LANDSCAPE OF CLINICAL EVIDENCE FOR PHARMACOGENETIC TESTING (PGT)
Summary of Current Evidence and Expert Perspectives

[ White Papers in Pharmacogenetics ]
EXECUTIVE SUMMARY

Precision medicine is rapidly becoming a reality in clinical practice today. Currently, there are over 10,000 genetic testing products available to clinicians for diagnosing, managing, and treating disease.¹ One rapidly growing sector of the genetic testing space is pharmacogenetics, which helps clinicians tailor and optimize medication therapy according to a patient’s genetic profile. Because pharmacogenetics provides information on medication response, rather than disease risk or vulnerability, it has been touted as a more clinically actionable facet of precision medicine.² The current report aims to provide a comprehensive overview of the evidence landscape for pharmacogenetics in key patient populations.

CENTRAL THEMES THAT EMERGED FROM THE LITERATURE INCLUDE:

1. There is a sizable clinical opportunity for pharmacogenetic intervention in key disease states, including cardiovascular, mental health, and chronic pain therapy.

2. Pharmacogenetic testing requires a paradigm shift for how evidence of clinical utility is generated compared to traditional models of medicine.

   The clinical evidence supporting validity of testing includes Food and Drug Administration (FDA)-approved labeling for over 100 gene-drug pairs and published expert guidelines for numerous commercially available tests. Such tests may provide the most actionable guidance to clinicians during patient care.

3. The existing clinical utility studies are encouraging and support the potential for pharmacogenetic testing to improve patient outcomes and reduce health care costs for specific gene-drug pairs.

4. There are a number of important considerations that can facilitate widespread implementation of pharmacogenetic testing in clinical practice.

   Multiple well-known US medical institutions and centers are paving the way for preemptive (pre-prescription) testing integrated with electronic medical/health records (EMR/EHR) that provide a template for best practices.
INTRODUCTION

Pharmacogenetics (known interchangeably as pharmacogenomics) is the science of how genetics impact an individual’s response to medications. Benefits of pharmacogenetics can range from helping clinicians target medications to improve patient outcomes to enhancing efficiency of pre-market clinical trials for new drug entities.  

**Various medication classes such as antidepressants, antipsychotics, analgesics, and oncologics can be ineffective for 20-75% of treated patients.**

<table>
<thead>
<tr>
<th>% patient population for which specific drug is ineffective, on average</th>
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</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>30-40%</td>
</tr>
<tr>
<td>SSRIs/SNRIs</td>
<td>38%</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>40%</td>
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<tr>
<td>Asthma drugs</td>
<td>40%</td>
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<tr>
<td>Arthritis drugs</td>
<td>50%</td>
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<tr>
<td>Alzheimer’s drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer drugs</td>
<td>75%</td>
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</tbody>
</table>

As clinicians and patients are well aware, optimizing medication therapy can be challenging because response to many commonly used drug classes is often unpredictable, highly variable, and sub-optimal.  

Compelling biological and clinical evidence suggests that genetic differences may explain an estimated 20-95% of the variability in medication effects, such as poor response or serious adverse drug reactions (ADRs). Testing for clinically relevant genetic variations may offer clinicians an objective tool to help better predict medication response for their patients. It may also offer significant economic benefits, both in the immediate term by helping clinicians avoid potentially unsafe or ineffective medications, as well as in the long term, since patients on targeted drug treatments are more likely to experience improved health outcomes.

Most commercially available pharmacogenetic tests (PGT) used in clinical practice today are in specialty care, such as oncology, cardiovascular, CNS, and chronic pain therapy. As primary care assumes an increasingly prominent role in treating patients with many of these conditions, PGT use is broadening into this clinical setting as well. Given the substantial health burden to patients and economic costs associated with these chronic diseases, the potential clinical value of pharmacogenetic testing is significant.

Over the past three decades, total US health care spending has approximately doubled to 16% of Gross Domestic Product (GDP) and is projected to reach almost 20% of GDP in 2016. As both public and private payers struggle with rising health care costs, PGT may provide one solution for improving health care quality and efficiency. For payers, PGT may represent an innovative, science-based tool for targeting use of often-expensive medications to patients most likely to benefit. For clinicians, PGT may provide a potentially faster and more effective path to optimizing medication management compared to traditional trial-and-error prescribing. For patients, PGT may offer a relatively simple, non-invasive tool to help them and their care providers maximize the benefits of drug therapy while minimizing the economic, physical, and emotional burdens of ineffective medication trials.
DEFINING THE OPPORTUNITY FOR PHARMACOGENETIC INTERVENTION

Many factors, including diet\textsuperscript{22}, lifestyle\textsuperscript{23}, and age\textsuperscript{24} contribute to inter-patient variability in medication response. However, genetics remains one of the most compelling targets to evaluate in clinical practice because of the relative ease of measuring and quantifying its impact on patient response. As such, genetic testing may provide a more consistent barometer for predicting medication response among patients compared to other clinical factors and it is also relatively easy to implement in clinical practice.\textsuperscript{4,17}

Nonetheless, it is important to understand that drug pharmacology and clinical response are complex processes that involve multiple biological players. Therefore, it is important to define opportunities for pharmacogenetic intervention, ideally according to clinically relevant gene-drug pairs rather than nonspecific or generic approaches.\textsuperscript{3} To date, the bulk of the scientific evidence has focused on gene-drug pairs involving metabolism pathways, in particular the CYP450 family of hepatic enzymes.\textsuperscript{25-29} Genetic variations in CYP450 enzymes may cause a drug to be metabolized either faster or slower than expected for a given patient compared to the reference (or normal) population. Consequently, such patients may have trouble processing and eliminating medications from the body, potentially increasing the risk of therapeutic failure or serious side effects. In general, the consequences may range from unpleasant to fatal depending on the specific gene-drug pair.\textsuperscript{27}

With respect to nomenclature for metabolism genes, the “genotype” denotes the specific DNA changes detected in the enzyme gene, while the “phenotype” describes how DNA variations change the functional activity of the protein encoded by the enzyme gene. Patients with variant (or non-normal) phenotypes can experience significant differences in their response to certain medications compared to the reference (or normal) phenotype.\textsuperscript{27}

CYP450 enzymes process approximately 90% of medications available in the US and the majority are known to be genetically variable in the general population.\textsuperscript{30} A systematic 2001 JAMA review reported that CYP450 metabolism pathways are also frequently associated with ADRs and are responsible for metabolizing almost 60% of commonly prescribed medications most frequently cited in adverse events.\textsuperscript{31} A large (N=607) follow-up study reported that over 1 in 4 primary care patients had received at least one of these “culprit” medications within the previous 12-month period.\textsuperscript{20}

<table>
<thead>
<tr>
<th>Predicted Phenotype</th>
<th>Definition</th>
<th>Liver Enzyme Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid Metabolizer (UM)</td>
<td>increased enzyme activity</td>
<td>CYP2C19, CYP2D6</td>
</tr>
<tr>
<td>Extensive Metabolizer (EM)</td>
<td>normal enzyme activity</td>
<td>CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/CYP3A5*</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>reduced enzyme activity</td>
<td>CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/CYP3A5*</td>
</tr>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>little or no enzyme activity</td>
<td>CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/CYP3A5</td>
</tr>
</tbody>
</table>

*CYP3A5/CYP3A5: Intermediate Metabolizer displays normal enzyme activity and Extensive Metabolizer displays increased enzyme activity.

Table 1. Phenotype categories denoting clinical impact of DNA variations in liver CYP450 genes on the functional activity of the translated protein.\textsuperscript{27}
For patients receiving cardiovascular, CNS, or analgesic medications, the emergence of ADRs or therapeutic failure can be particularly problematic because they can lead to additional costly treatments, hospitalization, or even death. A large study (N=30,397) of Medicare outpatients found that almost 40% of ADRs reported within a 12-month period were classified as serious, life threatening, or fatal; moreover, CNS, cardiovascular, and analgesics ranked in the top ten ADR-causing medication classes for this population.

These statistics clearly illustrate the clinical relevance of metabolism pharmacogenetics for certain therapeutic drug classes. They also prompt important questions including: (i) how common are such genetic variations in the general patient population and (ii) are a significant portion of patients with genetic variations taking medications expected to interact negatively with their genetics.

According to a recent retrospective study in a chronic pain cohort (N=102), the vast majority of patients (95%) are variant metabolizers for at least one enzyme pathway that is known to play a primary role in processing medications commonly prescribed in this population (e.g., opioids, benzodiazepines, and antidepressants). A larger retrospective study (N=1143) in a heterogeneous patient cohort reports similarly high rates of variant metabolizers. Most importantly, it also reports that the majority of patients (52.9%) are variant for two enzymes, while 1 in 10 are variant across three clinically relevant CYP450 pathways (CYP2D6, CYP2C19, and CYP2C9).
These frequency data are especially relevant to clinicians because they suggest that substantially more patients exhibit genetic variations when examined across multiple genes than expected from frequency distributions within a single gene and may therefore benefit from PGT. Verbeurgt and colleagues also demonstrate that many of these patients take medications that may negatively interact with their genetics. In fact, genetics were predicted to cause up to 35% of major medication interactions in this patient population. Thus, there is a significant opportunity for PGT in both specialty and primary care settings and it is only expected to grow in tandem with the accelerating pace of clinical research published daily. Presently, the most robust evidence exists for specific gene-drug pairs that satisfy parameters for being clinically actionable. These gene-drug pairs will be the focus of the current review of the evidence landscape.

EXPERT PERSPECTIVES ON EVIDENCE GENERATION

While the potential clinical benefits of PGT are clearly evident, there must be evidence of clinical value to justify routine adoption by clinicians. Payers have traditionally raised the bar even higher for prognostic tests and often require evidence of economic value to justify coverage and reimbursement. To facilitate evidence generation, the Centers for Medicare and Medicaid Services (CMS) have put forth certain criteria that establish a framework for evaluating the analytical, clinical, and economic value of molecular diagnostics used in patient care. These criteria provide rough benchmarks that diagnostic developers can use to generate evidence of value; however, there is no clear consensus among stakeholders on the type of studies and/or volume of data that constitute adequate evidence.

Historically, diagnostic laboratories and drug manufacturers have relied on an evidence-based approach that exclusively employs clinical trials that randomize patients into different treatment arms to demonstrate safety and efficacy of the intervention. Such “gold standard” randomized clinical trials (RCTs) are a staple of traditional medicine and provide effective models to detect the relative benefits and harms of direct interventions, such as drugs or medical devices, in large, representative patient populations. However, there are significant challenges to using the RCT model to validate diagnostics used in precision medicine, such as PGT. Precision medicine represents a new paradigm of health care that involves matching diagnosis and/or treatment strategies for a patient to their unique molecular makeup. Therefore, the clinical value of PGT is found almost exclusively at the individual patient level. Population-based studies often dilute the individual patient signal, and as such, can require sample sizes in the thousands to adequately detect significant genetic associations among treatment groups in RCTs. For PGT, this becomes both practically and economically unfeasible given the sheer number of genes and drugs that can be surveyed. Some experts have further reasoned that such evaluation may be clinically overzealous since PGT is not a direct intervention and its use carries negligible harms, especially compared to its potential benefits.
For clinicians weighing the decision to incorporate PGT into patient management, the decision may be ultimately guided by clinical relevance. In the postgenomic era of the last decade, the rate of published pharmacogenetic research has accelerated almost exponentially per year. Most published evidence to date derives from pragmatic, naturalistic studies conducted in real-world patients, which may provide the most valuable assessment of PGT in routine clinical practice according to some experts. Nonetheless, it remains challenging for clinicians to distinguish between PGT targets with actionable information that can be implemented immediately in patient care from investigational tests that may presently offer only preliminary value. However, as the clinical evidence mounts for specific gene-drug pairs, some clinical experts question whether we are shortchanging patient care by waiting for proof-of-value using potentially inadequate models of utility.

EVIDENCE FOR ANALYTICAL VALIDITY

Analytical validity evaluates the accuracy, sensitivity, and reproducibility of the technological platform used to perform PGT. As such, this parameter depends on the specific technology platform used to perform the genetic
The vast majority of commercially available PGTs are designated as laboratory developed test (LDTs). LDTs must meet federally mandated testing standards established by the Clinical Laboratory Improvement Amendments (CLIA) and administered by CMS. These testing standards stipulate criteria for test performance, validity, and quality control that meet specific thresholds for assay specificity, sensitivity, and accuracy. A thorough review of PGT technology platforms is beyond the scope of this paper. However, in general, many pharmacogenetic LDTs utilize microarray technology or some variation of polymerase chain reaction (PCR)-based detection. Both technologies are highly accurate and sensitive, however PCR-based techniques have been in existence for much longer. Microarrays are also limited in the number of genetic variants (alleles) that can be detected per array, while PCR can be easily modified to capture a theoretically unlimited number of variants. DNA sequencing technologies represent an emerging PGT platform that is not used widely in the commercial sector as yet.

**EVIDENCE FOR CLINICAL VALIDITY**

Clinical validity establishes a positive association between a patient’s genotype and the observed clinical phenotype for specific medications. Most of the clinical validity evidence to date has focused on metabolism pathways. These data demonstrate, for example, that a patient’s CYP2D6 genotype accurately predicts their clinical phenotype when prescribed medications primarily processed by the CYP2D6 pathway.

Pharmacogenetic associations between response to the anti-coagulant warfarin (Coumadin®) and variations in two genes, CYP2C9 and VKORC1, were some of the first to be described and currently have the strongest level of clinical evidence. In 2007, the FDA approved language in the prescribing information to guide clinicians in the use of CYP2C9/VKORC1 genetic information during warfarin administration. In recent years, specific algorithms have also been developed that predict precise warfarin maintenance doses based on both genetic and non-genetic factors. The platelet inhibitor and prodrug clopidogrel (Plavix®) represents another well-known cardiovascular PGT target. CYP2C19 poor metabolizers produce less active metabolite and are at higher risk of cardiovascular events, especially stent thrombosis.

Antidepressants represent another drug class with well documented pharmacogenetic associations. CYP2C19 poor metabolizers taking tricyclic antidepressants (TCAs) and SSRIs including sertraline (Zoloft®), citalopram (Celexa®), and escitalopram (Lexapro®) may have higher-than-expected plasma concentrations of active medication and are more likely to experience adverse effects. On the other hand, CYP2C19 ultra-rapid metabolizers show lower-than-expected plasma levels of active medication and may be at risk of therapeutic failure.

Genetic variations for CYP2D6 metabolism also correlate with ADRs and clinical response for many psychiatric medications. CYP2D6 poor metabolizers are at higher risk for side effects.

### Table 2. Commonly prescribed drugs metabolized by CYP2D6, CYP2C19, and CYP2C9 that have clinical evidence of associations with patient outcomes.

<table>
<thead>
<tr>
<th>ENZYME GENE</th>
<th>THERAPEUTIC AREA</th>
<th>DRUGS WITH GENETIC ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Analgesics</td>
<td>Codeine, Tramadol, Hydrocodone, Oxycodeone</td>
</tr>
<tr>
<td></td>
<td>Psychiatry</td>
<td>Venlafaxine, Paroxetine, Anpiprazole, Risperidone, Atomoxetine, TCAs, Metoprolol, Propanolol, Carvedilol (others)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>CYP2C19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Psychiatry</td>
<td>Citalopram, Sertraline, Escitalopram, Amtriptyline, Droxepin, Diazepam, Clopidogrel, Esomeprazole, Omeprazole, Pantoprazole, Carisoprodol</td>
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<tr>
<td></td>
<td>Cardiovascular</td>
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<td></td>
<td>Gastroenterology</td>
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<td></td>
<td>Musculoskeletal</td>
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<tr>
<td>CYP2C9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Analgesics</td>
<td>Celecoxib, Warfarin</td>
</tr>
<tr>
<td>CYP2B6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Analgesic</td>
<td>Methadone</td>
</tr>
<tr>
<td>CYP3A4/3A5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Analgesic</td>
<td>Fentanyl</td>
</tr>
</tbody>
</table>

<sup>a</sup>Refs: 10, 12, 16, 26, 64, 68-87, 102, 106, 120; <sup>b</sup>Refs: 10, 12, 16, 63-67, 88-94, 106; <sup>c</sup>Refs: 55-62, 96-99, 154-157; <sup>d</sup>Refs: 149-153; <sup>e</sup>Refs: 95
effects and discontinuation, while ultrarapid metabolizers are at risk for therapeutic failure with TCAs\textsuperscript{64}, other antidepressants\textsuperscript{68-70}, some antipsychotics\textsuperscript{71-73}, and the ADHD non-stimulant atomoxetine.\textsuperscript{74} Moreover, a small (N=28) retrospective and naturalistic study found that CYP2D6 poor metabolizers were almost 4-fold over-represented in patients experiencing ADRs due to antidepressants compared to the general population.\textsuperscript{75} Patients classified as non-responders to their antidepressant therapy were approximately 5-fold over-represented.\textsuperscript{75} Genetic variations in CYP450 enzymes can also significantly impact clinical outcomes during chronic opioid therapy. The pro-drug codeine is metabolized to its active metabolite morphine via the CYP2D6 pathway. CYP2D6 ultra-rapid metabolizers are at higher risk of toxic morphine accumulation and several cases of respiratory depression and/or death following codeine administration have been reported in children known to be CYP2D6 ultra rapid metabolizers.\textsuperscript{76-79} A recent population study reports a 16-fold higher risk of CNS depression for nursing infants of mothers that are CYP2D6 ultra-rapid versus poor metabolizers.\textsuperscript{79}

CYP2D6 poor metabolizers were almost 4-fold over-represented in patients who experienced ADRs due to antidepressants compared to the general population. Patients classified as non-responders to their antidepressant therapy were approximately 5-fold over-represented.\textsuperscript{75}

CYP2D6 variant metabolizers also exhibit poor clinical outcomes for other commonly used opioids\textsuperscript{80}, including tramadol\textsuperscript{81,82}, oxycodone\textsuperscript{83-85}, and hydrocodone.\textsuperscript{86} CYP2D6 genetic variation may also impact risk for opioid dependence.\textsuperscript{87} CYP2C19 ultra-rapid metabolizers taking the muscle relaxer carisoprodol (Soma\textsuperscript{86}) are at higher risk of CNS depression, coma, and sometimes death.\textsuperscript{88-90} CYP2C19 poor metabolizers may experience CNS depression and serotonin syndrome.\textsuperscript{88-90} CYP2C19 variant metabolizers are also at higher risk of sedation and CNS depression for a number of commonly used benzodiazepines, including diazepam (Valium\textsuperscript{89}).\textsuperscript{91-94} Finally, fentanyl (Duragesic\textsuperscript{86}) dosing requirements may be impacted by CYP3A4 and CYP3A5 genetic variations\textsuperscript{95}, while CYP2C9 variant metabolizers taking the NSAID pain reliever celecoxib (Celebrex\textsuperscript{86}) may be at increased risk of side effects.\textsuperscript{96-99} Previous studies also demonstrate that CYP2B6 variations are associated with patient drug-taking behavior,\textsuperscript{149-151} risk of methadone-induced fatality,\textsuperscript{152} and need for lower methadone doses in patients being treated for addiction.\textsuperscript{153}

**EVIDENCE FOR CLINICAL UTILITY**

Clinical utility studies evaluate whether PGT improves patient outcomes and associated health care costs.\textsuperscript{36} Given the inherent limitations of the RCT model, the majority of clinical utility evidence for PGT has employed naturalistic clinical trials in representative patient populations.\textsuperscript{45} The accumulated data clearly demonstrate that patients with genetically variant metabolism experience a wide variety of poor health outcomes compared to non-variant patients.\textsuperscript{100-118}

**RANDOMIZED CLINICAL TRIALS**

Despite their limitations, a number of RCTs have been successfully completed and published. Some have introduced innovative methodologies aimed at overcoming design challenges in order to detect specific patient outcomes. For example, one approach has been to enrich each study arm with equal proportions of randomly selected variant metabolizers to increase the signal-to-noise ratio.\textsuperscript{12} Otherwise, potentially thousands of patients would need
to be randomized to adequately power the study. A recent prospective year-long RCTs of schizophrenic patients (N=209) reported that CYP2D6 or CYP2C19 poor or ultra-rapid metabolizers demonstrated higher overall health care costs. Importantly, this study also showed that genetic testing prior to medication selection reduced these excess costs compared to patients that received standard care (no PGT).

Other studies evaluate multiple clinically related genes in the patient and interpret the results using a combined phenotype approach. Since the majority of patients are variant for at least two CYP450 enzymes, evaluating multiple clinically relevant enzymes may be a useful approach to improve the concordance of a patient’s genetics with their clinical presentation. Using this method, one prospective and blinded eight-week study in depressed patients (N=113) reports that more patients in the PGT-guided group achieved response and remission as evaluated by three validated and structured assessment tools (QIDS-C16, HAMD-17, PHQ-9) versus patients receiving standard care (no PGT).

Several recent RCTs have shown improved outcomes for patients receiving warfarin using PGT-guided dosing compared to standard care, with the primary endpoint being percentage of time in the therapeutic INR range. A national prospective study also showed a one-third reduction in hospitalization incidence when genotyping was performed prior to warfarin usage.

Finally, a double-blinded, placebo-controlled RCT (N=33) reported that CYP2D6 poor metabolizers experienced less analgesia with oxycodone than extensive metabolizers in three out of five well-validated pain tests. These results also demonstrated that poor metabolizers had statistically lower levels of oxycodone’s more analgesically potent metabolite oxymorphone.

### REAL-WORLD, PRAGMATIC CLINICAL TRIALS

Studies that employ pragmatic designs may include open-label (no comparator group), retrospective, or cross-sectional designs. These studies often have less stringent exclusion criteria and may recruit patients that are more representative of patients treated in routine clinical practice. For example, patients on complex polypharmacy or with co-morbid conditions may be frequently excluded from RCTs but recruited into pragmatic trials.

In depressed patients, naturalistic studies demonstrate that PGT-guided care results in greater therapeutic response and doubled remission rates compared to standard care in the same patient. In a retrospective study, patients with major depression who were
Mental health patients with variant metabolism used more health care resources and incurred higher costs when prescribed medications incompatible with their genetics.\textsuperscript{13}

Variant metabolizers incur higher direct and indirect costs (N=96)\textsuperscript{13}

\begin{table}
\begin{tabular}{|c|c|c|}
\hline
 & HIGH RISK MEDICATION & LOW RISK MEDICATION \\
\hline
ANNUAL MEAN HEALTH CARE UTILIZATION COST & $\ 8,627$ & $\ 3,453$ \\
\hline
 & $p=0.02$ & $p=0.03$ \\
\hline
\end{tabular}
\end{table}

Prospective 1-yr study finds that psychiatric patients with reduced CYP2D6 metabolism have substantially more ADRs and cost an extra $4,000–$6,000/year to treat.\textsuperscript{120}

CYP2D6 variants have more ADRs and higher care costs (N=100)\textsuperscript{120}

Compared to normal metabolizers, patients with CYP2D6 poor metabolism (N=254) are\textsuperscript{101}...

\begin{itemize}
  \item 4x MORE LIKELY TO SWITCH TO ANOTHER ANTIDEPRESSANT
  \item 2x MORE LIKELY TO CHANGE ANTIDEPRESSANT DOSING
  \item 2x MORE LIKELY TO CHANGE ANTIPSYCHOTIC DOSING
\end{itemize}

prescribed a medication that was later identified by genetic testing to be problematic had 69% more total health care visits, 67% more general medical visits, 3 times more sick days, and 4 times more disability claims compared to patients who were administered medications considered appropriate for their genetics. These patients also had an estimated greater health care cost of $5,188 per patient.\textsuperscript{16} Another open-label, year-long prospective study in psychiatric patients (n=100) receiving in-patient care found that CYP2D6 poor metabolizers are more expensive to treat and have greater ADR risk than extensive (normal) metabolizers’ patients.\textsuperscript{120} They were also more likely to experience adverse effects with some medications due to reduction in CYP2D6 activity.

One potential driver of health care costs in patients with genetic variations is pharmacy costs associated with ineffective medications. A retrospective study of psychiatric inpatients (N=254) found that the relative risk of medication switches or changes to dosing regimen were significantly greater for CYP2D6 poor metabolizers compared to extensive (normal) patients.\textsuperscript{101} Another large study (N=1198) in elderly outpatients found that CYP2D6 poor metabolizers receiving TCAs had a higher risk of switching to another antidepressant.\textsuperscript{102} Poor metabolizers also required a lower maintenance dose of antidepressants compared to extensive (normal) metabolizers.
For many chronic diseases, including depression, hypertension, and diabetes (type 2), lack of medication adherence poses a significant issue that contributes to higher overall medical costs.\textsuperscript{121-124} In fact, a comprehensive analysis conducted by Medco Health reports that between 50-90% of patients with common health conditions stop taking their prescribed medication by the end of the first year of treatment.\textsuperscript{125} Multiple studies have shown that medication discontinuation and non-adherence may be driven in part by a lack of medication response and/or medication intolerance.\textsuperscript{124}

Given the association between genetic variations and these drivers of non-adherence, optimizing medication therapy using PGT may improve adherence by reducing the risk of side effects or therapeutic failures. In fact, a number of preliminary studies have shown PGT-guided care may improve adherence rates and clinical outcomes for diabetes therapy\textsuperscript{121}, statins\textsuperscript{122}, and depression therapy.\textsuperscript{123} A recent large claims database study in depressed patients (N=681) found that PGT-guided treatment significantly improved medication adherence versus standard care and resulted in a relative total cost savings of almost 10% (or $562) over a 4-month follow-up period.\textsuperscript{123}

**Preliminary studies demonstrate that PGT may improve clinical outcomes and adherence for diabetes therapy\textsuperscript{121}, statins\textsuperscript{122}, and depression.\textsuperscript{123}**

By the end of the first year of treatment, 50-90% of patients stop taking their prescribed medications.\textsuperscript{124,125}

![Graph showing medication adherence rates over time for different conditions](image)

GUIDELINES AND EXPERT OPINION

In the wake of the accelerating pace of pharmacogenetic research being published, a number of expert consortia have convened to provide guidance on PGT that are considered clinically actionable according to the strength of published evidence. These consortia include members of NIH, FDA, academic experts, and industry representatives who review the available literature in order to develop and publish consensus guidelines for specific gene-drug pairs. These guidelines are intended for use by clinicians during decision making for patients with certain genetic variations receiving specific medications. The Clinical Implementation Pharmacogenetics Consortium (CPIC) was created in 2009 to identify genetic tests that have strong clinical evidence and to publish guidelines that recommend clinical actions based on genetic test results.\textsuperscript{126} The CPIC has published two CYP2C19 guidelines for TCAs\textsuperscript{64} and clopidogrel\textsuperscript{127}; and a CYP2C9/VKORC1 guideline for warfarin.\textsuperscript{55} The Coriell Personalized Medicine Collaborative has identified CYP2C19 and clopidogrel and CYP2D6 and codeine as gene-drug pairs with highly actionable genetic results.\textsuperscript{130} Finally, the Royal Dutch Association for the Advancement of Pharmacy has issued guidelines for the use of CYP2C19 genetic test results for 12 medications, including clopidogrel, certain antidepressants (sertraline, citalopram,
escitalopram, and tricyclic antidepressants), and proton pump inhibitors as well as for the use of CYP2D6 genetic test results for 35 medications, including codeine, antidepressants, and antipsychotics.\textsuperscript{131,132}

The FDA has approved drug labeling that provides dosing and administration guidance for over 120 medications according to pharmacogenetic information, including carisoprodol, atomoxetine, aripiprazole, celecoxib, clopidogrel, diazepam, codeine, risperidone, paroxetine, tramadol, pantoprazole, and venlafaxine.\textsuperscript{133} Clopidogrel and codeine include the FDA's strongest warning (boxed warning) to clinicians about increased risk of side effects or death, respectively, in variant metabolizers.\textsuperscript{133}

**Over 120 medications carry pharmacogenetic information in their FDA product label\textsuperscript{133}, including codeine, Risperdal®, Abilify®, Paxil®, Strattera®, and Ultram®.**

Medications with PGT guidance in FDA approved drug labeling\textsuperscript{133}

CONSIDERATIONS FOR ROUTINE CLINICAL IMPLEMENTATION

Although the evidence for the health and economic benefits of PGT is rapidly accumulating, there remain a number of considerations for successful implementation into routine clinical care.\textsuperscript{45,49,134} One important consideration is clinician awareness and preparedness to interpret and apply genetic test results to manage their patients. According to a number of surveys, the majority of clinicians across a variety of therapeutic specialties have a generally positive perception regarding the potential benefits of pharmacogenetic testing; however, only a small minority of clinicians report feeling adequately informed about this type of testing.\textsuperscript{135,136} Many medical organizations and experts are advocating for expanded education on pharmacogenetics in US medical schools and a few industry stakeholders have made efforts to provide non-branded education to clinicians.

Another important stepping stone to routine implementation is achieving consensus among stakeholders regarding the relevant criteria, definitions, and validation models used to assess genetic tests for clinical value.\textsuperscript{49,53,54} Stakeholders must also acknowledge the paradigm shift increasingly advocated by researchers that RCT models are not the only avenue for generating high quality evidence of clinical utility.\textsuperscript{49,53,54} Integrating PGT information into EMR/EHR systems and sharing patient results across providers is another consideration for routine implementation.\textsuperscript{46} Despite federal incentives to implement approved EMR systems with interoperable capacity, nationwide adoption of EMR systems that meet these basic criteria has been slow.\textsuperscript{137} In the absence of EMR/EHR systems, clinicians must be able to appropriately document PGT information within patient health records in ways that facilitate access for patient care.

**FUTURE DIRECTIONS**

A number of major US medical institutions and centers have implemented PGT into routine care and offer real-world models of best practices for practically translating the clinical value of PGT.\textsuperscript{138-143} Multiple centers have adopted an innovative approach that couples preemptive (pre-prescribing) PGT with popup alerts embedded within EMR/EHR systems to help guide patient care. Successful examples include preemptive CYP2D6 genotyping.
Some major medical institutions and centers in the US are testing patients preemptively (pre-prescription) using integrated EHR/EMR systems. In fact, Vanderbilt’s PREDICT program suggests that over 91% of patients had one or more actionable variants. Importantly, the authors report that when preemptive genotyping is used during patient care, fewer tests are performed compared to reactive testing. Similarly, Mayo’s RIGHT protocol recruited and tested 1,013 participants with the goal of developing best practices for wider implementation of PGT. The RIGHT protocol deploys preemptive CYP2D6 testing in addition to sequencing of 84 pharmacogenetically relevant genetic variants in a pilot effort to evaluate impacts of EMR-driven pre-prescription PGT during patient care. The RIGHT protocol also aims to circumvent the current clinical paradigm of ordering specific point-of-care PGT upon initiation of treatment, which can be expensive and potentially delay therapeutic decision-making.

Finally, the clinical literature continues to expand for new and emerging genetic targets and these data are likely to improve the precision of pharmacogenetic testing in predicting patient outcomes. These novel biomarkers include genes that encode transport proteins involved in cellular influx and efflux of drugs as well as cell surface receptors that interact with receptors to produce a therapeutic effect. Epigenetic biomarkers, which can alter protein expression independent of DNA variations, represent a novel and intensely researched area that may soon be translated from the research arena into clinical practice.

**SUMMARY**

In the decade following the decoding of the human genome in 2001, there have been substantial milestones achieved on the path to genomic medicine. Given the potential significance of PGT to patient care and the rapid pace of progress, we must continuously scan the evidence landscape to identify actionable gene-drug pairs for clinical implementation. In clinical practice today, clear examples of clinically relevant and robustly supported gene-drugs pairs that merit routine implementation during patient management have emerged from the evidence landscape.

“The power in tailored therapeutics is for us to say more clearly to payers, providers, and patients: ‘this drug is not for everyone, but it is for you.’ That is exceedingly powerful.”

- John C. Lechleiter, Ph.D.
President and Chief Executive Officer
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REFERENCES


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