Reviewer’s report

Title: Personalized medicine in psychiatry: problems and promises

Version: 1 Date: 2 December 2012

Reviewer: Gavin Reynolds

Reviewer’s report:

This manuscript addresses a highly topical area of research. It is impressive in its attempted scope; the authors have gone beyond risk factors related to the consequences of treatment (which could be a narrow definition of personalised medicine) to address risk factors and biomarkers associated with disease and diagnosis. However, the depth of coverage of each topic is very variable, with some aspects only dealt with superficially. This is perhaps inevitable in such a broad approach, however the reader needs some explicit guidance where a comprehensive assessment of the literature has not been attempted and the information provided is solely an example of the various findings, many of which may be more informative than those cited. I feel this makes for an imbalanced and inconsistent content, and is the issue underlying many of the specific comments I make below.

1. p2 the authors refer to "rare genetic variants" although many are in fact common but still account for a small percentage of heritability.

2. p3 In addressing TPH they authors could make clear the different functionality, distribution and hence relevance of the two subtypes.

3. p12 The authors make useful reference to SZgene but miss a w from the web address. However, they mention few of the risk genes, and arguably not the most important. Neuregulin1, RGS4, ZNF804A and others deserve some mention here, or at least there should be an indication that the genes discussed are two examples of several more.

4. p15 There is far more work on gene methylation in depression than the authors indicate. Essentially only one example is given here, although given the later discussion of BDNF, why do they not discuss this gene and its methylation, at least in relation to early life stress as a further risk factor, and in PTSD. Other genes - HTT, MTHFR - may also be relevant here.

5. The same goes for BD and schizophrenia - discussion of recent HTR1A and HTR2A methylation results would be valuable.

6. In discussion of biomarkers, there is some imbalance and selectivity in the topic discussed - measurement of CSF metabolites is not currently a realistic acceptable approach for clinical biomarker determination.

7. p22 BDNF discussion of serum vs plasma is not clear - the authors continue to mention "blood" levels.

8. p24 there is surprising focus on how the amount of alcohol intake is a correlate
of alcoholism. It is hard to take a valuable message from this point.

9. The authors discuss with clarity and depth the issue of environmental factors.

10. Much of the discussion around genetic correlates of treatment - which comes closer to what many think of as personalised medicine - is variable in its depth of coverage. There is a lot on MDD response, but little (perhaps rightly) on antidepressant side effects. In contrast in schizophrenia, the authors start by addressing genetics of TD, not a major problem for patients starting on current therapies, and then mention weight gain pharmacogenetics. This has been reviewed extensively in several recent reviews, and involves far more than 5-HT2C and leptin gene polymorphisms which have been frequently replicated, notwithstanding some failures. The authors are incorrect in stating that "the T-allele previously reported to be protective against weight gain was demonstrated to be associated with weight gain ... was subsequently supported by a meta-analysis". They also incorrectly imply weight gain to be a class effect of second generation drugs - early drugs such as chlorpromazine show weight gain.

11. Other than the results from the CATIE study, the authors only address dopamine D2 and D3 polymorphisms in schizophrenia symptom response, yet many other (and some replicated) candidate genes have been shown to have associations with response.

12. In the "emerging applications" section it would be valuable to acknowledge that there are already some gene-environment interaction studies yielding results in treatment response.

In conclusion, I feel that in attempting such a broad coverage, the authors have lost both depth (in many sections) and balance. This might be acceptable if they were to indicate what is being used solely as an example, acknowledging their lack of comprehensive coverage. Better, however, would be to focus on a component of this work - fewer disorders, perhaps, or the HPA axis and its related systems - and explore that in depth.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am consultant to a company, Optimal Medicine, that is developing clinical tools for personalised medicine.