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Letter to the Editor: Clinical versus statistical significance of pharmacogenomic-guided antidepressant therapy: What's really being measured and marketed?

To the Editor,

We are troubled by the data presentation and conclusions reported in the GUIDED study by Greden et al. (2019), in which higher antidepressant response and remission rates in major depressive disorder (MDD) were reported with use of a proprietary combinatorial pharmacogenomics (PGx) algorithm than during treatment-as-usual (TAU). The authors acknowledge that the primary outcome of their study (8-week change in 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) scores) was negative, but nevertheless emphasize the statistical significance of their secondary outcomes of response and remission rates. They fail to mention that they examined 25 secondary outcome measures (as registered on ClinicalTrials.gov: NCT02109939) but used an alpha level uncorrected for multiplicity. (Bonferroni correction renders the reported p-values nominal.) Also underemphasized for both the guided and TAU study arms are the meager actual response rates (26.0% and 19.9%, respectively) and remission rates (15.3% and 10.1%, respectively). Unacknowledged is the modest *clinical* significance of these differences.

From the reported proportions we can calculate a number needed to treat (NNT) for response of 17, with an absolute risk reduction (ARR) of 6%, and for remission an NNT of 19, with an absolute risk reduction of 5.4%. These numbers substantially exceed the single-digit NNT's advised for judging an intervention to be clinically meaningful, as proposed by the United Kingdom's National Institute for Clinical Excellence (NICE). From an economic perspective, this translates to a retail cost of nearly $40,000 (approximately $2000/patient) to achieve one additional remission.

A previous open label GeneSight MDD study reported a much higher PGx-guided response rate (43.1% by $HAMD_{17}$ scores) but a similar TAU response rate to that reported in GUIDED (26.9%), with a resulting NNT = 6 (Hall-Flavin et al., 2013). The substantially larger response rate but similar TAU rate in open versus blinded PGx trials suggests a considerable expectancy bias when patients are told they will receive "personalized treatment." Juxtaposed, these findings imply that expectancy bias may contribute more to the AAR than does improved prescribing guided by PGx.

Antidepressant response is well-recognized as a multi-determinate phenomenon, but the relative contribution of genetic versus nongenetic patient- and clinician-specific factors is largely unknown. The authors' moderator analysis included baseline depression severity scores and several demographic factors but omitted other known contributors to antidepressant response such as chronicity, age at onset, baseline anxiety, depressive subtypes, comorbid personality disorders, psychosis, social isolation, education, or employment status (Shelton and Trivedi, 2011), as well as histories of trauma (Williams et al., 2016).

Perhaps even more importantly, the study design fails to account for stratification owing to variation in treaters' knowledge and expertise in psychopharmacology. The real study subjects in GUIDED were the prescribing groups themselves, and the potential interaction effect between prescriber acumen and patient characteristics. The possible impact of the PGx protocol is difficult to infer if the treating groups were unbalanced for their distribution of psychiatrists versus non-psychiatrists, levels of training, years of experience, and degrees of proficiency in the psychopharmacology of depression. Macaluso and Preskorn (2018) recently showed that antidepressant prescribing decisions equivalent to those obtained using a PGx protocol could be made simply by avoiding drugs that undergo oxidative metabolism – suggesting that the report may serve simply as a primer on basic pharmacokinetics. Without accounting for the above moderating factors, the authors' conclusions that genetic mechanisms importantly influence antidepressant response is unsubstantiated.

Other investigators have noted that commercial PGx test manufacturers promote their products with a zeal that is disproportionate to the existing evidence base (de Leon, 2016; Zubenko et al., 2018) – particularly when marketing to the lay public and clinicians who are likely unfamiliar with the limited statistical power of candidate gene association studies. (By comparison, genome-wide association studies (GWAS) require p-values of about 5×10^{-8} to capture a true finding.) Such concerns are echoed by the recent FDA consumer warning that there is insufficient evidence to support commercial claims that PGx testing can predict antidepressant response, and that patients could be harmed if clinicians inappropriately discontinued (or refused to prescribe) effective pharmacotherapies solely because they fell in the "red bin" (https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm). Similar caution against routine pharmacogenetic testing before starting antidepressant pharmacotherapy has been voiced by the Centers for Disease Control Evaluation of Genomic Applications in Practice and Prevention (EGAPP) (https://www.cdc.gov/genomics/gtesting/EGAPP/recommend/CYP450.htm) and the American Psychiatric Association Council on Research Task Force for Novel Biomarkers and Treatments (Zeier et al., 2018). The American College of Neuropsychopharmacology notes that "the polygenicity and complexity of risk, diagnosis and treatment in psychiatric illness makes genetic testing … scientifically unsupportable for general clinical use and certainly inappropriate in the direct-to-consumer arena" (https://acnp.org/wp-content/uploads/2018/07/ACNP-Statement-on-Genetic-Testing-for-Neuropsychiatric-Disorders.pdf).

We share the GUIDED authors' hope that pharmacogenetics may someday meaningfully inform personalized medicine in psychiatry in ways analogous to oncology. However, at present, busy mental health clinicians and other stakeholders could easily misconstrue the oversimplified findings from GUIDED as evidence that a genetic test can now identify "which antidepressant will work," sans other clinical information about a given patient.

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Appendix A. Supplementary data

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