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Pharmacogenomics in the clinic

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Preface

After decades of discovery, inherited variation in approximately 20 genes affecting about 80 medications has been identified as actionable in the clinic. Additional somatically acquired genomic variants direct the choice of "targeted" anticancer drugs for individual patients. Current efforts that focus on the processes required to appropriately act on pharmacogenomic variability in the clinic are systematically moving pharmacogenomics from discovery to implementation as an evidenced-based strategy for improving the use of medications, thereby providing an important cornerstone for precision medicine.

Introduction

Pharmacogenomics focuses on the identification of genome variants that influence drug effects, typically via alterations in a drug's pharmacokinetics (i.e., absorption, distribution, metabolism, elimination) or via modulation of a drug's pharmacodynamics (e.g., modifying a drug's target or perturbing biological pathways that alter sensitivity to the drug's pharmacological effects). For diseases other than cancer and infectious diseases, the genome variations of interest are primarily in the germline DNA, either inherited from parents or *de novo* germline sequence changes that alter the function of gene products. In cancer, both inherited genome variations and somatically acquired genome variants can influence response to anticancer agents. For infectious diseases, genomic variation in the infectious agents themselves may alter their sensitivity to antimicrobials.[1] Advances in genome interrogation technology and in analytical approaches have facilitated evolution of the discovery paradigm from candidate gene studies to more agnostic genomewide analyses of populations of patients who have been characterized for specific drug response phenotypes (e.g., toxicity or desired pharmacologic effects). In fact, current technologies for genome sequence interrogation are sufficiently robust that rigorously defining the drug response phenotype has become the more difficult component of pharmacogenomics research. Once pharmacogenomic relationships have been discovered and validated, there are many obstacles to their translation into clinical practice. Such translation requires that effective alternative therapy is available for those with "high risk" genotypes, and requires

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Additional updated information from regulatory agencies can be found at:
http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
http://www.ema.europa.eu/ema/
http://www.pmda.go.jp/english/

improvements in health care systems, structured approaches to guide prescribing (e.g., algorithms), and implementation of point-of-care electronic clinical decision support (CDS) to make it feasible to appropriately utilize genetics to guide drug prescribing.

A decade ago, we laid out a vision of how evolving genome technologies could be deployed to facilitate pharmacogenomic discoveries,[2] and here we extend this to address how discoveries can best be translated into tools to optimize the use of medications in the clinic.

Review

Discovery research vs clinical implementation of pharmacogenomics---evolution to the clinic

The earliest origins of pharmacogenomics are unclear; perhaps it was in 510 BC when Pythagoras reported that a subset of people ingesting fava beans experienced potentially fatal hemolytic anemia, whereas others did not (Figure 1). Centuries later this was shown to be due to an inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD), which also predisposes to hemolysis from rasburicase and the antimalarial primaquine.[3] In 1909, studying another bean (Phaseolus vulgaris), Danish pharmacist Wilhelm Johannsen coined the terms genotype and phenotype, linking genotype to the effects of volatile organics, a presage to pharmacogenetics. A clustering of drug metabolizing enzyme activities by racial groups strongly suggested a genetic component to population variation.[4,5]

In 1959, Friedrich Vogel first coined the term “pharmacogenetics,”[6] a concept bolstered by landmark studies of Elliott Vesell and George Page showing that the pharmacokinetics of antipyrine were much more similar in monozygotic twins than in dizygotic twins.[7] The clinical relevance of pharmacogenetics was reinforced when family studies indicated that racial differences in isoniazid metabolism and its side effect of peripheral neuritis were inherited as an autosomal recessive trait.[8,9] Decades later the genetic polymorphism in isoniazid acetylation was shown to be caused by inherited variants in the gene encoding N-acetyltransferase 2 (*NAT2*).[10,11]

Additional family studies in the 1960s–1980s documented the pattern of inheritance for many drug effects, which eventually led to molecular genetic studies that revealed the inherited determinants for many of these traits, with *CYP2D6* being the first polymorphic human drug metabolizing gene to be cloned and characterized in 1987.[12] In the 1990s, the potential clinical utility of pharmacogenomics was clearly illustrated for several genes,[13,14] including the inherited deficiency of thiopurine-methyltransferase and hematopoietic toxicity from mercaptopurine and azathioprine[15] although implementation in the clinic progressed slowly at that time.[16]

Like most areas of genetics research, pharmacogenetic discoveries were accelerated by the human genome project and by advances in technologies for genome-wide interrogation of genetic variation. This shortened the timeline for discovery and enabled agnostic genome-wide studies of populations of patients who had been phenotyped for specific drug effects (treatment efficacy or toxicity), often leading to the identification of unanticipated genetic

variants that were statistically associated with drug effects. These genomewide strategies helped introduce "pharmacogenomics" into the lexicon.[17]

Discoveries emerging from genome-wide or candidate gene strategies require independent validation before their translation into clinical diagnostics, and this can be facilitated by elucidation of the underlying mechanism(s) by which genome variation alters drug response. Because genetic variants often differ according to ancestry, this can confound the translation of pharmacogenetic traits from one population to another, as recently exemplified by genetic polymorphisms in *CYP2C9* and *VKORC1* and their population-specific influence on warfarin's anticoagulant effects.[18] Furthermore, it is becoming increasingly evident that many drug effects are influenced by multiple variants in the same gene (some of which are rare) and/or by variants in multiple genes within the same patient. The UK's 100,000 Genomes Project and the US NIH's Pharmacogenomics Research Network are two of many ongoing efforts to facilitate genome discoveries and their translation into new diagnostics that may eventually be used to optimize the selection and dosing of medications in individual patients. Discovery and translation of inherited determinants of drug response and somatically acquired genome variants in cancer are prominent pharmacogenomic components of these and other initiatives.

Criteria for implementing diagnostic tests in the clinic; clinical implementation of pharmacogenomics compared to other genomic tests

It is widely stated that in order for a test to be used in clinical care, it must meet criteria of analytic validity, clinical validity, and clinical utility.[19] Several pharmacogenes are not trivial in terms of developing tests with analytic validity.[20] Clinical utility involves assessing whether the use of the test leads to improved health outcomes for patients who are subject to testing, and an assessment of the risks that occur as a result of testing. However, there is substantial heterogeneity as to precisely what outcome measures constitute clinical utility.[21,22] Some have broadened such assessments to go beyond the clinical utility for the tested individuals to include an assessment of the impact of broader use of testing on the entire health care system, including weighing the costs of genetic testing versus the costs of other health care interventions, and unintended consequences on behavior of clinicians. For example, the introduction of a pharmacogenetic screening policy in Hong Kong to test for the *HLA-B*1502* allele prior to prescribing antiepileptic drugs (to avoid use of carbamazepine in those at high risk for severe skin reactions) had the unintended consequence of clinicians foregoing prescribing carbamazepine at all and instead prescribing phenytoin. Because phenytoin can also cause severe skin reactions, but the risk factors are not as well defined, the overall incidence of severe skin reactions remained unchanged after implementing the *HLA-B*-specific screening policy.[23] For purposes of this review, we focus on the clinical utility of pharmacogenomic testing for individual patients, without consideration of possible untoward public health consequences based on unintended (and often unnecessary) changes in clinician prescribing behaviors.

With the continuing decline in cost of sequencing, many have predicted that in the not-too-distant future, every individual will have their entire inherited genome sequenced early in life, with the results available for clinical use throughout a lifetime of health care. Assuming

that this will be true (at least to some extent), we have called for a shift away from debating whether specific pharmacogenes should be tested prior to using specific drugs, and toward a model in which clinicians are provided with guidelines on how genomic variants should be interpreted and deployed to improve prescribing. This assumption underlies the efforts of the Clinical Pharmacogenetics Implementation Consortium (CPIC),[24,25] an open international group that creates standardized, evidence-based, peer-reviewed, publicly available, nonprofit gene/drug guidelines for how to use genomic data to inform prescribing.

The decision as to whether each set of pharmacogenomic results has the necessary evidence to support analytic validity, clinical validity, and clinical utility to warrant use in prescribing depends on many factors.[21] Analytic validity will depend on the quality of the data from genetic tests, and on performance characteristics such as positive and negative predictive value. Many types of data can be used to evaluate clinical validity and utility, including the penetrance of genetic variation on drug effects based on retrospective studies, the mechanism(s) by which genetic variation influences drug effects or a relevant endophenotype (such as drug metabolizing enzyme activity), *in vivo* pharmacokinetic or other functional studies, *in vitro* functional studies, pre-clinical and clinical studies linking pharmacologic effects or drug concentrations to genomic variation, case reports, family studies, and randomized clinical trials comparing outcomes of genetically-based prescribing versus “standard of care.” Other factors that are considered in deciding on the actionability of pharmacogenomic variation include the therapeutic index of a drug, the severity of drug toxicity, the severity of the underlying disease, and the consequences of suboptimal prescribing.

A key consideration for actionability of a gene/drug relationship is based on the availability of and evidence for alternative therapy, and may partly depend upon the mechanism of the gene/drug association. If the gene is affecting the drug by virtue of affecting active drug pharmacokinetics (e.g. *CYP3A5* catabolism of tacrolimus), there may be substantial literature supporting a dose adjustment based on extrapolation of pharmacokinetic effects, analogous to decisions often made in the clinic based on altered renal function, liver function, or age. Such dose adjustment decisions are particularly defensible if the drug is one for which therapeutic drug monitoring (based on measures of drug concentration in blood) is readily available. If genetic tests indicate that a particular drug is not effective in those with the high-risk genotype (e.g. those homozygous for inactive *CYP2D6* alleles cannot anabolize codeine to its active metabolite, morphine), then the recommendation for alternative therapy will be dependent upon weighing the evidence for both the efficacy and possible toxicity of an alternative medication; for codeine, there are generally several alternative opiate analgesics available with reasonable data on doses likely to achieve comparable analgesia.[26] If genetic tests indicate an extremely high risk for a serious adverse event (e.g. carriers of the *HLA-B*57:01* allele have a high risk of hypersensitivity to abacavir),[27,28] the alternative therapy would ideally be equally effective with an acceptable risk of adverse effects (which may or may not be influenced by other genetic variants).

Some treatment efficacy decisions are not all-or-none, but rather are based on a range of probabilities: for example, there are substantial data that efficacy against breast cancer recurrence is reduced in patients who have inherited two defective *CYP2D6* alleles, as they

have much lower levels of the active metabolite endoxifen than the majority of the population,[29–34] but whether the best alternative therapy is a different drug (e.g. a different selective estrogen receptor modulator) or an altered dose of tamoxifen is not clear, particularly in premenopausal women for whom there are a dearth of data supporting alternatives. These cases are the most difficult: it is clear from pharmacogenomics that the drug or drug dose is not optimal in a patient with the high-risk genotype compared to the majority of the population, but a lack of clinical data for alternative therapies makes it difficult or impossible to recommend alternative medications.

CPIC considers all such evidence in prioritizing which gene/drug pairs are clinically actionable. Given the high bar required for clinical actionability, the number of actionable inherited genes (those that have at least one actionable "high risk" diplotype) and the list of medications for which clinical actions can be recommended (pharmacogenetically "high risk" drugs) is relatively short (Table 1). We acknowledge that there are additional medications for which regulatory agencies include pharmacogenomic information in their labels;[35–37] however, not all such mentions are actionable. Information on genetic variation is sometimes included even when the effects are modest (and therefore don't translate into changes in the prescribing sections of the drug label), and have been included for some drugs when the evidence is weak or conflicting.

One item to note: there are currently very few examples of actionable pharmacogenes that also carry a disease risk. The only examples thus far are *UGTIA1* and Gilbert's disease,[38] and *G6PD* and hemolytic anemia.[39] Thus, many of the ethical concerns affecting clinical implementation of "disease risk" genomics have less relevance for pharmacogenomics.[40]

Critical issues for clinical implementation of pharmacogenomics

Drugs and genes—There are more than 1200 individual molecular entities approved as drugs by regulatory agencies in the US, Europe and Asia (i.e., FDA[41], -EU-EMA[35] and PMDA.[37] Although about 15% of EU-EMA and US-FDA approved medications contain pharmacogenomic information in their label[35] http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm), only a subset of these are deemed actionable. As summarized in Figure 2, the use of only about7% of medications have actionable germline pharmacogenetics (https://www.pharmgkb.org/cpic/pairs, corresponding to CPIC level A and level B genes/drugs---corresponding to actionable prescribing recommendations). Interestingly, in the US, these medications constitute ~18% of all prescriptions, indicating that there is a slight overrepresentation of pharmacogenomically high-risk medications among highly-prescribed medications (Figure 2).[42] Thus far, only 17 of ~ 18,000 human genes are considered clinically actionable for germline pharmacogenomics (https://www.pharmgkb.org/cpic/pairs). Not only is most human germline genetic variation unlikely to be actionable for medication prescribing, pharmacogenomics is unlikely to be useful for improving prescribing for the majority of drugs. However, for that relatively small set of medications for which genomics is actionable, prescribing could be improved and outcomes optimized if genetic testing were more widely and appropriately deployed clinically. And the number of such actionable gene drug pairs continues to grow, albeit at a relatively slow pace.

Somatically acquired genomic variation—A special case of pharmacogenomics applies to somatically acquired genomic variants that are specific to cancer tissue. In some cancer types, somatic genomic variations can guide the choice of anticancer agents, by virtue of identifying which malignancies are more or less likely to respond to specific anticancer agents.[43,44] The recognition that cancer tissue can be distinguished from normal host tissue by the presence of specific genomic abnormalities predates the human genome project, with early examples of genomic abnormalities such as unfavorable ploidy in neuroblastoma,[45] and cytogenetic abnormalities in acute lymphoblastic leukemia,[46] being used to determine the composition and aggressiveness of cytotoxic chemotherapy. In more recent years, the genetic testing of malignancies has become more specific, as several anticancer agents have been developed that are directed against or proven to be much more effective for tumors that harbor specific acquired genetic variants (Table 2). The US FDA has generally approved companion diagnostics concomitantly with new targeted anticancer agents, whereas the EU EMA requirements have been somewhat less stringent[47], but proposed changes in the EU framework would lead to greater harmonization.[48]

Single gene vs multi-gene panels; reactive vs pre-emptive genomic testing— Strong "monogenic" gene/drug associations, coupled with limitations in genotyping technology, led to the initial clinical practice of using single-gene pharmacogenetic tests,[49] as has been true for all of genetic testing. In this model, genetic tests are ordered one at a time on an "as needed" or reactive basis: the patient is likely to need a pharmacogenetically high-risk drug, and so the clinician orders the applicable genetic test. However, with improvements in technology, it is possible to interrogate multiple genes in a single assay, for far less expense than was formerly the case for single gene tests.

Most human diseases, including cancer, are influenced by multiple genes and genetic variants. Likewise, the pharmacokinetics and pharmacological effects of most medications are determined by multiple gene products (e.g., genes encoding drug metabolizing enzymes, transporters, targets, and disease modifying genes). Many of the pharmacogenes that have been identified to date are genes that have a strong effect on a drug's pharmacokinetics and/or pharmacodynamics (i.e., they represent the "low hanging fruit"). The genetic polymorphism in thiopurine methyltransferase (*TPMT*) and its strong effects on the risk of hematopoietic toxicity from thiopurine medications (e.g., mercaptopurine, azathioprine) nicely illustrates how such "low hanging fruit" are often merely the first step down a polygenic path. For example, it was found that after one adjusts the dosage of mercaptopurine based on *TPMT* genetic test results, then genetic polymorphisms in other genes surface as important (e.g., *ITPA*).[50] Furthermore, genetic polymorphisms in others genes along the same pharmacological pathway can emerge as important in populations of a different ancestry, as illustrated by the strong influence of an inherited variant in *NUDT15* on thiopurine toxicity. *NUDT15* variants are extremely uncommon in persons of European and African ancestry, but are relatively common among people of Asian ancestry,[51] explaining the relatively high frequency of thiopurine intolerance in Asians despite a relatively low frequency of *TPMT* variants. When a GWAS of thiopurine intolerance was eventually performed in a diverse population comprising people of European, Asian, African and Native American ancestry, both *TPMT* and *NUDT15* reached genomewide

significance,[52] revealing that *TPMT* variants were the major determinant of tolerated dose in patients of European and African ancestry, whereas *NUDT15* was the major genetic determinant in patients of Asian and Native American ancestry. Because the metabolism and effects of anticancer agents, including thiopurines, can be affected by both germline and somatic genome variation[53], this can further increase the complexity of cancer pharmacogenomics.

There are several other examples for which more than one gene is clinically actionable for a given medication, such as the anticoagulant warfarin (affected by both *CYP2C9* and *VKORC1*)[18] and tricyclic antidepressants (affected by both *CYP2C19* and *CYP2D6*). Given that one gene can affect multiple medications (Table 1), there are potential benefits of genotyping a panel of pharmacogenomic variants that may be applicable for multiple drugs that could be given throughout a patient's lifetime. For pharmacogenetic testing as for all of genetic testing, there is increasing evidence that genotyping multiple genes in a single test is more cost effective, makes better use of DNA, and allows for pre-emptive availability of genetic test information. Such multigene panels can change practice from a "reactive" approach (order a new genetic test every time in the patient's life that the results are deemed to be of interest) to a pre-emptive approach (test for likely-to-be actionable genes in a single sample, thereby providing a lifetime's worth of test results). Several groups have begun implementing such pre-emptive multigene panels for pharmacogenomics,[54–58] but the practice is by no means widespread at the present time.

Barriers to and resources for clinical implementation of pharmacogenomics— What is preventing the widespread use of pre-emptive multi-gene panels to guide drug prescribing? One barrier is the lack of incentives for health care systems to conduct tests or implement procedures to prevent adverse events in the future. There are relatively few studies proving the cost-effectiveness of pharmacogenetic testing,[59] and although a multi-gene panel approach is of course less expensive than ordering tests for one pharmacogene at a time, there are no data assessing the cost-effectiveness of a panel approach implemented early in life and usable for a patient's lifetime. Many health care systems do not provide financial reimbursement for preventive medicine services or for pre-emptive screening services, and thereby create a barrier to pharmacogenetic testing in the clinic.[60,61]

Layered onto the costs of the laboratory test of genome interrogation itself are the costs and complexity of computational approaches to identify, catalog, prioritize, and interpret genome variants that influence prescribing decisions. Even with a growing number of publicly availability computational tools to analyze genome variation, this process continues to evolve and generally requires a substantial level of expertise and manual interpretation to use successfully in the clinic. Computational tools for clinical decision support (CDS) will be required to prompt and guide clinicians to use genetic information when prescribing affected drugs, triggered by patient-specific alerts.[42,62,63] The costs associated with pharmacogenomics in clinical practice is quickly shifting from the cost of the laboratory test to the costs associated with linking genetic test results with evidence-based decisions that will robustly guide prescribing, and will be routinely updated as new evidence emerges. Again, with many healthcare systems, it is not clear who will take responsibility for ongoing updates of interpretations, and who will pay for such interpretations.

Another barrier to clinical uptake of pharmacogenomic testing is that there has been a lack of clear clinical guidelines for translating genomic variation into actionable recommendations, and there is sometimes disagreement among professional societies or other guideline generating groups on whether and how to proceed with pharmacogenetic testing. Examples for which there has been disagreement include testing for warfarin[64] and for clopidogrel[65], with a common reason for lack of support for genetic testing being the paucity of randomized prospective controlled trials comparing genetically guided testing vs conventional therapy, Also, many professional societies and guideline-generating groups have approached evaluations of pharmacogenomic tests from the standpoint of whether the clinician is obligated to order the genetic test.[49,64–66] However, with inexpensive multi-gene tests becoming increasingly available, the question is shifting from whether to order a genetic test, to how the genetic test results "already" generated can and should be used for prescribing decisions. For inherited genomic variation, CPIC has taken on the task of creating such guidelines that focus on how genetic test results should be translated into specific prescribing actions. A similar approach was taken by the Royal Dutch Association for the Advancement of Pharmacy.[67,68] Multiple resources exist to help guide cancer drug selection based on somatically acquired genomic variation (Table 2), although these are constantly changing based on new evidence.[69–72]

With more widespread deep sequencing, additional variants will be discovered in pharmacogenes.[73] As for other areas of clinical genetics, it will be challenging to catalog and annotate the additional novel variants. Given the importance of novel rare variants to both inherited [23] and cancer-related pharmacogenes, publicly available and easily updatable resources such as PharmGKB, ClinGen and ClinVar will be critical to feed into computational CDS in health care record systems to provide up-to-date recommendations based on genomic test results.[74–76] Currently, heterogeneity among genomic variation databases and among health care record systems, coupled with lack of common ontology for genomic test results and interpretations, limit interoperability and are hindering the use of pharmacogenetic test results longitudinally as well as across all of the health care systems each patient must navigate. Several groups are working to standardize pharmacogenetic test terminologies,[77–82] with an eye toward creating terminology that can drive CDS across health care record systems. Initiatives such as the Institute of Medicine Roundtable on Translating Genomic-Based Research for Health and CPIC are working to create terms and language that can be directly uploaded into electronic health care records' CDS, but heterogeneity across systems will at least initially slow creation and uptake of CDS to facilitate use of pharmacogenetic information.[81]

Additional barriers include the insatiable desire for more evidence, the lack of education amongst clinicians, the paucity of evidence-based implementation systems, and concerns about incidental or secondary findings from genetic testing, not to mention inertia for change in health care systems.[66,83–86] These barriers are not unique to pharmacogenomics, and the energy to overcome them will likely come from multiple sources, ranging from the "push" of patient advocates to the "pull" of courtrooms. For example, an advocate for pediatric patients expressed a disquieting lay perspective; "I am mystified by the resistance to a simple blood test that might save children's lives,"[16] As the general public becomes more aware of the potential of genetic tests to improve medication use, including direct-to-

consumer testing,[87,88] it is possible that their advocacy will grow even stronger. Meanwhile, the attorney general in Hawaii brought a lawsuit against the manufacturer of the anti-platelet drug clopidogrel because they marketed their drug in Hawaii without warning that a high percentage of the Hawaiian population has inherited low-function alleles of *CYP2C19*, which encodes the enzyme required to convert clopidogrel to its active metabolite.[89] This legal case asserts that it was known *a prior*i that *CYP2C19* variant allele frequencies are higher in East Asians and Pacific Islanders, which comprise about 40% and 10% of the Hawaiian population, respectively, and there was abundant evidence that the antithrombotic effects of clopidogrel are diminished in patients with low CYP2C19 activity (predisposing to an increased incidence of cardiovascular events such as stent thrombosis).[90,91] From an educational perspective, there are multiple accrediting agencies that are calling for pharmacogenomics to be part of curricula for health care students, trainees, and advanced practitioners,[92] and the availability of educational tools continues to grow.[93–95] Although the early adopters of clinical pharmacogenomics are establishing methods to advance treatment, broad clinical implementation remains elusive.

Organized efforts to facilitate clinical use of pharmacogenomics—Many groups are working worldwide to share resources to facilitate clinical implementation of germline pharmacogenetic tests.[96] The European Pharmacogenetics Implementation Consortium (http://www.eu-pic.net/) is an international consortium whose goal is to improve therapy by integrating pharmacogenetic information into clinical care.[97] Efforts to facilitate implementation have also been undertaken by the Royal Dutch Association for the Advancement of Pharmacy.[67,68] In the US, members of NIH's Pharmacogenomics Research Network organized a Translational Pharmacogenetics Project,[54–58,98–100] which is dedicated to sharing best practices for clinical implementation of CPIC pharmacogenomics guidelines, and the eMERGE and IGNITE networks are testing pharmacogenetic implementation strategies.[85,101,102] In Thailand and Singapore, where the *HLA-B*15:02* variant is common and strongly predisposes to severe skin toxicity after specific drugs, pharmacogenetic testing is common.[103–105] The Genomic Medicine Alliance (http://www.genomicmedicinealliance.org/)[106] facilitates the clinical use of pharmacogenomics and has created a database linking drugs with genes.[107] Population admixture in diverse populations must also be considered in global efforts for clinical implementation. [108]

Future directions

Clinicians are accustomed to making prescribing decisions based on patient characteristics such as age, renal function, liver function, drug/drug interactions, and patient preferences. Much of this prescribing, however, is taking place without optimal clinical decision support to assist in compiling those characteristics and matching them with evidenced-based choices on medications and their doses. As CDS improves and becomes more widespread, and as the evidenced supporting pharmacogenomic testing continues to grow, the momentum for clinical implementation of pharmacogenomics should accelerate. Going forward, there is a growing body of evidence that pharmacogenomics will be an expanding component of evidence-based precision medicine.

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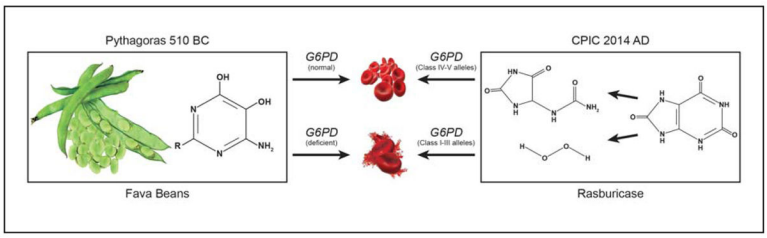

Figure 1.

Pythagoras is thought to have banned the consumption of fava beans (vicia fava) after observing that their ingestion caused hemolytic anemia in a subset of people (left). This was subsequently shown to occur predominantly in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, primarily persons who inherited the Class II "Mediterranean allele" of G6PD. The chemical moieties in fava beans thought to cause hemolysis in G6PD-deficient individuals are isouramil (R=OH) and divicine (R=NH_2), pyrimidine aglycones of two glucosides found in fava beans. (vicine and convicine). Multiple medications also cause oxidative stress and erythrocytes of G6PD deficient individuals produce insufficient NADPH to protect from oxidative damage, and hemolysis and methemoglobinemia can ensue.[39] Rasburicase is a recombinant form of urate oxidase that is used clinically to lower uric acid levels in the treatment of tumor lysis syndrome (right). The oxidative stress caused by hydrogen peroxide produced when rasburicase cleaves uric acid to allantoin and hydroperoxide is more likely to cause hemolytic anemia and methemoglobinemia in persons who have inherited G6PD deficiency; rasburicase is contraindicated in G6PD deficient individuals.[109]

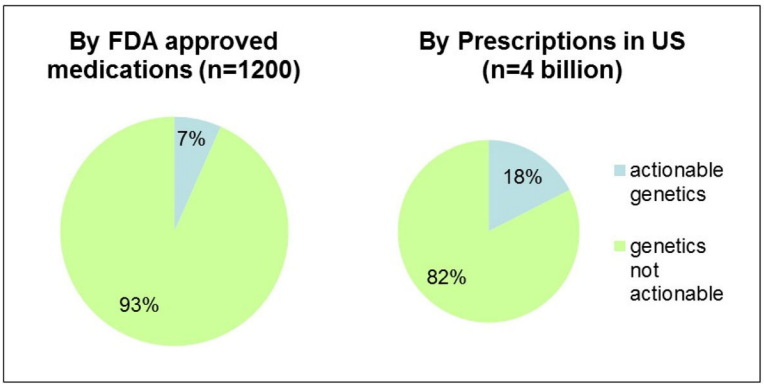

Figure 2.

Approximately 7% percentage of medications (FDA approved) are affected by actionable inherited pharmacogenes (right), whereas approximately 18% of outpatient prescriptions in the US are affected by actionable germline pharmacogenomics (left),[42] illustrating that several pharmacogenetically high-risk drugs are commonly prescribed.

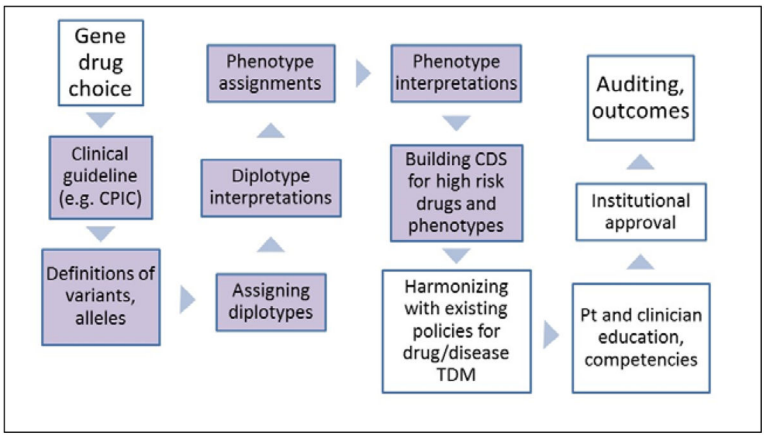

Figure 3.

Multiple steps in bringing pharmacogenomic tests to the clinic. These include prioritizing the choice of gene(s)/drug(s) for actionability; CPIC guidelines exist or are being developed for all actionable inherited pharmacogenes,[24] and the guidelines provide guidance for the steps shaded in lavender. Genotypes must be assigned to alleles, and diplotypes assigned to patients. The diplotypes must be translated into phenotypes (gene function) and interpreted with respect to drug therapy. Appropriate clinical decision support (CDS) should be built and deployed to provide prescribers with recommendations, and pharmacogenetic considerations must be harmonized with other policies for the affected medications, using therapeutic drug monitoring (TDM) where applicable. Education of clinicians and of patients should take place, and institutional oversight committees may approve prescribing recommendations and policies. Many groups are auditing clinical and prescribing outcomes to evaluate the impact of clinical implementation of pharmacogenomics.

Table 1

Actionable germline genetic variation and associated medications

Genetic Variation	Medication
TPMT	mercaptopurine, thioguanine, azathioprine
CYP2D6	codeine, tramadol, tricyclic antidepressants
CYP2C19	tricyclic antidepressants, clopidogrel, voriconazole
VKORC1	Warfarin
CYP2C9	warfarin, phenytoin
HLA-B	allopurinol, carbamazepine, abacavir, phenytoin
CFTR	Ivacaftor
DPYD	fluorouracil, capecitabine, tegafur
G6PD	rasburicase
UGT1A1	irinotecan, atazanavir
SLCO1B1	simvastatin
IFNL3 (IL28B)	interferon
CYP3A5	tacrolimus

From https://www.pharmgkb.org/cpic/pairs (accessed May 7, 2015)

Table 2

Actionable somatic genome variants in cancer cells and associated medications[1]

Genetic Abnormality[2]	HGVS Nomenclature[3]	Target[4]	Medications	Disease[5]
AKT Mut (Act)	p.Glu17Lys	mTOR	sirolimus, everolimus	RCC
BCR-ABL (SV)	t(9;22) (q34.1;q11.21)	ABL	imatinib, dasatinib	CML, Ph+ ALL
BCR-ABL (SV + Mut)	p.Val299Leu	ABL	bosutinib, nilotinib	imatinib resistant CML
BCR-ABL (T135I)	p.Thr135Ile	ABL	ponatinib	CML, Ph+ ALL
BCR-ABL (SV)	t(9;22) (q34.1;q11.21)	SRC	dasatinib	CML, Ph+ ALL
BRCA1/2 variants	too numerous to list	PARP	olaparib	ovarian
BRAF SNVs (V600E/K)	p.Val600Glu, p.Val600Lys, p.Val600Asp	BRAF	dabrafenib, vemurafenib	melanoma
BRAF SNVs (V600)	p.Val600Glu, p.Val600Lys, p.Val600Asp	MEK	trametinib	melanoma
EGFR (Ex 19 del., SNV L858R)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	afatinib, erlotinib	NSCLC (EGRF$^+$)
EGFR Mut (Act, Amp)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	gefitinib	NSCLC (EGRF$^+$)
EGFR$^+$ & WT *KRAS*	NA	EGFR	cetuximab, panitumumab	EGRF$^+$ colon (WT *KRAS*)
EML-ALK (SV)	inv(2)(p21p23)	ALK	crizotinib	NSCLC
FLT3 CNV (Amp)	p.D600_L601insFREYEYD, p.Asp835Tyr	FTL3	sunitinib, sorafenib	AML
HER2 (Amp)	NA	ERBB2	lapatinib, trastuzumab	HER2+ breast
KIT (Act Mut)	p.Trp557_Lys558del, p.Asp579del, p.Val559Asp	KIT	imatinib, sunitinib	RCC, GIST
PDGFR (Mut, SV)	p.Asp842Val	PDGFR	sunitinib, imatinib	RCC, GIST, pancreas
PI3K (Mut, Amp)	PIK3CA p.Glu542Lys, p.Glu545Lys; p.His1047Arg, p.His1047Leu	PI3K	idelalisib	CLL, NHL
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	tretinoin, alitretinoin	APL CTCL, Kaposi
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	arsenic trioxide	APL
SMO (Mut, Act)	p.Trp535Leu, p.Arg199Trp, p.Arg562Gln	Smoothen	vismodegib	basal cell
VHL (Mut)	too numerous to list	VEGFR	sorafenib	RCC, hepatic, thyroid
VEGF (Mut)	NA	VEGF	ziv-aflibercept	colon

[1]Medications targeting normal cell surface proteins that are expressed on some tumor cells (e.g., ER, PR, CD20, CD30, CD52) are not included in this summary of drugs targeting proteins with aberrant expression or function due to somatic genome variants.

[2]Act= activating; Amp= amplification, typically by CNV; CNV=copy number variant; Epigen= epigenetic; Mut=mutation; NA = not applicable; SNV= single nucleotide variant; SV= structural variant.

[3]Only representative examples of known mutations are shown.

[4]Targets are generally protein products encoded by the gene listed.

[5]ALCL= anaplastic large cell lymphoma; ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; CLL=chronic myeloid leukemia, CML= chronic myeloid leukemia; CTCL= cutaneous T-cell lymphoma; Ex= exon; GIST= gastrointestinal stromal tumor; NHL= non-Hodgkins lymphoma; NSCLC= non-small cell lung cancer; RCC= renal cell carcinoma.