REVIEW

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Pharmacogenomics in the clinic

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After decades of discovery, inherited variations have been identified in approximately 20 genes that affect about 80 medications and are actionable in the clinic. And some somatically acquired genetic 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 moving away from discovery and towards implementation of an evidenced-based strategy for improving the use of medications, thereby providing a cornerstone for precision medicine.

Pharmacogenomics focuses on the identification of genetic variants that influence drug effects, typically through alterations in pharmacokinetics — that is, how the drug is absorbed, distributed, metabolized or eliminated — or pharmacodynamics, by modifying its target or by perturbing the biological pathways that shape a patient's sensitivity to its pharmacological effects. In conditions apart from cancer and infectious diseases, the genetic variations of interest are primarily in germline DNA, and are inherited from a parent or are *de novo* changes that alter the function of gene products. In cancer, both inherited and somatically acquired variants can influence a patient's response to treatments. In infectious diseases, genetic variation can affect a pathogen's sensitivity to antimicrobial drugs[1]. Advances in genome interrogation technology and in analytical approaches have facilitated the evolution of a discovery model from candidate gene studies towards agnostic genome-wide analyses of patient populations with specific drug-response phenotypes — for example, toxicity or desired pharmacological effects. In fact, current technologies for genome interrogation are sufficiently robust that defining the drug-response phenotype has become the more difficult component of pharmacogenomics research. Once a pharmacogenomic relationship has been discovered and validated, there are many obstacles to translating it into clinical practice. Such translation requires that effective, alternative therapy is available for those with 'high-risk' genotypes, as well as improvements to healthcare systems, structured approaches to guide prescribing (for example, algorithms), and implementation of point-of-care electronic clinical decision support (CDS), to make it feasible to utilize genetics appropriately 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 in this Review, we extend this vision to address how these relationships can be translated into tools to optimize the use of medications in the clinic.

Evolution of pharmacogenomics

The earliest origins of pharmacogenomics are unclear; in 510 BC the Greek philosopher and mathematician Pythagoras reported that a subset of people who ingested broad beans (*Vicia faba*) experienced potentially fatal haemolytic anaemia (Fig. 1). Over two thousand years later, this reaction was attributed to an inherited deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD), which also predisposes patients to haemolysis from several medications, including rasburicase and the antimalarial primaquine[3]. In 1909, while studying the common bean *Phaseolus vulgaris*, the Danish pharmacist Wilhelm Johannsen coined the terms genotype and phenotype, linking genotype to the effects of volatile organics, a presage to pharmacogenetics[4]. A clustering of drug-metabolizing enzyme activities by racial group strongly suggested a genetic component to population variation[5,6].

In 1959, the German geneticist Friedrich Vogel was the first to use the term 'pharmacogenetics'[7], a concept that was bolstered by landmark studies by the pharmacologists Elliott Vesell and John G. Page showing that the pharmacokinetic profile of the pain-relieving drug antipyrine is more similar in monozygotic twins than in dizygotic twins[8]. The clinical relevance of the field was reinforced when family studies in different racial groups indicated that differences in the metabolism of isoniazid — a treatment for tuberculosis — and its side effect, peripheral neuritis, were inherited as an autosomal recessive trait[9,10]. Decades later, differences in the metabolism of isoniazid were shown to be caused by inherited variants in the *NAT2* gene, which encodes the *N*-acetyltransferase 2 enzyme[11,12].

Other family studies conducted between the 1960s and 1980s documented patterns of inheritance for many drug effects, which eventually led to molecular studies that revealed the inherited determinants for many of the traits. In 1987, *CYP2D6* became the first polymorphic human drug-metabolizing gene to be cloned and characterized[13]. In the 1990s, the potential clinical utility of pharmacogenomics was clearly illustrated for several genes[14,15], including *TPMT*, which encodes the enzyme thiopurine methyltransferase. People with an inherited deficiency in this enzyme were found to experience haematopoietic toxicity on administration of the antileukaemic and immunosuppressive thiopurine drugs mercaptopurine and azathioprine[16], although implementation of this finding in the clinic progressed slowly at that time[17].

As in most areas of genetics, the rate of pharmacogenetic discovery has been accelerated by the Human Genome Project and by improved technologies for the genome-wide interrogation of variation. This shortened the timeline for discovery and enabled agnostic genome-wide studies of populations of patients with specific drug-effect phenotypes, often leading to the identification of unanticipated genetic variants that were statistically associated with drug effects. These genome-wide strategies also helped to bring the term 'pharmacogenomics' into the pharmacology lexicon[18].

Discoveries that emerge from genome-wide or candidate-gene strategies require independent validation before they can be translated into clinical diagnostics. The validation process can be facilitated by elucidating the mechanisms that determine how the variation alters drug

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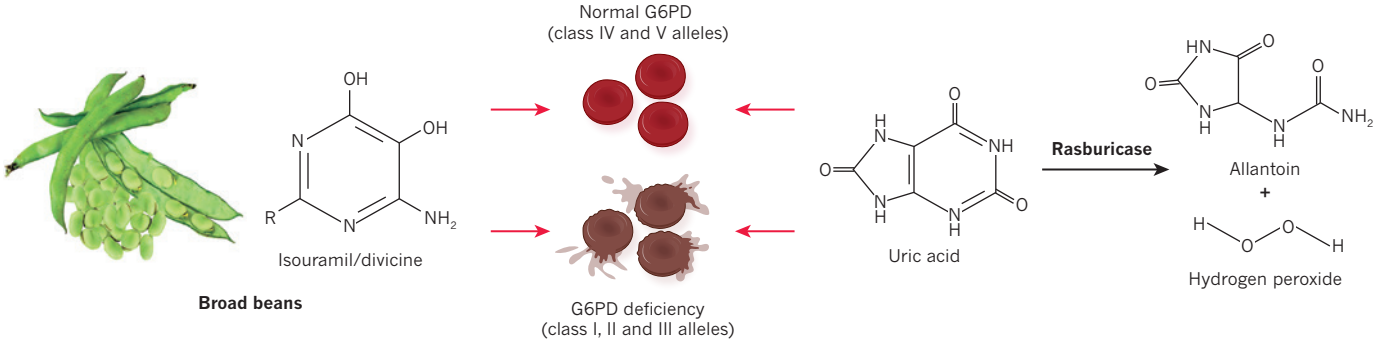

Figure 1 | Inherited G6PD deficiency and haemolysis. People with a deficiency in the enzyme glucose-6-dehydrogenase (G6PD) can develop haemolytic anaemia after eating broad beans (left) or when taking the drug rasburicase (right). In the case of broad beans, the reaction is the result of the chemical moieties isouramil (R = OH) and divicine (R = NH_2), and for rasburicase it is the hydrogen-peroxide product of the breakdown of uric acid. Red blood cells of G6PD-deficient individuals — primarily those with the class II 'Mediterranean' allele of *G6PD* — produce insufficient NADPH to protect from oxidative damage caused by these moieties, which leads to haemolysis. Consequently, rasburicase is contraindicated in G6PD-deficient individuals[112].

responses. Genetic variants often differ according to ancestry, which can confound the translation of pharmacogenetic traits from one population to another. For instance, genetic polymorphisms in the genes *CYP2C9* and *VKORC1* have a population-specific influence on the anticoagulant effects of warfarin[19]. 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 by variants in multiple genes within the same patient. The Genomics England 100,000 Genomes Project and the US National Institutes of Health (NIH) Pharmacogenomics Research Network are two of many ongoing efforts to facilitate genome discoveries and their translation into diagnostics. Their findings may eventually be used to optimize the selection and dosing of medications for individual patients. The discovery and translation of inherited determinants of drug response and somatically acquired genetic variants in cancer are prominent pharmacogenomic components of these and other initiatives.

Diagnostic testing

Before being used in a clinical setting, genetic tests must meet certain criteria concerning their analytical validity, clinical validity and clinical utility[20]. Developing genetic tests with analytical validity is nontrivial for pharmacogenes such as *CYP2D6* (ref. 21) because the gene is subject to germline copy number variation and the formation of hybrid gene fusions that are difficult to assay and interpret reliably. Clinical utility involves assessing whether the use of the test leads to improved health outcomes for patients who are subject to testing, as well as an assessment of the risks that occur as a result of testing. There is substantial difference of opinion as to precisely which outcomes constitute clinical utility[22,23]. Some studies have broadened their scope to assess the impact of testing on the entire health-care system, including comparing the costs of genetic testing with those of other health-care interventions, as well as understanding how such testing can influence the behaviour of clinicians. For example, Hong Kong introduced a policy to screen for the *HLA-B*1502* allele before prescribing antiepileptic drugs because patients with the allele are at high risk of developing severe skin reactions to the drug carbamazepine. But the policy led clinicians to forego prescribing carbamazepine at all and instead they began to prescribe phenytoin. Phenytoin can also cause severe skin reactions, but the risk factors are not well defined, as for carbamazepine, so the overall incidence of severe skin reactions remained unchanged[24]. For the purposes of this Review, we focus on the clinical utility of pharmacogenomic testing for individual patients without considering the possible public-health consequences of changes in prescribing behaviour.

As the cost of sequencing continues to fall, many have predicted that every individual will in the not-too-distant future have their germline genome sequenced early in life and the results will be available for clinical use throughout their lifetime. Assuming that this prediction is realized (to some extent, at least), we call for a shift away from the debate over whether patients should be tested for specific pharmacogenes before they are prescribed specific drugs, and instead, we suggest moving towards a model in which clinicians are provided with guidelines on how to interpret and deploy genetic variants to improve their prescribing. This assumption underlies the efforts of the Clinical Pharmacogenetics Implementation Consortium (CPIC)[25,26], an open, international non-profit group that creates standardized guidelines on how to use genomic data to inform prescribing. The guidelines are evidence-based, peer-reviewed and publicly available.

A number of factors are used to determine whether there is enough evidence to support the analytical validity, clinical validity and clinical utility of a pharmacogenomic test and to warrant its use in guiding the prescription of medications[22]. The analytical validity will depend on the quality of the data from genetic tests as well as the test's performance characteristics, such as the positive and negative predictive values. Many types of data can be used to evaluate clinical validity and utility, including the penetrance of genetic variation on drug effects, which can be determined from retrospective studies. The mechanism or mechanisms by which genetic variation influences drug effects or a relevant endophenotype (an intermediate phenotype, such as drug-metabolizing enzyme activity) can also be used. Additionally, data can be gathered from *in vivo* pharmacokinetic or other functional studies, *in vitro* functional studies,

Table 1 | Actionable germline genetic variation and associated medications

Genetic variation	Medications
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 ref. 44 (accessed on 7 May 2015). See ref. 44 for updates.

and preclinical and clinical studies that link pharmacological effects or drug concentrations to genetic variation. Further sources of data include case reports, family studies, and randomized clinical trials that compare the outcomes of genetics-based prescribing versus prescribing that is not based on genetic-test results. Other factors that are considered when deciding on the actionability of pharmacogenomic variation include the therapeutic index of a drug (the ratio of the toxic dose to the therapeutic dose), the severity of the drug's toxicity, the severity of the underlying disease and the consequences of suboptimal prescribing.

An important consideration for the actionability of a gene–drug relationship is the availability of an alternative therapy, which may partly depend on the mechanism of the gene–drug association. If the gene affects the pharmacokinetics of a drug (such as in the *CYP3A5*-mediated catabolism of the immunosuppressant drug tacrolimus), there could be substantial published evidence to support a dose adjustment in much the same way as doses are often adjusted according to age or kidney or liver function. Such dose-adjustment decisions are particularly defensible if the drug is one for which therapeutic drug monitoring (based on the concentration in the blood) is readily available. When tests indicate that a drug is either unlikely to be effective or could have unacceptable adverse effects in patients with a particular genotype, the recommendation for an alternative therapy will depend on the balance of evidence for both the efficacy and possible toxicity of the alternative. For example, individuals who are homozygous for inactive *CYP2D6* alleles are unable to convert the analgesic drug codeine into its active metabolite, morphine, but can respond to several other opiate analgesics[27]. If genetic tests indicate an extremely high risk for a serious adverse event — for example, carriers of the *HLA-B*57:01* allele have a high risk of hypersensitivity to the antiretroviral drug abacavir[28,29] — the alternative therapy should be equally effective but have an acceptable risk of adverse effects (that may or may not be influenced by other genetic variants).

Some treatment decisions are less clear cut. For example, there are substantial data to show that patients with two defective *CYP2D6* alleles are more likely to experience recurrence of breast cancer after treatment with tamoxifen. This is because these patients produce much lower levels of the active tamoxifen metabolite, endoxifen, than those without defective alleles[30–35]. However, it is unclear whether the best alternative is another drug (a different selective oestrogen-receptor modulator, for instance) or an altered dose of tamoxifen, particularly in premenopausal women for whom there is a shortage of data to support alternative treatments. Such cases are the most difficult to resolve: although clear from pharmacogenomic testing that the drug or drug dose is suboptimal in a patient with the high-risk genotype, a lack of clinical data for alternative therapies makes it difficult to recommend other medications.

The CPIC considers all such evidence when deciding which gene–drug pairs are clinically actionable. Given the high bar for clinical actionability, the number of actionable genes — those with at least one actionable high-risk diplotype — is small, and the list of medications for which clinical actions are recommended (pharmacogenetically high-risk drugs) is relatively short (Table 1). There are also additional medications that include pharmacogenomic information in their labels[36–38]. However, not all are actionable. Sometimes, information on genetic variation is included when the effects are modest and therefore do not require changes to be made to the prescribing section of the drug label. This information has also been included for some drug labels despite weak or conflicting evidence.

At present, there are only two examples of actionable pharmacogenes that also carry a disease risk: the gene *UGTIA1* and Gilbert's syndrome[39], and the gene *G6PD* and haemolytic anaemia[40]. Thus, many of the ethics concerns that affect the clinical implementation of disease-risk genomics have less relevance for pharmacogenomics[41].

Clinical implementation of pharmacogenomics

Genetic variants that influence the clinical effects of some medications can now be reliably assayed in the clinical setting. Prescribing decisions for such clinically actionable gene–drug pairs should be influenced by these genetic-test results.

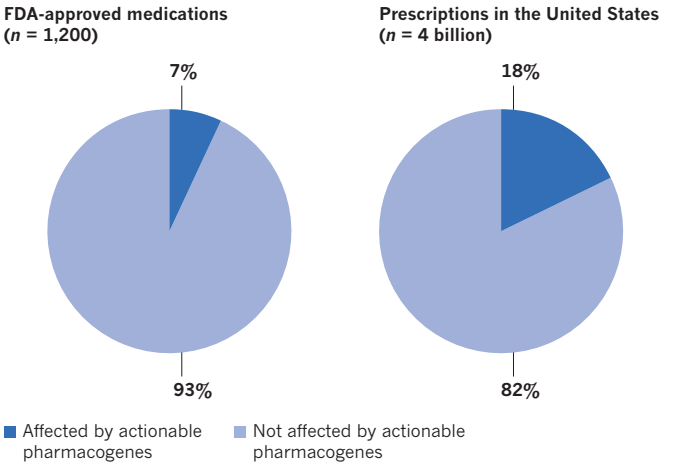

Figure 2 | Medications affected by actionable pharmacogenes. Approximately 7% of FDA-approved medications are affected by actionable inherited pharmacogenes (left), and approximately 18% of US outpatient prescriptions are affected by actionable germline pharmacogenomics (right)[45], which demonstrates that several pharmacogenetically high-risk drugs are commonly prescribed.

Drugs and genes

More than 1,200 individual molecular entities have been approved as drugs by the US Food and Drug Administration (FDA)[42], the European Medicines Agency (EMA)[36] or by Japan's Pharmaceuticals and Medical Devices Agency (PMDA)[38]. Although about 15% of the medications approved by the FDA and EMA contain pharmacogenomic information on their label[36,43], only a subset of the corresponding pharmacogenes is deemed actionable. As summarized in Fig. 2, 7% of medications have actionable germline pharmacogenetics. These correspond to CPIC level A or B gene–drug pairs[44] for which genetic information should or could be used to change the prescription pattern of the relevant drug. In the United States, these medications constitute 18% of all prescriptions, which indicates that pharmacogenomically high-risk medications are slightly overrepresented in highly prescribed medications (Fig. 2)[45]. So far, only 16 of the roughly 19,000 human genes are considered to be clinically actionable for germline pharmacogenomics[44]. Most human germline genetic variation is unlikely to be actionable for the prescription of medication, and pharmacogenomics is unlikely to be useful for improving the prescription of the majority of drugs. However, for the relatively small set of medications for which genomics is actionable, prescribing could be optimized if genetic testing were more widely and appropriately deployed in the clinic. In the meantime, the number of such actionable gene–drug pairs continues to grow, albeit at a slow pace.

Somatically acquired genomic variation

Genetic variants that are specific to cancer tissue represent a special case of pharmacogenomics. Somatic variation can identify which types of malignancy are likely to respond to various anticancer agents[46,47]. The recognition that cancer tissue can be distinguished from normal tissue by the presence of specific genomic abnormalities pre-dates the Human Genome Project. For example, in the 1980s and 1990s ploidy in neuroblastoma[48] and cytogenetic abnormalities in acute lymphoblastic leukaemia[49] were used to determine the composition and strength of the cytotoxic chemotherapy required to treat these cancers. The genetic testing of malignancies has since become more specific in response to the development of anticancer agents that are directed at — or more effective at — treating tumours that harbour certain acquired genetic variants (Table 2). Although the FDA generally requires that diagnostics be developed alongside targeted anticancer agents, the EMA is less stringent[50]. However, proposed changes to the European Union's framework would lead to greater harmonization between the United States and Europe[51].

Table 2 | Actionable somatic genetic variants in cancer cells and associated medications

Genetic abnormality	HGVS nomenclature*	Target†	Medications	Disease
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 cancer
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 ($EGFR^+$)
EGFR mut (act, amp)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	Gefitinib	NSCLC ($EGFR^+$)
$EGFR^+$ and WT *KRAS*	N/A	EGFR	Cetuximab, panitumumab	$EGFR^+$ colon cancer (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)	N/A	ERBB2	Lapatinib, trastuzumab	$HER2^+$ breast cancer
KIT mut (act)	p.Trp557_Lys558del, p.Asp579del, p.Val559Asp	KIT	Imatinib, sunitinib	RCC, GIST
PDGFR (mut or SV)	p.Asp842Val	PDGFR	Sunitinib, imatinib	RCC, GIST, pancreatic cancer
PI3K (mut or 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 sarcoma
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 carcinoma
VHL (mut)	Too numerous to list	VEGFR	Sorafenib	RCC, hepatic cancer, thyroid cancer
VEGF (mut)	N/A	VEGF	Ziv-aflibercept	Colon cancer

Medications targeting normal cell surface proteins that are expressed on some tumour cells (for example, ER, PR, CD20, CD30, CD52) are not included in this summary of drugs that target proteins with aberrant expression or function due to somatic genetic variants. Act, activating; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; amp, amplification (typically by CNV); APL, acute promyelocytic leukaemia; CLL, chronic lymphocytic leukaemia, CML, chronic myeloid leukaemia; CNV, copy number variant; CTCL, cutaneous T-cell lymphoma; del, deletion; ER, oestrogen receptor; ex, exon; GIST, gastrointestinal stromal tumour; HGVS, Human Genome Variation Society; ins, insertion; mut, mutation; N/A, not applicable; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; Ph, Philadelphia chromosome; PR, progesterone receptor; RCC, renal cell carcinoma; SNV, single nucleotide variant; SV, structural variant; WT, wild type.

*Only representative examples of known mutations are shown.

†In general, targets are protein products encoded by the gene listed.

Reactive and pre-emptive testing

Initially, clinical testing was deployed through single-gene pharmacogenetic tests — a practice that evolved from the coupling of strong 'monogenic' gene–drug associations with limitations in genotyping technology[52]. In this model, genetic tests are ordered one at a time on a reactive basis: if the patient might need a pharmacogenetically high-risk drug, the clinician orders the applicable test. However, improvements in technology mean that it is now possible to interrogate multiple genes in a single assay at lower cost than for multiple 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, such as drug-metabolizing enzymes, drug-transporting membrane proteins, drug targets and disease-modifying genes. Many of the actionable pharmacogenes that have been identified to date exert a strong effect on the pharmacokinetics or pharmacodynamics of their associated drug, which make them easy to identify. The strong effects of the polymorphism in the gene *TPMT* on the risk of haematopoietic toxicity from thiopurine medications are an excellent illustration of how 'low-hanging fruit' are often merely the first step down a polygenic path. Subsequent studies showed that when the dosage of mercaptopurine is adjusted in response to *TPMT* testing, polymorphisms in other genes — such as *ITPA* — begin to surface as important[53]. Furthermore, polymorphisms in other genes that form part of the same pharmacological pathway can emerge as being significant for populations of a different ancestry. An example of this is the strong influence of an inherited variant found in the gene *NUDT15* on thiopurine toxicity. *NUDT15* variants are extremely uncommon in individuals of European and African ancestry, but are relatively common in people of Asian descent[54]. This explains the high frequency of thiopurine intolerance in Asian populations despite the low frequency of *TPMT* variants. When a genome-wide association study of thiopurine intolerance was performed in a population that comprised people of European, Asian, African and Native American ancestry, germline variants in both *TPMT* and *NUDT15* reached genome-wide significance for their association with thiopurine intolerance[55]. *TPMT* variants were revealed to be the major determinant of the tolerated dose of thiopurine medications in patients of European and African ancestry, whereas *NUDT15* was the major genetic determinant in patients of Asian and Native American ancestry. Moreover, the metabolism and effects of anticancer agents, including thiopurines,

can be affected by both germline and somatic genetic variation[56], which further increases the complexity of cancer pharmacogenomics.

Several other examples exist in which more than one gene is clinically actionable for a given medication. These include the anticoagulant warfarin, which is affected by both *CYP2C9* and *VKORC1* (ref. 19), and tricyclic antidepressants, which are affected by both *CYP2C19* and *CYP2D6*. Given that a single gene can affect more than one medication (Table 1), there are potential benefits of genotyping a panel of pharmacogenomic variants that apply to a number of drugs that a patient might receive in their lifetime. There is increasing evidence to show that genotyping multiple genes in a single assay is more cost-effective, uses the DNA in the sample more efficiently, and facilitates the pre-emptive availability of genetic-test information. Such multigene panels can change practice from a reactive approach (in which a fresh genetic test is ordered every time it is required) to a pre-emptive approach (in which a single sample is assessed for many likely-to-be actionable genes at the same time), thereby providing the patient with a lifetime's worth of test results. Several groups have already begun to implement pre-emptive multigene panels for pharmacogenomics[57–61], but the practice is by no means widespread at present.

Clinical implementation

A number of barriers prevent the widespread use of pre-emptive multigene panels to guide the prescription of drugs. These include the lack of incentives for clinicians to conduct tests or implement procedures that might prevent adverse events. There are relatively few studies that prove the cost-effectiveness of pharmacogenetic testing[62]. Although a multigene panel approach is less expensive than ordering tests for one pharmacogene at a time, there are no data to assess the cost-effectiveness of the panel approach when implemented early on in life and used throughout a patient's lifetime. Many health-care systems do not provide financial reimbursement for preventive-medicine services or for pre-emptive screening, which creates a barrier to pharmacogenetic testing in the clinic[63,64].

The cost and complexity of the computational approaches needed to identify, catalogue, prioritize and interpret genetic variants that influence prescribing decisions present another barrier to the clinical uptake of pharmacogenomics testing. Although an increasing number of computational tools for analysing genetic variation are becoming available, a substantial level of expertise and manual interpretation is still required to apply this analysis successfully in the clinic (Fig. 3). Computational tools for CDS, triggered by patient-specific alerts, prompt and guide clinicians to use genetic information when prescribing affected drugs[45,65,66]. The costs associated with the use of pharmacogenomics in clinical practice are quickly shifting away from laboratory testing towards the process of linking genetic-test results with evidence-based decisions that will robustly guide the prescription of medications and will be updated as the latest evidence emerges. However, it is unclear who should take responsibility for updating and paying for such interpretations.

A further barrier to the clinical uptake of pharmacogenomic testing is the lack of clear guidelines for translating genetic variation into actionable recommendations. Professional societies and other guideline-generating groups sometimes disagree on whether to proceed with pharmacogenetic testing and, if so, how. Examples for which there has been disagreement include the drugs warfarin[67] and clopidogrel[68]. A common reason for the lack of support for genetic testing is the dearth of randomized prospective controlled trials that compare genetically guided testing with conventional therapy. Also, many professional societies and guideline-generating groups approach their evaluation of pharmacogenomic tests from the standpoint of whether the clinician is obligated to order the genetic test[52,67–69]. However, as inexpensive multigene tests become available, the question is shifting from whether to order a genetic test to how existing genetic-test results can and should be used to influence prescribing decisions. For inherited genetic variation, the CPIC has undertaken the task of creating guidelines that focus on how genetic-test results should be translated into specific prescribing actions. The Royal Dutch Pharmacists Association took a similar approach[70,71]. Multiple resources exist to guide the selection of cancer drugs on the basis of somatically acquired genetic variation (Table 2), although these constantly change as new evidence arises[72–75].

As deep sequencing becomes more widespread, further variants will be discovered in pharmacogenes[76]. The challenge will be to catalogue and annotate these variants. Given the importance of rare variants for both inherited[24] and cancer-related pharmacogenes, publicly available and easily updatable resources such as PharmGKB, ClinGen and ClinVar will be essential for providing the computational CDS in health-care record systems with up-to-date recommendations that are based on genetic-test results[77–79]. Current heterogeneity in genetic-variation databases and health-care record systems, coupled with a lack of a common ontology, limits interoperability and hinders the use of pharmacogenetic test results longitudinally as well as across each of the health-care systems the patient must navigate. Several groups are working to standardize the language of pharmacogenetic testing[80–85], with the aim of creating terminology that can drive CDS across health-care record systems. Initiatives such as an Institute of Medicine Roundtable on Translating Genomic-Based Research for Health and the CPIC are working to create terms and language that can be directly uploaded into

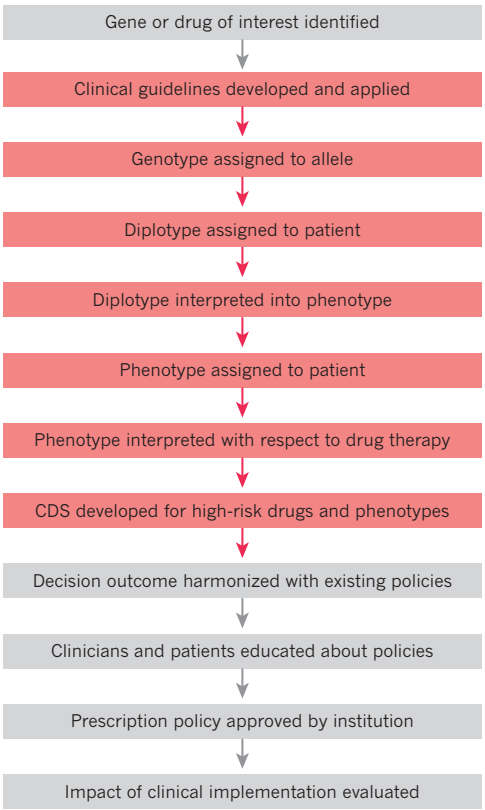

Figure 3 | Bringing pharmacogenomic testing to the clinic. Multiple steps are required before pharmacogenomic testing can be used in the clinic. First, genes or drugs for actionability are identified. Guidelines for all actionable inherited pharmacogenes, such as those developed by CPIC[25], exist for subsequent steps that are shaded in red. Next, genotypes are assigned to alleles, and diplotypes are assigned to patients. Diplotypes are then translated to phenotypes (that describe gene function), followed by their interpretion with respect to drug therapy. Appropriate CDS is deployed to provide clinicians with recommendations for prescribing medications. Pharmacogenetic considerations are harmonized with other policies for affected medications, including therapeutic drug monitoring, if applicable. Clinicians and patients are educated as to what the results mean, what type of CDS and information to expect and which medication might be affected. Institutional oversight committees can then approve prescribing recommendations and policies, if desired. Last, clinical and prescribing outcomes are audited by various groups to evaluate the impact of the clinical implementation of pharmacogenomics.

the CDS of electronic health records. However, heterogeneity across systems will initially slow the creation and uptake of CDS that facilitates the use of pharmacogenetic information[84].

Other barriers include the insatiable desire for more evidence, a lack of education in clinicians, the scarcity of evidence-based implementation systems, and concerns about incidental or secondary findings from genetic testing, not to mention inertia in health-care systems[69,86–89]. These barriers are not unique to pharmacogenomics, and the energy required to overcome them is likely to come from multiple sources that range from the 'push' of patient advocates to the 'pull' of the courtroom. The resistance by some clinicians to the ordering or use of pharmacogenetic testing can be perplexing to patients and their caregivers. For example, an advocate for paediatric patients expressed a disquieting lay perspective: "I am mystified by the resistance to a simple blood test that might save children's lives."[17] As the general public becomes more aware of the potential for genetic tests to improve the prescription of medications, including through direct-to-consumer testing[90,91], its advocacy could grow even stronger. In Hawaii, the attorney general brought a lawsuit against the manufacturer of clopidogrel because it marketed its drug in the state without warning that a high percentage of the Hawaiian population has inherited low-function alleles of the gene *CYP2C19*, which encodes the enzyme required to convert clopidogrel to its active metabolite[92]. The case asserts that it was already known that *CYP2C19* variant allele frequencies are higher in East Asian and Pacific Island populations, which comprise about 40% and 10% of the Hawaiian population, respectively. It also states that there was abundant evidence to show that the antithrombotic effects of clopidogrel are diminished in patients with low CYP2C19 activity (predisposing them to an increased incidence of cardiovascular events such as stent thrombosis)[93,94]. From an educational perspective, multiple accrediting agencies are calling for pharmacogenomics to become part of the curricula for health-care students, trainees and advanced practitioners[95]. The availability of pharmacogenomic educational tools continues to grow[96–98]. Although early adopters of clinical pharmacogenomics are now establishing methods to advance the treatment of patients, broad clinical implementation remains elusive.

Facilitating clinical use

Around the world, many groups are working to share resources that will facilitate the clinical implementation of germline pharmacogenetic tests[99]. The European Pharmacogenetics Implementation Consortium is an international body whose goal is to improve therapy by integrating pharmacogenetic information into clinical care[100]. The Royal Dutch Pharmacists Association has also made efforts to facilitate implementation[70,71]. In the United States, members of the NIH Pharmacogenomics Research Network organized the Translational Pharmacogenetics Project[57–61,101–103], which is dedicated to sharing best practices for the clinical implementation of CPIC pharmacogenomics guidelines. Meanwhile, the Electronic Medical Records and Genomics (eMERGE) and Implementing Genomics in Practice (IGNITE) networks are testing pharmacogenetic implementation strategies[88,104,106]. In Thailand and Singapore, where the *HLA-B*15:02* variant is widespread and strongly predisposes patients to severe skin toxicity after treatment with specific drugs, pharmacogenetic testing is common[106–108]. The Genomic Medicine Alliance[109] facilitates the clinical use of pharmacogenomics and has created a database that links drugs with genes[110]. Population admixture between previously isolated, diverse human populations must also be considered as part of the global effort towards clinical implementation[111].

Future directions

Clinicians are accustomed to making prescribing decisions on the basis of patient characteristics such as age, kidney or liver function, drug–drug interactions and personal preferences. Much of this takes place without optimal CDS to assist in compiling these characteristics and matching them with evidenced-based choices on medications and doses. As CDS improves and becomes more widespread, and as the evidence to support pharmacogenomic testing continues to grow, momentum for the clinical implementation of pharmacogenomics should accelerate. Going forward, there is a growing body of evidence to suggest that pharmacogenomics will become an important component of evidence-based precision medicine. ■

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