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# Response to: Goldberg et al. and Severance et al. Letters to the Editor: The clinical significance of improving remission over standard of care – The reality of treatment resistant-based therapies

We read with interest the letters from Goldberg et al, 2019. and Severance et al, 2019. regarding our publication on the GUIDED trial, which evaluated the utility of combinatorial pharmacogenomic testing to guide medication selection for patients with difficult-to-treat depression. The authors raised several concerns about the GUIDED trial, to which we would like to respond.

The authors of both letters questioned the clinical relevance of our findings and suggest that the response and remission rates in GUIDED were meager. Study participants had an average of 3.5 failed medication trials, so the response and remission rates in GUIDED are consistent with prior trials that report remission rates of < 15% in well-controlled studies of patients with treatment resistant depression (TRD) (Lam et al., 2008; Mahmoud et al., 2007; McGrath et al., 2006; Rush et al., 2006) This highlights clinical challenges associated with TRD rather than a shortcoming of the GUIDED results. The 50% relative improvement in remission rate reported for GUIDED is consistent with all prior studies of this pharmacogenomic test, including two open-label trials (Hall-Flavin et. al., 2012, 2013; Winner et al., 2013). Although a placebo effect likely contributed to greater symptom improvement and response in the open-label studies compared to GUIDED, it is extremely unlikely that this 'expectancy bias' would substantially impact remission. Thus, we would suggest that the statistically significant improvements in remission associated with pharmacogenomic testing in the GUIDED trial could be considered clinically important.

The authors also criticize the fact that the number needed to treat (NNT) was 17 for response and 19 for remission in GUIDED, suggesting that this is not clinically meaningful. Goldberg et al, 2019. refer to the UK's National Institute for Clinical Excellence (NICE) guidelines in stating that NNTs must be < 10 to be clinically meaningful. However, NNT typically refers to trials that compare active and inactive treatments – e.g., drug versus placebo. Even within that context, FDA approval studies comparing the antidepressants vilazodone and vortioxetine against placebo in patients with a lower level of treatment resistance (< 2 previous medication failures) achieved NNTs for remission of 15 and 13, respectively (Jacobsen et al., 2015; Khan et al., 2011). Although the current NICE guidance on depression does not mention that NNTs should be < 10 (National Institute for Health and Care Excellence, 2009), the British Association for Psychopharmacology (BAP) guidelines specify that NNTs > 10 may be clinically relevant in TRD (Cleare et al., 2015). In addition, Roose et al. question the clinical relevance of NNTs from highly controlled drug studies that do not reflect real-world conditions (Roose et al., 2016). In light of the well-documented challenges in TRD, improvements in response and remission with pharmacogenomic testing establishes real-world evidence in the GUIDED trial, representing a clinically meaningful change relative to *active standard of care treatment*.

Goldberg et al, 2019. correctly point out that the GUIDED protocol included many secondary outcomes using additional depression rating scales and that the primary findings presented for HAM-D17 were not corrected for multiplicity. The Bonferroni correction cited by Goldberg et al, 2019. is considered to be overly conservative for tests with positively correlated results (Conneely and Boehnke, 2007; Shi et al., 2012; Streiner, 2015), which is the case here for the evaluated patient outcome measures and depression scales. Still, when the Bonferroni correction is applied to the standard outcomes of symptom improvement, response, and remission for the primary outcome scale (HAM-D17), response and remission remain significant for the GUIDED trial.

Goldberg et al, 2019. also call attention to several factors that may have influenced the results from GUIDED, including several non-genetic factors that may impact patient outcomes and provider's expertise in psychopharmacology. Although we agree that these factors can affect outcomes, they would reduce the likelihood of the test producing a significant result between study arms. In addition, GUIDED was designed as a randomized trial to enhance equivalence between arms.

Goldberg et al, 2019. questioned the utility and safety of using pharmacogenomic testing to make medication selections, raising two contradictory points. The authors first indicate that identifying gene-drug interactions may not 'importantly influence antidepressant response,' citing a recent study that suggests an increased knowledge of medications and metabolic pathways could allow providers to predict and avoid medications with severe gene-drug interactions (red-bin medications) (Macalusco and Preskorn, 2018). The authors then go on to question the safety of taking patients off red-bin medications, citing a consumer warning from the FDA (U.S. Food and Drug Administration, 2018). This highlights conflicting approaches in the field and the need for adjunct tools to inform medication selection. To this end, the greatest benefit for pharmacogenomic testing was observed for patients who switched off of red-bin medications in the GUIDED trial and other studies of the same test. From a population health point of view, identifying gene-drug interactions results in actionable improvements in patient outcomes.

We agree with the FDA consumer warning about pharmacogenomic testing in depression and believe that that a high level of evidence is required to justify clinical use (U.S. Food and Drug Administration, 2018). In our study, we called attention to the fact that available pharmacogenomic tests are not identical. While the level of evidence varies for each pharmacogenomic test, the clinical validity, clinical utility, and analytical validity of the pharmacogenomic test utilized in GUIDED has been demonstrated in multiple studies (Altar et al., 2015; Hall-Flavin et. al., 2012, 2013; Jablonski et al., 2018; Winner et al., 2013). Goldberg et al, 2019. cite additional guidelines that caution against pharmacogenomic testing due to insufficient evidence; however, these guidelines are not applicable here, as they were written before all or most of the validation studies for the pharmacogenomic test used in GUIDED (American College of Neuropsychopharmacology, 2014; EGAPP Working Group, 2007).

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Both letters cite health care cost concerns associated with broad pharmacogenomic testing based on back-of-the-envelope calculations. However, the economic burden associated with TRD is substantial, and overall health care costs have been shown to rise with each treatment step (Johnston et al., 2019). To this end, formal cost effectiveness studies have demonstrated a net reduction in healthcare expenses associated with pharmacogenomic testing in patients with prior medication failures (Benitez et al., 2018; Brown et al., 2017; Winner et al., 2015).

Overall, we agree with the position by Goldberg et al, 2019. and Severance et al, 2019. that clinical utilization of pharmacogenomic testing requires a high level of evidence to ensure appropriate patient care. However, the findings presented from GUIDED - a large, randomized, controlled, blinded trial - add to the existing evidence that the clinical utilization of this pharmacogenomic test results in improved patient outcomes compared to TAU. The clinically significant improvements over active treatment in TAU, particularly in remission rate, always the desired outcome, represent an important step forward in addressing the clinical dilemma of treating patients with TRD.

## Conflict of interest statement

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## References


Altar, C.A., Carhart, J.M., Allen, J.D., Hall-Flavin, D.K., Dechairo, B.M., Winner, J.G., 2015. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenomics J. 15 (5), 443–451.

American College of Neuropsychopharmacology, 2014. ACNP statement on genetic testing for neuropsychiatric disorders. https://acnp.org/wp-content/uploads/2018/07/ACNP-Statement-on-Genetic-Testing-for-Neuropsychiatric-Disorders.pdf.

Benitez, J., Cool, C.L., Scotti, D.J., 2018. Use of combinatorial pharmacogenomic guidance in treating psychiatric disorders. Per Med 15 (6), 481–494.

Brown, L.C., Lorenz, R.A., Li, J., Dechairo, B.M., 2017. Economic utility: combinatorial pharmacogenomics and medication cost savings for mental health care in a primary care setting. Clin. Ther. 39 (3), 592–602 e591.

Cleare, A., Pariante, C.M., Young, A.H., Anderson, I.M., Christmas, D., Cowen, P.J., Dickens, C., Ferrier, I.N., Geddes, J., Gilbody, S., Haddad, P.M., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R.H., Ramchandani, P., Scott, J., Taylor, D., Uher, R., 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J. Psychopharmacol. 29 (5), 459–525.

Conneely, K.N., Boehnke, M., 2007. So many correlated tests, so little time! Rapid adjustment of P values for multiple correlated tests. Am. J. Hum. Genet. 81 (6), 1158–1168.

EGAPP Working Group, 2007. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet. Med. 9 (12), 819–825.

Goldberg, J.F., Rosenblat, J.D., Preskorn, S.H., McIntyre, R.S., de Leon, J., 2019. Letter to the Editor: Clinical Versus Statistical Significance of Pharmacogenomic-Guided Antidepressant Therapy: What's Really Being Measured and Marketed? Journal of Psychiatric Research. https://doi.org/10.1016/j.jpsychires.2019.04.002.

Hall-Flavin, D.K., Winner, J.G., Allen, J.D., Carhart, J.M., Proctor, B., Snyder, K.A., Drews, M.S., Eisterhold, L.L., Geske, J., Mrazek, D.A., 2013. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics Genom. 23 (10), 535–548.

Hall-Flavin, D.K., Winner, J.G., Allen, J.D., Jordan, J.J., Nesheim, R.S., Snyder, K.A., Drews, M.S., Eisterhold, L.L., Biernacka, J.M., Mrazek, D.A., 2012. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl. Psychiatry 2, e172.

Jablonski, M.R., King, N., Wang, Y., Winner, J.G., Watterson, L.R., Gunselman, S., Dechairo, B.M., 2018. Analytical validation of a psychiatric pharmacogenomic test. Pers. Med. 15 (3), 189–197.

Jacobsen, P.L., Mahableshwarkar, A.R., Serenko, M., Chan, S., Trivedi, M.H., 2015. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. J. Clin. Psychiatry 76 (5), 575–582.

Johnston, K.M., Powell, L.C., Anderson, I.M., Szabo, S., Cline, S., 2019. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. J. Affect. Disord. 242, 195–210.

Khan, A., Cutler, A.J., Kajdasz, D.K., Gallipoli, S., Athanasiou, M., Robinson, D.S., Whalen, H., Reed, C.R., 2011. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J. Clin. Psychiatry 72 (4), 441–447.

Lam, R.W., Chan, P., Wilkins-Ho, M., Yatham, L.N., 2008. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. Can. J. Psychiatr. 53 (9), 621–631.
Macalusco, M., Preskorn, S.H., 2018. Knowledge of the pharmacology of antidepressants and antipsychotics yields results comparable with pharmacogenetic testing. J. Psychiatr. Pract. 24 (6), 416–419.
Mahmoud, R.A., Pandina, G.J., Turkoz, I., Kosik-Gonzalez, C., Canuso, C.M., Kujawa, M.J., Gharabawi-Garibaldi, G.M., 2007. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann. Intern. Med. 147 (9), 593–602.
McGrath, P.J., Stewart, J.W., Fava, M., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Thase, M.E., Davis, L., Biggs, M.M., Shores-Wilson, K., Luther, J.F., Niederehe, G., Warden, D., Rush, A.J., 2006. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am. J. Psychiatry 163 (9), 1531–1541 quiz 1666.
National Institute for Health and Care Excellence, 2009. Depression in Adults: Recognition and Management (CG90). https://www.nice.org.uk/guidance/cg90.
Roose, S.P., Rutherford, B.R., Wall, M.M., Thase, M.E., 2016. Practising evidence-based medicine in an era of high placebo response: number needed to treat reconsidered. Br. J. Psychiatry 208 (5), 416–420.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatry 163 (11), 1905–1917.
Severance, A.J., Good, C.B., Schuster, J.M., 2019. Letter to the Editor: Pharmacogenomic testing is not ready for general use in psychiatry. Journal of Psychiatric Research. https://doi.org/10.1016/j.jpsychires.2019.04.003.
Shi, Q., Pavey, E.S., Carter, R.E., 2012. Bonferroni-based correction factor for multiple, correlated endpoints. Pharmaceut. Stat. 11 (4), 300–309.
Streiner, D.L., 2015. Best (but oft-forgotten) practices: the multiple problems of multiplicity-whether and how to correct for many statistical tests. Am. J. Clin. Nutr. 102 (4), 721–728.
U.S. Food & Drug Administration, 2018. The FDA Warns against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm.
Winner, J., Allen, J.D., Altar, C.A., Spahic-Mihajlovic, A., 2013. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl. Psychiatry 3, e242.
Winner, J.G., Carhart, J.M., Altar, C.A., Goldfarb, S., Allen, J.D., Lavezzari, G., Parsons, K.K., Marshak, A.G., Garavaglia, S., Dechairo, B.M., 2015. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr. Med. Res. Opin. 31 (9), 1633–1643.

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