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Schizophrenia and related psychoses CHAPTER 1 Genetic testing for clozapine treatment A great number of studies have sought to detect genetic predictors of clozapine outcomes, both therapeutic and adverse. Generally, only small effects have been uncovered and clinical utility is limited unless genetic variant effects are mathematically combined. Sensitivity (the likelihood of accurately predicting a specific outcome) is usually low but specificity (the likelihood of correctly excluding that outcome) is often very high. Numerical values for these categories can be combined with population incidence data to generate positive predictive value (PPV – the % of people who will experience the outcome when predicted) and negative predictive value (NPV – the % of people who will not experience that outcome when it is not predicted). This concept is applicable to genetic variants linked to agranulocytosis. The presence of a candidate variant (see PPV below) should provoke caution and perhaps more frequent testing. The absence of a candidate variant (see NPV) may give some reassurance about the likelihood of agranulocytosis, especially if the NPV is >99.6% (that is, 100 minus 0.4%, the risk of agranulocytosis in the wider population). Response Three variants have been reliably shown to predict therapeutic outcome with clozapine:1 HTR2A rs6313C CC carriers less likely to respond than T carriers CC 146/272 response, CT/TT 366/596 response (54% vs 62%) HTR2A rs6314 C allele more likely to respond than T allele C allele response 685/1,215, T allele 55/127 (56% vs 43%) HTR3A rs1062613 C allele less likely to respond than T allele C allele response 528/841, T allele 134/185 (63% vs 72%) Mathematical modelling of these three variants can generate an overall percentage chance of response with confidence intervals. Other variants may be linked to response. Agranulocytosis Several genetic variants are reliably associated with altered risk of agranulocytosis. Some variants are found only in certain ethnic groups. HLA-DQB1 Sequence variant 6672G>C (REC 21G) confers 1,175% higher risk of agranulocytosis than general population. Sensitivity 21.5%, specificity 98.4%.2 PPV 5.1%, NPV 99.7%. In people of European ancestry, sensitivity is 53.7% and this variant confers a 10-fold greater risk of agranulocytosis.3 HLA-DQB1 DQB1*0502 allele is associated with agranulocytosis in 5 of 7 studies (e.g. Dettling and colleagues,4 Yunis and colleagues5). Effect size variable.

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