Evaluation of the Detection Rate of Targeted Pharmacogenomic Tests for TPMT and NUDT15

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Introduction

Traditionally, targeted genotyping assays have been implemented in pharmacogenomic testing efforts. These assays test for a small number of relevant variants within a gene, lowering costs and simplifying genotyping results. This approach creates a risk of false negative test results, where patients are wrongly assumed to have default normal metabolizing variants. Patients of varying ethnic populations with different relevant variants potentially face an increased risk of false negative test results.

TPMT and NUDT15 play an important role in metabolizing thiopurines used for their immunosuppressive properties for a variety of indications. Patients with reduced metabolic activity of TPMT and NUDT15 face increased risk of serious side effects, such as leukopenia, neutropenia, and myelosuppression [1]. PGx testing of these genes prior to therapy is an important step that can limit the likelihood of these side effects. Continued evaluation of commercial PGx tests evaluating TPMT and NUDT15 allows patients and providers to select appropriate PGx tests to optimize thiopurine therapy minimizing risks of false-negative test results.

Objective

Our objective is to evaluate the influence of variant selection practices on ethnic background for TPMT and NUDT15 genes by available PGx tests.

Methods

We previously published method for determining detection rate [2]. Briefly, the Genetic Test Registry (GTR) was searched on October 11, 2021 to identify available targeted PGx tests [3]. Potential PGx tests were excluded if they used alternative sequencing technologies, and if variant selection data was not available. PGx test variant selection data combined with guidelines from the Clinical Pharmacogenetic Implementation Consortium (CPIC) and gene frequency data from PharmGKB allowed us to determine detection rates [4, 5]. The detection rate was defined as the percentage of a given population with an "altered metabolizer" genotype predicted phenotype where a PGx test targeted both gene variants in a diplotype (Equation 1).

$$\text{Detection Rate} = \frac{\text{Detectable altered metabolizer frequency}}{\text{Population altered metabolizer frequency}} x\ 100$$

Equation 1: *Detection rate equation using altered metabolizer frequencies*

A potential genotype predicted phenotype was considered an altered metabolizer when it resulted in thiopurine therapy modification based on CPIC guidelines. Thus, specifically intermediate and poor metabolizers of TPMT and NUDT15 were considered altered metabolizer. In addition to detection rate, we determined gene coverage percentage for each PGx test evaluated. Coverage percentage was calculated by taking the total number of variants selected by a PGx test divided by the total number of variants identified in the PharmGKB database.

Results

With search of the GTR, 193 total PGx tests were identified as using targeting sequencing technologies. Of this total, 18 (9%) assayed TPMT and 8 (4%) assayed NUDT15 (Figure 1). With respect to variant selection data, 44% (8 out of 18) PGx tests for TPMT had variant selection data available while 62% (5 out of 8) NUDT15 had this data.

The gene coverage percentage for PGx tests is highly variable, ranging from 7% to 86% for TPMT and 20 to 100% for NUDT15.

As expected, detection rates were influenced by test coverage percentage; the higher the coverage percentage the higher the detection rate (Figure 2). For TPMT, African-American/Afro-Caribbean (AAAC) had the lowest average detection rate across all PGx tests evaluated at 51%. All other ethnic groups had average values higher than 71. For NUDT15, European and Latino ethnic groups had average detection rates of 43% and 51%, while other groups had averages that were 70% or higher (Figure 2).

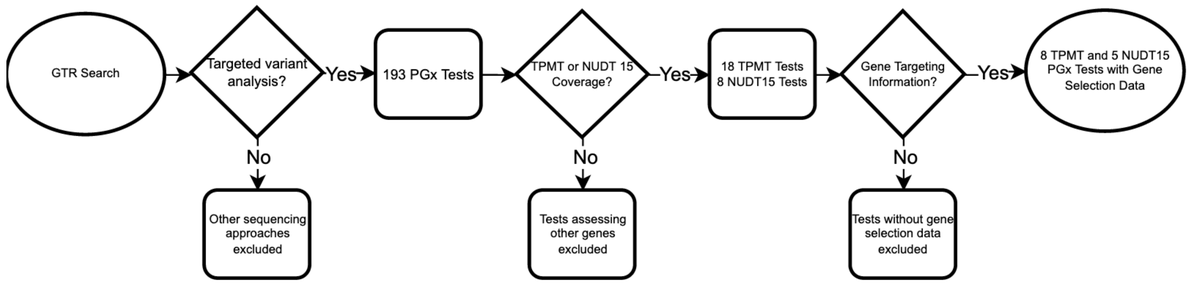

Figure 1: *Process of Genetic Testing Registry (GTR) search identifying PGx tests to be used in the study*

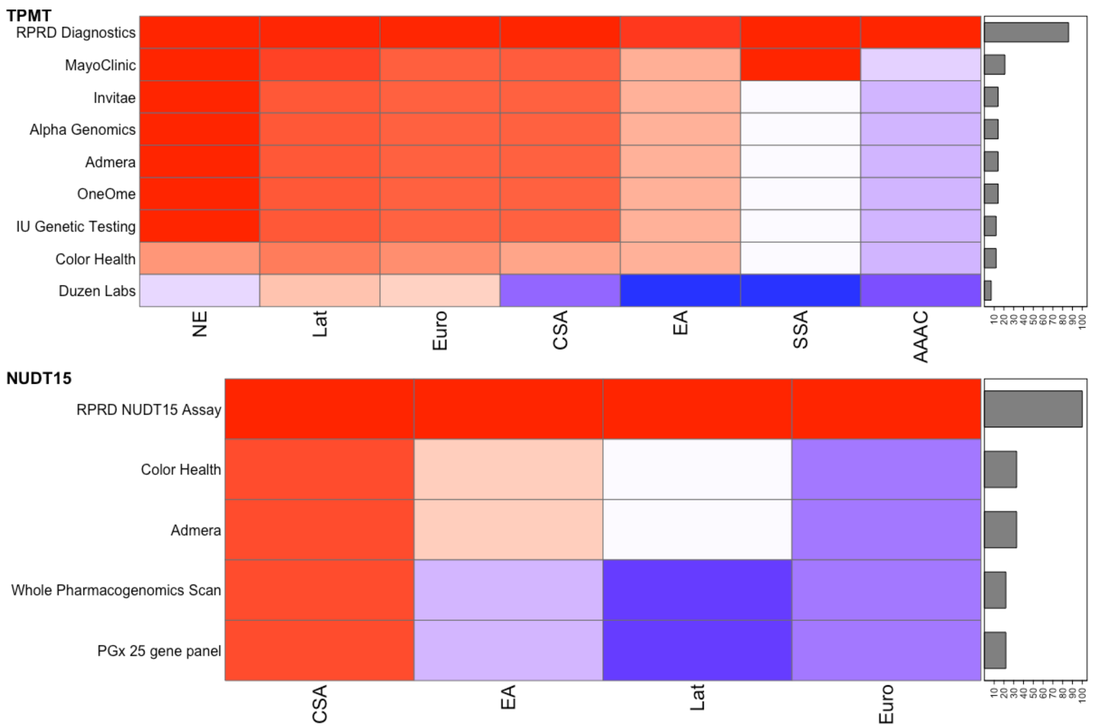

Figure 4: *Heatmap showing detection rates of PGx tests for TPMT and NUDT15. Abbreviations for ethnic groups are as follows: AAAC (African American/Afro-Caribbean), CSA (Central/South Asian), EA (East Asian), Euro (European), Lat (Latino), NE (Near Eastern), and SSA (Sub-Saharan African). Bar graphs along the right hand side of heatmaps represent the coverage percentage of each PGx test.*

Discussion and Conclusion

Less than half of the tests assaying TPMT had gene selection data available. A lack of gene selection data readily available for targeted PGx tests is problematic when trying to pick ideal tests for patients. There is a clear trend that the more variants that are included in a PGx test, the higher the detection rate. Additionally, the detection rate for prospective patients is clearly influenced by their ethnic background. With respect to TPMT, the African-American/Afro-Caribbean population had very low detection rates relative to other ethnic groups. For NUDT15 tests, the detection rates for Latino and European populations were much lower compared to other ethnic groups evaluated. We feel our results strongly support patients and providers taking into account the number of variants selected by a PGx tests and ethnic background. This would improve confidence in genotyping results and optimize thiopurine therapy.

Low detection rates for PGx tests indicate there is a high likelihood of patients receiving false negative test results. This would lead to providers potentially assuming a more rapid metabolism of these drugs, leading to higher dose than is warranted given their actual genotype, leading to potential toxicity and serious side effects. However, this risk can be minimized if variant selection and ethnic background are taken into account when selecting PGx tests.

Future Research

We hope to evaluate the effect of variant selection practices for other genes to evaluate any association between ethnic background and therapeutic efficacy in PGx guided therapy.

Acknowledgements

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References

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