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Advancing Pharmacogenomics from Single-Gene to Preemptive Testing

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Keywords

pharmacogenetics, pharmacogenomics, precision medicine, individualized medicine, personalized medicine, clinical decision support, genomic medicine

Abstract

Pharmacogenomic testing can be an effective tool to enhance medication safety and efficacy. Pharmacogenomically actionable medications are widely used, and approximately 90–95% of individuals have an actionable genotype for at least one pharmacogene. For pharmacogenomic testing to have the greatest impact on medication safety and clinical care, genetic information should be made available at the time of prescribing (preemptive testing). However, the use of preemptive pharmacogenomic testing is associated with some logistical concerns, such as consistent reimbursement, processes for reporting preemptive results over an individual's lifetime, and result portability. Lessons can be learned from institutions that have implemented preemptive pharmacogenomic testing. In this review, we discuss the rationale and best practices for implementing pharmacogenomics preemptively.

Annu. Rev. Genom. Hum. Genet. 2022.23:449-473. Downloaded from www.annualreviews.org
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INTRODUCTION

Pharmacogenomics is the study of how an individual's genetic makeup influences their response to medications. Although the role of genetics in drug response has been studied for decades, broad pharmacogenomic testing has only recently been integrated into prescribing decisions. Resources from groups such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have allowed for more informed integration of pharmacogenomics into prescribing decisions (9, 25, 93, 112, 113), but different perspectives on the evidence needed for implementation of drug–gene pairs exist (23, 69, 89). Furthermore, pharmacogenomics implementation approaches vary regarding the timing of when the test should be ordered. Some advocate that pharmacogenomic testing should be reactive and obtained only for certain medications prior to prescribing or after a patient has had an adverse reaction to the medication or is failing therapy. Others advocate for using a preemptive pharmacogenomic testing approach as a prevention and medication safety tool. In this review, we compare and contrast reactive and preemptive testing and discuss the rationale for implementing pharmacogenomics preemptively along with best practices for using preemptive pharmacogenomics as a preventive tool.

EVIDENCE AND RESOURCES FOR PHARMACOGENOMIC TESTING

The level of evidence needed to support the use of pharmacogenomics in routine clinical practice remains controversial (23, 69, 89). Although randomized clinical trials (RCTs) are considered the gold standard for evidence-based medicine, many argue that, for pharmacogenomics, RCTs are unnecessary and may be impractical because of their cost and the number of patients needed. In some cases, RCTs may even be unethical (23, 69, 89). Many decisions made for patient care are not based on RCT data, with notable examples being dosing adjustments based on renal dysfunction, liver dysfunction, drug interactions, and other patient-specific characteristics. For example, regulatory label requirements do not mandate that RCTs show equivalent clinical outcomes for dosing adjustments based on renal function (133).

In the absence of RCTs, pragmatic trials and observational studies are often used as evidence supporting the use of pharmacogenomics in patient care. Although observational data are prone to bias, they do have advantages over RCTs: Pragmatic and observational trials are conducted in the context of clinical practice, making them more generalizable, and they may be less costly than RCTs (12). Furthermore, the evidence paradigm for medication use and regulation is increasingly embracing data beyond RCTs (90, 106, 108, 132). For example, as part of the 21st Century Cures Act, the US Food and Drug Administration (FDA) was tasked with considering how to use real-world evidence (which typically consists of observational data) to support new indications and other postapproval data requirements, and the FDA released a framework for use of these data (90, 106, 108, 132). Finally, pharmacogenomics should be viewed as a patient safety intervention, and RCTs are not always performed for many widely used patient safety strategies (23, 112).

Current resources, such as CPIC and DPWG guidelines, provide recommendations for how to use available pharmacogenomic test results and do not focus on whether ordering a pharmacogenomic test is required. In most cases, institutions implementing pharmacogenomics use the CPIC and/or DPWG guidelines to guide gene–drug selection for implementation and prescribing recommendations (34, 41). CPIC guidelines are based on published evidence, adhere to National Academy of Medicine standards for clinical guidelines, and are updated, freely available, and peer reviewed. Furthermore, the data needed for many steps in clinical implementation can be downloaded from the CPIC database (25, 32).

Table 1 Common features of reactive versus preemptive pharmacogenomic testing

Feature	Reactive pharmacogenomic testing	Preemptive pharmacogenomic testing
Timing of ordering	Ordered as drug therapy is initiated or being contemplated	Ordered independently of medication use
Turnaround time	Often ~5–7 business days; can be a point-of-care test (only available for a limited set of genes; use is not widespread)	Test result already available in the electronic health record at the time of prescribing; results can be reused as other medications are prescribed
Prescriber knowledge about pharmacogenomics	Requires knowledge about which test to order	Clinical decision support alerts prompt prescriber for action
Cost	Routinely found to be cost effective or cost saving, but expensive relative to the potential benefit of one therapeutic decision	Approximately equivalent to the cost of two single-gene tests, and provides cost savings over years with continued use of genetic information for medication use
General testing platform used	Often single gene (one pharmacogenomic test result)	Often array based (multiple pharmacogenomic test results)

CHARACTERISTICS OF PHARMACOGENOMIC TESTING

Reactive Testing

Reactive testing is prompted by a medication prescribing decision, either one that has already taken place or one that is pending (**Table 1**). Reactive testing has the advantage that it is simple and consistent with what is often routine practice: Consider a therapeutic intervention and do appropriate testing to decide whether the intervention should be undertaken. Reactive pharmacogenomic tests are often single-gene tests because most actionable pharmacogenomic decisions are based on evidence regarding variants in a single gene. Because the results are not yet available at the time of prescribing, the initial prescription may need to change after the results are known. Depending on the turnaround time, this delay could be problematic, as it may be difficult to revise the prescription in a timely fashion if the test results require a change in pharmacotherapy. Quickly changing a prescription may be especially complex in an ambulatory setting after the prescription has been ordered and dispensed. For some medications, harm may come to the patient because of either drug toxicity or a lack of efficacy while the test result is still pending, when the patient could be receiving inappropriate therapy. Single-gene tests are inefficient in that panel testing for all actionable pharmacogenes can be performed at just slightly higher costs and using the same DNA as single-gene testing (150). Reactive testing is contrasted with preemptive testing, in which test results are available prior to medication prescribing decisions, often by using multigene arrays or DNA sequencing technologies (39, 41).

Point-of-care testing. Point-of-care testing is a type of reactive testing. Technically, point-of-care testing is performed at or near the patient (e.g., blood glucose monitoring tests). In some acute care settings, it may be important for a quick turnaround time to physically perform the test using an instrument that is in a clinic or inpatient unit. There are a few examples, such as anticipating the need for clopidogrel antiplatelet therapy after percutaneous coronary intervention, when the availability of quick turnaround times in or near the coronary procedure room could facilitate prescribing decisions needed the same day as the procedure (31, 102, 105, 114). Point-of-care testing has also been employed for warfarin (analyzing variants in *CYP2C9* and *VKORC1*), another example when decisions about prescribing and dosing the medication are somewhat urgent (46). Point-of-care testing has also been proposed for *HLA-B*57:01* with abacavir and for *TPMT* with thiopurines (143). Issues of technical performance for point-of-care devices have been reviewed (140).

Single-gene testing. Most reactive pharmacogenomic tests are done for a single gene, or occa-
sionally two or three genes, and are ordered in the context of prescribing a specific medication or
class of medications (47). The techniques used to interrogate the single gene can vary, from inter-
rogating only a handful of variants in that gene to complete gene sequencing. Because germline
pharmacogenomic tests for an individual can be performed from DNA extracted from a single
sample (usually blood or saliva) without regard to timing, sending multiple samples for interro-
gation of multiple single genes over a patient's lifetime is inherently redundant and an inefficient
use of the patient's DNA sample (150). Some clinical laboratories even market medication-specific
pharmacogenomic tests, treating tests for the same gene as different tests depending on the med-
ication being contemplated; for example, a *CYP2D6* tamoxifen test may be marketed separately
from a *CYP2D6* antidepressant test or a *CYP2D6*-containing pain panel, even though the gene test
itself is identical. Some clinical laboratories have their sample tracking and validation procedures
linked to obtaining a new sample for each pharmacogenomic test, and reimbursement incentives
favor obtaining a new sample for each gene test (74, 146, 150). Thus, single-gene tests continue
to dominate the clinical landscape of genomic testing.

Single-gene tests imply a practice model in which genes are contemplated one at a time as
each new medication is considered for the patient. With adequate interpretation and workflows,
single-gene test results may be reused over time for multiple affected medications that may be
ordered for the patient over time.

Single-gene tests can be ordered preemptively (pre-prescription). Examples include testing
for *DPYD* before starting fluoropyrimidine-based chemotherapy (59), testing for *CYP2C9* and
VKORC1 before prescribing warfarin (82), and testing for *HLA* before prescribing abacavir or car-
bamazepine (149). Despite their inefficiency compared with multigene panels, single-gene tests
have been shown to be cost effective or cost saving (14). The cost effectiveness is frequently sensi-
tive to pharmacogenomic test cost, which continues to decline, and the adverse effects that might
be caused without testing are expensive to manage or treat, such as severe neutropenia in patients
with cancer and increased cardiovascular adverse events in patients with acute coronary syndrome
(36, 151).

Preemptive Testing

Preemptive testing means that the test result is available in the medical record pre-prescription;
this could involve a single-gene test ordered preemptively because the patient is likely to need an
affected medication in the future (e.g., *TPMT* testing for all patients with an autoimmune disease
likely to need a thiopurine), but more commonly the test result is available preemptively because
it was included in a broad panel of multiple genes that has already been performed (41) (**Table 1**).
Preemptive testing has several advantages over reactive, single-gene testing (1, 115, 121). One
is efficiency: Ordering a single array of multiple actionable pharmacogenes avoids the need to
perform many single-gene tests, and often the cost of a multigene test is not much greater than
the cost of a single-gene test. This is partly because some of the cost of genetic testing is ascribed to
obtaining the patient sample and isolating DNA. Another advantage is that preemptive multigene
testing avoids the delay that would be incurred by reactive single-gene testing: Instead of needing
to order a gene test and then wait for the individual results, the results are already available in the
patient's medical record at the time of the prescribing decision.

It should be mentioned that pharmacogenomic testing may be initiated by the patient, espe-
cially as direct-to-consumer testing becomes more common. A major challenge for the healthcare
system will be to accommodate incorporating relevant information from patient-initiated testing
into the clinical workflow (45, 52, 56).

Multiple types of pharmacogenomic testing panels are available from clinical laboratories. These can include commercially available arrays, bundles of tests performed with a single technology (e.g., PCR), whole-exome or whole-genome sequencing, or hybrid models using a combination of technologies. The panels can be agnostic with regard to medication category (e.g., panels containing all actionable pharmacogenes) or can be disease specific (e.g., genes relevant for treating colon cancer, breast cancer, cardiovascular disease, or psychiatric disorders). Cancer gene panels that might include the somatic cancer-specific lesions that drive certain targeted therapies as well as likely important germline pharmacogenes have been proposed (73). It should be noted that a challenge for those offering panel testing (via an array or via DNA sequencing) is that several pharmacogenes present technical challenges, including HLA genes and *CYP2D6*, with the latter being subject to common partial- or whole-gene duplications and rearrangements (37, 72, 101, 118).

Although panel-based testing is accompanied by the complications of providing interpretations for many genes, and the costs incurred and methods needed to update interpretations over time have not been fully addressed, even limited panels have some evidence for cost effectiveness relative to usual care. For example, a preemptive panel with 30 test-return days that included the gene–drug pairs *CYP2C19*–clopidogrel, *CYP2C9/VKORC1*–warfarin, *DPYD*–fluoropyrimidines, and *SLCO1B1*–statins was found to be cost effective compared with usual care (36, 150).

Panel-based tests, particularly those based on DNA sequencing, present the problem that clinicians must decide how to handle the inclusion of variants whose actionability is uncertain. Certain institutions mask the results of genes or variants whose actionability is uncertain, whereas others return results for all tested variants to the electronic health record (EHR) (58). Some have argued that pharmacogenomic panel-based clinical testing should be restricted to clinically validated variants and that comprehensive testing should be used only for research purposes (81). Moreover, some panels include not only variants of unknown significance but even genes of unknown actionability. Returning such results to the medical record could place clinicians in the difficult position of having unimportant results obscure the important ones or of failing to act on results that might in the future become actionable. There are multiple descriptions of how panel-based preemptive testing has been handled at early-adopter sites (39, 80, 102, 122, 135). Some centers return all results into the patient's medical record, while others use an approach of returning results of pharmacogenes that have clinical recommendations for actionability in the CPIC or DPWG guidelines.

Rationale for Preemptive Pharmacogenomic Testing

Evidence for widespread use of pharmacogenomically actionable medications is now overwhelming. For example, examination of more than 70 million patient insurance records in the United States found that approximately half of all patients 40–64 years of age received at least one pharmacogenomically actionable medication and more than 25% received two or more actionable medications over only a 4-year period (119). A study of 56 actionable medications in more than 50,000 patients at Vanderbilt University Medical Center estimated that 65% of patients received a high-risk medication within a 5-year time period (120). An analysis of claims data in Austria for more than 6.7 million patients found that 72% of patients over 65 years of age received at least one actionable medication in a 2-year period (79). In Singapore, based primarily on 69 medications that were rated as CPIC level A or B (actionable), the 5-year risk of receiving any new pharmacogenomically actionable medication was approximately 43%, with the risk being higher for older patients and higher for Malays and Indians than Chinese (27). Of more than 1.3 million South Koreans, 47.4% were prescribed a pharmacogenomically high-risk medication in a 1-year period (76). More

than 84% of nursing home residents used pharmacogenomically high-risk medications (137). Of more than 7.7 million American veterans, 54.8% received at least one CPIC level A drug (actionable) over a 6-year period, with the most common gene–drug pairs being *SLCO1B1*–simvastatin, *CYP2D6*–tramadol, and *CYP2C9*–warfarin or *VKORC1*–warfarin (28). In a British primary care setting, 58% of patients were prescribed at least one high-risk medication over a 2-year period, but that increased to 80% over 20 years, with exposure increasing with age (77).

Despite the very high frequency of pharmacogenomically high-risk medication use in the general population, strategies to identify groups of patients with the highest likelihood of receiving a high-risk medication have been proposed to identify subsets in whom array-based preemptive genotyping would have the biggest payoff (124). When patients were grouped by clinic type and age in a US population, the percentage receiving a high-risk medication ranged from 12.7% in the outpatient pediatric psychiatry group to 75.7% in adult inpatients over 50 years of age (61).

The rationale for widespread panel-based preemptive testing is simple: Pharmacogenomically actionable medications are widely used in both inpatient and outpatient settings, and every individual (regardless of race or genetic ancestry) is extremely likely to harbor at least one actionable variant (**Figure 1**). Moreover, with results available preemptively, turnaround time for returning test results is not an issue (121). With preemptive testing, genotype results reside in EHRs and can be available immediately when a high-risk medication is ordered. More than 98% of American
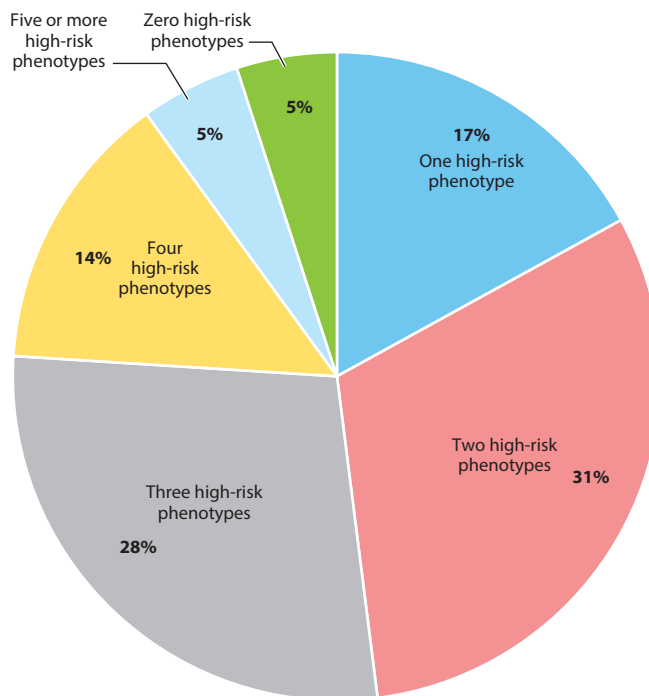
Figure 1

Proportions of patients preemptively genotyped at St. Jude Children's Research Hospital with high-risk phenotypes. Data are from the PG4KDS clinical trial and are shown as of November 1, 2021. The study genotyped 5,912 patients for the following 13 pharmacogenes: *CACNA1S*, *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A5*, *DPYD*, *G6PD*, *mt-RNR1*, *RYR1*, *SLCO1B1*, *TPMT*, and *UGT1A1*. Patients diagnosed with acute lymphoblastic leukemia were also genotyped for *NUDT15*. A high-risk phenotype is a result that has implications for the modification of therapy for at least one medication.

whites and blacks are estimated to have at least one high-risk actionable genotype (41). More than 99% of 44,000 Estonians had at least one high-risk genotype (118), with a similar percentage found at the Mayo Clinic in the United States (70). In studies that considered both medication use and the presence of actionable genotypes and analyzed more than 3 million patients receiving more than 3.6 million new prescriptions in the Netherlands, approximately 24% of new prescriptions involving 45 actionable medications represented an actionable gene–drug interaction (2, 10, 11).

Thus, theoretically, essentially all patients would benefit from having multigene preemptive pharmacogenomic tests. Whereas payers may be willing to pay for single-gene tests, largely because they see this as likely to be a limited market, many report being skeptical of the costs involved in universal panel-based preemptive testing (74). There is limited evidence for the cost effectiveness of a preemptive approach (145, 150, 151). In addition to the costs associated with genotyping and with the delivery of results and clinical decision support (CDS), some have described potential disadvantages of array-based preemptive testing. For example, there is a school of thought that says that having multiple pharmacogenomic test results makes it too complicated for clinicians to interpret the results (78). A preemptive testing approach also requires an excellent healthcare system with integration of laboratory results and electronic prescribing practices. Sustainability is a clear challenge: The problems of how to update interpretations over time (6, 58) and how to continue to make results follow patients as they age and progress in and out of multiple healthcare systems have not been successfully addressed. Some describe the liability involved in providing a large number of results when a portion of these results may not be used or adequately interpreted (19). Testing more genes and variants also increases the theoretical danger of having incidental findings that may impact disease risk and may not have been anticipated by the patient or provider at the time of testing (56, 83). Examples of incidental pharmacogenomic findings include discovery of Klinefelter syndrome based on males having two *G6PD* (X chromosome) alleles and discovery of Gilbert syndrome based on *UGT1A1* genotype test results.

Cascade genetic testing—the practice of extending testing to at-risk family members of an individual determined to have a high-risk genotype—may be indicated for select pharmacogenes (128). The genes that are most amenable to this approach are those that have autosomal dominant inheritance (placing family members at very high or even certain risk for having a high-risk genotype); the frequency of use of the affected medications may also affect the decision to implement cascade genetic testing of family members. For example, certain *RYR1* and *CACNA1S* variants are associated with a predisposition to develop malignant hyperthermia with the administration of certain inhaled anesthetics or succinylcholine. Because these two genes exhibit autosomal dominant inheritance, the observation of a high-risk *RYR1* and *CACNA1S* genotype in a patient may result in offering cascade genetic testing to family members (55).

Using whole-genome sequencing for preemptive pharmacogenomic testing instead of array-based techniques has been proposed. The challenges of generating large numbers of false negative or false positive results with genome sequencing have been presented (123). On the other hand, some studies have reported promising levels of concordance between genome sequencing results and microarrays (111, 148), so that one possible strategy is for centers to leverage genome sequencing already performed for other reasons to yield actionable pharmacogenomic results.

WORKFLOW PRACTICES FOR INCORPORATING PHARMACOGENOMIC TEST RESULTS INTO ELECTRONIC HEALTH RECORDS

For pharmacogenomic testing to be most useful, structured genetic test results (generally organized by gene) should be delivered into the EHR and coupled with CDS; structured results
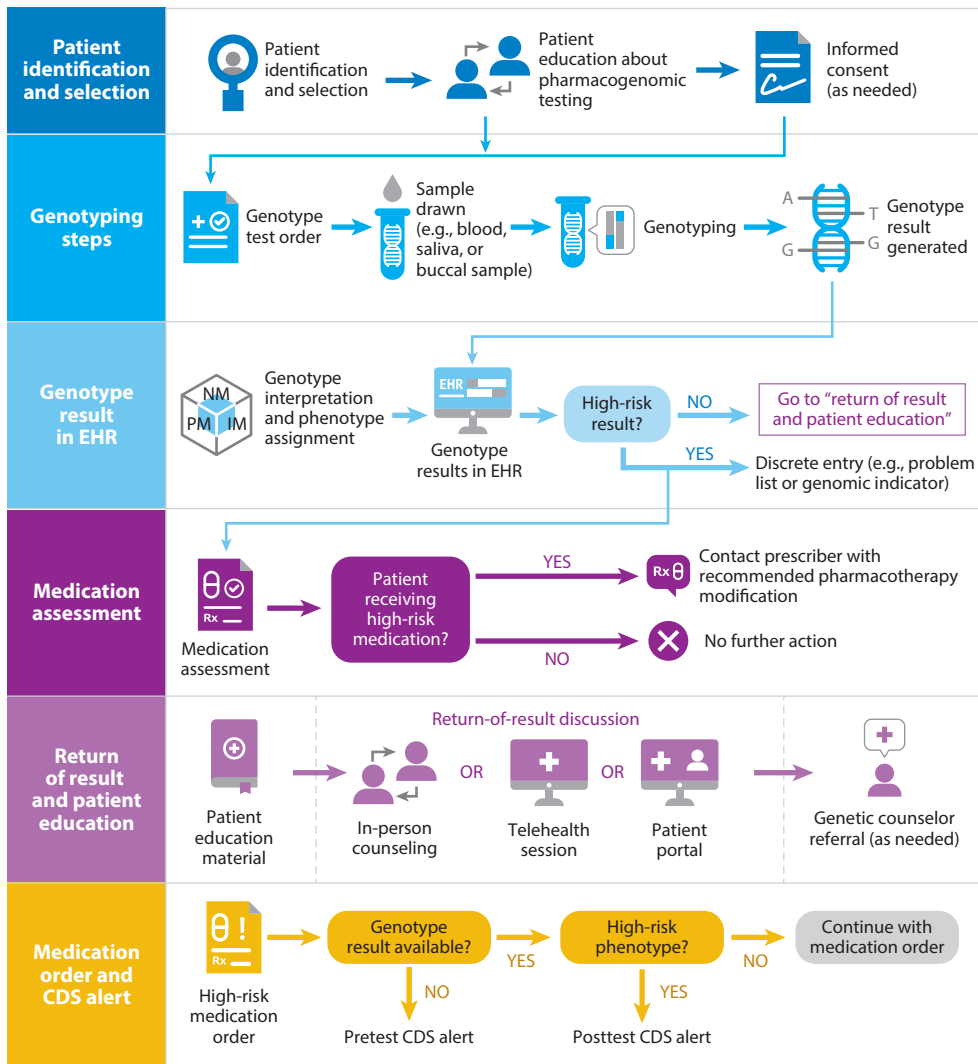
Figure 2

Preemptive pharmacogenomics service workflow process. Abbreviations: CDS, clinical decision support; EHR, electronic health record.

are particularly needed for multigene test results (6). Because the testing may have predated the relevant prescribing decision by months or even years, systems that can find past pharmacogenomic results and link the information with current prescribing decisions are needed. Thus far, workflows have been reported for 19 programs (88) and vary among institutions (6). However, there are several commonalities among these published workflows (6, 18, 21, 26, 38, 40, 60, 65, 68, 87, 88, 91, 96, 97, 107, 117, 125–127, 134).

Each clinical workflow encompasses the steps from ordering the pharmacogenomic test to making informed prescribing decisions to educating patients (**Figure 2**). Standardized terms for test names and test results facilitate standardizing the workflow and improving the interoperability of using the results across healthcare settings (24, 85). Some implementers propose combining

disease-risk genes (e.g., those included on the American College of Medical Genetics and Genomics list of disease-causing variants) and pharmacogenomic genes in one workflow (94), while others have separate workflows (7). Most workflows incorporate both active CDS presented at the time a high-risk medication is ordered and passive CDS in the form of a static written interpretive consultation (13, 63). Workflows have been described for point-of-care multigene implementations in ambulatory clinical settings (64, 71), as well as for panel-based preemptive testing in a large health center (87) and testing in cancer clinics (92). Some workflows include clinician and patient education (104). Toolboxes for workflows have been provided by the Implementing Genomics in Practice (IGNITE) network (42). Some sites set up a special pharmacogenomics clinic that incorporates patient encounters for testing and return of results (8, 40). Most sites incorporate pharmacogenomic testing into routine care workflows, and different considerations exist depending on the genes, medications, setting of care (i.e., ambulatory or inpatient), patient population, and other factors (21, 30, 107).

Some implementers establish a pharmacogenomics oversight committee, often as a subcommittee of a pharmacy and therapeutics committee, which can help prioritize the genes and medications for incorporation into the clinical workflow and can have external approval of CDS language (6, 13). Workflows can incorporate processes to distinguish clinically actionable results from other results, to ensure that only a portion of interrogated genetic results are reported or acted upon (8). Pharmacogenomic results can be incidental results from whole-genome or whole-exome sequencing (100), and workflows have been proposed based on using next-generation DNA sequencing methods (53).

Considerations for Identifying a Genetic Testing Laboratory and Interpreting Results

An important step in implementing preemptive pharmacogenomics is identifying an appropriate laboratory to perform the genetic test (138). When implementing preemptive testing using a multigene panel, consideration should be given to what genes are applicable to the clinical setting, what variants for each gene are interrogated, how much the testing costs, what type of sample is needed, how long the turnaround time will be, and how results will be reported. Many programs across the United States that have implemented pharmacogenomics rely on the CPIC guidelines to aid in gene and variant selection (139). Considerations for selecting a laboratory have been reviewed (138).

It is important to translate the genotype data into a clinical phenotype (e.g., *CYP2D6*4/*4* into CYP2D6 poor metabolizer), as this phenotype designation often drives therapeutic decisions. For example, CPIC guideline recommendations are generally built around phenotype groups rather than individual diplotypes. Furthermore, an advantage of this approach is that CDS alerts can be coded to alert from a limited number of phenotype assignments as opposed to multiple individual diplotype calls. For example, *CYP2D6* has more than 10,000 possible diplotypes but only 4 primary phenotypes. A system that provides alerts for all 10,000 diplotypes would be time consuming to build and maintain and is not necessary. Grouping diplotypes into clinical phenotypes for the purpose of designing CDS rules has been standard for pharmacogenomics implementation across multiple sites (41) (**Figure 3**).

Returning Pharmacogenomic Results and Incorporating Genetic Test Results into Electronic Health Records

For clinical pharmacogenomics to be truly used as a preventive service, test results must be incorporated into EHRs with CDS, so that results may be used to individualize therapy at any future
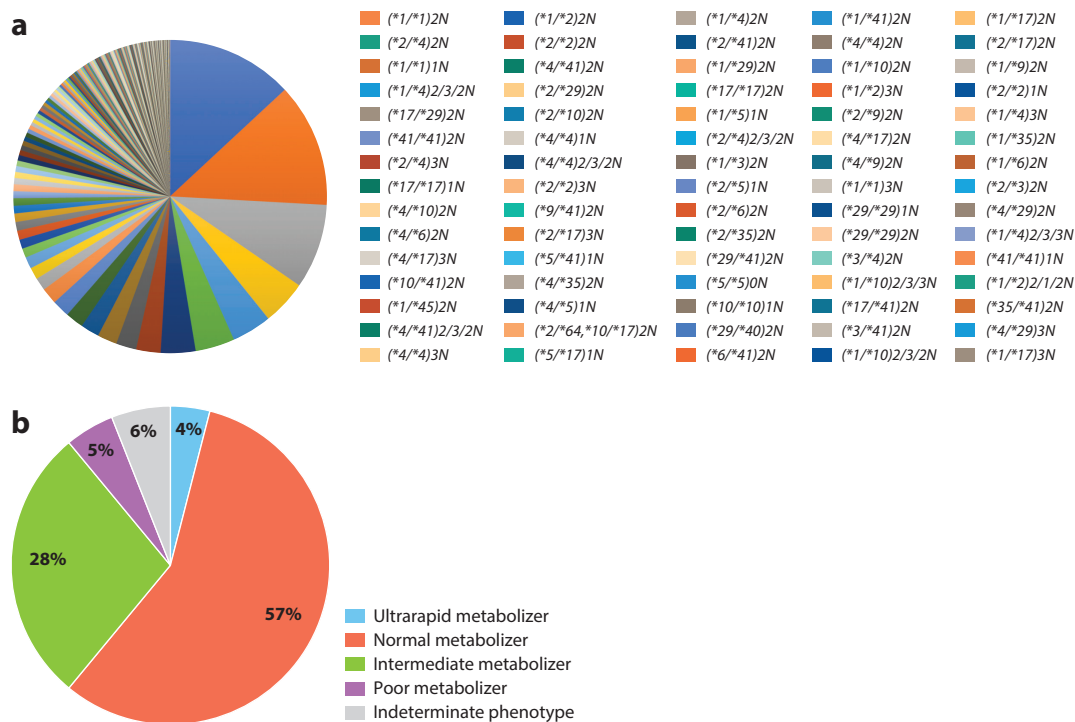
Figure 3

Demonstration of the reduction in complexity of pharmacogenomic result interpretation by utilizing phenotype instead of genotype. In this example, 406 unique *CYP2D6* genotype (diplotype) results (panel *a*) can be classified into 4 distinct phenotypes (panel *b*), with a small percentage left as indeterminate. This approach simplifies result interpretation for clinicians and enables clinical decision alerts to be triggered based on phenotype instead of diplotype.

time point (63, 67, 142). Most EHR vendors do not have a pharmacogenomics framework built into their system as a core function, and the major medication knowledge vendors used in EHRs are slowly adding pharmacogenomic content. Therefore, currently, incorporating pharmacogenomics into EHRs with CDS requires careful integration of pharmacogenomic knowledge from external resources (such as CPIC guidelines) combined with configuration of the EHR vendor's custom clinical rule capabilities. The CPIC Informatics Working Group provides informatics resources with each CPIC guideline (66) that include point-of-care CDS workflows, example text for decision support alerts, and templates for interpretive consultations. Most successful clinical implementation programs have relied on the integration of pharmacogenomic results and clinical phenotypes as discrete elements of EHRs to prompt CDS alerts that notify prescribers of special consideration for pharmacotherapy (13, 20, 22, 62, 65, 87). Some level of customization of the health system's EHR instance may be required to fully support pharmacogenomic CDS. While health systems may chafe at customization of their EHR systems, innovations for both genomics and patient safety often require some new approaches and a higher level of informatics support (44, 109). The growth in the number of healthcare systems implementing pharmacogenomic CDS using different EHR vendors demonstrates that the approach is feasible and can be scaled to more health systems (15, 21, 54, 91, 103, 110, 134, 142).

There are two main categories of CDS, both of which have value for preemptive pharmacogenomics. Instead of expecting clinicians to search for pharmacogenomic results in the EHR system

(passive CDS), or sometimes even to search for the results in a separate system, interruptive alerts that guide clinicians to make changes should also be used (active CDS). Many programs have published on the different types of CDS alerts used in pharmacogenomics as well as the differences in how they are used across implementer sites (75, 142), which are briefly reviewed below.

Passive clinical decision support. Information can be passively made available to the ordering clinician as a genetic test interpretation, generally in the form of a written consultation from a pharmacogenomics expert (63). While useful, passive CDS interpretations have limitations: (*a*) passive CDS tools rely first on the prescriber remembering the potential for a gene–drug interaction at the point of care and knowing the location of the pharmacogenomic test results in the EHR system, (*b*) pharmacogenomic interpretation reports consist of static consultations and may not be updated regularly to reflect new prescribing information (e.g., a newly published pharmacogenomic guideline), and (*c*) the location of pharmacogenomic results differs across EHR systems, and finding a location that works for all has been challenging (35).

Active clinical decision support. Active or interruptive CDS alerts stop the clinician's workflow during the medication ordering phase to inform them of the availability of pharmacogenomic information (i.e., a pretest alert) or to present pharmacotherapy recommendations on a high-risk pharmacogenomic test result (i.e., a posttest result).

Pretest alerts inform prescribers that they are attempting to order a medication affected by pharmacogenomic variation but the associated genotype test has not yet been ordered, the result is still pending, or the result has not been recorded using standardized terminology that the CDS system uses to identify the absence or presence of pharmacogenomic results. This type of alert generally informs clinicians of the potential risks associated with prescribing the medicine without a known genotype, provides recommendations for alternative medications to use or select, and offers the option of ordering the genotype test, often from within the alert window itself (13). Alternative agent selection in the alert text should consider the applicable medication formulary system and patient populations who are usually prescribed the medicine. For example, a pretest alert presented to a clinician trying to order codeine for treatment of pain should ideally recommend alternative analgesic medications that are part of the formulary system of the hospital and would have the same route of administration or formulation that the clinician was attempting to prescribe. A benefit to preemptive pharmacogenomic testing is that pretest alerts are infrequent if a process is in place to test patients before a medication is ordered. In many cases, the pharmacogenomic test results should already be in the patient's EHR.

Posttest alerts interrupt the normal medication ordering or dispensing process, usually by presenting a new window explaining the need to modify pharmacotherapy based on the patient's high-risk pharmacogenomic test result (high-risk phenotype). Ideally, the posttest alert should have a concise message to the clinician that explains the risk if the patient were to receive the medication at the dose ordered. The alert should provide clear alternatives and functions to guide the prescriber to these alternatives. Like pretest alerts, it is important to tailor the selection of alternative agents to the institution's medication formulary system and ideally to match the route of administration and formulation of the medication that was originally intended to be prescribed. Drug–drug interaction alerts can also be combined with gene–drug information, as in the case of paroxetine, which is a strong inhibitor of CYP2D6. The coadministration of paroxetine may lead to a clinical CYP2D6 phenotype that is different from the genotype-defined phenotype, a process referred to as phenoconversion (16, 29). Additionally, multifactorial alert rules can be created to incorporate other clinical elements that influence medication dosing and selection, such as age, route of administration, previous medication use, previous therapeutic drug monitoring, or hepatic and

renal dysfunction (63). In some cases, sophisticated alert logic and other features within the EHR can decrease the need for a posttest alert, thus decreasing the chance of clinician alert fatigue (63).

Result Portability

Pharmacogenomic test results are relevant across a patient's life span, with use of high-risk pharmacogenomic medications tending to increase with age (77, 119). Processes need to be developed to make it routine for pharmacogenomic results to be available to clinicians at any future encounter that may start or change medication therapy. The fragmented and reactive nature of healthcare in many countries creates challenges for the optimal use of pharmacogenomic information over time. There is a need for systems that will exchange results and/or a registry of pharmacogenomic results, akin to vaccination registries.

The challenges of creating a workflow that allows for long-term sustainability and handoffs with providers outside the original implementation program have been described (130). Some suggest embracing patients as the keepers of their pharmacogenomic results, creating tools such as QR-code-compliant pharmacogenomic passports that patients can present to various providers (136). This issue of result portability remains one of the biggest and toughest barriers to positioning pharmacogenomics as a routine preventive measure.

Pharmacogenomic Education

As pharmacogenomics moves from single-gene reactive tests to more comprehensive panels preemptively ordered or directly obtained by consumers, prescribers may be faced with incorporating a genetic test result into a therapeutic selection and counseling a patient for a test they did not order. One of the most cited barriers to implementing pharmacogenomics is a lack of knowledge or education of clinicians and patients to support the interpretation of results (17, 49).

Healthcare provider education strategies. Preemptive programs have addressed the knowledge gap in pharmacogenomics education by developing comprehensive educational programs aimed at clinicians, including physicians, pharmacists, advanced practice nurses, and others. These programs fall under several categories: just-in-time education and resources for clinical implementers, education in professional schools, postdoctoral training (e.g., residencies, fellowships, and graduate programs), and certification programs.

Structured onsite educational in-services for clinicians are often recognized as crucial when establishing a pharmacogenomics program (41, 68, 88, 104). Educational in-services can be tailored to pharmacists or a relevant specialty within a health system or can provide general education across all clinical staff. Once a preemptive program is launched, the most immediate and real-time form of provider education includes just-in-time education embedded in provider workflows (48, 147). Methods of just-in-time education include active CDS presented to the prescriber within the clinical workflow, which provides clinicians with information required to interpret an individual patient's pharmacogenomic results. Active CDS is enhanced by passive CDS, as discussed above. A review of pharmacogenomics programs found that individual programs have also included messages to clinicians' inboxes, dedicated webpages, and on-site in-services for providers (88). Combining institutional education with access to available resources such as CPIC guidelines is key in educating the workforce so that pharmacogenomic results can be used once they have been implemented at an institution.

Accreditation standards for some schools of medicine and pharmacy now include pharmacogenomics as foundational content in predoctoral education. Including pharmacogenomic concepts in medical and pharmacy school curricula will ensure that graduates are poised to integrate

pharmacogenomics into patient care. For practicing clinicians, continuing education programs focused on therapeutic areas or practice settings are offered. The Inter-Society Coordinating Committee for Practitioner Education in Genomics, supported by the National Human Genome Research Institute, is a collaborative group aimed at improving healthcare provider genomics education by developing educational resources (98). Competencies are also well established, especially for pharmacists (51, 116). In addition, the National Human Genome Research Institute's Genetics/Genomics Competency Center website (**https://www.genomicseducation.net**) contains freely accessible genomics-related competency material for healthcare professionals.

Despite the increased presence of pharmacogenomics education and training for clinicians in medical and pharmacy school curricula, there is a need for some clinicians to complete specialty training via residencies, fellowships, or graduate programs (99, 144). Significant expansion of preemptive pharmacogenomics programs has led to novel pharmacist-led pharmacogenomic services and outpatient clinics and thus has created a need for leadership roles at the level of individual health systems. Accordingly, the American Society of Health-System Pharmacists has developed accreditation standards for specialty postgraduate year-two pharmacy residencies in clinical pharmacogenomics (3, 57). In the United States, nine pharmacogenomics residency programs either have been accredited by the American Society of Health-System Pharmacists or have preaccreditation status, and additional programs continue to apply for accreditation (4). The accreditation standards ensure that pharmacists who successfully complete an accredited postgraduate year-two clinical pharmacogenomics residency are prepared for advanced patient care, academic positions, or other specialized positions in the field. Fellowships and graduate programs in pharmacogenomics are other avenues of specialized training in the field. Several established pharmacogenomics programs and professional organizations offer certification in pharmacogenomics for practitioners. Certificate programs are most often offered as continuing education modules that may be self-paced and focus on principles of pharmacogenomics and applying them at a patient care level.

Patient education strategies. Educating patients about their individual results, which have lifelong implications, is an important aspect of a preemptive pharmacogenomics program. Preemptive programs have published several methods for patient education (88). Methods for educating patients about their individual results vary. General education about genetic tests can occur at the time that the pharmacogenomic testing is being ordered (68, 88, 141). At the time that results are placed in a patient's EHR, individualized patient education can be included in the workflow (**Figure 2**). Patients may be provided with information about their results in person, in writing, or via a patient portal (41, 68, 86). Programs may provide information about medications and pharmacogenes through a dedicated webpage (e.g., 129) or via educational videos (68, 95).

ECONOMIC AND REIMBURSEMENT CHALLENGES FOR PREEMPTIVE PHARMACOGENOMIC TESTING

Although the cost of a pharmacogenomic test can vary across different testing companies and platforms, many single-gene tests range from approximately $100 to $500, while a multigene panel can cost approximately the same or twice as much as a single-gene test (5). Even though a multigene panel would be less expensive than multiple single-gene tests, many payers are reluctant to reimburse for the multigene panels that would be used for preemptive pharmacogenomics implementation. Clinical utility is a requirement for coverage and reimbursement, and demonstrating clinical utility for preemptive testing can be difficult, as it is unclear exactly how the test results would be used clinically at the time the test is ordered (e.g., a patient may not take a medication that would be affected by pharmacogenomic test results for some time). Proving clinical utility for

reactive testing is more straightforward, as the test is being ordered with a medication in mind and prior to administration of a high-risk medication, but even reimbursement for single-gene tests remains a challenge.

However, more consistent reimbursement for pharmacogenomics in the United States may be on the horizon (43). Recently, building on previous decisions from public and private payers, local coverage determinations for the Molecular Diagnostic Services (MolDx) program were released, adding expanded coverage of pharmacogenomic tests for Medicare patients in select states and mentioning that "PGx [pharmacogenomic] tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines" (131). The new local coverage determinations now allow for coverage of all CPIC level A and B drugs [prescribing action recommended by CPIC (33)] and gene–drug pairs listed in FDA labeling. More importantly for preemptive pharmacogenomic testing, the local coverage determination does cover multigene tests, albeit only if the patient is receiving or may receive a medication covered by at least one gene on the panel (43).

The cost of the pharmacogenomic test is only one financial aspect of preemptive pharmacogenomics implementation. As discussed above, a multidisciplinary team of clinicians, informaticians, and laboratory specialists is required to adequately implement preemptive pharmacogenomics in EHRs with CDS. Once the infrastructure has been set up, monitoring of evolving evidence for pharmacogenomics and guidelines will need to continue on an ongoing basis, and the CDS will need to be updated (58, 87).

A DECADE OF PREEMPTIVE PHARMACOGENOMICS AT ST. JUDE CHILDREN'S RESEARCH HOSPITAL

St. Jude Children's Research Hospital established an institution-wide preemptive pharmacogenomics program through the PG4KDS protocol in May 2011 (68, 129). Patients and their families meet with a member of the hospital's Clinical Pharmacogenomics Service, who explains to them what pharmacogenomics is and have a consent discussion where they indicate whether they agree to have the child genotyped. As of October 2021, 95% of patients (6,171 out of 6,508) approached for consent have agreed to genotyping. Reasons for refusal of genotyping vary and include concern over extra blood collection, enrollment in too many clinical trials, distrust of DNA research, and privacy concerns. Genomic DNA is obtained from a blood sample, and genotyping is performed by RPRD Diagnostics using the PharmacoScan array from Thermo Fisher Scientific.

The results of 14 pharmacogenes are used to guide therapy using 66 drugs (**Figures 4** and **5**) for all patients who have been genotyped. Pharmacogenomic test results are displayed in a dedicated pharmacogenomics specialty flow-sheet tab and are presented independently of the date that the tests were performed. When pharmacogenomic test results are returned in the EHR system, a written consultation assigning a phenotype and explaining the implications of the result is generated and verified by a trained pharmacist (62). The consultation notes are a passive decision support tool and concisely convey useful information to clinicians who may not have deep knowledge of pharmacogenomics. The interpretive consultation language is also broad enough to be useful over time as new medications related to that gene are implemented. The genotype result and consultation note are viewable in the patient's online portal. For all patients with a high-risk diplotype, a member of the Clinical Pharmacogenomics Service also assesses the medications that the patient is receiving to address therapy changes that may be necessary based on the patient's pharmacogenomic profile.
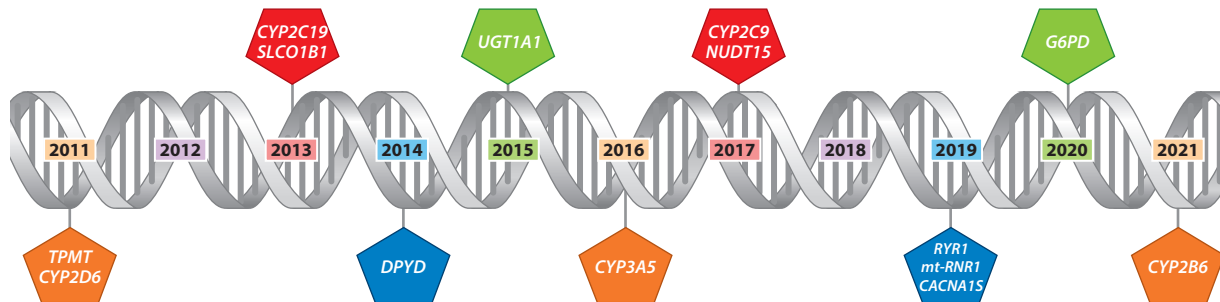
Figure 4

Example of a preemptive implementation timeline for pharmacogene testing, showing the rollout of gene test results over time in St. Jude Children's Research Hospital's PG4KDS study. All genes were interrogated starting in 2011 and were placed in the EHR system when at least one drug affected by that gene had a CDS alert recommendation for a change in pharmacotherapy. All gene–drug pair rollouts were approved by the hospital's Pharmacogenomics Oversight Committee. Abbreviations: CDS, clinical decision support; EHR, electronic health record.

When a patient is prescribed a high-risk medication and has a corresponding high-risk phenotype, structured and discrete data in the EHR facilitate presenting an interruptive CDS alert to the prescriber (13). The alert language is provided in a standard format that recommends a dosage change or selection of an alternative regimen and reminds the prescriber that more
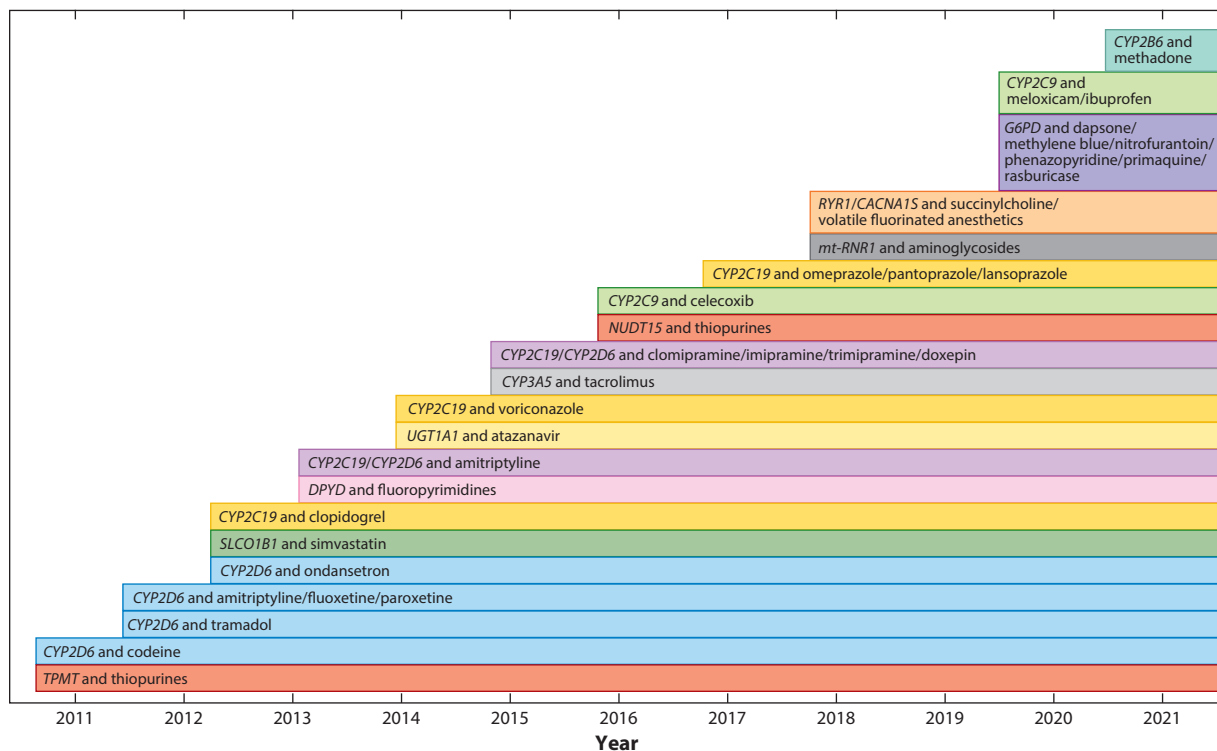
Figure 5

Genes and medications implemented at St. Jude Children's Research Hospital. Test results for some genes (e.g., *CYP2C19*; *yellow bars*) were implemented as early as 2013, but CDS for additional drugs was implemented over time for different drugs (clopidogrel in 2013, voriconazole in 2015, and proton pump inhibitors in 2017). Abbreviation: CDS, clinical decision support.

information is available in the EHR or by contacting a pharmacist (63). The clinician acceptance of the pharmacotherapy modification recommendation is greater than 90% for *CYP2D6*–codeine (50) and *TPMT*–thiopurines (13). As pharmacogenomic knowledge develops and evolves, some results require updating and reinterpretation (58). For example, prior to 2017, patients with a *CYP2C19* genotype of **1/*17* were assigned a CYP2C19 ultrarapid metabolizer phenotype. As new evidence emerged about the functional status of CYP2C19 enzymes in patients with this genotype, the phenotype assignment was changed to a rapid metabolizer phenotype. This update in phenotype assignment has implications for medication therapy recommendations; for example, initial dosing recommendations for omeprazole differ for a CYP2C19 rapid metabolizer compared with a CYP2C19 ultrarapid metabolizer (84).

The hospital's Pharmacogenomics Oversight Committee provides oversight of the activities of the Clinical Pharmacogenomics Service. This committee, chaired by the principal investigator of the PG4KDS protocol, meets at least quarterly and is structured as a subcommittee of the Pharmacy and Therapeutics Committee, which reports to the Medical Executive Committee. It includes clinician champions representing all major clinical services across the institution, informatics specialists, an external pathologist, and an external advisor who is an internationally recognized leader in the clinical implementation of pharmacogenomics. Beyond connecting pharmacogenomics implementation to medication use, the committee approves the priority of future gene–drug implementations and the wording, logic, and rules of active CDS alerts and rules.

Pharmacogenomics is established as a patient safety strategy at St. Jude. Consistent with the institutional approach to transparently share quality and patient safety data across the institution, pharmacogenomics is included as a quality indicator, and data are available to the entire institution. A primary metric is the proportion of thiopurine-naive patients diagnosed with acute lymphoblastic leukemia for whom both *TPMT* and *NUDT15* (as of April 2017) genotypes are placed in the EHR before thiopurine therapy is initiated (**Figure 6**). Approximately 22 new thiopurine-naive patients are started on thiopurine therapy each quarter at St. Jude. Our goal is that 100% of these patients will receive pharmacogenomics-guided dosing at the time thiopurine therapy is initiated. For rare cases of patients who did not have *TPMT* or *NUDT15* genotype results available before thiopurine was prescribed, we investigate the cause of the missed genotyping and implement improvement actions based on the findings. Examples of improvements made based on this ongoing data monitoring include adding an order for *TPMT/NUDT15* genotyping in the prebuilt order sets of all patients newly diagnosed with leukemia and changing the name of the test from thiopurine genotype to *TPMT/NUDT15* genotype, thereby allowing clinicians to more easily find the order. These data metrics are reported quarterly to the Pharmacogenomics Oversight Committee and incorporated into the hospital's medication safety dashboard.

ADVANCING PREEMPTIVE PHARMACOGENOMICS INTO PRACTICE

Examples of successful preemptive pharmacogenomics programs exist across practice settings, and some of these programs have been in place for over a decade (6, 18, 21, 26, 38, 40, 60, 65, 68, 87, 88, 91, 96, 97, 107, 117, 125–127, 131). Use of medications that are impacted by pharmacogenomic tests is common. Likewise, genetic variation that can result in adverse medication outcomes is common. The necessary technology—both testing and informatics—is well established. However, gaps in knowledge, incomplete reimbursement, the need for processes for reporting of preemptive results over time, and poor result portability across healthcare encounters are tangible barriers that need to be addressed in order to fully embrace a preemptive approach to pharmacogenomics. Continued standardization and use of established resources such as CPIC's can advance implementing preemptive pharmacogenomics (24). One barrier is that some clinicians and payers
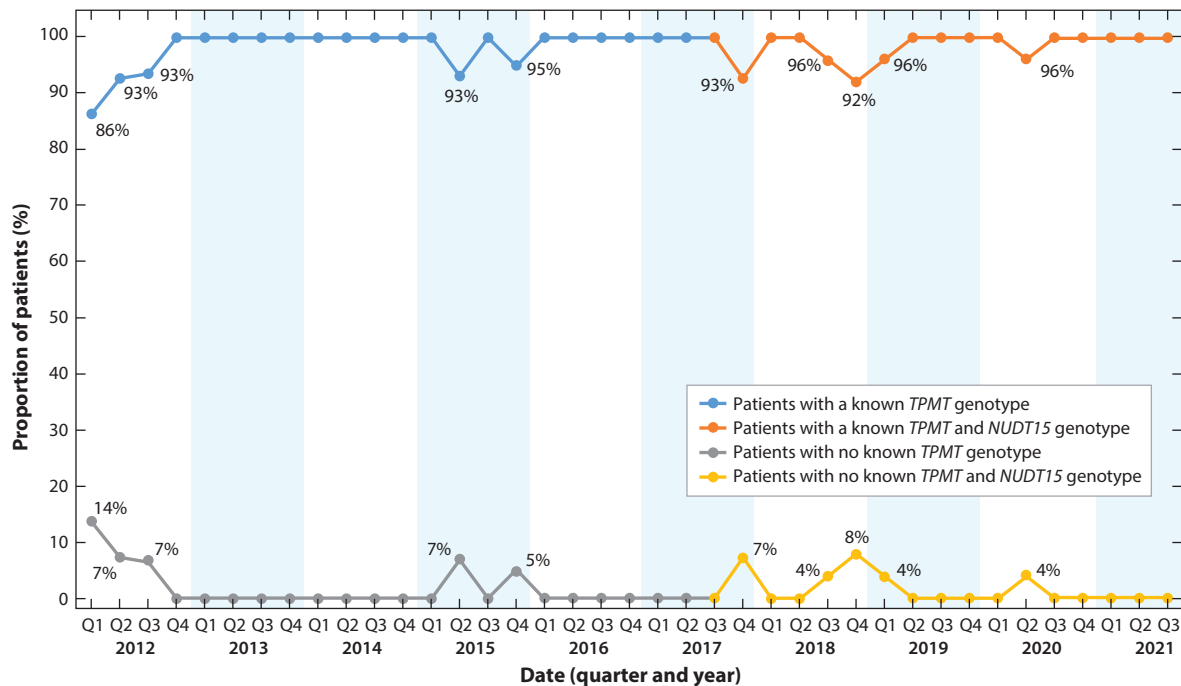
Figure 6

Percentage of thiopurine-naive patients diagnosed with acute lymphocytic leukemia who had a known *TPMT* and *NUDT15* genotype prior to initiating thiopurine therapy at St. Jude Children's Research Hospital, by quarter. *TPMT* genotyping was implemented prior to 2012; *NUDT15* genotyping was implemented in 2017. The goal quality metric is 100% for the top curve and 0% for the bottom curve. Approximately 22 patients per quarter were included in this metric.

consider some amount of trial and error to be an inevitable part of medication use, especially for less expensive medications (74). To embrace preemptive pharmacogenomics, this mind set must shift from accepting poor prescribing outcomes toward preventing harm and using all available information to select the right medication and dose for the patient from the first prescription.

DISCLOSURE STATEMENT

ACKNOWLEDGMENTS

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Contents

Errata

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