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Response to "DPYD genotyping panels: Impact of population diversity".

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REPLY

Response to "*DPYD* genotyping panels: Impact of population diversity"

We thank Dr. Suarez-Kurtz for his Letter to the Editor on our publication "*DPYD* HapB3 haplotype structure and implications for pharmacogenomic testing".[1]

In response to our findings, the Clinical Pharmacogenetics Implementation Consortium (CPIC) posted an update to their online guideline for fluoropyrimidines and *DPYD*[2] to promote awareness that the c.1236G>A variant may not always be linked to the causal, deep intronic c.1129-5923C>G variant. Based on our "*All of US*" data, false-positive calls due to the presence of c.1236G>A, while c.1129-5923C>G is absent, are most likely presenting in patients of European ancestry (13 cases had European ancestry and one was "Other"). This finding does, of course, not preclude such cases also being found in admixed populations such as Brazilians or even being discovered in people without European ancestry.

We agree with Suarez-Kurtz's comment that pharmacogenetic tests developed for one population may not directly be translatable to all ancestral compositions but should rather be tailored toward the targeted patient population. Replacing c.1679T>G (rs55886062, also known as **13*) with c.557A>G (rs115232898), which is more likely to be detected in Brazilian patients with cancer, is one example of how regional testing can be adapted to focus on more prevalent variants within the population. However, although the frequency of rs55886062 is exceedingly low, it cannot be inferred that this risk variant will be completely absent within any population. The American Molecular Pathology (AMP) Pharmacogenomics Working Group plans to develop recommendations for clinical *DPYD* allele testing in the near future, which includes c.557A>G. These guidelines use a Tier-system for testing a minimum set of variant alleles ("Tier 1") and an extended list of variant alleles ("Tier 2") that aids clinical laboratories/implementers in the development of tests that include variants of relevance for their patient populations, with the overarching goal to better serve patients across the globe.

In regard to Suarez-Kurtz's comment that CPIC is acknowledging the importance of c.557A>G for people with African ancestry but not including this variant among the four decreased function variants of primary relevance due to their population frequency, we would like to emphasize that CPIC does not recommend whether testing should be performed, or which variants should be tested, but rather provides clinical recommendations if a pharmacogenetic test result is available. Commercial tests may not include c.557A>G, which is clearly a limitation. Testing this variant in populations with African ancestry should indeed be considered given its functional consequence and frequency.

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CONFLICT OF INTEREST STATEMENT

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