Introduction
The cytochrome P450 family 2 subfamily D member 6 (CYP2D6) gene is involved in the metabolism of numerous important prescription drugs. CYP2D6 is highly polymorphic and harbors structural variation due to its homology with the pseudogene CYP2D7, making it challenging to genotype. This not only hampers efforts to apply CYP2D6 genotyping in a clinical setting but also limits the ability of researchers to uncover novel drug associations with CYP2D6 variants.

- We present a comprehensive assessment of CYP2D6 variation in a cohort of 30,000 individuals.
- Our clinically validated pipeline reports 106 star alleles, including structural variants and amplifications.
- We find that less comprehensive tests are potentially miss-genotyping 17% of samples. This leads to the mischaracterization of 7.7% of ultrarapid metabolizers and 4.4% of poor metabolizers.

What current tests are missing
Commercial PGx tests typically report on the most common CYP2D6 star alleles, omitting a large fraction of the 100+ alleles documented by the Pharmacogene Variation Consortium (PharmVar.org). Using a panel of star alleles based on Del Tredici et al [1] that is representative of these commercial tests (‘short panel’ below), we quantify the consequences of using panels that are not comprehensive.

Methods
Our method builds upon existing NGS-based star allele callers Aldy [2] and Stargazer [3]:
1. Reads mapping to the CYP2D6-CYP2D7 locus are filtered and processed.
2. Allele depths at 97 variants and read counts per exon are determined.
3. The most likely allele combination that explains the data observed in step 2 is reported, along with a quality score.

This method is clinically validated with average accuracy of 99.5%.

References: