowers the likelihood that chronic ischemic heart disease is the under lying cause. The absence of a resting tachycardia and thyroid gland enlargement reduces the likelihood of hyperthyroidism in a patient with paroxysmal atrial fibrillation. The acuity of a patient's illness may override considerations of prevalence and the other issues described above. "Diagnostic impera tives" recognize the significance of relatively rare but potentially catastrophic conditions if undiagnosed and untreated. For example, clinicians should consider aortic dissection routinely as a possible cause of acute severe chest discomfort. Although the typical present ing symptoms of dissection differ from those of MI, dissection may mimic MI, and because it is far less prevalent and potentially fatal if mistreated, diagnosing dissection remains a challenging diagnostic imperative (Chap. 291). Clinicians taking care of acute, severe chest pain patients should explicitly and routinely inquire about symptoms suggestive of dissection, measure blood pressures in both arms for dis crepancies, and examine for pulse deficits. When these are all negative, clinicians may feel sufficiently reassured to discard the aortic dissec tion hypothesis. If, however, the chest x-ray shows a possible widened mediastinum, the hypothesis should be reinstated and an appropriate imaging test ordered (e.g., thoracic CT angiography or transesophageal echocardiogram). In nonacute situations, the prevalence of potential alternative diagnoses should play a much more prominent role in diag nostic hypothesis generation. Cognitive scientists studying the thought processes of expert clini cians have observed that clinicians group data into packets, or "chunks," that are stored in short-term or "working memory" and manipulated to generate diagnostic hypotheses. Because short-term memory is limited (classically humans can accurately repeat a list of 7 ± 2 numbers read to them), the number of diagnoses that can be actively considered in hypothesis-generating activities is similarly limited. For this reason, the cognitive shortcuts discussed above play a key role in the generation of diagnostic hypotheses, many of which are discarded as rapidly as they are formed, thereby demonstrating that the distinction between analytic and intuitive reasoning is an arbitrary and simplistic, but nonetheless useful, representation of cognition. Research into the hypothetico-deductive model of reasoning has had difficulty identifying the elements of the reasoning process that distinguish experts from novices. This has led to a shift from examining the problem-solving process of experts to analyzing the

organization of their knowledge for pattern matching as exemplars, prototypes, and illness scripts. For example, diagnosis may be based on the resemblance of a new case to patients seen previously (exemplars). As abstract mental models of disease, prototypes incorporate the likeli hood of various disease features. Illness scripts include risk factors, pathophysiology, and symptoms and signs. Experts have a much larger store of exemplar and prototype cases, an example of which is the visual long-term memory of experienced radiologists. However, clinicians do not simply rely on literal recall of specific cases but have constructed elaborate conceptual networks of memorized information or models of disease to aid in arriving at their conclusions (illness scripts). That is, expertise involves an enhanced ability to connect symptoms, signs, and risk factors to one another in meaningful ways; relate those findings to possible diagnoses; and identify the additional information necessary to confirm the diagnosis. No single theory accounts for all the key features of expertise in medical diagnosis. Experts have more knowledge about presenting symptoms of diseases and a larger repertoire of cognitive tools to employ in problem solving than nonexperts. One definition of exper tise highlights the ability to make powerful

distinctions. In this sense, expertise involves a working knowledge of the diagnostic possibilities and those features that distinguish one disease from another. Memo rization alone is insufficient, e.g., photographic memory of a medical textbook would not make one an expert. But having access to detailed case-specific relevant information is critically important. In the past, clinicians primarily acquired clinical knowledge through their patient experiences, but now clinicians have access to a plethora of information sources. Clinicians of the future will be able to leverage the experiences of large numbers of other clinicians using electronic tools, but, as with the memorized textbook, the data alone will be insufficient to create expertise. Despite all the research seeking to understand expertise in medi cine and other disciplines, it remains uncertain whether any didactic program can actually accelerate the progression from novice to expert or from experienced clinician to master clinician. Deliberate effortful practice (over an extended period of time, sometimes said to be 10 years or 10,000 practice hours) and personal coaching are two strategies often used outside medicine (e.g., music, athletics, chess) to develop expertise. Their use in the context of medical practice has not yet been adequately explored. Some studies in medicine suggest that the most beneficial approach to education exposes students to both the signs and symptoms of specific diseases (disease pattern recognition) and, in addition, the lists of diseases that can present with specific symptoms and signs (differential diagnosis). Active learning opportunities useful for those in training include developing a personal learning system, e.g., systematically reflecting on diagnostic processes used (metacogni tion) and following up to identify diagnoses and treatments for patients in their care. ■ ■PERSONALIZED DECISION-MAKING The modern ideal of medical therapeutic decision-making is to “per sonalize” treatment recommendations. In the abstract, personalizing treatment involves combining the best available evidence about what works with an individual patient’s unique features (e.g., risk factors, genomics, and comorbidities) and their preferences and health goals to craft an optimal treatment recommendation with the patient. Opera tionally, two different and complementary levels of personalization are possible: individualizing the risk of harm and benefit for the options being considered based on the specific patient characteristics (preci sion medicine) and personalizing the therapeutic decision process by incorporating the patient’s preferences and values for the possible health outcomes. This latter process is sometimes referred to as shared decision-making and typically involves clinicians sharing their knowl edge about the options and the associated consequences and trade-offs and patients sharing their health goals (e.g., avoiding a short-term risk of dying from coronary artery bypass grafting to see their grandchild get married in a few months). Individualizing the evidence about therapy does not mean relying on physician impressions of benefit and harm from their personal

experience. Because of nonrandom selection, small sample sizes, and rare events, the chance of drawing erroneous causal inferences from one’s own clinical experience is very high. For most chronic diseases, the treatment response is a counterfactual concept, only demonstrable statistically in large patient populations. Because of this, it would be incorrect to infer with any certainty, for example, that treating a hyper tensive patient with angiotensin-converting enzyme (ACE) inhibitors necessarily prevented a stroke from occurring during treatment, or that an untreated patient would definitely have avoided their stroke had they been treated. For many chronic diseases, a majority of patients will remain event free over long periods of time regardless of treatment choices; some will have events regardless of which treatment is selected; and those who avoided having an event through treatment cannot be individually identified. Blood pressure lowering, a readily observable surrogate endpoint, does not have a tightly coupled relationship with

strokes prevented. Consequently, in most situations, demonstrating therapeutic effectiveness cannot rely simply on observing the outcome of an individual patient but should instead be based on large groups of patients carefully studied and properly analyzed. Therapeutic decision-making, therefore, should be based on the best available evidence from clinical trials and well-done outcome studies. Trustworthy clinical practice guidelines that synthesize such evidence offer normative guidance for many testing and treatment decisions. However, all guidelines recognize that “one size fits all” recommenda tions may not apply to individual patients. Increased research into the heterogeneity of treatment effects seeks to understand how best to adjust group-level clinical evidence of treatment harms and benefits to account for the absolute level of risks faced by subgroups and even by individual patients, using, for example, validated clinical risk scores. ■ ■NONCLINICAL INFLUENCES ON CLINICAL DECISION-MAKING More than three decades of research on variations in clinician prac tice patterns have identified important nonclinical forces that shape clinical decisions. These factors can be grouped conceptually into three overlapping categories: (1) factors related to an individual physician’s practice, (2) factors related to practice setting, and (3) factors related to payment systems. Practice Style To ensure that necessary care is provided at a high level of quality, physicians fulfill a key role in medical care by serv ing as the patient’s advocate. Factors that influence performance in this role include the physician’s knowledge, training, and experience. Clearly, physicians cannot practice EBM if they are unfamiliar with the evidence. As would be expected, specialists generally know the evidence in their field better than do generalists. Beyond published evidence and practice guidelines, a major set of influences on physi cian practice can be subsumed under the general concept of “practice style.” The practice style serves to define norms of clinical behavior. Differing practice styles may be based on training, personal experi ence, and medical evidence. Beliefs about effectiveness of different therapies and preferred patterns of diagnostic test use are examples of different facets of a practice style. For example, cardiologists evaluating patients with lower risk chest pain symptoms often conceptualize their primary diagnostic objective as maximizing the detection of ischemia. For this reason, they may strongly favor stress imaging. Internists car ing for the same patients may be more comfortable with initial use of exercise electrocardiogram (ECG) testing without imaging. This latter practice style focuses less on ischemia detection and more on follow ing guideline recommendations that indicate no outcome advantage for stress imaging in this context. Cardiologists, relative to general internists, may also favor a more liberal use of coronary angiography and revascularization in patients with stable ischemic symptoms, i.e., the “oculostenotic reflex.” Beyond the patient’s welfare, physician perceptions about the risk of a malpractice suit resulting from either an erroneous decision or a bad outcome may drive clinical decisions and create a practice referred to as defensive medicine. This practice involves ordering tests and therapies with very small marginal benefits, ostensibly to preclude

future criticism should an adverse outcome occur. Over time, such patterns of care may become accepted as part of the practice norm, thereby perpetuating their overuse, e.g., annual cardiac exercise testing in asymptomatic patients.

CHAPTER 4 Practice Setting Factors in this category relate to work systems including tasks and workflow (e.g., interruptions, inefficiencies, work load), technology (e.g., electronic health record design or implemen tation issue,), organizational characteristics (e.g., culture, leadership, staffing, scheduling), and the physical environment (e.g., noise, light ing, layout). Physician-induced demand is a term that refers to the repeated observation that once medical facilities and

technologies become available to physicians, they will find ways to use them. Other environmental factors that can influence decision-making include the local availability of specialists for consultations and procedures; “high-tech” advanced imaging or procedure facilities such as magnetic resonance imaging (MRI) machines and proton beam therapy centers; and fragmentation of care. Decision-Making in Clinical Medicine Payment Systems Economic incentives are closely related to the other two categories of practice-modifying factors. Financial issues can exert both stimulatory and inhibitory influences on clinical practice. Historically, physicians have been paid on a fee-for-service, capitation, or salary basis. In fee-for-service, physicians who do more generally get paid more, thereby encouraging overuse, consciously or unconsciously. When fees are reduced (discounted reimbursement), clinicians tend to increase the number of services provided to maintain revenue. Capitation, in contrast, provides a fixed payment per patient per year to encourage physicians to consider a global population budget in managing individual patients and ideally reducing the use of interven tions with small marginal benefit. In recognition of the unsustainability of continued growth in medical expenditures and the opportunity costs associated with that (funds that might be more beneficially applied to education, energy, social welfare, or defense), current efforts seek to transition to a value-based payment system to reduce overuse and to reflect benefit. Work to define how to tie payment to value has mostly focused so far on “pay for performance” models. High-quality clinical trial evidence for the effectiveness of these models is still mostly lacking. ■ ■DIAGNOSTIC TEST PERFORMANCE: UNDERSTANDING TEST ACCURACY The purpose of performing a test on a patient is to reduce uncertainty about the patient’s diagnosis or prognosis to facilitate appropriate management. Although diagnostic tests commonly refer to laboratory (e.g., blood count) or imaging tests or procedures (e.g., colonoscopy or bronchoscopy), any information that changes a clinician’s understand ing of the patient’s problem qualifies as a diagnostic test. Thus, even the history and physical examination can be considered as diagnostic tests. In clinical medicine, it is common to reduce the results of a test to a dichotomous outcome, such as positive or negative, normal or abnor mal. Although this simplification often suppresses useful information (such as the degree of abnormality), it facilitates illustrating some important principles of test interpretation that are described below. The accuracy of any diagnostic test is best assessed relative to a “gold standard,” where a positive gold standard test defines the patients who have disease and a negative test securely rules out disease (Table 4-1). Characterizing the diagnostic performance of a new test requires identifying an appropriate population (ideally, patients representative of those in whom the new test would be used) and applying both the new and the gold standard tests to all subjects. Biased estimates of test performance occur when diagnostic accuracy is defined using an inappropriate population or one in which gold standard determina tion of disease status is incomplete. The accuracy of the new test in distinguishing disease from health is determined relative to the gold standard results and summarized in four estimates. The sensitivity or true-positive rate reflects how well the new test identifies patients with disease. It is the proportion of patients with disease (defined by the gold standard) who have a positive test. The proportion of patients with disease who have a negative test is the false-negative rate, calculated as

TABLE 4-1 Measures of Diagnostic Test Accuracy DISEASE STATUS TEST RESULT PRESENT ABSENT Positive True positives (TP) False positives (FP) Negative False negatives (FN) True negatives (TN) PART 1 The Profession of Medicine Test Characteristics in Patients with Disease True-positive rate (sensitivity) = TP/(TP + FN) False-negative rate = FN/(TP + FN) = 1 – true-positive rate Test Characteristics in Patients without Disease True-negative rate (specificity) =

TN/(TN + FP) False-positive rate = FP/(TN + FP) = 1 – true-negative rate 1 – sensitivity. The specificity, or true-negative rate, reflects how well the new test correctly identifies patients without disease. It is the pro portion of patients without disease (defined by the gold standard) who have a negative test. The proportion of patients without disease who have positive test is the false-positive rate, calculated as 1 – specificity. A theoretically perfect test then would have a sensitivity of 100% and a specificity of 100% and would completely distinguish patients with disease from those without it. A useful mnemonic to help remember the somewhat paradoxical relationship between what the test is best at technically versus what it is most useful for clinically is: a test with a very high sensitivity (Sn) when negative (N) helps rule out (out) disease (SnNout), and a test with a very high specificity (Sp) when positive (P) helps rule in (in) disease (SpPin). Calculating sensitivity and specificity requires selection of a thresh old value or cut point above which the test is considered “positive.” Making the cut point “stricter” (e.g., raising it) lowers sensitivity but improves specificity, while making it “laxer” (e.g., lowering it) raises sensitivity but lowers specificity. This dynamic trade-off between more accurate identification of patients with disease versus those without disease is often displayed graphically as a receiver operating charac teristic (ROC) curve (Fig. 4-1) by plotting sensitivity (y axis) versus 1 – specificity (x axis). Each point on the curve represents a potential cut point with an associated sensitivity and specificity value. The area under the ROC curve often is used as a quantitative measure of the information content of a test. Values range from 0.5 (no diagnostic information from testing at all; the test is equivalent to flipping a coin) to 1.0 (perfect test). The choice of cut point should ideally reflect the relative harms and benefits of treatment for those without versus those with disease. For example, if treatment was safe with substantial ben efit, then choosing a high-sensitivity cut point (upper right of the ROC curve) for a low-risk test may be appropriate (e.g., phenylketonuria in newborns), but if treatment had substantial risk for harm, then choos ing a high-specificity cut point (lower left of the ROC curve) may be appropriate (e.g., chemotherapy for cancer). The choice of cut point may also depend on the prevalence of disease, with low prevalence placing a greater emphasis on the harms of false-positive tests (e.g., HIV testing in marriage applicants) or the harms of false-negative tests (e.g., HIV testing in blood donors). ■ ■MEASURES OF DISEASE PROBABILITY AND BAYES’ RULE In the absence of perfect tests, the true disease state of the patient remains uncertain after every test. Bayes’ rule provides a way to quan tify the revised uncertainty using simple probability mathematics (and thereby avoid anchoring bias). It calculates the posttest probability, or likelihood of disease after a test result, from three parameters: the pretest probability of disease, the test sensitivity, and the test specificity. The pretest probability is a quantitative estimate of the likelihood of the diagnosis before the test is performed and is usually estimated from the prevalence of the disease in the underlying population (if known) or clinical context (e.g., age, sex, and type of chest pain). For some common conditions, such as CAD, existing nomograms and statistical models generate estimates of pretest probability that account for his tory, physical examination, and test findings. The posttest probability

0.9 0.8 0.7 True-positive rate 0.6 0.5 0.4 0.3 0.2 Good Fair No predictive value 0.1

0.1 0.2 0.3 0.4 False-positive rate 0.5 0.6 0.7 0.8 0.9

FIGURE 4-1 Each receiver operating characteristic (ROC) curve illustrates a tradeoff that occurs between improved test sensitivity (accurate detection of patients with disease) and improved test specificity (accurate detection of patients without disease), as the test value defining when the test turns from “negative” to “positive” is

varied. A 45° line would indicate a test with no predictive value (sensitivity = specificity at every test value). The area under each ROC curve is a measure of the information content of the test. Thus, a larger ROC area signifies increased diagnostic accuracy. (also called the predictive value of the test, see below) is a recalibrated statement of

the probability of the diagnosis, accounting for both pre test probability and test results. For the probability of disease following a positive test (i.e., positive predictive value), Bayes’ rule is calculated as:

× × + × Posttest probability Pretest probability test sensitivity Pretest probability test sensitivity (1–Pretest probability) (false-positive

test rate) For example, consider a 64-year-old woman with atypical chest pain who has a pretest probability of 0.50 and a “positive” diagnostic test result (assuming test sensitivity = 0.90 and specificity = 0.90). Posttest probability (0.50)(0.90) (0.50)(0.90) (0.50)(0.10) 0.90

- = The term predictive value has often been used as a synonym for the posttest probability. Unfortunately, clinicians commonly misinterpret reported predictive values as intrinsic measures of test accuracy rather than calculated probabilities. Studies of diagnostic test performance

compound the confusion by calculating predictive values from the same sample used to measure sensitivity and specificity. Such calcula tions are misleading unless the test is applied subsequently to popula tions with exactly the same disease prevalence. For these reasons, the more descriptive term, posttest probability following a positive or a negative test, is preferred over predictive value. The nomogram version of Bayes' rule (Fig. 4-2) helps us to under stand at a conceptual level how it estimates the posttest probability of disease. In this nomogram, the impact of the diagnostic test result is summarized by the likelihood ratio, which is defined as the ratio of the probability of a given test result (e.g., "positive" or "negative") in a

0.1 0.1 0.5 0.2

0.5 0.5

0.5

0.05 0.1 0.2

0.02

0.01

0.5

0.2

0.1

Pretest Probability, % Posttest Probability, % Likelihood Ratio Pretest Probability, % Posttest Probability, % Likelihood Ratio FIGURE 4-2 Nomogram version of Bayes' theorem used to predict the posttest probability of disease (right-hand scale) using the pretest probability of disease (left-hand scale) and the likelihood ratio for a positive or a negative test (middle scale). See text for information on calculation of likelihood ratios. To use, place a straightedge connecting the pretest probability and the likelihood ratio and read off the posttest probability. The right-hand part of the figure illustrates the value of a positive exercise treadmill test (likelihood ratio 4, green line) and a positive exercise thallium single-photon emission CT perfusion study (likelihood ratio 9, broken brown line) in a patient with a pretest probability of coronary artery disease of 50%. (Adapted from Centre for Evidence-Based Medicine: Likelihood ratios. Available at http://www.cebm.net/likelihood-ratios/.) patient with disease to the probability of that result in a patient without disease, thereby providing a measure of how well the test distinguishes those with from those without disease. The likelihood ratio for a positive test is calculated as the ratio of the true-positive rate to the false-positive rate (or sensitivity/[1 – specificity]). For example, a test with a sensitivity of 0.90 and a specificity of 0.90 has a likelihood ratio of 0.90/(1 – 0.90), or 9. Thus, for this hypotheti cal test, a "positive" result is 9 times more likely in a patient with the disease than in a patient without it. Most tests in medicine have likeli hood ratios for a positive result between 1.5 and 20. Higher values are associated with tests that more substantially increase the posttest likelihood of disease. A very high likelihood ratio positive (>10) usually implies high specificity, so a positive high-specificity test helps "rule in" disease (the "SpPin" mnemonic introduced earlier). If sensitivity is

excellent but specificity is less so, the likelihood ratio positive will be reduced substantially (e.g., with a 90% sensitivity but a 55% specificity, the likelihood ratio positive is 2.0). The corresponding likelihood ratio for a negative test is the ratio of the false-negative rate to the true-negative rate (or [1 – sensitivity]/ specificity). Lower likelihood ratio negative values more substan tially lower the posttest likelihood of disease. A very low likelihood ratio negative (falling below 0.10) usually implies high sensitivity, so a negative high-sensitivity test helps “rule out” disease (the SnNout mnemonic). The hypothetical test considered above with a sensitivity of 0.9 and a specificity of 0.9 would have a likelihood ratio for a nega tive test result of (1 – 0.9)/0.9, or 0.11, meaning that a negative result

is about one-tenth as likely in patients with disease than in those without dis ease (or about 10 times more likely in those without disease than in those with disease).

CHAPTER 4

■ ■APPLICATIONS TO DIAGNOSTIC TESTING

IN CAD Consider two tests commonly used in the diagnosis of CAD: an exercise treadmill and an exercise single-photon emission CT (SPECT) myocardial per fusion imaging test (Chap. 248). A positive treadmill ST-segment response has an average sensitivity of ~60% and an average specificity of ~75%, yielding a likelihood ratio positive of 2.4 (0.60/ [1 – 0.75]) (consistent with modest discriminatory ability because it falls between 2 and 5). A 41-year-old man with atypical chest pain and no other risk factors has about a 10% pretest probability of CAD. After a positive result, the posttest probability of disease rises to only ~30%. For a 60-year-old man with typical angina and multiple risk factors, the pretest probability of CAD is about 80%. After a positive test result, the posttest probability of disease rises to ~95%.

Decision-Making in Clinical Medicine

0.5 0.05 0.1 0.2

0.02 0.01

0.5 0.2 In contrast, exercise SPECT myo cardial perfusion test is more accurate for diagnosis of CAD. For simplicity, assume that the finding of a revers ible exercise-induced perfusion defect has both a sensitivity and a specificity of 90% (a bit higher than reported), yielding a likelihood ratio for a positive test of 9.0 (0.90/[1 – 0.90]) (consistent with intermediate discriminatory abil ity because it falls between 5 and 10). For the same 10% pretest probability patient, a positive test raises the probability of CAD to 50% (Fig. 4-2). However, despite the differences in posttest probabilities between these two tests (30 vs 50%), the more accurate test may not improve diag nostic likelihood enough to change patient management (e.g., decision to refer to cardiac catheterization) because the more accurate test has only moved the physician from being fairly certain that the patient did not have CAD to a 50:50 chance of disease. In a patient with a pretest probability of 80%, exercise SPECT test raises the posttest probability to 97% (compared with 95% for the exercise treadmill). Again, the more accurate test does not provide enough improvement in posttest confidence to alter management, and neither test has improved much on what was known from clinical data alone. 0.1 In general, positive results with an accurate test (e.g., likelihood ratio

for a positive test of 10) when the pretest probability is low (e.g., 20%) do not move the posttest probability to a range high enough to rule in disease (e.g., 80%). In screening situations, pretest probabilities are often particularly low because patients are asymptomatic. In such cases, specificity becomes especially important. For example, in screen ing first-time female blood donors without risk factors for HIV, a posi tive test raised the likelihood of HIV to only 67% despite a specificity of 99.995% because the prevalence was 0.01%. Conversely, with a high pretest probability, a negative test may not rule out disease adequately if it is not sufficiently sensitive. Thus, the largest change in diagnostic likelihood following a test result occurs when the clinician is most uncertain (i.e., pretest probability between 30 and 70%). For example, a 70-year-old woman with typical angina and multiple risk factors has a

pretest probability for CAD of ~50%. A positive exercise treadmill test moves the posttest probability to 80%, and a positive exercise SPECT perfusion test moves it to 90% (Fig. 4-2).

As presented above, Bayes' rule employs a number of important simplifications that should be considered. First, few tests provide only "positive" or "negative" results. Many tests have multidimensional out comes (e.g., extent of ST-segment depression, exercise duration, and exercise-induced symptoms with exercise testing). Although Bayes' theorem can be adapted to this more detailed test result format, it is computationally more complex to do so. Similarly, when multiple sequential tests are performed, the posttest probability may be used as the pretest probability to interpret the second test. However, this simplification assumes conditional independence—that is, that the results of the first test do not affect the likelihood of the second test result—and this is often not true. PART 1 The Profession of Medicine Finally, many texts assert that sensitivity and specificity are prevalence-independent parameters of test accuracy. This statistically useful assumption, however, is often incorrect. A treadmill exercise test, for example, has a sensitivity of ~30% in a population of patients with one-vessel CAD, whereas its sensitivity in patients with severe three-vessel CAD approaches 80%. Thus, the best estimate of sensitiv ity to use in a particular decision may vary, depending on the severity of disease in the local population. A hospitalized, symptomatic, or referral population typically has a higher prevalence of disease and, importantly, a higher prevalence of more advanced disease than does an outpatient population. Consequently, test sensitivity will likely be higher in hospitalized patients and test specificity higher in outpatients. ■ ■RISK PREDICTION MODELS Bayes' rule, when used as presented above, is useful in studying diag nostic testing concepts, but predictions based on multivariable statisti cal models can more accurately address these more complex problems by simultaneously accounting for additional relevant patient charac teristics. These models explicitly account for multiple, even possibly overlapping, pieces of patient-specific information and assign a relative weight to each on the basis of its unique independent contribution to the prediction in question. For example, a logistic regression model to predict the probability of CAD ideally considers all the relevant inde pendent factors from the clinical examination and diagnostic testing and their relative importance instead of the limited data that clinicians can manage in their heads or with Bayes' rule. However, despite this strength, prediction models are usually too complex computationally to use without a calculator or computer. Guideline-driven treatment recommendations based on statistical prediction models available online, e.g., the American College of Cardiology/American Heart Association risk calculator for primary prevention with statins and the CHA2DS2-VASC calculator for anticoagulation for atrial fibrilla tion, have generated more widespread usage. Some predictive models are now embedded into electronic health record (EHR)

systems, most commonly addressing issues related to thrombosis/anticoagulation and to sepsis. Evidence about the impact of these EHR-based models on patient outcomes is mostly observational and suggests more work is needed to deliver the risk information to the right clinician at the right time in a way that supports clinical workflow. One reason for limited clinical use is that, to date, only a handful of prediction models have been validated sufficiently (e.g., Wells criteria for pulmonary embolism; Table 4-2). The importance of independent validation in a population separate from the one used to develop the model cannot be overstated. An unvalidated risk prediction model should be viewed with the skepticism appropriate for any new drug or medical device that has not had rigorous clinical trial testing. When statistical survival models in cancer and heart disease have been compared directly with clinicians' predictions, the survival mod els have been found to be more consistent, as would be expected, but not always more accurate. On the other hand, comparison of clinicians with websites and apps that generate lists of possible diagnoses to help patients with self-diagnosis found that physicians outperformed the currently available programs. For students and less-experienced clinicians, the biggest value of diagnostic decision support may be in

TABLE 4-2 Wells Clinical Prediction Rule for Pulmonary

Embolism (PE) CLINICAL FEATURE POINTS Clinical signs of deep-vein thrombosis

Alternative diagnosis is less likely than PE

Heart rate >100 beats/min 1.5 Immobilization ≥3 days or surgery in previous 4 weeks 1.5 History of deep-vein thrombosis or PE 1.5 Hemoptysis

Malignancy (with treatment within 6 months) or palliative

INTERPRETATION Score >6.0 High Score 2.0–6.0 Intermediate Score <2.0 Low extending diagnostic possibilities and triggering "rational override," but their impact on knowledge, information-seeking, and problemsolving needs additional research. FORMAL DECISION SUPPORT TOOLS ■ ■DECISION SUPPORT SYSTEMS AND ARTIFICIAL INTELLIGENCE Over the past 50 years, many attempts have been made to develop computer systems to aid clinical decision-making and patient man agement. Conceptually, computers offer several levels of potentially useful support for clinicians. At the most basic level, they provide ready access to vast reservoirs of information, which may, however, be quite difficult to sort through to find what is needed. At higher levels, computers can support care management decisions by making accu rate predictions of outcome, or can simulate the whole decision pro cess, and provide algorithmic guidance. Computer-based predictions using Bayesian or statistical regression models inform a clinical deci sion but do not actually reach a "conclusion" or "recommendation." Recent advances in artificial intelligence (AI) suggest that medicine is on the threshold of developing much more powerful digital tools, but current enthusiasm for such tools still exceeds demonstrated utility in clinical care. Work on AI dates back to the 1950s and can be separated into three major subtypes: neural networks, machine learning (and its subtype deep learning), and generative AI. Machine learning methods are being applied to pattern recognition tasks such as the examination of skin lesions and the interpretation of x-rays. Generative AI (AI models that generate new content) is a term that covers several differ ent types of systems, including large language models (which gener ate language-

based content; an example is GPT-4). Large language models offer some promise in helping to create clinical notes. Their use in support of clinical decision-making, however, is still at a very preliminary stage with need for independent validation in a popula tion separate from the one used to develop the model. Early evidence suggests that clinicians are willing to rely on AI-based tools even when the information provided is clearly inaccurate or contradictory. Concerns about model confabulation and the potential for patient harms mandate careful and comprehensive testing before AI tools are implemented in clinical care. Reminder or protocol-directed systems do not make predictions but use existing algorithms, such as guidelines or appropriate utiliza tion criteria, to direct clinical practice. In general, however, decision support systems have so far had little impact on practice. Reminder systems built into EHRs have shown the most promise, particularly in correcting drug dosing and promoting adherence to guidelines. Check lists may also help avoid or reduce errors. ■ ■DECISION ANALYSIS Compared with the decision support methods discussed earlier, decision analysis represents a normative prescriptive approach to decision-making in the face of uncertainty. Its principal application

is in complex decisions. For example, public health policy decisions often involve trade-offs in length versus quality of life, benefits versus resource use, population versus individual health, and uncertainty regarding efficacy, effectiveness, and adverse events as well as values or preferences regarding mortality and morbidity outcomes. One recent analysis using this approach involved the optimal screening strategy for breast cancer, which has remained controversial, in part because a randomized controlled trial to determine when to begin screening and how often to repeat screening mammography is impractical. In 2016, the National Cancer Institute–sponsored Cancer Intervention and Surveillance Network (CISNET) examined eight strategies differing by whether to initiate mammography screening at age 40, 45, or 50 years and whether to screen annually, biennially, or annually for women in their forties and biennially thereafter (hybrid). The six simulation models found biennial strategies to be the most efficient for average-risk women. Biennial screening for 1000 women from age 50–74 years versus no screening avoided seven breast cancer deaths. Screening annually from age 40–74 years avoided three addi tional deaths but required 20,000 additional mammograms and yielded 1988 more false-positive results. Factors that influenced the results included patients with a two- to fourfold higher risk for developing breast cancer in whom annual screening from age 40–74 years yielded similar benefits as biennial screening from age 50–74. For average-risk patients with moderate or severe comorbidities, screening could be stopped earlier, at age 66–68 years. This analysis involved six models that reproduced epidemiologic trends and a screening trial result, accounted for digital technology and treatments advances, and considered quality of life, risk factors, breast density, and comorbidity. It provided novel insights into a public health problem in the absence of randomized clinical trials examining alter native start age, stop age, and screening frequencies, and helped weigh the pros and cons of such a health policy recommendation. Although such models have been developed for selected clinical problems, their benefit and application to individual real-time clinical management has yet to be demonstrated. DIAGNOSIS AS AN ELEMENT OF

QUALITY OF CARE High-quality medical care begins with accurate diagnosis. The inci dence of diagnostic errors has been estimated by a variety of methods including postmortem examinations, medical record reviews, and medical malpractice claims, with each yielding complementary but different estimates of this quality of care patient-safety problem. In the past, diagnostic errors tended to be viewed as a failure of individual clinicians. The modern view is that they are mostly a

system of care deficiencies. Current estimates suggest that nearly everyone will expe rience at least one diagnostic error in their lifetime, leading to mortal ity, morbidity, unnecessary tests and procedures, costs, and anxiety. Solutions to the “diagnostic errors as a system of care” problem have focused on system-level approaches, such as decision support and other tools integrated into EHRs. The use of checklists has been proposed as a means of reducing some of the cognitive errors discussed earlier in the chapter, such as premature closure. While checklists have been shown to be useful in certain medical contexts, such as operating rooms and intensive care units, their value in preventing diagnostic errors that lead to patient adverse events remains to be shown.
EVIDENCE-BASED MEDICINE Clinical medicine is defined traditionally as a practice combining medical knowledge (including scientific evidence), intuition, and judg ment in the care of patients (Chap. 1). EBM updates this construct by placing much greater emphasis on the processes by which clinicians gain knowledge of the most up-to-date and relevant clinical research to determine for themselves whether medical interventions alter the disease course and improve the length or quality of life. The phrase “evidence-based medicine” is now used so often and in so many differ ent contexts that many practitioners are unaware of its original mean ing. The intention of the EBM program, as described in the early 1990s

by its founding proponents at McMaster University, becomes clearer through an examination of its four key steps:

1. Formulating the management question to be answered
2. Searching the literature and online databases for applicable research CHAPTER 4 data
3. Appraising the evidence gathered with regard to its validity and relevance
4. Integrating this appraisal with knowledge about the unique aspects of the patient (including the patient’s preferences about the possible outcomes) Decision-Making in Clinical Medicine The process of searching the world’s research literature and apprais ing the quality and relevance of studies can be time-consuming and requires skills and training that most clinicians do not possess. In a busy clinical practice, the work required is also logistically not fea sible. This has led to a focus on finding recent systematic overviews of the problem in question as a useful shortcut in the EBM process. Sys tematic reviews are regarded by some as the highest level of evidence in the EBM hierarchy because they are intended to comprehensively summarize the available evidence on a particular topic. To avoid the potential biases found in narrative review articles, predefined repro ducible explicit search strategies and inclusion and exclusion criteria seek to find all of the relevant scientific research and grade its quality. The prototype for this kind of resource is the Cochrane Database of Systematic Reviews. When appropriate, a meta-analysis is used to quantitatively summarize the systematic review findings (discussed further below). Unfortunately, systematic reviews are not uniformly the acme of the EBM process they were initially envisioned to be. In select cir cumstances, they can provide a much clearer picture of the state of the evidence than is available from any individual clinical report, but their value is less clear when only a few trials are available, when trials and observational studies are mixed, or when the evidence base is only observational. They cannot compensate for deficiencies in the under lying research available, and many are created without the requisite clinical insights. The medical literature is now flooded with systematic reviews of varying quality and clinical utility. The peer review system has, unfortunately, not proved to be an effective arbiter of quality of

these papers. Therefore, systematic reviews should be used with cir cumspection in conjunction with selective reading of some of the best empirical studies. ■ ■SOURCES OF EVIDENCE: CLINICAL

TRIALS AND REGISTRIES The notion of learning from observation of patients is as old as medi cine itself. Over the past 50 years, physicians' understanding of how best to turn raw observation into useful evidence has evolved consider ably. Medicine has received a hard refresher lesson in this process from the COVID-19 pandemic. Starting in the spring of 2020, case reports, personal and institutional anecdotal experience, and small singlecenter case series started appearing in the peer-reviewed literature and within months turned into a flood of confusing and often contradic tory evidence. Observational reports of treatments for COVID-19 fueled the confusion. Despite >40,000 publications appearing in the first 7 months of the pandemic, an enormous amount of uncertainty around prevention, diagnosis, treatment, and prognosis of the dis ease remained. Many of the early 2020 publications were either small observational series or reviews of published series, neither of which can resolve the key uncertainties clinicians need to address in caring for these patients. These small observational studies often have sub stantial limitations in validity and generalizability, and although they may generate important hypotheses or be the first reports of adverse events or therapeutic benefit, they have no role in formulating modern standards of practice. The major tools used to develop reliable evidence consist of randomized clinical trials supplemented strategically by large (high-quality) observational registries. A registry or database typically is focused on a disease or syndrome (e.g., different types of cancer, acute or chronic CAD, pacemaker capture, or chronic heart failure), a clinical procedure (e.g., bone marrow transplantation, coronary

revascularization), or an administrative process (e.g., claims data used for billing and reimbursement).

By definition, in observational data, the investigator does not con trol patient care. Carefully collected prospective observational data, however, can at times achieve a level of evidence quality approaching that of major clinical trial data through trial emulation (specifying eligibility criteria, interventions, outcome, follow-up, causal contrast, and statistical analysis) using causal inference methods. At the other end of the spectrum, data collected retrospectively (e.g., chart review) are limited in form and content to what previous observers recorded and may not include the specific research data being sought (e.g., claims data). Advantages of observational data include the inclusion of a broader population as encountered in practice than is typically represented in clinical trials because of their restrictive inclusion and exclusion criteria. In addition, observational data provide primary evidence for research questions when a randomized trial cannot be performed. For example, it would be difficult to randomize patients to test diagnostic or therapeutic strategies that are unproven but widely accepted in practice, and it would be unethical to randomize based on sex, racial/ethnic group, socioeconomic status, or country of residence or to randomize patients to a potentially harmful intervention, such as smoking or deliberately overeating to develop obesity. PART 1 The Profession of Medicine A well-done prospective observational study of a particular man agement strategy differs from a well-done randomized clinical trial most importantly by its lack of protection from treatment selection bias. The use of observational data to compare diagnostic or thera peutic strategies assumes that sufficient uncertainty and heteroge neity exists in clinical practice to ensure that similar patients will be managed differently by diverse physicians. In short,

the analysis assumes that a sufficient element of randomness (in the sense of disorder rather than in the formal statistical sense) exists in clini cal management. In such cases, statistical models attempt to adjust for important imbalances to “level the playing field” so that a fair comparison among treatment options can be made. When manage ment is clearly not random (e.g., all eligible left main CAD patients are referred for coronary bypass surgery), the problem may be too confounded (biased) for statistical correction, and observational data may not provide reliable evidence. In general, the use of concurrent controls is vastly preferable to that of historical controls. For example, comparison of current surgical management of left main CAD with medically treated patients with left main CAD during the 1970s (the last time these patients were routinely treated with medicine alone) would be extremely misleading because “medical therapy” has substantially improved in the interim. Randomized controlled clinical trials include the careful prospective design features of the best observational data studies but also include the use of random allocation of treatment. This design provides the best protection against measured and unmeasured confounding due to treatment selection bias (a major aspect of internal validity). However, the randomized trial may not have good external validity (generaliz ability) if the process of recruitment into the trial resulted in the exclu sion of many potentially eligible subjects or if the nominal eligibility for the trial describes a very heterogeneous population. Consumers of medical evidence need to be aware that randomized trials vary widely in their quality and applicability to practice. The process of designing such a trial often involves many compromises. For example, trials designed to gain U.S. Food and Drug Administra tion (FDA) approval for an investigational drug or device must fulfill regulatory requirements (such as the use of a placebo control) that may result in a trial population and design that differ substantially from what practicing clinicians would find most useful. ■ ■META-ANALYSIS The Greek prefix meta signifies something at a later or higher stage of development. Meta-analysis is research that combines and sum marizes the available evidence quantitatively. Although it is used to examine nonrandomized studies, meta-analysis is most useful for summarizing all available randomized trials examining a particular therapy used in a specific clinical context. Ideally, unpublished trials

should be identified and included to avoid publication bias (i.e., miss ing “negative” trials that may not be published). Furthermore, the best meta-analyses obtain and analyze individual patient-level data from all trials rather than using only the summary data from published reports. Nonetheless, not all published meta-analyses yield reliable evidence for a particular problem, so their methodology should be scrutinized carefully to ensure proper study design and analysis. The results of a well-done meta-analysis are likely to be most persuasive if they include at least several large-scale, properly performed random ized trials. Meta-analysis can especially help detect benefits when individual trials are inadequately powered (e.g., the benefits of strep tokinase thrombolytic therapy in acute MI demonstrated by ISIS-2 in 1988 were evident by the early 1970s through meta-analysis). However, in cases in which the available trials are small or poorly done, metaanalysis should not be viewed as a remedy for deficiencies in primary trial data or trial design. Meta-analyses typically focus on summary measures of relative treatment benefit, such as odds ratios or relative risks. Clinicians should also examine what absolute risk reduction (ARR) can be expected from the therapy. A metric of absolute treatment benefit that is frequently reported is the number needed to treat (NNT) to prevent one adverse outcome event (e.g., death, stroke). NNT should not be interpreted literally as a causal statement. NNT is simply 1/ARR. For example, if a hypothetical therapy reduced mortality rates over a 5-year follow-up by 33% (the relative treatment benefit) from 12% (control arm) to 8% (treatment arm), the ARR would be 12% – 8% =

4% and the NNT would be 1/0.04, or 25. This does not mean literally that 1 patient benefits and 24 do not. However, it can be conceptualized as an informal measure of treatment efficiency. If the hypothetical treatment was applied to a lower-risk population, say, with a 6% 5-year mortal ity, the 33% relative treatment benefit would reduce absolute mortality

by 2% (from 6 to 4%), and the NNT for the same therapy in this lowerrisk group of patients would be 50. Although often not made explicit, comparisons of NNT estimates from different studies should account for the duration of follow-up used to create each estimate. In addition, the NNT concept assumes a homogeneity in response to treatment that may not be accurate. The NNT is simply another way of summarizing the absolute treatment difference and does not provide any unique information. ■ ■CLINICAL PRACTICE GUIDELINES Per the 1990 Institute of Medicine definition, clinical practice guide lines are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” This definition emphasizes several crucial features of modern guideline development. First, guidelines are created by using the tools of EBM. In particular, the core of the development process is a systematic literature search followed by a review of the relevant peer-

reviewed literature. Second, guidelines usually are focused on a clinical disorder (e.g., diabetes mellitus, stable angina pectoris) or a health care intervention (e.g., cancer screening). Third, the primary objective of guidelines is to improve the quality of medical care by identifying care practices that should be routinely implemented, based on high-quality evidence and high benefit-to-harm ratios for the interventions. Guidelines are intended to “assist” decisionmaking, not to define explicitly what decisions should be made in a particular situation, in part because guideline-level evidence alone is never sufficient for clinical decision-making (e.g., deciding whether to intubate and administer antibiotics for pneumonia in a terminally ill individual, in an individual with dementia, or in an otherwise healthy 30-year-old mother). Guidelines are narrative documents constructed by expert panels whose composition often is determined by interested professional organizations. These panels vary in expertise and in the degree to which they represent all relevant stakeholders. The guideline docu ments consist of a series of specific management recommendations, a summary indication of the quantity and quality of evidence sup porting each recommendation, an assessment of the benefit-to-harm ratio for the recommendation, and a narrative discussion of the

05 - 5 Precision Medicine and Clinical Care

5 Precision Medicine and Clinical Care

recommendations. Many recommendations simply reflect the expert consensus of the guideline panel because literature-based evidence is insufficient or absent. An examination of this issue in cardiovascular guidelines showed that <15% of guideline recommendations were based on the highest level of clinical trial evidence, and this proportion had not improved in 10 years despite a substantial number of trials being conducted and published. The final step in guideline construc tion is peer review, followed by a final revision in response to the critiques provided. Guidelines are closely tied to the process of quality improvement in medicine through their identification of evidence-based best practices. Such practices can be used as quality indicators. Examples include the proportion of acute MI patients who receive aspirin upon admission to a hospital and the proportion of heart failure patients with a depressed ejection fraction treated with an ACE inhibitor. CONCLUSIONS Thirty years after the introduction of the EBM movement, it is tempt ing to think that all the difficult decisions practitioners face have been or soon will be solved and digested into practice guidelines and com puterized reminders. However, EBM provides practitioners with an ideal rather than a finished set of tools with which to manage patients. Moreover, even with such evidence, it is always worth remembering that the response to therapy of the “average” patient represented by the summary clinical trial outcomes may not be what can be expected for the specific patient sitting in front of a clinician in the clinic or hospital. In addition, meta-analyses cannot generate evidence when no adequate randomized trials exist, and most of what clinicians confront in practice will never be thoroughly tested in a randomized trial. For the foreseeable future, excellent clinical reasoning skills and experience supplemented by well-designed quantitative tools and a keen apprecia tion for the role of individual patient preferences in their health care will continue to be of paramount importance in the practice of clinical medicine. ■ ■FURTHER READING Chen JH et al: Decoding artificial intelligence to achieve diagnostic excellence. JAMA 328:709, 2022. Fanaroff AC et al: Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018. JAMA 321:1069, 2019. Goldberg CB et al: To do no harm - and the most good - with AI in health care. Nat Med 30:623, 2024. Hernán MA, Robins JM: Causal Inference: What If. Boca Raton, FL, Chapman & Hall/CRC, 2020. Khera R et al: Automation bias and assistive AI. Risk of harm from AI-driven clinical decision support. JAMA 330:2255, 2023. Mandelblatt JS et al: Collaborative modeling of the benefits and harms of associated with different U.S. breast cancer screening strate gies. Ann

Intern Med 164:215, 2016. Monteior S et al: The 3 faces of clinical reasoning: Epistemological explorations of disparate error reduction strategies. J Eval Clin Pract 24:666, 2018. Murthy VK et al: An inquiry into the early careers of master clini cians. J Grad Med Educ 10:500, 2018. Park YJ et al: Assessing the research landscape and clinical utility of large language models: A scoping review. BMC Med Inform Decis Mak 12:72, 2024. Richards JB et al: Teaching clinical reasoning and critical thinking: From cognitive theory to practical application. Chest 158:1617, 2020. Royce CS et al: Teaching critical thinking: A case for instruction in cognitive biases to reduce diagnostic errors and improve patient safety. Acad Med 94:187, 2019. Saposnik G et al: Cognitive biases associated with medical decisions: A systematic review. BMC Med Inform Decis Mak 16:138, 2016. Schuwirth LWT et al: Assessment of clinical reasoning: three evolu tions of thought. Diagnosis (Berl) 7:191, 2020.

The Editors

Precision Medicine

and Clinical Care CHAPTER 5 ■ ■DISEASE NOSOLOGY AND PRECISION MEDICINE Modern disease nosology arose in the late nineteenth century and repre sented a clear departure from the holistic, limited descriptions of disease dating to Galen. In this rubric, the definition of any disease is largely based on clinicopathologic observation. As the correlation between clinical signs and symptoms with pathoanatomy required autopsy mate rial, diseases tended to be characterized by the end organ in which the primary syndrome was manifest and by late-stage presentations. Mor gagni institutionalized this framework with the publication of De Sedi bus et Causis Morborum per Anatomen Indagatis in 1761, in which he correlated the clinical features of patients with more than 600 autopsies at the University of Padua, demonstrating an anatomic basis for disease pathophysiology. Clinicopathologic observation served as the basis for inductive generalization coupled with the application of Occam’s razor in which disease complexity was reduced to its simplest possible form. While this approach to defining human disease has held sway for over a century and facilitated the conquest of many diseases previously consid ered incurable, overly inclusive and simplified Oslerian diagnostics suf fer from significant shortcomings. These include, but are not limited to, failure to distinguish the underlying etiology of different diseases with common pathophenotypes. For example, many different diseases can cause end-stage kidney disease or heart failure. Over time, the classifi cation of neurodegenerative disorders or lymphomas, as well as many other diseases, is becoming more refined and precise as the underlying molecular etiologies are identified. These distinctions are important for providing predictable prognostic information for individual patients with even highly prevalent diseases. Additionally, therapies may be inef fective owing to a lack of understanding of the often subtle molecular complexities of specific disease drivers. Precision Medicine and Clinical Care Beginning in the mid-twentieth century, the era of molecular medicine offered the idealized possibility of identifying the underlying molecular basis of every disease. Using a conventional reductionist paradigm, physician-scientists explored disease mechanism at ever-

increasing molecular depth, seeking the single (or limited number of) molecular cause(s) of many human diseases. Yet, as effective as this now conventional scientific approach was at uncovering many disease mechanisms, the clinical manifestations of very few diseases could be explained on the basis of a single molecular mechanism. Even knowl edge of the globin β chain mutation that causes sickle cell disease does not predict the many different manifestations of the disease (stroke

syn drome, painful crises, and hemolytic crisis, among others). Clearly, the profession had expected too much from oversimplified reductionism and failed to take into consideration the extraordinary biologic variety and its accompanying molecular and genetic complexity that underpin both normal and pathologic diversity. The promise of the Human Genome Project provided new tools and approaches and unleashed efforts to identify a monogenic, oligogenic, or polygenic cause for every disease (allowing for environmental influences). Yet, once again, disappointment reigned as the pool of genomes expanded without the expected revelations (aside from rare variants). These shortcomings are explained in part by the important roles of epigenetics, which is significantly modulated by environmental exposures and individual experiences. The arc of progressive reductionism (as illustrated for tuberculosis in Fig. 5-1) in refining and explaining disease reached a humbling plateau, revealing the need for new approaches to under stand better the etiology, manifestations, and progression of most diseases. The stage was set for a return to holism. However, in contrast to the holism of ancient physicians, a more useful approach is one that is integrative, taking genomic context into account in all dimensions. In the course of elaborating this complex pathobiological landscape,

PART 1 The Profession of Medicine 18th century – Sick person – Phthisis 21st century – The challenge of reassembly FIGURE 5-1 Arc of reductionism in medicine. (From JA Greene, J Loscalzo: Putting the patient back together–social medicine, network medicine, and the limits of reductionism. N Engl J Med 377:2493, 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) disease definition must become more precise and progressively more individualized, setting the stage for precision medicine. Oversimplification of phenotype is a natural outgrowth of the obser vational scientific method. Categorizing individuals as falling into groups or clusters that are reasonably similar simplifies the task of the diagnostician and also facilitates the application of “specific” therapies more broadly. Biomedicine has been viewed as less quantitative and precise than other scientific disciplines, with biological and pathobio logical diversity (biologic “noise”) viewed as the norm. Thus, distilling such observational complexity to a fundamental group of symptoms or signs that are reasonably invariant across a group of sick individuals has served as the basis for the approach to disease and its treatment since the earliest days of medicine. This approach to diagnosis and therapy has remained in place into the twenty-first century, serving as the basis for the development of standard diagnostic tests and of broadly applied drug therapies. Targeting larger groups of patients is efficient when applied to large populations. As successful as this approach has been in advancing medical care, it is important to point out its limitations, which include significant predictive inaccuracies and sizeable segments of the disease population that do not respond to the most “effective” drugs (upward of 60% by some estimates). Clearly, a more nuanced approach to diagnosis and therapy is required to achieve better prognostic and therapeutic outcomes. Turning first to phenotype, astute clinicians know full well the subtle and vivid differences in presentation that are often manifest among individuals with the same disease. In some cases, these differences in pathophenotype lead to new subclassifications of the disease, such as heart failure with preserved ejection fraction versus heart failure with

Early 19th century – Lesions of organs and tissues – Caseating granulomata Late 19th century – Lesions of cells and microbes – M. tuberculosis identification Late 20th century – Lesions detected at molecular level – Interferon testing reduced ejection fraction. Often, these relatively crude efforts at mak ing diagnoses more precise are driven by new technologies or new ways of applying

established technologies. In other cases, differences in pathophenotype are more subtle, not necessarily clinically apparent, and often driven by measures of endophenotype, such as distinctions among vasculitides facilitated by refinements in serologies or immu nophenotyping. The impetus to create these subclasses of disease is largely determined by the need to improve prognosis and apply more precise and effective therapies. Based on these guiding principles, many experienced clinicians will argue—and rightly so—that they have been practicing personalized, precision medicine throughout their careers: they characterize each patient's illness in great detail and choose thera pies that respect and are guided by those individualized clinical and laboratory features, limited though they may be. For many diseases, genomic variation, whether inherited or acquired, provides opportunities to refine diagnostic precision with even greater fidelity and predictive accuracy. For this reason, the field of preci sion medicine has now entered a new era that couples the molecular reductionism of the last century with an integrative, systems-level understanding of the basis for pathophenotype. Equally important, modern genomics has established that genomic context, sometimes referred to as modifier genes, is distinctive for each individual person; hence, understanding that context provides the insight necessary to predict how a primary disease driver or drivers may manifest a clinical pathophenotype—e.g., why some individuals with sickle cell anemia will develop stroke, while others will develop acute chest syndrome. This concept that primary genetic and/or environmental drivers of a disease differentially affect disease expression based on an individual's

unique genomic context serves as the ultimate basis for much of what is now called precision medicine. To develop a precision medicine strategy for any disease, the clini cian needs to be aware of two important, confounding principles. First, patients with different diseases can manifest similar pathophenotypes, i.e., convergent phenotypes. Examples of this principle include the hypertrophied myocardium found in hypertrophic cardiomyopathy, infiltrative cardiomyopathies, critical aortic stenosis, and untreated, long-standing hypertension; and the thrombotic microangiopathy found in malignant hypertension, scleroderma renal crisis, thrombotic thrombocytopenic purpura, eclampsia, and antiphospholipid syn drome. As genetic analysis has been applied to neoplasms originating from the same organ and sharing a common name, substantial hetero geneity has been detected often with pathophysiologic and therapy-

affecting consequences. Second, patients with the same basic disease can manifest very different pathophenotypes, i.e., divergent phenotypes (Chap. 479). Examples of this principle include the different clinical manifestations of cystic fibrosis or sickle cell disease and the incom plete penetrance of many common genetic diseases. These common presentations of different diseases and different presentations of the same disease are both a consequence of genomic context coupled with unique exposures over an individual's lifetime (Fig. 5-2). Understand ing the interplay among these many complex molecular determinants of disease expression is essential for the success of precision medicine. Given the complexity of the genomic and environmental context of an individual, one must ask the question: How precise do we need to be in order to practice effective precision medicine? Complete knowledge of a person's comprehensive genome (DNA, gene expression, mito chondrial function, proteome, metabolome, posttranslational modi fication of the proteome, and metagenome, among others) and quantitative assessments of environmental and social history are not possible to acquire; yet, this shortcoming does not render the general problem intractable. Ultimately, more precision is needed when it is actionable; otherwise, it leads to excessive testing, anxiety, and accompanying risks. Owing to the fact that the molecular

networks that govern phenotype are overdetermined (i.e., redundant) and that there are primary drivers of disease expression that are modified in a weighted way by other genomic features of an individual, the practice of precision medicine can be real ized without complete knowledge of all dimensions of the genome. Examples of how best to realize this strategy are discussed later in this chapter. ■ ■REQUIREMENTS FOR PRECISION MEDICINE The essential elements of any precision medicine effort include phenotyping, endophenotyping (defining the char acteristics of a disorder that are not readily observable), genomic profiling, and understanding social determinants of health (Fig. 5-3). While subtle distinctions among indi viduals with the same disease are well known to clinicians, formalizing these nuanced differences is critical for achiev ing more precise phenotypes. Deep phenotyping requires a detailed history, including family history and environmen tal exposures, as well as relevant (physiologic) functional studies and imaging, including molecular imaging where appropriate. Biochemical, immunologic, and molecular tests of body fluids provide additional detail to the overall phenotype. Importantly, these objective laboratory tests together with functional studies compose an assessment of the endophenotype (or endotype) of an individual, refin ing the overall discriminant power of the evaluation. One additional concept that has gained traction in recent years is the notion of orthogonal phenotyping, i.e., assessing clinical, molecular, imaging, or functional (endo)pheno types seemingly unrelated to the clinical presentation. These features further enhance the ability to distinguish (sub)phenotypes and derive from the fact that diseases can

be subtly (subclinically) manifest in organ systems different from that in which the primary symptoms or signs are expressed. While some diseases are well known to affect multiple organ systems (e.g., sys temic lupus erythematosus) and in many cases involvement of those many systems is assessed at initial diagnosis, such is not the case for most other diseases. As we begin to understand the differences in the organ-specific expression of genomic variants that drive or modify disease, it is becoming increasingly apparent that orthogonal— or more appropriately, unbiased comprehensive—phenotyping should become the norm.

CHAPTER 5 Precision Medicine and Clinical Care Genomic profiling must next be coupled to detailed phenotyping. The complex levels of genomic assessment continue to mature and include DNA sequencing (exome, whole genome), gene expression (mRNA and protein expression), and metabolomics. In addition, the epigenome, the posttranslationally modified proteome, and the metagenome (the personal microbiome of an individual) are gaining traction as additional elements of comprehensive genomics (Chap. 497). Most of these genomic features are not yet available for clinical labora tory testing, and those that are available are largely confined to blood testing. An emerging area is immunophenotyping, using the immune system as an indicator of disease or prior exposures, as well as a sens ing system for the emergence of new diseases. While DNA sequencing using whole blood would generally apply to any organ-based disease, gene expression, metabolomics, and epigenomics are often tissue-specific. As tissue specimens cannot always or easily be obtained from the organ of interest, attempts at correlating whole-blood mRNA, protein, or metabolite profiles with those of the involved organ are critical for precise prognostics and therapeutic choices. In many cases, systemic Hypertrophic cardiomyopathy – Mutations in >11 sarcomeric proteins (>1400 variants) – Hypertensive heart disease – Aortic stenosis – Fabry’s disease – Pompe’s disease Thrombotic microangiopathy – TTP – HUS – Malignant hypertension – Scleroderma renal crisis – Preeclampsia/eclampsia – HELLP – Antiphospholipid syndrome A Aortic stenosis – Syncope – Heart failure – Angina pectoris Antiphospholipid syndrome – Venous

thromboembolism – Thrombotic stroke – Mesenteric thrombosis – Coronary thrombosis – Livedo reticularis B FIGURE 5-2 Convergent and divergent phenotypes. Examples of the former (A) include hypertrophic cardiomyopathy and thrombotic microangiopathy, and examples of the latter (B) include aortic stenosis and antiphospholipid syndrome, each of which can have several distinct clinical presentations. HELLP, hemolysis, elevated liver enzymes, and a low platelet count; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

Genomic network Transcriptomic network Proteomic network Metabolomic network Psychosocial network Clinical phenotypes PART 1 The Profession of Medicine Integration: Network of Networks HO O Single-cell analyses Post-translational modifications Epigenomic modifications Environmental exposures FIGURE 5-3 Universe of precision medicine. The totality of precision medicine incorporates multidimensional biologic networks, the integration of which leads to a network of networks whose components interact with each other and with environmental exposures to yield a distinctive phenotype or pathophenotype. (Reproduced with permission from LYH Lee, J Loscalzo: Network medicine in pathobiology. Am J Pathol 189:1311, 2019.) consequences to an organ-specific disease (e.g., systemic inflammatory responses in individuals with atherosclerosis) can be ascertained and may provide useful prognostic information or therapeutic strategies. These biomarker signatures are the subject of ongoing discovery and have provided useful guidance toward improved diagnostic precision in many diseases. However, in many diseases, the correlations between these plasma or blood markers and organ-based diseases are weak, indicating a need to analyze each condition and each resulting signa ture before applying it to clinical decision-making. It is important to note that one of the key determinants of the functional consequences of a genetic variant believed to drive a disease phenotype is not simply its expression in a tissue of interest but, more importantly, the coex pression of protein binding partners in that same tissue comprising specific (dys)functional pathways that govern phenotype (Fig. 5-4). An alternative strategy currently under investigation is the conversion of induced pluripotent stem cells from a patient into a cell type of interest for gene expression or metabolomics study. As rational as this approach seems from first principles, it is important to note that gene expression patterns in these induced, differentiated cell types are not completely consonant with their native counterparts, offering often limited addi tional information at potentially great additional expense. Single-cell gene expression data are yet another area of modern genomics that will add even more complexity to understanding the genesis of disease phenotype. These data are becoming increasingly available for different cell and tissue types, including their spatial dis tribution. What role this differential expression may have on ultimate integrative pathophenotype and how intercellular communication (homologous and heterologous) within an organ or tissue may influ ence gene expression or be influenced by differential gene expression remain interesting questions of ongoing study. While phenotype features of many chronic diseases are assessed longitudinally, at the current time, genomic features tend to be limited to single time point sampling. Time trajectories are extremely informa tive in precision genotyping and phenotyping, with gene expression patterns and phenotypes changing over time in different ways among different patients with the same overarching phenotype. Cost, feasible sampling frequency, predictive power, and therapeutic choices will all drive the optimal strategy for the acquisition of timed samples in any given patient; however, with continued cost reduction in genomics

Improved understanding of (patho)biology Complex disease reclassification Disease prevention Network-targeted therapies O OH Precision medicine Microbiome interactions technologies, this limitation may be progressively mitigated and clini cal application may become a reality. One important class of diseases that does not have most of these limitations in genomic profiling is cancer. Cancers can be (and are) sampled (biopsied) frequently to monitor temporal changes in the somatically mutating oncogenome and its consequences for the limited number of well-defined oncogenic driver pathways (Chap. 76). A unique limitation of cancer in this regard, however, is that the frequency of somatic mutations over time (and, especially, with treatment) is great and the functional consequences of many of these mutations unknown. Equally important, assessment of single-cell mRNA sequencing pat terns demonstrates great variability between apparently similar cells, challenging functional interpretation. Lastly, in solid tumors, stromal cells interact in a variety of ways (e.g., metabolically) with the associ ated malignant cells, and their gene expression signatures are also modified by the changing somatic mutational landscape of the primary malignancy. Thus, while much more information can be obtained over time in most cancer patients, the interpretation of these rich data sets continues to remain largely semi-empirical. The possibility of identifying specific therapeutic targets remains a major goal of precision medicine. Doing so usually requires more than simple DNA sequencing and may include analysis of some level of gene expression, ideally in the involved organ(s). In addition to demonstrat ing the expression of a variant protein in the organ, one must ideally also demonstrate its functional consequences, which requires ascer taining the expression of binding partner proteins and the functional pathways they comprise. To achieve this goal, a variety of approaches have been tried, one of the most successful of which is the construction of the protein-protein interaction network (the interactome), which is a comprehensive network map of the protein-protein interactions in a cell or organ of interest (Chap. 499). This template provides informa tion on the subnetworks that govern a disease phenotype (disease mod ules), which can be further individualized by incorporating individual variants and differentially expressed proteins that are patient specific. This type of analysis leads to the creation of an individual “reticulome” or reticulotype (after the Latin for network), which links the genotype to the phenotype of an individual (Fig. 5-5). Using this approach, one can identify potential drug targets in a rational way or can even repurpose existing drugs by demonstrating the proximity of a known

I. Human Interactome colored nodes are disease genes II. Expression Data Node size = expression level Non-disease genes DATA: Genes of disease A Genes of disease B Significance threshold Genes of disease C A Disease-Tissue Network Lipid metabolism disorders Multiple sclerosis Tauopathies Macular degeneration Spinalcord Hypothalamus Muscular dystrophies Nutritional and metabolic diseases Medulla oblongata Cingulate cortex Arthritis, rheumatoid Psoriasis CD14 Monocytes Lupus erythematosus, systemic Liver Bonemarrow Smooth muscle Anemia, hemolytic Appendix Placenta Blood protein disorders Skeletal muscle Blood platelet disorders Whole blood Blood coagulation disorders Pancreatic islet Adrenal cortex Anemia, aplastic Classification Adrenal gland diseases Bronchial epithelial cells Multiple Cardiomyopathy, hypertrophic Aneurysm Crohn disease Cardiovascular Digestive Endocrine Immune Integumentary Musculoskeletal Nervous Reproductive Respiratory Total genes expressed in a tissue: B FIGURE 5-4 Tissue-specific gene expression and phenotype. A. The human protein-protein interactome is constructed, and a specific disease module is identified (I); gene expression within this module is ascertained (II); and the tissue specificity of gene expression is determined (III). This analysis leads to a reduction of the total number of disease module genes that govern phenotype in a specific organ, which is a

reflection of the specific pathway (or pathways) that is (or are) expressed in their functional entirety in that tissue. B. A disease-tissue bipartite network is constructed wherein specific tissues are placed within the circle and linked to diseases shown on the circumference. Nodes are colored according to tissue classification, the sizes of nodes are proportional to the total number of genes expressed in them, and the widths (shades) of the lines or edges correspond to the significance of the associations with specific diseases. (From M Kitsak et al: Tissue specificity of human disease module. Sci Rep 6:35241, 2016, Figure 4.)

III. Tissue-specific Interactome Subgraph of significantly expressed genes CHAPTER 5 Precision Medicine and Clinical Care highest Gene expression 13,460 Proteins 141,296 Interactions 70 Diseases 64 Tissues lowest Basal ganglia diseases Cerebrovascular disorders Alzheimer’s disease Thalamus Amygdala Whole brain Charcot-Marie-Tooth disease Prefrontal cortex Peroxisomal disorders Pituitary Glomerulonephritis Tonsil Lymphnode Lung diseases, obstructive X721 B lymphoblasts BDCA4 Dentritic cells Asthma CD56 NKCells Lung Thyroid Mycobacterium infections Sarcoma Heart CD8 Tcells Carbohydrate metabolism, inborn errors CD34 Amino acid metabolism, inborn errors Leukemia, myeloid, acute CD105 Endothelial Cardiac myocytes CD4 Tcells Breast neoplasms Prostate Lysosomal storage diseases Tongue Colorectal neoplasms Cardiomyopathies Association significance: z = 18.2 z = 1.6

Individual 1 PART 1 The Profession of Medicine DNA RNAs Proteins Metabolites Microbiome Clinical/exposures Multi-omic molecular analysis Interrogation of patient-specific molecular perturbations in individualized network contexts “Reticulotyping” Reticulotype Genotype Phenotype Genotype Phenotype Genotype Phenotype Individualized targeted therapeutics FIGURE 5-5 Reticulotype. Patient-specific genotype-phenotype relationships by multiomic network structures are depicted for three individuals. Each individual’s unique molecular perturbations (genetic variants, differentially expressed genes) are examined within the context of the subject’s unique integrative biologic network or reticulome derived from these multiomic analyses. These unique reticulotypes then serve as the basis for patient-specific, precision therapies. (Reproduced with permission from LY-H Lee, J Loscalzo: Network medicine in pathobiology. Am J Pathol 189:1311, 2019.) drug target to a disease module of interest (Fig. 5-6). For example, in multicentric Castleman’s disease, a disorder of unclear etiology, recognition that the PI3K/Akt/mTOR pathway is highly activated led to trials with an existing drug approved for other purposes, sirolimus. Precision medicine offers additional opportunities for optimizing the utilization of a drug by assessing the individualized pharmacogenom ics of its disposition and metabolism, as demonstrated for the adverse Network-Based Drug Target ID Network-Based Drug Repurposing: The Proximity Hypothesis Disease module S1 S2 Disease module Disease gene Drug target Shortest path to the closest disease gene Drug target FIGURE 5-6 Network-based precision drug repurposing. (Adapted from F Cheng et al: A genome-wide positioning systems network algorithm for in silico drug repurposing. Nat Commun 10:3476, 2019.)

Individual 2 Individual 3 DNA RNAs Proteins Metabolites Microbiome Clinical/exposures DNA RNAs Proteins Metabolites Microbiome Clinical/exposures Reticulotype Reticulotype consequences of variants in TPMT on azathioprine metabolism and variants in CYP2C19 on clopidogrel metabolism (Chap. 72). ■ ■EXAMPLES OF PRECISION MEDICINE APPLICATIONS The field of precision medicine did not appear abruptly in medical history but, rather, evolved gradually as clinicians became more aware of differences among patients with the same disease. With the advent of modern genom ics,

in the ideal situation, these phenotype differences can now be mapped to genotype differences. Thus, we can consider preci sion medicine from the perspective of the pregenomic era and the postgenomic era. Pregenomic precision medicine was applied to many diseases as therapeutic classes expanded for those disorders. For exam ple, many endocrine disorders (i.e., type 1 diabetes mellitus) are treated with a goal of restoring metabolic normality, precisely titrating hormone treatments (i.e., insu lin) to a metabolic endpoint (i.e., glucose). Another prime example of this approach is in the field of heart failure, where diuretics, digoxin, beta blockers, afterload-reducing agents, venodilators, renin-angiotensin-

aldosterone inhibitors, and brain natriuretic t1 t2 S3

peptide (nesiritide) are commonly used in some combination for most patients. The choice of agents is governed by the evidence basis for their use, but tailored to the primary pathophysiologic phenotypes manifest in a patient, such as congestion, hypertension, and impaired contractility. These treatments were developed in the latter half of the last century based on empiric observation, reductionist experiments of specific pathways believed to be involved in the pathophysiology, and clinical response in prospective trials. As phenotyping became more refined (e.g., echocardiographic assessments of ventricular function and tissue Doppler characterization of ventricular relax ation), the syndrome was subclassified into heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, the latter of which does not respond well to most of the classes of therapeutic agents currently available. In the postgenomic era, ever more refined and detailed methods are under investigation to char acterize pathophenotypes as well as genotypes, which may then be matched to the idealized combination of therapeutic classes of agents. Pulmonary arterial hypertension is another disease for which definitive therapies straddle the pre- and postgenomic eras of preci sion medicine. Prior to the 1990s, there were no effective therapies for this highly morbid and lethal condition. With the advent of molecular and biochemical characterization of vascular abnormalities in indi viduals with established disease, however, therapies with agents that restored normal vascular function improved morbidity and mortality. These included calcium channel blockers, prostacyclin congeners, and endothelin receptor antagonists. As genomic characterization of the disease has progressed over the past two decades, there is increasing recognition of distinct genotypes that yield unique pheno types (Chap. 294), such as the demonstration of a primarily fibrotic endophenotype governed by the (oxidized) scaffold protein NEDD-9 and its aldosterone-dependent, TGF-β–independent enhancement of collagen III expression. This approach will continue to evolve as therapies become more effective (e.g., for perivascular fibrosis) and therapeutic choices better targeted to individual patients. Precision diagnostics has also led to a new classification of the dementias, conditions previously thought to have a single cause with varied clinical expression. These disorders can now be categorized based on the genes and pathways involved and the site where aggre gated proteins first form and then spread in the nervous system. For example, the varied clinical presentations of frontotemporal dementia, including progressive aphasia, behavioral disturbances, and dementia with amyotrophic lateral sclerosis, can now be linked to specific genotypes and susceptible cell types (Chap. 443). In prion diseases, the clinical phenotype is determined by specific germline mutations present in the prion protein (Chap. 449). Discovery of autoantibodies against aquaporin-4 (AQP-4) and myelin oligoden drocyte glycoprotein (MOG) has allowed neuromyelitis optica, previ ously considered a multiple sclerosis–like disorder, to be classified as a separate entity requiring different treatment (Chap. 456). Similarly, in myasthenia gravis, the identification of novel

autoantibodies now permits stratification and a more finely tuned precision approach to therapy (Chap. 459). Precision medicine approaches to cancers have, of course, become the prime example of the opportunity that this strategy offers. In the pregenomic era, chemotherapy was widely used based upon the tissue affected and histologic characteristics of the tumors. Treat ment success was variable despite continued efforts to characterize the molecular features of the specific tumors and their semi-empiric responses to specific chemotherapeutic agents. As cancer genome sequencing evolved, however, it became apparent that there are a limited number of oncogenic pathways (<20) that are represented in the great majority of malignancies, without regard for the organ in which the disease is primarily manifest. These genomic signatures served as a template for precisely targeted therapies that have led to dramatic changes in response to treatment, including, for example, imatinib (and congeners) for Bcr-Abl tyrosine kinase activity in chronic myeloid leukemia, erlotinib for EGFR-mutant non-small cell lung cancers, and ibrutinib for Bruton tyrosine kinase in chronic lymphocytic leukemia, among many others.

As exciting as these approaches have been, at least four primary challenges associated with precision therapeutics are unique to can cer: (1) the mutational landscape continues to evolve as the disease progresses, and therapy often (if not invariably) leads to selection for resistant clones; (2) the likelihood that any cancer can be definitively cured by any single agent, no matter its exquisite precision, is quite limited, necessitating the development of rational polypharmaceutical approaches that take into account alternative pathways that achieve the same oncogenic goals as the primary targeted pathway, complicating drug development; (3) marked genomic heterogeneity characterizes many malignancies, arguing that targeting a specific pathway—even with multiple drugs—may not ultimately succeed over the long term owing to the continued and heterogeneous evolution of the genomic landscape within a tumor within a patient; and (4) there is variability in the characteristics of patients and their ability to withstand treatment and mount a complementary immune response to neoplastic cells. Despite these serious shortcomings, the application of progressively more refined and precisely targeted therapies used alone and in com bination, such as with immune modulators, continues to offer great promise for the treatment of these diseases.

CHAPTER 5 Precision Medicine and Clinical Care In some ways, these approaches in cancer mirror earlier strate gies in the treatment of infectious diseases in which the identi fication of the causative organism and its sensitivity to potential antimicrobials allows precision approaches to treatment. Combi natorial antimicrobial treatments represent an effective strategy to address acquired resistance. These diagnostic and therapeutic strategies can be applied without detailed knowledge of personal ized responses to the infection or treatment (aside from serious adverse effects) with good outcomes in most cases. Yet, individuals do respond differently to specific infections and their treatments, possibly driven by different endophenotypes (e.g., different inflam matory responses), suggesting that more precise knowledge of these precise mechanistic differences may yield improved prognosis and therapeutic approaches. As with cancer, immune modulation, par ticularly for immune exhaustion in chronic infections, represents a new frontier, again amenable to the personalized, precise analyses described above. ■ ■THE FUTURE OF PRECISION MEDICINE Precision medicine clearly holds great promise for the future of the practice of medicine. For precision medicine to continue to evolve successfully, however, several requirements will need to be met. First, both deeply refined personal phenotypic data and genomic data are essential as the information with which precision analysis is per formed. These data sets are quite large and require sufficient storage for analysis, especially for individuals in whom time

trajectories are acquired (as should be the case for every person whenever feasible). Equally important, the analytical methods required to extract use ful information from these data sets are evolving and themselves quite complex. While great progress has been made in genomics and biochemical testing, our ability to capture meaningful immunologic endophenotypes and environmental exposures is limited by compari son. Machine learning and artificial (auxiliary) intelligence methods will be essential for extracting optimal information from these data sets, which include not only pathways that can be uniquely targeted therapeutically but also individualized genomic or phenotypic signa tures that are highly predictive of outcome, with or without therapy. Gathering sufficient information on the “normal” segments of the population is also required to ensure appropriate comparison data sets for optimal prediction. Second, phenotyping must continue to expand and become dimensionally richer. The phenotypic features included in this data gathering must incorporate not only data relevant to the clinical presentation but also orthogonal phenotypic data that may yield use ful information on disease trajectory or preclinical disease markers. Personal device data, environmental exposure history, social network interactions, and health system data will all be incorporated increas ingly in defining phenotype and will require great efforts on the

Health system data ‘Omic’ data PART 1 The Profession of Medicine Study-participantgenerated data Exposome/social determinants Motivations and behaviours A Microbiome Precision participant descriptor Electronic health-care system of the future Dynamic phenotype Data curation and user-friendly display B C FIGURE 5-7 Big data in precision medicine. A. Six dimensions by which individuals may be characterized in the precision medicine era are described. B. The precision participant descriptor integrates the data from these six dimensions and varies over time. C. The electronic medical record increasingly must evolve to provide curated precision data in a user-friendly way. (Reproduced with permission from E Antman, J Loscalzo: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016.) part of the medical informatics community to harmonize data sets, standardize data collection, and optimize/standardize data analysis (Fig. 5-7). Third, perhaps the greatest challenge to making precision medicine the standard approach to illness will be to determine the minimal data set required to predict outcome and response to therapy. Gathering data is comparatively simple; however, analyzing it to eliminate redundant information in these overdetermined biologic systems, weighting the determinants of an outcome, and using the data as phenomic/genomic signatures that are easier to collect than comprehensive, unbiased data sets are the ideal goals—a major challenge, but not insurmountable. Rapidly evolving machine learning and artificial intelligence strategies will also be essential for maximal success. To return to the question of how precise precision medicine needs to be in order to be useful, please refer to Fig. 5-8 where the approaches to clinical trial design meant to improve therapeutic signal are illus trated. Decreasing heterogeneity and enriching the study population will enhance the effect size, but these strategies are based on analyses of prior data sets that define those individuals who are more likely than not to respond to a therapy. By contrast, the notion of predic tive enrichment follows from the information provided by a detailed, big data–driven analysis of individuals that explores phenotypic and genomic features used to predict response. These features need not be precisely met by each patient; however, they can be collated or clustered to define a reasonably sized cohort predicted to respond in a particular way within certain confidence bounds. In this way, the boundaries to the practice of precision medicine are imprecise strictly speaking, but sufficiently predictive to be practical from the perspectives of clinical care and cost-effectiveness.

Disease Sample Enrichment strategies Decreased heterogeneity Prognostic enrichment Predictive enrichment FIGURE 5-8 The basis for precision medicine. The notion of precision medicine evolved, in part, from clinical trial design. From the entire population of patients with the disease of interest, a sample cohort of individuals is enrolled in the trial that ideally is representative of the entire distribution. Enrichment strategies developed to decrease heterogeneity or increase the representation of individuals with a high risk of observed outcomes (prognostic enrichment) facilitate trial conduct but do not necessarily improve precision in defining treatment response. The predictive enrichment strategy utilizes both trial participant characteristics and data from experiments conducted before or during (adaptive design) the trial to improve the prediction of who is likely to have a more pronounced response to the treatment under study. (Reproduced with permission from E Antman, J Loscalzo: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016.) ■ ■FURTHER READING

Antman EM, Loscalzo J: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016. Cheng F et al: A genome-wide positioning systems network algorithm for in silico drug repurposing. Nat Commun 10:3476, 2019. Cheng F et al: Comprehensive characterization of protein-protein interactions perturbed by disease mutations. Nat Genet 53:342, 2021. Greene JA, Loscalzo J: Putting the patient back together—Social medicine, network medicine, and the limits of reductionism. N Engl J Med 377:2493, 2017. Gupta RM et al: Multiomic analysis and CRISPR perturbation screens identify endothelial cell programs and novel therapeutic targets for coronary artery disease. Arterioscler Thromb Vasc Biol 43:608, 2023. Kitsak M et al: Tissue specificity of human disease module. Sci Rep 6:35241, 2016. Lee LY, Loscalzo J: Network medicine in pathobiology. Am J Pathol 189:1311, 2019. Leopold JA et al: The application of big data to cardiovascular disease: Paths to precision medicine. J Clin Invest 130:29, 2020. Loscalzo J et al: Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. Mol Syst Biol 3:124, 2007. Loscalzo J et al: Molecular interaction networks and drug develop ment: Novel approach to drug target identification and drug repur posing. FASEB J 37:e22660, 2023. Maiorino E, Loscalzo J: Phenomics and robust multiomics data for cardiovascular disease subtyping. Arterioscler Thromb Vasc Biol 43:1111, 2023. Maron BA et al: Individualized interactomes for network-based preci sion medicine in hypertrophic cardiomyopathy with implications for other clinical pathophenotypes. Nat Commun 12:873, 2021. Menche J et al: Disease networks. Uncovering disease-disease relation ships through the incomplete interactome. Science 347:1257601, 2015. Samokhin AO et al: NEDD9 targets COL3A1 to promote endothe lial fibrosis and pulmonary arterial hypertension. Sci Transl Med 10:eaap7294, 2018.

06 - 6 Screening and Prevention of Disease

6 Screening and Prevention of Disease

Gary J. Martin

Screening and Prevention

of Disease A primary goal of health care is to prevent disease or detect it early enough that intervention will be more effective. Tremendous progress has been made toward this goal over the past 50 years. Screening tests are available for many common diseases and encompass biochemical (e.g., cholesterol, glucose), physiologic (e.g., blood pressure, growth curves), radiologic (e.g., mammogram, bone densitometry), and cyto logic (e.g., Pap smear) approaches. Effective preventive interventions have resulted in dramatic declines in mortality from many diseases, particularly infections. Preventive interventions include counseling about risk behaviors, vaccinations, medications, and, in some relatively uncommon settings, surgery. Preventive services (including screening tests, preventive interventions, and counseling) are different than other medical interventions because they are proactively administered to healthy individuals instead of in response to a symptom, sign, or diag nosis. Thus, the decision to recommend a screening test or preventive intervention requires a particularly high bar of evidence that testing and intervention are both practical and effective. Because population-based screening and prevention strategies must be extremely low risk to have an acceptable benefit-to-harm ratio, the ability to target individuals who are more likely to develop disease could enable the application of a wider set of potential approaches and increase efficiency. Currently, there are many types of data that can predict disease incidence in an asymptomatic individual. Germline genomic data have received the most attention to date, at least in part because mutations in high-penetrance genes have clear implications for preventive care (Chap. 480). Women with mutations in either BRCA1 or BRCA2, the two major breast cancer susceptibil ity genes identified to date, have a markedly increased risk (five- to twentyfold) of breast and ovarian cancer. Genetic counseling should be provided. Screening and prevention recommendations often include prophylactic oophorectomy and breast magnetic resonance imaging (MRI), both of which are considered to incur too much harm for women at average cancer risk. Some women with BRCA mutations opt for prophylactic mastectomy to greatly reduce their breast cancer risk. Although the proportion of common disease explained by highpenetrance genes appears to be relatively small (5–10% of most dis eases),

mutations in rare, moderate-penetrance genes and variants in low-penetrance genes also contribute to the prediction of disease risk. Most recently, polygenic risk scores combining information about vari ants across hundreds of genes are being evaluated for identifying indi viduals at high risk of coronary heart disease and other conditions. The advent of affordable whole exome/whole genome sequencing is likely to speed the dissemination of these tests into clinical practice and may transform the delivery of preventive care. Other forms of “omic” data also have the potential to provide impor tant predictive information. Proteomics and metabolomics can provide insight into gene function, but it has proven challenging to develop reliable, predictive measures using these platforms. More recently, it has become possible to measure the presence of mutations in DNA circulating in the bloodstream and in stool, with early promising evidence that these assays can be used to detect cancer before existing screening tests. In addition to “omic” data, imaging data are increasingly being integrated into risk-stratified prevention approaches as evidence grows about the predictive ability of these data. For example, coronary com puted tomography (CT) scans are used in many preventive cardiology programs to inform decisions about beginning statin therapy when there is conflicting or uncertain information from other risk assess ment approaches. Of course, these data may also be helpful in predict ing the risk of harms from screening or prevention, such as the risk of a false-positive mammogram.

TABLE 6-1 Principles of Screening The condition should be an important health problem. There should be a treatment for the condition. Facilities for diagnosis and treatment should be available. CHAPTER 6 There should be a latent stage of the disease. There should be a test or examination for the condition. The test should be acceptable to the population. The natural history of the disease should be adequately understood. There should be an agreed policy on whom to treat. Screening and Prevention of Disease The cost of finding a case should be balanced in relation to overall medical expenditure. Source: Reproduced with permission from The basic principles of screening populations for disease. World Health Organization; 1968. In addition to advances in risk prediction, there are several other reasons that screening and prevention are likely to gain importance in medical care in the near term. New imaging modalities are being developed that promise to detect changes at the cellular and subcellular levels, greatly increasing the probability that early detection improves outcomes. The rapidly growing understanding of the biologic pathways underlying initiation and progression of many common diseases has the potential to transform the development of preventive interventions, including chemoprevention. Furthermore, screening and prevention offer the promise of both improving health and sparing the costs of dis ease treatment, an issue that will continue to gain importance as long as health care costs in the United States remain a concern to patients, government agencies, and insurers. This chapter will review the basic principles of screening and pre vention in the primary care setting. Recommendations for specific disorders such as cardiovascular disease, diabetes, and cancer are pro vided in the chapters dedicated to those topics. ■ ■BASIC PRINCIPLES OF SCREENING The basic principles of screening populations for disease were pub lished by the World Health Organization in 1968 (Table 6-1). In general, screening is most effective when applied to relatively common disorders that carry a large disease burden (Table 6-2). The five leading causes of mortality in the United States are heart diseases, malignant neoplasms, chronic obstructive pulmonary dis ease, accidents, and cerebrovascular diseases. Thus, many screening strategies are targeted at these conditions. From a global health per spective, these conditions are priorities, but malaria, malnutrition, AIDS, tuberculosis, and violence also carry a heavy disease burden (Chap. 485). Having an effective treatment for early disease has proven challeng ing for some common diseases. For example,

although Alzheimer’s disease is the sixth leading cause of death in the United States, there are no curative treatments and a paucity of data that early treatment improves outcomes. Lack of facilities for diagnosis and treatment is a particular challenge for developing countries and may change screen ing strategies, including the development of “see and treat” approaches such as those currently used for cervical cancer screening in some countries. A long latent or preclinical phase where early treatment increases the chance of cure is a hallmark of many cancers; for exam ple, polypectomy prevents progression to colon cancer. Similarly, early identification of hypertension or hyperlipidemia allows therapeutic TABLE 6-2 Lifetime Cumulative Risk Breast cancer for women 10% Colon cancer 6% Cervical cancer for womena 2% Domestic violence for women Up to 15% Hip fracture for white women 16% aAssuming an unscreened population without HPV vaccination.

interventions that reduce the long-term risk of cardiovascular or cere brovascular events. In contrast, lung cancer screening has historically proven more challenging because most tumors are not curable by the time they can be detected on a chest x-ray. However, the length of the preclinical phase also depends on the level of resolution of the screen ing test, and this situation changed with the development of chest CT. Low-dose chest CT scanning can detect tumors earlier and has been demonstrated to reduce lung cancer mortality by 20% in individuals who had at least a 30-pack-year history of smoking. The short interval between the ability to detect disease on a screening test and the devel opment of incurable disease also contributes to the limited effective ness of mammography screening in reducing deaths from some forms of breast cancer. At the other end of the spectrum, the early detection of prostate cancer may not lead to a difference in the mortality rate because the disease is often indolent and competing morbidities, such as coronary artery disease, may ultimately cause mortality (Chap. 75). This uncertainty about the natural history is also reflected in the contro versy about treatment of prostate cancer, further contributing to the challenge of screening in this disease. Finally, screening programs can incur significant economic costs that must be considered in the con text of the available resources and alternative strategies for improving health outcomes.

METHODS OF MEASURING HEALTH BENEFITS Because screening and preventive interventions are recommended to asymptomatic individuals, they are held to a high standard for demonstrating a favorable risk-benefit ratio before implementation. In general, the principles of evidence-based medicine apply to dem onstrating the efficacy of screening tests and preventive interventions, where randomized controlled trials (RCTs) with mortality outcomes are the gold standard. However, because RCTs are often not feasible, observational studies, such as case-control designs, have been used to assess the effectiveness of some interventions such as colonoscopy for colorectal cancer screening. For some strategies, such as Pap smear screening for cervical cancer, the only data available are ecologic data demonstrating dramatic declines in mortality. Irrespective of the study design used to assess the effectiveness of screening, it is critical that disease incidence or mortality is the pri mary endpoint rather than length of disease survival. This is important because lead time bias and length time bias can create the appearance of an improvement in disease survival from a screening test when there is no actual effect. Lead time bias occurs because screening identifies a case before it would have presented clinically, thereby creating the perception that a patient lived longer after diagnosis simply by moving the date of diagnosis earlier rather than the date of death later. Length time bias occurs because screening is more likely to identify slowly pro gressive disease than

rapidly progressive disease. Thus, within a fixed period of time, a screened population will have a greater proportion of these slowly progressive cases and will appear to have better disease survival than an unscreened population. Disease-free survival is an alternative to consider since many metastatic cancers are controllable for many years with newer therapies. Differences in cancer mortality may not be as easily detected, but years of chemotherapy would still be worth avoiding. A variety of endpoints are used to assess the potential gain from screening and preventive interventions.

1. The absolute and relative impact of screening on disease incidence or mortality. The absolute difference in disease incidence or mortality between a screened and nonscreened group allows the comparison of size of the benefit across preventive services. A meta-analysis of Swedish mammography trials (ages 40–70) found that ~1.2 fewer women per 1000 would die from breast cancer if they were screened over a 12-year period. By comparison, at least ~3 lives per 1000 would be saved from colon cancer in a population (aged 50–75) screened with annual fecal occult blood testing (FOBT) over a 13-year period, and an estimated 20–24 lives per 1000 would be saved over the entire 25-year period. Based on this analysis, colon

TABLE 6-3 Estimated Average Increase in Life Expectancy for a Population SCREENING OR PREVENTIVE INTERVENTION AVERAGE INCREASE Mammography: Women, 40–50 years 0–5 days Women, 50–70 years 1 month Pap smears, age 18–65 2–3 months Getting a 35-year-old smoker to quit 3–5 years Beginning regular exercise for a 40-year-old man

(30 min, 3 times a week) 9 months–2 years cancer screening may actually save more women’s lives than does mammography. However, the relative impact of FOBT (30% reduc tion in colon cancer death) is similar to the relative impact of mam mography (14–32% reduction in breast cancer death), emphasizing the importance of both relative and absolute comparisons. 2. The number of subjects screened to prevent disease or death in one individual. The inverse of the absolute difference in mortality is the number of subjects who would need to be screened or receive a preventive intervention to prevent one death. For example, 731 women aged 65–69 would need to be screened by dual-energy x-ray absorptiometry (DEXA) (and treated appropriately) to prevent one hip fracture from osteoporosis. 3. Increase in average life expectancy for a population. Predicted increases in life expectancy for various screening and preventive interventions are listed in Table 6-3. It should be noted, however, that the increase in life expectancy is an average that applies to a population, not to an individual. In reality, the vast majority of the population does not derive any benefit from a screening test. A small subset of patients, however, will benefit greatly. For example, Pap smears do not benefit the 98% of women who never develop cancer of the cervix. However, for the 2% who would have developed cervical cancer, Pap smears may add as much as 25 years to their lives. Some studies suggest that a 1-month gain of life expectancy is a reasonable goal for a population-based screening or prevention strategy. ■ ■ASSESSING THE HARMS OF SCREENING

AND PREVENTION Just as with most aspects of medical care, screening and preventive interventions also incur the possibility of adverse outcomes. These adverse outcomes include side effects from preventive medica tions and vaccinations, false-positive screening tests, overdiagnosis of disease from screening tests, anxiety, radiation exposure from some screening tests, and

discomfort from some interventions and screening tests. The risk of side effects from preventive medications is analogous to the use of medications in therapeutic settings and is considered in the U.S. Food and Drug Administration (FDA) approval process. Side effects from currently recommended vaccinations are primarily limited to discomfort and minor immune reactions. How ever, the concern about associations between vaccinations and serious adverse outcomes continues to limit the acceptance of many vaccina tions despite the lack of data supporting the causal nature of these associations. The possibility of a false-positive test occurs with nearly all screen ing tests, although the definition of what constitutes a false-positive result often varies across settings. For some tests such as screening mammography and screening chest CT, a false-positive result occurs when an abnormality is identified that is not malignant, requiring either a biopsy diagnosis or short-term follow-up. For other tests such as Pap smears, a false-positive result occurs because the test identifies a wide range of potentially premalignant states, only a small percent age of which would ever progress to an invasive cancer. This risk is closely tied to the risk of overdiagnosis in which the screening test identifies dis ease that would not have presented clinically in the patient's lifetime.

Assessing the degree of overdiagnosis from a screening test is very difficult given the need for long-term follow-up of an unscreened population to determine the true incidence of disease over time. Recent estimates suggest that as much as 15–40% of breast cancers identified by mammography screening and 15–37% of prostate cancers identified by prostate-specific antigen testing may never have presented clinically. Screening tests also have the potential to create unwarranted anxiety, particularly in conjunction with false-positive findings. Although multiple studies have documented increased anxiety through the screening process, there are few data suggesting this anxiety has longterm adverse consequences, including subsequent screening behavior. Screening tests that involve radiation (e.g., mammography, chest CT) add to the cumulative radiation exposure for the screened individual. The absolute amount of radiation is very small from any of these tests, but the overall impact of repeated exposure from multiple sources is still being determined. Some preventive interventions (e.g., vaccina tions) and screening tests (e.g., mammography) may lead to discomfort at the time of administration, but again, there is little evidence of longterm adverse consequences. ■ ■WEIGHING THE BENEFITS AND HARMS The decision to implement a population-based screening and preven tion strategy requires weighing the benefits and harms, including the economic impact of the strategy. The costs include not only the expense of the intervention but also time away from work, down stream costs from false-positive results, "incidentalomas" or adverse events, and other potential harms. Cost-effectiveness is typically assessed by calculating the cost per year of life saved, with adjustment TABLE 6-4 Screening Tests Recommended by the U.S. Preventive Services Task Force for Average-Risk Adults DISEASE TEST POPULATION FREQUENCY CHAPTER Abdominal aortic aneurysm Ultrasound Men 65–75 who have ever smoked Once Alcohol misuse Alcohol Use Disorders Identification Test All adults Unknown

Breast cancer Mammography with or without clinical breast examination Cervical cancer Pap smear Women 21–65 Every 3 years

Pap smear and/or HPV testing Women 30–65 Every 5 years if HPV negative Chlamydia/gonorrhea Nucleic acid amplification test on urine or cervical swab Colorectal cancer Fecal occult blood testing 45–75 Every year 75, 86 Fecal immunochemical-DNA 45–75 Every 1–3 years

Sigmoidoscopy 45–75 Every 5 years Colonoscopy (or occult blood testing combined with sigmoidoscopy) Depression+anxiety Screening questions All adults Periodically Diabetes Fasting blood glucose or HgbA1c Adults overweight, obese, or with hypertension Hepatitis C Anti-HCV antibody followed by confirmatory PCR HIV Reactive immunoassay or rapid HIV followed by confirmatory test Hyperlipidemia Cholesterol 40–75 Unknown

Hypertension Blood pressure All adults Periodically

Intimate partner violence Screening questions Women of childbearing age Unknown Lung cancer Low-dose computed tomography Adults 50–80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years Obesity Body mass index All adults Unknown

Osteoporosis DEXA Women >65 or >60 with risk factors Unknown

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; HPV, human papillomavirus; PCR, polymerase chain reaction. Source: Adapted from the U.S. Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations.

for the quality of life impact of different interventions and disease states (i.e., quality-adjusted life-year). Typically, strategies that cost $50,000–100,000 per quality-adjusted year of life saved are considered “cost-effective” (Chap. 4).

The U.S. Preventive Services Task Force (USPSTF) is an indepen dent panel of experts in preventive care that provides evidence-based recommendations for screening and preventive strategies based on an assessment of the benefit-to-harm ratio (Tables 6-4 and 6-5). Because there are multiple advisory organizations providing rec ommendations for preventive services, the agreement among the organizations varies across the different services. For example, all advisory groups support screening for hyperlipidemia and colorectal cancer, whereas consensus is lower for breast cancer screening among women in their forties and for prostate cancer screening. Because the guidelines are only updated periodically, differences across advisory organizations may also reflect the data that were available when the guideline was issued. CHAPTER 6 Screening and Prevention of Disease For many screening tests and preventive interventions, the balance of benefits and harms may be uncertain for the average-risk population but more favorable for individuals at higher risk for disease. Although age is the most commonly used risk factor for determining screen ing and prevention recommendations, the USPSTF also recommends some screening tests in populations based upon the presence of other risk factors for the disease. In addition, being at increased risk for the disease often supports initiating screening at an earlier age than that recommended for the average-risk population. For example, when there is a significant family history of colon cancer, it is prudent to initiate screening 10 years before the age at which the youngest family member was diagnosed with cancer. Women (40?) 50–75 Every 2 years

Sexually active women <25 Unknown

45–75 Every 10 years Every 3 years

18–79 Once

15–65 At least once

Yearly

TABLE 6-5 Preventive Interventions Recommended for Average-Risk Adults INTERVENTION DISEASE POPULATION FREQUENCY CHAPTER Adult immunization 127, 129 COVID-19 Tetanus-diphtheria

> 18 18 PART 1 The Profession of Medicine Varicella Susceptibles only, >18 Two doses Measles-mumps-rubella Women, childbearing age One dose Pneumococcal 64 20 valent option or 15/23 Influenza 18 Yearly Human papillomavirus Up to age 27 If not done prior Zoster 60 Once Chemoprevention Aspirin Cardiovascular disease Aged 40–59 years with a ≥10% 10-year cardiovascular disease risk (bleeding risk may = benefit for some groups) Folic acid Neural tube defects in baby Women planning or capable of pregnancy Tamoxifen/raloxifene Breast cancer Women at high risk for breast cancer Vitamin D Fracture/falls 64 at increased risk for falls Although informed consent is important for all aspects of medi cal care, shared decision-making may be a particularly important approach to decisions about preventive services when the benefit-toharm ratio is uncertain for a specific population. For example, many expert groups, including the American Cancer Society, recommend an individualized discussion about prostate cancer screening because the decision-making process is complex and relies heavily on personal issues. Some men may decline screening, whereas others may be more willing to accept the risks of an early detection strategy. Another example of shared decision-making involves the choice of techniques for colon cancer screening (Chap. 75). In controlled studies, the use of annual FOBT reduces colon cancer deaths by 15–30%. Flexible sig moidoscopy reduces colon cancer deaths by ~40–60%. Colonoscopy appears to offer a greater benefit than flexible sigmoidoscopy with a reduction in risk of ~50–70% under optimal conditions of adherence and adenoma detection rates, but its use incurs additional costs and risks. These screening procedures have not been compared directly in the same population, but models suggest that appropriate frequen cies of each technique may be associated with similar numbers of lives saved and cost to society per life saved ($10,000–25,000). Thus, although one patient may prefer the ease of preparation and less time disruption of a DNA-based stool test, others may prefer the sedation, thoroughness, and time interval of colonoscopy. ■ ■COUNSELING ON HEALTHY BEHAVIORS In considering the impact of preventive services, it is important to recognize that tobacco and alcohol use, diet, and exercise constitute the vast majority of factors that influence preventable deaths in developed countries. Perhaps the single greatest preventive health care measure is to help patients quit smoking (Chap. 465). However, efforts in these areas frequently require behavior changes (e.g., weight loss, exercise) or the management of addictive conditions (e.g., tobacco and alcohol use) that are

often recalcitrant to intervention. Although these are chal lenging problems, evidence strongly supports the role of counseling by health care providers (Table 6-6) in effecting health behavior change. Educational campaigns, public policy changes, and community-based interventions have also proven to be important parts of a strategy for addressing these factors in some settings. Although the USPSTF found that the evidence was conclusive to recommend a relatively small set of counseling activities, counseling in areas such as physical activity and injury prevention (including seat belts and bicycle and motorcycle helmets) has become a routine part of primary care practice. Prevent ing and treating excess weight is also a top priority given the multiple complications of obesity (Chap. 414).

Every 10 years ■ ■IMPLEMENTING DISEASE PREVENTION

AND SCREENING The implementation of disease prevention and screening strategies in practice is challenging. A number of techniques can assist physicians with the delivery of these services. An appropriately configured elec tronic health record can provide reminder systems that make it easier for physicians to track and meet guidelines. Some systems give patients secure access to their medical records, providing an additional means to enhance adherence to routine screening. Systems that provide nurses and other staff with standing orders are effective for immunizations. The USPSTF has developed flow sheets and electronic tools to assist clinicians (https://www.uspreventiveservicestaskforce.org/uspstf/aboutuspstf/task-force-resources). Many of these tools use age categories to help guide implementation. Age-specific recommendations for screen ing and counseling are summarized in Table 6-7. Many patients see a physician for ongoing care of chronic ill nesses, and this visit provides an opportunity to include a “measure of prevention” for other health problems. For example, a patient seen for management of hypertension or diabetes can have breast cancer screening incorporated into one visit and a discussion about colon cancer screening at the next visit. Other patients may respond more favorably to a clearly defined visit that addresses all relevant screening and prevention interventions. Because of age or comorbidities, it may be appropriate with some patients to abandon certain screening and prevention activities, although there are fewer data about when to “sunset” these services. For many screening tests, the benefit of screen ing does not accrue until 5–10 years of follow-up, and there are gener ally few data to support continuing screening for most diseases past age 75. In addition, for patients with advanced diseases and limited life expectancy, there is considerable benefit from shifting the focus from screening procedures to the conditions and interventions more likely to affect quality and length of life. TABLE 6-6 Preventive Counseling Recommended by the

U.S. Preventive Services Task Force (USPSTF) TOPIC CHAPTER REFERENCE Alcohol and drug use 464, 467, 468 Genetic counseling for BRCA1/2 testing among women at increased risk for deleterious mutations 84, 480 Nutrition and diet 343, 344 Sexually transmitted infections 141, 208 Sun exposure

Tobacco use

TABLE 6-7 Age-Specific Causes of Mortality and Corresponding Preventive Options LEADING CAUSES OF

AGE-SPECIFIC MORTALITY SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION AGE GROUP 15–24

1. Accident
2. Homicide
3. Suicide
4. Malignancy
5. Heart disease • Counseling on routine seat belt use, bicycle/motorcycle/ATV helmets (1) • Counseling on diet and exercise (5) • Discuss dangers of alcohol use while driving, swimming, boating (1) • Assess and update vaccination status (tetanus, diphtheria, hepatitis B, MMR, rubella, varicella, meningitis, HPV, COVID-19) • Ask about gun use and/or gun possession (2,3) • Assess for substance abuse history including alcohol (2,3) • Screen for domestic violence (2,3) • Screen for depression and/or suicidal/homicidal ideation (2,3) • Pap smear for cervical cancer screening after age 21 (4) • Discuss skin, breast awareness, and testicular self-examinations (4) • Recommend UV light avoidance and regular sunscreen use (4) • Measurement of blood pressure, height, weight, and body mass index (5) • Discuss health risks of tobacco use, consider emphasis on cosmetic and economic issues to improve quit rates for younger smokers (4,5) • Chlamydia and gonorrhea screening and contraceptive counseling for sexually active females, discuss STD prevention • Hepatitis B, and syphilis testing if there is high-risk sexual behavior(s) or any prior history of sexually transmitted disease • Hepatitis C screening starting at age 18 to 79 • HIV testing • Continue annual influenza vaccination 25–44
6. Accident
7. Malignancy
8. Heart disease
9. Suicide
10. Homicide
11. HIV As above plus consider the following: • Readdress smoking status, encourage cessation at every visit (2,3) • Obtain detailed family history of malignancies and begin early screening/prevention program if patient is at significant increased risk (2) • Assess all cardiac risk factors (including screening for diabetes and hyperlipidemia); consider statin therapy for higher-risk patients • Assess for chronic alcohol abuse, risk factors for viral hepatitis, or other risks for development of chronic liver disease • Consider individualized breast cancer screening with mammography at age 40 (2) 45–64
12. Malignancy
13. Heart disease
14. Accident
15. Diabetes mellitus
16. Cerebrovascular disease
17. Chronic lower respiratory • Consider prostate cancer screen with annual PSA and digital rectal examination at age 50 (or possibly earlier in African Americans or patients with family history) (1) • Begin colorectal cancer screening at age 45 or 50 with fecal occult blood testing, stool DNA testing, flexible sigmoidoscopy, or colonoscopy (1) • Reassess

and update vaccination status at age 50 and vaccinate all smokers against Streptococcus pneumoniae at age 50 (6) • Consider screening for coronary disease in higher-risk patients (2,5) • Zoster vaccination at age 60 • Begin mammography screening by age 50 • Lung cancer screening at age 50–80 years if a 20-pack-year smoking history and currently smoke or have quit disease

18. Chronic liver disease and cirrhosis
19. Suicide within the past 15 years, yearly ≥65
20. Heart disease
21. Malignancy
22. Cerebrovascular disease
23. Chronic lower respiratory As above plus consider the following: • Readdress smoking status, encourage cessation at every visit (1,2,3,4) • One-time ultrasound for AAA in men 65–75 who have ever smoked • Consider pulmonary function testing for all long-term smokers to assess for development of chronic obstructive disease
24. Alzheimer's disease
25. Influenza and pneumonia
26. Diabetes mellitus
27. Kidney disease
28. Accidents
29. Septicemia pulmonary disease (4,6) • Screen all postmenopausal women (and all men with risk factors) for osteoporosis • Continue annual influenza vaccination and vaccinate against S. pneumoniae at age 65 (4,6) • Screen for visual and hearing problems, home safety issues, and elder abuse (9) • Consider fall prevention exercise intervention if at higher risk (9) Note: The numbers in parentheses refer to areas of risk in the mortality column affected by the specified intervention. Abbreviations: AAA, abdominal aortic aneurysm; ATV, all-terrain vehicle; HPV, human papillomavirus; MMR, measles-mumps-rubella; PSA, prostate-specific antigen;

STD, sexually transmitted disease; UV, ultraviolet. Acknowledgment The author is grateful to Dr. Katrina A. Armstrong for contributions to this chapter in prior editions of Harrison's. ■ ■FURTHER READING Bretthauer M et al: Effect of colonoscopy screening on risks of colorectal cancer and related death. N Engl J Med 387:1547, 2022.

CHAPTER 6 Screening and Prevention of Disease Davidson KW et al: Screening for colorectal cancer: US Preventive Ser vices Task Force recommendation statement. JAMA 325:1965, 2021. Hugosson J et al: Mortality results from the Goteborg randomized popu lation-based prostate-cancer screening trial. Lancet Oncol 11:725, 2010. Woloshin S et al: The new USPSTF mammography recommendations—a dissenting view. N Engl J Med 389:1061, 2023.

07 - 7 The Safety and Quality of Health Care

7 The Safety and Quality of Health Care

David W. Bates

The Safety and Quality

of Health Care PART 1 The Profession of Medicine Safety and quality are two of the central dimensions of health care. In recent years, it has become easier to measure safety and quality, and it is increasingly clear that performance in both dimensions could be much better. The public is—with good justification—demanding measure ment and accountability, and payment for services will increasingly be based on performance in these areas. Thus, physicians must learn about these two domains, how they can be improved, and the relative strengths and limitations of the current ability to measure them. Safety and quality are closely related but do not completely overlap. The Institute of Medicine has suggested in a seminal series of reports that safety is the first part of quality and that the health care system must first and foremost guarantee that it will deliver safe care, although quality is also pivotal. In the end, it is likely that more net clinical ben efit will be derived from improving quality than from improving safety, though both are important and safety is in many ways more tangible to the public. The first section of this chapter will address issues relating to the safety of care and the second will cover quality of care. ■ ■SAFETY IN HEALTH CARE Safety Theory and Systems Theory Safety theory clearly points out that individuals make errors all the time. Think of driving home from the hospital: you intend to stop and pick up a quart of milk on the way home but find yourself entering your driveway without realizing how you got there. Everybody uses low-level, semiautomatic behavior for many activities in daily life; this kind of error is called a slip. Slips occur often during care delivery—e.g., when people intend to write an order but forget because they must complete another action first. Mistakes, by contrast, are errors of a higher level; they occur in new or nonstereotypic situations in which conscious decisions are being made. An example would be dosing of a medication with which a physician is not familiar. The strategies used to prevent slips and mistakes are often different. Systems theory suggests that most accidents occur as the result of a series of small failures that happen to line up in an individual instance so that an accident can occur (Fig. 7-1). It also suggests that most individuals in an industry such as health care are trying to do the right thing (e.g., deliver safe care) and that most accidents thus result from defects in systems. Systems should be designed both to make

errors less likely and to identify those that do inevitably occur. Hazards Some holes due to active failures Other holes due to latent conditions (resident “pathogens”) Losses Successive layers of defenses, barriers, and safeguards FIGURE 7-1 “Swiss cheese” diagram. Reason argues that most accidents occur when a series of “latent failures” are present in a system and happen to line up in a given instance, resulting in an accident. Examples of latent failures in the case of a fall might be that the unit is unusually busy and the floor happens to be wet. (Adapted from J Reason: BMJ 320:768, 2000.)

Factors That Increase the Likelihood of Errors Many factors ubiquitous in health care systems can increase the likelihood of errors, including fatigue, stress, interruptions, complexity, and transitions. The effects of fatigue in other industries are clear, but its effects in health care have been more controversial until recently. For example, the acci dent rate among truck drivers increases dramatically if they work over a certain number of hours in a week, especially with prolonged shifts. A study of house officers in the intensive care unit demonstrated that they were about one-third more likely to make errors when they were on a 24-h shift than when they were on a schedule that allowed them to sleep 8 h the previous night. The American College of Graduate Medical Education moved to address this issue by putting in place the 80-h workweek. Although this stipulation is a step forward, it does not address the most important cause of fatigue-related errors: extendedduty shifts. High levels of stress and heavy workloads also can increase error rates. Thus, in extremely high-pressure situations, such as cardiac arrests, errors are more likely to occur. Strategies such as using proto cols in these settings can be helpful, as can simple recognition that the situation is stressful. Interruptions also increase the likelihood of error and occur fre quently in health care delivery. It is common to forget to complete an action when one is interrupted partway through it by a page, for example. Approaches that may be helpful in this area include minimiz ing interruptions and setting up tools that help define the urgency of an interruption. Complexity represents a key issue that contributes to errors. Providers are confronted by streams of data (e.g., laboratory tests and vital signs), many of which provide little useful information but some of which are important and require action or suggest a specific diagnosis. Tools that emphasize specific abnormalities or combinations of abnormalities may be helpful in this area. Transitions between providers and settings are also common in health care, especially with the advent of the 80-h workweek, and gen erally represent points of vulnerability. Tools that provide structure in exchanging information—for example, when transferring care between providers—may be helpful. The Frequency of Adverse Events in Health Care Most large studies focusing on the frequency and consequences of adverse events have been performed in the inpatient setting; some data are available for nursing homes, but much less information is available about the outpatient setting. The Harvard Medical Practice Study, one of the largest studies to address this issue, was performed with hospitalized patients in New York. The primary outcome was the adverse event: an injury caused by medical management rather than by the patient’s underlying disease. In this study, an event either resulted in death or disability at discharge or prolonged the length of hospital stay by at least 2 days. Key findings were that the adverse event rate was 3.7% and that 58% of the adverse events were considered preventable. Although New York is not representative of the United States as a whole, the study was replicated later in Colorado and Utah, where the rates were essentially similar. Several recent studies suggest that the frequency of harm related to medical care now approaches one in four admissions. The rates appear to be higher for several reasons—the techniques for finding events have improved with the use of “triggers” such as an unexpected transfer to the intensive care unit; records are now elec

tronic and are easier to search; and the complexity of care continues to grow. Overall, it is quite concerning that rates remain so high, even though the frequency of some types of harm such as hospital-acquired infections appears to have decreased. In the Harvard Medical Practice Study, adverse drug events (ADEs) were most common, accounting for 19% of all adverse events, and were followed in frequency by wound infections (14%) and technical com plications (13%). Almost half of adverse events were associated with a surgical procedure. Among nonoperative events, 37% were ADEs, 15% were diagnostic mishaps, 14% were therapeutic mishaps, 13% were procedure-related mishaps, and 5% were falls. ADEs have been studied more than any other error category. Stud ies focusing specifically on ADEs have found that they appear to be

much more common than was suggested by the Harvard Medical Practice Study, although most other studies use more inclusive crite ria. Detection approaches in the research setting include chart review and the use of a computerized ADE monitor, a tool that explores the database and identifies signals that suggest an ADE may have occurred. Studies that use multiple approaches find more ADEs than does any individual approach, and this discrepancy suggests that the true underlying rate in the population is higher than would be identi fied by a single approach. About 6–10% of patients admitted to U.S. hospitals experience an ADE. Injuries caused by drugs are also common in the outpatient setting. One study found a rate of 21 ADEs per every 100 patients per year when patients were called to assess whether they had had a problem with one of their medications. The severity level was lower than in the inpatient setting, but approximately one-third of these ADEs were preventable. The period immediately after a patient is discharged from the hospi tal appears to be very risky. A recent study of patients hospitalized on a medical service found an adverse event rate of 19%; about one-third of those events were preventable, and another one-third were ameliorable (i.e., they could have been made less severe). ADEs were the single leading error category. Prevention Strategies Most work on strategies to prevent adverse events has targeted specific types of events in the inpatient setting, with nosocomial infections and ADEs having received the most attention. Nosocomial infection rates have been reduced greatly in intensive care settings, especially by using checklists. For ADEs, several strategies have been found to reduce the medication error rate, although it has been harder to demonstrate that they reduce the ADE rate overall, and no studies with adequate power to show a clinically meaningful reduc tion have been published. Implementation of checklists to ensure that specific actions are car ried out has had a major impact on rates of catheter-associated blood stream infection and ventilator-associated pneumonia, two of the most serious complications occurring in intensive care units. The checklist concept is based on the premise that several specific actions can reduce the frequency of these issues; when these actions are all taken for every patient, the result has been an extreme reduction in the frequency of the associated complication. These practices have been disseminated across wide areas in the state of Michigan. Computerized physician order entry (CPOE) linked with clinical decision support reduces the rate of serious medication errors, defined as those that harm someone or have the potential to do so. In one study, CPOE, even with limited decision support, decreased the serious medication error rate by 55%. CPOE can prevent medication errors by suggesting a default dose, ensuring that all orders are complete (e.g., that they include dose, route, and frequency), and checking orders for allergies, drug–drug interactions, and drug–laboratory issues. In addi tion, clinical decision support can suggest the right dose for a patient, tailoring it to the level of renal function and age. In one study, patients with renal insufficiency received the appropriate dose only one-third of the time without decision support, whereas that fraction increased to approximately two-thirds with decision support; moreover, with

such support, patients with renal insufficiency were discharged from the hospital half a day earlier. As of 2019, over 95% of U.S. hospitals had implemented CPOE, although the decision support often is still limited. Another technology that can improve medication safety is bar cod ing linked with an electronic medication administration record. Bar coding can help ensure that the right patient gets the right medica tion at the right time. Electronic medication administration records can make it much easier to determine what medications a patient has received. Studies to assess the impact of bar coding on medication safety are under way, and the early results are promising. Another tech nology to improve medication safety is “smart pumps.” These pumps can be set according to which medication is being given and at what dose; the health care professional will receive a warning if too high a dose is about to be administered.

The National Safety Picture Several organizations, including the National Quality Forum and The Joint Commission, have made rec ommendations for improving safety. The National Quality Forum has released recommendations to U.S. hospitals about what practices will most improve the safety of care, and all hospitals are expected to imple ment these recommendations. Many of these practices arise frequently in routine care. One example is “readback,” the practice of recording all verbal orders and immediately reading them back to the physician to verify the accuracy of what was heard. Another is the consistent use of standard abbreviations and dose designations; some abbreviations and dose designations are particularly prone to error (e.g., 7U may be read as 70).

CHAPTER 7 The Safety and Quality of Health Care Measurement of Safety Measuring the safety of care is difficult and expensive, since adverse events are, fortunately, rare. Most hos pitals rely on spontaneous reporting to identify errors and adverse events, but the sensitivity of this approach is very low, with only ~1 in 20 ADEs reported. Promising research techniques involve searching the electronic record for signals suggesting that an adverse event has occurred. These methods are not yet in wide use but will probably be used routinely in the future. Claims data have been used to identify the frequency of adverse events; this approach works much better for surgical care than for medical care and requires additional validation. The net result is that, except for a few specific types of events (e.g., falls and nosocomial infections), hospitals have little idea about the true frequency of safety issues. Nonetheless, all providers have the responsibility to report prob lems with safety as they are identified. All hospitals have spontaneous reporting systems, and if providers report events as they occur, those events can serve as lessons for subsequent improvement. Conclusions about Safety It is abundantly clear that the safety of health care can be improved substantially—nearly one inpatient in four suffers harm today. As more areas are studied closely, more problems are identified. Much more is known about the epidemiology of safety in the inpatient setting than in outpatient settings. Many effective strate gies for improving inpatient safety have been identified, and they are increasingly being applied. Some effective strategies are also available for the outpatient setting. Transitions appear to be especially risky. The solutions to improving care often entail the consistent use of systematic techniques such as checklists and often involve leveraging of informa tion technology. Nevertheless, solutions will also include many other domains, such human factors techniques, team training, and a culture of safety. ■ ■QUALITY IN HEALTH CARE Assessment of quality of care has remained somewhat elusive, although the tools for this purpose have increasingly improved. Selection of health care and measurement of its quality are components of a com plex process. Quality Theory Donabedian has suggested that quality of care can be categorized by type of measurement into structure, process, and outcome. Structure refers to whether a particular characteristic is appli cable in a particular setting—e.g.,

whether a hospital has a catheteriza tion laboratory or whether a clinic uses an electronic health record (EHR). Process refers to the way care is delivered; examples of process measures are whether a Pap smear was performed at the recommended interval or whether an aspirin was given to a patient with a suspected myocardial infarction. Outcome refers to what happens—e.g., the mor tality rate in myocardial infarction. It is important to note that good structure and process do not always result in a good outcome. For instance, a patient may present with a suspected myocardial infarction to an institution with a catheterization laboratory and receive recom mended care, including aspirin, but still die because of the infarction. Quality theory also suggests that overall quality will be improved more in the aggregate if the performance level of all providers is raised rather than if a few poor performers are identified and punished. This view suggests that systems changes are especially likely to be helpful in improving quality, since large numbers of providers may be affected simultaneously.

Adopt or abandon strategies based on results Identify potential improvement strategies Plan Act PART 1 The Profession of Medicine Check Do Measure effectiveness of strategies Try out strategies FIGURE 7-2 Plan-Do-Check-Act cycle. This approach can be used to improve a specific process rapidly. First, planning is undertaken, and several potential improvement strategies are identified. Next, these strategies are evaluated in small “tests of change.” “Checking” entails measuring whether the strategies have appeared to make a difference, and “acting” refers to acting on the results. The theory of continuous quality improvement suggests that organi zations should be evaluating the care they deliver on an ongoing basis and continually making small changes to improve their individual processes. This approach can be very powerful if embraced over time. Several specific tools have been developed to help improve process performance. One of the most important is the Plan-Do-Check-Act cycle (Fig. 7-2). This approach can be used for “rapid cycle” improve ment of a process—e.g., the time that elapses between a diagnosis of pneumonia and administration of antibiotics to the patient. Some statistical tools, such as control charts, are often used in conjunction to determine whether progress is being made. Because most medical care includes one or many processes, this tool is especially important for improvement. Factors Relating to Quality Many factors can decrease the level of quality, including stress to providers, high or low levels of produc tion pressure, and poor systems. Stress can have an adverse effect on quality because it can lead providers to omit important steps, as can a high level of production pressure. Low levels of production pressure sometimes can result in worse quality, as providers may be bored or have little experience with a specific problem. Poor systems can have a tremendous impact on quality, and even extremely dedicated providers typically cannot achieve high levels of performance if they are operat ing within a poor system. Data About the Current State of Quality A study published by the RAND Corporation in 2006 provided the most complete picture of quality of care delivered in the United States to date. The results were sobering. The authors found that, across a wide range of quality param eters, patients in the United States received only 55% of recommended care overall; there was little variation by subtype, with scores of 54% for preventive care, 54% for acute care, and 56% for care of chronic conditions. The authors concluded that, in broad terms, the chances of getting high-quality care in the United States were little better than those of winning a coin flip. Work from the Dartmouth Atlas of Health Care evaluating geo graphic variation in use and quality of care demonstrates that, despite large variations in utilization, there is no positive correlation between the two variables at the regional level. An array of data demonstrate, however, that providers with larger volumes for specific conditions, especially for surgical conditions, do have better outcomes. Strategies for Improving Quality and Performance

Many specific strategies can be used to improve quality at the individual level, including rationing, education, feedback, incentives, and penalties. Rationing has been effective in some specific areas, such as persuading physicians to prescribe within a formulary, but it generally has been resisted. Education is effective in the short run and is necessary for

changing opinions, but its effect decays fairly rapidly with time. Feed back on performance can be given at either the group or the individual level. Feedback is most effective if it is individualized and is given in close temporal proximity to the original events. Incentives can be effec tive, and many believe that they will prove to be a key to improving quality, especially if pay-for-performance with sufficient incentives is broadly implemented (see below). Penalties produce provider resent ment and are rarely used in health care. Another set of strategies for improving quality involves changing the systems of care. An example would be introducing reminders about which specific actions need to be taken at a visit for a specific patient—a strategy that has been demonstrated to improve performance in certain situations, such as the delivery of preventive services. Another approach that has been effective is the development of “bundles” or groups of quality measures that can be implemented together with a high degree of fidel ity. Many hospitals have implemented a bundle for ventilator-associated pneumonia in the intensive care unit that includes five measures (e.g., ensuring that the head of the bed is elevated). These hospitals have been able to improve performance substantially. Another technique is SCAMPs, or Standardized Clinical Assessment and Management Plans. These are care guidelines developed by clinicians who identify key steps in workflow and decisions to help improve the process outcomes. Perhaps the most pressing need is to improve the quality of care for chronic diseases. The Chronic Care Model has been developed by Wagner and colleagues (Fig. 7-3); it suggests that a combination of strategies is necessary (including self-management support, changes in delivery system design, decision support, and information systems) and that these strategies must be delivered by a practice team com posed of several providers, not just a physician. Available evidence about the relative efficacy of strategies in reduc ing hemoglobin A1c (HbA1c) in outpatient diabetes care supports this general premise. It is especially notable that the outcome was the HbA1c level, as it has generally been much more difficult to improve outcome measures than process measures (such as whether HbA1c was measured). In this meta-analysis, a variety of strategies were effective, but the most effective ones were the use of team changes and the use of a case manager. When cost-effectiveness is considered in addition, it appears likely that an amalgam of strategies will be needed. However, the more expensive strategies, such as the use of case managers, proba bly will be implemented widely only if pay-for-performance takes hold. The evidence linking better performance on quality metrics assess ing process and outcomes varies greatly by condition. For example, there is strong evidence that performing Pap smears results in better Community Resources and policies Health System Organization of health care Selfmanagement Support Decision support Clinical information systems Delivery system design Informed, activated patient Prepared, proactive practice team Productive interactions Improved Outcomes FIGURE 7-3 The Chronic Care Model, which focuses on improving care for chronic diseases, suggests that (1) delivery of high-quality care requires a range of strategies that must closely involve and engage the patient and (2) team care is essential. (From EH Wagner et al: Eff Clin Pract 1:2, 1998.)

outcomes in patients who develop cervical cancer, but the evidence for many other conditions is far more tenuous. National State of Quality Measurement In the inpatient set ting, quality

measurement is now being performed by a very large proportion of hospitals for several conditions, including myocardial infarction, congestive heart failure, pneumonia, and surgical infection prevention; 20 measures are included in all. This is the result of the Hospital Quality Initiative, which represents a collaboration among many entities, including the Hospital Quality Alliance, The Joint Com mission, the National Quality Forum, and the Agency for Healthcare Research and Quality. The data are housed at the Centers for Medi care and Medicaid Services, which publicly releases performance data on the measures on a website called Hospital Compare (www. cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ HospitalQualityInits/HospitalCompare.html). These data are reported voluntarily and are available for a very high proportion of the nation's hospitals. Analyses demonstrate substantial regional variation in qual ity and important differences among hospitals. Analyses by The Joint Commission for similar indicators reveal that performance on mea sures by hospitals has improved over time and that, as might be hoped, lower performers have improved more than higher performers. The biggest change recently in this domain is that Medicare is now moving to electronic clinical quality metrics (ECQMs). Histori cally, care has been measured mainly through claims data, but now it is being measured through data being extracted from EHRs, though these new metrics need to be validated. https://www.cms.gov/medicare/ regulations-guidance/promoting-interoperability-programs/electronicclinical-quality-measures-basics#:~:text=CMS%20has%20finalized%20 the%20Electronic%20clinical%20quality%20measure,to%20measure%20 the%20quality%20of%20health%2. Public Reporting Overall, public reporting of quality data is becoming increasingly common. There are now commercial websites that have quality-related data for most regions of the United States, and these data can be accessed for a fee. Similarly, national data for hospitals are available. The evidence to date indicates that patients have not made much use of such data, but that the data have had an important effect on provider and organization behavior. Instead, patients have relied on provider reputation to make choices, partly because little information was available until very recently and the information that was available was not necessarily presented in ways that were easy for patients to access. Problems still exist with quality metrics; many can be "gamed," and even though providers are now nearly universally using EHRs, most metrics come from claims that include many inaccuracies. More metrics that leverage EHRs are sorely needed. However, many authorities think that, as more information about quality becomes available, it will become increasingly central to patients' choices about where to access care. Pay-for-Performance Currently, providers in the United States get paid the same amount for a specific service, regardless of the qual ity of care delivered. The pay-for-performance theory suggests that, if providers are paid more for higher-quality care, they will invest in strategies that enable them to deliver that care. The current key issues in the pay-for-performance debate relate to (1) how effective it is, (2) what levels of incentives are needed, and (3) what perverse consequences are produced. The evidence on effectiveness is limited, although several studies are ongoing. With respect to incentive levels, most quality-based performance incentives have accounted for merely 1–2% of total payment in the United States to date. In the United Kingdom, however, 40% of general practitioners' salaries have been placed at risk according to performance across a wide array of parameters; this approach has been associated with substantial improvements in reported quality performance, although it is still unclear to what extent this change represents better performance versus better reporting. The potential for perverse consequences exists with any incentive scheme. One problem is that, if incentives are tied to outcomes, there may be a tendency to transfer the sickest patients to other providers and systems. Another concern is that providers will pay too much attention to qual ity measures with

incentives and ignore the rest of the quality picture.

The validity of these concerns remains to be determined. Nonetheless, it appears likely that, under health care reform, the use of various payfor-performance schemes is likely to increase.

■ ■CONCLUSIONS The safety and quality of care in the United States could be improved substantially. Many available interventions have been shown to improve the safety of care and should be used more widely; others are under going evaluation or soon will be. Quality also could be dramatically better, and the science of quality improvement continues to mature. Medicare is rapidly moving toward electronic clinical quality measures. Implementation of value-based approaches such as accountable care that include pay-for-performance related to safety and quality should make it much easier for organizations to justify investments in improv ing safety and quality parameters, including health information tech nology. However, many improvements will also require changing the structure of care—e.g., moving to a more team-oriented approach and ensuring that patients are more involved in their own care. Payment reform focusing on value seems very likely to progress and will likely include both positive incentives and penalties related to safety and quality performance. Measures of safety are still relatively immature and could be made much more robust; it would be particularly useful if organizations had measures they could use in routine operations to assess safety at a reasonable cost, and substantial research is address ing this. Although the quality measures available are more robust than those for safety, they still cover a relatively small proportion of the entire domain of quality, and more measures need to be developed. The public and payers are demanding better information about safety and quality as well as better performance in these areas. The clear implication is that these domains will have to be addressed directly by providers. CHAPTER 7 The Safety and Quality of Health Care ■ ■FURTHER READING Bates DW et al: Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 280:1311, 1998. Bates DW et al: The safety of inpatient health care. N Engl J Med 388:142, 2023. Bates DW et al: Two decades since to err is human: An assessment of progress and emerging priorities in patient safety. Health Aff (Millwood) 37:1736, 2018. Berwick DM: Era 3 for medicine and health care. JAMA 315:1329, 2016. Brennan TA et al: Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med 324:370, 1991. Centers for Medicare and Medicaid Services: Inspector General's Report. https://www.cms.gov/medicare/regulations-guidance/promoting-

interoperability-programs/electronic-clinical-quality-measures-

basics#:~:text=CMS%20has%20finalized%20the%20Electronic%20clini cal%20quality%20measure,to%20measure%20the%20quality%20of%20 health%20care%20provided. Chertow GM et al: Guided medication dosing for inpatients with renal insufficiency. JAMA 286:2839, 2001. Institute of Medicine: Report: To err is human: Building a safer health system. 1999. https://www.nap.edu/resource/9728/To-Err-is-

Human-1999–report-brief.pdf. Institute of Medicine: Crossing the quality chasm: A new health system for the 21st century. 2001. https://www.nap.edu/catalog/10027/ crossing-the-quality-chasm-a-new-health-system-for-the. Landrigan C et al: Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med 351:1838, 2004. McGlynn EA et al: The

quality of health care delivered to adults in the United States. N Engl J Med 348:2635, 2003. Pronovost P et al: An intervention to decrease catheter-related blood stream infections in the ICU. N Engl J Med 355:2725, 2006. Erratum in: N Engl J Med 356:2660, 2007. Starmer AJ et al: Rates of medical errors and preventable adverse events among hospitalized children following implementation of a resident handoff bundle. JAMA 310:2262, 2013.

08 - 8 The Value of the Physical Examination in Modern Medicine

8 The Value of the Physical Examination in Modern Medicine

Abraham Verghese, Steven McGee

The Value of the Physical Examination in Modern Medicine PART 1 The Profession of Medicine Medicine is experiencing unprecedented progress in understanding the biology of disease and developing new therapies; concurrently, artificial intelligence (AI), with its ability to train on and interpret large medical data sets, is transforming many aspects of clinical medicine. Meanwhile, the rising costs of health care in the United States and many other nations have led to the merging of health care systems and the decline of individual physician practices. For the patient, the profoundly personal and often isolating nature of the illness experience remains largely unchanged since antiquity: individuals who are ill want to feel they are in the hands of a caring and attentive physician, and they will judge the quality of their care based on that interaction. It is not uncommon to hear patient dissatisfaction expressed as “my doctor never touched me” or “never laid a hand on me.” ■ ■HISTORICAL EVOLUTION OF THE PHYSICAL EXAMINATION A student of ancient medical texts finds few good descriptions of physi cal findings of disease; longstanding proscriptions against dissecting the dead meant that for centuries physicians had a poor understanding of normal anatomy or physiology. One exception is in the writings of Hippocrates (460–370 BCE), who described clubbing in the setting of empyema and the “succussion splash” (heard without a stethoscope) in a patient with hydropneumothorax. Only in 1543, with the publication of Vesalius’s De Humani Corporis Fabrica Libri Septem (On the fabric of the human body in seven books) did things begin to change. The Dawn of Physical Diagnosis In 1761, the Viennese physi cian Leopold Auenbrugger published his treatise, Inventum Novum ex Percussione Thoracis Humani Interni Pectoris Morbos Detegendi (A new discovery that enables the physician from the percussion of the human thorax to detect the diseases hidden within the chest). He recalled his father, an innkeeper, tapping the sides of casks of wine and listening for where the sound changed in character, thereby revealing the position of the fluid meniscus and how much wine remained. Auenbrugger could similarly, by tapping on his patients’ chests, detect

cardiomegaly as well as the presence of fluid in the pleural space. He confirmed the validity of his findings in a few autopsies. His discovery was revolutionary because it was the first means of "looking" into the living body; it was the ultrasound of its day. Auenbrugger's text was so complete that little new has been added to the art of percussion since, with the exception of "Skodaic resonance" (an arc of hyperresonance above a pleural effusion) and "Kronig's isthmus" (a narrow band of resonance in the supraclavicular area connecting the resonance of the front and back of the chest, an isthmus that is narrowed on one side in the presence of apical lobe diseases such as tuberculosis). New Bedside Instruments Soon after percussion came the inven tion of the stethoscope by Laënnec in 1816, the ophthalmoscope by Helmholtz in 1850, the clinical thermometer by Wunderlich in 1868, the reflex hammer to elicit the muscle stretch reflexes described by Erb and Westphal in 1875, and the blood pressure cuff by Riva-Rocci in 1896. In the 1800s, Paris was the place to learn clinical skills under individuals such as Corvisart, Laënnec, Dupuytren, Bichat, and Pierre Louis. By the 1850s, the "German School" epitomized by Johannes Müller emerged, with its emphasis on experimental medicine and laboratory skills. For many North American physicians, includ ing William Osler (1849–1919), who shaped medical education in America, a sojourn in Europe was obligatory. The use of tuning forks, oximeters, electronic stethoscopes, and Dopplers (for pulse detection and for ankle brachial index) and other ultrasound devices brings us to the present. Just as modern physicians are adopting point-of-care

ultrasound and even pocket ultrasounds, the addition of new instru ments has always been part of the evolution of physical diagnosis. An Illustration of Clinical Examination Excellence Almost all diseases in the latter part of the nineteenth century and the early twentieth century were defined by their bedside findings, as clinical imaging had not yet developed. Physicians therefore prioritized care ful bedside examination by means of inspection, palpation, percussion, and auscultation. Professor Joseph Bell (1837–1911) at the University of Edinburgh was legendary for his inferential skills. Among his medical students was the future physician and writer, Arthur Conan Doyle, who based his famous sleuth, Sherlock Holmes, on Professor Bell. The fol lowing anecdote in Lancet (by another one of Bell's students) illustrates Bell's skill in inspection before he begins palpation, percussion, and auscultation. A woman with a small child was shown in. Joe Bell said good morning to her and she said good morning in reply. "What sort of a crossing di' ye have fra' Burntisland?" "It was guid." "And had ye a guid walk up Inverleith Row?" "Yes." "And what did ye do with th' other wain (child)?" "I left him with my sister in Leith." "And would ye still be working at the linoleum factory?" "Yes I am." Dr. Bell then explains to the students: "You see gentlemen, when she said good morning I noted her Fife accent, and, as you know, the nearest town in Fife is Burntisland. You noticed the red clay on the edges of the soles of her shoes, and the only such clay within 20 miles of Edinburgh is in the Botanical Gardens. Inverleith Row borders the gardens and is her nearest way here from Leith. You observed that the coat she carried over her arm is too big for the child who is with her, and therefore she set out from home with two children. Finally she has a dermatitis on the fingers of the right hand which is peculiar to workers in the linoleum factory at Burntisland." With the ascendance of diagnostic technology and laboratory test ing, bedside examination skills declined, a trend that began in the 1970s and has accelerated. "Assessment drives learning" is an axiom of education; in medicine, the use of multiple-choice exams without a clinical assessment by direct observation of trainees as they examine patients with known physical findings diminishes the trainee's incen tive to develop these skills. ■ ■FIVE REASONS THE PHYSICAL EXAMINATION REMAINS VERY RELEVANT The bedside examination remains important and necessary for at least the following five reasons:

1. For a host of disorders, there are no laboratory or imaging studies that make the diagnosis, and thus the bedside findings are the gold standard; Parkinson's disease is an example.
2. Focused evidence-based physical examination maneuvers allow the physician to assign a greater or smaller value to the probability of a particular disease than prior to the examination and can thus direct and complement imaging and laboratory testing.
3. The physical examination frequently uncovers clues to other disease states that are asymptomatic or unrelated to the patient's presenting complaint but that are potentially treatable.
4. Missing critical findings in the examination can lead to errors that delay diagnosis and treatment; subject the patient to unnecessary contrast, radiation, or even surgery; and at times lead to significant morbidity and death. Such errors are embarrassing to the physician and can lead to malpractice claims.
5. The physical examination, when viewed through an anthropologic lens, has all the classic markers of a ritual. When performed well, the ritual elicits the patient's confidence and trust, while at the same time symbolically validating and localizing their disease or

symptom on the canvas of their body and in an organ, as opposed to on an image or biopsy report. It is also worth noting that the physical examination is safe, imme diately accessible, has no added cost, and uses no technology beyond the instruments carried by the clinician or available in the room. Its pedagogic value with trainees is in the opportunity to teach proper examination techniques as well as clinical reasoning. It allows the cli nician to model empathy, consideration for the patient's comfort, and the establishment of a connection that builds trust and reduces anxiety. The five themes are elaborated below, with particular attention to the second theme above. When the Physical Examination Is the Sole Means of Mak ing a Diagnosis For numerous medical disorders, the physical examination findings are the gold standard, the only means of making a diagnosis. This is the case for many diseases of the skin and of the eye (a reason why internists should be well versed in examining both organs and be familiar with common disorders associated with these). Amyotrophic lateral sclerosis is diagnosed principally by the clinical examination—there are no diagnostic blood tests or imaging findings. Table 8-1 lists other examples. Evidence-Based Physical Examination Improves Diagnosis and Complements Imaging and Laboratory Testing Trainees often assume that evidence-based medicine (EBM) is properly focused on "external" data such as from laboratory tests or diagnostic images; these are perceived as more "objective." However, as the late clinical epidemiologist Alvan Feinstein (often thought of as one of the fathers of EBM and whose book Clinical Judgment remains a seminal work) took pains to emphasize, the clinical evidence base is of great impor tance. He wrote, "clinicians can bring science to clinical judgment by better exercise of the very human capacities that appear to impair it, and by giving increased attention not to laboratory substances and inanimate technology, but to sick people and the human methods of evaluating sick people." Rather than devaluing the objective data to be TABLE 8-1 Selected Examples of Conditions in Which the Physical Exam Is the Diagnostic Standard or the Primary Method of Diagnosis DISEASE CONDITIONS NOTES Dermatology (selected list) Cellulitis, psoriasis, rosacea, acne vulgaris, eczema, urticaria, pityriasis rosea, cutaneous lichen planus, erythema multiforme, hereditary hemorrhagic telangiectasia, rubella, measles, herpes zoster, erythema nodosum • Many dermatologic conditions are diagnosed by observation, even if confirmatory tests may exist • Skin biopsy not needed for the selected examples unless there is diagnostic uncertainty • Only the neurologic exam can determine the functional deficit, if any, of

an abnormality on computed tomography Neurology Amyotrophic lateral sclerosis, Parkinson's disease (tremor, bradykinesia, rigidity; absence of atypical features), Bell's palsy scan or magnetic resonance imaging • Peripheral neuropathy is common; diagnosis is by symptoms and signs (decreased sensation, decreased or absent reflexes, and motor weakness); electromyography and nerve conduction studies are painful and must be ordered for specific reasons • Sensory testing for pain and temperature (carried by small unmyelinated fibers) may be more sensitive than conventional nerve conduction tests, which test larger myelinated nerves fibers • Patterns of sensory loss help localization: glove and stocking (peripheral neuropathy); radicular (root); BrownSequard type (spinal cord); "crossed" signs (cranial nerve deficits on one side and motor deficit on the other with brainstem lesions) • The clinical exam is essential for diagnosis and follow-up • In rheumatoid arthritis or lupus, serology alone does not make the diagnosis. A positive rheumatoid factor without Rheumatology Rheumatoid arthritis, lupus erythematosus, scleroderma, relapsing polychondritis, patterns suggesting vasculitis (acute mononeuritis, palpable purpura) multiple joint involvement, constitutional symptoms, rheumatoid nodules, morning stiffness, palpable synovitis, etc., is likely falsely positive. Seronegative rheumatoid arthritis is a clinical diagnosis • Diagnosis depends on combinations of characteristic chest pain, pericardial friction rub, and characteristic Cardiology Pericarditis electrocardiogram; 34–50% have normal echocardiograms • "Red eye": the internist must recognize symptoms and signs that require immediate ophthalmology referral, including Ophthalmology Diabetic retinopathy, conjunctivitis, suspicion of keratitis, iritis, scleritis, acute angle glaucoma, retinal infarction peri-limbic erythema (ciliary flush), photophobia, acute progressive pain, vision loss, foreign body sensation, anisocoria, fluid in the anterior chamber (hypopyon) • With conjunctivitis, the redness is most intense on the palpebral and peripheral bulbar conjunctiva • Bacterial versus viral versus allergic causes of conjunctivitis: bacterial discharge is purulent, sticky; eyes are stuck shut and crusted. Viral and allergic conjunctivitis can have mucoid, watery discharge. History of hay fever, itching, and previous episodes suggests allergic

found on the clinical examination, physicians should take pride in its careful collection. These data include not just the physical findings but also the physician's unique understanding of the patient's history, back ground, social situation, work environment, aspirations, beliefs, family structure, and local trends in disease.

CHAPTER 8 BEYOND THE STUDENT'S FIRST PHYSICAL DIAGNOSIS TEXTBOOK

Medical students typically learn their patient examination skills in preclinical courses that utilize one of several excellent physical diag nosis textbooks. In later years, however, few students revisit these texts to remind themselves of the rationale for each test or the correct technique. This might be because when the student enters the hospital in their clinical years, they often find that the workflow revolves more around the virtual patient in the computer, the ordering and retrieving of tests, and data entry, with less emphasis on examining the embodied patient. The introductory physical examination texts remain an impor tant and fundamental base from which to build skills. The trainee in internal medicine should progress to more advanced texts that embody Feinstein's philosophy of "bringing science to clinical judgment," such as Evidence-Based Physical Diagnosis by Steven McGee and the JAMA Rational Clinical Exam series begun in 1998 by David Simel and Drummond Rennie. The Value of the Physical Examination in Modern Medicine Trainees may falsely believe that physical examination findings are unreliable because clinicians can disagree about the

presence or absence of a finding. Also, trainees may incorrectly assume that chest radiograph, computed tomography (CT) scan, or tissue biopsy reports are “gold standards,” while physical examination findings are inaccurate. RELIABILITY Whether it is the interpretation of a bedside finding or of a CT scan, human observations are accompanied by a certain degree of interobserver disagreement. In clinical studies, interobserver agree ment is captured by the test statistic kappa or κ, which is a normalized measure of the increase in observed agreement over what would be expected by chance. Its value ranges from 0 (for agreement by chance) to 1 (for perfect agreement); 0.2–0.4 is considered fair agreement,

0.4–0.6 is moderate agreement, and 0.6–0.8 is substantial agreement. It might surprise the trainee to learn, for example, that there is only fair to moderate agreement (κ of 0.38–0.58) in recognizing the presence of an infiltrate on chest radiograph, while there is better agreement (κ of 0.83) for recognizing interstitial edema. The interobserver agreement for the classification of coronary artery lesions on angiogram is only fair (κ of 0.33); it is slightly better for determining the severity of val vular regurgitation on echocardiogram (κ of 0.32–0.55). Pathologists interpreting liver biopsies show fair agreement in noting cholestasis (κ of 0.4) and moderate agreement on the existence of cirrhosis (κ of 0.59).

PART 1 The Profession of Medicine In the same manner, physical signs have varying degrees of interob server agreement. Some signs, such as percussing for liver span or the use of auscultatory percussion, have notoriously low interobserver agreement and should be abandoned, while other signs have high agreement. A wide range in κ for a physical examination maneuver often reflects studies of varying rigor, different levels of training and experience, the transient nature of a sign, and other factors. Deter mining whether neck veins are normal or elevated shows a κ ranging from 0.08 to 0.71. Nevertheless, when the method of examination is agreed upon and the technique performed correctly, the interobserver agreement for many physical signs is good. The clock-drawing test (Wolf-Klein method) for dementia has a κ of 0.73; eliciting a positive abdominojugular test has a κ of 0.92, or almost perfect agreement. DIAGNOSTIC ACCURACY: PRETEST PROBABILITY, LIKELIHOOD RATIO, AND POSTTEST PROBABILITY From the patient’s history, the expe rienced clinician formulates hypotheses that are then accepted or rejected, or new ones are added as data are obtained by the physical examination (iterative hypothesis testing). For example, in a patient with cough and fever, the clinician might suspect pneumonia, and with those symptoms, the pretest probability of pneumonia is between 15 and 35%. It is useful for the clinician to have handy or memorize the pretest probabilities for common diagnoses, given particular clinical settings (Table 8-2). In a patient with cirrhosis, for example, the pretest probability of their having hepatopulmonary syndrome (HPS), which considerably alters their prognosis, is in the range from 14 to 37%. The finding of clubbing in this patient has a high specificity of 64–96% for HPS, but a variable sensitivity of 12–91%. Of more utility than sensitivity and specificity is the likelihood ratio (LR), a measure that allows the clinician to rapidly estimate posttest probability. The LR is calculated as the ratio of the probability of a particular finding in patients with disease (i.e., the sensitivity) divided by the probability of the identical finding in patients with mimicking conditions but without disease (i.e., the false-positive probability, which is 1 minus the specificity). LRs serve as diagnostic weights: values

> 1 increase probability from pretest to posttest (and the greater the LR, the more the probability increases); LRs with values <1 decrease TABLE 8-2 Pretest Probability of Selected Conditionsa CLINICAL SETTING DIAGNOSIS Hospitalized with fever Bacteremia

7–37 Cough and fever Pneumonia

15–35 Pleuritic chest pain, dyspnea, or hemoptysis Pulmonary embolism

9–43 Murmur of aortic regurgitation Moderate-to-severe aortic regurgitation

24–56 Chronic liver disease Hepatopulmonary syndrome

14–37 Abdominal distension Ascites

24–33 Ankle injury Ankle fracture

10–14 Lymphadenopathy persisting several weeks Serious disease (mostly cancer)

14–41 Diabetic foot ulcer Osteomyelitis

52–68 Acute calf pain or swelling Deep venous thrombosis

6–43 aThese pretest probabilities derive from published studies of physical findings. Clinicians can further refine them by considering their own clinical experience. For example, the pretest probability of hepatopulmonary syndrome (range, 14–37%) is probably closer to 14% in primary care patients with liver disease and closer to 37% in hepatology patients. Source: Adapted from SR McGee: Evidence-Based Physical Diagnosis, 5th ed. Philadelphia, Elsevier, 2022.

TABLE 8-3 Physical Signs and Their Likelihood Ratios LIKELIHOOD RATIO IF FINDING IS: DIAGNOSIS AND FINDING PRESENT ABSENT Diagnosing ascites in patients with abdominal distension Edema 3.8 0.2 Flank dullness NS 0.3 Fluid wave 5.0 0.5 Shifting dullness 2.3 0.4 Diagnosing hepatopulmonary syndrome in patients with chronic liver disease Clubbing 4.3 0.6 Cyanosis 4.4 0.7 Ascites NS NS Jaundice NS NS Diagnosing pneumonia in patients with cough and fever Percussion dullness 3.6 NS Egophony 4.1 NS Crackles 2.8 0.8 Bronchial breath sounds 3.3 0.9 Diagnosing elevated left heart filling pressures in patients with chest pain and dyspnea Heart rate >100 beats/min 5.5 NS Crackles NS NS Displaced apical impulse 5.8 NS Positive abdominojugular test 8.0 0.3 S3 gallop 3.9 0.8 Abbreviation: NS, not significant (i.e., the likelihood ratio of the finding is statistically no different from the value of 1.0 and therefore useless to the clinician when considering this diagnosis). Source: Adapted from SR McGee: Evidence-Based Physical Diagnosis, 5th ed. Philadelphia, Elsevier, 2022. probability (and the closer the value is to zero, the more probability decreases). McGee has popularized a useful rule of thumb in interpret ing LRs: LRs of 2, 5, and 10 translate to increased probability of disease of 15, 30, and 45%, respectively, whereas LRs of 0.5, 0.2, and 0.1 reduce the probability of disease by 15, 30, and 45%, respectively. These esti mates are accurate to within 5–10% of the actual calculated posttest probability and serve well

for bedside decisions. In the previous example of the patient with cirrhosis, the finding of finger clubbing in detecting HPS has an LR of 4.3 (Table 8-3). Suppose the clinician's estimate of pretest probability of HPS is about 30%: the PRETEST PROBABILITY (%) MEDIAN RANGE

ELEVATED LEFT HEART FILLING PRESSURE Decrease Probability Increase +45% –45% –30% –15% +15% +30% LRs LRs 0.1 0.2 0.5

Normal Valsalva response Positive abdominojugular test Abnormal Valsalva response Pulse increment ≥10% during Valsalva Displaced apical impulse Negative abdominojugular test Heart rate >100/min at rest S3 gallop Elevated jugular venous pressure Bendopnea test FIGURE 8-1 With just a glance, the clinician can immediately identify those few findings that significantly increase probability of heart failure (right side of ruler, likelihood ratio [LR] = 3 or more) and those that significantly decrease it (left side of ruler, LR = 0.3 or less). For example, the figure shows that the presence of S3 gallop (LR = 3.9) and presence of displaced apical impulse (LR = 5.8) significantly increase probability of heart failure. On the other hand, the absence of either finding does not appear on the ruler because these LRs lie between 0.3 and 3.0 (Table 8-3) and therefore are diagnostically unhelpful. (Reproduced with permission from

SR McGee: Evidence-Based Physical Diagnosis, 4th ed. Philadelphia, Elsevier; 2022.) LR of 4.3 raises the probability of HPS by about 25–30%; adding this to the pretest probability results in a posttest probability of HPS of about 55–60%. One can also combine findings, if they have different patho genesis (i.e., are independent). If the same patient with cirrhosis and clubbing also has cyanosis, which has an LR of 4.4 (increasing prob ability another 25–30%), the posttest probability of HPS (combining the two findings and their probabilities with the pretest probability) is now about 80–90%. LRs allow the clinician to compare all traditional physical find ings for a given diagnosis and quickly identify those few findings that accurately increase or decrease probability, a practice that improves the clinician's accuracy, efficiency, and confidence. Table 8-3 provides selected findings for four different conditions. If contemplating the diagnosis of ascites, for example, the clinician consults the table and focuses only on those findings with large LR values (3.0 or more, which increase probability) and those findings with LRs close to zero (0.3 or less, which decrease probability), disregarding those findings with values close to 1 (i.e., 0.3–3.0) because these latter values change probability minimally or not at all. In the example of abdominal disten sion, only the presence of the fluid wave (LR = 5) and edema (LR = 3.8) increase probability sufficiently, and only the absence of edema (LR = 0.2) and absence of flank dullness (which is the same as presence of flank tympany, LR = 0.3) decrease probability. These are the only findings the clinician applies at the bedside. LRs for a variety of conditions can be easily looked up in the two sources mentioned above. In EvidenceBased Physical Diagnosis, McGee has created an original and easily remembered graphic representation of physical signs related to a host of conditions (Fig. 8-1). TABLE 8-4 Bedside Rules That Decrease Probability of Serious Conditions ("Stop Rules") CONDITION DIAGNOSIS BEDSIDE RULEa LIKELIHOOD RATIO IF BEDSIDE RULE SATISFIED Ankle injury Ankle fracture Negative Ottawa ankle rule 0.1 Acute calf pain and swelling Deep venous thrombosis Original Wells score 0 or lessb 0.2 Acute sustained vertigo, nausea, and vomiting Posterior circulation stroke HINTS peripheral 0.02 Acute abdominal pain Acute appendicitis Alvarado score 4 or less 0.1 Acute cough and fever Pneumonia Heckerling score 0 or 1 0.3 Diabetic foot ulcer Osteomyelitis Negative probe-to-bone test 0.2 aDefinition of rules: for "Ottawa ankle rule," "Original Wells rule," and "Alvarado score," see reference (McGee); for "HINTS peripheral" see text;

for “Heckerling score,” the clinician scores 1 point for each of the following findings if present: temperature >37.8°C, heart rate >100 beats/min, crackles, diminished breath sounds, and absence of asthma; for “probe-to-bone” test, the clinician gently probes the foot ulcer with a blunt metal probe and identifies a rock-hard, gritty base without intervening soft tissue (positive test) or fails to observe this (negative test). bClinicians combine a Wells score ≤0 with negative quantitative D-dimer before stopping workup. Source: Adapted from SR McGee: Evidence-Based Physical Diagnosis, 5th ed. Philadelphia, Elsevier, 2022.

PHYSICAL SIGNS AS DECISION POINTS IN PATIENT MANAGEMENT The clinician should also master some common physical diagnosis maneu vers and “rules” that are helpful in distinguishing serious conditions from more benign ones (Table 8-4). These are sometimes called “stop rules” because the workup can safely end if all the conditions of the rule are met. One example is the HINTS battery (Head Impulse, Nys tagmus, Skew Deviation Test) in evaluating the patient with dizziness: in emergency room patients with acute sustained vertigo, nausea, and vomiting, the combination of positive head impulse test, absence of direction-changing nystagmus, and absence of skew deviation mark edly decreases the probability of posterior circulation stroke (LR = 0.02). This and a few other useful maneuvers and clinical rules are shown in Table 8-4.

CHAPTER 8 The Value of the Physical Examination in Modern Medicine Finding Clues to Unsuspected and Asymptomatic

Disorders The attentive physician often picks up clues to diseases that the patient may be unaware of but that could be consequential. Noting diffuse enlargement of the thyroid (in goiter or in Grave’s dis ease), or xanthelasma (hypercholesterolemia), or acanthosis nigricans (in insulin resistance) presents the opportunity to intervene. Such clues abound, as an observant physician in busy public places such as airports cannot help but notice. A common observation is the coxalgic gait: the patient’s trunk leans dramatically to the side (the “lateral lurch”) when bearing weight on a painful hip. On the other hand, if the patient’s lat eral lean over the hip is less dramatic and accompanied by a drop in the contralateral pelvis, the opposing sways of the shoulder and pelvis give the impression of a hinge between sacrum and lumbar spine. This is the Trendelenburg gait, a sign of weakness of the hip abductor, the gluteus medius. At one time, the Trendelenburg gait was commonly seen after polio or other neuromuscular diseases, or with congenital hip disloca tion; more recently, it can be seen after damage to the gluteus medius or the superior gluteal nerve after hip arthroplasty by the lateral approach. Another commonly observed gait abnormality is “circumduction” of the foot (which swings in a small semicircle with each step instead of moving forward directly), along with a reduced arm swing on the same side, suggesting past hemiplegia. Table 8-5 lists some other such obser vations that are meaningful to the clinical eye. Developing this type of clinical gaze requires conscious practice and alertness. Too narrow an examination based on the presenting symptom can miss important clues and be a disservice to the patient. Conversely, detecting such find ings is satisfying because it might present the opportunity to intervene earlier in the course of a disease. Medical Error from Oversights in the Physical Examination

Failure to do the examination, or an incomplete examination, can lead to diagnostic delay, inappropriate or delayed treatment, unneces sary exposure of the patient to radiation, surgical misadventure, or even death. Examples abound: the febrile patient whose petechiae or ecchymosis

is missed because clothing is not completely removed, delaying the consideration of and empiric treatment for suspected Rocky Mountain spotted fever or meningococcemia; the patient with wrist and ankle pain seen by the primary care physician and referred

PART 1 The Profession of Medicine TABLE 8-5 Important Clues to Disorders That May Not Be Related to the Patient's Presenting Symptoms TYPE OF OBSERVATION, WITH SELECTED EXAMPLES NOTES Faces and expression Acromegaly, Parkinson's disease, Cushing's syndrome, myxedema, hyperthyroidism, myasthenia gravis, Hippocratic facies, amiodarone facies, myotonic dystrophy, multiple endocrine neoplasia 2b (MEN2b), Down's syndrome, congenital syphilis, facial lipodystrophy with antiretroviral therapy in HIV, scleroderma • Blue pigmentation around malar region with amiodarone • Myotonic dystrophy: "hatchet face" from temporal and facial muscle wasting, baldness in males, cataracts. • MEN2b: mucosal neuromas on lips, tongue, marfanoid habitus Gait Coxalgic gait, Trendelenburg gait, high-stepping gait, Parkinson's gait, hemiplegic gait, diplegic gait or spastic gait, ataxic gait, sensory ataxic gait • Parkinson's features are short, shuffling steps, forward flexion, appearance of hurrying up ("festination"), hesitancy in turning, absent arm swing, tremor • Peripheral neuropathy or posterior column disease cause sensory ataxia with broad-based "stamping" gait—striking foot down hard; worse at night when visual cues are diminished • Both hemiplegic and diplegic or "spastic" gait have hypertonia in upper limb flexors and lower limb extensors and adductors, with ankles extended and toes pointed in, circumduction with each step, "scissor gait" with diplegia (cerebral palsy) Hands (Selected examples in the right column.) There are many eponymous nail changes (Beau's line, Terry's nails, Mee's line, Muehrcke's lines, halfand-half nails, etc.); they are frequently seen but not diagnostically helpful as they are associated with multiple conditions, including renal failure, liver failure, past or current severe illness, and hypoproteinemia. Koilonychia is associated with iron deficiency anemia but not exclusively. Pitting is seen in psoriasis and many other conditions. • Cardiac conditions: splinter hemorrhages, Osler's nodes, Janeway lesions in endocarditis; "fingerization of the thumb" in Holt-Oram syndrome (with atrial septal defect); Marfan syndrome with arachnodactyly, thumb and wrist sign; Ehlers-Danlos syndrome with joint hypermobility, lax thin skin • Liver dysfunction: palmar erythema, spider angioma, white nails, asterixis • Endocrine: moist, warm, tremulous extremities, onycholysis in hyperthyroidism • Neurologic: myotonic grip with myotonic dystrophy; wrist drop of radial palsy; claw hand of ulnar nerve palsy • Rheumatology: nail fold and capillary changes in vasculitis; Heberden's and Bouchard's nodes in osteoarthritis; swan neck deformity, subluxation and ulnar deviation of fingers in rheumatoid arthritis and other chronic inflammatory arthritis; telescoping hand in destructive psoriatic or rheumatoid arthritis • Pulmonary: nicotine staining; clubbing; cyanosis • Congenital/developmental changes: Single transverse palmar crease in Down's syndrome Odors • Odor of tobacco on clothing • Grapelike odor of Pseudomonas wound infection • Fetid breath of anerobic lung abscess • Uriniferous odor in renal failure • Ammoniacal mousy odor in hepatic failure • Acetone-like fruity odor in diabetic ketoacidosis • Fish odor in trimethylaminuria • Bitter almond scent with cyanide poisoning • Alcohol metabolites with intoxication or alcohol-induced delirium Clothing • Inappropriate clothing for the ambient weather in hypothyroidism and hyperthyroidism • Neglect of clothing or color mismatch in dementia or delirium • Untied shoelaces in edema, toe of shoe cut out in chronic gout Stature • Short stature (growth hormone deficiency, Turner's syndrome) • Tall stature in Marfan syndrome and those with a Marfanoid habitus. In one study, the phenotypic features that favor Marfan syndrome are pectus carinatum, reduced elbow extension, high-arched or "gothic" palate, arm span–to–height ratio (ASHR) >1.05, hindfoot deformity, downslanting

palpebral fissures, the thumb sign, lens subluxation, myopia, dental crowding, joint laxity, and micrognation Source: Adapted from multiple sources including SL Berk, A Verghese: General Appearance, in Clinical Methods: The History, Physical, and Laboratory Examinations, 3rd ed. Walker HK et al (eds). Boston, Butterworths, 1990. to consultants in rheumatology or orthopedics, and serologic tests for lupus, vasculitis, and other conditions ordered, until at some point the presence of clubbing (and even Horner's syndrome) is noted, suggest ing pulmonary hypertrophic osteoarthropathy caused by a malignancy in the lung; or the patient with chest pain taken to the cardiac catheter ization lab where contrast is injected before a rash looking like "dew drops on rose petals" involving a dermatome on the left chest is noted (herpes zoster). Studies show that when patients with "cellulitis" are first routed through a dermatology clinic, about a third will have an alternative diagnosis such as eczema or lymphedema, avoiding hospi talization and antibiotics. RADIOLOGISTS REPORTING WHAT SHOULD HAVE BEEN OBVIOUS ON THE EXAMINATION It is unfortunately commonplace in hospital practice for the physician to be notified by the radiologist on the day after admission that the admission plain films of the abdomen show the patient labeled "gastroenteritis" has strangulated bowel in a hernial orifice or has gas in the scrotal tissue (Fournier's gangrene). These represent surgical emergencies that should be diagnosed by physical examination. Radiologists often report breast masses on CT scan of the chest, gynecomastia in a male, or thyroid masses, all of which should have been palpable. Such errors are consequential to the patient and an embarrassment to the clinician. Conversely (and less frequently), a careful physical examination might raise doubt on a radiologic inter pretation. For example, even though all patients with acute atraumatic third cranial nerve palsy should undergo urgent neuroimaging, the "rule of the pupil" still applies: a dilated pupil suggests a compressive etiology such as an aneurysm, whereas a normal pupil suggests an ischemic cause. One particular study described two patients whose pupillary findings challenged the radiologic report. One patient's image showed a cavernous meningioma, which was suggested as causal, yet the pupil was spared; the clinicians elected to follow the patient, who made a full recovery, suggesting ischemia was the cause. A second patient had an abnormal pupil but a normal CT angiogram; noting

this discrepancy, the clinicians discussed the dilated pupil with the radiologist, and on restudying the image, a posterior communicating aneurysm was noted. THE CAUSE OF OVERSIGHTS IN THE PHYSICAL EXAMINATION This variety of medical error usually goes unnoted and is difficult to study. In one paper based on physician-reported anecdotes of such over sights (either their own or those of others), it was because the physical examination was cursory or had not been done, although the patient's chart suggested a complete exam. The electronic medical record with its templates, dropdown boxes, and cut-and-paste functions makes it easy to suggest (and bill for) a complete examination. These errors of omission and commission are magnified by rapid patient turnover; frequent "handoffs" from the emergency room to the night team and then to the morning admitting team, with overreliance placed on the initial diagnosis; and insufficient continuity of care for any particular physician to be fully invested in the patient. Pride in their profession and a desire to avoid egregious mistakes that harm the patient should give clinicians a healthy skepticism for diagnostic labels given to new patients handed over for continuing care. The Physical Examination as a Ritual Meaningful to Patient and Physician Busy physicians may not appreciate that what may be routine for them—seeing a patient in the clinic or the hospital—is far from routine for the patient. An ethnographer observing a new patient–physician encounter sees one stranger presenting themselves to another stranger and revealing personal and sensitive information that they may not admit to their spouse or their spiritual advisor; the setting is a room that has unique

furnishings not to be found in either individual’s home. One of the two participants might be wearing a white shamanistic garment with specialized tools in the pockets, while the other is asked to don a cloth or paper gown for the occasion. Then, at some point, one participant disrobes and allows the other to touch and manipulate their limbs and body; peer into their eyes, ears, and throat; probe their hernial orifices; and at times, examine the genitalia and rectum. These actions are far from the norm in society and could even be construed as assault. The great privilege of being a physician is that the physical examination is part of the contractual agreement to provide care for the patient, and it therefore comes with great fiduciary responsibility. To the ethnographer, the patient–physician encounter has all the trappings of a ritual. CHARACTERISTICS OF RITUALS All rituals (such as weddings, baptisms, funerals, inaugurations, or graduations) are characterized by the cross ing of a threshold, by a commitment, and by some type of transforma tion. The physical examination ritual can signal the patient’s transition from self-sufficiency to seeking help, or from illness to wellness; it also signals the placement of trust in the physician. The willingness to dis robe and allow touch—markers of vulnerability—indicates the patient’s acceptance that this ritual is important for the transfer of knowledge. PATIENTS ARE EXPERT JUDGES OF RITUAL Patients of different eth nicities and cultural backgrounds, and with differing beliefs about illness, nevertheless recognize and appreciate ritual, even when the physician fails to see it. Patients are also good judges of the skills of other professionals such as automobile mechanics, hairdressers, or cooks, and they can tell if the work is being done well and with pride. In studies where lay subjects assess videos of surgeons operating (crowdsourced assessment), the subjects’ assessments when compared to that of experienced surgeons rating the same videos showed moder ate to strong correlation. Patients can feel let down when a physical examination feels perfunctory, such as when it consists only of a prod ding of the belly and the placing of the stethoscope on the clothing instead of on the skin. To quote William Osler, “Remember, however, that every patient upon whom you wait will examine you critically and form an estimate of you by the way in which you conduct yourself at the bedside. Skill and nicety in manipulation, whether in the simple act of feeling the pulse or in the performance of any minor operation, will do more towards establishing confidence in you than a string of

Diplomas, or the reputation of extensive hospital experience.” When well executed, the physical examination preserves the patient’s sense of identity and affirms their humanity and personhood. It validates the presenting symptoms by localizing them on their soma, on and in their body, rather than on a distant radiologic report or a lab test. Imaging and laboratory tests strip away the markers of individuality and personhood. Patients who chance to see their own imaging studies see little that is recognizable to them as self.

CHAPTER 8 PASSING ON THE SKILLS Skilled rituals are typically learned by a lengthy apprenticeship. The gradual erosion of bedside rounds in teaching hospitals, replaced by rounds in a conference room where the patient’s data on the computer are discussed, is detrimental to trainees. Bedside skills can only be passed on by role models who, by repeated demonstration, by observing the trainees’ technique, and by giving appropriate feedback, keep this useful and essential skill alive. The Value of the Physical Examination in Modern Medicine PLACEBO, NOCEBO, AND THE PHYSICAL EXAMINATION The physi cal examination can be dehumanizing when done poorly, but when done well, it can have a salutary effect. Research on the placebo effect shows that a placebo can be something other than an inert tablet. One can have a “placebo without a placebo,” meaning that the context, the ritual and its manner of execution, the setting, and the

tone of voice of the examiner induce measurable change in levels of neurotransmitters and can produce a psychobiological effect. Trainees must appreciate their role in bringing about this effect. When patient expectations of the physical examination rituals are fulfilled, there is a positive effect; conversely, a clumsy and indifferent examination could have a nocebo (unpleasant or harmful) effect that impairs subsequent interactions. ■ ■CONCLUSION The physical examination of the patient remains a critical element in diagnosis as well as in the ongoing assessment of the patient. The his tory generates hypotheses that are subsequently confirmed by useful evidence-based physical examination maneuvers, which then allow judicious ordering of further diagnostic tests. The ritual epitomizes the art and science of medicine and is itself an important means of satisfying the patient's need to feel cared for in a uniquely human and personal way. Physicians who over a lifetime cultivate skill in "reading the body" will find their practice more rewarding, will excite those apprenticing with them, and will pass on this important aspect of medicine to another generation. Acknowledgment The authors thank George Verghese, PhD, for his close reading and invalu able input. ■ ■FURTHER READING Elder A et al: How valuable is physical examination of the cardiovas cular system? BMJ 354:i3309, 2016. Elder A et al: The road back to the bedside. JAMA 323:1672, 2020. Maitra A, Verghese A: Diagnosis and the illness experience: Ways of knowing. JAMA 326:1907, 2021. McGee S: Evidence-Based Physical Diagnosis, 5th ed. Philadelphia, Elsevier, 2022. Osler W: Valedictory address to the graduates in Medicine and Surgery, McGill University. Can Med Sur J 3:433-42, 1874-75. https://www

.canadiana.ca/view/oocihm.8_05177_34/4 Simel DL, Rennie D (eds): The Rational Clinical Examination: Evidence-Based Clinical Diagnosis. New York, McGraw-Hill Education, 2009. Ongoing updates at https://jamaevidence.mhmedical.com/content. aspx?bookid=845&sectionid=61356244. Verghese A et al: The bedside evaluation: Ritual and reason. Ann Intern Med 155:550, 2011. Verghese A et al: Inadequacies of physical examination as a cause of medical errors and adverse events: A collection of vignettes. Am J Med 128:1322, 2015. Zaman J et al: The value of physical examination: A new conceptual framework. South Med J 109:754, 2016.

09 - 9 Physician Well-Being

9 Physician Well-Being

Lisa M. Bellini, Vivek H. Murthy

Physician Well-Being PART 1 The Profession of Medicine PHYSICIAN WELL-BEING: AN HISTORICAL PERSPECTIVE The practice of medicine is often viewed as a calling and as a way of life. The term resident originated from Dr. William Osler in 1890, when he established the first full-time, live-in medical residency training program at Johns Hopkins Hospital in Baltimore, Maryland. There, residents lived in the administration building. With the duration of their training undefined, many stayed for years. Personal sacrifices came at the cost of professional expectations and norms of the time. The twentieth century ushered an era of standards and policies for medical education, and for the profession more broadly. In 1904, the American Medical Association (AMA) formed the Council for Medical Education (CME) to strengthen medical education training programs and policies. In 1910, the AMA supported an evaluation of the quality of these programs in the United States and Canada, which resulted in the Flexner Report, which called for the creation of a new model for medical education by recommending that medical schools enact higher admission and graduation standards and adhere strictly to the proto cols of mainstream science in their teach ing and research. There was no reference to physician well-being. The AMA's CME supported the report, leading to the birth of the Federation of State Medical Boards in 1912, the American Board of Medical Specialties in 1933, the Licensing Com mission of Medical Education (LCME) in 1972, and the Accreditation Council of Graduate Medical Education (ACGME) in 1981. Again, physician well-being was not prioritized in causes for reform. Through this time, residents worked long hours, with little sleep or days off for ill ness and time with their families. Most were expected to work 36 hours every other night, often exceeding 100 hours per week. Factors associated with burnout among health workers Societal and Cultural Concerns mounted about the potential impact of fatigue on resident well-being and patient care; both were inevitably and inextricably linked. Yet, changes in policy were slow to follow. In 1975, New York City medical residents went on strike calling for fewer hours on duty. The tragic death of Libby Zion in 1984, following a misdiagnosis, was linked to medical resi dent fatigue and inadequate supervision. By 1989, New York became the first state to regulate resident duty hours. These regulations limited duty hours to an aver age of no more than 80 hours per week, with no more than 24 hours of continuous duty, and at least 24 hours free from clini cal duties weekly. Subsequently, medical residents across the country petitioned the Occupational Safety and Health Administration in 2001 to nationally limit duty hours. The ACGME responded to concerns by 2003 with national standards limiting resident duty hours for all of its programs. Organizational Workplace and Learning Environment FIGURE 9-1 Factors associated with burnout among health workers. (Adapted from Addressing Health Worker Burnout: The U.S. Surgeon General's Advisory on Building a Thriving Health Workforce, p. 12. Available at https://www.hhs.gov/sites/default/files/health-worker-wellbeing-advisory.pdf.) In 2000, the Institute of

Medicine (IOM) landmark report “To Err Is

Human: Building a Safer Health System” shifted the discourse away from individual-level factors toward system-level changes needed to address alarming patient safety concerns. Efforts soon after acceler ated to ensure patient safety and quality of care alongside physician well-being. Over the past 20 years, there has been an increasing focus on physi cian well-being with the introduction of wellness programs to promote self-care. Such programs have diffused into undergraduate medical education and biomedical training, but there are fewer standards governing physicians in independent practice. While individual-level stressors are important determinants of physician well-being, the most important drivers are the workplace systems in which students and residents learn and where physicians work. CHALLENGES IN THE CURRENT HEALTH CARE LANDSCAPE As health care systems have grown more complex and the demand for care has outpaced resources, chronic workplace stress and burnout have defined the contemporary experience of many physicians. Burn out is an occupational syndrome resulting from chronic workplace stress due to an imbalance between job demands and resources and other organizational, societal, and cultural factors in health care. The concept and contributing factors are included in the 11th Revision of the International Classification of Diseases (ICD-11) and the Surgeon General’s Advisory on Addressing Health Worker Well-Being (Fig. 9-1). • Politicization of science and public health • Structural racism and health inequities • Health misinformation • Mental health stigma • Unrealistic expectations of health workers • Limitations from national and state regulation • Misaligned reimbursement policies • Burdensome administrative paperwork • Poor care coordination • Lack of human-centered technology Health Care System • Lack of leadership support • Disconnect between values and key decisions • Excessive workload and work hours • Biased and discriminatory structures and practices • Barriers to mental health and substance use care • Limited flexibility, autonomy, and voice • Lack of culture of collaboration and vulnerability • Limited time with patients and colleagues • Absence of focus on health worker well-being • Harassment, violence, and discrimination “This is beyond my control...” Office of the U.S. Surgeon General

It is characterized by a high degree of emotional exhaustion, deperson alization (e.g., job cynicism), and a low sense of personal achievement at work. In 2014, the Institute for Healthcare Improvement advanced the Quadruple Aim, adding a fourth goal to improve health workforce well-being, directly acknowledging that the existing goals in health care—to enhance the patience experience, improve population health, and reduce costs—cannot be met without the health and well-being of our nation’s healers. Subsequently, in 2017, the National Academy of Medicine (NAM) formed a Clinician Well-Being Action Collaborative, gathering leaders to highlight and act on the alarming burnout crisis across all health care specialties and settings. NAM declared “crisis levels” of burnout in 2019, even before the pandemic, with 35–54% of nurses and physicians and 45–60% of medical students and residents experiencing varying degrees of burnout. The COVID-19 pandemic acutely brought the nation’s attention to the unprecedented demands placed on physicians and other health workers. It also highlighted the moral distress, moral injury, and com passion fatigue experienced by many physicians and other health care providers who were forced to choose between caring for patients and keeping their families safe; who witnessed countless patients suffer and die, without family or friends at their bedside; and who had to help lessly ration inadequate supplies, beds, or treatment to their patients. One survey published in Mayo Clinic Proceedings found that an alarm ing 63% of physicians reported burnout during the pandemic in 2021, compared with 38% in 2020 and 44% in 2017. Decades of research and evidence have

found, as referenced by the Surgeon General's Advisory on Addressing Health Worker Burnout in 2022, that chronic work stress and burnout have harmful effects on physician health and well-being. Chronic work stress is associated with poor health outcomes such as impaired cognitive function, increased risk of cardiovascular disease, type 2 diabetes, fertility issues, sleep disruptions, isolation, relationship conflict, and risk for substance use and misuse. Burnout is also associated with mental health challenges including anxiety, depression, and suicidal ideation. Surveys by health care professional associations have also found widening gender and racial gaps, especially among female physicians and groups underrep resented in medicine. Physicians and other health workers who report burnout are more likely to reduce working hours, report intent to leave jobs or medical school, or leave medicine altogether. One in every five physicians has reported intent to leave medical practice due to burnout, contributing to a projected shortfall of up to 86,000 physicians in the United States by 2036. These shortages will only compound the vicious cycle of increasing physician work demands that often lead to burnout. CORE ELEMENTS FOR BUILDING A THRIVING PHYSICIAN WORKFORCE A thriving physician workforce requires a dynamic, multipronged, and collective approach to solve the complex array of institutional, structural, cultural, and societal factors that impact physician health and well-being (Figs. 9-1 and 9-2). Fundamental change in the orga nizational environment, including the systems and cultures where all physicians learn, train, and work, is the necessary first step. ■ ■PROTECTION FROM HARM Strengthen physician protections from physical and psychological harms in the clinical learning and work environment. This includes ensuring adequate personal protective equipment during and outside of public health emergencies, sufficient staffing, shift coverage and rest, and clearly communicated policies that protect physicians from all threats and acts of harassment, intimidation, and violence at work and in their communities. The Joint Commission released workplace violence prevention standards in 2021 to guide leaders with implemen tation. Health care organizations must also explicitly support inclusion and equitable access to policies and programs (e.g., paid leave, career advancement) that can comprehensively address diversity and acces sibility. Doing so can address the microaggressions, implicit bias, dis crimination, and racism that many physicians face.

Increase access to quality mental health care for all physicians, including residents and students. These services can be offered on-site or via telehealth options including peer support groups, confidential physician health programs, or employee assistance program (EAP) ser vices (e.g., counseling, referrals, caregiver support). It is most impor tant to ensure that access to any service is convenient, meeting unique needs and work schedules.

CHAPTER 9 In the 2023 Physicians Foundation Survey of America's Current and Future Physicians, more than half of physicians (up since 2021) reported knowing of a physician who has ever considered, attempted, or died by suicide. A proactive, evidence-based approach to suicide prevention must be incorporated to embed voluntary, anonymous screening and tailored referrals and follow-up care. Physician Well-Being Furthermore, we must end barriers to mental health care, specifi cally stigma and policies that deter physicians and other health workers from mental health support services. Many physicians may be reluctant to seek formal short-term and recovery care for mental health chal lenges and conditions, given concerns regarding potential repercus sions on their license, hospital credentials, careers, and credibility. Health care organizations, academic institutions, and policymakers at all levels can review and remove intrusive, stigmatizing questions on all applications and forms, ensuring alignment with national recom mendations set by The Joint

Commission in 2020. ■ ■REDUCE ADMINISTRATIVE BURDENS Administrative burdens must be reduced to give physicians more time for what matters—their patients. A rapidly changing health care eco system, with new payment options, market consolidation, insurance and regulatory requirements, and advances in health information tech nology, has contributed to the loss of physician autonomy and a signifi cant reduction in time for patient care. For example, with the growing consolidation of the health care market and the corporate privatization of practices, many physicians feel their voices, decision-making, and sense of value have diminished over time. Systems-level changes are needed to ensure that the physician–patient relationship is at the very center of the health care system. Further, there are additional organiza tion-level practice changes that can also address inefficiencies and give physicians time back. Improve and streamline workflow processes (e.g., documentation requirements, inbox notifications, prior authorizations). As an exam ple, changes to documentation guidelines for outpatient evaluation and management (E/M) visit codes were updated in 2021 to better align with current medical practice and patient care. Health professional associations offer practical tools, including the AMA Saving Time Playbook and Electronic Health Records (EHR) Playbook. Researchers have found notable progress across health systems when leaders visibly apply the “Getting Rid of Stupid Stuff,” or GROSS, model, seeing mea surable reductions in the volume of unnecessary daily documentation tasks for physicians and the care team. Eliminate unnecessary and inefficient prior authorizations. In 2022, a majority of physicians surveyed (94%) reported that prior authoriza tions from insurers delayed access to necessary care. Many physicians also reported treatment abandonment by their patients because of prior authorization delays. Many policymakers and health profes sional association programs exempt clinicians from prior authorization requirements if they meet specific performance measures. Although evidence is mixed on the benefits of these efforts, it seems likely that any measurable reduction in administrative burden will improve costs and, if thoughtfully implemented, improve quality of care. With workforce shortages, organizations can harness, adopt, and implement technology in a physician- and patient-centered way. While the role of the physician will always be indispensable, particularly for direct patient interactions and complex clinical decision-making, there are growing opportunities to leverage trustworthy artificial intelligence (AI), machine learning, and other digital automation tools to support various stages of patient care, such as previsit planning, encounter documentation, prior authorizations, and follow-up communication. Importantly, AI companies have the responsibility to also ensure that such platforms safeguard patient safety and privacy, mitigate risk of

Thriving together: Solutions to health worker burnout We must shift burnout from a “me” problem to a “we” problem. PART 1 The Profession of Medicine Leadership commitment and organizational values Diverse and empowered health workforce Accessible mental health and substance use care Culture of healing, community and connection Human-centered technology Health Insurers and Payers Health Care Organizations Federal, State, Local, Tribal Governments Researchers Family Members, Friends, and Communities FIGURE 9-2 Thriving together: solutions to health worker burnout. (Adapted from Addressing Health Worker Burnout: The U.S. Surgeon General’s Advisory on Building a Thriving Health Workforce, p. 20. Available at https://www.hhs.gov/sites/default/files/health-worker-wellbeing-advisory.pdf.) clinical harm, and measurably improve the quality of care. Further, EHR companies must strengthen platforms to focus on key features needed for patient care and design the systems to meet the needs of clinicians in ways that optimize usability as a clinical decision support tool. Finally, health care technology companies must work with physi cians and other health workers to ensure accessible,

meaningful, and unbiased processes and data. This includes assurance that interven tions do not add more burden onto the health care team. ■ ■BUILD CONNECTION AND COMMUNITY Opportunities for strengthening social connection and community in medical education, clinical training programs, and all health care work environments should be integrated into our systems. Physicians, including students and residents, should be included in these social networks, as appropriate. They may have fewer routine opportunities to connect meaningfully with colleagues and identify new colleagues

Reduced administrative burdens Safe and inclusive environments Community partnership Trust Academic Institutions Licensing and Accreditation Bodies Office of the U.S. Surgeon General and mentors, particularly when new to the community. The value of workplace connection and social support for physicians cannot be overstated, especially in an era of widespread societal loneliness and social isolation. Acknowledging that the common experience of loneli ness and isolation can be felt at all stages of medical education and throughout a career in medicine is a necessary and important first step. Peers, faculty, and health care organization and academic institution leaders are each well-positioned to model and foster opportunities for social connection and community. This can be through applying team work and team-based care models, establishing peer support groups and informal learning networks, reviving the modern-day doctors' lounge, and investing in mentoring and coaching programs. These efforts to cultivate social connection must be operationalized with protected time and infrastructure built into core working hours and the physical environment. This can help all physicians feel seen and heard, with time to pause and reflect on challenging circumstances

and morally distressing dilemmas together with peers and mentors. These efforts also help physicians build trusting relationships with one another and promote a culture that values connection within the workplace. Finally, such efforts also offer necessary time and space to reinforce connection through shared purpose, professional fulfilment, and a celebration of collective achievements in health care, research, and medicine. ■ ■BOLSTER THE HEALTH WORKFORCE Investments that bolster the health workforce need to be expanded. Health workforce shortages across all specialties and settings can negatively impact timely access, quality, and patient safety. As noted earlier, the American Academy of Medical Colleges has estimated a major shortage of physicians in the United States, and the challenge is much greater in most parts of the world. Health care needs will only increase as we address the ongoing mental health crises and a growing and aging population and strengthen our responses to climate change and its impact on health. Despite these gaps, there are hopeful signs and solutions. According to data compiled by the Federation for State Medical Boards, the U.S. physician workforce is 20% larger than it was over a decade ago. New medical schools and postgraduate training programs are being devel oped at an unprecedented rate in most industrialized countries and in many less developed parts of the world. There are renewed efforts to increase and diversify the workforce, especially to ensure more cul turally appropriate care. Many of these efforts encourage practice in specialties with shortages and in rural and underserved communities. We can also ensure support for equitable pathways via scholarships and tuition support. Additional career advancement, faculty salary support, and apprenticeship training programs can further retain and sustain instructors, preceptors, and mentors in the nursing, direct patient care, and behavioral health workforce. We must also sustain and increase investments for addressing unmet underlying social needs, such as housing, food, and transportation. Doing so can not only reduce demands upstream for health care but can also

address the moral distress physicians may experience when they encounter root causes of their patients' suffering and the obstacles to quality care that they cannot address. An annual survey by the Phy sicians Foundation in 2022 found that many (61%) felt they had little to no time to effectively address their patients' social determinants of health. Social determinants of health are estimated to account for upward of 80–90% of modifiable factors to health outcomes (Chap. 11). Health systems, together with community leaders in public health, are well-poised to focus on prevention and whole-person care, investing in evidence-informed models that keep individuals and communities healthy for the long term. ■ ■FOSTER A CULTURE OF PHYSICIAN WELL-BEING The culture of medicine must be transformed to center on physician health and well-being. For medical education and training programs, institutions can begin by addressing the hidden curriculum—the unwritten and unofficial values, and unintended lessons, that students learn by observing a teacher's actions, which may be at odds with the formalized curriculum. The American College of Physicians (ACP) reported that more than half of medical students experienced discon nect between what they were explicitly taught and what they perceived from faculty behaviors in practice. The ACP 2018 position paper is a helpful resource for physician leaders and faculty with recommenda tions and strategies for fostering values of respect, honesty, empathy, inquiry, and ethics, while promoting clinician wellness. Across any organization, leadership is critical in fostering a culture that values physician health and well-being. Concrete steps include operationalizing well-being as an organizational value; integrating it into strategic plans, performance indicators, and training; and establishing a chief well-being officer role. This position must have dedicated resources and decision-making authority. The role should collaborate with leadership in health care administration, human resources and talent management, finances, health information technology (IT), and equity, while proactively engaging physician

and other health worker representatives. They must regularly assess the work environment for factors contributing to chronic work stress and burnout while also evaluating changes in policies and programs that impact the role, function, and well-being of physicians. NAM's Action Collaborative offers a compendium of resources, with vali dated tools for engaging staff, measuring physician well-being, and benchmarking success.

CHAPTER 9 All health care leaders must model and create environments where conversations about physical and mental health are normalized. Phy sicians should be able to talk openly about work stressors and their mental health without stigma or fear of repercussions on their licens ing, credentialing, or careers. This includes encouraging open and honest conversations about the mental health challenges they face in their day-to-day work and offering support and validation along their journey. This must begin early in medical training. Periodic physician well-being support and awareness campaigns can help physicians feel heard, supported, and valued and serve as useful tools for communicat ing information and updates about well-being services. The National Institute for Occupational Safety and Health, the NAM Action Collab orative, and numerous professional associations offer practical tools to support leaders with this type of communication and programming to support physician well-being. Physician Well-Being THE FUTURE OF PHYSICIAN WELL-BEING Medicine remains a calling, yet one that should be built on, not at the expense of, the well-being of our nation's healers. Failing to value and center their health and well-being at the core of our health care system puts us all at risk. When physicians look ahead, they should see a future where their dedication is not taken for granted, but one where their health, safety, and well-being are as much a priority as the well-being of the people and communities in their care. ■

■FURTHER READING The Complexities of Physician Supply and Demand: Projections From 2021 to 2036. https://www.aamc.org/media/75236/download?attachment. Accessed April 29, 2024. Kohn L et al (eds): To Err Is Human: Building a Safer Health System. Institute of Medicine (U.S.) Committee on Quality of Health Care in America, Washington, DC, National Academies Press, 2000. https:// pubmed.ncbi.nlm.nih.gov/25077248/. Lehmann LS et al: Hidden curricula, ethics, and professionalism: Optimizing clinical learning environments in becoming and being a physician. A position paper of the American College of Physicians, 2018. Ann Intern Med 168:506, 2018. Linzer M et al: Trends in clinician burnout with associated mitigat ing and aggravating factors during the COVID-19 pandemic. JAMA Health Forum 3:11, 2022. Lyubarova R et al: Gender differences in physician burnout: Driving factors and potential solutions. Perm J 27:2, 2023. National Academy of Medicine: National Plan for Health Workforce Well-Being. Washington, DC: The National Academies Press. https:// doi.org/10.17226/26744. Accessed July 28, 2023. Philibert I, Taradejna C: Duty hour standards. Chapter 2: A brief history of duty hours and resident education, in Enhancing Quality of Care, Supervision, and Resident Professional Development. ACGME, 2011. https://www.acgme.org/globalassets/pdfs/jgme-11-00-5-111.pdf. Shanafelt T et al: Physician well-being 2.0: Where are we and where are we going? Mayo Clin Proc 96:10, 2021. US Department of Health and Human Services: Addressing Health Worker Burnout: The U.S. Surgeon General's Advisory on Building a Thriving Health Workforce. https://www.hhs.gov/sites/ default/files/health-worker-wellbeing-advisory.pdf. Accessed July 28, 2023. ■ ■WEBSITES American Medical Association: www.ama-assn.org/ Physicians Foundation: www.physiciansfoundation.org/

10 - 10 Diagnosis- Reducing Errors and Improving Quality

10 Diagnosis: Reducing Errors and Improving Quality

Gordon Schiff

Diagnosis: Reducing

Errors and Improving

Quality PART 1 The Profession of Medicine Diagnosing patients’ illnesses is the essence of medicine. Patients pres ent to doctors seeking an answer to the question, “What is wrong with me?” Ideally, no clinician would want to treat a patient without knowing the diagnosis or, worse yet, erroneously treat a misdiagnosed illness. From the earliest moments of medical school, the defining quest toward becoming a knowledgeable and proficient physician is learning how to put a diagnostic label on patients’ symptoms and physical findings, and clinicians pride themselves on being “good diagnosticians.” Yet the centuries-old paradigm of mastering a long list of diseases, understand ing their pathophysiology, and knowing the cardinal ways they manifest themselves in signs and symptoms, while still of fundamental impor tance, is being challenged by new insights illuminated by the glaring spotlight of diagnostic errors. Basic internal medicine diseases, such as asthma, pulmonary embolism, congestive heart failure, seizures, strokes, ruptured aneurysms, depression, and cancer, are misdiagnosed at shock ingly high rates, often with 20–50% of patients either being mislabeled as having these conditions (false-positive diagnoses) or having their diag nosis missed or delayed (false negatives). How and why do physicians so often get it wrong, and what can we do to both diagnose and treat the problem of delayed diagnosis or misdiagnosis? Diagnosis is both an ancient art and a modern science. The current sci ence of diagnosis, however, goes far beyond what typically comes to clini cians’ and patients’ minds when they conjure up images of state-of-the-art molecular, genetic, or imaging technologies. Improvements in diagnosis are just as likely to come from other areas, many with origins outside of medicine, as they are from advanced diagnostic testing modalities. These diverse sciences that the field of diagnostic safety has, and must, draw from include systems and human factors engineering, reliability science, cognitive psychology, decision sciences, forensic science, clinical epide miology, health services research, decision analysis, network medicine, learning health systems theory, medical sociology, team dynamics and communication, risk assessment and communication, information and

knowledge management, and health information technology, especially artificial intelligence and clinical decision support. A clinician read ing this chapter is likely to find this list of overlapping and intersecting domains quite daunting. However, rather than feeling overwhelmed, we urge readers to view them as the basic science supports that will ultimately make their lives easier and diagnosis more accurate and timely. Rather than feeling intimidated, clinicians should feel a sense of relief and assur ance in understanding that good diagnosis does not rest entirely on their shoulders. Instead, it is a systems property, where an infrastructure and a team, one that especially includes the patient, can in a coordinated way work together to achieve more reliable and optimal diagnosis. ■ ■EMERGENCE OF DIAGNOSIS ERROR AS AN IMPORTANT PATIENT SAFETY ISSUE Over the past two decades, a series of studies culminating in a land mark report from the U.S. National Academy of Medicine (NAM), Improving Diagnosis in Health Care, have shone a spotlight on diagnos tic errors. Reports from patient surveys, malpractice claims, and safety organizations have found that diagnostic errors are the leading type of medical error. Although errors in diagnosis can be defined in various ways, the NAM Committee defined diagnostic error as "the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient."* *Source: National Academies of Sciences, Engineering, and Medicine. 2015. Improving Diagnosis in Health Care. https://doi.org/10.17226/21794. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

Adverse Outcomes Diagnostic Process Failures Delayed, Missed, or Wrong Diagnosis FIGURE 10-1 What is a diagnosis error? (Adapted from GD Schiff et al: Diagnosing diagnosis errors: Lessons from a multi-institutional collaborative project, in Advances in Patient Safety: from Research to Implementation. Vol. 2 Concepts and Methodology, Rockville, MD, 2005, pp. 255-278, and GD Schiff, L Leape: Acad Med 87:135, 2012.) One way to visualize diagnostic errors is through a Venn diagram

(Fig. 10-1), which illustrates the fact that many things can go wrong in the diagnostic process (e.g., failure to ask an important history question, physical examination sign overlooked, laboratory specimen erroneously switched between two patients, x-ray not followed up), but this usually does not result in a wrong diagnosis or patient harm. Similarly, a patient can be misdiagnosed but unharmed, without any identifiable error in the care received. Our greatest concern is where these three circles intersect, with conservative estimates suggesting that 40,000–80,000 patients die each year in U.S. hospitals alone from diagnostic errors. The NAM report outlined eight recommendations that are the foundation for this chapter (Table 10-1). ■ ■NEW WAYS TO THINK ABOUT DIAGNOSIS AND DIAGNOSTIC ERRORS Medical textbooks have historically given attention to "clinician reasoning" and associated cognitive heuristics and biases. Errors in clinical reasoning can be summarized in three broad groups: (1) hasty judgments, (2) biased judgments, and (3) inaccurate probability esti mates. Research from cognitive psychology has identified scores of common mental shortcuts or "heuristics" humans are prone to use in everyday life, many of which are useful for efficient diagnosis but can also lead to biases and errors. Table 10-2 lists some of the common cognitive biases that can lead diagnosis astray (this topic is discussed further in Chap. 4). TABLE 10-1 National Academy of Medicine Recommendations for Improving Diagnosis in Health Care

1. Facilitate more effective teamwork in the diagnostic process among health care professionals, patients, and their families.
2. Enhance professional education and training in the diagnostic process in areas such as clinical reasoning; teamwork; communication with patients, families, and other health care professionals; and appropriate use of diagnostic tests.
3. Ensure that health information technologies support patients and health care professionals in the diagnostic process.
4. Develop and deploy approaches to identify, learn from, and reduce diagnostic errors and near misses in clinical practice including providing systematic feedback on diagnostic performance.
5. Establish a work system and culture that supports the diagnostic process and improvements in diagnostic performance.
6. Develop a reporting environment and medical liability system that facilitates improved diagnosis by learning from diagnostic errors and near misses.
7. Design a payment and care delivery environment that supports the diagnostic process.
8. Provide dedicated funding for research on the diagnostic process and diagnostic errors. Source: National Academies of Sciences, Engineering, and Medicine. 2015. Improving Diagnosis in Health Care. https://doi.org/10.17226/21794. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

TABLE 10-2 Selected Cognitive Biases Contributing to Diagnostic Errors

1. Premature closure: accepting a diagnosis before it has been fully verified
2. Anchoring: tendency to fixate on a specific symptom or piece of information early in the diagnostic process with subsequent failure to appropriately adjust
3. Confirmation bias: tendency to look for confirming evidence to support one’s diagnostic hypothesis, rather than disconfirming evidence to refute it
4. Search satisficing: tendency to call off a search, satisfied once a piece of data or presumed explanation is found, and not considering/searching for additional findings or diagnoses
5. Availability bias: tendency to give too much weight to diagnoses that come more readily to mind (e.g., recent dramatic case)
6. Base-rate neglect: failing to adequately take into account prevalence of a particular disease (e.g., erroneously interpreting a positive test as indicating disease in a low-prevalence population using a test with 5% false-positive rate)
7. Knowledge deficit (on part of provider, with accompanying lack of awareness)
8. Framing bias: judgement overly influenced by the way the problem was presented (how it was framed in words, settings, or situations)
9. Social/demographic/stereotype bias: biases from personal or cultural beliefs about women, historically marginalized populations such as African Americans, people with differing sexual identities, or other patient groups for whom prejudices may distort diagnostic assessment However, clinicians will also benefit from having a better under standing of diagnosis as a “system” rather than just what takes place in clinicians’ minds. Classic teaching exhorting trainees and practicing physicians to have a broad differential and “high index of suspicion” for various diseases is challenged not only by these

unconscious biases but also by limitations of human memory, information shortfalls, constrained encounter time, system process failures, and the myriad nonspecific symptoms that patients bring to clinicians. Many symp toms are self-limited, defy a precise diagnosis or etiology, and do not portend harmful outcomes. Insights from safety and cognitive sciences call for rethinking traditional approaches to diagnosis and suggest new approaches to overcome current limitations (Table 10-3). TABLE 10-3 New Models for Conceptualizing Diagnosis and Diagnosis Improvement TRADITIONAL WAYS OF THINKING ABOUT DIAGNOSIS AND DIAGNOSTIC ERROR NEW PARADIGMS/BETTER WAYS TO THINK ABOUT DIAGNOSIS AND IMPROVING DIAGNOSIS General A good diagnostician gets it right the first time, almost all of the time Diagnosis is an inexact science with inherent uncertainties Goal is to minimize errors and delays via more reliable systems and follow-up Lore of masterful/skillful academic expert diagnostician who knows/recalls everything; need to look to them if seeking diagnostic excellence Less reliance on (fallible) human memory Quality diagnosis is based on well-coordinated distributed network/team of people and reliable processes All patients entitled to receive quality diagnosis, regardless of where and from whom they receive care Diagnosis is the doctor’s job Co-production of diagnosis among clinicians (including lab, radiology, specialists, nurses, social workers) and, especially, the patient and family Patients often viewed as overly anxious, exaggerating, time-consuming, questioning, with sometimes unreasonable demands and expectations Patients are key allies in diagnosis; hold key information Need to address understandable/legitimate fears, desires for explanations Leveraging patient questions and questioning of diagnosis to stimulate rethinking the diagnosis where needed Diagnosis and treatment as separate stages in patient care (i.e., make a diagnosis, then treat) Prioritizing diagnostic efforts to target treatable conditions More integrated strategies and timing for testing and treatment depending on urgency for treatment Clinical practices Order lots of tests to avoid missing diagnoses Judicious ordering: targeted, well-organized data and testing Appreciation of test limitations (false positives or negatives, incidental findings, overdiagnosis, test risks) and resulting harms More referrals to avoid missing rarer/specialized diagnoses; concomitant utilization barriers (copays, prior authorization) to minimize overuse “Pull systems” to lower barriers and make it easier to pose questions, obtain real-time virtual consults Co-management approaches to enable collaborative watch-and-wait conservative strategies where appropriate Frequent empirical drug trials when uncertain of diagnosis Conservative use of drugs to avoid confusing clinical picture or labeling patients with diseases they may not have Physician attention/efforts to ensure disease screening Automating, delegating clerical functions; teamwork to free up physician cognitive time

■ ■UNCERTAINTY IN DIAGNOSIS Given variations in ways patients present, illnesses evolve, and tests per form, it is often not possible or practical to “make” a definitive diagnosis, particularly in the primary care setting early in the course of a patient’s illness. Clinicians need to harness these uncertainties to both have enhanced situational awareness of where things can go wrong and create safety nets to protect patients against harms from delayed diagnosis and misdiagnosis. Terms such as preliminary diagnosis, working diagnosis, dif ferential diagnosis, deferred diagnosis, undiagnosed illness, diagnoses with uncertain or multifactorial etiologies, intermittent diagnoses, multiple/dual diagnoses, self-diagnosis, or at times contested diagnosis need to be part of our vocabulary, thinking, and communications with patients to convey that diagnosis is often

imprecise. Anxious patients worried about a con dition, for example, cancer, COVID-19 infection, or a diagnosis to which a relative or a friend has recently succumbed, come seeking reassurance and may not welcome an uncertain answer. Thus, we have to work with patients, listen to and respect their concerns, and take their symptoms seriously yet modestly acknowledge our limitations. We need to tailor this approach to patients' differing levels of health literacy, trust in our clinical advice, and experiences with the health system.

CHAPTER 10 Diagnosis: Reducing Errors and Improving Quality
■ ■DON'T MISS DIAGNOSES AND RED FLAGS Uncertainty should not be a license for complacency. Particularly for diseases that (1) progress rapidly, (2) require specific treatments that depend on making the correct diagnosis, or (3) have public health or contagion implications, clinicians need to be poised, and systems designed, to consider and, where appropriate, pursue critical "don't miss" diagnoses. While clinicians are generally aware of more com mon "don't miss" diagnoses (e.g., acute myocardial infarction, sepsis), Table 10-4 illustrates examples of less common diagnoses that warrant similar consideration. Throughout this textbook, readers should orient themselves to recognize such critical diagnoses and think about pre sentations and syndromes where they may be lurking. An important related concept is so-called "red flags" or "alarm symptoms." This construct has its origins in guidelines for back pain but has increasingly been applied to many other problems, such as headache, red eye, swollen joint, or even abdominal pain and chest (Continued)

TABLE 10-3 New Models for Conceptualizing Diagnosis and Diagnosis Improvement TRADITIONAL WAYS OF THINKING ABOUT DIAGNOSIS AND DIAGNOSTIC ERROR NEW PARADIGMS/BETTER WAYS TO THINK ABOUT DIAGNOSIS AND IMPROVING DIAGNOSIS Diagnosis errors and challenges Diagnostic error viewed as a personal failing Errors classified as either "system" or "cognitive" Many errors/delays rooted in processes and system design/failures Errors multifactorial with interwoven, interacting, and inseparable cognitive and system factors PART 1 The Profession of Medicine Errors are infrequent; hit-and-miss ways to learn about errors Errors are common; systematic proactive follow-up is needed to recognize potential for errors Surveilling of high-risk situations and one's own diagnostic performance and outcomes Clinicians' reactions: denial, defensive, others to blame, pointing to others also making similar errors Culture of actively and nondefensively seeking to uncover, dig deep to learn from, and share errors and lessons Dreading complex, frustrating diagnostic dilemmas Welcoming/enjoying intellectual/professional challenges Adequate support (time, help, consultations) for more complex patients Diagnoses as distinct labels, events Diagnoses can be indistinct, interacting comorbidities, socially constructed, multifactorial, evolving over time, or have overlapping genotype-phenotype expressions Documentation/communication Viewed as time-consuming, mindless, primarily to document for billing code and/or bulwark against malpractice claims Documentation as useful tool for reflecting, crafting, sharing assessments, differential diagnosis, reflecting about unanswered questions Opportunities for decision support interacting with computer Notes open for patients to read to help understand and critique diagnosis Say and write as little as possible about uncertainties, lest it be used against you in malpractice allegation Share uncertainties to maximize communication and engagement with other caregivers, patients Don't let patient know about errors so they don't become angry, mistrustful, or sue Patients have right to honest disclosure; often find out about errors anyway (e.g., cancer evolves); anticipate, engage their concerns Patients advised to call if not better; no news is good news (test results: "We'll call if anything is abnormal.") Systematic proactive follow-up to close loop on all tests and any worrisome symptoms, to check how patient is

doing, monitor outcomes Global remedies Knowing/memorizing more medical knowledge Knowing more about the patient (including psychosocial, past history, environmental contexts) Attention to the “objective” data (physical exam, tests) to reliably make diagnoses Renewed emphasis on history, history-taking, listening Acknowledgment of ubiquitous subjective cognitive biases; efforts to anticipate, recognize, counteract Exhortations to have “high index of suspicion” of various diagnoses Less reliance on memory recall of lectures/reading; more just-in-time info look-up Affordances, alerts to red flags engineered into workflow Delineation of “don’t miss” diagnoses with design of context-relevant decision support reminders Ensuring physician is copied on everything, thorough/ voluminous notes, widespread reminders/alerts Biggest problem no longer lack of access to information, but rather information overload; strategies to organize, minimize Continuing medical education (CME) courses to expand medical knowledge Real-time, context-aware reminders of pitfalls, critical differential diagnoses, and key differentiating features. Ready access to medical references, second opinions Redundancies, double-checks Recognition that single, highly reliable systems are often better than multiple halfway solutions Clear delineation of responsibilities for follow-up tasks Fear of malpractice suits to motivate physicians to be more careful and practice defensive medicine Drive out fear, make it safe to learn from and share errors Shared situational awareness of where pitfalls lurk More accountability, financial incentives, and penalties tied to performance metrics Clinician engagement in improvement based on trust, collaboration, professionalism, financial neutrality Metric modesty, recognizing many best practices yet to be defined/proven More rules, requirements; target outlier physicians for better compliance Standardization with flexibility; learning from deviations More time with patients Better time spent with patients: offloading distractions, more efficient history collection/organization, longitudinal continuity, and, where needed, additional time to talk/think/explain during, before, or after visits Easier access for patients to reach or be seen by clinicians when experiencing concerning symptoms Reflex changes in response to errors Avoiding “tampering,” which entails understanding/diagnosing difference between “special cause” versus “common cause” (random) variation Source: Modified from GD Schiff: Quality and Safety in Health Care 2013. pain. Examples of widely cited red flags for back pain that should trig ger consideration of more serious etiologies include fever, weight loss, history of malignancy or intravenous drug use, or neurologic signs and symptoms. In theory, many presenting syndromes could benefit from identification of such clues to more serious diagnoses. Evidence-based medicine calls for better data on the sensitivity, specificity, yield, and discriminatory ability of various clinical “red flag” clues; yet few have been rigorously evaluated. Nonetheless, clinicians find them useful as simple ways to reassure themselves and their patients that a common symptom such as back pain or headache is, or is not, likely an indicator of more urgent or serious pathology. Interwoven with the challenges of not missing critical diagno ses is the problem of overtesting and overdiagnosis—performing

(Continued) unnecessary and even potentially harmful tests whose benefit does not justify the risks or costs or that may lead to diagnoses that would have never caused any symptoms or problems. Diagnosticians need to weigh carefully this “other side of the coin” of missed diagnosis to avoid such harms and expenses. Thus, being more conservative in diagnostic testing should not be primarily about conserving resources, but more an approach for ensuring laboratory or imaging studies truly benefit patients, while minimizing short- and longer-term harms. ■ ■DIAGNOSTIC PITFALLS One of the important ways of learning in medicine is learning from the missteps of those who have walked the path ahead of us. By learn ing about commonly missed diagnoses and the ways accurate, timely

TABLE 10-4 Examples of “Don’t Miss” Diagnoses METABOLIC/ HEMATOLOGIC/ ENVIRONMENTAL INFECTIONS/ INFLAMMATION CARDIAC/ISCHEMIC/ BLEEDING Spinal epidural abscess Aortic dissection Leaking/ruptured abdominal aortic aneurysm Diabetes ketoacidosis Hyperosmolar hyperglycemia Necrotizing fasciitis Pericardial tamponade Myxedema/ thyrotoxicosis Meningitis Wolff-Parkinson-White Prolonged QT Addison’s disease Endocarditis Pulmonary embolism B12 deficiency anemia Peritonsillar abscess Tension pneumothorax von Willebrand’s disease Tuberculosis-active pulmonary, other Acute mesenteric ischemia Sigmoid volvulus Hemochromatosis COVID-19 infection Esophageal, bowel perforation Celiac sprue Guillain-Barré syndrome Cerebellar hemorrhage Carbon monoxide, lead, pesticide poisoning Ebola infection Spinal cord compression Food poisoning Temporal arteritis Testicular, ovarian torsion Malignant hyperthermia Rhabdomyolysis Ectopic pregnancy Alcohol, benzodiazepine, barbiturate withdrawal Angioedema Retroperitoneal hemorrhage Tumor lysis syndrome Hypo-/hypercalcemia diagnosis went astray, we can avoid making similar mistakes. Anticipat ing the potential for similar types of errors can both create situational awareness of traps to avoid and contribute to learning from our own personal and collective patterns of mistakes. Several studies have examined common or recurring pitfalls in diagnosis. An example of a common disease-specific diagnostic pitfall in breast cancer diagnosis is ordering a mammogram for a woman with a palpable breast lump and, when the mammogram returns as normal, reassuring her that cancer has been “ruled out” by the negative test. Any unexplained mass or lesion palpable on physical examination needs assessment including further testing and biopsy, where warranted. Diagnostic pitfalls can be classified into a number of generic scenarios (Table 10-5). We now have large databases that have the potential to track “diagnoses outcomes”— i.e., whether a new diagnosis emerges that suggests an initial diagnosis was incorrect or a diagnosis of a patient’s symptoms was suboptimally delayed. This should, in the future, allow us to more rigorously focus on these cases, to identify contributing factors and recurring patterns, and to help point the way for systemwide improvement strategies. ■ ■DIAGNOSIS SAFETY CULTURE Just as diagnosing bacterial infections relies on a proper culture medium to grow and identify etiologic organisms, good diagnosis also requires a healthy safety culture that will allow it to grow and flourish. While clinicians may be inclined to view “safety culture” as something too subjective to be important in their quest to make a definitive diagnosis, this view is misguided. Multiple studies have demonstrated adverse consequences resulting from organizational cultures that inhibit openness, learning, and sharing and create a climate where staff and patients are afraid to speak up when they observe problems or have questions. Most importantly, patients need to be encouraged to ques tion diagnoses and be heard, particularly when they are not responding to treatment as expected or developing symptoms that are either not consistent with the diagnosis or represent possible red flags for other diagnoses or complications. Studies examining “high-reliability organizations” outside of medi cine and “learning health care organizations” have distilled a series of fundamental properties that are correlated with more reliable and safer outcomes. Just as a thermometer or recording of a pulse can suggest how ill a patient is, we now have instruments that can measure safety culture.

TABLE 10-5 Generic Types of Diagnostic Pitfalls PITFALL EXAMPLES • Aortic dissection misdiagnosed as Disease A mistaken for disease B Diseases often mistaken/misdiagnosed with each other acute myocardial infarction • Bipolar disorder misdiagnosed as CHAPTER 10 depression • Breast lump dismissed after Misinterpretation of test result(s) False-positive or false-negative results with failure to recognize test limitations negative mammogram • Negative COVID-19 test early or late in course Diagnosis: Reducing Errors and Improving Quality

• Apathetic hyperthyroidism • Sepsis in elderly patient who is Failure to recognize atypical presentation, signs, and symptoms afebrile or hypothermic • Compartment syndrome • Pericardial tamponade • Tension pneumothorax Failure to assess appropriately the urgency of diagnosis Urgency of the clinical situation was not appreciated and/or delays critical diagnoses • “Lucid interval” in traumatic Perils of intermittent symptoms or misleading evolution Intermittent symptoms dismissed due to normal findings (exam, lab, electrocardiogram) when initially seen epidural hematoma • Paroxysmal arrhythmias • Intermittent hydrocephalus (Bruns’ syndrome) • Empiric treatment with steroids, Confusion arising from response/ masking by empiric treatment proton pump inhibitors, antibiotics, pain medication erroneously masking serious diagnosis • Septic joint signs misattributed to Chronic disease or comorbidity presumed to account for new symptoms Especially in medically complex patients chronic rheumatoid arthritis • Mental status change due to infection or medication misattributed to underlying dementia • Many; fortunately, by definition, Rare diagnosis: failure to consider or know rare, but still warrant consideration especially if urgent or treatable • Ventricular arrhythmia related to Drug or environmental factor not considered/overlooked Underlying etiology causing/ contributing to symptoms, or disease progression not sought, uncovered QT-prolonging drug • Achilles tendon rupture related to quinolone • Family history of breast, colorectal Failure to appreciate risk factors for particular disease cancer not solicited and/or weighed in diagnostic evaluation or screening • Overweighing absence of Failure to appreciate limitations of physical exam Now with ↑ telemedicine, missing physical exam entirely tenderness, swelling in deep vein thrombosis • Missing pill-rolling tremor during telemedicine visit These safety measurement tools typically are validated staff surveys that assess (1) communication about errors with staff willingness to report mistakes because they do not feel these mistakes are held against them; (2) openness and encouragement to talk about hospital/office problems; (3) existence of a learning culture that seeks to learn from errors and improve based on lessons learned; (4) leadership commitment to safety, prioritizing safety over production speed and the “bottom line” by pro viding adequate staffing and resources to operate safely; and (5) account ability and transparency for following up safety events and concerns. Each of these generic culture attributes translates into specific implica tions for diagnostic safety. These include the following: • Making it “safe” for clinicians to admit and share diagnostic errors • Proactive identification, ownership, and accountability regarding error-prone diagnostic workflow processes (particularly around test results, referrals, and patient follow-up) • Leadership making diagnosis improvement a top priority based on recognition that patients and malpractice insurers report that diag nostic errors are the leading patient safety problem

• Mutual trust and respect for challenges that clinicians often face in

making diagnoses and caution in applying the lens of hindsight bias in judging what in retrospect might seem like an “obvious” diagnosis that a clinician initially missed. ■ ■HEALTH INFORMATION TECHNOLOGY AND THE FUTURE OF DIAGNOSIS Clinicians now spend more time interacting with computers than they do interacting with patients. This is especially true for diagnosis and will likely be even more so in the future. Interactions with patients, consultants, and other staff are increasingly mediated through the computer. Key activities, such as collecting patients’ history (past and current), interpreting data to make a diagnosis, conveying diagnostic assessments (to others on the team and, increasingly, to the patient via open notes), and tracking diagnostic trajectories as they evolve over time, are now computer based. With the rise of telemedicine, even elements of the physical examination have been rerouted to electronic encounters, with important

implications for diagnostic safety. PART 1 The Profession of Medicine While many complain the computer has “gotten in the way” of good diagnosis, distracting clinicians from quality time listening to patients and miring doctors in reading and writing notes filled with copied/ pasted/templated information of questionable currency and accuracy, medicine needs to harness the computer’s capabilities to improve diag nosis (Table 10-6). Although supporting these basic diagnosis capa bilities should be the foundation of health information technology and everyday workflows, electronic medical records have historically been largely designed around other needs, such as ordering medications, billing, and documentation to guard against malpractice claims. They instead need to be redesigned radically to better support diagnostic pro cesses, as well as save clinicians time. With the rise of generative artificial intelligence large language learning models, many are looking to the computer to take over the job of making diagnoses, answering patients’ diagnostic questions, or resolving diagnostic dilemmas. However, despite its significant cabilities for image and data analysis, pattern recognition, creating clinical notes, and decision support including generating dif ferential diagnoses, there are fundamental limitations, challenges, and unanswered questions related to data accuracy and how to incorporate human relational elements into AI-driven diagnostic processes. ■ ■DIAGNOSIS OF DIAGNOSIS ERRORS AND SAFETY: PRACTICAL CONCLUSIONS In practice, there are frequent and meaningful opportunities for improving diagnosis in each of the three NAM-defined areas to make it (1) more reliable and (2) timely, and (3) to improve diagnosis-related communication with patients. Clinicians in training, practicing physi cians, nurses, and others should develop the habit of regularly asking themselves three questions about individual patients in their care, and another three questions regarding the systems in which they work. For each patient being assessed, clinicians should ask:

1. What else might this be? (forcing a differential diagnosis to be made)
2. What doesn’t fit? (making sure unexplained abnormal findings are not dismissed)
3. What critical diagnoses are important not to miss? (injecting con sideration of “don’t miss” diagnoses, red flags, and known pitfalls) And to diagnose safely, each practitioner must recognize that they are working within a larger system. Questions to be asking continually, ensuring we are maximizing reliability and timeliness and minimizing potential for errors, include:
4. Do we have reliable “closed loop” systems to provide reliable, ideally automated tracking and following up of patients’ symptoms, abnormal laboratory or imaging findings, and critical referrals that we order?
5. What is the culture-of-safety climate in our organization, office, or clinic?
6. How does the electronic (or even paper) medical record as currently implemented help versus impair efficient, timely, accurate, and failsafe diagnosis, and how can it be improved? The challenge will be to take these questions to the next develop mental stage in order to ensure diagnostic errors are recognized both in individual patients as well as prioritized for systemic changes in

TABLE 10-6 Areas Where Health Information Technology Has Potential to Help Improve Diagnosis and Reduce Errors FUNCTION EXAMPLES Facilitate collection/ gathering of information • Quickly access past history from prior care at same and outside institutions • Electronic collection of history of present illness, review of systems, and social determinant risks in advance of visits Enhanced information entry, organization, and display • Visually enhanced flowsheets showing trends, relationships to treatment • Reorganized notes to facilitate summarization and

simplification and prevent items from getting lost Generating differential diagnosis • Automated creation of lists of diagnoses to consider based on patient's symptoms, demographics, risks • ChatGPT augmenting physician's diagnostic considerations Weighing diagnoses likelihoods • Tools to assist in calculation of posttest (Bayesian) probabilities Aids for formulating diagnostic plan, intelligent test ordering • Entering a diagnostic consideration (e.g., celiac disease, pheochromocytoma) and computer suggests most appropriate diagnostic test(s) and how to order Access to diagnostic reference information • Info-buttons instantly linking symptom- or diagnosis-relevant questions to Harrison's, Up-toDate chapters, references Ensuring more reliable follow-up • Hardwiring "closed loops" to ensure abnormal labs, missed referrals, worrisome symptoms are tracked and followed up Support screening for early detection • Collaborative tools that patients, clinicians, and offices can use to know when due, order and track screening based on individualized demographics, risk factors, prior tests Collaborative diagnosis; access to specialist • Real-time posing/answering of questions • Electronic consults; virtual co-management Facilitating feedback on diagnoses • Feeding back new diagnoses (from downstream providers, patients) that emerge suggesting potential misdiagnosis/errors to clinicians, emergency rooms that saw patient previously Source: Modified from G Schiff, DW Bates: N Engl J Med 362:1066, 2010, and R El-Karah et al: BMJ Qual Saf Suppl 2:ii40, 2013. medicine. In the decade following the ground-breaking National Acad emy of Medicine report there have been a host of quality improvement and research efforts to better understand the epidemiology, causes, and ways to prevent diagnostic errors. While these efforts have had mixed success, they have enhanced understanding of where, how, and why things go wrong. Transforming diagnostic safety culture, ensur ing reliable follow-up and feedback, learning from diagnostic errors, leveraging health IT, and more deeply partnering with patients will be essential elements for highest quality diagnosis in the future. ■ ■FURTHER READING Moore Foundation: Viewpoint series aims to broaden understand ing of diagnostic excellence. https://www.moore.org/article-detail?

newsUrlName=viewpoint-series-aims-to-broaden-understanding-of-

diagnostic-excellence. National Academies of Sciences, Engineering, and Medicine. 2015. Improving Diagnosis in Health Care. https://doi.org/10.17226/21794. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, DC. Newman-Toker D et al: Rate of diagnostic errors and serious misdiagnosisrelated harms for major vascular events, infections, and cancers: Toward a national incidence estimate using the "Big Three." Diagnosis 8:1, 67, 2021. Schiff GD et al: Ten principles for more conservative, care-full diagnosis. Ann Intern Med 169:643, 2018. Singh H et al: Developing the Safer Dx Checklist of ten safety recom mendations for health care organizations to address diagnostic errors. Jt Comm J Qual Pat Saf 48:581, 2022. Society to Improve Diagnosis in Medicine (SIDM): Resource page. https://www.improvediagnosis.org/resources-for/.

11 - 11 Racial and Ethnic Disparities in Health Care

11 Racial and Ethnic Disparities in Health Care

Lenny López, Joseph R. Betancourt

Racial and Ethnic

Disparities in Health Care Over the course of its history, the United States has experienced dramatic improvements in overall health and life expectancy, largely as a result of initiatives in public health, health promotion, disease prevention, and chronic care management. Our ability to prevent, detect, and treat diseases in their early stages has allowed us to target and reduce rates of morbidity and mortality. Despite interventions that have improved the overall health of the majority of Americans, racial and ethnic minorities (blacks, Hispanics/Latinos, Native Americans/ Alaskan Natives, Asian/Pacific Islanders) have benefited less from these advances than whites and have suffered poorer health outcomes from many major diseases, including cardiovascular disease, cancer, and diabetes. In 2018, the estimated economic burden of racial and ethnic health inequities was between $421 billion and $451 billion and between $940 billion and $978 billion for adults without a 4-year college degree. These disparities highlight the importance of recogniz ing and addressing the multiple factors that impact health outcomes, including structural racism, social determinants of health (SDOH), access to care, and health care quality. On this last point, research has revealed that minorities may receive less care and lower-quality care than whites, even when confounders such as stage of presentation, comorbidities, and health insurance are controlled. These differences in quality are called racial and ethnic disparities in health care. These health care disparities have taken on greater importance with the sig nificant transformation of the U.S. health care system and value-based purchasing. The shift toward creating financial incentives and disin centives to achieve quality goals makes focusing on those who receive lower-quality care more important than ever before. This chapter will provide an overview of racial and ethnic disparities in health and health care, identify root causes, and provide key recommendations to address these disparities at both the clinical and health system levels. Non-Hispanic Asian female Hispanic female Non-Hispanic Asian male Non-Hispanic White female Non-Hispanic Black female Non-Hispanic White male Hispanic male Non-Hispanic American Indian or Alaska Native female Non-Hispanic Black male Non-Hispanic American Indian or Alaska Native male

Age (years) FIGURE 11-1 Life expectancy at birth, by Hispanic origin and race and sex: United States, 2020. (From E Arias, JQ Xu: United States life tables, 2020. National Vital Statistics Reports; vol 71 no 1. Hyattsville, MD: National Center for Health Statistics. 2022. Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-01.pdf.)

■ ■NATURE AND EXTENT OF DISPARITIES Life expectancy at birth is an important measure of the health of a nation's population. Although the overall life expectancy in the United States has been increasing since 1900, differences due to race/ethnicity, education, and socioeconomic status have persisted. For example, at every level of education and income, African Americans have lower life expectancy at age 25 than whites and Hispanics/Latinos. Blacks with a college degree or more education have lower life expectancy than whites and Hispanics who graduated from high school. Blacks have had lower life expectancy compared to whites for as long as data have been collected. From 1975 to 2003, the largest difference in life expectancy between blacks and whites was substantial (6.3 years for males and 4.5 years for females). The gap in life expectancy between the black and white populations decreased by 2.3 years between 1999 and 2013 from 5.9 to 3.6 years (4.4 years for males and 3.0 years for women). During 1999–2017, mortality decreases occurred in all racial/ethnic groups except non-Hispanic American Indian and Alaskan Native adults, who experienced steady increases in midlife mortality through 2017. The pattern of high midlife mortality rates among non-Hispanic American Indian and Alaskan Native and non-Hispanic black adults exceeded rates among other racial/ethnic groups. This pattern remained through 2020, with male non-Hispanic American Indian or Alaskan Native and black males having the lowest life expectancies at birth (Fig. 11-1).

CHAPTER 11 Racial and Ethnic Disparities in Health Care The life expectancy gap is augmented by worse health and higher disease burden. Cardiovascular-related diseases remain the leading cause of black-white differences in life expectancy. If all cardiovascular causes and diabetes are considered together, they account for 35% and 52% of the gap for males and females, respectively. During the COVID-19 pandemic, the U.S. population experienced the most sig nificant 2-year decline in life expectancy in roughly a century, dispro portionately impacting people of color and exacerbating longstanding racial disparities in life expectancy. While overall U.S. life expectancy declined by 2.7 years between 2019 and 2021, American Indian and Alaskan Native people experienced a decline of 6.6 years and Hispanic people and black people experienced a decline of 4.2 and 4 years, respectively, compared to a decline of 2.4 years for white people and 2.1 years for Asian people. Finally, place matters for health. Analysis of data from 2010 to 2015 demonstrate large geographic life expectancy 85.9 81.3 81.1 80.1 75.4 74.8 74.6 70.7 67.8 63.8

PART 1 The Profession of Medicine Life Expectancy at birth (Quintiles) 56.9–75.1 75.2–77.5 77.6–79.5 79.6–81.6 81.7–97.5 Geographic areas with no data available are filled in gray FIGURE 11-2 Life expectancy at birth for U.S. census tracts, 2010–2015. (From A New View of Life Expectancy, Surveillance and Data - Blogs and Stories, Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/surveillance/blogs-stories/life-expectancy.html.) gap variation at the census tract level (Fig. 11-2). Socioeconomic and race/ethnicity factors, behavioral and metabolic risk factors (preva lence of obesity, leisure-time physical inactivity, cigarette smoking, hypertension, diabetes), and health care factors (percentage of the pop ulation younger than 65 years who are insured, primary care access and quality, number of physicians per capita) explained 60%, 74%, and 27% of county-level variation in life expectancy, respectively. Combined, these

factors explained 74% of this variation. Most of the association between socioeconomic and race/ethnicity factors and life expectancy was mediated through behavioral and metabolic risk factors. In addition to racial and ethnic disparities in health, there are racial and ethnic disparities in the quality of care for persons with access to the health care system. Seminal studies over several decades have con sistently documented disparities in health care. For instance, studies have documented disparities in the treatment of pneumonia and con gestive heart failure, with blacks receiving less optimal care than whites when hospitalized for these conditions. Moreover, blacks with endstage renal disease are referred less often to the transplant list than are their white counterparts (Fig. 11-3). Disparities have been found, for example, in the use of cardiac diagnostic and therapeutic procedures (with blacks being referred less often than whites for cardiac catheter ization and bypass grafting), prescription of analgesia for pain control (with blacks and Hispanics/Latinos receiving less pain medication than whites for long-bone fractures and cancer), and surgical treatment of lung cancer (with blacks receiving less curative surgery than whites for non-small-cell lung cancer). Again, many of these disparities have occurred even when variations in factors such as insurance status, income, age, comorbid conditions, and symptom expression are taken into account. Finally, disparities in the quality of care provided at the sites where minorities tend to receive care have been shown to be an important additional contributor to overall disparities. The 2022 National Healthcare Quality and Disparities Report, released by the Agency for Healthcare Research and Quality, tracks more than 400 health care process, outcome, and access measures,

across many diseases and settings. This annual report is particularly important because most studies of disparities have not been longitu dinally repeated with the same methodology to document trends and changes in disparities over time. This report found that some dispari ties were getting smaller from 2000 through 2016–2018, but disparities persisted and some even worsened, especially for poor and uninsured populations. For about 45% of quality measures, blacks (85 of 190 mea sures) and American Indians and Alaska Natives (47 of 110 measures) received worse care than whites. For more than one-third of quality mea sures, Hispanics (73 of 190 measures), Asians, and Native Hawaiians/

Pacific Islanders received worse care than whites, but Asians also received better care for about 28% of quality measures (Fig. 11-4). Of note, for those quality measures that demonstrated disparities at baseline, >90% of these measures showed no improvement since 2000 (Fig. 11-5). ■ ■ROOT CAUSES OF DISPARITIES Race, Racism, and Health Race and racism are core elements of any explanatory model on racial and ethnic disparities in health and health care. Our nation’s history of slavery, segregation, separate but “equal” health care, and medical experimentation, among a myriad of other ways in which racism has manifested in the United States, has played a key role in the existence and persistence of these dispari ties. It is now well accepted that race is a social category without biologic foundation and a product of historical racism. Nevertheless, it is clear that racism has a biologic impact as a form of psychosocial stress. It is now well established that psychosocial stress negatively impacts health through psychophysiologic reactivity causing hyper stimulation of the sympathetic-adrenal-medullary system and the hypothalamic-pituitary-adrenal axis, leading to vascular inflamma tion, endothelial dysfunction, and neurohormonal dysregulation, causing an acceleration of cardiovascular disease. Behavioral changes occurring as adaptations or coping responses to stressors such as

15,000 12,500 10,000 Number of Patients

Year

White Black Hispanic Asian Native American NH/PI FIGURE 11-3 Number of end-stage renal disease patients added to the waitlist for a kidney transplant, 2010–2020. NH/PI, Native Hawaiian/Pacific Islander. (From US Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/7-transplantation. Accessed October 25, 2023.) increased smoking, decreased exercise and sleep, and poorer adher ence to medical regimens provide an additional important pathway through which stressors influence disease risk. This accelerated disease risk, aging, and premature death has been termed the weathering effect. While most empiric research focuses on interpersonal racial/

ethnic discrimination, structural racism (sometimes called institu tional racism) provides a more holistic framework. Structural rac ism refers to the totality of ways that a society fosters, sustains, and reinforces discrimination through sociopolitical, legal, economic, and health structures that determine differential access to risks, opportuni ties, and resources that drive health and health care disparities. Struc tural racism explains how racism's structure and ideology can persist in governmental and institutional policies in the absence of individual actors who are explicitly racially prejudiced. For example, the history of residential segregation has had lasting negative effects generationally on equal access for racial/ethnic minorities to employment, banking, earnings, high-quality education, and health care. Policies that do not 100%

80% 60%

40%

20%

0% AI/AN (n=110) Hispanic (n=190) NHPI (n=73) Black (n=190) Asian (n=172) Better Same Worse FIGURE 11-4 Number and percentage of quality measures for which members of selected groups experienced better, same, or worse quality of care compared with white people for the most recent data year, 2017, 2018, 2019, or 2020. AI/AN, American Indian or Alaska Native; NHPI, Native Hawaiian/Pacific Islander (From 2022 National Healthcare Quality and Disparities Report. Rockville, MD: Agency for Healthcare Research and Quality; October 2022. AHRQ Publication No. 22(23)-0030. https://www. ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/2022qdr-appendix-combined.pdf. Accessed October 25, 2023.)

 address root structural causes will not address health and health care inequities. With the promise of individualizing clinical decisions, the use of race in clinical and risk assessment algorithms has long been a part of modern medicine. The evidence is now clear that race is not a reliable proxy for genetic difference and that race adjustment has the potential to create inadvertent disparities in health care. One clinical example is from nephrology. Blacks have higher rates of end-stage kidney disease and death due to kidney failure than the overall population. The most widely used cohort-

derived equation to estimate glomerular filtration rate (GFR), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, has the limitation that it produces 80–90% esti mated GFR (eGFR) values that are within ±30% of a patient's measured GFR. In addition, this equation uses a black race-related factor, which increases eGFR for any given serum creatinine by 15.9% compared to a nonblack patient with the same age, sex, and serum creatinine. The increase in eGFR is likely to disadvantage blacks for early referral to a nephrologist, early treatment of advanced chronic kidney dis ease, and kidney transplantation. It is also not clear how to apply the race factor when the patient's race is unknown and/or ambiguous, as in those who are multiracial. This disparity-inducing scenario could be avoided through the use of cys tatin C–based eGFR estimation, which has been demonstrated to be more accurate than the CKD-EPI equation and for which race is not required in estimation.

The application of artificial intelligence (AI) analytics to large amounts of clinical electronic data—big data—holds the prom ise to better understand health care costs, utilization, resource allocation, and population health monitoring. Machine learning models can identify the statisti cal patterns in large amounts of

100%

80% PART 1 The Profession of Medicine 60%

40% 20%

0% AI/AN (n=38) Hispanic (n=58) NHPI (n=18) Black (n=72) Asian (n=43) Improving Not Changing Worsening FIGURE 11-5 Number and percentage of quality measures with disparity at baseline for which disparities related to race and ethnicity were improving, not changing, or worsening over time, 2000–2020. AI/AN, American Indian or Alaska Native; NHPI, Native Hawaiian/Pacific Islander. (From 2022 National Healthcare Quality and Disparities Report. Rockville, MD: Agency for Healthcare Research and Quality; October 2022. AHRQ Publication No. 22(23)-0030. https://www.ahrq.gov/sites/ default/files/wysiwyg/research/findings/nhqrdr/2022qdr-appendix-combined.pdf. Accessed October 25, 2023.) historically collected data. These data naturally contain the patterning of preexisting health care disparities created by socially and historically structured inequities. This biased patterning can lead to incorrect pre dictions, withholding of resources, and worse outcomes for vulnerable populations. Recently, analysis of a commercial, national, proprietary prediction algorithm, affecting millions of patients, exhibited racial bias. Historical cost data were used to predict clinical risk and allocate additional clinical services for high-cost patients. Algorithmic bias arose because black patients historically have less access to health care and thus less money is spent on their care compared to white patients. Thus, blacks, who tended to be sicker than white patients, received lower clinical risk scores and thus were less likely to receive additional clinical services. The observed allocation bias was remedied using direct measures of illness and illness severity. Thus, machine learning algorithms are not inherently free of bias and should be assessed for accuracy and fairness. In summary, there are many ways in which racism has contributed and does and will continue to contribute to racial and ethnic disparities in health and health care. ■ ■SOCIAL DETERMINANTS OF HEALTH Minority Americans have poorer health outcomes than whites from preventable and treatable conditions such as cardiovascular disease, diabetes, asthma, cancer, and HIV/AIDS. Multiple factors contribute to these racial and ethnic

disparities in health. The landmark National Academy of Medicine (formerly, the Institute of Medicine [IOM]) report, Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care, published in 2002, summarized the scientific evidence on health disparities and provided an important framework for con ceptualizing and defining racial/ethnic disparities. Since the Unequal Treatment report, there has been a growing empiric evidence base on how racism and the SDOH, often working in synergy, create and sustain disparities. Mechanistically, the biopsychosocial model brings together the social and physical characteristics of the environment with individual physical and psychological attributes. These environmental and individual characteristics, in turn, influence health behaviors and stress-related physiologic pathways that directly impact health. The National Institute on Minority Health and Health Disparities SDOH model builds on prior models and adds the time element across the life course of the individual in recognition of the long-lasting health effects of socioeconomic exposures (Fig. 11-6). The resulting matrix has the domains of influence of health (biological, behavioral, physical and built environment, sociocultural environment, health care system) along the y-axis and the levels of influence on health (individual, inter personal, community, societal) along the x-axis. Cells are not mutually

exclusive, and examples of factors within each cell are illustrative and not comprehensive. This frame work emphasizes the complex mul tidomain etiologies of disparities across the factors in the conceptual matrix, thus highlighting the limi tation of individual-level focused research and policy. The Centers for Disease Control and Prevention’s (CDC) Social Vul nerability Index (SVI) is one of the most comprehensive indicators of SDOH for every U.S. county and census tract (Fig. 11-7). The 15 social factors are grouped into four broad themes: (1) socioeconomic status (below poverty, unemployed, income level, and no high school diploma); (2) household composition and dis ability (aged 65 years or older, aged 17 years or younger, individuals

> “ 5 years with a disability, and

single-parent households); (3) minor ity status and language (minority and individual speaks English “less than well”); and (4) housing type and transportation (multiunit structure, mobile home, crowding, group quarters, and no vehicle). Recent studies using national databases have demonstrated a strong geographic concen tration of negative factors by counties and regions in the United States. States in the highest tertile of social vulnerability had predominantly black and Hispanic adults, lower levels of education, lower income, and higher rates of unemployment and substance use. These individuals also had higher rates of hypertension, diabetes, hyperlipidemia, chronic kidney disease, smoking, and atherosclerotic cardiovascular disease compared with those living in counties in the first tertile of SVI. Importantly, there is a graded increase in mortality related to cancer, cardiovascular disease, and comorbid cancer and cardiovascular disease in U.S. counties with the worst SVI. In addition to race and racism, Unequal Treatment identified a set of root causes that included health system, provider-level, and patientlevel factors. Health System Factors • HEALTH SYSTEM COMPLEXITY Even among persons who are insured and educated and who have a high degree of health literacy, navigating the U.S. health care system can be complicated and confusing. Some individuals may be at higher risk for receiving substandard care because of their difficulty navigating the sys tem’s complexities. These individuals may include those from cultures unfamiliar with the Western model of health care delivery, those with limited

English proficiency, those with low health literacy, and those who are mistrustful of the health care system. These individuals may have dif ficulty knowing how and where to go for a referral to a specialist; how to prepare for a procedure such as a colonoscopy; or how to follow up on an abnormal test result such as a mammogram. Since people of color in the United States tend to be overrepresented among the groups listed above, the inherent complexity of navigating the health care system has been seen as a root cause for racial/ethnic disparities in health care. OTHER HEALTH SYSTEM FACTORS Racial/ethnic disparities are due not only to differences in care provided within hospitals but also to where and from whom minorities receive their care; i.e., certain spe cific providers, geographic regions, or hospitals are lower-performing on certain aspects of quality. For example, one study showed that 25% of hospitals cared for 90% of black Medicare patients in the United States and that these hospitals tended to have lower performance scores on certain quality measures than other hospitals. That said, health systems generally are not well prepared to measure, report, and inter vene to reduce disparities in care. Few hospitals or health plans stratify their quality data by race/ethnicity or language to measure disparities, and even fewer use data of this type to develop disparity-targeted

Individual Interpersonal Biological Vulnerability and Mechanisms Caregiver–Child Interaction Family Microbiome Biological Health Behaviors Coping Strategies Behavioral Domains of Influence (Over the Lifecourse) Household Environment School/Work Environment Physical/Built Environment Personal Environment Sociodemographics Limited English Cultural Identity Response to Discrimination Social Networks Family/Peer Norms Interpersonal Discrimination Sociocultural Environment Insurance Coverage Health Literacy Treatment Preferences Patient–Clinician Relationship Medical Decision-Making Health Care System Health Outcomes Individual Health FIGURE 11-6 National Institute on Minority Health and Health Disparities social determinants research framework. *Health disparity populations: race/ethnicity, low socioeconomic status, rural, sexual and gender minority. Other fundamental characteristics: sex and gender, disability, geographic region. (From National Institute on Minority Health and Health Disparities. NIMHD Research Framework. 2017. Retrieved from https://www.nimhd.nih.gov/about/overview/research-framework.html.)

16.0 8.0

HR (95% CI) Cumulative mortality (%) 4.0

2.0

1.0

Log-rank p<0.0001

Number at risk No unfavorable SDoH One unfavorable SDoH Two unfavorable SDoH Three unfavorable SDoH Four unfavorable SDoH Five unfavorable SDoH Six or more unfavorable SDoH

FIGURE 11-7 Premature all-cause mortality and hazard ratios (HRs) in U.S. adults aged 20–74 years according to the number of unfavorable social determinants of health (SDoHs). Kaplan-Meier curves show cumulative mortality by age and number of unfavorable SDoHs. Bar chart shows HRs of premature all-cause mortality associated with number of unfavorable SDoHs, adjusted for age,

gender, and race and ethnicity; error bars are 95% confidence intervals. (Reproduced with permission from JD Bundy et al: Social determinants of health and premature death among adults in the USA from 1999 to 2018: A national cohort study. Lancet Public Health 8:e422, 2023.)

Levels of Influence* Community Societal CHAPTER 11 Sanitation Immunization Pathogen Exposure Community Illness Exposure Herd Immunity Family Functioning School/Work Functioning Policies and Laws Community Functioning Racial and Ethnic Disparities in Health Care Community Environment Community Resources Societal Structure Social Norms Societal Structural Discrimination Community Norms Local Structural Discrimination Quality of Care Health Care Policies Availability of Services Safety Net Services Family/ Organizational Health Community Health Population Health

≥6

Number of unfavorable SDoH

Age (years)

How do we link communication to outcomes? Communication Patient satisfaction PART 1 The Profession of Medicine Adherence Health outcomes FIGURE 11-8 The link between effective communication and patient satisfaction, adherence, and health outcomes. (From the Institute of Medicine. 2003. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. https://doi. org/10.17226/12875. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.) interventions. Similarly, despite regulations concerning the need for professional interpreters, research demonstrates that many health care organizations and providers fail to routinely provide this service for patients with limited English proficiency. Despite the link between limited English proficiency and health care quality and safety, few pro viders or institutions monitor performance for patients in these areas. Provider-Level Factors • PROVIDER–PATIENT COMMUNICATION

Significant evidence highlights the impact of sociocultural factors, race, ethnicity, and limited English proficiency on health and clinical care. Health care professionals frequently care for diverse populations with varied perspectives, values, beliefs, and behaviors regarding health and well-being. The differences include variations in the recognition of symptoms, thresholds for seeking care, comprehension of management strategies, expectations of care (including preferences for or against diagnostic and therapeutic procedures), and adherence to preven tive measures and medications. In addition, sociocultural differences between patient and provider influence communication and clinical decision-making and are especially pertinent: evidence clearly links provider–patient communication to improved patient satisfaction, regimen adherence, and better health outcomes (Fig. 11-8). Thus, when sociocultural differences between patient and provider are not appreciated, explored, understood, or communicated effectively during the medical encounter, patient dissatisfaction, poor adherence, poorer health outcomes, and racial/ethnic disparities in care may result. A survey of 6722 Americans ≥18 years of age is particularly relevant to this important link between provider–patient communication and health outcomes. Whites, African Americans, Hispanics/Latinos, and Asian Americans who had made a medical visit in the past 2 years were asked whether they had trouble understanding their doctors; whether they felt the

doctors did not listen; and whether they had medical questions they were afraid to ask. The survey found that 19% of all patients experienced one or more of these problems, yet whites experienced them 16% of the time as opposed to 23% of the time for African Americans, 33% for Hispanics/Latinos, and 27% for Asian Americans (Fig. 11-9). In addition, in the setting of even a minimal language barrier, provider–patient communication without an interpreter is recognized as a major challenge to effective health care delivery. These commu nication barriers for patients with limited English proficiency lead to frequent misunderstanding of diagnosis, treatment, and follow-up plans; inappropriate use of medications; lack of informed consent for surgical procedures; high rates of adverse events with more seri ous clinical consequences; and a lower-quality health care experience than is provided to patients who speak fluent English. Physicians who have access to trained interpreters report a significantly higher quality of patient–physician communication than physicians who use other methods. Communication issues related to discordant language dis proportionately affect minorities and likely contribute to racial/ethnic disparities in health care. CLINICAL DECISION-MAKING Theory and research suggest that varia tions in clinical decision-making may contribute to racial and ethnic

Percent of adults with one or more communication problems*

33% 27% 23% 19% 16%

Total White African American Hispanic Asian American Base: Adults with health care visit in past two years *Problems include understanding doctor, feeling doctor listened, had questions but did not ask. FIGURE 11-9 Communication difficulties with physicians, by race/ethnicity. The reference population consisted of 6722 Americans ≥18 years of age who had made a medical visit in the previous 2 years and were asked whether they had had trouble understanding their doctors, whether they felt that the doctors had not listened, and whether they had had medical questions they were afraid to ask. (Reproduced with permission from the Commonwealth Fund Health Care Quality Survey, 2001.) disparities in health care. Two factors are central to this process: clinical uncertainty and stereotyping. First, a doctor’s decision-making process is nested in clinical uncer tainty. Doctors depend on inferences about severity based on what they understand about illness and the information obtained from the patient. A doctor caring for a patient whose symptoms he or she has difficulty understanding and whose “signals”—the set of clues and indi cations that physicians rely on to make clinical decisions—are hard to read may make a decision different from the one that would be made for another patient who presents with exactly the same clinical condition. Given that the expression of symptoms may differ among cultural and racial groups, doctors—the overwhelming majority of whom are white—may understand symptoms best when expressed by patients of their own racial/ethnic groups. The consequence is that white patients may be treated differently from minority patients. Differences in clinical decisions can arise from this mechanism even when the doctor has the same regard for each patient (i.e., is not prejudiced). Second, the literature on social cognitive theory highlights how nat ural tendencies to stereotype may influence clinical decision-making. Stereotyping can be defined as the way in which people use social cat egories (e.g., race, gender, age) in acquiring, processing, and recalling information about others. Faced with enormous information loads and the need to make many decisions, people often subconsciously simplify the decision-making process and lessen cognitive effort by using “cat egories” or “stereotypes” that bundle information into groups or types that can be processed more quickly. Although functional, stereotyping can be systematically biased, as people

are automatically classified into social categories based on dimensions such as race, gender, and age. Many people may not be aware of their attitudes, may not consciously endorse specific stereotypes, and paradoxically may consider them selves egalitarian and not prejudiced. Stereotypes may be strongly influenced by the messages presented consciously and unconsciously in society. For instance, if the media and our social/professional contacts tend to present images of minori ties as being less educated, more violent, and nonadherent to health care recommendations, these impressions may generate stereotypes that unnaturally and unjustly impact clinical decision-making. As signs of racism, classism, gender bias, and ageism are experienced (con sciously or unconsciously) in our society, stereotypes may be created that impact the way doctors manage patients from these groups. On

the basis of training or practice location, doctors may develop certain perceptions about race/ethnicity, culture, and class that may evolve into stereotypes. For example, many medical students and residents are trained—and minorities cared for—in academic health centers or public hospitals located in socioeconomically disadvantaged areas. As a result, doctors may begin to equate certain races and ethnicities with specific health beliefs and behaviors (e.g., “these patients” engage in risky behaviors, “those patients” tend to be noncompliant) that are more associated with the social environment (e.g., poverty) than with a patient’s racial/ethnic background or cultural traditions. This “conditioning” phenomenon may also be operative if doctors are faced with certain racial/ethnic patient groups who frequently do not choose aggressive forms of diagnostic or therapeutic intervention. The result over time may be that doctors begin to believe that “these patients” do not like invasive procedures; thus, they may not offer these procedures as options. A wide range of studies have documented the potential for provider biases to contribute to racial/ethnic disparities in health care. For example, one study measured physicians’ unconscious (or implicit) biases and showed that these were related to differences in decisions to provide thrombolysis for a hypothetical black or white patient with a myocardial infarction. It is important to differentiate stereotyping from prejudice and discrimination. Prejudice is a conscious prejudgment of individuals that may lead to disparate treatment, and discrimination is conscious and intentional disparate treatment. All individuals stereotype subcon sciously, yet, if left unquestioned, these subconscious assumptions may lead to lower-quality care for certain groups because of differences in clinical decision-making or differences in communication and patientcenteredness. For example, one study tested physicians’ unconscious racial/ethnic biases and showed that patients perceived more biased physicians as being less patient-centered in their communication. What is particularly salient is that stereotypes tend to be activated most in environments where the individual is stressed, multitasking, and under time pressure—the hallmarks of the clinical encounter. In fact, in a survey of close to 16,000 physicians, 42% admitted that bias—including by race and ethnicity—impacted their clinical decision-making. Inter estingly, emergency medicine physicians, who work in environments of stress, time pressure, risk, and where they are multitasking, topped the list by discipline at 62%. Patient-Level Factors Lack of trust has become a major concern for many health care institutions today. For example, an IOM report, To Err Is Human: Building a Safer Health System, documented alarming rates of medical errors that made patients feel vulnerable and less trust ful of the U.S. health care system. The increased media and academic attention to problems related to quality of care (and of disparities them selves) has clearly diminished trust in doctors and nurses. Trust is a crucial element in the therapeutic alliance between patient and health care provider. It facilitates open communication and is directly correlated with adherence to the physician’s recommendations and the patient’s satisfaction. In other words, patients who

mistrust their health care providers are less satisfied with the care they receive, and mistrust of the health care system greatly affects patients' use of services. Mistrust can also result in inconsistent care, "doctor-shopping," self-medication, and an increased demand by patients for referrals and diagnostic tests. On the basis of historic factors such as discrimination, segregation, and medical experimentation, blacks may be especially mistrustful of providers. The exploitation of blacks by the U.S. Public Health Service during the Tuskegee syphilis study from 1932 to 1972 left a legacy of mistrust that persists even today among this population. Other populations, including Native Americans/Alaskan Natives, Hispanics/ Latinos, and Asian Americans, also harbor significant mistrust of the health care system. A national survey conducted by the Kaiser Family Foundation found that there is significant mistrust for the health care system among minority populations. Of the 3884 individuals surveyed, 36% of Hispanics and 35% of blacks (compared to 15% of whites) felt they were treated unfairly in the health care system in the past based on their race and ethnicity. Perhaps even more alarming—65% of blacks

Whites Blacks Latinos Tx based on race/ethnicity

Past unfair

CHAPTER 11

Future unfair Tx based on race/ethnicity

Racial and Ethnic Disparities in Health Care

Percent FIGURE 11-10 Patient perspectives regarding unfair treatment (Tx) based on race/ ethnicity. The reference population consisted of 3884 individuals surveyed about how fairly they had been treated in the health care system in the past and how fairly they felt they would be treated in the future on the basis of their race/ethnicity. (From Race, Ethnicity & Medical Care: A Survey of Public Perceptions and Experiences. Kaiser Family Foundation, 2005.) and 58% of Hispanics (compared to 22% of whites) were afraid of being treated unfairly in the future based on their race/ethnicity (Fig. 11-10). This mistrust may contribute to wariness in accepting or following recommendations, undergoing invasive procedures, or participat ing in clinical research, and these choices, in turn, may lead to mis understanding and the perpetuation of stereotypes among health professionals. ■ ■KEY RECOMMENDATIONS TO ADDRESS RACIAL/ ETHNIC DISPARITIES IN HEALTH CARE Unequal Treatment provides recommendations to address the root causes of racial/ethnic disparities organized as health system inter ventions, provider interventions, patient interventions, and general recommendations. Health System Interventions • COLLECTING, REPORTING, AND TRACKING OF DATA ON HEALTH CARE ACCESS AND USE, BY PATIENTS' RACE/ETHNICITY Unequal Treatment found that the appropriate systems to track and monitor racial and ethnic disparities in health care are lacking and that less is known about the disparities affect ing minority groups other than African Americans (Hispanics, Asian Americans, Pacific Islanders, Native Americans, and Alaskan Natives). For instance, only in the mid-1980s did the Medicare database begin to collect data on patient groups outside the standard categories of "white," "black," and "other." Federal, private, and state-supported datacollection efforts are scattered and unsystematic, and many health care systems and hospitals still do not collect data on the race, ethnicity, or primary language of enrollees or patients. A survey by the Institute for Diversity in Health Management and

the Health Research and Educational Trust in 2015 found that 98% of 1083 U.S. hospitals col lected information on race, 95% collected data on ethnicity, and 94% collected data on primary language. However, only 45% collected data on race, 40% collected data on ethnicity, and 38% collected data on primary language to benchmark gaps in care. A survey by America's Health Insurance Plans Foundation in 2008 and 2010 showed that the proportion of enrollees in plans that collected race/ethnicity data of some type increased from 75 to 79%; however, the total percentage of plan enrollees whose race/ethnicity and language are recorded is still much lower than these figures. COLLECTING, REPORTING, AND TRACKING OF SDOH DATA In 2014, the IOM Committee on Recommended Social and Behavioral Domains and Measures for Electronic Health Records recommended the routine collection, in the electronic health record, of a parsimonious panel of clinically significant SDOH measures that may be obtained by self-

report in advance of or during the health care encounter and, when used together, provide a psychosocial vital sign. The IOM-recommended questionnaire includes 25 items addressing the following domains: race

and ethnicity, education, financial resource strain, stress, depression, physical activity, tobacco use, alcohol use, social connection or isola tion, intimate partner violence, residential address, and geocoded cen sus tract median income. Implementation studies have demonstrated that collection of these data takes about 5 minutes, and both patients and providers saw this data collection as appropriate and important. Given that data access and monitoring is an essential component to disparities elimination, we highlight several important sources of upto-date racial/ethnic disparities monitoring initiatives that are available to the general public and are updated regularly. We highlight only three examples of national data sources.

PART 1 The Profession of Medicine • Since 2003, the Agency for Healthcare Research and Quality has led the yearly compilation of The National Healthcare Quality and Disparities Report, which reports trends for measures related to access to health care, affordable care, care coordination, healthy liv ing, patient safety, and the quality of care across acute and chronic disease management by race/ethnicity, income, and other SDOH (https://www.ahrq.gov/research/findings/nhqrdr/index.html). • Since 2011, the Geospatial Research, Analysis, and Services Program (GRASP) created and maintains the CDC SVI. This database maps, for all U.S. Census tracts, 15 social factors (grouped in four SDOH categories: socioeconomic status, housing composition and disabil ity, minority status and language, and housing and transportation) and is updated every 2 years (https://www.atsdr.cdc.gov/placeand health/svi/index.html). • Launched in 2018, the Health Opportunity and Equity (HOPE) Ini tiative benchmarks and tracks 27 indicators by race, ethnicity, and socioeconomic status. The indicators measure social and economic factors, community and safety, physical environment, access to health care, and health outcomes for the United States (https://www. nationalcollaborative.org/our-programs/hope-initiative-project/). INCREASE INSURANCE COVERAGE AND ACCESS Lack of access to high-quality health care is an important driver of racial/ethnic dispari ties. Signed into law in 2010, the Affordable Care Act (ACA) funda mentally transformed health insurance by decreasing the uninsured population from 16.3% in 2010 (~49.9 million) to 8.8.% in 2016 (~28.1 million) to 7.7% in early 2023. This represents the largest expansion of health insurance since the creation of Medicare and Medicaid in 1965. Prior to the ACA, non-Hispanic blacks were 70% and Hispan ics nearly three times more likely to be uninsured than non-Hispanic whites. Of note, Medicaid

expansion accounted for an estimated 60% of the ACA's effect through a combination of expanded eligibility and increased enrollment of previously eligible but unenrolled people. This is important given the higher number of racial/ethnic minorities who obtain insurance through Medicaid. Many studies have demon strated that increased insurance coverage has also translated to greater improvement for blacks and Hispanics in access to care, more access to a usual source of care, and improved health outcomes. In 2023, as Medicaid returns to normal eligibility rules following the end of the COVID-19 public health emergency, many Americans are likely to transition out of Medicaid coverage with the concomitant risk of returning to high uninsurance rates in the United States among poor people and racial/ethnic minorities. ENCOURAGEMENT OF THE USE OF EVIDENCE-BASED GUIDELINES AND QUALITY IMPROVEMENT Unequal Treatment highlights the subjec tivity of clinical decision-making as a potential cause of racial and ethnic disparities in health care by describing how clinicians—despite the existence of well-delineated practice guidelines—may offer (con sciously or unconsciously) different diagnostic and therapeutic options to different patients on the basis of their race or ethnicity. Therefore, the widespread adoption and implementation of evidence-based guide lines is a key recommendation in eliminating disparities. For instance, evidence-based guidelines are now available for the management of diabetes, HIV/AIDS, cardiovascular diseases, cancer screening and management, and asthma—all areas where significant disparities exist. As part of ongoing quality-improvement efforts, particular attention should be paid to the implementation of evidence-based guidelines for all patients, regardless of their race and ethnicity.

SUPPORT FOR THE USE OF LANGUAGE INTERPRETATION SERVICES IN THE CLINICAL SETTING As described previously, a lack of efficient and effective interpreter services in a health care system can lead to patient dissatisfaction, to poor comprehension and adherence, and thus to ineffective/lower-quality care for patients with limited English proficiency. Unequal Treatment's recommendation to support the use of interpretation services has clear implications for delivery of quality health care by improving doctors' ability to communicate effectively with these patients. INCREASES IN THE PROPORTION OF UNDERREPRESENTED MINORI TIES IN THE HEALTH CARE WORKFORCE Data for 2021 from the Association of American Medical Colleges indicate that of active phy sicians, 63.9% identified as white, 6.9% identified as Hispanic, 5.7% identified as black or African American, and 0.3% identified as Native American or Alaskan Natives. Furthermore, U.S. national data show that only 3.6% of full-time faculty are black or African American, and 5.5% are Hispanic, Latino, or of Spanish origin (alone or in combina tion with another race/ethnicity), compared to 63.9% who identified as white. Longitudinal data demonstrate that minority faculty are more likely to be at or below the rank of assistant professor, whereas whites composed the highest proportion of full professors. Similarly, several studies have found that both Hispanic and black faculty were promoted at lower rates than their white counterparts. Despite representing ~30% of the U.S. population (a number projected to almost double by 2050), minority students are still underrepresented in medical schools. In 2018, matriculates to U.S. medical schools were 6.2% Latino, 7.1% African American, 0.1% Native Hawaiian or Other Pacific Islander, and 0.2% Native American or Alaskan Native. These percentages have decreased or remained nearly the same since 2007. It will be difficult to develop a diverse physician workforce that can meet the needs of an increasingly diverse population without dramatic changes in the racial and ethnic composition of medical student bodies. Long-term investment in pathway programs and the nearly universal adoption of holistic admissions (a process by which schools consider each applicant individually to determine how they might contribute to the learning environment and the workforce instead of

relying just on test scores and grades) have produced modest results. Institutional change in medical schools, focused on creating nurturing, inclusive, and equity-focused environments that dismantle the structural racism that has created the opportunity gap faced by many minority students, is needed to address this important workforce challenge. Provider Interventions • INTEGRATION OF CROSS-CULTURAL EDUCATION INTO THE TRAINING OF ALL HEALTH CARE PROFESSIONALS

The goal of cross-cultural education is to improve providers' ability to understand, communicate with, and care for patients from diverse backgrounds. Such education focuses on enhancing awareness of sociocultural influences on health beliefs and behaviors and on build ing skills to facilitate understanding and management of these factors in the medical encounter. Cross-cultural education includes curricula on health care disparities, use of interpreters, and effective communi cation and negotiation across cultures. These curricula can be incor porated into health professions training in medical schools, residency programs, nursing schools, and other health professions programs, and can be offered as a component of continuing education. Despite the importance of this area of education and the attention it has attracted from medical education accreditation bodies, a national survey of senior resident physicians by Weissman and colleagues found that up to 28% felt unprepared to deal with cross-cultural issues, including caring for patients who have religious beliefs that may affect treatment, patients who use complementary medicine, patients who have health beliefs at odds with Western medicine, patients who mistrust the health care system, and new immigrants. In a study at one medical school, 70% of fourth-year students felt inadequately prepared to care for patients with limited English proficiency. Efforts to incorporate crosscultural education into medical education will contribute to improving communication and to providing a better quality of care for all patients.

INCORPORATION OF TEACHING ON THE IMPACT OF RACE, ETHNICITY, AND CULTURE ON CLINICAL DECISION-MAKING Unequal Treatment and more recent studies found that stereotyping by health care provid ers can lead to disparate treatment based on a patient's race or ethnicity. The Liaison Committee on Medical Education, which accredits medi cal schools, issued a directive that medical education should include instruction on how a patient's race, ethnicity, and culture might uncon sciously impact communication and clinical decision-making. Patient Interventions Difficulty navigating the health care sys tem and obtaining access to care can be a hindrance to all populations, particularly to minorities. Similarly, lack of empowerment or involve ment in the medical encounter by minorities can be a barrier to care. Patients need to be educated on how to navigate the health care system and how best to access care. Interventions should be used to increase patients' participation in treatment decisions. General Recommendations • INCREASE AWARENESS OF RACIAL/ ETHNIC DISPARITIES IN HEALTH CARE Efforts to raise awareness of racial/ethnic health care disparities have done little for the general public but have been fairly successful among physicians, according to a Kaiser Family Foundation report. In 2006, nearly 6 in 10 people sur veyed believed that blacks received the same quality of care as whites, and 5 in 10 believed that Latinos received the same quality of care as whites. These estimates are similar to findings in a 1999 survey. Despite this lack of awareness, most people believed that all Americans deserve quality care, regardless of their background. In contrast, the level of awareness among physicians has risen sharply. In 2002, the majority (69%) of physicians said that the health care system "rarely or never" treated people unfairly on the basis of their racial/ethnic background. In 2005, less than one-quarter (24%) of physicians disagreed with the statement that "minority

patients generally receive lower-quality care than white patients.” More recently, a survey by WebMD showed that 42% of 16,000 physicians admitted that their own personal biases impact their clinical decision-making, including on characteristics such as race and ethnicity. Increasing awareness of racial and ethnic health disparities, and their root causes, among health care profession als and the public is an important first step in addressing these dispari ties. The ultimate goals are to generate discourse and to mobilize action to address disparities at multiple levels, including health policymakers, health systems, and the community. CONDUCT FURTHER RESEARCH TO IDENTIFY SOURCES OF DIS PARITIES AND PROMISING INTERVENTIONS While the literature that formed the basis for the findings reported and recommendations made in Unequal Treatment provided significant evidence for racial and ethnic disparities, additional research is needed in several areas. First, most of the literature on disparities focuses on black-versus-white dif ferences; much less is known about the experiences of other minority groups. Improving the ability to collect racial and ethnic patient data should facilitate this process. However, in instances where the neces sary systems are not yet in place, racial and ethnic patient data may be collected prospectively in the setting of clinical or health services research to more fully elucidate disparities for other populations. Second, much of the literature on disparities to date has focused on defining areas in which these disparities exist, but less has been done to identify the multiple factors that contribute to the disparities or to test interventions to address these factors. There is clearly a need for research that identifies promising practices and solutions to disparities. ■ ■IMPLICATIONS FOR CLINICAL PRACTICE Individual health care providers can do several things in the clinical encounter to address racial and ethnic disparities in health care. Be Aware That Disparities Exist Increasing awareness of racial and ethnic disparities among health care professionals is an important first step in addressing disparities in health care. Only with greater awareness can care providers be attuned to their behavior in clinical practice and thus monitor that behavior and ensure that all patients receive the highest quality of care, regardless of race, ethnicity, or culture.

Practice Culturally Competent Care Previous efforts have been made to teach clinicians about the attitudes, values, beliefs, and behaviors of certain cultural groups—the key practice “dos and don’ts” in caring for “the Hispanic patient” or the “Asian patient,” for example. In certain situations, learning about a particular local community or cultural group, with a goal of following the principles of community- oriented primary care, can be helpful; when broadly and uncritically applied, however, this approach can actually lead to stereotyping and oversimplification of culture, without respect for its complexity.

CHAPTER 11 Cultural competence has thus evolved from merely learning infor mation and making assumptions about patients on the basis of their backgrounds to focusing on the development of skills that follow the principles of patient-centered care. Patient-centeredness encompasses the qualities of compassion, empathy, and responsiveness to the needs, values, and expressed preferences of the individual patient. Cultural competence aims to take things a step further by expanding the reper toire of knowledge and skills classically defined as “patient-centered” to include those that are especially useful in cross-cultural interactions (and that, in fact, are vital in all clinical encounters). This repertoire includes effectively using interpreter services, eliciting the patient’s understanding of their condition, assessing decision-making prefer ences and the role of family, determining the patient’s views about biomedicine versus complementary and alternative medicine, recog nizing sexual and gender issues, and building trust. For example, while it is important to understand all patients’ beliefs about health, it may be particularly crucial to

understand the health beliefs of patients who come from a different culture or have a different health care experi ence. With the individual patient as teacher, the physician can adjust their practice style to meet the patient’s specific needs. Racial and Ethnic Disparities in Health Care Avoid Stereotyping Several strategies can allow health care provid ers to counteract, both systemically and individually, the normal tendency to stereotype. For example, when racially/ethnically/culturally/socially diverse teams in which each member is given equal power are assembled and are tasked to achieve a common goal, a sense of camaraderie devel ops and prevents the development of stereotypes based on race/ethnicity, gender, culture, or class. Thus, health care providers should aim to gain experiences working with and learning from a diverse set of colleagues. In addition, simply being aware of the operation of social cognitive fac tors allows providers to actively check up on or monitor their behavior. Physicians can constantly reevaluate to ensure that they are offering the same things, in the same ways, to all patients. Understanding one’s own susceptibility to stereotyping—and how disparities may result—is essen tial in providing equitable, high-quality care to all patients. Work to Build Trust Patients’ mistrust of the health care system and of health care providers impacts multiple facets of the medical encounter, with effects ranging from decreased patient satisfaction to delayed care. Although the historic legacy of discrimination can never be erased, several steps can be taken to build trust with patients and to address disparities. First, providers must be aware that mistrust exists and is more prevalent among minority populations, given the history of discrimination in the United States and other countries. Second, providers must reassure patients that they come first, that everything possible will be done to ensure that they always get the best care avail able, and that their caregivers will serve as their advocates. Third, interpersonal skills and communication techniques that demonstrate honesty, openness, compassion, and respect on the part of the health care provider are essential tools in dismantling mistrust. Finally, patients indicate that trust is built when there is shared, participatory decision-making and the provider makes a concerted effort to under stand the patient’s background. When the doctor–patient relationship is reframed as one of solidarity, the patient’s sense of vulnerability can be transformed into one of trust. The successful elimination of disparities requires trust-building interventions and strengthening of this relationship. ■ ■CONCLUSION The issue of racial and ethnic disparities in health care has gained national prominence, both with the release of the IOM report Unequal

12 - 12 Ethical Issues in Clinical Medicine

12 Ethical Issues in Clinical Medicine

Treatment and with more recent articles that have confirmed their persistence and explored their root causes. Furthermore, another influential IOM report, Crossing the Quality Chasm, has highlighted the importance of equity—i.e., no variations in quality of care due to personal characteristics, including race and ethnicity—as a central principle of quality. Current efforts in health care reform and transfor mation, including a greater focus on value (high-quality care and cost control), will sharpen the nation's focus on the care of populations who experience low-quality, costly care. Addressing disparities will become a major focus, and there will be many obvious opportunities for inter ventions to eliminate them. Greater attention to addressing the root causes of disparities will improve the care provided to all patients, not just those who belong to racial and ethnic minorities.

PART 1 The Profession of Medicine ■ ■FURTHER READING Buchmueller TC et al: The ACA's impact on racial and ethnic dis parities in health insurance coverage and access to care. Health Aff (Millwood) 39:395, 2020. Dwyer-lindgren L et al: Inequalities in life expectancy among us counties, 1980 to 2014: Temporal trends and key drivers. JAMA Intern Med 177:1003, 2017. Kreuter MW et al: Addressing social needs in health care settings: Evidence, challenges and opportunities for public health. Annu Rev Public Health 42:11, 2021. Krieger N: Measures of racism, sexism, heterosexism, and gender binarism for health equity research: From structural injustice to embodied harm: An ecosocial analysis. Annu Rev Public Health 41:37, 2020. LaVeist TA et al: The economic burden of racial, ethnic, and educa tional health inequities in the US. JAMA 329:1682, 2023. Medscape: Medscape Lifestyle Report 2016: Bias and burnout. http://www.medscape.com/features/slideshow/lifestyle/2016/public/overview. Vyas DA et al: Hidden in plain sight: Reconsidering the use of race cor rection in clinical algorithms. N Engl J Med 383:874, 2020. Williams DR et al: Racism and health: Evidence and needed research. Annu Rev Public Health 40:105, 2019. Christine Grady, Bernard Lo

Ethical Issues in Clinical Medicine Physicians face both enduring and novel ethical dilemmas that can be perplexing and emotionally draining and can sometimes lead to moral distress. For example, physicians may worry about the intensity of care that is appropriate at the end of life, how to distribute time between critically ill patients, or their responsibilities for patients with

limited access to needed care. Newer technologies such as artificial intelligence promise more coordinated and efficient care, but also raise concerns about confidentiality, the doctor–patient relationship, and accountability. New social and economic developments, such as greater attention to health disparities and the growth of for-profit enterprises, present additional issues. This chapter suggests how physicians can address important vexing ethical issues they encounter in their work. Physicians make ethical judgments about clinical situations every day and should prepare for lifelong learning about ethical issues so they can respond appropriately. Traditional professional codes and ethical principles provide instructive guidance but need to be interpreted and applied to each situation. When facing a challenging ethical issue, phy sicians may need to reevaluate their basic convictions, tolerate uncer tainty, and act in a manner that maintains their integrity. Physicians

should articulate their concerns and reasoning, listen to and respect the views of others involved in the patient's care, and utilize available resources, including members of the interdisciplinary health care team as well as ethics consultants in some cases. Ethics consultation services or a hospital ethics committee can help to clarify issues and identify strategies for resolution, including improving communication and dealing with strong or conflicting emotions. Through these efforts, physicians can gain deeper insight into the ethical issues they face and reach mutually acceptable resolutions to complex problems. APPROACHES TO ETHICAL PROBLEMS Several approaches are useful for addressing ethical issues, including approaches based on ethical principles, virtue ethics, professional oaths, and personal values. Sometimes these various sources of guid ance may seem to conflict. In a diverse society, different individuals may turn to different sources of moral guidance. In addition, general moral precepts often need to be interpreted and applied to particular clinical situations. ■ ■ETHICAL PRINCIPLES Ethical principles serve as general guidelines to help physicians deter mine the right thing to do. Respecting Patients Physicians should always treat patients with respect, which entails understanding patients' goals, providing infor mation, communicating effectively, obtaining informed and voluntary consent, respecting informed refusals, and protecting confidentiality. Different clinical goals and approaches are often feasible, and interven tions can result in both benefit and harm. Individuals differ in how they value health and medical care and weigh the benefits and risks of medical interventions. Generally, physicians should respect patients' values and informed choices. Respect is especially important when patients are responding to experiences of, or concerns about, disrespect and discrimination. Physicians should consider patient confidentiality, professional boundaries, and therapeutic relationships in all spoken and written communications. GOALS AND TREATMENT DECISIONS Physicians should provide rel evant and accurate information for patients about current clinical circumstances, diagnoses, expected future course, prognosis, treatment options, and uncertainties, and discuss how different options might realize patients' goals of care. Physicians may be tempted to withhold a serious diagnosis, misrepresent it by using ambiguous terms, or limit discussions of prognosis or risks for fear that patients will become anxious or depressed. However, providing honest information about clinical situations promotes patients' autonomy and trust. When shar ing bad news with patients, physicians should adjust the pace of dis closure, offer empathy and hope, provide emotional support, and call on other resources such as spiritual care or social work. Some patients may choose not to receive such information or may ask surrogates to make decisions on their behalf, as is common with serious diagnoses in some cultures. SHARED DECISION-MAKING AND OBTAINING INFORMED CONSENT

Physicians should engage in shared decision-making with patients, whenever appropriate. Physicians promote shared decision-making by informing and educating patients, eliciting and answering their questions, checking that they understand key issues, making recom mendations, and helping them to deliberate. Medical jargon, needlessly complicated explanations, or the provision of too much information at once may overwhelm patients. Increasingly, decision aids can help patients play a more active role in decision-making, improve the accu racy of their perception of risk and benefit, and help them clarify their values and goals. Informed consent is more than obtaining signatures on consent forms and involves disclosure of honest and understand able information to promote understanding and choice. Competent, informed patients may refuse recommended interventions and choose among reasonable alternatives. In an emergency, treatment can be given without informed consent if patients cannot give their own consent and delaying treatment while surrogates are contacted would

jeopardize patients' lives or health. People are presumed to want such emergency care unless they have previously indicated otherwise, such as through a portable order for life-sustaining treatment (POLST). Respect for patients does not entitle patients to insist on any care or treatment that they want. Physicians are not obligated to provide inter ventions that have no physiologic rationale, have already failed, or are contrary to evidence-based practice recommendations or good clinical judgment. Public policies and laws also dictate certain decisions—e.g., allocation of scarce medical resources during public health crises such as the COVID-19 pandemic, use of cadaveric organs for transplanta tion, and responding to requests for physician aid in dying. CARING FOR PATIENTS WHO LACK DECISION-MAKING CAPACITY

Patients with decision-making capacity can express choices and appre ciate their medical situation; the nature, risks, and benefits of proposed care; and the consequences of each alternative. Patient choices should be consistent with their values and not the result of delusions, hal lucinations, or misinformation. Physicians should use available and validated assessment tools, resources such as psychiatry or ethics consultation, and clinical judgment to ascertain whether individuals have the capacity to make decisions for themselves. Some patients are unable to make informed decisions because of unconsciousness, advanced dementia, delirium, or other medical conditions that impair cognition. Courts have the legal authority to determine that a patient is legally incompetent, but physicians usually determine when patients lack the capacity to make particular health care decisions and arrange for authorized surrogates to make decisions, without involving the courts. Patients who disagree with recommendations or refuse treat ment should not be assumed to lack capacity. Such decisions should be probed, however, to ensure the patient is not deciding based on misunderstandings and has the capacity to make an informed decision. When impairments are fluctuating or reversible, decisions should be postponed if possible and revisited when the patient recovers decisionmaking capacity. Physicians seek an appropriate surrogate for patients who lack decision-making capacity. Patients may designate a health care proxy through a POLST or an advance directive; such choices should be respected (see Chap. 13). For patients who lack decision-making capacity and have not previously designated a health care proxy, family members usually serve as surrogate decision-makers. Statutes in most U.S. states delineate a priority order of relatives to make medical deci sions. For unrepresented patients who do not have relatives or friends who can be found and no previously appointed proxy, making deci sions presents difficult dilemmas and should follow a fair and careful institutional or legal process. Patients' values, goals, and previously expressed preferences, when known, should guide surrogate decisions. However,

the patient’s current best interests may sometimes justify overriding earlier preferences if an intervention is likely to provide significant benefit, previous statements do not fit the situation well, or the patient gave the surrogate leeway in decisions. MAINTAINING CONFIDENTIALITY Maintaining confidentiality is essential to respecting patients’ autonomy and privacy; it encourages patients to seek treatment and discuss problems candidly. However, confidentiality may be overridden to prevent serious harm to third parties or to the patient. Exceptions to confidentiality are justified when the risk is serious and probable, no less restrictive measures can avert risk, and the adverse effects of overriding confidentiality are minimized and deemed acceptable by society. For example, laws require physicians to report cases of tuberculosis, sexually transmitted infections, elder or child abuse, and domestic violence. Beneficence or Acting in Patients’ Best Interests The prin ciple of beneficence requires physicians to act for the patient’s benefit. Patients typically lack medical expertise, and illness often makes them vulnerable. Patients rely on and trust physicians to treat them with compassion and provide sound recommendations and treatments aimed to promote their well-being. Physicians encourage such trust and have a fiduciary duty to act in the best interests of patients, which should prevail over physicians’ self-interest or the interests of third

parties such as hospitals or insurers. A related principle, “first do no harm,” obliges physicians to prevent unnecessary harm by recom mending interventions that maximize benefit and minimize harm and forbids physicians from providing known ineffective interventions or acting without due care. Although often cited, this precept alone provides limited guidance because many beneficial interventions also pose serious risks.

CHAPTER 12 Physicians often provide care within interdisciplinary teams and rely on consultation with or referral to specialists. Team members and consultants contribute different expertise to the provision of compre hensive, high-quality care for patients. Physicians should collaborate with and respect the contributions of interdisciplinary team members and should initiate and participate in regular communication and plan ning to avoid diffusion of responsibility and ensure accountability for quality patient care. Ethical Issues in Clinical Medicine INFLUENCES ON PATIENTS’ BEST INTERESTS Conflicts arise when patients’ refusals or requests for interventions thwart their own goals for care, cause serious harm, or jeopardize their best medical inter ests. For example, simply accepting a young asthmatic adult’s refusal of mechanical ventilation for readily reversible respiratory failure, in the name of respecting autonomy, is morally constricted. Physicians should elicit patients’ expectations and concerns, correct their misun derstandings, and try to persuade them to accept beneficial therapies. If disagreements persist after such efforts, physicians should call on institutional resources for assistance, but patients’ informed choices and views of their own best interests should prevail. Drug prices and out-of-pocket expenses for patients have escalated in many parts of the world and may compromise care in the patients’ best interests. Physicians should recognize that patients, especially those with high copayments or inadequate insurance, may not be able to afford prescribed tests and interventions. Physicians should strive to prescribe indicated medications that are affordable and acceptable to the patient. Knowing what kind of insurance, if any, the patient has and whether certain medications are likely to be covered may help in determining appropriate prescriptions. Physicians or their team should follow up with patients who don’t fill prescriptions, don’t take their medications, or skip doses to explore whether cost and affordability are obstacles. Clinical pharmacists, technicians, or social workers can help the prescribing physician appeal for coverage or find funding for needed medications. It may be reasonable for physicians to advocate for coverage of nonformulary products for sound reasons,

such as when the formulary drugs are ineffective or not tolerated. Organizational policies and workplace conditions may sometimes conflict with patients' best interests. Physicians' focus and dedication to the well-being and interests of patients may be negatively influenced by perceived or actual staffing inadequacies, unfair wages, deficiencies in equipment or infrastructure, work-hour limitations, corporate culture, violence, and other risks in the workplace. Physicians should work with institutional leaders to ensure that policies and practices support their ability to provide quality care focused on patients' best interests. Patients' interests are served by the increasing use of evidence-based practice guidelines and performance benchmarking. However, practice guideline recommendations may not serve the interests of each indi vidual patient when another plan of care would provide substantially greater benefits. In prioritizing their duty to act in the patient's best interests, physicians should be familiar with relevant practice guide lines, be able to recognize situations that might justify exceptions, and advocate for reasonable exceptions. Acting Justly The principle of justice provides guidance to physi cians about how to ethically treat patients and make decisions about allocating important resources, including their own time. Justice in a general sense means fairness: people should receive what they deserve or are owed. Justice also entails similar treatment of people who are similar in ethically relevant ways, in order to avoid arbitrary, biased, and unfair decisions. Justice forbids discrimination in health care based on race, religion, gender, sexual orientation, disability, age, or other personal characteristics (Chap. 11). Distributive justice requires fair

and equitable allocation of limited health care resources, which should be distributed equally or according to relevant moral considerations such as need, probability of benefit, or other factors.

ALLOCATION OF RESOURCES Universal access to medically needed health care remains an unrealized moral aspiration in the United States and around the world. Patients with no or inadequate health insurance, especially those with chronic diseases, often cannot afford needed care and lack access to safety-net services. Even among insured patients, insurers sometimes deny coverage for interventions recommended by their physician. Physicians should advocate for patients' affordable access to indicated care, try to help patients obtain needed care, and work with institutions and policies to promote wider access. PART 1 The Profession of Medicine Allocation of health care resources is unavoidable when resources are limited, such as during medication shortages due to manufacturing and quality problems or during public health crises. Allocation policies should be fair, transparent, accountable, responsive to the concerns of those affected, and proportionate to the situation, including the supply relative to the need. Difficult decisions about allocation of available scarce resources are inevitable. A fair process should aim to prioritize patients who are likely to have a large and irreversible decrement in health outcomes without the interventions; avoid discrimination; mitigate health disparities; save the most lives; and promote the good of the community. First-come, first-served allocation is often not fair, because it disad vantages patients who experience barriers to accessing care. To avoid discrimination, allocation decisions should not consider personal social characteristics such as race, gender, or disability, nor consider insurance status or wealth. Allocation policies should aspire to reduce health care disparities often due to social determinants of health including poverty, unhealthy living conditions, and poor access to health care. Fair and well-considered guidelines help mitigate emotional and moral distress for clinicians and patients when difficult allocation decisions are made. Physicians should act as patient advocates within constraints set by society, reasonable insurance policies, and evidencebased practice. Ad hoc resource allocation by individual physicians may be

inconsistent, unfair, and ineffective. Many allocation decisions are made at the institutional or public policy level with physician and public input, for example, decisions and criteria for allocating cadaveric organs for transplantation. ■ ■VIRTUE ETHICS Virtue ethics focuses on physicians' character and qualities, with the expectation that doctors will cultivate virtues such as compassion, trustworthiness, intellectual honesty, humility, and integrity. Propo nents argue that, if such characteristics become ingrained, they help guide physicians in unforeseen situations. Moreover, simply following ethical precepts or principles without any of these virtues could lead to uncaring doctor–patient relationships. ■ ■PROFESSIONAL OATHS AND CODES Professional oaths and codes are useful guides for physicians. Most physicians take oaths during their medical training, and many are members of professional societies with codes of ethics. Physicians pledge to the public and to their patients that they will be guided by the principles and values in these oaths or codes and commit to the spirit of the ethical ideals and precepts represented in oaths and professional codes of ethics. ■ ■PERSONAL VALUES Personal values, cultural traditions, and religious beliefs are important sources of personal morality that help physicians address ethical issues and cope with any moral distress they may experience in practice. While essential, personal morality alone is a limited ethical guide in clinical practice. Physicians have role-specific ethical obligations that go beyond their obligations as good people, including the duties to obtain informed consent and maintain confidentiality discussed earlier. Furthermore, in a culturally and religiously diverse world, physicians should expect that many patients and colleagues will have personal moral beliefs that differ from their own.

ETHICALLY COMPLEX PROFESSIONAL ISSUES FOR PHYSICIANS ■ ■CLAIMS OF CONSCIENCE Some physicians, based on personal values, have legally protected conscientious objections to providing, or referring patients for, certain treatments such as contraception, abortion, or physician aid in dying. Although physicians should not be asked to violate deeply held moral beliefs or religious convictions, patients need medically appropriate and timely care, rely on physicians for medical advice, and should always be treated with respect. Institutions such as clinics and hospitals have a collective ethical duty to provide medical care that will avert serious risks and suffering to patients while accommodating health care workers' conscientious objections—for example, when possible, by arranging for another professional to provide the service in ques tion or by referral to another institution. Ethically, patients seeking a relationship with a doctor or health care institution should be notified in advance of any conscientious objections to the provision of specific interventions. Since insurance often constrains patients' selection of physicians or health care facilities, switching providers can be prob lematic after an illness is recognized. There are also important limits on claims of conscience. Health care workers may not insist that patients receive unwanted medical interventions or refuse to treat or illegally discriminate against patients because of their race, ethnicity, disability, genetic information, or diagnosis. Refusal to treat patients because of personal characteristics, such as sexual orientation, gender identity, or immigration status is ethically inappropriate because it falls short of helping patients in need and respecting them as persons. Importantly, some physicians may object to laws, institutional policies, or insurance policies that restrict them from providing or even describing medically appropriate care to their patients. In some of these cases, work arounds are justified on the ethical basis of sound clinical practice. ■ ■PHYSICIAN AS GATEKEEPER In some cases, patients may ask their physicians to facilitate access to services that the physician has ethical and clinical qualms about providing. For example, a patient might request a prescription for a cognitive enhancing medication to temporarily augment cognitive abilities in order to take an exam or apply for employment, or request that the physician

sign a disability form when the patient does not meet disability criteria. Patients may request more pain medication than the physician believes is warranted for the given situation, or the physician may feel uncomfortable prescribing attention-deficit/hyperactivity disorder medications to a young child because of concerns that the possible benefit does not justify the risks despite the parent's request. In these and similar circumstances, the physician should work with the patient or parent to understand reasons for their requests, some of which might be legitimate. In addition to considering possible risks and benefits to the patient, the physician should consider how meeting the request might affect other patients, societal values, and public trust in the medical profession. If the physician determines that fulfilling the request requires deception, is unfair, jeopardizes professional responsi bilities, could undermine the physician's credibility or trustworthiness, or is inconsistent with the patient's best medical interests, the physician should decline and explain the reasons to the patient. ■ ■OCCUPATIONAL RISKS AND BURDENS Physicians accept some risks in fulfilling their professional responsi bilities, including exposure to infectious agents or toxic substances, abuse from patients or families, distress, and violence or threats in the workplace. Nonetheless, most physicians, nurses, and other hospital staff willingly care for patients, despite personal risk, grueling hours, and sometimes inadequate resources or information. Health care institutions are responsible for preventing and addressing occupational risks and burdens and for providing proper information, training and supervision, resources, infrastructure and workflow modifications, and emotional and psychological support. Clinical leaders should acknowl edge fears about personal safety and take steps to mitigate the impact of work on family responsibilities, moral distress, and burnout.

■ ■MORAL DISTRESS AND WELL-BEING Clinicians, including residents, medical students, and experienced physi cians, experience moral distress when they feel that ethically appropriate action is hindered by institutional policies or culture, decision-making hierarchies, limited resources, or other reasons. Moral distress can lead to anger, anxiety, depression, frustration, fatigue, work dissatisfaction, and burnout. A physician's health and well-being can affect how they care for patients and interact with colleagues. Discussing complex or unfamiliar clinical situations with colleagues and seeking assistance with difficult decisions can help mitigate moral distress, as can a healthy work environment characterized by open communication, mutual respect, adequate support and resources, and an emphasis on the common goal of good patient care. In addition, physicians should take good care of their own health and well-being and be aware of the personal and system factors associated with stress, burnout, and depression. Health care orga nizations should provide a supportive work environment, counseling, and other support services as needed. CONFLICTS OF INTEREST Acting in patients' best interests may sometimes conflict with a physi cian's self-interest or the interests of third parties such as insurers or hospitals. From an ethical viewpoint, patients' interests are paramount. Transparency, appropriate disclosure, and management of conflicts of interest are essential to maintain the trust of patients, colleagues, and the public. Disclosure requirements vary for different purposes, and available software can assist physicians in complying with specific requirements. Importantly, not all conflicts are financial. Physicians sometimes face conflicts of commitment between their patient's inter ests and their own personal interests, professional goals, responsibili ties, and aspirations or the interests of the health care institutions or corporations that employ them. Physicians should prioritize patients' interests while recognizing possible conflicts and use disclosure, dis cussion with institutional officials, and management of the conflict or recusal when appropriate. Medical institutions themselves may have conflicts of interest arising from patent rights, industry-funded research

programs, donations from individuals and companies, and priorities of the health care system, pharmacy benefits managers, insurers, and private equity or corporate owners. Institutions should be transparent about the presence and amount of such relationships and about the steps taken to prevent such relationships from influencing clinical or financial decisions. Institutions should take steps not to benefit from donations or honor donors when there is good evidence that a donor breached ethical or legal standards. ■ ■FINANCIAL INCENTIVES Physicians have financial incentives to improve the quality or effi ciency of care that might lead some to avoid patients who are older, chronically ill, or have more complicated problems, or to focus on benchmarked outcomes even when not in individual patients' best interests. In contrast, fee-for-service payments might encourage physi cians to order more interventions than necessary or to refer patients to laboratory, imaging, or surgical facilities in which they have a financial stake. Regardless of financial incentives, physicians should recommend available care that is in the patient's best interests—no more and no less. ■ ■RELATIONSHIPS WITH PHARMACEUTICAL COMPANIES Financial relationships between physicians and industry are increasingly scrutinized. Many medical centers have banned drug-company gifts, including branded pens or notepads or meals to physicians, to reduce risk of undue influence or subconscious feelings of reciprocity and to decrease possible influences on public trust or the costs of health care. The federal Open Payments website provides public information on the payments and amounts that drug and device companies give to individual physicians. The challenge is to distinguish payments for scientific consulting and research contracts—which should be encour aged as promoting professional and academic missions—from those for promotional speaking and other activities that aim to increase sales of company products.

■ ■LEARNING CLINICAL SKILLS Medical students', residents', and physicians' interests in learning, which fosters the long-term goal of benefiting future patients, may sometimes conflict with the short-term goal of providing optimal care to current patients. When trainees are learning procedures on patients, they lack the proficiency of experienced physicians, and patients may experi ence inconvenience, discomfort, longer procedures, or increased risk. Increasingly, institutions are developing simulation-based clinical skills laboratories and requiring students to demonstrate proficiency before carrying out procedures such as venipuncture and intravenous lines in patients. Furthermore, teaching hospitals are establishing proceduralist services in which procedure-specialist faculty members directly super vise interns for procedures such as lumbar puncture and thoracentesis and certify their proficiency. Medical students may need to defer learn ing such invasive procedures until internship. It is always important to seek patients' consent for trainee participation in their care, par ticularly for intimate examinations, such as pelvic, rectal, breast, and testicular examinations, and for invasive procedures. Patients should be told who is providing care and how trainees are supervised. Failing to introduce students or trainees who will be performing procedures undermines trust, may lead to more elaborate deception, and hin ders patients' informed choices about their care. Most patients, when informed, allow trainees to play an active role in their care.

CHAPTER 12 Ethical Issues in Clinical Medicine ■ ■RESPONSE TO MEDICAL ERRORS Errors are inevitable in clinical medicine, and some errors cause harm to patients. Most errors are caused by lapses of attention or flaws in the system of delivering health care; only a small number result from blameworthy individual behavior. Many health care institutions have adopted a communication and resolution system that encourages open and honest reporting of errors as essential to quality of

care and shifts the focus from individual blame to system redesign for improvement in quality and safety (Chap. 7). This approach is more likely than a punitive approach to improve patient safety. However, professional discipline is appropriate for cases of gross incompetence, reckless behavior, physician impairment, and boundary violations. Physicians and students may fear that disclosing errors will damage their careers. Physicians and health care institutions show respect for patients by disclosing and explaining errors, offering apologies, offering appropri ate compensation for harm done, and using errors as opportunities to improve the quality of care. ■ ■PHYSICIAN IMPAIRMENT Physicians may hesitate to intervene when colleagues impaired by alco hol, drugs, or psychiatric or medical illness place patients at risk. How ever, society relies on physicians to regulate themselves. Colleagues of an impaired physician should take steps to protect patients and help their impaired colleague, starting with reporting their concerns to their clinical supervisor or director, and institutions should have programs in place for assessing physician competence. ETHICAL ISSUES IN CLINICAL RESEARCH Clinical research is essential to translate scientific discoveries into beneficial interventions for patients. However, clinical research raises ethical concerns because participants face inconvenience and risks in research designed to advance scientific knowledge and not specifically to benefit them. Ethical guidelines require researchers to rigorously design and conduct research, minimize risk to participants, and obtain informed and voluntary participant consent and approval from an institutional review board (IRB). IRBs determine whether risks to par ticipants are acceptable and adequately minimized, and recommend appropriate additional safeguards when research includes vulnerable participants. Physicians may be clinical research investigators themselves or in a position to refer or recommend research participation to their patients. Physician-investigators are likely to feel some inherent tension between conducting research and providing health care. Awareness of this ten sion, familiarity with research ethics, collaboration with research and clinical team members, and utilizing research ethics consultation can

13 - 13 Palliative and End-of-Life Care

13 Palliative and End-of-Life Care

help to mitigate tensions. Before starting clinical research, investigators should complete training in the ethics of clinical research, which is widely available. Physicians also should be critical consumers of clini cal research results and keep up with research advances that change standards of practice.

Forms of research that generate knowledge useful for improving health might pose concerns about informed consent, privacy and con fidentiality, and psychosocial risk without physical risks. Research with routinely collected clinical data available in electronic health records, leftover clinical specimens, data from mobile devices, administra tive data, and combinations could encompass traditional discovery research as well as quality improvement, comparative effectiveness research, and learning health care systems. PART 1 The Profession of Medicine EMERGING TECHNOLOGIES Scientific advances in genome sequencing, gene editing (e.g., with CRISPR-Cas9), machine learning, artificial intelligence, brain–computer interfaces, cell-based therapies, and other technologies offer great promise for research and clinical care with the ultimate goal of improv ing the prediction, prevention, and treatment of disease. Groundbreak ing innovations that have strong scientific plausibility still need to be evaluated in rigorous clinical studies for efficacy and safety. Physicians should keep up to date on the status of novel and often complex technologies as research evolves, data emerge, and technolo gies are incorporated into clinical practice. They can help their patients understand research findings and the evidence for clinical use, correct any misunderstandings, facilitate shared decision-making, and advo cate for fair access to such therapies. Furthermore, physicians should engage in professional and public discussion related to allocation of resources and fair access to expensive new therapies and emerging technologies and their impact on overall health care affordability. Certain cell-based therapies, such as peripheral blood stem cell transplantation (Chap. 119) and chimeric antigen receptor (CAR)-T cell therapy (Chap. 78), are approved for use in several serious hema tologic disorders. Somatic cell gene therapies have been approved as safe and effective for clinical use in β thalassemia, hemophilia A, sickle cell disease, and some rare pediatric-onset diseases. Numerous other gene therapy applications are under review by regulatory agencies. The approved therapies have a very high cost, which often limits access. Germline gene editing in blastocysts or embryos raises many ethical questions and is not permitted in the United States and many other countries. Some patients may request cell-based, gene, or other complex, highly technical, and expensive therapies for unproven indications. Yet, claims of cures through unproven stem cell or gene-based “therapies” pose significant health and financial risks to patients without evidence of benefit.

Physicians should help patients distinguish approved thera pies from unproven claims and refer interested patients to well-designed clinical trials. Artificial intelligence (AI) using computers to carry out tasks typi cally done by humans, and machine learning (ML), a type of AI that automatically learns and improves its performance without explicit programming, are increasingly used in clinical practice. AI clinical algorithms are used to make diagnoses using images from radiology studies, retinal scans, pathology slides, or skin photographs; to search for potential diagnoses associated with a genomic sequence; and to predict outcomes for patients, such as surgical complications, hospital readmissions, or not coming to scheduled appointments. Physicians should use these predictive algorithms when they are confident that they are clinically meaningful, are unbiased, and do not lead to worse patient outcomes. Generative AI, large language models (LLMs), or chatbots (Chap. 501) promise to help reduce burdensome adminis trative tasks that contribute to health care worker burnout, such as drafting clinical notes and summaries for patients and writing letters to obtain authorization or appeal denials of insurance coverage. Although rapidly evolving in sophistication, LLMs can sometimes “hallucinate” and provide false information. Physicians should be confident that the LLM or bots they use are providing medically accurate information and advice. Collaboration between AI developers and clinicians can

utilize the strengths of each. The impact of AI on clinician workflow and satisfaction, as well as patient outcomes, needs to be assessed. Physicians should stay informed of emerging evidence about such technologies and the ethical challenges that accompany their use and always keep their patients’ best interests and informed preferences at the forefront. GLOBAL CONSIDERATIONS ■ ■INTERNATIONAL RESEARCH Clinical research is often conducted across multiple sites and across national borders. Societal, legal, and cultural norms and perspectives about research may vary, and there are many ethical challenges. Physician-investigators involved in international research should be familiar with federal regulations, applicable international regulatory and good clinical practice guidelines, as well as national and local laws where research is taking place. Partnering with local researchers and communities is essential not only to demonstrate respect but also to facilitate successful clinical research. ■ ■INTERNATIONAL CLINICAL EXPERIENCES Providing patient care in international settings can be a humanitarian service and/or broaden clinical experience. Such arrangements, how ever, raise ethical challenges—for example, as a result of differences in beliefs about health and illness, expectations regarding health care and physicians’ roles, standards of clinical practice, resource limitations, and cultural norms regarding disclosure and other issues. Visiting physicians and trainees should receive training and mentoring about cultural and clinical practices in the host community, respect local cus toms and values, collaborate closely with local professionals and staff, and recognize their own limits. ■ ■CONCLUSION Ethical issues are common in clinical medicine and occur in circum stances that may be foreseeable, novel, or unexpected. Physicians address these ethical issues by being prepared, informed, and reflective, and using appropriate available resources. ■ ■FURTHER READING Beauchamp T, Childress J: Principles of Biomedical Ethics, 8th ed. New York, Oxford University Press, 2019. Berwick D: Salve Lucrum: The existential threat of greed in US health care. JAMA 329:629, 2023. Harris L: Divisions, new and old: Conscience and religious freedom at HHS. N Engl J Med 378:1369, 2018. Hightower M et al: Is medicine ready for AI: Intention to treat epi sode 6. N Engl J Med 388:e49, 2023. National Academy of Medicine. Action Collaborative on Clinician Wellbeing and Resilience. https://nam.edu/initiatives/clinician-resilience-

and-well-being/. Ezekiel J. Emanuel, John W. Urwin

Palliative and

End-of-Life Care EPIDEMIOLOGY ■ ■CAUSES OF DEATH In 2019, before the COVID-19 pandemic, 2,854,838 individuals died in the United States (Table 13-1). Approximately 74% of these deaths occurred in those aged ≥65 years. The epidemiology of death has changed significantly since 1900 and even since 1980. In 1900, heart

TABLE 13-1 Ten Leading Causes of Death in the United States and Britain UNITED STATES (2019) ENGLAND AND WALES (2019) NUMBER OF DEATHS, ALL AGES (%) CAUSE OF DEATH All deaths 2,854,838 2,117,332 530,841 449,047 Heart diseasea 659,041 (23.1) 531,583 (25.1) 87,095 (16.4) 74,967 (16.7) Malignant neoplasms 599,601 (21.0) 435,462 (20.6) 147,419 (27.8) 118,982 (26.5) Chronic lower respiratory diseases 156,979 (5.5) 133,246 (6.3) 31,221 (5.9) 28,235 (6.3) Accidents 173,040 (6.1) 60,527 (2.9) 15,141 (2.9) 8999 (2.0) Cerebrovascular diseases 150,005 (5.3) 129,193 (6.1) 29,816 (5.6) 27,210 (6.0) Alzheimer's disease 121,499 (4.3) 120,090 (5.7) 20,400 (3.8) 20,279 (4.5) Diabetes mellitus 87,647 (3.1) 62,397 (2.9) 6528 (1.2) 5552 (1.2) Influenza and pneumonia 49,783 (1.7) 40,399 (1.9) 26,398 (5.0) 24,269 (5.4) Nephritis, nephritic syndrome, nephrosis 51,565 (1.8) 42,230 (2.0) 3575 (0.7) 3323 (0.7) Intentional self-harm 47,511 (1.7) — 4832 (0.9) 751 (0.2) aCalculated using International Classification of Diseases codes I00–I09, I11, I13, I20–I51. Source: National Center for Health Statistics (United States, 2019), http://www.cdc.gov/nchs; National Statistics (Great Britain, 2019), http://www.statistics.gov.uk.

disease caused ~8% of all deaths, and cancer accounted for <4% of all deaths. In 1980, heart disease accounted for 38.2% of all deaths, cancer 20.9%, and cerebrovascular disease 8.6% of all deaths. By 2019, there had been a dramatic drop in deaths from cardiovascular and cerebrovascular diseases. In 2021, 23.1% of all deaths were from car diovascular disease and just 5.3% from cerebrovascular disease. Deaths attributable to cancer, however, had increased slightly to 21.0%. The proportions of deaths due to chronic lower respiratory disease, dia betes, Alzheimer's, and suicide have increased. Interestingly, in 2019, HIV/AIDS accounted for <0.18% of all U.S. deaths. While unlikely to continue being a leading cause of death in the future, COVID-19 was the cause for >600,000 deaths in 2020–2021, and the official figure is almost certainly an undercount of the actual death toll. This change in the epidemiology of death is also reflected in the costs of illness. In the United States, about 90% of all health care spend ing goes to patients with chronic illnesses, and around 10% of total personal health care spending—slightly <$450 billion in 2022—goes to the 0.98% of the population in the last year of their lives. In upper-middle- and upper-income countries, an estimated 70% of all deaths are preceded by a disease or condition, making it reason able to plan for dying in the foreseeable future. Cancer has served as the paradigm for terminal care, but it is not the only type of illness 50.00 45.00 40.00 35.00 Decedents, % 30.00 25.00 20.00 15.00 10.00 5.00 0.00 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 FIGURE 13-1 Graph showing trends in cancer decedents' site of death 1999–2019. (Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2019 on CDC WONDER Online Database. http://wonder.cdc.gov.)

NUMBER OF DEATHS, PEOPLE ≥65 YEARS OF AGE NUMBER OF DEATHS, ALL AGES (%) NUMBER OF DEATHS, PEOPLE ≥65 YEARS OF AGE CHAPTER 13 Palliative and End-of-Life Care with a recognizable and predictable terminal phase. Since heart failure, chronic obstructive pulmonary disease (COPD), chronic liver failure, dementia, and many other conditions have recognizable

terminal phases, a systematic approach to end-of-life care should be part of all medical specialties. Many patients with chronic illness–related symp toms and suffering benefit from palliative care regardless of prognosis. Palliative care is an essential part of comprehensive care for all chroni cally ill patients. Strong evidence demonstrates that palliative care can be improved by coordination between caregivers, doctors, and patients for advance care planning, as well as dedicated teams of physicians, nurses, and other providers. ■ ■SITE OF DEATH Where patients die varies by country. In Belgium and Canada, for instance, over half of all cancer patients still die in the hospital. The past few decades have seen a steady shift, both in the United States and other countries like the Netherlands, out of the hospital, as patients and their families list their own homes as the preferred site of death. In the early 1980s, approximately 70% of American cancer patients died in the hospital. Today, that percentage is closer to 25% (Fig. 13-1). Since 2000, there has been a shift in the United States from inpatient to home deaths, especially for patients with cancer, COPD, congestive heart Inpatient Hospice facility Decedent’s home Year

failure (CHF), and dementia. For instance, among Medicare beneficia ries, 30.1% of deaths due to cancer in 2000 occurred in acute care hos pitals; by 2009, this figure had dropped to 22.1%; by 2015, it was 19.8%.

Paradoxically, while deaths in acute care hospitals have declined in the United States since 2000, both hospitalizations in the last 90 days of life and—even more troublingly—admission to the intensive care unit (ICU) in the last 30 days have actually increased. Over 40% of cancer patients in the United States are admitted to the ICU in their last 6 months of life, and >25% of cancer patients are admitted to the hospital in the last 30 days. PART 1 The Profession of Medicine The shift in deaths out of the hospital has been accompanied by an increase in the use of hospice in the United States. In 2000, 21.6% of Medicare decedents used hospice at the time of death; by 2009, 42.2% were using hospice; and by 2019, 51.6% of Medicare decedents were enrolled in hospice at the time of death. Among those aged 85 or older, 60.8% of Medicare decedents were enrolled in hospice in 2021. Since the COVID-19 pandemic, this number has been a 29% over the 20212023 time period. Among cancer patients, ~60% were using hospice at the time of death. Hospice is also increasingly being used by noncancer patients. Today, cancer patients constitute only 25% of hospice users. Indeed, since 2014, the proportion of patients with other diagnoses using hospice has grown substantially. Those with cardiovascular dis ease has grown significantly, from 14% in 2014 to 29% in 2021, while neurocognitive disorders now account for 24% of cases. Of 2019 Medi care hospice decedents, 51.5% died at home, 17.4% in a nursing facility, 12.8% in a hospice inpatient facility, and 12.3% in assisted living. Unfortunately, significant racial disparities exist in end-of-life care and the use of hospice, especially for noncancer deaths. Racial and ethnic minorities are less likely to receive hospice services than white decedents and are more likely to receive invasive or aggressive care in end-of-life treatment. Of people who died of head and neck cancers between 1999 and 2017, African Americans and Asians/Pacific Islanders were less likely to die at home or in hospice. Among Medicare benefi ciaries who had a pancreatectomy for pancreatic cancer and lived at least 30 days, racial and ethnic minority patients remained 22% less likely than white patients to have hospice care before death. In 2008, for the first time, the American Board of Medical Special ties (ABMS) offered certification in hospice and palliative medicine. With the shortening of hospital stays, many serious conditions are now being treated at home or on an outpatient basis. Consequently, providing optimal palliative and end-of-life care requires ensuring that appropriate services are available in a variety of settings, especially noninstitutional settings.

HOSPICE AND THE PALLIATIVE

CARE FRAMEWORK Central to this type of care is an interdisciplinary team approach that typically encompasses pain and symptom management, spiritual and psychological care for the patient, and support for family caregivers during the patient's illness and the bereavement period. One of the more important changes in this field is beginning pal liative care many months before death in order to focus on symptom relief and then switching to hospice in the patient's last few months. This approach avoids leaving hospice until the very end by introducing palliative care earlier, thereby allowing patients and families time to accommodate and transition. Phasing palliative care into end-of-life care means that patients will often receive palliative interventions long before they are formally diagnosed as terminally ill, or likely to die within 6 months. Fundamental to ensuring quality palliative and end-of-life care is a focus on four broad domains: (1) physical symptoms; (2) psychologi cal symptoms; (3) social needs that include interpersonal relationships, caregiving, and economic concerns; and (4) existential or spiritual needs. ■ ■ASSESSMENT AND CARE PLANNING Comprehensive Assessment Standardized methods for con ducting a comprehensive assessment focus on evaluating the patient's

condition in all four domains affected by the illness: physical, psycho logical, social, and spiritual. A comprehensive assessment should follow a modified version of the traditional medical history and physical examination and should emphasize both physical and psychological or mental symptoms. Questions should aim to elucidate symptoms, discern sources of suffer ing, and gauge how much those symptoms interfere with the patient's quality of life. Standardized and repeated assessments to evaluate the effectiveness of interventions are critical. Thus, clinicians should use shorter, validated instruments, such as (1) the revised Edmon ton Symptom Assessment Scale; (2) Condensed Memorial Symptom Assessment Scale (MSAS); (3) MD Anderson Brief Symptom Inven tory; (4) Rotterdam Symptom Checklist; (5) Symptom Distress Scale; (6) Patient-Reported Outcomes Measurement Information System; and (7) Interactive Symptom Assessment and Collection (ISAAC) tool. MENTAL HEALTH With respect to mental health, many practices use the Patient Health Questionnaire-9 (PHQ-9) to screen for depression and the Generalized Anxiety Disorder-7 (GAD-7) to screen for anxiety. Using such tools ensures that the assessment is comprehensive and does not focus excessively on only pain. INVASIVE TESTS Invasive tests are best avoided in end-of-life care, and even minimally invasive tests should be evaluated carefully for their benefit-to-burden ratio for the patient. Aspects of the physical exami nation that are uncomfortable and unlikely to yield useful information that changes patient management should be omitted. SOCIAL NEEDS Health care providers should also assess the status of important relationships, financial burdens, caregiving needs, and access to medical care. Relevant questions include the following: How often is there someone to feel close to? How has this illness been for your family? How has it affected your relationships? How much help do you need with things like getting meals and getting around? How much trouble do you have getting the medical care you need? EXISTENTIAL NEEDS To determine a patient's existential needs, providers should assess distress, the patient's sense of emotional and existential well-being, and whether the patient believes they have found purpose or meaning. Helpful assessment questions can include the fol lowing: How much are you able to find meaning since your illness began? What things are most important to you at this stage? PERCEPTION OF CARE In addition, it can be helpful to ask how the patient perceives their care: How much do you feel your doctors and nurses respect you? How clear is the information from us about what to expect regarding your illness? How much do you feel that

the medical care you are getting fits with your goals? If concern is detected in any of these areas, deeper evaluative questions are warranted. Communication Particularly when an illness is life-threatening, there exists the potential for many emotionally charged and potentially conflict-creating moments—collectively called “bad news” situations— in which empathic and effective communication skills are essential. Those moments include the sharing of a terminal diagnosis with the patient and/or family, the discussion of the patient’s prognosis and any treatment failures, the consideration of deemphasizing efforts to cure and prolong life while focusing more on symptom management and palliation, advance care planning, and the patient’s actual death. Although these conversations can be difficult, research indicates that end-of-life discussions can lead to earlier hospice referrals, rather than overly aggressive treatment, ultimately benefiting quality of life for patients and improving the bereavement process for families. Just as surgeons prepare for major operations and investigators rehearse a presentation of research results, physicians and health care providers caring for patients with significant or advanced ill nesses should develop a standardized approach for sharing important information and planning interventions. In addition, physicians must be aware that families often care not only about how prepared the physician was to deliver bad news, but also the setting in which it was delivered. For instance, one study found that 27% of families making critical decisions for patients in an ICU desired better and more private physical space to communicate with physicians.

Multiple communications frameworks and guides have been devel oped to assist clinicians prepare for and conduct these serious illness conversations, including SPIKES, GUIDE, BREAKS, SHARE, ABCDE, and the Serious Illness Conversation Guide. SPIKES is the oldest and perhaps most commonly used in practice guide and consists of a six-step process for communicating bad news: (1) set up a suitable environment, (2) begin the discussion by finding out what the patient and/or family’s perception and understand of their condition is, (3) obtain the patient’s invitation to receive new information and determine how much they want to know, (4) provide needed new knowledge accordingly, (5) allow for emotional responses empathetically, and (6) summarize and share next steps in care (Table 13-2). Continuous Goal Assessment Major barriers to providing high-quality palliative and end-of-life care include the difficulty in determining an accurate prognosis and the emotional resistance of patients and their families to accepting the implications of a poor prognosis. A practical solution to these barriers is to integrate pallia tive care interventions or home visits from a palliative care visiting nurse months before the estimated final 6 months of life. Under this approach, palliative care no longer conveys the message of failure, having no more treatments, or “giving up hope.” The transition from TABLE 13-2 Elements of Communicating Bad News—The P-SPIKES Approach ACRONYM STEPS AIM OF THE INTERACTION PREPARATIONS, QUESTIONS, OR PHRASES P Preparation Mentally prepare for the interaction with the patient and/or family. S Setting of the interaction Ensure the appropriate setting for a serious and potentially emotionally charged discussion. P Patient’s perception and preparation Begin the discussion by establishing the baseline and whether the patient and family can grasp the information. Ease tension by having the patient and family contribute. I Invitation and information needs Discover what information needs the patient and/or family have and what limits they want regarding the bad information. K Knowledge of the condition Provide the bad news or other information to the patient and/or family sensitively. E Empathy and exploration Identify the cause of the emotions— e.g., poor prognosis. Empathize with the patient’s and/or family’s feelings. Explore by asking open-ended questions. S Summary and planning Delineate for the patient and the family the next steps, including additional tests or interventions. Source: Adapted from R

Buckman: How to Break Bad News: A Guide for Health Care Professionals. Baltimore, Johns Hopkins University Press, 1992.

palliative to end-of-life care or hospice also feels less hasty and unex pected to the family. Fundamental to integrating palliative care with curative therapy is the inclusion of a continuous goal assessment as part of the routine patient reassessments that occur at most patientphysician encounters.

CHAPTER 13 Goals for care are numerous, ranging from curing a specific disease, to prolonging life, to relieving a particular symptom, to adapting to a progressive disability without disrupting the family, to finding peace of mind or personal meaning, to dying in a manner that leaves loved ones with positive memories. Discerning a patient's goals for care can be approached through a seven-step protocol: (1) ensure that medical and other information is as complete as reasonably possible and is under stood by all relevant parties (see above); (2) explore what the patient and/or family is hoping for, while also identifying relevant and realistic goals; (3) share all the options with the patient and family; (4) respond with empathy as they adjust to changing expectations; (5) make a plan that emphasizes what can be done to achieve the realistic goals; (6) follow through with the plan; and (7) periodically review the plan and consider at every encounter whether the goals of care should be revised with the patient and/or family. Each of these steps need not be followed in rote order, but together they provide a helpful framework for interactions with patients and their families regarding their goals Palliative and End-of-Life Care Review what information needs to be communicated. Plan how you will provide emotional support. Rehearse key steps and phrases in the interaction. Ensure that patient, family, and appropriate social supports are present. Devote sufficient time. Ensure privacy and prevent interruptions by people or beeper. Bring a box of tissues. Start with open-ended questions to encourage participation. Possible questions to use: What do you understand about your illness? When you first had symptom X, what did you think it might be? What did Dr. X tell you when Dr. X sent you here? What do you think is going to happen? Possible questions to use: If this condition turns out to be something serious, do you want to know? Would you like me to tell you all the details of your condition? If not, who would you like me to talk to? Do not just dump the information on the patient and family. Check for patient and family understanding. Possible phrases to use: I feel badly to have to tell you this, but… Unfortunately, the tests showed… I'm afraid the news is not good… Strong feelings in reaction to bad news are normal. Acknowledge what the patient and family are feeling. Remind them such feelings are normal, even if frightening. Give them time to respond. Remind the patient and family you won't abandon them. Possible phrases to use: I imagine this is very hard for you to hear. You look very upset. Tell me how you are feeling. I wish the news were different. We'll do whatever we can to help you. It is the unknown and uncertain that can increase anxiety. Recommend a schedule with goals and landmarks. Provide your rationale for the patient and/or family to accept (or reject). If the patient and/or family are not ready to discuss the next steps, schedule a follow-up visit.

for care. Such interactions can be especially challenging if a patient or family member has difficulty letting go of an unrealistic goal. In such cases, the provider should help them refocus on more realistic goals and should also suggest that while it is fine to hope for the best, it is still prudent to plan for other outcomes as well.

PART 1 The Profession of Medicine Advance Care Planning • PRACTICES Advance care planning is the process of planning for future medical care in case the patient becomes incapable of making medical decisions. A 2010 study of adults aged ≥60 who died between 2000 and 2006 found that while 42% of adults were required to make treatment decisions in their final days of life, 70% lacked decision-making capacity. Among those lack ing decision-making capacity, approximately one-third did not have advance planning directives. Ideally, such planning would occur before a health care crisis or the terminal phase of an illness. Unfortunately, diverse barriers prevent this. Approximately 80% of Americans endorse advance care planning and living wills. However, few Americans have completed advance care documents. One systematic review of the literature from 2017 found that 38.2% of chronically ill patients com pleted advance care documents, higher than 32.7% of healthy adults. Importantly, 45.6% of older adults completed documents, but fewer than a third of people under 65 did so. According to a 2020 Gallup sur vey, 45% of American adults claim to have a living will. Other studies report that even fewer Americans—with some estimates as low as 26% of adults—have filled out advance care directives. Overall, the results suggest that between 55 and 67% of adults have not completed advance TABLE 13-3 Steps in Advance Care Planning STEP GOALS TO BE ACHIEVED AND MEASURES TO COVER USEFUL PHRASES OR POINTS TO MAKE Introduce advance care planning Ask the patient what they know about advance care planning and if they have already completed an advance care directive. Indicate that you as a physician have completed advance care planning. Have you thought about the type of care you would want if you ever became too sick to speak for yourself? That is the purpose of advance care planning. Indicate that you try to perform advance care planning with all patients regardless of prognosis. Explain the goals of the process as empowering the patient and ensuring that you and the proxy understand the patient's preferences. Provide the patient relevant literature, including the advance care directive that you prefer to use. Recommend the patient identify a proxy decision-maker who should attend the next meeting. Have a structured discussion of scenarios with the patient Affirm that the goal of the process is to follow the patient's wishes if the patient loses decision-making capacity. Elicit the patient's overall goals related to health care. Elicit the patient's preferences for specific interventions in a few salient and common scenarios. Help the patient define the threshold for withdrawing and withholding interventions. Define the patient's preference for the role of the proxy. Review the patient's preferences After the patient has made choices of interventions, review them to ensure they are consistent and the proxy is aware of them. Document the patient's preferences Formally complete the advance care directive and have a witness sign it. Provide a copy for the patient and the proxy. Insert a copy into the patient's medical record and summarize it in a progress note. Update the directive Periodically, and with major changes in health status, review the directive with the patient and make any modifications. Apply the directive The directive goes into effect only when the patient becomes unable to make medical decisions for themself. Reread the directive to be sure about its content. Discuss your proposed actions based on the directive with the proxy. Abbreviation: CPR, cardiopulmonary resuscitation.

care documents. However, larger numbers of adults, between 50 and 70%, claim to have talked with someone about their treatment wishes. Americans aged 65 and older are more likely to complete an advance directive compared to younger adults (46 vs 32%), but this is still a minority of patients who are likely to need to plan. Effective advance care planning should follow six key steps: (1) introducing the topic, (2) structuring a discussion, (3) reviewing plans that have been discussed by the patient and family, (4) document ing the plans, (5) updating them periodically,

and (6) implementing the advance care directives (Table 13-3). Two of the main barriers to advance care planning are problems in raising the topic and difficulty in structuring a succinct discussion. Raising the topic can be done efficiently as a routine matter, noting that it is recommended for all patients, analogous to purchasing insurance or estate planning. Many of the most difficult cases have involved unexpected, acute episodes of brain damage in young individuals. Structuring a focused discussion is an important communication skill. To do so, a provider must first identify the health care proxy and recommend their involvement in the advance care planning process. Next, a worksheet must be selected that has been demonstrated to produce reliable and valid expressions of patient preferences, and the patient and proxy must be oriented to it. Such worksheets exist for both general and disease-specific situations. The provider should then dis cuss with the patient and proxy one example scenario to demonstrate how to think about the issues. It is often helpful to begin with a scenario in which the patient is likely to have settled preferences for care, such I'd like to talk with you about something I try to discuss with all my patients. It's called advance care planning. In fact, I feel that this is such an important topic that I have done this myself. Are you familiar with advance care planning or living wills? There is no change in health that we have not discussed. I am bringing this up now because it is sensible for everyone, no matter how well or ill, old or young. Have many copies of advance care directives available, including in the waiting room, for patients and families. Know resources for state-specific forms (available at www.nhpco.org). Use a structured worksheet with typical scenarios. Begin the discussion with persistent vegetative state and consider other scenarios, such as recovery from an acute event with serious disability; then ask the patient about their preferences regarding specific interventions, such as ventilators, artificial nutrition, and CPR; finally, proceeding to less invasive interventions, such as blood transfusions and antibiotics.

as being in a persistent vegetative state. Once the patient's preferences for interventions in this scenario are determined, the provider should suggest that the patient and proxy discuss and complete the worksheet for each other. If appropriate, the patient and proxy should consider involving other family members in the discussion. During a subse quent return visit, the provider should go over the patient's preferences, checking and resolving any inconsistencies. After having the patient and proxy sign the document, the provider should place the document in the patient's medical chart and make sure that copies are provided to relevant family members and care sites. Since patients' preferences can change, these documents must be reviewed periodically. TYPES OF DOCUMENTS Advance care planning documents are of two broad types. The first includes living wills, also known as instructional directives; these are advisory documents that describe the types of deci sions that should direct a patient's care. Some are more specific, delin eating different scenarios and interventions for the patient to choose from. Among these, some are for general use and others are designed for use by patients with a specific type of disease, such as cancer, renal failure, or HIV. Less specific directives can be general statements, such as not wanting life-sustaining interventions, or forms that describe the values that should guide specific discussions about terminal care. The second type of advance directive allows the designation of a health care proxy (sometimes also referred to as a durable attorney for health care), an individual selected by the patient to make decisions. The choice is not either/or; a combined directive that includes a living will and des ignates a proxy is often used, and the directive should indicate clearly whether the specified patient preferences or the proxy's choice takes precedence if they conflict. Some states have begun to put into practice a "Physician Orders for Life-Sustaining Treatment (POLST)" directive, which builds on communication between providers and patients by including guidance for

end-of-life care in a color-coordinated form that follows the patient across treatment settings. The procedures for com pleting advance care planning documents vary according to state law. A potentially misleading distinction relates to statutory, as opposed to advisory, documents. Statutory documents are drafted to fulfill rel evant state laws. Advisory documents are drafted to reflect the patient's wishes. Both are legal, the former under state law and the latter under common or constitutional law. LEGAL ASPECTS As of 2024, 48 states and the District of Columbia had enacted living will legislation. Massachusetts and Michigan are the two states without living will legislation. Indiana has a life-prolonging procedures declaration. States differ in the requirements for advanced directives, including whether they need to be witnessed and, if so, by how many witnesses and whether they need to be notarized. Impor tantly, in 26 states, the laws state that the living will is not valid if a woman is pregnant. All states except Alaska have enacted durable power of attorney for health care laws that permit patients to designate a proxy decision-maker with authority to terminate life-sustaining treatments. Only in Alaska does the law prohibit proxies from termi nating life-sustaining treatments for pregnant women. The U.S. Supreme Court has ruled that patients have a constitutional right to decide any issues related to refusing or terminating medical interventions, including life-sustaining interventions, and that men tally incompetent patients can exercise this right by providing "clear and convincing evidence" of their preferences. Since advance care directives permit patients to provide such evidence, commentators agree that they are constitutionally protected. Most commentators believe that a state is required to honor any clear advance care directive, regardless of whether it is written on an "official" form. Many states have enacted laws for the explicit purpose of honoring out-of-state directives. If a patient is not using a statutory form, it may be advisable to attach a statutory form to the advance care directive being used. State-specific forms are readily available free of charge for health care providers, patients, and families through the website of the National Hospice and Palliative Care Organization (http://www.nhpco.org). The National Hospice and Palliative Care Organization website also has created CaringInfo (https://www.caringinfo.org/), a free online resource

that contains free patient-centered educational materials on end-of-life care and advanced care planning.

REIMBURSEMENT As of January 1, 2016, the Centers for Medicare and Medicaid Services amended the physician fee schedule to reim burse discussions of advance care planning under Current Procedural Terminology codes 99497 and 99498. The session must be voluntary and include an explanation of advance care planning but need not include a completed advance care document. There can be multiple bills for the discussion if it extends over several encounters. A study found that patients who engaged in a billed advance care planning encounter were more likely to be enrolled in hospice and less likely to receive intensive therapies, despite being more likely to be hospital ized in the ICU. However, a billing incentive in and of itself may not increase advance care planning discussions by clinicians. In 2016, just 1.6% of Medicare Advantage patients had a discussion of advance care planning that was billed. Moreover, one retrospective study examin ing Medicare claims data from 2016 to 2018 found that only 15% of practices billed for any advanced care planning visits. Factors beyond reimbursement, such as clinicians' lack of comfort and skill in carry ing out advance care planning discussions and lack of time, appear to impede discussions of advance care planning. CHAPTER 13 Palliative and End-of-Life Care INTERVENTIONS ■ ■PHYSICAL SYMPTOMS AND THEIR MANAGEMENT Great emphasis has been placed on addressing dying patients' pain. In order to emphasize its importance, pain assessment has frequently been included

as the fifth vital sign. Heightened consideration of pain has been advocated by large health care systems such as the Veterans' Administration and accrediting bodies such as The Joint Commission. Although this embrace of pain has been symbolically important, avail able data suggest that making pain the fifth vital sign does not lead to improved pain management practices. In light of the opioid crisis in the United States, the emphasis on pain management has begun to be reexamined. For instance, in 2017 standards, The Joint Commission recommends nonpharmacologic pain treatment as well as identifica tion of psychosocial risk factors for addiction. Importantly, good palliative care requires much more than good pain management. The frequency of symptoms varies by disease and other factors. The most common physical and psychological symptoms among all terminally ill patients include pain, fatigue, insomnia, anorexia, dyspnea, depression, anxiety, nausea, and vomiting. In the last days of life, terminal delirium and excessive secretions are also common. Assessments of patients with advanced cancer have shown that patients experienced an average of 11.5 different physical and psychological symptoms (Table 13-4). TABLE 13-4 Common Physical and Psychological Symptoms of Terminally Ill Patients PHYSICAL SYMPTOMS PSYCHOLOGICAL SYMPTOMS Pain Anxiety Fatigue and weakness Depression Dyspnea Hopelessness Insomnia Meaninglessness Dry mouth Irritability Anorexia Impaired concentration Nausea and vomiting Confusion Constipation Delirium Cough Loss of libido Swelling of arms or legs Itching Diarrhea Dysphagia Dizziness Fecal and urinary incontinence Numbness/tingling in hands/feet

In the vast majority of cases, evaluations to determine the etiology of these symptoms should be limited to the history and physical examina tion. In some cases, radiologic or other diagnostic examinations will provide sufficient benefit in directing optimal palliative care to warrant the risks, potential discomfort, and inconvenience, especially to a seri ously ill patient. Only a few of the common symptoms that present dif ficult management issues will be addressed in this chapter. Additional information on the management of other symptoms, such as nausea and vomiting, insomnia, and diarrhea, can be found in Chaps. 48, 33, and 49, respectively. Information on the management of patients with cancer is provided in Chaps. 73 and 74.

PART 1 The Profession of Medicine Pain • FREQUENCY The frequency of pain among terminally ill patients varies significantly. Cancer (~85%), CHF (~75%), and HIV/ AIDS have been associated with a higher prevalence of pain compared to other advanced illnesses, such as COPD (~45%), chronic kidney disease (~40%), and dementia (~40%). One meta-analysis of adults with advanced or terminal illness found pain prevalence of 30–94% in patients with cancer, compared to 21–77% for COPD, 14–78% for CHF, 11–83% for end-stage renal disease, 14–63% for dementia, and 30–98% for AIDS. ETIOLOGY There are two types of pain: nociceptive and neuropathic. Nociceptive pain is further divided into somatic or visceral pain. Somatic pain is the result of direct mechanical or chemical stimulation of nociceptors and normal neural signaling to the brain. It tends to be localized, aching, throbbing, and cramping. The classic example is bone metastases. Visceral pain is caused by nociceptors in gastrointes tinal (GI), respiratory, and other organ systems. It is a deep or colicky type of pain classically associated with pancreatitis, myocardial infarc tion, or tumor invasion of viscera. Neuropathic pain arises from disor dered nerve signals. It is described by patients as burning, electrical, or shock-like pain. Classic examples are poststroke pain, tumor invasion of the brachial plexus, and herpetic neuralgia. ASSESSMENT Pain is a subjective experience. Depending on the patient's circumstances, perspective, and physiologic condition, the MILD PAIN Acetaminophen: 500 mg 2 tablets every 4–6 h Ibuprofen: 400 mg every 6 h; max 8

tablets per day (2400 mg/d qid) Pain persists or increases MODERATE PAIN Codeine: 30–60 mg every 4–8 h; maximum daily dose for pain 240 mg Tramadol: 25 mg PO every 6 h; max 400 mg/d Add to acetaminophen, NSAIDs Pain persists or increases SEVERE PAIN Morphine: 2.5–5 mg every 3–6 h orally Hydromorphone: 1–2 mg every 3–6 h orally Fentanyl transdermal: 1000-µg patch for 72 h Hydrocodone: 5–10 mg every 3–6 h orally Add to acetaminophen, NSAIDs
Difficult to Control Pain Specialist Consultation (Consideration of surgical procedures such as nerve blocks) FIGURE 13-2 Terminal pain management flow chart. NSAIDs, nonsteroidal anti-inflammatory drugs.

same physical lesion or disease state can produce different levels of reported pain and need for pain relief. Systematic assessment includes eliciting the following: (1) type: throbbing, cramping, burning, etc.; (2) periodicity: continuous, with or without exacerbations, or incident; (3) location; (4) intensity; (5) modifying factors; (6) effects of treatments; (7) functional impact; and (8) impact on patient. Several validated pain assessment measures may be used, including the Visual Analogue Scale (VAS), the Defense and Veterans Pain Rating Scale (DVPRS), the Brief Pain Inventory (BPI), or the Numerical Pain Rating Scale (NRS-11). Other scales have been developed for neuropathic pain, such as the Neuropathic Pain Scale and the DN4 Questionnaire. Frequent reassessments on a consistent scale are essential to assess the impact of and need to readjust interventions.
INTERVENTIONS Interventions for pain must be tailored to each individual, with the goal of preempting chronic pain and relieving breakthrough pain. At the end of life, there is rarely reason to doubt a patient’s report of pain. With the opioid crisis in the United States, there is more emphasis on making opioids one component of mul timodal analgesia. Nevertheless, at the end of life, pain medications, especially opioids, remain the cornerstone of management (Fig. 13-2). If they are failing and nonpharmacologic interventions—including radiotherapy and anesthetic or neurosurgical procedures such as peripheral nerve blocks or epidural medications—are required, a pain consultation is appropriate. Pharmacologic interventions still largely follow the World Health Organization three-step, “analgesic ladder” approach, which involves nonopioid analgesics, “mild” opioids, and “strong” opioids, with or without adjuvants (Chap. 14). Nonopioid analgesics, especially non steroidal anti-inflammatory drugs (NSAIDs), are the initial treatments for mild pain. They work primarily by inhibiting peripheral prosta glandins and reducing inflammation but may also have central ner vous system (CNS) effects. Additionally, NSAIDs have a ceiling effect. Ibuprofen, up to 2400 mg/d qid, has a minimal risk of causing bleeding and renal impairment and is a good initial choice. In patients with a history of severe GI or other bleeding, however, ibuprofen should be NOCICEPTIVE PAIN cramping, throbbing, aching, sharp, prickling, stabbing, deep and constant, dull and gnawing e.g., pancreatitis, bone metastases, tumor invasion, obstruction (of ureters, colon, gastric outlet, gallbladder, etc.) Treatment NSAIDs or acetaminophen with opioids NEUROPATHIC PAIN burning, electrical, shock-like e.g., poststroke pain, tumor invasion of brachial plexus, herpetic neuralgia Treatment Gabapentin: 100–300 mg bid or tid, with 50–100% dose increments every 3 days; 3600 mg/d in 2 or 3 days

avoided. In patients with a history of mild gastritis or gastroesophageal reflux disease (GERD), acid-lowering therapy, such as a proton pump inhibitor, should be used. Acetaminophen is an alternative in patients with a history of GI bleeding and can be used safely at up to 4 g/d qid. In patients with liver dysfunction due to metastases or other causes and in patients with heavy alcohol use, doses should be reduced. Patients with cirrhosis can receive doses up to 2 g/d. If nonopioid analgesics are insufficient, opioids should be intro duced. Opioids primarily work by

interacting with μ opioid receptors to activate pain-inhibitory neurons in the CNS, although they also interact variably with δ and κ receptors. Receptor agonists, such as morphine, codeine, and fentanyl, produce analgesia by activating paininhibitory neurons in the CNS. Partial agonists, such as buprenor phine, have a ceiling effect for analgesia and a lower potential for abuse. They are useful for postacute pain but should not be used for chronic pain in end-of-life care. Pure antagonists, such as naloxone and meth ylnaltrexone, are used for reversal of opioid effects. Traditionally, “weak” opioids such as codeine were used first. If they failed to relieve pain after dose escalation, “strong” opioids like morphine were used in doses of 5–10 mg every 4 h. However, this breakdown between “weak” and “strong” opioids is no longer com monly accepted, with smaller doses of “stronger” opioids frequently being preferred over similar or larger doses of “weaker” opioids, and different pain syndromes having different preferred therapies. Regard less, nonopioid analgesics should be combined with opioids, as they potentiate the effect of opioids. Importantly, the goal is to prevent patients from experiencing pain. Consequently, for continuous pain, opioids should be administered on a regular, around-the-clock basis consistent with their duration of analgesia, and the next dose should occur before the effect of the previ ous dose wears off. They should not be provided only when the patient experiences pain. Patients should also be provided rescue medication, such as liquid morphine, for breakthrough pain, generally at 20% of the baseline dose. Patients should be informed that using the rescue medication does not obviate the need to take the next standard dose of pain medication. If the patient’s pain remains uncontrolled after 24 h and recurs before the next dose, requiring the patient to utilize the rescue medication, the daily opioid dose can be increased by the total dose of rescue medications used by the patient or by 50% of the standing opioid daily dose for moderate pain and 100% for severe pain. It is inappropriate to start with extended-release preparations. Instead, an initial focus on using short-acting preparations to deter mine how much is required in the first 24–48 h will allow clinicians to determine opioid needs. Once pain relief is obtained using short-acting preparations, the switch should be made to extended-release prepara tions. Even with a stable extended-release preparation regimen, the patient may experience incident pain, such as during movement or dressing changes. Short-acting preparations should be taken before such predictable episodes. Although less common, patients may have “end-of-dose failure” with long-acting opioids, meaning that they develop pain after 8 h in the case of an every-12-h medication. In these cases, a trial of giving an every-12-h medication every 8 h is appropriate. Due to differences in opioid receptors, cross-tolerance among opi oids is incomplete, and patients may experience different side effects with different opioids. Therefore, if a patient is not experiencing pain relief or is experiencing too many side effects, a change to another opi oid preparation is appropriate. When switching, one should begin with 50–75% of the published equianalgesic dose of the new opioid. Unlike NSAIDs, opioids have no ceiling effect; therefore, there is no maximum dose, no matter how many milligrams the patient is receiv ing. The appropriate dose is the dose needed to achieve pain relief. This is an important point for clinicians to explain to patients and families. Addiction or excessive respiratory depression is extremely unlikely in the terminally ill; fear of these side effects should neither prevent esca lating opioid medications when the patient is experiencing insufficient pain relief nor justify using opioid antagonists. Opioid side effects should be anticipated and treated preemptively. Nearly all patients experience constipation that can be debilitating (see below). Failure to prevent constipation often results in noncompliance

with opioid therapy. The preferred treatment is prevention. Fiber supplementation with bulk-forming agents (psyllium 1 tbsp qd) as well as osmotic laxatives (polyethylene glycol 1 tbsp qd)

and stimulant laxa tives (senna 2 tbsp qhs) are considered first-line treatment. For refrac tory cases, opioid antagonists or other therapies, such as lubiprostone, should be considered.

CHAPTER 13 Methylnaltrexone is the best-studied opioid antagonist for use in refractory opioid-induced constipation. It reverses opioid-induced constipation by blocking peripheral opioid receptors, but not central receptors, for analgesia. In placebo-controlled trials, it has been shown to cause laxation within 24 h of administration. As with the use of opioids, about a third of patients using methylnaltrexone experience nausea and vomiting, but unlike with opioid usage, tolerance usually develops within a week. Therefore, when one is beginning opioids, an antiemetic such as metoclopramide or a serotonin antagonist is often prescribed prophylactically and stopped after 1 week. Olanzapine has also been shown to have antinausea properties and can be effective in countering delirium or anxiety, with the advantage of some weight gain. Palliative and End-of-Life Care Drowsiness, a common side effect of opioids, also usually abates within a week. For refractory or severe cases, pharmacologic therapy should be considered. The best-studied agents are the psychostimu lants dextroamphetamine, methylphenidate, and modafinil, although evidence regarding their efficacy is weak. Modafinil has the advan tage of once-a-day dosing compared to methylphenidate’s twice daily dosing. Seriously ill patients who require chronic pain relief rarely become addicted. Suspicion of addiction should not be a reason to withhold pain medications from terminally ill patients. Nonetheless, patients and families may withhold prescribed opioids for fear of addiction or dependence. Physicians and health care providers should reassure patients and families that the patient will not become addicted to opioids if they are used as prescribed for pain relief; this fear should not prevent the patient from taking the medications around the clock. However, diversion of drugs for use by other family members or illicit sale may occur. It is necessary to advise the patient and caregiver about secure storage of opioids. Contract writing with the patient and family can help. If that fails, transfer to a safe facility may be necessary. Tolerance describes the need to increase medication dosage for the same pain relief without a concurrent change in disease. In the case of patients with advanced disease, the need for increasing opioid dos age for pain relief usually is caused by disease progression rather than tolerance. Physical dependence is indicated by symptoms resulting from the abrupt withdrawal of opioids and should not be confused with addiction. In recent years, the potential dangers of opioid drugs have become increasingly apparent. To help mitigate the risk of these powerful drugs, several strategies should be used to reduce the risk of aberrant drug use. To start, all patients should be assessed for their individual levels of risk. While there are multiple surveys available, including the Opioid Risk Tool, none have gained widespread use or validation. It is also important to screen for prior substance use disorder, major psy chiatric disorders, and in-state and out-of-state controlled substance fill histories. For patients deemed to be high risk, a multidisciplinary effort should be pursued to reduce the risk of adverse consequences, such as addiction and diversion. Prescribing strategies include selecting opioids with longer durations of action and lower street values, such as methadone, and prescribing smaller quantities with more frequent follow-up. Monitoring options include periodic urine screening and referral to pain specialists. In some cases, it may also be reasonable to consider not offering short-acting opioids for breakthrough pain. In no situation, however, should adequate pain relief be withheld due to risk. Adjuvant analgesic medications are nonopioids that potentiate the analgesic effects of opioids. They are especially important in the management of neuropathic pain. Gabapentin, an anticonvulsant ini tially studied in the setting of herpetic neuralgia, is now the first-line treatment for neuropathic pain resulting from a variety of causes. It is begun at 100–300 mg bid or tid, with 50–100% dose increments

every

3 days. Usually 900–3600 mg/d in two or three doses is effective. The combination of gabapentin and nortriptyline may be more effective than gabapentin alone. Two potential side effects of gabapentin to be aware of are confusion and drowsiness, especially in the elderly. Other effective adjuvant medications include pregabalin, which has the same mechanism of action as gabapentin but is absorbed more efficiently from the GI tract. Several antidepressants have also been shown to be beneficial, including duloxetine, venlafaxine, nortriptyline, and amitriptyline. Second-line agents include topical medications such as capsaicin cream and lidocaine patches. Lamotrigine is a novel agent whose mechanism of action is unknown but has been shown to be effective. It is recommended to begin at 25–50 mg/d, increasing to 100 mg/d. Carbamazepine, a first-generation agent, has been proven effective in randomized trials for neuropathic pain. Other potentially effective anticonvulsant adjuvants include topiramate (25–50 mg qd or bid, rising to 100–300 mg/d) and oxcarbazepine (75–300 mg bid, rising to 1200 mg bid).

PART 1 The Profession of Medicine Glucocorticoids, preferably dexamethasone given once a day, can be useful in reducing inflammation that causes pain, while also elevating mood, energy, and appetite. Its main side effects include confusion, sleep difficulties, and fluid retention. Glucocorticoids are especially effective for bone pain and abdominal pain from distention of the GI tract or liver. Other drugs, including clonidine and baclofen, can be effective in providing pain relief. These drugs are adjuvants and gen erally should be used in conjunction with—not instead of—opioids. Methadone, carefully dosed because of its unpredictable half-life in many patients, has activity at the N-methyl-D-aspartame (NMDA) receptor and is useful for complex pain syndromes and neuropathic pain. It is generally reserved for cases in which first-line opioids (morphine, oxycodone, hydromorphone) are either ineffective or unavailable. Radiation therapy can treat bone pain from single metastatic lesions. Bone pain from multiple metastases can be amenable to radiopharma ceuticals such as strontium-89 and samarium-153. Bisphosphonates, such as pamidronate (90 mg every 4 weeks) and calcitonin (200 IU intranasally once or twice a day), also provide relief from bone pain but have multiday onsets of action. Constipation • FREQUENCY Constipation is reported in up to 70–100% of patients requiring palliative care. ETIOLOGY Although hypercalcemia and other factors can cause con stipation, it is most frequently a predictable consequence of the use of opioids for pain and dyspnea relief and of the anticholinergic effects of tricyclic antidepressants, as well as due to the inactivity and poor diets common among seriously ill patients. If left untreated, constipation can cause substantial pain and vomiting and also is associated with confu sion and delirium. Whenever opioids and other medications known to cause constipation are used, preemptive treatment for constipation should be instituted. ASSESSMENT Assessing constipation can be difficult because people describe it differently. Four commonly used assessment scales are the Bristol Stool Form Scale, the Constipation Assessment Scale, the Con stipation Visual Analogue Scale, and the Eton Scale Risk Assessment for Constipation. The Bowel Function Index can be used to quan tify opioid-induced constipation. The physician should establish the patient’s previous bowel habits, as well as any changes in subjective and objective qualities such as bloating or decreased frequency. Abdominal and rectal examinations should be performed to exclude impaction or an acute abdomen. Radiographic assessments beyond a simple flat plate of the abdomen in cases in which obstruction is suspected are rarely necessary. INTERVENTION Any measure to address constipation during end-oflife care should include interventions to reestablish comfortable bowel habits and to relieve pain or discomfort. Although physical activity,

adequate hydration, and dietary treatments with fiber can be help ful, each is limited in its effectiveness for most seriously ill patients, and fiber may exacerbate problems in the setting of dehydration or if impaired motility is the etiology. Fiber is contraindicated in the

TABLE 13-5 Medications for the Management of Constipation INTERVENTION DOSE COMMENT Stimulant laxatives These agents directly stimulate peristalsis and may reduce colonic absorption of water. Prune juice 120–240 mL/d Work in 6–12 h. Senna (Senokot) 2–8 tablets PO bid Bisacodyl 5–15 mg/d PO, PR Osmotic laxatives These agents are not absorbed. They attract and retain water in the gastrointestinal tract. Lactulose 15–30 mL PO q4–8h Lactulose may cause flatulence and bloating. Magnesium hydroxide 15–30 mL/d PO Lactulose works in 1 day, magnesium products in 6 h. (Milk of Magnesia) Magnesium citrate 125–250 mL/d PO Stool softeners These agents work by increasing water secretion and as detergents, increasing water penetration into the stool. Sodium docusate 300–600 mg/d PO Work in 1–3 days. (Colace) Calcium docusate 300–600 mg/d PO Suppositories and enemas Bisacodyl 10–15 PR qd Sodium phosphate PR qd Fixed dose, 4.5 oz, Fleet’s. enema presence of opioid use. Stimulant and osmotic laxatives, stool softeners, fluids, and enemas are the mainstays of therapy (Table 13-5). To pre vent constipation from opioids and other medications, a combination of a laxative and a stool softener (such as senna and docusate) should be used. If after several days of treatment a bowel movement has not occurred, a rectal examination to remove impacted stool and place a suppository is necessary. For patients with impending bowel obstruc tion or gastric stasis, octreotide to reduce secretions can be helpful. For patients in whom the suspected mechanism is dysmotility, metoclo pramide can be helpful. Nausea • FREQUENCY Up to 70% of patients with advanced cancer have nausea, defined as the subjective sensation of wanting to vomit. ETIOLOGY Nausea and vomiting are both caused by stimulation at one of four sites: the GI tract, the vestibular system, the chemoreceptor trigger zone (CTZ), and the cerebral cortex. Medical treatments for nausea are aimed at receptors at each of these sites: the GI tract con tains mechanoreceptors, chemoreceptors, and 5-hydroxytryptamine type 3 (5-HT3) receptors; the vestibular system probably contains hista mine and acetylcholine receptors; and the CTZ contains chemorecep tors, dopamine type 2 receptors, and 5-HT3 receptors. An example of nausea that most likely is mediated by the cortex is anticipatory nausea before a dose of chemotherapy or other noxious stimuli. Specific causes of nausea include metabolic changes (liver failure, uremia from renal failure, hypercalcemia), bowel obstruction, consti pation, infection, GERD, vestibular disease, brain metastases, medica tions (including antibiotics, NSAIDs, proton pump inhibitors, opioids, and chemotherapy), and radiation therapy. Anxiety can also contribute to nausea. INTERVENTION Medical treatment of nausea is directed at the ana tomic and receptor-mediated cause revealed by a careful history and physical examination. When no specific cause of nausea is identified, many advocate beginning treatment with metoclopramide; a serotonin type 3 (5-HT3) receptor antagonist such as ondansetron, granisetron,

palonosetron, dolasetron, tropisetron, or ramosetron; or a dopamine antagonist such as chlorpromazine, haloperidol, or prochlorperazine. When decreased motility is suspected, metoclopramide can be an effective treatment. When inflammation of the GI tract is suspected, glucocorticoids, such as dexamethasone, are an appropriate treatment. For nausea that follows chemotherapy and radiation therapy, one of the 5-HT3 receptor antagonists or neurokinin-1 antagonists, such as apre pitant or fosaprepitant, is recommended. Clinicians should attempt prevention of postchemotherapy nausea, rather than simply providing treatment after the fact. Current clinical guidelines recommend tailor ing the strength of treatments to the specific emetic

risk posed by a specific chemotherapy drug. When a vestibular cause (such as “motion sickness” or labyrinthitis) is suspected, antihistamines, such as mecli zine (whose primary side effect is drowsiness), or anticholinergics, such as scopolamine, can be effective. In anticipatory nausea, patients can benefit from nonpharmacologic interventions, such as biofeedback and hypnosis. The most common pharmacologic intervention for anticipatory nausea is a benzodiazepine, such as lorazepam. As with antihistamines, drowsiness and confusion are the main side effects. The use of medical marijuana or oral cannabinoids for palliative treatment of nausea is controversial, as there are no controlled tri als showing its effectiveness for patients at the end of life. A 2018 meta-analysis concluded that “there is reasonable evidence that can nabinoids improve nausea and vomiting after chemotherapy,” and such treatments are not as good as 5-HT3 receptor antagonists and can sometimes even cause cannabis hyperemesis syndrome. Older patients, who compose the vast majority of dying patients, seem to tolerate can nabinoids poorly. Dyspnea • FREQUENCY Dyspnea is the subjective experience of being short of breath. Over 50%, and as many as 75%, of dying patients, especially those with lung cancer, metastases to the lung, CHF, and COPD, experience dyspnea at some point near the end of life. Dyspnea is among the most distressing of physical symptoms and can be even more distressing than pain. ASSESSMENT As with pain, dyspnea is a subjective experience that may not correlate with objective measures of PO_2, PCO_2, or respira tory rate. Consequently, measurements of oxygen saturation through pulse oximetry or blood gases are rarely helpful in guiding therapy. Despite the limitations of existing assessment methods, physicians should regularly assess and document patients’ experience of dyspnea and its intensity. Guidelines recommend visual analogue dyspnea scales to assess the severity of symptoms and the effects of treatment. Potentially reversible or treatable causes of dyspnea include infection, pleural effusions, pulmonary emboli, pulmonary edema, asthma, and tumor encroachment on the airway. However, the risk-versus-benefit ratio of the diagnostic and therapeutic interventions for patients with little time left to live must be considered carefully before undertaking diagnostic steps. Frequently, the specific etiology cannot be identi fied, and dyspnea is the consequence of progression of the underlying disease that cannot be treated. The anxiety caused by dyspnea and the choking sensation can significantly exacerbate the underlying dyspnea in a negatively reinforcing cycle. INTERVENTIONS When reversible or treatable etiologies are diag nosed, they should be treated as long as the side effects of treatment, such as repeated drainage of effusions or anticoagulants, are less bur densome than the dyspnea itself. More aggressive treatments such as stenting a bronchial lesion may be warranted if it is clear that the dys pnea is due to tumor invasion at that site and if the patient and family understand the risks of such a procedure. Usually, treatment will be symptomatic (Table 13-6). Supplemental oxygen does not appear to be effective. “A systematic review of the literature failed to demonstrate a consistent beneficial effect of oxygen inhalation over air inhalation for study participants with dyspnea due to end-stage cancer or cardiac failure.” Therefore, oxygen may be no more than an expensive placebo. Low-dose opioids reduce the sensitivity of the central respiratory center and relieve the sensation of dyspnea. If patients are not receiving opioids, weak opioids can be

TABLE 13-6 Medications for the Management of Dyspnea INTERVENTION DOSE COMMENTS Weak opioids For patients with mild dyspnea Codeine (or codeine 30 mg PO q4h For opioid-naïve patients CHAPTER 13 with 325 mg acetaminophen) Hydrocodone 5 mg PO q4h Strong opioids For opioid-naïve patients with moderate to severe dyspnea Palliative and End-of-Life Care Morphine 5–10 mg PO q4h For patients already taking opioids for pain or other symptoms 30–50% of baseline opioid dose q4h Oxycodone 5–10 mg PO q4h Hydromorphone 1–2 mg PO q4h

Anxiolytics Give a dose every hour until the patient is relaxed; then provide a dose for maintenance Lorazepam 0.5–2.0 mg PO/SL/IV qh then q4–6h Clonazepam 0.25–2.0 mg PO q12h Midazolam 0.5 mg IV q15min initiated; if patients are already receiving opioids, morphine or other stronger opioids should be used. Controlled trials do not support the use of nebulized opioids for dyspnea at the end of life. Phenothiazines and chlorpromazine may be helpful when combined with opioids. Benzodiazepines can be helpful in treating dyspnea, but only if anxiety is present. Benzodiazepines should not be used as first-line therapy or if there is no anxiety. If the patient has a history of COPD or asthma, inhaled bronchodilators and glucocorticoids may be helpful. If the patient has pulmonary edema due to heart failure, diuresis with a medication such as furosemide is indicated. Excess secretions can be transdermally or intravenously dried with scopolamine. More general interventions that medical staff can perform include sitting the patient upright, removing smoke or other irritants like perfume, ensuring a supply of fresh air with sufficient humidity, and minimizing other fac tors that can increase anxiety. Fatigue • FREQUENCY Fatigue is one of the most commonly reported symptoms not only of cancer treatment but also of the pal liative care of multiple sclerosis, COPD, heart failure, and HIV. More than 90% of terminally ill patients experience fatigue and/or weakness. Fatigue is frequently cited as one of the most distressing symptoms in these patients. ETIOLOGY The multiple causes of fatigue in the terminally ill can be categorized as resulting from the underlying disease; from disease-induced factors such as tumor necrosis factor and other cytokines; and from secondary factors such as dehydration, anemia, infection, hypothy roidism, and drug side effects. In addition to low caloric intake, loss of muscle mass and changes in muscle enzymes may play an important role in fatigue during terminal illness. The importance of changes in the CNS, especially the reticular activating system, have been hypoth esized based on reports of fatigue in patients receiving cranial radia tion, experiencing depression, or having chronic pain in the absence of cachexia or other physiologic changes. Finally, depression and other causes of psychological distress can contribute to fatigue. ASSESSMENT Like pain and dyspnea, fatigue is subjective, as it represents a patient’s sense of tiredness and decreased capacity for physical work. Objective changes, even in body mass, may be absent. Consequently, assessment must rely on patient self-reporting. Scales used to measure fatigue, such as the Edmonton Functional Assessment Tool, the Fatigue Self-Report Scales, and the Rhoten Fatigue Scale, are usually appropriate for research but not clinical purposes. In clinical

practice, a simple performance assessment such as the Karnofsky per formance status or the Eastern Cooperative Oncology Group (ECOG)’s question “How much of the day does the patient spend in bed?” may be the best measure. In the ECOG 0–4 performance status assessment, 0 = normal activity; 1 = symptomatic without being bedridden; 2 = requir ing some, but <50%, bed time; 3 = bedbound more than half the day; and 4 = bedbound all the time. Such a scale allows for assessment over time and correlates with overall disease severity and prognosis. A 2008 review by the European Association of Palliative Care also described several longer assessment tools that contained 9–20 items, including the Piper Fatigue Inventory, the Multidimensional Fatigue Inventory, and the Brief Fatigue Inventory (BFI).

PART 1 The Profession of Medicine INTERVENTIONS Reversible causes of fatigue, such as anemia and infection, should be treated. However, at the end of life, it must be realistically acknowledged that fatigue will not be “cured.” The goal is to ameliorate fatigue and help patients and families adjust expecta tions. Behavioral interventions should be utilized to avoid blaming the patient for inactivity and to educate both the family and the patient that the underlying disease causes

physiologic changes that produce low energy levels. Understanding that the problem is physiologic and not psychological can help alter expectations regarding the patient's level of physical activity. Practically, this may mean reducing routine activi ties such as housework, cooking, and social events outside the house and making it acceptable to receive guests while lying on a couch. At the same time, the implementation of exercise regimens and physical therapy can raise endorphins, reduce muscle wasting, and decrease the risk of depression. In addition, ensuring good hydration without wors ening edema may help reduce fatigue. Sleep hygiene should also be emphasized, and effort should be taken to eliminate poor sleep hygiene behaviors. Discontinuing medications that worsen fatigue may help, including cardiac medications, benzodiazepines, certain antidepres sants, or opioids if the patient's pain is well-controlled. As end-of-life care proceeds into its final stages, fatigue may protect patients from further suffering, and continued treatment could be detrimental. Only a few pharmacologic interventions target fatigue and weak ness. Randomized controlled trials suggest glucocorticoids can increase energy and enhance mood. Dexamethasone (8 mg/d) is preferred for its once-a-day dosing and minimal mineralocorticoid activity. Benefit, if any, is usually seen within the first month. For fatigue related to anorexia, megestrol (480–800 mg) can be helpful. Psychostimulants such as dextroamphetamine (5–10 mg PO) and methylphenidate (2.5–5 mg PO) may enhance energy levels, although controlled trials have not shown these drugs to be effective for fatigue induced by mild to moderate cancer. Doses should be given in the morning and at noon to minimize the risk of counterproductive insomnia. Modafinil and armodafinil, developed for narcolepsy, have had mixed results in the treatment of fatigue but have the advantage of once-daily dosing. Their precise role in fatigue at the end of life has not been documented but may be worth trying if other interventions are not beneficial. ■ ■PALLIATIVE SEDATION Palliative sedation is used in distressing situations that cannot be addressed in other ways. When patients experience severe symptoms, such as pain or dyspnea, that cannot be relieved by conventional interventions or experience acute catastrophic symptoms, such as uncontrolled seizures, then palliative sedation should be considered as an intervention of last resort. It can be abused if done to hasten death (which it usually does not), when done at the request of the family rather than according to the patient's wishes, or when there are other interventions that could still be tried. The use of palliative sedation in cases of extreme existential or spiritual distress remains controver sial. Typically, palliative sedation should be introduced only after the patient and family have been assured that all other interventions have been tried and after the patient and their loved ones have been able to "say goodbye." Palliative sedation can be achieved by significantly increasing opi oid doses until patients become unconscious and then putting them on a continuous infusion. Another commonly used medication for

palliative sedation is midazolam at 1–5 mg IV every 5–15 min to calm the patient, followed by a continuous IV or subcutaneous infusion of

1 mg/h. In hospital settings, a continuous propofol infusion of 5 µg/kg per min can be used. There are also other, less commonly used medications for palliative sedation that include levomepromazine, chlorpromazine, and phenobarbital. PSYCHOLOGICAL SYMPTOMS AND THEIR MANAGEMENT Depression • FREQUENCY AND IMPACT Depression at the end of life presents an apparently paradoxical situation. Many people believe that depression is normal among seriously ill patients because they are dying. People frequently say, "Wouldn't you be depressed?" Although sadness, anxiety, anger, and irritability are normal responses to a serious condition, they are typically of modest intensity and transient. Persistent sadness and anxiety and the physically

disabling symptoms that they can lead to are abnormal and suggestive of major depression. The precise number of terminally ill patients who are depressed is uncertain, primarily due to a lack of consistent diagnos tic criteria and screening. Careful follow-up of patients suggests that while as many as 75% of terminally ill patients experience depressive symptoms, ~25% of terminally ill patients have major depression. Depression at the end of life is concerning because it can decrease the quality of life, interfere with closure in relationships and other separa tion work, obstruct adherence to medical interventions, and amplify the suffering associated with pain and other symptoms. ETIOLOGY Previous history of depression, family history of depres sion or bipolar disorder, and prior suicide attempts are associated with increased risk for depression among terminally ill patients. Other symptoms, such as pain and fatigue, are associated with higher rates of depression; uncontrolled pain can exacerbate depression, and depres sion can cause patients to be more distressed by pain. Many medica tions used in the terminal stages, including glucocorticoids, and some anticancer agents, such as tamoxifen, interleukin 2, interferon α, and vincristine, also are associated with depression. Some terminal con ditions, such as pancreatic cancer, certain strokes, and heart failure, have been reported to be associated with higher rates of depression, although this is controversial. Finally, depression may be attributable to grief over the loss of a role or function, social isolation, or loneliness. ASSESSMENT Unfortunately, many studies suggest that most depressed patients at the end of life are not diagnosed, or if they are diagnosed, they are not properly treated. Diagnosing depression among seriously ill patients is complicated, as many of the vegetative symptoms in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for clinical depression—insomnia, anorexia and weight loss, fatigue, decreased libido, and difficulty concentrating—are associated with the process of dying itself. The assessment of depres sion in seriously ill patients therefore should focus on the dysphoric mood, helplessness, hopelessness, and lack of interest, enjoyment, and concentration in normal activities. It is now recommended that patients near the end of life should be screened with either the PHQ-9 or the PHQ-2, which asks “Over the past 2 weeks, how often have you been bothered by any of the following problems? (1) Little interest or pleasure in doing things and (2) feeling down, depressed or hopeless.” The answer categories are as follows: not at all, several days, more than half the days, and nearly every day. Other possible diagnostic tools include the short form of the Beck Depression Index or a visual analogue scale. Certain conditions may be confused with depression. Endocrinopa thies, such as hypothyroidism and Cushing’s syndrome, electrolyte abnormalities, such as hypercalcemia, and akathisia, especially from dopamine-blocking antiemetics such as metoclopramide and prochlor perazine, can mimic depression and should be excluded. INTERVENTIONS Undertreatment of depressed, terminally ill patients is common. Physicians must treat any physical symptom, such as pain, that may be causing or exacerbating depression. Fostering adaptation to the many losses that the patient is experiencing can also be helpful.

Unfortunately, there are few randomized trials to guide such inter ventions. Thus, treatment typically follows the treatment used for non–terminally ill depressed patients. In the absence of randomized controlled trials, nonpharmacologic interventions, including group or individual psychological counseling, and behavioral therapies such as relaxation and imagery can be helpful, especially in combination with drug therapy. Pharmacologic interventions remain at the core of therapy. The same medications are used to treat depression in terminally ill as in non–terminally ill patients. Psychostimulants may be preferred for patients with a poor prognosis or for those with fatigue or opioid-induced somnolence. Psychostimulants are comparatively fast-acting, working within a few days instead of the weeks required for selective serotonin reuptake inhibitors (SSRIs).

Dextroamphetamine or methylphenidate should be started at 2.5–5.0 mg in the morning and at noon, the same starting doses used for treating fatigue. The doses can eventually be escalated up to 15 mg bid. Modafinil is started at 100 mg qd and can be increased to 200 mg if there is no effect at the lower dose. Pemoline is a nonamphetamine psychostimulant with minimal abuse potential. It is also effective as an antidepressant beginning at 18.75 mg in the morning and at noon. Because it can be absorbed through the buc cal mucosa, it is preferred for patients with intestinal obstruction or dysphagia. If it is used for prolonged periods, liver function must be monitored. The psychostimulants can also be combined with more traditional antidepressants while waiting for the antidepressants to become effective, then tapered down after a few weeks if necessary. Psychostimulants have side effects, particularly initial anxiety, insom nia, and very rarely paranoia, which may necessitate lowering the dose or discontinuing treatment. Mirtazapine, an antagonist at the postsynaptic serotonin receptors, is a promising psychostimulant. It should be started at 7.5 mg before bed and titrated up no more than once every 1–2 weeks to a maximal dose of 45 mg/d. It has sedating, antiemetic, and anxiolytic properties, with few drug interactions. Its side effect of weight gain may be beneficial for seri ously ill patients; it is available in orally disintegrating tablets. For patients with a prognosis of several months or longer, SSRIs, including fluoxetine, sertraline, paroxetine, escitalopram, and cita lopram, and serotonin-noradrenaline reuptake inhibitors, such as venlafaxine and duloxetine, are the preferred treatments, due to their efficacy and comparatively few side effects. Because low doses of these medications may be effective for seriously ill patients, one should use half the usual starting dose as for healthy adults. The starting dose for fluoxetine is 10 mg once a day. In most cases, once-a-day dosing is possible. The choice of which SSRI to use should be driven by (1) the patient’s past success or failure with the specific medication and (2) the most favorable side effect profile for that specific agent. For instance, for a patient in whom fatigue is a major symptom, a more activating SSRI (fluoxetine) would be appropriate. For a patient in whom anxiety and sleeplessness are major symptoms, a more sedating SSRI (parox etine) would be appropriate. Importantly, it can take up to 4 weeks for these drugs to have an effect. Atypical antidepressants are recommended only in select cir cumstances, usually with the assistance of a specialty consultation. Trazodone can be an effective antidepressant but is sedating and can cause orthostatic hypotension and, occasionally, priapism. Therefore, it should be used before bed and only when a sedating effect is desired and is often used for patients with insomnia at a dose starting at 25 mg. Bupropion can also be used. In addition to its antidepressant effects, bupropion is energizing, making it useful for depressed patients who experience fatigue. However, it can cause seizures, preventing its use for patients with a risk of CNS neoplasms or terminal delirium. Finally, alprazolam, a benzodiazepine, starting at 0.25–1.0 mg tid, can be effec tive in seriously ill patients who have a combination of anxiety and depression. Although it is potent and works quickly, it has many drug interactions and may cause delirium, especially among very ill patients, because of its strong binding to the benzodiazepine–γ-aminobutyric acid (GABA) receptor complex. Unless used as adjuvants for the treatment of pain, tricyclic anti depressants are not recommended. While they can be effective, their

therapeutic window and serious side effects typically limit their util ity. Similarly, monoamine oxidase (MAO) inhibitors are not recom mended because of their side effects and dangerous drug interactions.

Psychedelic drugs, such as psylocibin, have been tried for patients with cancer and major depressive disorder and shown promise. In smaller trials, psylocibin (a single dose of 25 mg) has

been shown to be effective in up to 70% of patients. Importantly, psylocibin has a rela tively rapid onset of relief of depressive symptoms—within 1 week—that can last for months. While still not U.S. Food and Drug Administration approved for general clinical use, there are multiple trials that may be available for patients. CHAPTER 13 Palliative and End-of-Life Care Delirium (See Chap. 29) • FREQUENCY In the weeks or months before death, delirium is uncommon, although it may be significantly underdiagnosed. However, delirium becomes relatively common in the days and hours immediately before death. Up to 85% of patients dying from cancer may experience terminal delirium. ETIOLOGY Delirium is a global cerebral dysfunction characterized by alterations in cognition and consciousness. It is frequently preceded by anxiety, changes in sleep patterns (especially reversal of day and night), and decreased attention. In contrast to dementia, delirium has an acute onset, is characterized by fluctuating consciousness and inattention, and is reversible, although reversibility may be more theoretical than real for patients near death. Delirium may occur in a patient with dementia; indeed, patients with dementia are more vulnerable to delirium. Causes of delirium include metabolic encephalopathy arising from liver or renal failure, hypoxemia, or infection; electrolyte imbalances such as hypercalcemia; paraneoplastic syndromes; dehydration; and primary brain tumors, brain metastases, or leptomeningeal spread of tumor. Among dying patients, delirium is commonly caused by side effects of treatments, including radiation for brain metastases and medications, such as opioids, glucocorticoids, anticholinergic drugs, antihistamines, antiemetics, benzodiazepines, and chemotherapeutic agents. The etiology may be multifactorial; e.g., dehydration may exac erbate opioid-induced delirium. ASSESSMENT Delirium should be recognized in any terminally ill patient exhibiting new onset of disorientation, impaired cognition, somnolence, fluctuating levels of consciousness, or delusions with or without agitation. Delirium must be distinguished from acute anxiety, depression, and dementia. The central distinguishing feature is altered consciousness, which usually is not noted in anxiety, depression, or dementia. Although “hyperactive” delirium, characterized by overt confusion and agitation, is probably more common, patients should also be assessed for “hypoactive” delirium, which is characterized by sleep-wake reversal and decreased alertness. In some cases, use of formal assessment tools such as the MiniMental Status Examination (which does not distinguish delirium from dementia) and the Delirium Rating Scale (which does distinguish delirium from dementia) may be helpful in distinguishing delirium from other processes. The patient’s list of medications must be evalu ated carefully. Nonetheless, a reversible etiologic factor for delirium is found in fewer than half of all terminally ill patients. Given that most terminally ill patients experiencing delirium are very close to death and often at home, extensive diagnostic evaluations such as lumbar punc tures and neuroradiologic examinations are inappropriate. INTERVENTIONS One of the most important objectives of terminal care is to provide terminally ill patients the lucidity to say goodbye to the people they love. Delirium, especially when in combination with agitation during the final days, is distressing to family and caregivers. A strong determinant of bereavement difficulties is witnessing a difficult death. Thus, terminal delirium should be treated aggressively. At the first sign of delirium, such as day-night reversal with slight changes in mentation, the physician should let the family members know that it is time to be sure that everything they want to say has been said. The family should be informed that delirium is common just before death. If medications are suspected of being a cause of the delirium, unnec essary agents should be discontinued. Other potentially reversible

TABLE 13-7 Medications for the Management of Delirium INTERVENTIONS DOSE Neuroleptics Haloperidol 0.5–5 mg q2–12h, PO/IV/SC/IM Thioridazine 10–75 mg q4–8h, PO

of Medicine Chlorpromazine 12.5–50 mg q4–12h, PO/IV/IM Atypical neuroleptics Olanzapine 2.5–5 mg qd or bid, PO Risperidone 1–3 mg q12h, PO Anxiolytics Lorazepam 0.5–2 mg q1–4h, PO/IV/IM Midazolam 1–5 mg/h continuous infusion, IV/SC Anesthetics Propofol 0.3–2.0 mg/h continuous infusion, IV causes, such as constipation, urinary retention, and metabolic abnor malities, should be treated. Supportive measures aimed at providing a familiar environment should be instituted, including restricting visits only to individuals with whom the patient is familiar and eliminating new experiences; orienting the patient, if possible, by providing a clock and calendar; and gently correcting the patient's hallucinations or cog nitive mistakes. Pharmacologic management focuses on the use of neuroleptics and, in extreme cases, anesthetics (Table 13-7). Haloperidol remains the first-line therapy. Usually, patients can be controlled with a low dose (1–3 mg/d), given every 6 h, although some may require as much as 20 mg/d. Haloperidol can be administered PO, SC, or IV. IM injec tions should not be used, except when this is the only way to address a patient's delirium. Olanzapine, an atypical neuroleptic, has shown significant effectiveness in completely resolving delirium in cancer patients. It also has other beneficial effects for terminally ill patients, including antinausea, antianxiety, and weight gain. Olanzapine is use ful for patients with longer anticipated life expectancies because it is less likely to cause dysphoria and has a lower risk of dystonic reactions. Additionally, because olanzapine is metabolized through multiple pathways, it can be used in patients with hepatic and renal dysfunc tion. Olanzapine has the disadvantage that it is only available orally and takes a week to reach steady state. The usual dose is 2.5–5 mg PO bid. Chlorpromazine (10–25 mg every 4–6 h) can be useful if sedation is desired and can be administered IV or PR in addition to PO. Dystonic reactions resulting from dopamine blockade are a side effect of neu roleptics, although they are reported to be rare when these drugs are used to treat terminal delirium. If patients develop dystonic reactions, benztropine should be administered. Neuroleptics may be combined with lorazepam to reduce agitation when the delirium is the result of alcohol or sedative withdrawal. If no response to first-line therapy is observed, a specialty consulta tion should be obtained with a goal to change to a different medica tion. If the patient fails to improve after a second neuroleptic, sedation with either an anesthetic such as propofol or continuous-infusion midazolam may be necessary. By some estimates, as many as 25% of patients at the very end of life who experience delirium, especially restless delirium with myoclonus or convulsions, may require sedation. Physical restraints should be used with great reluctance and only when patients' violence is threatening to themselves or others. If restraints are used, their appropriateness should be frequently reevaluated. Insomnia • FREQUENCY Sleep disorders, defined as difficulty initiating sleep or maintaining sleep, sleep difficulty at least 3 nights a week, or sleep difficulty that causes impairment of daytime function ing, occurs in 19–63% of patients with advanced cancer. Some 30–74% of patients with other end-stage conditions, including HIV/AIDS, heart disease, COPD, and renal disease, experience insomnia. ETIOLOGY Patients with cancer may experience changes in sleep effi ciency, such as an increase in stage I sleep. Insomnia may also coexist

with both physical illnesses, like thyroid disease, and psychological ill nesses, like depression and anxiety. Medications, including antidepres sants, psychostimulants, glucocorticoids, and β agonists, are significant contributors to sleep disorders, as are caffeine and alcohol. Multiple over-the-counter medications contain caffeine and antihistamines, which can contribute to sleep disorders. ASSESSMENT Assessments should include specific questions concern ing sleep onset, sleep maintenance, and early-morning wakening, as these will provide clues to both the causative agents and management of insomnia. Patients should be asked about previous sleep problems, screened

for depression and anxiety, and asked about symptoms of thyroid disease. Caffeine and alcohol are prominent causes of sleep problems, and a careful history of the use of these substances should be obtained. Both excessive use and withdrawal from alcohol can be causes of sleep problems. INTERVENTIONS The mainstays of any intervention include improve ment of sleep hygiene (encouragement of regular time for sleep, decreased nighttime distractions, and elimination of caffeine and other stimulants and alcohol), interventions to treat anxiety and depression, and treatment for the insomnia itself. For patients with depression who have insomnia and anxiety, a sedating antidepressant such as mir tazapine can be helpful. In the elderly, trazodone, beginning at 25 mg at nighttime, is an effective sleep aid at doses lower than those that cause its antidepressant effect. Zolpidem may have a decreased incidence of delirium in patients compared with traditional benzodiazepines, but this has not been clearly established. When benzodiazepines are prescribed, short-acting ones (such as lorazepam) are favored over longer-

acting ones (such as diazepam). Patients who receive these medications should be observed for signs of increased confusion and delirium. ■ ■SOCIAL NEEDS AND THEIR MANAGEMENT Financial Burdens • FREQUENCY Dying can impose sub stantial economic strains on patients and families, potentially causing distress. This is known as financial toxicity. In the United States, which has the least comprehensive health insurance systems among wealthy countries, a fifth to a half of families coping with end-stage cancer report that care was a major financial burden. Among caregivers of Medicare beneficiaries with cancer, average out-of-pocket costs within the last year of life ranged from $4,645 to $10,547 (14–28% household income). Between 10 and 30% of families are forced to sell assets, use savings, or take out a mortgage to pay for the patient’s health care costs, while around 40% of primary caregivers felt forced to quit their jobs due to caregiving requirements. The patient is likely to reduce hours worked and eventually stop working altogether. In 20% of cases, a family member of the terminally ill patient also must stop working to provide care. The major underly ing causes of economic burden are related to poor physical function ing and care needs, such as the need for housekeeping, nursing, and personal care. More debilitated patients and poor patients experience greater economic burdens. INTERVENTION The economic burden of end-of-life care should not be ignored as a private matter. It has been associated with a number of adverse health outcomes, including preferring comfort care over lifeprolonging care, as well as consideration of euthanasia or physicianassisted suicide (PAS). Economic burdens increase the psychological distress of the families and caregivers of terminally ill patients, and poverty is associated with many adverse health outcomes. Importantly, studies have found that “patients with advanced cancer who reported having end-of-life conversations with physicians had significantly lower health care costs in their final week of life. Higher costs were associated with worse quality of death.” Assistance from a social worker, early on if possible, to ensure access to all available benefits may be helpful. Many patients, families, and health care providers are unaware of options for long-term care insurance, respite care, the Family Medical Leave Act (FMLA), and other sources of assistance. Some of these options (such as respite care) may be part of a formal hospice program, but others (such as the FMLA) do not require enrollment in a hospice program.

Relationships • FREQUENCY Settling personal issues and clos ing the narrative of lived relationships are universal needs. When asked if sudden death or death after an illness is preferable, respondents often ini tially select the former, but soon change to the latter as they reflect on the importance of saying goodbye. Bereaved family members who have not had the chance to say goodbye often have a more difficult grief process. INTERVENTIONS Care of seriously ill patients

requires efforts to facilitate the types of encounters and time spent with family and friends that are necessary to meet those needs. Family and close friends may need to be accommodated in hospitals and other facilities with unre stricted visiting hours, which may include sleeping near the patient, even in otherwise regimented institutional settings. Physicians and other health care providers may be able to facilitate and resolve strained interactions between the patient and other family members. Assistance for patients and family members who are unsure about how to create or help preserve memories, whether by providing materials such as a scrapbook or memory box or by offering them suggestions and infor mational resources, can be deeply appreciated. Taking photographs and creating videos can be especially helpful to terminally ill patients who have younger children or grandchildren. Family Caregivers • FREQUENCY Caring for seriously ill patients places a heavy burden on families. Families are frequently required to provide transportation and homemaking, as well as other services. Typically, paid professionals, such as home health nurses and hospice workers, supplement family care; only about a quarter of all caregiving consists of exclusively paid professional assistance. Over the past 40 years, there has been a significant decline in the United States of deaths occurring in hospitals, with a simultaneous increase in deaths in other facilities and at home. Over a third of deaths occur in patients' homes despite 70% of Americans expressing a preference to die at home. This increase in out-of-hospital deaths increases reliance on families for end-of-life care. Increasingly, family members are being called upon to provide physical care (such as moving and bathing patients) and medical care (such as assessing symptoms and giving medications) in addition to emotional care and support. Three-quarters of family caregivers of terminally ill patients are women—wives, daughters, sisters, and even daughters-in-law. Since many are widowed, women tend to be able to rely less on family for caregiving assistance and may need more paid assistance. About 20% of terminally ill patients report substantial unmet needs for nursing and personal care. The impact of caregiving on family caregivers is substan tial: both bereaved and current caregivers have a higher mortality rate than that of non-caregiving controls. INTERVENTIONS It is imperative to inquire about unmet needs and to try to ensure that those needs are met either through the family or by paid professional services when possible. Community assistance through houses of worship or other community groups often can be mobilized by telephone calls from the medical team to someone the patient or family identifies. Sources of support specifically for family caregivers should be identified through local sources or nationally through groups such as the National Family Caregivers Association (www.nfcacares.org), the American Cancer Society (www.cancer.org), and the Alzheimer's Association (www.alz.org). ■ ■EXISTENTIAL NEEDS AND THEIR MANAGEMENT Frequency Religion and spirituality are often important to dying patients. Nearly 70% of patients report becoming more religious or spiritual when they became terminally ill, and many find comfort in religious or spiritual practices such as prayer. However, ~20% of ter minally ill patients become less religious, frequently feeling cheated or betrayed by becoming terminally ill. For other patients, the need is for existential meaning and purpose that is distinct from, and may even be antithetical to, religion or spirituality. When asked, patients and family caregivers frequently report wanting their professional caregivers to be more attentive to religion and spirituality. Assessment Health care providers are often hesitant about involv ing themselves in the religious, spiritual, and existential experiences

of their patients because it may seem private or not relevant to the current illness. But physicians and other members of the care team should be able at least to detect spiritual and existential needs. Screen ing questions have been developed for a physician's spiritual history taking. Spiritual

distress can amplify other types of suffering and even masquerade as intractable physical pain, anxiety, or depression. The screening questions in the comprehensive assessment are usually suffi cient. Deeper evaluation and intervention are rarely appropriate for the physician unless no other member of a care team is available or suit able. Pastoral care providers may be helpful, whether from the medical institution or from the patient's own community.

CHAPTER 13 Palliative and End-of-Life Care Interventions Precisely how religious practices, spirituality, and existential explorations can be facilitated and improve end-of-life care is not well established. What is clear is that for physicians, one main intervention is to inquire about the role and importance of spirituality and religion in a patient's life. This will help a patient feel heard and help physicians identify specific needs. In one study, only 36% of respondents indicated that a clergy member would be comforting. Nevertheless, the increase in religious and spiritual interest among a substantial fraction of dying patients suggests inquiring of individual patients how this need can be addressed. Some evidence supports specific methods of address ing existential needs in patients, ranging from establishing a supportive group environment for terminal patients to individual treatments emphasizing a patient's dignity and sources of meaning. MANAGING THE LAST STAGES ■ ■PALLIATIVE CARE SERVICES: HOW AND WHERE Determining the best approach to providing palliative care to patients will depend on patient preferences, the availability of caregivers and specialized services in close proximity, institutional resources, and reimbursement. Hospice is a leading, but not the only, model of pal liative care services. In the United States, slightly more than a third— 35.7%—of hospice care is provided in private residential homes, with 14.5% of hospice care in nursing homes. In the United States, Medicare pays for hospice services under Part A, the hospital insurance part of reimbursement. Two physicians must certify that the patient has a prognosis of ≤6 months if the disease runs its usual course. Progno ses are probabilistic by their nature; patients are not required to die within 6 months but rather to have a condition from which half the individuals with it would not be alive within 6 months. While many have advocated for allowing hospice patients to continue with curative treatments, Medicare does not cover hospice services if patients are receiving curative therapy related to their terminal illness. However, hospice patients can still receive medical services for other comorbid conditions. Patients also can withdraw enrollment and reenroll later; the hospice Medicare benefit can be revoked later to secure traditional Medicare benefits. Payments to the hospice are per diem (or capitated), not fee-for-service. Payments are intended to cover physician services for the medical direction of the care team; regular home care visits by registered nurses and licensed practical nurses; home health aide and homemaker services; chaplain services; social work services; bereave ment counseling; and medical equipment, supplies, and medications. No specific therapy is excluded, and the goal is for each therapy to be considered for its symptomatic (as opposed to disease-modifying) effect. Additional clinical care, including services of the primary physi cian, is covered by Medicare Part B even while the hospice Medicare benefit is in place. The Affordable Care Act directed the secretary of Health and Human Services to gather data on Medicare hospice reimbursement with the goal of reforming payment rates to account for resource use over an entire episode of care. The legislation also required additional evaluations and reviews of eligibility for hospice care by hospice physicians or nurses. The Center for Medicare and Medicaid Innovation (CMMI) sponsors and carries out demonstration projects to test models and evaluate the potential of new methods. Between 2012 and 2021, CMMI carried out four palliative care demonstration projects that demonstrated improve ment in patient and caregiver experience of care and quality of life. For

instance, the Medicare Care Choices Model (MCCM) that ran from 2016 to 2021 offered participants supportive services without forgoing payment for curative services and found that offering supportive ser vices reduced expenditures per beneficiary by 14% ($7,254 per capita), driven by a reduction in utilization of resource-intensive services at the end of life, notably a 38% reduction in ICU days, a 26% reduction in inpatient admissions, and a 14% reduction in emergency department visits. The Medicare Advantage (MA) Value-Based Insurance Design (VBID) Model, which was started in 2021 and extended through 2030, is currently testing the inclusion of hospice in MA, which covers 8% of the market and includes important health plans.

PART 1 The Profession of Medicine By 2021, the average length of enrollment in a hospice for Medicare beneficiaries was 92 days. However, the median length of stay was just 17 days, suggesting most patients are in hospice for a short time. In fact, over a third of patients referred to hospice die within 7 days of arriving and 1 in 10 die within 72 h. Around 5% of patients live longer than 6 months, with patients with neurologic diagnoses (155 days), COPD (140 days), and heart/circulatory disease (104 days) having the longest average lengths of hospice. Such short stays create barriers to establish ing high-quality palliative services in patients' homes and also place financial strains on hospice providers since the initial assessments are resource intensive. Physicians should initiate early referrals to the hos pice to allow more time for patients to receive palliative care. Several cognitive biases predispose physicians to referring patients to hospice services late. Studies have shown that when asked to prog nosticate, physicians are both inaccurate and systematically optimistic. When asked to predict the number of days patients referred to hospice would survive, the referring providers overestimated prognosis by a factor of 5.3. Only one in five predictions was within 33% of actual survival, while two-thirds were overestimated by over a third. Notably, the longer physicians had been with their patient and the more recently they had seen them, the less accurate their predictions were, suggesting that physicians overestimate how long patients will live the better they knew them. In response to these innate biases, the "surprise question" was developed as a clinical heuristic. Using this tool, instead of asking "Do I expect this patient to do X in the next Y period of time," the clini cian instead asks the question "Would I be surprised if this patient did X in the next Y period of time?" While the "surprise question" was originally studied to predict 12-month mortality to aid in referral to palliative care in the primary care setting, it has since been validated in trials in a variety of settings, including dialysis patients, cancer patients, overall 1-year mortality, and overall 1-month mortality. In the United States, hospice care has been the main method for securing palliative services for terminally ill patients. However, leading physicians have increasingly emphasized the need to introduce pallia tive care much earlier in a patient's illness, and efforts are being made to develop palliative care services that can be provided before the last 6 months of life and across a variety of settings. Studies of terminally ill patients indicate that those who received in-home palliative care delivered by an interdisciplinary team compared to usual care were more satisfied, more likely to die at home, and had fewer visits to the emergency room and lower per-day costs. More companies and home health agencies are now offering nonhospice palliative care services in patients' homes in an effort to increase quality of life and forestall emergency room visits and hospitalizations. Similarly, palliative care services are increasingly available via consultation, rather than being available only in hospital, day care, outpatient, and nursing home settings. Palliative care consul tations for nonhospice patients can be billed as for other consultations under Medicare Part B. It is argued that using palliative care earlier in a patient's illness allows patients and family members to become more acculturated to avoiding life-sustaining treatments, facilitating a

smoother transition to hospice care closer to death. ■ ■WITHDRAWING AND WITHHOLDING

LIFE-SUSTAINING TREATMENT Legal Aspects For centuries, it has been deemed ethical to with hold or withdraw life-sustaining interventions. The current legal

consensus in the United States and most wealthy countries is that patients have a moral as well as legal right to refuse medical interven tions. American courts also have held that incompetent patients have a right to refuse medical interventions. For patients who are incompetent and terminally ill and who have not completed an advance care direc tive, next of kin can exercise that right, although this may be restricted in some states, depending on how clear and convincing the evidence is of the patient's preferences. Courts have limited families' ability to terminate life-sustaining treatments in patients who are conscious and incompetent but not terminally ill. In theory, a patient's right to refuse medical therapy can be limited by four countervailing interests: (1) preservation of life, (2) prevention of suicide, (3) protection of third parties such as children, and (4) preservation of the integrity of the medical profession. In practice, these interests almost never override the right of competent patients and incompetent patients who have left explicit wishes or advance care directives. For incompetent patients who either appointed a proxy without specific indications of their wishes or never completed an advance care directive, three criteria have been suggested to guide the decision to terminate medical interventions. First, some commentators suggest that ordinary care should be administered but extraordinary care could be terminated. Because the ordinary/extraordinary distinction is too vague, courts and commentators widely agree that it should not be used to justify decisions about stopping treatment. Second, many courts have advocated the use of the substituted-judgment criterion, which holds that the proxy decision-makers should try to imagine what the incompetent patient would do if they were competent. However, multi ple studies indicate that many proxies, even close family members, can not accurately predict what the patient would have wanted. Therefore, substituted judgment becomes more of a guessing game than a way of fulfilling the patient's wishes. Finally, the best-interests criterion holds that proxies should evaluate treatments by balancing their benefits and risks and select those treatments where the benefits maximally out weigh the burdens of treatment. Clinicians have a clear and crucial role in this by accurately and dispassionately explaining the known benefits and burdens of specific treatments. Yet even when that information is as clear as possible, different individuals can have very different views of what is in the patient's best interests, and families may have disagree ments or even overt conflicts. This criterion has been criticized because there is no single way to determine the balance between benefits and burdens; it depends on a patient's personal values. For instance, for some people, being alive even if mentally incapacitated is a benefit, whereas for others, it may be the worst possible existence. As a matter of practice, physicians rely on family members to make decisions that they feel are best and object only if those decisions seem to demand treatments that the physicians consider not beneficial. Practices Withholding and withdrawing acutely life-sustaining medical interventions from terminally ill patients are now standard practice. More than 90% of American patients die without cardiopul monary resuscitation (CPR), and just as many forgo other potentially life-sustaining interventions. For instance, in ICUs in the period of 1987–1988, CPR was performed 49% of the time, but it was performed only 10% of the time in 1992–1993 and on just 1.8% of admissions from 2001 to 2008. On average, 3.8 interventions, such as vasopressors and transfusions, were stopped for each dying ICU patient. However, up to 19% of decedents in hospitals received interventions such as extubation, ventilation, and surgery in the 48 h preceding death. There is wide variation in

practices among hospitals and ICUs, suggesting an important element of physician preferences rather than consistent adherence to professional society recommendations. Mechanical ventilation may be the most challenging intervention to withdraw. The two approaches are terminal extubation, which is the removal of the endotracheal tube, and terminal weaning, which is the gradual reduction of the fraction of inspired oxygen (FIO2) or ventilator rate. One-third of ICU physicians prefer to use the terminal weaning technique, and 13% extubate; the majority of physicians utilize both techniques. The American Thoracic Society's 2008 clinical policy guidelines note that there is no single correct process of ventilator

withdrawal and that physicians use and should be proficient in both methods but that the chosen approach should carefully balance ben efits and burdens as well as patient and caregiver preferences. Some recommend terminal weaning because patients do not develop upper airway obstruction and the distress caused by secretions or stridor; however, terminal weaning can prolong the dying process and not allow a patient's family to be with the patient unencumbered by an endotracheal tube. To ensure comfort for conscious or semiconscious patients before withdrawal of the ventilator, neuromuscular blocking agents should be terminated and sedatives and analgesics adminis tered. Removing the neuromuscular blocking agents permits patients to show discomfort, facilitating the titration of sedatives and analgesics; it also permits interactions between patients and their families. A com mon practice is to inject a bolus of midazolam (2–4 mg) or lorazepam (2–4 mg) before withdrawal, followed by a bolus of 5–10 mg of mor phine and continuous infusion of morphine (50% of the bolus dose per hour) during weaning. In patients who have significant upper airway secretions, IV scopolamine at a rate of 100 µg/h can be administered. Additional boluses of morphine or increases in the infusion rate should be administered for respiratory distress or signs of pain. Higher doses will be needed for patients already receiving sedatives and opioids. The median time to death after stopping of the ventilator is 1 h. However, up to 10% of patients unexpectedly survive for 1 day or more after mechanical ventilation is stopped. Women and older patients tend to survive longer after extubation. Families need to be reassured about both the continuations of treatments for common symptoms, such as dyspnea and agitation, after withdrawal of ventilatory support and the uncertainty of length of survival after withdrawal of ventilatory support. ■ ■FUTILE CARE Beginning in the late 1980s, some commentators argued that physi cians could terminate futile treatments demanded by the families of terminally ill patients. Although no objective definition or standard of futility exists, several categories have been proposed. Physiologic futility means that an intervention will have no physiologic effect. Some have defined qualitative futility as applying to procedures that "fail to end a patient's total dependence on intensive medical care." Quantitative futility occurs "when physicians conclude (through personal experience, experiences shared with colleagues, or consid eration of reported empiric data) that in the last 100 cases, a medi cal treatment has been useless." The term conceals subjective value judgments about when a treatment is "not beneficial." Deciding whether a treatment that obtains an additional 6 weeks of life or a 1% survival advantage confers benefit depends on patients' preferences and goals. Furthermore, physicians' predictions of when treatments are futile deviate markedly from the quantitative definition. When residents thought CPR was quantitatively futile, more than one in five patients had a >10% chance of survival to hospital discharge. Most studies that purport to guide determinations of futility are based on insufficient data and therefore cannot provide statistical confidence for clinical decision-making. Quantitative futility rarely applies in ICU settings. Many commentators reject using futility as a criterion for withdraw ing care, preferring instead to consider futility

situations as ones that represent conflict that calls for careful negotiation between families and health care providers. Importantly, the American Medical Asso ciation clearly states that “respecting patient autonomy does not mean that patients should receive specific interventions simply because they (or their surrogates) request them.” That is, ethically, physicians can refuse patient or caregiver requests for treatments. The American Medical Association and other professional societies have developed process-based approaches to resolving cases clinicians feel are futile. These process-based measures mainly suggest involving consultants and/or ethics committees when there are seemingly irresolvable dif ferences. Some hospitals have enacted “unilateral do-not-resuscitate” policies to allow clinicians to provide a do-not-resuscitate order in cases in which consensus cannot be reached with families and medical opinion is that resuscitation would be futile if attempted. This type of a

policy is not a replacement for careful and patient communication and negotiation but recognizes that agreement cannot always be reached.

In 1999, Texas enacted the so-called Futile Care Act. Other states, such as Virginia, Maryland, and California, have also enacted such laws that provide physicians a “safe harbor” from liability if they refuse a patient’s or family’s request for life-sustaining interventions. It appears that 19 state laws protect a physician’s futility judgment. For instance, in Texas, when a disagreement about terminating interventions between the medical team and the family has not been resolved by an ethics consultation, the physician is tasked with trying to facilitate transfer of the patient to an institution willing to provide treatment. If this fails after 10 days, the hospital and physician may unilaterally withdraw treatments determined to be futile. The family may appeal to a state court. Data suggest that the law increases futility consultations for the ethics committee and that, although most families concur with with drawal, ~10–15% of families refuse to withdraw treatment. As of 2007, there had been 974 ethics committee consultations on medical futil ity cases and 65 in which committees ruled against families and gave notice that treatment would be terminated. In 2007, a survey of Texas hospitals showed that 30% of hospitals had used the futility law in 213 adult cases and 42 pediatric cases. Treatment was withdrawn for 27 of those patients, and the remainder were transferred to other facilities or died while awaiting transfer. CHAPTER 13 Palliative and End-of-Life Care ■ ■EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE Euthanasia and PAS are defined in Table 13-8. Terminating life-sustaining care and providing opioid medications to manage symptoms such as pain or dyspnea have long been considered ethical by the medical pro fession and legal by courts and should not be conflated with euthanasia or PAS. Some advocates, especially in the United States, urge the use of the term physician-assisted death (PAD), rather than physician-assisted suicide (PAS), on the idea that it is not suicide. This is not accepted in many countries, and the terms themselves remain under dispute and are used inconsistently. For instance, in the Netherlands, PAD applies to terminating life-sustaining treatments, such as a ventilator, not providing pills to a patient who takes them to end their life. In the United Kingdom, PAD applies to prescribing life-ending interventions to terminally ill patients, while PAS applies to prescribing life-ending interventions to patients who are not necessarily terminally ill. Thus, TABLE 13-8 Definitions of Physician-Assisted Suicide and Euthanasia TERM DEFINITION LEGAL STATUS Voluntary active euthanasia Intentionally administering medications or other interventions to cause the patient’s death with the patient’s informed consent Netherlands, Belgium, Luxembourg, Canada, Colombia, Spain, Western Australia, New Zealand Involuntary active euthanasia Intentionally administering medications or other interventions to cause the patient’s death when

the patient was competent to consent but did not—e.g., the patient may not have been asked Nowhere Passive euthanasia Withholding or withdrawing life-sustaining medical treatments from a patient to let the patient die (terminating life-sustaining treatments) Everywhere Physicianassisted suicide A physician provides medications or other interventions to a patient with the understanding that the patient can use them to commit suicide Netherlands, Belgium, Luxembourg, Canada, Colombia, Germany, Switzerland, Oregon, Washington, Montana, Vermont, California, Colorado, District of Columbia, Hawaii, Maine, New Jersey, New Mexico

in many countries, PAD is a misnomer if it is meant to replace or cover PAS. That is why we use the term PAS.

Legal Aspects Euthanasia and PAS are legal in the Netherlands, Belgium, Luxembourg, Colombia, Canada, Spain, Portugal, Western Australia, and New Zealand. Euthanasia was legalized in the Northern Territory of Australia in 1996, but that legislation was repealed 9 months later in 1997. Under certain conditions, a layperson in Switzerland or Germany can legally elect assisted suicide. In the United States, PAS is legal in Washington, D.C., and 10 states: Oregon, Washington State, Montana, Vermont, California, Colorado, Hawaii, Maine, New Jersey, and New Mexico. No state in the United States has legalized euthana sia. In 2009, the state supreme court of Montana ruled that state law permits PAS for terminally ill patients. In 2021 and 2023, respectively, Spain and Portugal became the most recent countries to legalize both euthanasia and PAS. Many other countries are actively debating the legalization of euthanasia and/or PAS. PART 1 The Profession of Medicine In the United States, multiple criteria must be met for PAS: the patient must have a terminal condition of <6 months and must be determined eligible through a process that includes a 15-day wait ing period. Many countries, such as the Netherlands, do not require patients to be terminally ill to obtain euthanasia or PAS. Instead, the key criterion is that patients must have “unbearable suffering” regardless of whether they have a terminal illness. In Canada, patients requesting euthanasia or PAS need not be terminally ill. Canadian law allows patients with chronic conditions to receive euthanasia or PAS. Practices Fewer than 10–20% of terminally ill patients actually consider euthanasia and/or PAS for themselves. Use of euthanasia and PAS is increasing but remains relatively rare. In all countries, even the Netherlands and Belgium where these practices have been tolerated and legal for many years, at most 5% of deaths occur by euthanasia or PAS. As of the most recent data in the Netherlands, 5.1% of all deaths were by euthanasia or PAS (2022) and 2.5% of all deaths were by euthanasia in Belgium (2013). Canada enacted its Medical Assistance in Dying Laws <8 years ago and expanded which patients could be eligible in 2021. In 1 year, the use of euthanasia or PAD increased 30% with >4% of all deaths in Canada being euthanasia or PAS. Conversely, after 25 years of enactment, just 0.82% of all deaths in Oregon in 2023 (367 of 44,681 deaths) and 0.53% of all deaths in Washington State in 2022 (363 of 69,116 deaths) were reported to be by PAS, although these may be underestimates since the cause of some deaths of patients who received medications could not be verified. In Belgium, the Netherlands, Oregon, and Washington, >70% of patients utilizing these interventions are dying of cancer; <10% of deaths by euthanasia or PAS involve patients with AIDS or amyotrophic lateral sclerosis. While the numbers are small, in the Netherlands, the numbers of euthanasia or PAS cases in patients with psychiatric disor ders, dementia, and the accumulation of health issues are increasing. Pain is not the primary motivator for patients’ requests for or interest in euthanasia and/or PAS. Among the first patients to receive PAS in Oregon, only 1 of the 15 patients had inadequate pain control, compared with 15 of the 43 patients in a control group who experienced

inadequate pain relief. In 2022, 31% of patients in Oregon seeking PAS currently cite pain or fear of pain as their main reason for doing so compared to 46% in Washington. Concerningly, the percentage of patients who cite inadequate pain control has increased over the past 15 years, with only 10% of patients in Oregon and 25% of patients in Washington citing inadequate pain control as a motivating factor in 2009. Conversely, depression and hopelessness are strongly associated with patient interest in euthanasia and PAS. Losing autonomy (86% Oregon [OR], 83% Washington [WA]), not being able to enjoy activities (89% OR, 83% WA), and fear of losing dignity (62% OR, 69% WA) are the most-cited end-of-life concerns in both states. Impor tantly, a recent study of 25 years of experience in Oregon reported that “there was an increase in patients feeling a burden and describing financial concerns as reasons for choosing an assisted death.” A study from the Netherlands showed that depressed terminally ill cancer patients were four times more likely to request euthanasia and confirmed that uncontrolled pain was not associated with greater interest in euthanasia.

Importantly, a growing number of cases in Oregon appear to be transactional rather than arising from a long-standing physician– patient relationship. Over 25 years, there has been a substantial decline in physician–patient relationship before the doctor provides medications, from an average of 18 weeks to just 5 weeks. More over, <1% of patients are referred for formal psychiatric assessment before prescription. Similarly, in Canada, where >4.1% of all deaths are accounted for by medically assisted suicide, the two most common motivating fac tors for assisted suicide are loss of ability to engage in meaningful life activities (86%) and loss of ability to perform activities of daily living (82%). Again, concerningly, 59% cited inadequate pain control, 47% cited inadequate symptom control, and 35% cited feeling like they were a burden on their family, friends, or caregivers as motivating factors. In addition, cases of health care providers not just responding to patients’ inquiries for euthanasia or PAS but actively encouraging them to use these interventions have been reported. Euthanasia and PAS are no guarantee of a painless, quick death. Data from the Netherlands indicate that in as many as 20% of eutha nasia and PAS cases, technical and other problems arose, including patients waking from coma, not becoming comatose, regurgitating medications, and experiencing a prolonged time to death. Data from Oregon between 1998 and 2017 and Washington between 2009 and 2017 indicate that of patients who received PAS prescriptions, 81% died at home and prescribers were present in 9.7% of cases. The time between drug intake and coma ranged from 1 min to 11 h, and the time from drug intake to death ranged from 1 min to 104 h. The median time from ingestion to coma was 5 min and from ingestion to death was 25 min. In Oregon between 1998 and 2015, 53% of patients had no complications, 44% of patients had no data on complications, and 2.4% of patients had regurgitation after taking the prescribed medicine as the only complication. In addition, six patients awakened. In Washington State between 2014 and 2015, 1.4% of patients had regurgitation, one patient had a seizure, and the reported range of time to death extended to 30 h. In the Netherlands, problems were significantly more common in PAS, sometimes requiring the physician to intervene and provide euthanasia. Regardless of whether they practice in a setting where euthanasia is legal or not, many physicians over the course of their careers will receive a patient request for euthanasia or PAS. In the United States, 18% of physicians have received a request for PAS and 11% have received a request for euthanasia. Three percent complied with a request for PAS, while 5% complied with a request for euthanasia. In the Netherlands, where the practices are legal, 77% of physicians have received a request for PAS or euthanasia and 60% have performed these interventions. In Oregon in 2022, 167 physicians participated in PAS out of a total of ~6300 (2.6%). Competency in dealing

with such a request is crucial. Although challenging, the request can also provide a chance to address intense suffering. After receiving a request for euthanasia and/or PAS, health care providers should carefully clarify the request with empathic, openended questions to help elucidate the underlying cause for the request, such as, “What makes you want to consider this option?” Endorsing either moral opposition or moral support for the act tends to be coun terproductive, giving an impression of being judgmental or of endors ing the idea that the patient’s life is worthless. Health care providers must reassure the patient of continued care and commitment. The patient should be educated about alternative; less laden options, such as symptom management and withdrawing any unwanted treatments; and the reality of euthanasia and/or PAS, since the patient may have misconceptions about their effectiveness as well as the legal implica tions of the choice. Depression, hopelessness, and other symptoms of psychological distress, as well as physical suffering and economic bur dens, are likely factors motivating the request, and such factors should be assessed and treated aggressively. After these interventions and clarification of options, most patients proceed with another approach, declining life-sustaining interventions, possibly including refusal of nutrition and hydration.

■ ■CARE DURING THE LAST HOURS Most laypersons have limited experiences with the actual dying process and death. They frequently do not know what to expect of the final hours and afterward. The family and other caregivers must be pre pared, especially if the plan is for the patient to die at home. Patients in the last days of life typically experience extreme weakness and fatigue and become bedbound; this can lead to pressure sores. The issue of turning patients who are near the end of life, however, must be balanced against the potential discomfort that movement may cause. Patients stop eating and drinking with drying of mucosal membranes and dysphagia. Careful attention to oral swabbing, lubricants for lips, and use of artificial tears can provide a form of care to substitute for attempts at feeding the patient. With loss of the gag reflex and dys phagia, patients may also experience accumulation of oral secretions, producing noises during respiration sometimes called “the death rattle.” Scopolamine can reduce the secretions. Patients also experi ence changes in respiration with periods of apnea or Cheyne-Stokes breathing. Decreased intravascular volume and cardiac output cause tachycardia, hypotension, peripheral coolness, and livedo reticularis (skin mottling). Patients can have urinary and, less frequently, fecal TABLE 13-9 Managing Changes in the Patient’s Condition during the Final Days and Hours CHANGES IN THE PATIENT’S CONDITION POTENTIAL COMPLICATION FAMILY’S POSSIBLE REACTION AND CONCERN ADVICE AND INTERVENTION Profound fatigue Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain Patient is lazy and giving up. Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted. Use an air mattress if necessary. Anorexia None Patient is giving up; patient will suffer from hunger and will starve to death. Dehydration Dry mucosal membranes

(see below) Patient will suffer from thirst and die of dehydration. Dysphagia Inability to swallow oral medications needed for palliative care Do not force oral intake. Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives. If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration. “Death rattle”— noisy breathing Patient is choking and suffocating. Apnea, Cheyne-Stokes respirations, dyspnea Patient is suffocating. Reassure family and caregivers that unconscious patients do not experience suffocation or air hunger. Apneic episodes are frequently a premorbid change. Opioids

or anxiolytics may be used for dyspnea. Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process. Urinary or fecal incontinence Skin breakdown if days until death Potential transmission of infectious agents to caregivers Patient is dirty, malodorous, and physically repellent. Agitation or delirium Day/night reversal Hurt self or caregivers Patient is in horrible pain and going to have a horrible death. Dry mucosal membranes Cracked lips, mouth sores, and candidiasis can also cause pain Odor Patient may be malodorous, physically repellent.

incontinence. Changes in consciousness and neurologic function gen erally lead to two different paths to death.

Each of these terminal changes can cause patients and families dis tress, requiring reassurance and targeted interventions (Table 13-9). Informing families that these changes might occur and providing them with an information sheet can help preempt problems and minimize distress. Understanding that patients stop eating because they are dying, not dying because they have stopped eating, can reduce family and caregiver anxiety. Similarly, informing the family and caregivers that the “death rattle” may occur and that it is not indicative of suf focation, choking, or pain can reduce their worry from the breathing sounds. CHAPTER 13 Palliative and End-of-Life Care Families and caregivers may also feel guilty about stopping treat ments, fearing that they are “killing” the patient. This may lead to demands for interventions, such as feeding tubes, that may be inef fective. In such cases, the physician should remind the family and caregivers about the inevitability of events and the palliative goals. Interventions may prolong the dying process and cause discomfort. Physicians also should emphasize that withholding treatments is both legal and ethical and that the family members are not the cause of the Reassure family and caregivers that the patient is not eating because they are dying; not eating at the end of life does not cause suffering or death. Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life. Reassure family and caregivers that dehydration at the end of life does not cause suffering because patients lose consciousness before any symptom distress. Intravenous hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong the dying process. Reassure the family and caregivers that this is caused by secretions in the oropharynx and the patient is not choking. Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d). Reposition patient to permit drainage of secretions. Do not suction. Suction can cause patient and family discomfort and is usually ineffective. Remind family and caregivers to use universal precautions. Frequent changes of bedclothes and bedding. Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output. Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain. Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modifying medications. Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam. Use baking soda mouthwash or saliva preparation q15–30 min. Use topical nystatin for candidiasis. Coat lips and nasal mucosa with petroleum jelly q60–90 min. Use ophthalmic lubricants q4h or artificial tears q30 min.

patient’s death. This reassurance may have to be provided multiple times.

Hearing and touch are said to be the last senses to stop functioning. Whether this is the case or not, families and caregivers can be encour aged to communicate with the dying patient. Encouraging them to talk directly to the patient, even if the patient is unconscious, and hold the patient’s hand or demonstrate affection in other ways can be an effec tive way to channel their

urge “to do something” for the patient. PART 1 The Profession of Medicine When the plan is for the patient to die at home, the physician must inform the family and caregivers how to determine that the patient has died. The cardinal signs are cessation of cardiac function and respira tion; the pupils become fixed; the body becomes cool; muscles relax; and incontinence may occur. Remind the family and caregivers that the eyes may remain open even after the patient has died. The physician should establish a plan for who the family or care givers will contact when the patient is dying or has died. Without a plan, family members may panic and call 911, unleashing a cascade of unwanted events, from arrival of emergency personnel and resus citation to hospital admission. The family and caregivers should be instructed to contact the hospice (if one is involved), the covering phy sician, or the on-call member of the palliative care team. They should also be told that the medical examiner need not be called unless the state requires it for all deaths. Unless foul play is suspected, the health care team need not contact the medical examiner either. Just after the patient dies, even the best-prepared family may experi ence shock and loss and be emotionally distraught. They need time to assimilate the event and be comforted. Health care providers are likely to find it meaningful to themselves and the patient’s caregivers to write a bereavement card or letter to the family. The purpose is to com municate about the patient, perhaps emphasizing the patient’s virtues and the honor it was to care for the patient, and to express concern for the family’s hardship. Some physicians attend the funerals of their patients. Although this is beyond any medical obligation, the presence of the physician can be a source of support to the grieving family and provides an opportunity for closure for the physician. Death of a spouse is a strong predictor of poor health, and even mortality, for the surviving spouse. It may be important to alert the spouse’s physician about the death so that they are aware of symptoms that might require professional attention. ■ ■FURTHER READING Emanuel E et al: Attitudes and practices of euthanasia and physician-

assisted suicide in the United States, Canada, and Europe. JAMA 316:79, 2016. Kelley AS, Meier DE: Palliative care—A shifting paradigm. N Engl J Med 363:781, 2010.

Kelley AS et al: Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay. Health Aff 32:552, 2012. Kelley AS et al: Palliative care for the seriously ill. N Engl J Med 373:747, 2015. Mack JW et al: Associations between end-of-life discussion character istics and care received near death: A prospective cohort study. J Clin Oncol 30:4387, 2012. Murray SA et al: Illness trajectories and palliative care. BMJ 330:1007, 2005. Neuman P et al: Medicare per capita spending by age and service: New data highlights oldest beneficiaries. Health Aff (Millwood) 34:335, 2015. Nicholas LH et al: Regional variation in the association between advance directives and end-of-life Medicare expenditures. JAMA 306:1447, 2011. Ornstein KA et al: Evaluation of racial disparities in hospice use and end-of-life treatment intensity in the REGARDS cohort. JAMA Netw Open 3:e2014639, 2020. Quinn KL et al: Association of receipt of palliative care interventions with health care use, quality of life, and symptom burden among adults with chronic noncancer illness: A systematic review and metaanalysis. JAMA 324:1439, 2020. Teno JM et al: Change in end-of-life care for Medicare beneficiaries: Site of death, place of care, and health transitions in 2000, 2005, and 2009. JAMA 309:470, 2013. Teno JM et al: Site of death, place of care, and health care tran sitions among US Medicare beneficiaries, 2000-2015. JAMA 320:264, 2018. Van Den Beuken-VanEverdingen MH et al: Update on prevalence of pain in patients with cancer: Systematic review and meta-analysis. J Pain Symptom Manage 51:1070, 2016. ■
■WEBSITES American Academy of Hospice and Palliative Medicine: www. aahpm.org Center to

Advance Palliative Care: http://www.capc.org Education in Palliative and End of life Care (EPEC): http:// www.epec.net Family Caregiver Alliance: http://www.caregiver.org National Hospice and Palliative Care Organization (including state-specific advance directives): http://www.nhpco.org NCCN: The National Comprehensive Cancer Network palliative care guidelines: http://www.nccn.org Our Care Wishes Advance Care Planning Tool: https://www

.ourcarewishes.org