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The Utility of Using Pharmacogenomics Testing in Clinical Practice

An Overview of Pharmacogenomic Testing

Medical providers prescribe medications aimed toward beneficial patient outcomes. However, drug impact (e.g., drug efficacy and toxicity) can differ between patients diagnosed for any given disorder. This is due partly to gene-mediated differentiations in each patient's body. The completion of Human Genome Mapping in 2003 enabled development of the emerging pharmacogenomics (PGx) field. As a result, this increased human genome knowledge has promoted the capacity to incorporate an understanding of a patient's genome in determining the best drug treatment regimen. It has been estimated that genetics account for up to 95% of the variability in drug disposition and effect[1].

What is PGx Testing

PGx testing is a diagnostic tool utilized to predict how a given patient will respond to a prescribed pharmaceutical agent (which was formerly limited); a therapeutic dose of the same drug could produce a positive effect in one patient, while producing an unwanted effect reaction in another patient—creating a challenge for physicians prescribing drug therapy. Since understanding the patient's likely response is vital to treatment plans, PGx testing is an emerging modality for clinicians to better target an individual patient's care. Among avoidable hospitalizations, those attributable to adverse drug reactions (ADRs) may be decreased as a result of more tailored drug interventions obtained from the use of PGx tests[2].

Phases of Drug Physiological Interactions

Following drug administration, sequential interactive phases occur that impact drug absorption, distribution, metabolism, and excretion. Meanwhile, genetic mediation of drug-metabolizing enzymes, transporters, targets, and receptors can alter a prescribed drug's pharmacokinetic/pharmacodynamic properties. Thus, a patient's innate genetic variations can potentially modify any interactive phase, thereby contributing to the variability of the drug response in terms of efficacy, safety and toxicity[1,3,4].

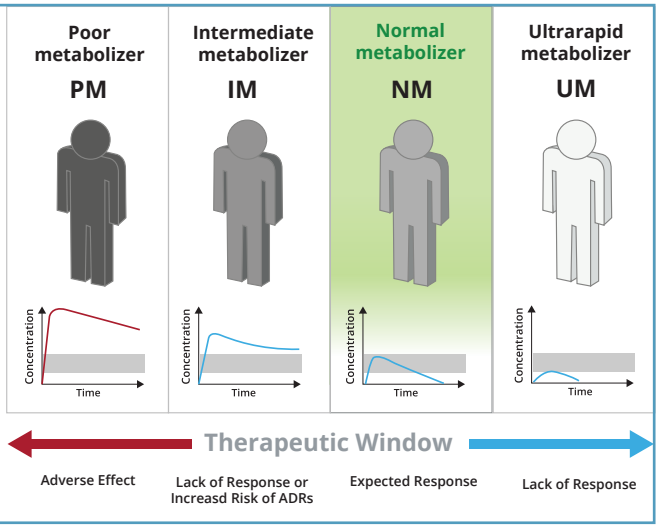
Figure 1: Example of the potential clinical consequence of CYP2C19 variable phenotypes on Citalopram (Celexa®)[5].

Poor metabolizer (PM):
Significantly reduced inactivation and increased response and side effects

Intermediate metabolizer (IM):
Reduced inactivation and increased response and side effects

Normal metabolizer:
Normal or expected clinical response

Ultrarapid metabolizer (UM):
Significantly increased inactivation and reduced response

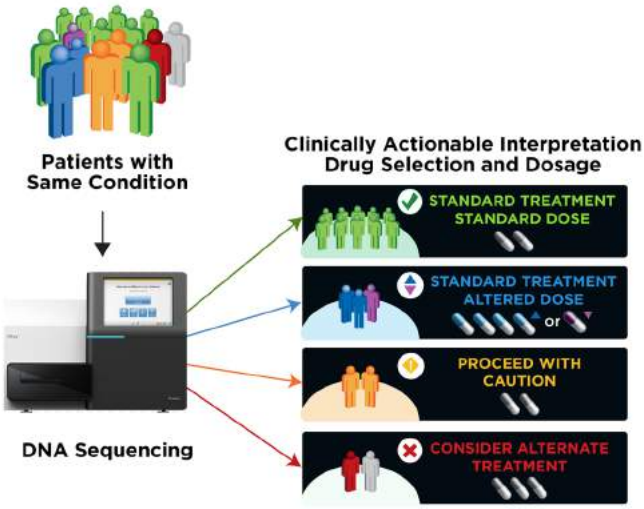


Example of Difference in Drug Impact Resulting from Genetic Variation

CYP2C19 is a drug-metabolizing enzyme that metabolizes many routinely-prescribed drugs (*e.g.*, certain proton pump inhibitors, anticonvulsants, and antimicrobials). The most common CYP2C19 genetic variants are: CYP2C19*2 and CYP2C19*3[4]. As two examples, these "variants" can result in different metabolizer phenotypes, categorized as the following: Poor metabolizer (PM), Intermediate metabolizer (IM), Extensive metabolizer (EM), and Ultrarapid metabolizer (UM)[4] ***(Figure 1)***[5].

Consequently, the use of a PGx test can enable physician incorporation of gene-targeted knowledge to better determine the most efficacious and least toxic drug treatment/dose for a given patient ***(Figure 2)***.

Figure 2: Pharmacogenomics Testing
"Individualize therapy" approach based on genetic makeup.



Economic and Clinical Benefits of Pharmacogenomics Testing

Increasing US healthcare costs can impact patients, payers and providers. Healthcare costs continue to rise due to inconsistent prescribing behavior, poor patient monitoring, non-compliance, and an aging population. For every dollar spent on prescription drugs, an additional fifty cents is spent solely in treating ADRs—calculated as $136 B of preventable excess healthcare spending, per the *US Food and Drug Administration (FDA)*[2,6].

According to the *Center for Medicare & Medicaid Services (CMS)*, US healthcare spending grew 4.3% in 2016 (averaging $10,348/person)[2]. Moreover, prescription drug spending increased to $328.6 B in 2016, and national hospital expenditures increased in 2016 to $11 T. Additionally, US healthcare spending is projected to continue growing at an average annual rate of 5.9%[2].

PGx testing may aid in reducing preventable healthcare costs, by increasing physicians' overall capacity to:

- Reduce the need for trial-and-error treatment planning[7]
- Maximize drug efficacy[8]
- Minimize Adverse Drug Reactions (ADRs)[8,9]
- Improve patient quality of life[8,9]
- Decrease lifetime healthcare costs[10]
- Improve medication compliance[11]

Effective Medication Management in Older Adults:

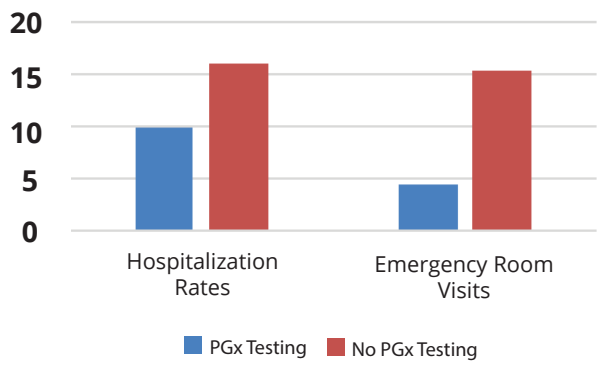
The US population aged ≥65 years continues to rise, with at least 71 million patients aged ≥65 by 2030[6]. Co-morbid chronic illnesses (necessitating multiple medications [polypharmacy]) are also increased in elderly adults. Wide consensus exists that polypharmacy-exhibiting patients most often take >5 drugs concurrently, and tend to be at highest risk for drug interactions and ADRs[6]. The estimated US cost-burden associated with mismanaging polypharmacy-exhibiting patients was $1.3 billion in 2012[6].

IMS Health reported that 42% of patients >65 years old consumed >5 or more drugs in 2012 (from 5 drugs at age 65, this increased to 7 drugs by age 85)[6]. The opportunity for healthcare cost savings is possible by incorporating PGx testing into the treatment decision.

Recent published findings from a randomized (controlled) clinical trial revealed that $621/patient on average may be saved through incorporation of PGx results into patient medication management ***(Figure 3)***[12]. Additionally, PGx testing resulted in a 38% increase in patients identified as benefiting from pharmaceutical treatment modification (as compared with analyzed data from similar patients not receiving PGx diagnostic testing).

Furthermore, a study comparing the impact of PGx testing with non-testing in human subjects aged >65 years old showed a much lower hospitalization rate for the PGx-tested group (9.8%) than the non-tested group (16.1%). After PGx testing, 50% of those on >5 medications were safely able to eliminate or modify at least one drug from their drug treatment plan[13].

Figure 3: Cost-Burden Associated with Hospital Stays and Emergency Room Visits were Reduced Utilizing PGx Test.



Improve Medication Adherence:

Poor medication adherence is a significant US economic burden (with a cost-burden of $105 B in 2012, of which 69% was spent on hospitalization)[6]. This US cost-burden has since risen to $300 B[14]. Moreover, prescription nonadherence is most commonly linked to chronic disorders (*e.g.*, hypertension, hypercholesterolemia, and diabetes ***(Table 1)***[6]. PGx studies have shown that genetic variations may be associated with more untoward side effects, resulting in drug nonadherence and/or discontinuation. Genomic testing has been found to have a positive relationship with improved medication adherence. On the other hand, nonadherence leads to increased overall healthcare costs via higher rates of ED visits, prolonged hospital stays, and increased short-term disability claims[10].

Table 1: Selected complications resulting from nonadherence[7]

Disease	Complication as a Result of Nonadherence
Hypercholesterolemia	Acute myocardial infarction
Diabetes	Stroke
Hypertension	Acute myocardial infarction
Psychiatry	Treatment failure

PGx-focused studies on medication adherence:

A PGx study that investigated the impact of PGx on identified nonadherent psychiatric patients showed nonadherence linked to a 69% increase in clinician visits, along with increased healthcare costs of >$5,188/person[15]. Likewise, another study showed a 6.3% increase in prescription drug adherence after PGx testing (and saving $562 in *per patient* outpatient costs over a four-month period)[10]. Yet a third PGx-focused study reported a 72% adherence improvement among diabetes patients[16].

The conclusion reinforced by diverse research studies' findings is that PGx testing can increase adherence and improve clinical outcome. This is additional to study findings revealing that clinician ability to proactively identify specific patients with a high likelihood of intolerance to a particular medication (or medication combination) is increased through utilization of PGx testing.

PGx has the potential to substantially **reduce** both direct and indirect **healthcare costs** while improving a patient's quality of life[6].

Reduction in Adverse Drug Reaction (ADR):

ADRs are a leading mortality cause[17], and ADR risk increases exponentially in patients prescribed ≥4 medications[6]. Moreover, ADRs are the cause of 1 out of every 5 injuries or deaths to hospitalized patients[18]. Frequently observed in patients with either PM or UM genetic precursors, ADRs can easily lead to[13]:

- Increased Emergency Department (ED) visits;
- Extended hospital stays;
- Hospital re-admissions (resulting in Medicare penalties for preventable readmissions).

Approximately 20-30% of ADRs are estimated as preventable; improved clinical outcome has been demonstrated if PGx testing is adopted[17]. Studies have also shown that—once PGx testing was provided to screen CYP2D6 for both poor or ultra-rapid metabolism—healthcare costs were reduced by 28% for those diagnosed with schizophrenia and other psychiatric illnesses[19]. In addition, results from a systemic review of economics evaluations regarding ADR prevention showed that PGx testing to prevent ADR to *Abacavir* (HLA-B*5701), *Clopidogrel* (CYP2C19), and *Warfarin* (CYP2C9 and VKORC1) was cost-effective ***(Table 2)***.

Table 2: Gene-drug combinations with actionable PGx are examples of potentially preventable adverse drug reaction[20]

Drug	Gene	ADR
Abacavir	HLA-B	Hypersensitivity
Clopidogrel	CYP2C19	Myocardial Infarction Stroke Bleeding
Codeine	CYP2D6	Respiratory Depression
Irinotecan	UGT1A1	Neutropenia Diarrhea
Simvastatin	SLCO1B1	Myopathy
Warfarin	CYP2C9, VKORC1	Bleeding

Pharmacogenomics Practice Guidelines

Pharmacogenomics is becoming more prevalent in clinical practice, however, one barrier is to translate genetic results into clinical application of pharmacogenomics in the treatment decision. Several clinical and drug dosing guidelines have been established that provides clinical guidance, therapeutic drug monitoring and recommendations to help clinicians in clinical settings. Two important pharmacogenomics practice guidelines are:

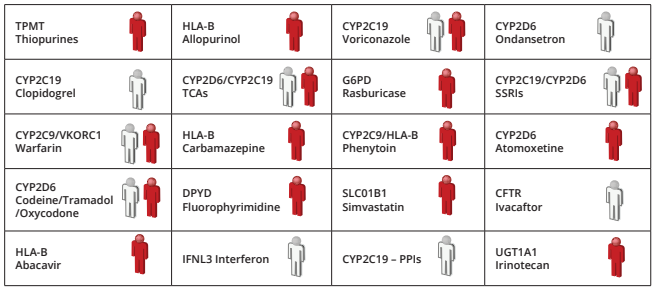
FDA U.S. FOOD & DRUG ADMINISTRATION

The value of PGx testing has been recognized by the ***Food and Drug Administration (FDA)***. Hence, the pharmacogenomics data is critically reviewed by FDA and incorporated into the drug label for more than 170 drugs[21]. Pharmacogenomic information appears in different sections of the labeling depending on the actions (See: **https://www.fda.gov**).

CPIC Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetic Implementation Consortium (CPIC) has published around 47 medication dosing guidelines. CPIC guidelines were designed to help clinicians understand HOW genetic test results should be used to optimize drug therapy[22] (See: **https://cpicpgx.org)** ***(Figure 4)*.**

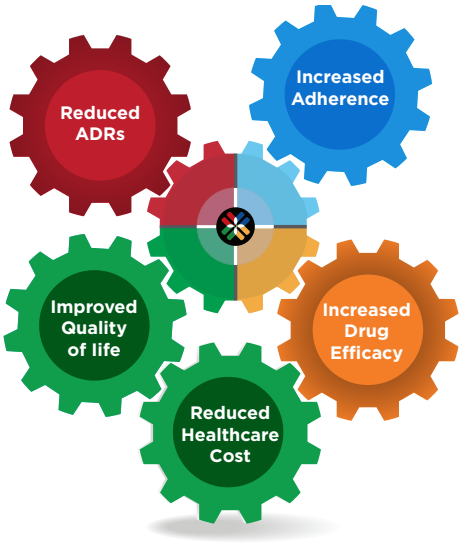
Figure 4:** **Examples of the clinical consequence of High risk Gene-Drug pair provided by FDA and dosing guidelines designed by CPIC



*Adapted with permission from Henry M. Dunnenberger

Risk of Therapeutic Failure Risk of Adverse Events

PGxOne™ Plus Benefits



PGxOne™ Plus Utilizes Superior Molecular Diagnostic Techniques

While PGx testing can be performed using a variety of genotyping technologies, the *PGxOne™ Plus* test utilizes Next Generation Sequencing (NGS), which is a form of high output or massively-parallel sequencing. Compared with non-NGS genotyping technologies, NGS can more robustly detect a broader spectrum of variant types, has superiority in scalability, speed, and resolution; and is able to detect single nucleotide polymorphisms (SNP), insertions & deletions (Indels), and copy number variants (CNV) in a single assay[23-25].

A commonly-experienced prior obstacle to the adoption of NGS technology was the required expertise necessary for the interpretation of results. However, *Admera Health*'s Actionable Genomic Interpretation System (AGIS™), addresses this obstacle by automating the interpretation of sequencing results, as well as by providing useful information for patients in the form of actionable reports[23-25].

Major Therapeutic Areas Covered By *PGxOne™ Plus*

Cardiology | Infectious Disease | Oncology | Pain Management | Psychiatry/Neurology

PGxOne™ Plus Logistics

Step 1

Provide a buccal swab, mouth wash, blood, or saliva sample

Step 2

Ship the specimen to Admera Health

Step 3

Admera Health scientists sequence and Interpret DNA

AGTCAGT
CGTAGTC
CAGCTGT...

Step 4

Receive a personalized genetic report

Clinical Application of Pharmacogenomics Testing in Specialty Areas

Cardiology - Clopidogrel (Plavix®)

Clopidogrel is an antiplatelet medication. It is commonly prescribed for acute coronary disease and/or following Percutaneous Coronary Intervention (PCI). Physiologically, this "pro-drug" requires activation via an active metabolite by the patient's CYP2C19 enzyme. Twenty-five percent of patients experience substantial variability in inhibition of platelet aggregation, leading to a potentially reduced drug response[8,26]. Well-recognized is that poor metabolizers (PMs) are at greater risk of adverse cardiovascular events as compared to patients prescribed Clopidogrel who were non-carriers of CYP2C19 reduced-function alleles[27]. In consequence, the *FDA* issued a "black box" warning to identify PMs prior to initiating Clopidogrel, and recommended administration of alternative medication in identified CYP2C19 PMs[26].

From a financial perspective as related to Clopidogrel ***(Table 3)***, studies have shown incorporating a genotype-guided treatment approach resulted in an annual cost-saving of around $445/person[28]. Therefore, utilizing PGx-testing has both the potential to improve drug prescribing and yield healthcare system economic benefits[8].

Table 3. Total Estimated Annual Costs of Clinical Outcomes Associated with Antiplatelet Treatment[28].

Outcomes	Estimates
Nonfatal MI	$26,086
Nonfatal Stroke	$28,053
CVD	$22,267
Nonfatal Bleeding	$24,829
Fatal Bleeding	$12,562

CVD=cardiovascular disease, MI = myocardial infarction

Cardiology - Warfarin (Coumadin®)

Warfarin is the most commonly-prescribed anticoagulant to prevent (and treat) thromboembolic events, AFib, or the need for cardiac valve replacement[29]. CYP2C9 is responsible for the metabolic clearance of Warfarin. Variation in the CYP2C9 gene (specifically *2 and *3 alleles) are known to cause slow metabolism of Warfarin. Therefore, this typically results in higher Warfarin blood concentration plus increased bleeding risk[29,30]. Conversely, the therapeutic effect of Warfarin is mediated by the Enzyme Vitamin K Epoxide Reductase Complex 1 (VKORC1). Variation in the VKORC1 gene results in reduced activity, and subsequently reduced synthesis of coagulation factors[29,30]. Warfarin has a narrow therapeutic window; achieving the desired International Normalized Ratio (INR) range can take several months.

Treatment variability of Warfarin is associated with heightened ADR and complication risk, leading to a higher incidence of Emergency Department (ED) visits and drug-related deaths[31]. The *FDA*-added dosing recommendation was based on scientific recognition of CYP2C9 and VKORC1 genetic variation[29]. A study focused on Warfarin impact revealed that proactive PGx testing could reduce hospitalization rates of Warfarin patients by 30% (saving the healthcare industry at least $1,800 per new Warfarin patient annually)[31]. Based on an estimated two million new Warfarin patients/year, the potential annual US cost-savings has been calculated as $3.6 B[32].

Infectious - Voriconazole (Vfend®)

Voriconazole is an antifungal agent that is used for the treatment of Invasive Fungal Infections (IFIs), which are more prevalent in immunocompromised patients (i.e., with Acute Myeloid Leukemia [AML])[33]. IFI sepsis is also associated with high morbidity and mortality, and therefore, steady serum concentration maintenance of Voriconazole is crucial for IFI eradication[34]. CYP2C19 is primarily involved in the metabolism of Voriconazole and genetic polymorphism in the CYP2C19 gene can significantly influence serum trough concentration (and therefore yield high patient variability in clinical response). UMs *(i.e.*, patients found to have the CYP2C19 *17 allele) are at the greatest risk of inadequate Voriconazole concentration (this occurs consequent to the too-rapid removal of Voriconazole from the bloodstream).

Sub-therapeutic trough concentration of Voriconazole is strongly correlated with Voriconazole therapeutic failure[34,35]. Published study findings focused on 100 severely neutropenic AML patients undergoing Voriconazole prophylaxis concluded an expected reduced total treatment cost-burden of $41,467 (combined with greater treatment efficacy). Also concluded was that this positive outcome was due to medical provider utilization of PGx testing[36] ***(Table 4)***.

Table 4. **Result of CYP2C19-Guided Voriconazole Analysis [36]**

Marginal Cost	Events	Cost	Total
Screening All Patients for ***CYP2C19*17***	100	($291.80)	($291.80)
Variconazole Level for UMs	36	($18.68)	($675)
		Total	($29,803)
Marginal Savings	**Events**	**Cost**	**Total**
Fungal Infection Avoided	2.3	$3,0952	$7,1270
		Total	$7,1270
Total Savings			**$41,467**
Total Savings Per Patient			**$415**

Pain Management - Codeine

Codeine is an opioid analgesic indicated for mild to moderately-severe pain[37]. Opioids are the most potent analgesics available. Clinical response to opioid medications as painkillers can vary as much as 40-fold among patients requiring analgesics[38]. As a "prodrug", the analgesic effect of Codeine is dependent on its conversion to Morphine by the enzyme CYP2D6. Biochemically, Morphine exhibits a 200-fold higher affinity than Codeine for μ-opioid receptors[39]. Meanwhile, genetic variations in CYP2D6 can result in wide therapeutic response variability. For example, CYP2D6 PMs derive little (or no) analgesic effect. In contrast, rapid conversion in UMs results in their experiencing a higher-than-expected Morphine blood concentration—even when prescribed at a standard dosage. Studies reporting related fatalities in UMs showed the postmortem Morphine levels as substantially higher than the therapeutic range;[37-39] consequently, the *FDA* has issued a concomitant "black-box" warning[37]. PGx testing has the potential to predict response to a specific analgesic by improving pain management and reducing overall healthcare costs attributable to pain management[38].

Psychiatry - Citalopram (Celexa®)

Citalopram is a selective serotonin reuptake inhibitor utilized in treating depression[40]. Approximately 50% of patients diagnosed with clinical depression fail initial SSRI treatment. An estimated 25,000 psychiatrically-distressed patients seek treatment annually due to related ADRs[40]. Serious drug side effects (*e.g.*, arrhythmias caused by QT prolongation) have been linked to SSRIs (particularly in patients who are CYP2C19 PMs). Consequently, the FDA recommends a maximum dose of 20 mg *per day* in CYPC19 PMs[40]. Utilizing PGx testing can identify PMs, and thereby guide SSRI therapy selection (and avoid the prolonged trial-and-error approach common to clinical depression management)[7]. Study results revealed both a significant cost savings ($1,000 annually per patient) in psychiatric patients who received PGx-guided medication therapy[19], as well as improved medication adherence[11].

Oncology - Irinotecan (Camptosar®)

Irinotecan is a topoisomerase inhibitor prescribed as first-line therapy for patients diagnosed with metastatic colon or rectum carcinomas[41]. It is associated with a high incidence of toxicity (*e.g.*, severe neutropenia and diarrhea)[42]. Irinotecan is converted to an active metabolite termed SN-38. Notably, SN-38 is inactivated and detoxified by enzyme UGT1A1[41]. The presence of UGT1A1*28 results in reduced excretion of the active metabolite SN-38. This leads to increased active Irinotecan metabolites in the person's body; side effects of SN-38 accumulation include diarrhea, myelosuppression, and neutropenia. Cancer patients with *28 homozygous genotypes are at higher risk of developing life-threatening, Irinotecan-induced ADRs[41,42]. The clinical validity of UGT1A1 *28 polymorphism in predicting Irinotecan-related severe toxicity has been demonstrated in several studies. It has been reported that *28 allele carriers have a six-fold increased Irinotecan accumulation as compared to *28 allele non-carriers[42]. The *FDA* recommends a reduction in the starting dose of Irinotecan by at least one level for patients known to be homozygous for the UGT1A1*28 allele. Similarly, a toxicity prevention strategy has also been suggested in several studies investigating the UGT1A1 *28 allele[41,42].

Conclusions
Clinician and Patient "Take-Aways"

- PGx testing has the ability to alleviate the burden of patient genetic variability and provide targeted clinical information; this can enable better individualization of drug selection and dosing to promote maximization of drug efficacy and reduction of ADRs. Thus, this type of testing can ultimately enhance patient care.
- By fostering the capacity for healthcare clinicians to more specifically tailor drug treatments to patients' ongoing health needs, PGx testing has the potential to decrease healthcare expenditures.

"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.
Former Chairman, President, and CEO, Eli Lilly and Company

About Admera Health

Admera Health is an advanced molecular diagnostics company focused on personalized medicine, non-invasive cancer testing and digital health. Dedicated to developing cutting-edge diagnostics that span the continuum of care, Admera Health fulfills unmet medical needs with cost-effective tests and accurate analysis to guide patient care. Utilizing next generation technology platforms and advanced bioinformatics, Admera Health seeks to redefine disease screening, diagnosis, treatment, monitoring, and management through its innovative, personalized solutions. It is our mission to deliver innovative and valuable solutions for patients, physicians, and clinical researchers. We are committed to improving the health and well-being of our global community through the direct delivery of personalized, medically actionable results.

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