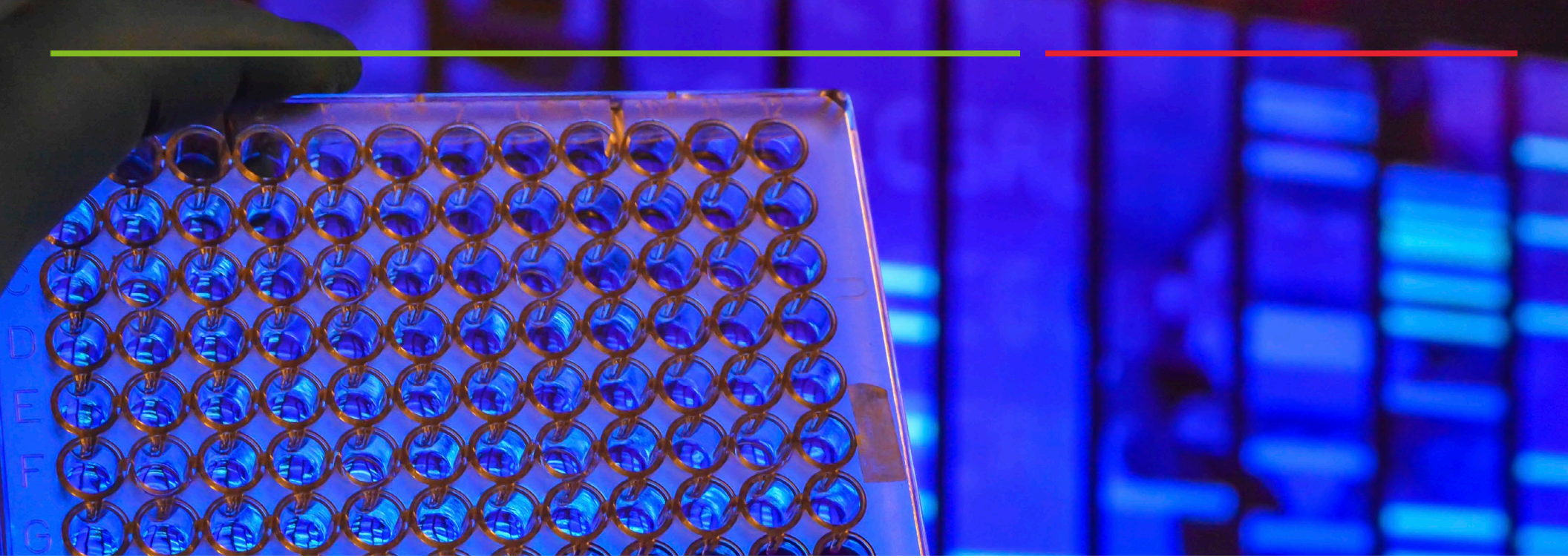


Pharmacogenomics:

Engaging and uniting teams is key to advancing care

Wolters Kluwer

Drug therapy cannot be viewed as one-size-fits-all

More than 90% of individuals carry at least one potentially actionable pharmacogenetic variation[1], giving pharmacogenomics (PGx) growing importance in clinical decision support. Additionally, non-European populations carry a greater frequency of variants, many not yet captured by current PGx allele definitions, that are predicted to be harmful.[2] Without knowledge of pharmacogenetic factors, improper drug selection and administration can result in reduced therapeutic response or serious adverse drug reactions (ADRs), the latter of which is estimated to be the the sixth leading cause of death worldwide and the fourth leading cause in the United States and Canada.[3]

With the widespread prevalence of PGx variance, it should not be surprising that the U.S. Food and Drug Administration (FDA) has identified more than 450 drugs with actionable PGx considerations.[4] This includes over 100 drugs with published clinical guidance.[5] Some examples of clinically significant genomic variants influencing mediation therapy include:

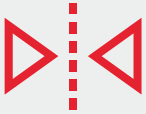
- Reduced cytochrome P450-mediated opioid metabolism, which could lead to excessive respiratory depression and death.
- Effects of decreased TPMT metabolism on thiopurine treatment, which could predispose to serious blood toxicities.
- Effects of reduced liver uptake of simvastatin, which could lead to significant muscle damage.

However, preemptive pharmacogenomics testing is still emerging as best practice, translating genotypes into actionable phenotypes. While PGx is a subject that intrigues many clinicians, transitioning it into a practical component of the diagnostic and treatment routine will require access to consistent, evidence-based PGx data and a team-based approach involving healthcare professionals from prescribers, pharmacists, and nurses, to lab technicians and those managing benefits.

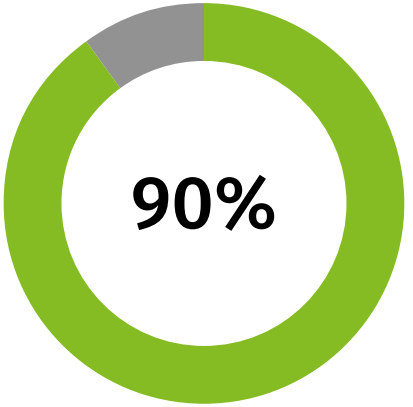
3 Steps to Putting PGx into Practice

Awareness:
Engaging clinicians on how, when, and why to use PGx

Alerting:
Getting the right data into clinicians' hands



Alignment:
PGx works best when care teams work together



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Awareness: Engaging clinicians on how, when, and why to use PGx

Clinicians are aware of the impact of genetic factors on drug therapy, but don't always feel prepared to implement that information into their daily practice:

- A U.S. national survey of 10,303 physicians indicated that although 97.6% of them agreed that genetic variation may influence drug response, only 29% of them had received any education in pharmacogenomics and only 10.3% felt adequately informed about PGx testing. Fewer than 40% of them had recently ordered a test or anticipated ordering a test in the near future.[6]
- Similarly, a Japanese study found that, while the majority of pharmacists surveyed felt PGx had potential to improve patient care, only 26% were involved in PGx testing and 12.4% had received specific PGx-related education.[7]
- A survey of 285 physicians from five of the Implementing GeNomics In pracTiCe (IGNITE) clinical trial network sites revealed that most physicians felt unprepared to use genetic information in their practice and believed steps needed to be taken to develop tools and training for physicians. Those with five years or fewer in practice were more likely to report that their training had prepared them to care for genetically high-risk patients compared with those with over five years' experience (41% vs 25%).[8]
- Another study, involving 597 primary care physicians in the U.S., found that although the majority of respondents had heard of pharmacogenomics testing and anticipated that it would be useful to their patients, only 13% felt comfortable ordering such tests and 22% reported that they had not received any education in pharmacogenomics.[9]

It may not always be clear to clinicians when ordering a test could be beneficial. Labs that conduct PGx tests often provide FAQs and other guides to help clinicians better understand why they might want to order PGx testing. However, direct marketing from commercial labs may not always include the complete context a clinician needs, especially if they are not sufficiently trained in possible interpretations of the pharmacogenetic tests. Simply being persuaded to order tests without knowing how to apply the results may cause more confusion than benefit.

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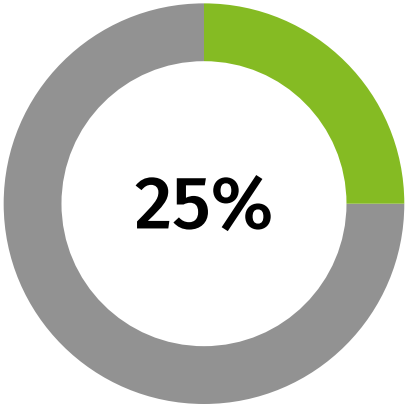
Recognizing the need to help clinicians understand the importance of pharmacogenomics early on, Wolters Kluwer has curated clinically relevant PGx content since 2003 and is widely recognized as a leader in providing extensive and actionable clinical guidance on important PGx interactions. This content covers the prevalence of genomic variants in patient populations, the utility and interpretation of laboratory testing, and subsequent clinical recommendations.[10]

For clinicians working at the point of care, drug-gene summary monographs provide testing and patient management recommendations from authoritative, clinically-actionable guidelines.[11] These concise summaries also offer a proprietary evidentiary rating that affords the clinician a more robust perspective on the true overall clinical importance of genetic testing. Actionable summaries are vital for frontline clinicians who need immediate guidance on drug-gene questions in direct care situations without the time to engage in in-depth drug information research.

When more comprehensive research data is required, clinicians need access to in-depth pharmacogenomics content. To accommodate this need, UpToDate® Lexidrug™ core drug monographs contain links to detailed, extensively referenced gene-based monographs which provide an overview of the population incidence of the most common or clinically-important gene variations and the relevance to drug response.

Online and mobile pharmacogenomics drug references also offer benefits outside of the direct care arena, providing valuable genetic research information for medical affairs departments and R&D and important safety context for healthcare benefits businesses, which have been slowly expanding coverage for gene testing over the past decade.



Only 25% of clinicians practicing more than five years say they feel prepared to manage genetically high-risk patients.[8]

Alerting: Getting the right data into clinicians' hands

Interviews with general practitioners in the United Kingdom revealed that most saw value in PGx, but felt there were many obstacles to primary care embracing it in everyday practice, including educating clinicians, managing cost-effectiveness, and incorporating the information into electronic health records.[12]

Currently, integrating genomic data and clinical decision support tools into electronic medical records (EMR) is one of the largest barriers to more widespread adoption of preemptive pharmacogenomics testing.

The Electronic Medical Records and Genomics (eMERGE) Network is leading the way in piloting and implementing PGx and integrating the results within EMR and clinical decision support systems in the U.S.

A survey of 10 of the sites within the network reported that delays in the process were not stemming from the pharmacogenomics testing itself, but more likely to be related to health information technology, among other logistical issues.[13]

As more medications commonly used in primary care include labeled indications for pharmacogenomic testing, it becomes increasingly important to include these guidelines and precautions in EMR and other clinical decision support screening. Additionally, laboratory technologies to perform multiplexed genotyping are rapidly becoming more affordable and reliable, furthering the demand for safety screening within clinical and pharmacy systems.

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Pharmacogenomic data embedded within an EMR, clinical, or pharmacy system serves as a powerful tool for getting vital data before the clinicians' eyes at the right time in the decision-making process. A smartly designed system with evidence-based data can help prevent high-risk patients from being exposed to "dangerous" drugs due to their genetic predispositions. Such a system would provide appropriate dosage recommendations based on relevant genetic variance and would only alert on known risky combinations, optimizing the alerts that fire in the system.

Clinicians can overcome some of those technological barriers by infusing Medi-Span® embedded drug data modules with evidence-based and actionable pharmacogenomic data that aligns with UpToDate Lexidrug content and by providing clear guidance and best practices on how to optimize and apply relevant pharmacogenomics data.

Powered by a dedicated Medical Condition Picklist of distinct pharmacogenomic phenotypes, more than 350 drug-phenotype associations are recognized within the Medi-Span Drug Disease Contraindications API to alert and advise clinicians at the point of care on the risks of using certain medications in patients with specific genetic conditions. Genomic conditions may be identified as an input for screening based off the patient's medical problem list as a selected phenotype within the EMR or pharmacy system, or by way of a submitted SNOMED CT® code to which that phenotype concept is mapped.

Furthermore, these phenotype conditions are also integrated within Medi-Span Dose Screening and Drug Orders API as patient-specific context to properly adjust dose range alerts in sensitive individuals. This is critical functionality for avoiding potentially harmful drug overdoses in patients with diminished metabolic capacity.

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Alignment: PGx works best when care teams work together

With resources available at the point of care and in the EMR, the final element to successful adoption of PGx is human. Many clinical and non-clinical personnel need to collaborate, communicate, and align resources to fully integrate PGx into an organization's regular practice.

Some experts recommend a team including a selection of the following:

- Prescribers who understand when testing is required and how drug therapy might be affected
- Labs/ technicians trained to administer and advise on appropriate testing
- Pharmacists to advise on pharmacokinetics and pharmacodynamics and recommend proper drug choice and drug dose
- Genetic counselors or others with appropriate training to advise on application/ interpretation of test results / Personnel to discuss risks, benefits, and limitations of testing

Furthermore, organizations should consider systems or infrastructure to support these needs:

- IT/EMR set-up and maintenance of appropriate PGx screening and alerts
- Process for documentation of relevant medication and family histories
- Billable-service provider
- Mechanism for reporting results

Wolters Kluwer's investment in pharmacogenomics content seeks to benefit all members of this multi-disciplinary care team by providing solutions that centralize and standardize delivery of this content to the right provider, at the right time, providing insight and context relevant to the right patient.

Conclusion

A Canadian study of 180 patients using antidepressant/antipsychotic medications who underwent PGx testing found that genotyping led to 81 medication changes in 33 unique patients (representing 22% of study participants). The study authors determined that the cost of performing the testing and adjusting the drug therapies amounted to less than $25 CAD per patient and was, therefore, both efficiently handled by the pharmacy team and well worth the cost.[14]

As more clinicians adopt, adapt, and learn about personalized medicine and pharmacogenomics, it will only increase medication safety in the future. Peter Bonis, MD, Chief Medical Officer for Wolters Kluwer Health, notes that "scientific advances continue to offer new options for medications that have the potential to improve and save lives.
The affordability of these drugs has spawned vigorous public debate. Equally important – but less in the public dialogue – are efforts to ensure that drugs are used both wisely and safely. Pharmacogenomics represents one such approach toward precision prescribing."

[1] Van Driest et al, Clin Pharmacol Ther. 2014 Apr; 95(4): 423–431.
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