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Pharmacogenomics: An evolving clinical tool for precision medicine

ABSTRACT

Pharmacogenomics, ie, the study of how an individual's genomic profile influences his or her response to drugs, has emerged as a clinical tool to optimize drug therapy. Certain variants in some genes increase the risk of severe, life-threatening adverse effects from certain drugs. Integrating pharmacogenomics into clinical practice to assist in drug selection and dosing has the potential to improve the outcomes of treatment, reduce the risk of drug-induced morbidity and death, and be cost-effective.

KEY POINTS

Most people carry a genetic variant that causes an abnormal response to specific drugs, making many vulnerable to potentially life-threatening events.

Codeine is metabolized to morphine by an enzyme that has more than 100 genetic variants with a continuum of activity; children who were ultrarapid metabolizers have died after receiving codeine.

Challenges to using pharmacogenomics in prescribing drugs include developing the infrastructure to routinely store and report test results, educating physicians on the use of testing, and obtaining third-party payment.

Many variants are rare or are common only in certain ethnic groups, so that adequately powered studies are difficult to perform.

Dr. Hicks has disclosed membership on advisory committee or review panels for 23andMe, research or independent contracting for OneOme, and consulting for Quest Diagnostics.

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PHARMACOGENOMICS can improve patient care by optimizing the choice and dosage of medications, thereby lessening the risk of adverse events and increasing patient and provider satisfaction through the practice of personalized medicine. Over the past decade, the technology for genetic testing has advanced, clinical evidence supporting integration of pharmacogenomics into clinical practice has gotten stronger, and the cost of testing has gone down. However, although rapidly advancing research and growing demand are bringing pharmacogenomic-guided therapy closer to reality, barriers remain.

This article reviews the clinical evidence supporting pharmacogenomics, the commonly prescribed drug classes influenced by known pharmacogenes, the costs of testing, research challenges, and what is needed for clinical implementation.

■ WHAT ARE PHARMACOGENES?

Genetic variants have been identified that affect the pharmacokinetics (ie, absorption, distribution, metabolism, elimination) or pharmacodynamics (ie, pharmacologic effects) of specific drugs. A patient who has a variant allele of one of these genes may experience severe and even life-threatening adverse events when exposed to certain drugs. Such events are a leading cause of morbidity and death in the United States and are costly to manage, and nearly half are estimated to be preventable.^{1,2}

More than 90% of patients are thought to carry at least 1 genetic variant that should prompt a change in dosing or medication if certain drugs are prescribed.^{3,4} Based on this estimate, a significant number are likely to be at

TABLE 1

Clinical Pharmacogenetics Implementation Consortium drug-gene pairs with evidence-based guidelines

Drugs	Genes	Drugs	Genes	Drugs	Genes
Abacavir ^a	HLA-B*57:01	Efavirenz	CYP2B6	Rasburicase	G6PD
Allopurinol	HLA-B*58:01	Escitalopram	CYP2C19	Ribavirin	IFNL3 (IL28B)
Amitriptyline ^a	CYP2C19, CYP2D6	Fluorouracil ^a	DPYD	Sertraline	CYP2C19
Atazanavir	UGT1A1	Fluvoxamine	CYP2D6	Simvastatin	SLCO1B1
Atomoxetine ^a	CYP2D6	Imipramine ^a	CYP2C19, CYP2D6	Succinylcholine	RYR1, CACNA1S
Azathioprine ^a	TPMT, NUDT15	Ivacaftor	CFTR	Tacrolimus	CYP3A5
Capecitabine ^a	DPYD	Mercaptopurine ^a	TPMT, NUDT15	Tamoxifen	CYP2D6
Carbamazepine ^a	HLA-A*31:01, HLA-B*15:02	Nortriptyline ^a	CYP2D6	Tegafur	DPYD
Citalopram ^a	CYP2C19	Ondansetron	CYP2D6	Thioguanine ^a	TPMT, NUDT15
Clomipramine ^a	CYP2C19, CYP2D6	Oxcarbazepine ^a	HLA-B*15:02	Trimipramine ^a	CYP2C19, CYP2D6
Clopidogrel ^a	CYP2C19	Paroxetine	CYP2D6	Tropisetron	CYP2D6
Codeine ^a	CYP2D6	Peg-interferon alfa-2a	IFNL3 (IL28B)	Volatile anesthetics	RYR1, CACNA1S
Desipramine ^a	CYP2D6	Peg-interferon alfa-2b	IFNL3 (IL28B)	Voriconazole	CYP2C19
Doxepin ^a	CYP2C19, CYP2D6	Phenytoin ^a	CYP2C9, HLA-B*15:02	Warfarin ^a	CYP2C9, CYP4F2, VKORC1

^aThe drug also has US Food and Drug Administration-designated pharmacogenetic labeling as a boxed warning, a contraindication, a warning and precaution, or a dosing and administration recommendation.

From the Clinical Pharmacogenetics Implementation Consortium, <https://cpicpgx.org/genes-drugs>.

risk of poor treatment outcomes due to a gene-drug interaction. Using pharmacogenomics as a clinical tool to guide drug selection and dosage adjustments may be an effective and potentially cost-saving risk-mitigation strategy.

CLINICAL UTILITY OF PHARMACOGENOMICS

Strong evidence indicates that variants in about 20 genes affecting more than 60 drugs could affect one’s response to these medications. Evidence-based, peer-reviewed guidelines are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (www.cpicpgx.org), an initiative funded by the US National Institutes of Health to help clinicians interpret the results of genomic tests and apply them to patient care.⁵ Table 1 lists the currently recognized gene-drug pairs for which

clinical guidelines are available.

Numerous examples for implementing pharmacogenomic testing have been published, with strategies ranging from preemptively testing everyone with panels of genes to testing single genes before prescribing certain drugs.⁶⁻⁹ But regardless of the implementation model, clinicians face challenges in deciphering the clinical evidence, and institutions face the challenge of creating the infrastructure to store genomic information that may be relevant throughout a patient’s life.

OPIOIDS AND CYP2D6

Ultrarapid metabolizers can overdose on codeine

Codeine is a prodrug with weak affinity for the mu-opioid receptor. It exerts most of its

analgesic effect after it is activated to morphine, primarily by cytochrome P450 2D6 (CYP2D6). The *CYP2D6* gene has more than 100 variants that can result in a continuum of enzyme activity, ranging from ultrarapid to poor metabolism of CYP2D6 substrates.¹⁰

After taking codeine, people who are CYP2D6 ultrarapid metabolizers have higher concentrations of morphine in their blood, increasing the risk of severe opioid toxicity. Numerous cases of codeine-induced toxicity have been reported in children who were CYP2D6 ultrarapid metabolizers undergoing tonsillectomy or adenoidectomy; 10 children died and 3 experienced severe respiratory depression.¹¹ In addition, infant deaths from opioid toxicity have been attributed to breastfeeding mothers who were CYP2D6 ultrarapid metabolizers taking codeine for postpartum pain.¹²

After these case reports, the US Food and Drug Administration (FDA) amended codeine labeling to contraindicate its use in all children younger than 12 years old and in patients under 18 after tonsillectomy or adenoidectomy.

Children with sickle cell disease may be the most adversely affected by this contraindication, as codeine is recommended as an initial opioid to manage pain during crises.¹³ This contraindication prohibits the use of acetaminophen with codeine, the only non-schedule II opioid (for which prescriptions can be refilled over the phone) as an option for managing pain in pediatric patients.

Other opioids pose similar problems

Although the current CPIC guideline focuses on codeine, several other opioids are also CYP2D6 substrates, including hydrocodone, oxycodone, and tramadol. The guideline specifically states that tramadol should not be used as an alternative to codeine¹⁴; it, like codeine, is activated through CYP2D6 to a more active metabolite and increases the risk of respiratory depression in CYP2D6 ultrarapid metabolizers. Tramadol carries the same US boxed warning as codeine, contraindicating its use in children.

Poor metabolizers may get little pain relief

Patients who are CYP2D6 intermediate or poor metabolizers are at risk of inadequate pain relief because of decreased metabolism.

Testing could increase the judicious prescribing of opioids by preventing CYP2D6 poor metabolizers from receiving an opioid that would result in inadequate pain relief, and have the effect of reducing opioid prescriptions in circulation.^{15,16}

Gammal et al¹⁷ described a strategy of employing CYP2D6 pharmacogenomic clinical decision support alerts to identify pediatric patients who are at low risk for opioid toxicity or inadequate pain control with codeine administration. Such a system may serve as an alternative to the current broadly restrictive approach.¹⁷

A pragmatic study conducted by Smith et al¹⁸ showed that better pain control was achieved with a strategy of guided prescribing of codeine, hydrocodone, and tramadol with CYP2D6 genotype-guided prescribing. In more than 75% of those who were CYP2D6 intermediate metabolizers or poor metabolizers, an opioid was replaced with a nonopioid for pain management.

■ ANTIDEPRESSANTS AND CYP2D6, CYP2C19, SLC6A4, HTR2A, AND HTR2C

Antidepressants are one of the most commonly prescribed drug classes in the United States.¹⁹ But in an estimated 30% to 50% of patients, initial antidepressant drug therapy fails because of ineffectiveness or drug-induced adverse effects.²⁰

Most antidepressants are metabolized by CYP2D6 or CYP2C19, or both. Emerging data suggest that genomic variation in serotonin transporters (eg, SLC6A4) and receptors (eg, HTR2A, HTR2C) is also associated with antidepressant response. Guidelines are available to assist with selection and dosage of serotonin reuptake inhibitors and tricyclic antidepressants based on the *CYP2D6* and *CYP2C19* genotype.^{21,22}

Pharmacogenomic guidance improves outcomes

Multicenter, randomized controlled trials have evaluated the impact of genotype-guided antidepressant drug prescribing using questionnaires to measure depressive symptoms. These studies employed combinatorial pharmacogenomic approaches consisting of panels that interrogate multiple genes (eg, *CYP2D6*,

A patient with a genetic variant may be at increased risk for developing severe, life-threatening adverse effects

CYP2C19, *SLC6A4*, *HTR2A*, and *HTR2C*), and recommend antidepressants based on patient genotypes. Patients randomized to genotype-guided treatment fared significantly better in standardized depression rating scores or response and remission rates compared with patients receiving usual clinical management.^{23,24} In addition to improved clinical outcomes, pharmacogenomic-guided antidepressant drug selection may also reduce healthcare resource usage and lower medication-related costs of antidepressant therapy.²⁵

■ **CLOPIDOGREL AND CYP2C19**

To inhibit platelets, clopidogrel must undergo activation by *CYP2C19*, and patients with decreased *CYP2C19* activity have less active metabolite formation. Current evidence-based guidelines recommend using an alternative antiplatelet agent in patients who are intermediate or poor metabolizers of *CYP2C19*.²⁶

CYP2C19-clopidogrel dosing guidelines have mostly focused on patients undergoing percutaneous coronary intervention, but recent evidence also indicates that the *CYP2C19* genotype affects the efficacy of clopidogrel when prescribed for other indications, such as ischemic stroke.²⁷

Multiple large observational studies have demonstrated the clinical impact of *CYP2C19* genotype-guided antiplatelet drug selection. These studies, which included thousands of patients, found that intermediate or poor metabolizers of *CYP2C19* who received clopidogrel had significantly worse cardiovascular outcomes than patients who received antiplatelet therapy that matched genotype-guided recommendations, although the assessed composite outcomes differed among the studies.^{28–30}

The Tailored Antiplatelet Therapy Following Percutaneous Coronary Intervention (TAILOR-PCI; NCT01742117) trial is currently accruing patients. This large, prospective, randomized controlled trial is designed to further evaluate the clinical utility of genotype-guided clopidogrel prescribing.

■ **OTHER CLINICAL CONSIDERATIONS**

Sometimes genotyping may not be useful

Although pharmacogenomics is an important

consideration when prescribing many common drugs, other patient characteristics are also pertinent to prescribing decisions. For instance, interactions with other drugs can significantly alter enzymatic activity, which could reduce the reliability of pharmacogenomic-guided dosing.³¹

Medication decisions may also be influenced by specific practice formularies or insurance coverage, which can affect the relevance of pharmacogenomic testing. For example, the American College of Rheumatology recommends screening for carriers of *HLA-B*5801* before starting allopurinol in high-risk patients to reduce the risk of allopurinol-induced severe cutaneous adverse reactions.³² But for patients with normal renal function who are receiving reduced doses of allopurinol, the risk of a cutaneous reaction is typically lower, and preemptive genotyping is arguably less warranted.³³ Third-party payers may not reimburse for preemptive testing, and the use of alternatives to allopurinol may be restricted or allocated to those in a higher copay group. These considerations may limit the clinical utility of *HLA-B*5801* testing in certain patients.

Other times, it can reduce morbidity and save money

In some circumstances, preemptive testing can prevent adverse effects that lead to expensive medical care.

In a case at our institution, a 76-year-old woman with rheumatoid arthritis inadequately controlled with steroids and methotrexate was subsequently switched to azathioprine 100 mg daily. About 6 weeks later, she was admitted to the hospital with pancytopenia, subdural hematoma, and cellulitis that resulted in more than a 2-week hospital stay, empiric use of antibiotics, multiple transfusions, and an evaluation for aplastic anemia vs azathioprine-induced pancytopenia.

Azathioprine-induced severe myelosuppression may be caused by genetic variants in thiopurine S-methyltransferase (TPMT), the enzyme that catabolizes azathioprine to less pharmacologically active compounds. Subsequent *TPMT* genotyping found that the patient was a *TPMT*-poor metabolizer, and the use of azathioprine should have been avoided.³⁴

Pharmacogenomics could increase the judicious prescribing of opioids

■ ADDRESSING CHALLENGES TO PHARMACOGENOMIC TESTING

Prospective, randomized clinical trials to assess the utility of pharmacogenomics can be difficult to carry out, particularly if testing for rare variants that would require a sample size of thousands to be sufficiently powered. Certain pharmacogenetic variants are more or less common in different ethnic groups; it would be difficult for any study population to adequately reflect all ethnic groups, making the large number needed to power a trial to demonstrate clinical utility a significant limitation.

Validity of clinical trial results may be limited by not testing for clinically important variants carried by the population being studied. Two randomized controlled trials for genotype-guided warfarin therapy illustrate this issue:

The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial³⁵ compared fixed warfarin dosing vs genotype-guided dosing and found better outcomes with genotype guidance. More than 90% of the study's participants identified as white.

The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial³⁶ compared patients who had warfarin dosage determined either by an algorithm based only on clinical variables or on clinical variables plus genotype data. In this trial, almost 30% of participants self-identified as black. Overall, no improvement in anticoagulation control was found, and in black patients, control was actually poorer in the genotype-guided group. A possible explanation for the poorer control in black patients is that *CYP2C9* genotyping did not include decreased-function alleles (eg, *CYP2C9*8*) that are commonly found in patients of African ancestry.

It is possible that the different dosing strategies between the 2 trials may have contributed to their opposite outcomes, suggesting that genotype-guided dosing may not be superior to algorithm-based dosing.³⁷

The subsequent large Genetics Informatics Trial (GIFT)³⁸ randomized elderly patients to either an algorithm based on clinical variables alone to guide warfarin dosing or one based on clinical variables plus *CYP2C9*, *CYP4F2*, and *VKORC1* genetic data. Similar to the EU-

PACT trial, this study's population was more than 90% white. The genotype-guided warfarin dosing arm had a reduction in the composite outcome of major bleeding, international normalized ratio greater than 4, venous thromboembolism, and death. These findings suggest that a genotype-guided algorithm is superior to a clinically guided algorithm when the appropriate genetic variants are included for the population being studied.

Alternatives to randomized trials

In most cases, pharmacogenomics can help guide selection between multiple medications that have similar efficacy and safety for the indication of interest. In such cases, it may not be necessary to conduct extensive, randomized clinical trials, but rather to rely on pragmatic trials focused on implementing pharmacogenomics to improve patient care.

Given the number of smaller studies including different racial and ethnic groups, meta-analyses of certain gene-drug pairs may be useful. In addition, identifying and validating pharmacogenetic associations by other methods, such as comparing prospective pharmacogenetic-guided therapy to matched historical controls, or evaluating results of well-designed retrospective studies, should be considered when determining the value of pharmacogenomics in practice.

In some situations, randomized controlled trials cannot be done because they would be considered unethical. When pharmacogenetic associations are known to predict life-threatening adverse events, prescribing a medication to a patient who carries the high-risk variant for the purpose of creating a control group would not be justifiable.

■ IS PHARMACOGENOMIC TESTING COST-EFFECTIVE?

The cost of pharmacogenomic testing may be an important barrier to implementation because of limited reimbursement. In a survey of 14 US payer organizations that cover 122 million patients, payers expressed concern about the initial costs and perceived uncertainty of benefits from preemptive pharmacogenomic testing. In particular, they pointed out that many low-cost generic drugs are often available that patients could be prescribed before

Genotype-based guidelines are available for selective serotonin reuptake inhibitors and tricyclic antidepressants

resorting to a new drug that would require panel genotyping before safely using it.³⁹

But several studies have shown that preemptive pharmacogenomic testing could not only benefit patients, it may also be cost-effective over the long term. In a systematic review, Verbelen et al⁴⁰ assessed 44 economic evaluations that covered 10 of the known pharmacogenomic-associated drugs listed by the FDA. They found that 57% supported reactive pharmacogenomic testing, with 30% being cost-effective (ie, benefits are large compared with costs) and 27% estimated to be cost-saving (ie, costs are reduced). If genetic testing had negligible costs, 75% of the studies would support pharmacogenomic testing, with 25% rated as cost-effective and 50% as cost-saving. Although panel testing can be costly, depending on the platform and number of genes tested, prices would be expected to fall over time, and cost savings would be realized as patients require additional pharmacogenomic-associated treatments.

Analysis of the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program at Vanderbilt University Medical Center found that 91% of nearly 10,000 preemptively genotyped patients had at least 1 actionable variant, and 42% of these patients had been exposed to a risk-associated medication in the past.³ If a separate test had been ordered before prescribing each of the drugs examined in this study, 14,656 tests would have had to be performed vs the 9,589 multiplex tests actually performed as part of this study, a rate 1.7 times higher.

In a hypothetical cohort, Borse et al⁴¹ compared 3 treatment strategies: universal clopidogrel, universal prasugrel, and CYP2C19-guided prescribing. They found that 658 major cardiovascular or bleeding events could be avoided over 30 days by guided therapy per 10,000 patients treated. Guided therapy also led to \$50,308 saved over 1 year per patient compared with the other groups.

In a model of CYP2C19-guided voriconazole prophylaxis in patients diagnosed with acute myeloid leukemia, Mason et al⁴² predicted a modest cost savings per patient, while reducing the incidence of invasive fungal infections and shortening average length of hos-

pital stay.

A study by Sluiter et al⁴³ of CYP2D6 genotyping for antidepressants was less conclusive. They found a wide incremental cost-effectiveness ratio ranging from \$22,500 to \$377,500, likely due to the many assumptions the model required. They did not include the effects of CYP2C19 genotyping, which also has significant clinical impact on antidepressant medications.

The biggest obstacle to determining the cost-effectiveness of pharmacogenomic testing is a lack of real-world economic data. Most pharmacogenomic studies that try to assess cost-effectiveness are based on estimated costs and clinical parameters from the literature rather than direct reporting of costs before and after testing. As pragmatic studies are being designed, investigators should consider incorporating economic end points to generate more accurate estimates of costs and use of healthcare services. This would provide direct evidence of the financial impact of pharmacogenomic testing that may improve future economic models.

■ DIRECT-TO-CONSUMER TESTING

Increasing interest in pharmacogenomic testing may in part be due to decreasing costs of panel genotyping. However, genomic direct-to-consumer tests may also be a driving force.

Genomic direct-to-consumer testing has a tumultuous history starting about 15 years ago. Technologies quickly outpaced clinical evidence, regulations, and ethical considerations, resulting in concerns about what information consumers should be allowed to receive without guidance by medical professionals. The FDA sent warning letters to reference laboratories, telling them to discontinue direct-to-consumer health-related genetic tests.

In recent years, clinical evidence has strengthened, guidelines have emerged, and genomic medicine is becoming integrated into routine care for certain disease states, such as some cancers. Recently, the FDA approved direct-to-consumer tests for pharmacogenomics, cancer risk (eg, BRCA1 and BRCA2 testing), and propensity to develop certain conditions (eg, Parkinson and Alzheimer diseases). Because the recent FDA authorization has better

Intermediate or poor metabolizers of CYP2C19 who received clopidogrel had worse cardiovascular outcomes

defined limits and costs have become lower, it is unlikely that these tests will be going away.

The FDA has stated that direct-to-consumer genomic test results should not be used to guide therapy, and an independent clinical test to confirm results is needed before making medical decisions. Clinicians should be prepared to discuss with patients direct-to-consumer pharmacogenomic testing, indications for confirmatory testing, and resources that are available when results arrive. Several educational resources are available, including those from the CPIC, the Pharmacogenomics Knowledgebase (PharmGKB), and the National Institutes of Health.

■ EDUCATION AND INFRASTRUCTURE NEEDED

Challenges to incorporating pharmacogenomics into clinical medicine include a lack of infrastructure to store and report test results and limited clinician confidence in interpreting, applying, and communicating results to patients.⁶⁻⁹ A survey of 47 general practitioners and 375 specialist physicians also identified the paucity of guidelines surrounding pharmacogenomic testing and lack of provider familiarity with pharmacogenomics as major barriers to adoption.⁴⁴ As with other clinical guidelines, CPIC guidelines are updated regularly to incorporate growing evidence.⁵ Despite this, it can be overwhelming to synthesize the recommendations, especially for patients prescribed multiple medications.

To overcome these challenges, interdisciplinary teams should be developed to incorporate the expertise of many healthcare professionals. Informatics experts can develop the infrastructure to enable adding pharmacogenomic test results to the medical record in a clinically meaningful way. They can also work with pharmacists and clinicians to develop clinical decision support rules to alert end users of significant drug-gene interactions at the point of prescribing, and provide alternative recommendations. Pharmacists and genetics counselors can train clinicians in the use of pharmacogenomic tests and communicate the meaning of test results directly to patients.

Implementation efforts often need to be customized to individual institutions, as rec-

ommendations may differ depending on available formulary agents and characteristics of the patient population.^{8,9}

■ DEVELOPING PHARMACOGENOMIC SERVICES

A few institutions are making efforts to incorporate preemptive pharmacogenomics testing, which can serve as models for their use.

Hicks et al⁸ described implementing clinical pharmacogenomic testing of 3 gene-drug pairs (*HLA-B*57:01*-abacavir, *HLA-B*15:02*-carbamazepine, and *TPMT*-thiopurines) in a large healthcare system. Custom rules and alerts were developed and integrated into the electronic health record to provide support for point-of-care decision-making. Such a system could be designed to also incorporate panel genotyping and triggering of clinical decision support alerts for those with an actionable genotype without further testing. A pharmacogenomics clinic was also established consisting of medical geneticists, genetic counselors, and a pharmacist with specialized training in pharmacogenomics, who assessed the need for pharmacogenomic testing in individual patients and provided results and interpretation and medication recommendations. Patients were educated on the benefits, risks, limitations, and financial costs of pharmacogenomics before testing.

Surgical services are conducting pilot studies to evaluate preemptive pharmacogenomic testing to better manage acute postoperative pain, reduce opioid consumption, and minimize recovery time after surgery. Senagore et al⁴⁵ compared overall benefit of analgesia scores and narcotic consumption in 2 groups: 50 patients who received pharmacogenomic-guided pain management after colorectal resection or major ventral hernia repair and a historical control group managed by an enhanced recovery protocol. The pharmacogenomic-guided group had significantly lower scores (indicating better pain control) and consumed 50% less narcotics compared with the control group.⁴⁵ Given that poor analgesia and adverse effects from medications may result in an unplanned admission to intensive care or lengthier hospital stays, preemptive pharmacogenomic testing could help minimize such events.

Third-party payers may not reimburse for preemptive testing

■ POISED TO IMPROVE CARE

As healthcare focuses on value-based care, pharmacogenomics is poised to improve patient care by optimizing pharmacotherapy, mitigating risk of adverse events, and increasing patient and provider satisfaction through the practice of personalized medicine. However, several barriers remain, including inte-

gration of pharmacogenomic results into existing electronic medical records to provide meaningful therapeutic recommendations at the appropriate time. With further research, education, and growing demand, the concept that an individual's therapy will be guided by pharmacogenomics will continue to become a reality. ■

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