Medication Response™ Test: Personalized Pharmacogenomic (PGx) Analysis Powered by Next-Generation Sequencing (NGS)

Executive Summary

The Medication Response™ test, a component of the MyOme Proactive Health Plus suite of products, uses next-generation sequencing (NGS) and a proprietary variant calling platform to provide an analysis of 15 known pharmacogenes and their actionable variants for interpretation by a trained healthcare provider.

In the study described herein, the Medication Response test was validated by comparing its performance to orthogonal methods using reference sample DNA and whole-genome sequencing (WGS) data.

The validation assessment found the Medication Response test to have high concordance with orthogonal methods, establishing its reliability as a useful tool for trained healthcare providers to gain meaningful insights that may inform personalized care.

Introduction

What is Pharmacogenomics?

Pharmacogenomics (PGx) refers to the study of pharmacogenes, which encode proteins that can influence how a drug is broken down and processed by the body (pharmacokinetics) or how a drug interacts with the body to carry out its intended physiological effect (pharmacodynamics). Due to natural genetic variation, some individuals carry variants that can affect the normal function of their encoded proteins, resulting in an altered medication response.[1] Identifying an individual's pharmacogenomic variants using WGS can provide valuable, personalized insights for interpretation by a trained healthcare provider.
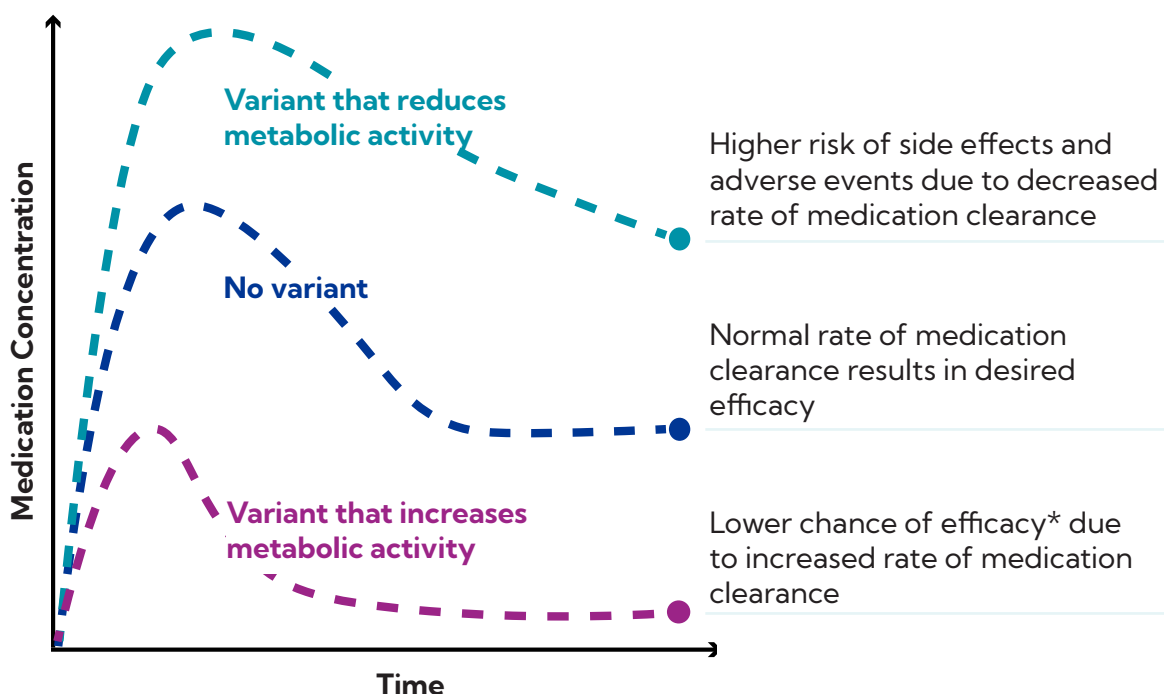
Introduction

How Genes Influence Medication Responses

Some pharmacogenomic variants lead to changes in protein function, which can in turn have clinical implications, such as affecting the risk of side effects and adverse events, determining optimal doses, or modifying the likelihood of efficacious treatment responses. Pharmacogenes can be classified according to the molecular processes they influence:

Classes of Pharmacogenes

1. **Medication metabolizer pharmacogenes** normally regulate medication clearance, but certain genetic variants can alter enzyme activity, resulting in suboptimal medication concentrations that may be associated with increased the risk of side effects and reduced efficacy (**Figure 1**).

2. **Medication transporter pharmacogenes** help transport drugs in or out of target cells. Variants that reduce or increase drug uptake can thus cause medication build-up in the body or in cells, increasing the risk of adverse events and affecting efficacy.

3. **Pathway-specific pharmacogenes** encode proteins that normally play a role in a biological pathway that is targeted or influenced by a medication. Variants alter these pathways, which can result in lower efficacy or increased risk of side effects.

Figure 1: Medication Metabolizer Pharmacogenes

*In cases where metabolic activity converts medications to their active form, an increase in metabolic activity can increase the chance of efficacy and the likelihood of side effects associated with excessive activation.

Introduction

Pharmacogenes of all three classes are analyzed by the Medication Response™ test, as shown in **Table 1**. Specific examples of pharmacogene variants analyzed in the test and their associated clinical implications are also described in **Table 1**.

Table 1: Examples of Pharmacogene Variants and Clinical Implications

Class	Genes Included in Test	Example of Gene–Medication Response and Clinical Implication
Medication Metabolizers	Cytochrome P450 (*CYP*) superfamily genes, *NUDT15, TPMT, UGT1A1, DPYD*	The CYP superfamily of proteins metabolize over 90% of clinically used drugs. Variants in *CYP* genes can alter their metabolic activity, affecting drug concentrations and thus optimal doses. For example, individuals with certain *CYP2C9* gene variants have a reduced ability to clear the anticoagulant drug warfarin from their system. As a result, lower doses of warfarin should be given to these patients to avoid serious complications like excessive bleeding and hemorrhage.[5]
Medication Transporters	*SLCO1B1*	The SLCO1B1 protein facilitates the uptake of cholesterol–lowering medications called statins from the blood and into liver cells. Some variants in the *SLCO1B1* gene reduce liver cell uptake of certain statins, causing statin build–up in the blood and associated adverse events like muscle pain and weakness.[6]
Pathway Influencers	*F5, IFNL3, VKORC1*	The *F5* gene encodes a protein involved in coagulation. Certain *F5* variants prolong its functional activity and increase the risk of excessive blood clotting and thrombosis. Individuals with these variants may benefit from avoiding certain medications that are known to increase the risk of blood clotting, such as oral contraceptives.[7]

The Medication Response™ Test

How Test Results are Generated

The Medication Response report is generated using MyOme's proprietary small variant calling platform (based on a modified version of Aldy*) that analyzes WGS data obtained from Illumina sequencing of genomic DNA isolated from submitted samples (blood, saliva, or buccal). The test detects variants rec–ommended by the Association for Molecular Pathology (AMP) PGx Working Group[9] in 15 pharmacogenes with gene–drug interactions described in the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines[10] and the Food and Drug Administration (FDA) Table of Pharmacogenetic Associations.[11]

How Test Results are Presented

Results are categorized and presented as shown in **Figure 2**. Of note, the phenotype column contains information that may enable trained healthcare providers to tailor medication regimens based on known pharmacogenetic associations. Depending on the gene, the phenotype describes (1) whether a variant is present or absent or (2) whether a variant is associated with normal, increased, decreased, or poor function.

Figure 2: Medication Response Test Results

GENE INFORMATION
Lists the specific genes analyzed.

DIPLOTYPE
Indicates the specific genetic

PHENOTYPE
Describes the predicted impact of variants on medication responses.

PHARMACOGENOMIC SUMMARY

To facilitate the use of pharmacogenomic guidance, we report known variants in genes associated with response to common medications. Our test examines 15 genes with alleles with known pharmacogenomic implications. For additional guidance on how the findings in this report might affect drug response please refer to https://www.cpicpgx.org/genes-drugs/ and https://www.pharmgkb.org/ **You should always consult your healthcare provider prior to making any changes to your medication regimen.**

Gene	Diplotype	Phenotype
CYP2B6	*6 / *22	Intermediate Metabolizer
CYP2C19	*1 / *1	Normal Metabolizer
CYP2C9	*1 / *1	Normal Metabolizer
CYP2D6	*4 / *29	Intermediate Metabolizer
CYP3A4	*1 / *36	Variant Present
CYP3A5	*1 / *3	Intermediate Metabolizer
CYP4F2	*1 / *1	Variant Absent
DPYD	*1 / *1	Normal Metabolizer
IFNL3	rs12979860 T/T	Variant Present
NUDT15	*1 / *1	Normal Metabolizer
SLCO1B1	*1 / *1	Normal Function
TPMT	*1 / *1	Normal Metabolizer

*Aldy is a computational tool developed by National Cancer Institute researchers for calling polymorphic pharmacogenes and reporting their phased star–alleles.[8]

The Medication Response™ Test

For genes that impact how the body metabolizes a medication, the phenotype column includes one of four classifications, listed and described in **Table 2**.[12]

Table 2: Metabolizer Phenotype Classifications

Classification	Definition	Risk of Adverse Events at Standard Dose
Normal Metabolizer	Associated medications are metabolized at a normal rate.	LOW ▬▬ HIGH
Poor Metabolizer	Associated medications are metabolized at a markedly decreased rate compared to normal metabolizers, potentially leading to an increased risk of adverse events.	LOW ▬▬▬▬ HIGH
Intermediate Metabolizer	Associated medications are metabolized at a slower rate compared to normal metabolizers, potentially leading to an increased risk of adverse events.	LOW ▬▬▬ HIGH
Ultrarapid Metabolizer	Associated medications are metabolized at a markedly increased rate compared to normal metabolizers, potentially leading to an increased risk of adverse events and reduced efficacy.	LOW ▬▬▬▬ HIGH

How Test Results are Interpreted

Results can be used by healthcare professionals to assess the likelihood of side effects, determine appropriate dosages, and better understand the chance of efficacious responses for over 70+ medications indicated for a range of clinical areas including pain management, behavioral health, and cardiology. The Medication Response test has the po–tential to impact current or future medication plans for up to 95% of patients.

95%

of patients carry at least one variant in an established pharmacogene that would influence medication–related outcomes and would be deemed actionable.[13–15]

Validation of the Medication Response™ Test

Introduction

The ability of the Medication Response™ test to detect single nucleotide variants (SNVs) and small insertions and deletions (indels) in 15 pharmacogenes as well as copy number variants (CNVs) in *CYP2D6* was validated by comparing the Medication Response results to results derived through orthogonal methods. Test sensitivity metrics were also calculated from the results of this validation study.

Methods

To validate the Medication Response test process and variant calling pipeline (the "Medication Response caller"), 15 commercially available samples–part of the Center for Disease Control's GeT-RM collection–were obtained from The Coriell Institute for WGS analysis. Genomic DNA was extracted from samples for WGS using Illumina technology, followed by proprietary bioinformatic processing in which the Medication Response caller was used to call SNVs, star alleles, and CNVs and to assign pharmacogenomic diplotypes.

To further validate the Medication Response caller, publicly available WGS data for 71 samples previously analyzed using orthogonal methods were obtained from the European Nucleotide Archive (PRJEB19931).

The Medication Response test analyzed Tier 1 variant alleles for *CYP2C19, CYP2C9, CYP2D6, TPMT* and *NUDT15* and Tier 2 variant alleles for *CYP2C19, CYP2C9, CYP2D6* (excluding hybridizations), as recommended by the AMP PGx Working Group[9] for all CPIC[10] covered pharmacogenes (**Table 3**).

Concordance between the genotype/diplotype calls produced by the Medication Response test for both datasets were compared to benchmark calls to validate the test's ability to accurately and precisely detect pharmacogenomic variants.

Table 3: Analyzed Genes and Alleles

Gene	Allele(s)
CYP2B6	*4; *6; *9; *18; *22
CYP2C9	*2, *3; *4; *5; *6; *8; *11; *12; *13; *15; *16; *26; *28; *29; *30; *31; *42; *55
CYP2C19	*2; *3; *4; *5; *6; *7; *8; *9; *10; *17; *35
CYP2D6	*2; *3; *4; *5; *6; *7; *8; *9; *10; *11; *12; *14; *15; *17; *21; *29; *31; *40; *41; *42; *49; *56; *59;*100; *114
CYP3A4	*22; *36
CYP3A5	*3; *6; *7
CYP4F2	*3
DPYD	rs3918290; rs55886062; rs59086055; rs67376798; rs75017182+rs56038477; rs112766203; rs115232898; rs14635695; rs183385770
F5	rs6025
IFNL3	rs12979860
NUDT15	*3; *4; *9
SLO181	*5; *9; *14; *20
TPMY	*2; *3A; *3B; *3C; *4; *11; *29
UGT1A1	*6; *27
VKORC1	rs9923231

Validation of the Medication Response™ Test

Results

To assess analytical validity, the concordance between the results produced from 15 DNA samples processed by MyOme's CLIA-certified lab and analyzed by the Medication Response™ test and results from the GeT-RM collection was calculated. The genotype/diplotype calls produced by the Medication Response caller had a 99.4% concordance with benchmark GeT-RM calls (**Table 4**). Of the 15 pharmacogenes included in the test, 13 had SNVs or indels detected by both the Medication Response test and orthogonal tests. Both datasets detected *CYP2D6* CNVs in 4 samples. Detection and assignment of *CYP2D6* CNVs by the Medication Response test had 100% concordance with the GeT-RM collection calls.

As a result of an analysis of existing WGS data derived from 71 samples, the concordance between variants identified by the Medication Response test and previously assigned variants was 100% (**Table 4**). For these samples, both datasets detected SNVs and indels in 14/15 included pharmacogenes. Further, both data-sets detected *CYP2D6* CNVs in 13 samples.

Table 4: Genotype/diplotype Concordance Results

Cohort	Concordance
Reference DNA	178/179 **(99.4%)**
Reference WGS Data	816/816 **(100%)**
Reference DNA + WGS Data	994/995 **(99.9%)**

In 10/71 samples, Medication Response test calls for *CYP2D6* were *CYP2D6-CYP2D7* gene hybridizations and thus fell outside of the reportable range as expected failures.

After combining the total genotype/diplotype concordance results per gene for both reference cohorts, the Medication Response test had 99.9% concordance with the orthogonal datasets (**Table 4**). Thus, the Medication Response test showed robust analytical validity akin to widely accepted pharmacogenomic methods.

Of note, the concordance between two intra-run replicates and two inter-run replicates was 100% for two separate batches of samples analyzed by the Medication Response test, thus validating reproducibility. Further, the following test metrics were derived based on the per gene performance from the samples discussed above:

- >98.5% per gene accuracy for diplotypes and phenotypes
- >99% sensitivity for *CYP2D6* gene duplications and deletions
- >99% sensitivity for pharmacogenomic SNVs and indels
- >99.5% of pharmacogenomic variants at ≥10x depth 30x average genome-wide coverage

Conclusion

The results produced from the validation assessment of the MyOme Medication Response test demonstrated high concordance with validated orthogonal methods based on a dataset of nearly 1,000 assigned diplotypes. These results support the use of the Medication Response test as a reliable tool for informing plans of care.

Get Started With MyOme

MyOme provides a customizable end-to-end solution to enhance both the provider and patient experience.

User-friendly Online Portal

Submit test orders, access test results, schedule genetic counseling sessions, and connect with MyOme resources in one convenient place.

Assured Data Privacy

Our platform is HIPAA-compliant and features enterprise-scale data encyrption. We never sell or share patient data without explicit consent.

Support at Every Step

We are committed to helping providers communicate complex topics by providing resources, customer support, and genetic counseling.

Questions?
Contact support@myome.com or visit our website for more information.

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