Letter to the editor: reply to Bousman *et al.*

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“The benefit of pharmacogenetic-informed prescribing is not distributed uniformly across a cohort but is derived from a minority of patients.”

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We read with interest the meta-analysis of pharmacogenetic-informed prescribing in the management of patients with depression [1]. Despite the acknowledged heterogeneity in the patient populations, genes analyzed, prescribing practices, study durations and effect sizes, the pooled relative risk of remission (RRR) in the informed versus noninformed cohorts across five randomized control trials was 1.71 (95% CI: 1.17–2.48). This pooled RRR is highly relevant for the development of treatment guidelines and the funding of pharmacogenetic testing.

The benefit of pharmacogenetic-informed prescribing is not distributed uniformly across a cohort but is derived from a minority of patients. A cohort's rate of remission reflects the remission rates in those participants with actionable genotypes taking congruent medication, in those with actionable genotypes taking noncongruent medication and in those with nonactionable genotypes having 'treatment as usual'. The pooled RRR for a cohort is the average of these three rates weighted by the proportions of patients in each category. It is an increase in the proportion of patients in the first category that drives the pooled RRR reported from a clinical trial.

Clinicians will be interested in the potential benefit of pharmacogenetic-informed prescribing for an individual patient with an actionable genotype, in other words, the RRR for patients with actionable genotypes who receive congruent versus noncongruent medications. This describes the utility of informed prescribing for an individual patient ('patient-specific RRR') rather than for a cohort as a whole ('pooled RRR'). The patient-specific RRR will always be more than the pooled RRR because the latter reflects the dilution of the benefit from the minority of patients with actionable genotypes and congruent medication across the other two patient categories.

The trials included in the meta-analysis did not report these three rates and the associated frequencies in test and control cohorts. Hence, it was not possible to directly determine this patient-specific RRR across all studies. However, it is possible to model the relationship of the pooled RRR, patient-specific RRR and the frequency of actionable genotypes in the cohort. This modeling requires that reasonable assumptions be made about the other rates and frequencies. The figure shows the relationship between the pooled RRR (x-axis) and the patient-specific RRR (y-axis) for different frequencies of actionable genotypes. For example, if the pooled RRR is 1.7 and the frequency of actionable genotypes is 40%, the patient-specific RRR in this model is 3.2. In this case, we assumed the remission rate in patients with actionable genotypes on concordant medication (30%), the remission rate in patients with nonactionable genotypes (1.1-fold the rate in those with actionable genotypes on nonconcordant medication) and the proportions of patients with actionable genotypes on concordant medication in the test and control cohorts (100 and 10%, respectively) (Figure 1).

Figure 1. Modelled pooled versus patient-specific RRR.
RRR: Relative risk of remission.

The degree to which the patient-specific RRR exceeds the pooled RRR clearly depends on parameter values that, in this instance, are unknown. We do not seek to defend the values we assumed, and simply note that the patient-specific RRR rises faster than the pooled RRR, especially at low frequencies of actionable genotypes.

This simple modeling is no substitute for real data, but such data are rarely reported. In one of the trials in the meta-analysis, Greden *et al.* [2] reported a pooled RRR of 1.51. However, among the 213 patients with actionable genotypes, the patient-specific RRR for those on congruent versus noncongruent medications was 2.50, in keeping with the results of our modeling.

Pharmacogenetics is, in principle, an attempt to improve the efficacy and/or safety of drug therapy for a subset of the total patient population. We encourage those involved in randomized control trials of pharmacogenetics to include both pooled and patient-specific metrics as primary outcome measures. These data will inform our understanding of both the cohort-level and the individual-level benefits of pharmacogenetic-informed prescribing.

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Disclaimer

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