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***CYP2D6*'s functional status associated with the length of hospitalization stay in psychiatric patients: a twist in the tale or evidence that matters?**

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The recently published paper by Ruaño *et al.* [1] addresses an urgent need for evidence-based clinical applications of *CYP2D6* pharmacogenomics in the area of psychiatry, in this case in the potential impact on a clinically relevant complex outcome (i.e., length of hospitalization stay [LOS]) of pharmacogenetic testing for guiding therapy of psychiatric inpatients with major depressive disorders at a mental health institution in the New England (CT, USA) area. In doing so, the authors computed a prospectively defined 'drug metabolic reserve' index for each participant, based on individual *CYP2D6* genotypes, to infer their innate metabolic capacity through this enzymatic pathway, and then tested whether an association with the LOS was observed.

Two previous studies in Europeans have addressed this question previously, with mixed results [2,3]. To our knowledge, this is the first time it has been tested in a multiethnic, highly heterogeneous cohort that also included a subgroup of admixed, often marginally represented and medically underserved, Hispanics (n = 41; 27%). Their findings are relevant insofar as they provide a functional scoring of *CYP2D6* carrier status with a potential impact on the quality of care, patient satisfaction and the utilization of healthcare resources in psychiatry, as well as other pharmacoeconomic issues related to an optimal therapeutic management strategy. Notably, those functionally deficient patients (*CYP2D6* metabolic reserve <2; n = 66) clearly segregated from the rest to show a longer LOS, and were also more likely to have an extended time on therapy with a psychiatric drug [1]. In fact, the

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CYP2D6 metabolic reserve index alone accounted for approximately 6% of the observed variability in the LOS after regression analysis.

Although some concerns in the experimental design could be raised, which might lead readers to be cautious about drawing conclusions from the observational study, it is important to bear in mind that the authors of this study enrolled participants in a more naturalistic setting (rather than following a typical ‘controlled’ scenario), which implies minimal protocol constraints on patients and related covariates that could further limit external validation.

Indeed, in order for them to achieve their objectives, they rather prefer to employ a ‘quasi-experimental’ design, which has been a well-established means of evaluating an intervention in an environment with significant natural variability in clinically oriented practices [4–6]. This design strategy enabled them to enroll a wider and more representative range of psychiatric patients than typically observed in randomized, controlled trials (RCTs). It is also important to mention that an alternative study design has to be considered in situations where RCTs are either not feasible or unethical, and this seems to be the case.

Although not explicitly discussed, concerns about potential confounders such as the exposure to a variety of treatments, comorbidities and ethnicity of participants seemed to be partially addressed by the authors in the study design because all individuals were recruited from the same participating medical institution in the same region (Institute of Living, CT, USA). Accordingly, once stratified by the postulated ‘metabolic reserve index’ into two major categories (i.e., individuals with scores <2 and scores ≥ 2), both groups are expected to be fairly balanced, therefore having the same access to care. It is also reasonable to assume they were similar in their relative risk for adverse drug reactions at the time of commencing the study, and in other unmeasured covariates (including lack of efficacy, compliance and multiple-drug therapies based on hospital formulary and guidance) as well.

On the other hand, the measured LOS in the subfunctional group of CYP2D6 metabolizers was significantly longer than that in the functional and suprafunctional groups combined ($p = 0.002$). Therefore, small differences in other randomly distributed covariates are not expected to have a substantial impact on their findings.

However, additional variables and/or alternatives (e.g., stratification by admixture and CYP2D6 substrates) should be taken into consideration in order to further account for unexplained variance in LOS, but also to control for potential confounders while maintaining the ‘naturalistic setting’, as well as generalizability. Owing to these potential limitations, most of them being acknowledged by the authors, results from this study need to be further validated externally in an RCT protocol before a final conclusion can be made about expected clinical benefits (i.e., reducing length of hospitalization) of genetic testing for psychiatric patients.

We congratulate the authors for this excellent work and firmly believe the study is of upmost importance for the translation of the knowledge gained from *CYP2D6* pharmacogenetic studies into clinical practice.

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