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Pharmacogenetic testing: Clinical integration and application for chronic pain management

Abstract: NPs commonly prescribe pharmaceutical therapies such as opiates, antidepressants, and/or other analgesics to improve the health and well-being of patients experiencing chronic pain. This article provides NPs with pharmacogenetic testing knowledge, such as readiness for clinical implementation, considerations for choosing a testing service, and testing costs for chronic pain management.

By Karin M. Fredrikson, MS and Tracy Fasolino, PhD, FNP-BC

Chronic noncancer pain is a common and costly healthcare problem with prevalence as high as 20.4% in US adults, or 50 million individuals.[1] An additional 8.0%, or 19.6 million US adults, have high-impact chronic pain, defined as persistent pain with substantial restriction of life activities lasting 6 months or more. According to the National Pain Strategy published in 2016 by the Interagency Pain Research Coordinating Committee, high-impact chronic pain restricts participation in work, social, recreational, or self-care activities.[2] The economic cost to the US for chronic pain management, including both direct medical costs and lost productivity, range from $560 to $635 billion annually.[3] NPs commonly prescribe opiates, antidepressants, and other analgesics to control chronic pain. Updated approaches to

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Genetic and pharmacogenetic terminology[5,6]

Allele	Alternate forms (usually two or more) of a specific DNA sequence occurring at a particular gene locus; the more common allele is typically referred to as "normal," "wild-type," or "reference."
Gene	Functional unit of heredity consisting of a linear string of nucleotides, occupying a specific locus on a chromosome; directs formation of a specific enzyme or other protein.
Genotype	Genetic constitution of an individual gene; may refer to the set of alleles present in an individual.
Pharmacogenetic metabolizers:	
• Poor metabolizer (PM)	No functional alleles; lacking the capacity to metabolize a substrate through the specific pathway of the gene.
• Intermediate metabolizer (IM)	One normal or reduced-function and one nonfunctional allele or one nonfunctional and one increased-function allele; less than normal capacity to metabolize a substrate through the specific pathway of the gene.
• Normal metabolizer (NM)	Two functional alleles or one full-function allele and one nonfunctional or reduced-function allele; normal capacity to metabolize a substrate through the specific pathway of the gene.
• Rapid metabolizer (RM)	One normal function and one increased-function allele.
• Ultrarapid metabolizer (UM)	Two increased-function alleles or more than two copies of functional alleles; enhanced capacity to metabolize a substrate through the specific pathway of the gene.
Phenotype	Observable clinical characteristics of an individual resulting from the expression of their specific genotype.
Phenotype, actionable	Those phenotypes currently associated with prescriptive recommendations.
Phenotype, informative	An observable phenotype that has little or no known association with efficacy or safety outcome data.
Single-nucleotide polymorphism (SNP)	A type of variant involving the substitution of a single nucleotide (adenine, cytosine, guanine, or thymine) with a different nucleotide at a specific location in the genome; pronounced "snip." For instance, a SNP at position 94780653 at NC_000010.11 (Homo sapiens chromosome 10, GRCh38.p2) is defined as a G nucleotide in the wild-type allele with the polymorphism of an A nucleotide for the *3 allele of CYP2C19. The presence of this SNP is associated with an IM phenotype.
Variant	Broadly, exhibiting genotypic or phenotypic diversity; narrowly, a change in the DNA sequence at a gene locus that may be harmful, beneficial, or neutral in the effect on cell function.

prescribing practices should address unrelieved pain and associated debility as well as methods to mitigate the current opioid crisis. Choosing the most efficacious analgesic at the most appropriate dosage at the initiation of pain management is a challenge for the clinician treating patients with chronic pain.[4] NPs can incorporate pharmacogenetic testing results, which highlight the patient's genetic alleles linked to drug metabolism, into prescribing practices across multiple classes of medications.

The study of pharmacogenetic loci (or the position of genes on the chromosome) provides evidence for genetic differences in an individual's response to medications. The patient's genotype is the set of genes responsible for a particular trait, whereas the phenotype is the physical expression of those genes. Currently, correlations between pharmacogenetic genotypes and the clinical phenotype are examined at the individual level. Each pharmacogenetic locus contains one allele (one of two or more versions of a given gene) inherited from each parent, and together they are referred to as the patient's diplotype. The phenotypes are genetically defined by two star alleles. Genetic testing provides the patient's diplotype, which is then converted into their associated drug metabolism phenotype, classified as either a normal, intermediate, poor, rapid, or ultrarapid metabolizer (see *Genetic and pharmacogenetic terminology*).[5] Clinical selection of medications is based on several factors, including age, gender, weight, and renal and liver function as well as patient-specific

history.[7] Adding in the patient's phenotype, as determined through pharmacogenetic genotype, along with clinical factors, can improve response to therapy and ultimately quality of life. Awareness of the patient's pharmacogenetic phenotype would improve NPs' decision-making for drug(s) selection and effective dose(s) and duration selection as well as avoid significant events and adverse reactions.[8]

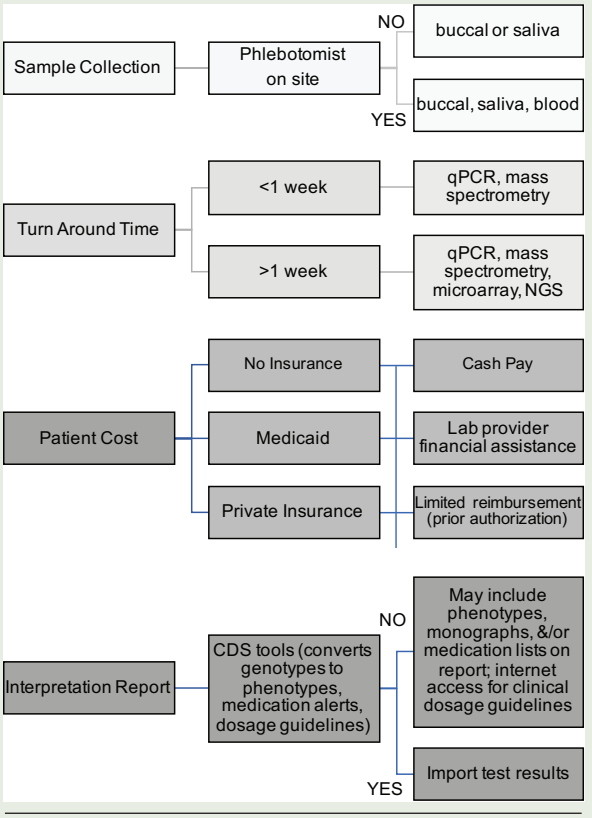
Overview

For the purpose of this discussion, the focus of pharmacogenetic testing is to tailor medication regimens for treatment of chronic noncancer pain in adults. The goal of pharmacogenetic testing is to provide accurate and clinically meaningful test results at the appropriate time during the clinical sequence to maximize benefit to the patient. Clinical utility and validity of pharmacogenetic testing are primary considerations when deciding to implement testing.[9] Considerations of clinical utility include the timing and type of the test in the clinical sequence, availability of the test and clinical decision support (CDS) tools, and practicality of implementation. Timing of pharmacogenetic testing could be preemptive (testing prior to medication selection) and more comprehensive across classes of drugs versus reactive (testing after adverse reactions or insufficient therapeutic pain relief) and sequential as each medication is added to care management. Given that pharmacogenetic testing is a subset of genetic testing, it may be performed with any of the current genetic testing technologies, such as quantitative polymerase chain reaction (qPCR), microarray, mass spectrometry, or next generation sequencing (NGS).

CDS tools for medication dosing based upon pharmacogenetic testing are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC), Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and Dutch Pharmacogenetics Working Group (DPWG).[10-12] More sophisticated CDS tools are being developed to integrate into the electronic health record for broader implementation, such as by the Implementing Genomics in Practice (IGNITE) Network funded by the National Institutes of Health (NIH).[13] The readiness for pharmacogenetic testing in clinical practice varies across medications, as the body of clinical evidence continues to grow and clinical resources are developed.

The practicality of pharmacogenetic testing includes educating NPs and other providers on testing procedures and interpretations, counseling patients and caregivers on the results and implications, reviewing associated costs of the test, and determining insurance or self-pay options. Choices made for each of these factors will impact the use and costs of pharmacogenetic testing within the clinical setting (see *Pharmacogenetic testing process*).

Pharmacogenetic testing process



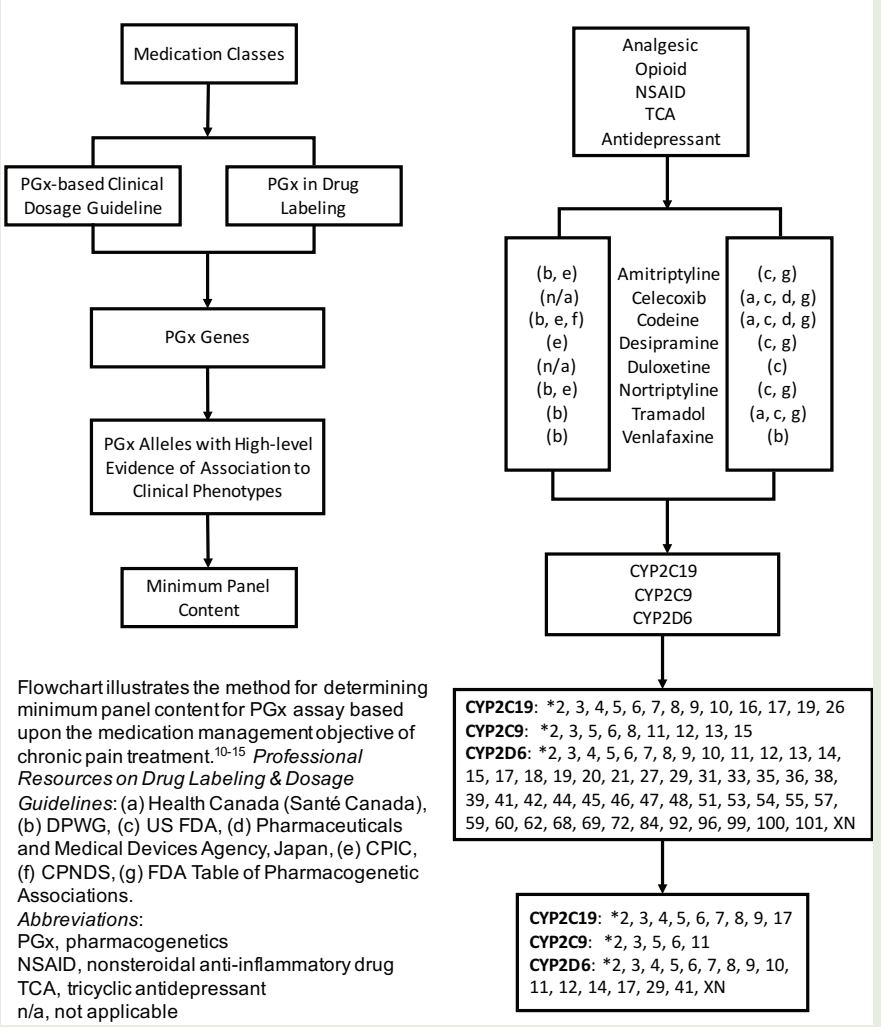
Abbreviations:
qPCR, quantitative polymerase chain reaction
NGS, next-generation sequencing
CDS, clinical decision support

Implementation of pharmacogenetic testing

In selecting the most appropriate pharmacogenetic test for chronic pain management, NPs should be assured that the test has enough scientific evidence. In February 2020, the FDA published a list of pharmacogenetic associations believed to be scientifically supported for subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes that would likely alter drug metabolism.[14] For example, codeine-*CYP2D6* interaction in the affected subgroup of ultrarapid metabolizers would yield higher systemic

active metabolite concentrations resulting in adverse reactions, such as respiratory depression or death. A web-based resource from the FDA distinguishes between three levels of scientific evidence, listing drugs alongside the pharmacogene, affected subgroups (metabolizer phenotypes), and a short description of the gene-drug interaction.[14] The three levels of scientific evidence contain several medications utilized for chronic pain management, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and opioid analgesics; these levels are indicated by data supporting therapeutic management recommendations, data indicating potential impact on safety or response, and data demonstrating potential impact on pharmacokinetic properties only.

Method for determining minimum panel content for pharmacogenomics assay[15-20]



Flowchart illustrates the method for determining minimum panel content for PGx assay based upon the medication management objective of chronic pain treatment.[10-15] *Professional Resources on Drug Labeling & Dosage Guidelines*: (a) Health Canada (Santé Canada), (b) DPWG, (c) US FDA, (d) Pharmaceuticals and Medical Devices Agency, Japan, (e) CPIC, (f) CPNDS, (g) FDA Table of Pharmacogenetic Associations.
Abbreviations:
PGx, pharmacogenetics
NSAID, nonsteroidal anti-inflammatory drug
TCA, tricyclic antidepressant
n/a, not applicable

First steps in implementing pharmacogenetic testing in clinical practice would be to obtain a list of clinically relevant medications to match with a preemptive pharmacogenetic assay offered by a lab. For those medications with pharmacogenetic information, the NPs would focus on the pharmacogenes and associated alleles with high-level evidence of association to clinical phenotypes listed on drug labels and clinical dosing guidelines (see *Method for determining minimum panel content for pharmacogenomics assay*).

Selecting the most clinically appropriate pharmacogenetic testing panel begins with the medication classes of interest to the clinical presentation; the example given is for addressing chronic pain. Drug label information and dosage guidelines from professional organizations guide the subset of medications applicable to pharmacogenetic testing and the pharmacogenes associated with phenotypes of altered drug metabolism. The star allele designations with high evidence suggest the core set for the genotyping panel when selecting an appropriate clinical pharmacogenetic testing facility. In chronic pain management, three pharmacogenes qualify for inclusion in a preemptive pharmacogenetic assay: *CYP2C19, CYP2C9,* and *CYP2D6*. In assessing the pharmacogenetic testing content, the NP would also consider the wild-type allele (defined as the most common genotype). Wild-type designation is based upon a quantitative representation or estimation of the normal allele in a population and

is denoted as star one (*1). An important caveat for all genotyping tests is that the decision to assign an allele a wild-type status is based upon a genotyping test that cross-examines only the most common and already proven sites of functional variation. It is always possible that a novel, previously undiscovered (and therefore uninterrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a nonfunctional allele being erroneously designated as wild-type.

The interpretation and usability of pharmacogenetic test results can impact their successful implementation in medication management planning.

In assessing pharmacogenetic testing assay content, the *1 allele is not genotyped directly within the lab test. Instead, the *1 allele is assigned during the conversion of genotypes into allele designation by default, through the absence of single nucleotide polymorphisms (SNPs) in the other components of the assay. As such, rare, personal, and novel alleles cannot be detected in most genotyping technologies (except sequencing), resulting in a possible erroneous designation as wild-type.

Practical considerations

Sample collection for pharmacogenetic testing includes three possible options: buccal swabs, saliva, or blood. In an online survey of pharmacogenetic testing labs, the majority accepted one of three possible samples: buccal swabs (59 labs), saliva (16 labs), or blood (15 labs) collected in a lavender-top tube.[21] Approximately 26% of labs surveyed did not specify the sample sources accepted.[21] The buccal swabs or saliva can easily be collected by NPs after a brief training session.

Cost considerations

An important consideration for pharmacogenetic testing within the clinical setting is the cost for the patient. Insurance reimbursement for the test is uncommon, except for warfarin, clopidogrel, and drugs used for oncology treatment. Reviewing the insurance reimbursement policy for coverage prior to ordering is recommended. Keep in mind, the more established the lab provider, the more likely they are to have a multistep billing process. A suggested process flow begins with the patient completing a preauthorization form followed by determining insurance coverage, such as copays or deductibles, and if the lab is considered in-network or out-of-network. In situations where the insurer authorizes all or part of the cost for the test, it is preferable for the lab to submit the insurance claim on behalf of the patient. Where insurance coverage is not available, the patient is uninsured, or the patient prefers not to bill their plan, a self-pay rate is offered and provides transparency of the associated costs.

Several pharmacogenetic testing providers offer financial support options to help alleviate financial burden due to out-of-pocket costs, including prompt-pay discount, zero-interest payment plan, or pro-rated costs determined by income-based guidelines. Only half of surveyed labs list payment information related to pharmacogenetic testing, and a quarter describe reimbursement processes but do not list the actual cost of the testing panel.[21] Currently, 10 labs offer pharmacogenetic testing panels through a web-based resource with prices ranging from $199 to $749 with a median cost of $350. Overall, approximate cost for a pharmacogenetic pain panel test appears in three groups: price-points of $250 to $350, $500, or $750 to $1000.[22-31] Most insurers, such as Medicare, Aetna, Cigna, and Humana, consider pharmacogenetic testing for pain management investigational use and do not authorize reimbursement.[32-34]

The interpretation and usability of pharmacogenetic test results can impact their successful implementation in medication management planning. While there are no standards on the content and organization of reports, there are similarities across the interpretation reporting service providers.

Pharmacogenetic test reports

The simplest format of a pharmacogenetic test report lists the patients' genotypes translated into the pharmacogenetic allele designations. A more useful report has information about the clinical phenotypes translated from the pharmacogenetic alleles, particularly with listing of medications impacted and sources for dosage selection and adjustment. In support of clinical implementation, the availability of online and mobile applications along with laboratory information system

(LIS), electronic medical record (EMR), and CDS system integration may be useful for clinics with limited resources in these areas. Delineating between actionable and informative pharmacogenetic phenotypes by drug with clinical dosing guidance along with drug-drug interactions is particularly useful when clinical pharmacogenetic information has not yet been incorporated into a CDS.

Clinical resources

Clinical practice guidelines from the American Academy of Family Physicians, the American Academy of Pain Medicine, and the Department of Health and Human Services (HHS) Pain Management Best Practices Inter-Agency Task Force Report emphasize patient-centered, individualized care based upon a biopsychosocial model of care.[35-37] A growing set of resources is available to the clinician for implementing pharmacogenetic testing into clinical practice, from organizations such as the NIH, consortia, and insurers to private sources. For implementation of pharmacogenetic testing into clinical decision-making, PharmGKB is the leading central repository for scientific evidence of genetic annotations, associations between genotyped alleles and phenotypes, drug label annotations, and clinical dosing guidelines published by scientific consortia.[38] Its website contains information from the three scientific consortia leading implementation efforts around the world (CPIC, DPWG, and CPNDS), along with annotations on approved drug labels across the FDA; European Medicines Agency; Pharmaceuticals and Medical Devices Agency, Japan; and Health Canada (Santé Canada).

The implementation of pharmacogenetic testing supports the risk assessment of medication treatment approaches, preceding the development of a treatment plan during the diagnostic evaluation. The HHS Task Force lists genetics as one of the contributing biological factors in their Biopsychosocial Model of Pain Management.[37] Pharmacotherapy for chronic pain can include both opioid and nonopioid categories of medications, with several medications in each broad class associated with pharmacogenetic information. Clinical dosing guidelines informed with testing results data are currently available for codeine and tramadol in the opioid class.[39-41] In the nonopioid class, such guidelines are available for the SNRI venlafaxine, nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib, and the tricyclic antidepressants (TCAs) amitriptyline, desipramine, and nortriptyline.[42-47]

Training and certification programs related to pharmacogenetic testing are available through the University of California, San Diego, with the Pharmacogenomics Education (PharmGenEd™) Program, the Mayo Clinic School of Continuous Professional Development with the online Pharmacogenomics Fundamentals for Today's Clinicians continuing education, and the Pitt Pharmacy Test2Learn™ interactive web application.[48-50] Private industries are also expanding their online training for clinicians and patients. Examples of white papers, Frequently Asked Question lists, podcasts, and brochures can be found online at Clinical Laboratory Improvement Amendments (CLIA) regulated labs specializing in pharmacogenetic testing.[22-31] Many of the individual institutes such as the National Institute of General Medical Sciences at the NIH have public-facing summaries of pharmacogenetics and the utility of testing.[51] The website for the National Human Genome Research Institute contains sections devoted to genomics teaching tools and general as well as pharmacogenetic-specific terms.[52]

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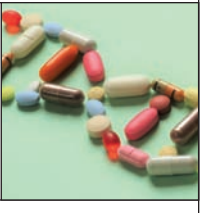

A rapidly evolving field

Preemptive pharmacogenetic testing across multiple medication classes provides greater value to patients over a longer period, although the promise of a lifetime of use for a single panel test is premature. Recommended panels for pharmacogenetic testing will remain in flux while clinical evidence for pharmacogenetic alleles still accrues at a rapid pace. Additional research is needed in underrepresented populations to increase clinical utility broadly. Discovery of new alleles will need to be screened for frequency and functionally validated to be incorporated into clinical guidelines. The interplay of patient populations and technical and cost considerations for implementing pharmacogenetic testing means that there is not yet a

one-size-fits-all solution. Despite these concerns, a core set of alleles are supported by clinical evidence and dosage guidelines for implementation in chronic pain management.

A general knowledge of the basic characteristics of genetic technologies is necessary when discerning between offerings of genetic lab service providers. Limitations of different genetic testing technologies influence the applicability for the patient population being served by the practice, as well as reinterpretation of panel results when evidence levels change for specific alleles. Where a known and tested variant of an allele changes in the evidence level or phenotype, an updated report may be requested from the lab service provider regardless of the testing technology. However, when a novel variant is elevated to clinical testing from a known pharmacogene, the only testing technology likely to contain the raw data that would allow for an updated interpretation report would be either Sanger or NGS sequencing.[53] Other genetic testing technologies are designed to test only the variants of interest defined at the creation of the panel test. The choice of lab service provider is a combination of the testing technology, appropriateness of pharmacogenetic allele content for pain medication metabolism, and associated costs to the patient.

Conclusion

Evidence of clinical utility and validity of pharmacogenetic testing continues to increase, along with clinical training resources and support tools. Challenges remain, related to testing access, professional clinical guidelines, integration with EMRs, and CDS alerts. The rapid growth of commercial testing facilities and lab-developed test options within CLIA facilities across the US are a sign of growing interest by both patients and clinicians. Focusing on the well-established drug-gene interactions and phenotypes with clinical relevance may reduce the barriers to pharmacogenetic incorporation into guiding therapy. Implementation of pharmacogenetic testing is another tool in evidence-based medication management for patients with chronic pain. NP

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