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The Promise and Challenges of Using Combined Moderator Methods to Personalize Mental Health Treatment

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Personalized medicine approaches depend on identifying moderators. In a randomized clinical trial (RCT), a moderator is a pre-treatment characteristic that provides information about who is likely to have a favorable outcome with which treatment. (In contrast, a non-specific predictor is a pre-treatment characteristic that provides information about who is likely to have a favorable outcome, regardless of treatment.) To illustrate, a recent RCT found that set-shifting performance moderated the effect of aripirazole (versus placebo) on remission in older adults with venlafaxine-resistant major depression (1). In people without set-shifting impairment, aripiprazole increased the likelihood of remission relative to placebo; but in people with set-shifting impairment, aripiprazole augmentation was no more efficacious than placebo. Theoretically, such moderators could be used to personalize treatment decisions in practice as well as to generate hypotheses regarding which core deficits must be addressed in non-responders.

Given that moderators are integral for advancing personalized medicine, why has there been limited progress implementing them clinically? While the answer is multifaceted, one key explanation lies in the traditional practice of searching for single treatment moderators in isolation from one another (2). Single treatment moderators tend to have relatively small effect sizes (e.g., see 3-6), limiting their ability to meaningfully inform clinical practice. Furthermore, if multiple separate moderators are identified, they can suggest conflicting treatment indications for the same patient. For example, consider a hypothetical scenario where gender and set-shifting performance both moderated the response to a drug treatment, such that the drug was efficacious in females and people without set-shifting impairment. How would these two moderator findings be used to guide treatment for a male without set-shifting impairment?

To address these limitations, an optimal combined moderator (OCM) approach was developed (2) and successfully demonstrated in recent years (e.g., see 3-6). This approach derives a composite moderator that is an optimally weighted combination of multiple individual moderators. This composite moderator can indicate which treatment is preferable for a patient based on multiple pre-treatment characteristics simultaneously, and has consistently been shown to have a larger effect size than any of its individual component moderators. But despite its promise, the OCM approach is rooted in a regression framework and thus carries specific assumptions regarding how moderators can be combined, a feature that could potentially limit the resulting combined moderator effect size. In this issue, Zilcha-Mano et al. demonstrate a