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Pharmacogenetics in clinical practice: how far have we come and where are we going?

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Abstract

Recent years have seen great advances in our understanding of genetic contributors to drug response. Drug discovery and development around targeted genetic (somatic) mutations has led to a number of new drugs with genetic indications, particularly for the treatment of cancers. Our knowledge of genetic contributors to variable drug response for existing drugs has also expanded dramatically, such that the evidence now supports clinical use of genetic data to guide treatment in some situations, and across a variety of therapeutic areas. Clinical implementation of pharmacogenetics has seen substantial growth in recent years and groups are working to identify the barriers and best practices for pharmacogenetic-guided treatment. The advances and challenges in these areas are described and predictions about future use of genetics in drug therapy are discussed.

Keywords

clinical implementation; pharmacogenetics; pharmacogenomics

The Human Genome Project (HGP) was completed in 2001 and its completion heralded the significant medical advances that would result from that large, international effort. At the time of the announcement, then director of the HGP and current director of the NIH, Francis Collins highlighted the expectations for the advances that would stem from the HGP. Prominent among them were expectations about the impact on pharmacological therapies [1]. First was the expectation of advances in targeted drug discovery based on genetic findings. Next was the expectation that genetic information could be used to predict drug responsiveness, with a specific statement that correlations with genetics and drug response would be found for many drugs within the proceeding 10 years (i.e., by 2011). He also projected that by 2020 “the pharmacogenomics approach for predicting drug responsiveness will be standard practice for quite a number of disorders and drugs” [1].

As we sit at approximately the midpoint of Collins’ two decade projection timeline, how close are we to those projections? One can argue his projections were indeed quite accurate,

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particularly given the difficulty of projecting advances one to two decades in the future. The advances and challenges in genetic-guided drug discovery and development, pharmacogenetics and use of pharmacogenetics to guide treatment are discussed herein.

Genetic-guided drug discovery & development: advances & challenges

There have been notable advances in the use of genomic information to guide drug discovery and development, particularly in the area of cancer. Table 1 highlights the drugs with genotype-specific indications. In many cases, development of these drugs was targeted around specific mutations, based on the role of the mutation in the cancer of interest. While most of the drugs listed in Table 1 are for the treatment of cancer, there are two exceptions. One is maraviroc, which is indicated for CCR5-tropic HIV infection. The other is the recently approved ivacaftor, indicated for cystic fibrosis patients with the *CFTR* G551D mutation [2].

Not only have there been a number of drugs developed through a genetically guided approach, it is well accepted in the clinical setting to test for the relevant genetic mutation or downstream protein expression, prior to use of these therapies. A number of factors likely contribute to the widespread clinical adoption of genetic testing to guide use of agents in Table 1. These factors include strong data pointing to poor efficacy in individuals lacking the genetic mutation, or absence of data in those lacking the mutation but lack of efficacy is presumed in the absence of the mutation. Additionally, there are strong statements in the product labels that the drug should only be used in patients with specific mutations, and in many cases a genetic test has been codeveloped with the drug. The very high cost for most of these drugs also produces sensitivity within the medical and payor communities to use them only in those patients with the potential for benefit based on genotype.

Review of Table 1 may also be instructive regarding the future potential for genetically targeted drug development. The only drug on this list that was approved at the time of completion of the HGP is trastuzumab, for HER2-positive breast cancer, the poster-child for targeted therapy. Like trastuzumab, all but two of the drugs in Table 1 target somatic mutations in cancer. Cancer drug development will continue to be highly focused on targeted mechanisms, further aided by genomics and systems biology approaches [3]. Maraviroc targets a specific mutation in the HIV virus, not human genetic variation. Only ivacaftor targets a germline mutation, and this is in the gene that causes the monogenic disease, cystic fibrosis. Thus, while there been substantial advances in genetic-guided drug development in the last decade, it has been almost exclusively in cancer. It is unclear whether cancer and infectious diseases represent the low-hanging fruit for genetically informed drug discovery and development and examples in common complex diseases will follow, or if such approaches will not be widely successful for discovery and development of drugs for common complex diseases. The latter seems more likely.

The common, complex diseases have environmental and multiple genetic influences, with each gene contributing in smaller ways, thus it is quite possible that the targeted approach, focused on specific mutations, that has been highly successful in cancer will not see the same success for chronic disease treatments. However, it is possible that genes identified through genome-wide association and other studies may still identify important protein targets. Several examples come from lipid regulation and drug development for treatment of lipid disorders, including *CETP* and CETP inhibitors, and *PCSK9* and PCSK9 inhibitors. Polymorphisms in *CETP* and *PCSK9* are associated with high levels of high-density lipoprotein and low levels of low-density lipoprotein, respectively [4,5] and inhibitors of CETP and PCSK9 show promise for their ability to raise high-density lipoprotein and lower levels of low-density lipoprotein, respectively [6,7]. Though these drugs do not target the

specific polymorphisms, the genetic literature supported these proteins as drug targets and the early data strongly support that they have the anticipated effects on the respective lipid subclass. The next decade will provide clarity about whether genetic/genomic-guided approaches to drug discovery and development will largely remain within therapies for cancer and infectious diseases, or will also become a common, widespread approach to the development of drugs for chronic diseases.

Pharmacogenetics to guide drug therapy decisions in the clinical setting

The other major advance predicted by Francis Collins in 2001 was that there would be increased literature on the genetic associations with drug response, and that by 2020 it would be common to use genetic information to guide drug therapy decisions. Certainly in the past decade there have been substantial advances in discoveries of genetic associations with drug response, spurred on in part by major funding from the NIH for the Pharmacogenomics Research Network (PGRN) and from similar large-scale funding in other countries. Prior to February 2001, the time of the announcement of completion of the HGP, there were 2316 papers in PubMed using the search terms pharmacogenetics or pharmacogenomics. By the end of 2012 that number was approaching 15,000; or approximately 1000 papers/year since completion of the HGP. This growth in the literature supports the theory that there is increased knowledge of genetic associations with drug response.

Over the last decade, the US FDA has also been aggressive in not only providing genetic labeling on new drugs, including the ones highlighted in Table 1, but has also provided updates to the product labels for a number of existing therapies, including some very old drugs like warfarin and 6-mercaptopurine. At present there are over 100 drugs that have pharmacogenetics information in their FDA product label. A current listing of all drugs with pharmacogenetic labeling in the product label can be found at [101]. Pharmacogenetic information in product labels ranges from boxed warnings, the highest level of warning in the product label, to information in the clinical pharmacology section.

It can also be argued that we are on our way to the vision of genetic information being used commonly by 2020 to guide drug therapy in the clinic. The Clinical Pharmacogenetic Implementation Consortium (CPIC) was formed in 2009 with the recognition that there are examples of clinically actionable pharmacogenetic drug–gene pairs, yet these have seen limited implementation in the clinical setting. CPIC set out to provide a comprehensive review of the existing literature on targeted pharmacogenetic examples, and to provide guidelines, authored by experts in the field, on the clinical use of pharmacogenetic information, if such information was available [8]. CPIC assumes that with continued advances in whole genome SNP genotyping and genome sequencing, it will be increasingly common for genetic information about patients to be available. As a result, CPIC elected to not focus on whether pharmacogenetic tests should be ordered, but builds guidelines based on an assumption that such genetic data are available. If such data are available, the clinician needs to know if the pharmacogenetic associations are sufficiently robust to use the information clinically, and if so, how to use the genetic information to guide drug therapy. By early 2013, eight CPIC guidelines had been published, which include *TPMT* and thiopurines [9], *CYP2C19* and clopidogrel [10], *VKORC1/CYP2C9* and warfarin [11], *CYP2D6* and codeine [12], *HLA-B* and abacavir [13], *SLCO1B1* and simvastatin [14], *HLA-B* and allopurinol [15], and *CYP2D6/CYP2C19* and tricyclic antidepressants [16]. These guidelines are summarized in Table 2. Production of a number of other guidelines is ongoing and a listing of in progress guidelines can be found at [102].

Clinical implementation of pharmacogenetics

Use of *HLA-B*5701* genotyping prior to initiation of abacavir, to prevent hypersensitivity reaction, has been endorsed not only by CPIC but by the US Department of Health and Human Services [103] and by HIV consensus panels [17,18]. As a result *HLA-B*5701* genotyping is standard practice in most centers prior to initiation of abacavir therapy. This rapid adoption into practice was aided not only by the numerous consensus recommendations, but also by a double-blind, prospective, randomized controlled trial (PREDICT-1) that showed clear benefit of genetic testing to prevent the hypersensitivity reaction [19].

Pharmacogenetic testing for other examples has not seen such widespread adoption, but in recent years, such testing is occurring with increasing frequency. For example, *TPMT* genotyping for 6-mercaptopurine therapy has been standard at St Jude Children's Research Hospital for over a decade for patients with acute lymphoblastic leukemia [20], and is increasingly common elsewhere, but is not standard at all centers treating acute lymphoblastic leukemia patients. *TPMT* genotyping (or phenotyping) for 6-mercaptopurine or azathioprine is also used with some regularity in patients with inflammatory bowel disease, and such is recommended in US treatment guidelines [21]. Implementation of *CYP2C19* genotyping for clopidogrel treatment in patients undergoing percutaneous coronary intervention is also occurring with increasing frequency, and centers that have adopted this approach include Scripps Health, Vanderbilt [22] and University of Florida [23], University of North Carolina at Chapel Hill, among others. Also, psychiatric groups within academic medical centers, such as the Mayo Clinic, have been using *CYP2D6* genotype to guide treatment decisions with antidepressants and antipsychotics since the AmpliChip received approval from the FDA in 2004 [24]. However, use of pharmacogenetic data in clinical practice is far from the norm.

Approaches to clinical pharmacogenetics implementation range from single targeted tests (e.g., for the SNPs required to define a drug-metabolism phenotype for a specific drug-metabolizing enzyme) to broader chip-based approaches. For the single test approach, there is great interest in rapid turnaround methods, including point-of-care tests, and several recent papers have highlighted the potential of point-of-care genetic testing [25,26], which can be particularly helpful for scenarios like clopidogrel, where a delay in therapy while awaiting a genotype result may be unrealistic. The chip-based approaches generate larger amounts of information, on broader gene panels, and in most cases, these are being used in settings where the primary goal is to create pre-emptive genetic data that can be available for future use in the patient's care [22,23,27,28]. This approach more closely mimics the expected future reality where large amounts of genetic information will be available on patients.

Thus, there are examples in place that provide clear evidence that we are moving toward the clinical use of pharmacogenetics, as predicted by Francis Collins, and movement in this direction has gained significant speed since 2011.

Barriers/challenges to clinical implementation of pharmacogenetics

Despite clear advances in clinical implementation of pharmacogenetics, there is much yet to be done before reaching the 2020 prediction of widespread use of pharmacogenetic information to guide drug therapy decisions for a number of drugs. There are a variety of barriers and many institutions have begun to actively identify and seek to remedy those barriers [20,22,23,28,29]. Examples of commonly identified barriers are summarized in box 1.

Box 1

Examples of identified barriers to clinical implementation of pharmacogenetics

Test-related barriers

- Pharmacogenetic test available in CLIA/CAP-compliant laboratory
- Remembering to order test or identifying patients for whom test is appropriate
- Turnaround time for test results
- Cost of test and potential lack of reimbursement for test

Knowledge barriers

- Insufficient knowledge of pharmacogenetic data
- Uncertainty about pharmacogenetic genetic test interpretation
- Uncertainty about drug therapy decision based on pharmacogenetic test

Evidence barriers

- 'Genetic exceptionalism' for genetic and pharmacogenetic tests
- Lack of randomized controlled trials documenting superiority of pharmacogenetic-guided treatment approach

ELSI barriers

- Concerns about inclusion of genetic information in the medical record and potential for genetic discrimination
- Questions about importance of sharing pharmacogenetic findings with family members
- Defining importance of ELSI in pharmacogenetics versus disease genetics

Adapted with permission from [23,28].

CAP: College of American Pathologists; CLIA: Clinical Laboratory Improvement Amendments; ELSI: Ethical, legal and social implications.

Test-related barriers—Advancement of pharmacogenetics into clinical practice requires recognition of these barriers and efforts to overcome them. The test-related barriers represent true logistical barriers. In order for the information to be used clinically (in the USA), the test must be performed in a regulated clinical laboratory but increasing numbers of clinical laboratories are offering such tests. Turnaround time is particularly important in clinical scenarios where a delay in therapy is not possible, and the genotype is needed quickly for it to be of clinical value. In some clinical situations, the genetic information is most useful if it is available within a few hours, whereas the turnaround time, particularly if the test is sent to a national reference laboratory, might be up to 2 weeks. This is why many centers are focusing on pre-emptive genotyping, so that the genetic information is available at the time it is needed in the course of clinical care, thus making turnaround time irrelevant [22,23,27,28]. Additionally, based on advances in chip-based genotyping technologies, the incremental costs of testing hundreds of SNPs is relatively small or absent compared to the cost of genotyping a few SNPs. This is another potential advantage of a pre-emptive, chip-based approach [23]. Academic centers, particularly those in the NIH PGRN and the NIH Electronic Medical Record and Genomics (eMERGE) Network are working to define

strategies for selection of patients for pre-emptive genotyping. Furthermore, it is expected that in the future, SNP genotyping will be replaced by sequencing and when this occurs the idea of testing a few SNPs in a single gene will seem as outdated as using a typewriter seems today. Nonetheless, to achieve this vision will require new models for reimbursement that focus less on the actual test performance, and rely more on the interpretation of the multiple results that can arise from the single test over a long period of time.

Knowledge barriers—There are also knowledge barriers among clinicians that must be overcome. Increased genetics education among medical, pharmacy and other health professional students is clearly needed, but this will only be the tip of the iceberg for educational efforts [30]. For example, recent surveys of practicing physicians indicate a majority are aware of pharmacogenetic testing, and most believe that it will represent an important tool in their drug therapy decision-making [31,32]. However, very few (10–15%) feel comfortable with their knowledge of pharmacogenetics or with ordering a pharmacogenetic test and most indicate they have not had any education on pharmacogenetics [31,32]. In order for pharmacogenetics to move forward in a substantial way, the knowledge base and comfort level of practicing physicians with pharmacogenetics will need to improve.

It is unlikely however that educational efforts will be sufficient. Those institutions that have built pharmacogenetics implementation programs have identified the importance of interpretive clinical decision support tools in the electronic medical record to aid the clinical translation of pharmacogenetics [20,22,23,28]. It is unrealistic that clinicians will remember what a specific genotype means (e.g., *CYP2C19*1*2*, or *VKORC1-1639 AA*) and clinical decision support tools will ensure that they do not have to know the data at this level of granularity. Clinical decision support tools can also provide clear guidance on the therapeutic options based on the genotype. These will not only help to advance the decisions based on pharmacogenetic information in the clinical setting, but will also serve as an educational tool.

Evidentiary barriers/controversies on level of evidence required for clinical use—There is also controversy about the level of evidence required for clinical implementation of pharmacogenetics. Some in the clinical community have argued there is not sufficient evidence to warrant clinical use of pharmacogenetic testing. For example, recent consensus guidelines for warfarin and clopidogrel recommend against routine pharmacogenetic testing, based on the lack of evidence of benefit of such testing [33–36]. These guidelines do not necessarily challenge the data on the genetic association with dose (warfarin) or antiplatelet effect and outcomes (clopidogrel) but rather argue that there are not data showing that a genotype-guided approach improves outcomes. This argument implicitly suggests there must be randomized, controlled trials documenting the benefit of a genotype-guided approach. Such trial was conducted with abacavir, and the benefit of genotyping was confirmed[19]. Similarly, these types of trials are underway for warfarin, with the US-based (COAG) [37] and European-based (EU-PACT) [38] warfarin pharmacogenetics trials expected to be completed in 2013. However, it is unrealistic to expect that such trials will be conducted for each example, or even most examples within pharmacogenetics. If this is the evidentiary bar that is required by the clinical community, then it is clear we will never reach the 2020 prediction of pharmacogenetics being commonly used to guide therapy.

Randomized controlled trial data are essential for judging the efficacy and effectiveness of a drug to enter into practice. However, it is not a level of evidence that has been applied in the setting of diagnostic, or laboratory-based tests, and so it remains unclear why it should generally be applied to pharmacogenetics. For example, there are no randomized, controlled trial data documenting that use of serum creatinine for dose adjustment of renally cleared

drugs is superior to not using this information; rather it is well accepted that serum creatinine is a biomarker that can be used to guide use of a drug and its dosing in an individual patient. In fact, FDA product labels routinely provide serum creatinine-based dosing guidance for renally cleared drugs. There are uncountable laboratory and diagnostic tests that are widely utilized but lack randomized controlled trial evidence showing that using the laboratory data to guide clinical decisions is superior to not using the information. Some have referred to the apparently higher evidentiary bar for genetic and pharmacogenetic tests as 'genetic exceptionalism' [39,40]. Indeed, it has been argued that for pharmacogenetics, non-inferiority to the standard of care should usually be sufficient [40]. Clearly in situations where the pharmacogenetic data might be used to withhold therapy, and when the therapy is used to treat a highly morbid or mortal condition, then the level of evidence for adoption of pharmacogenetics into practice should be very high. One example is use of *CYP2D6* to guide tamoxifen therapy. There is substantial debate in the literature on treatment-related outcomes in breast cancer based on *CYP2D6* genotype [41]. While some have advocated *CYP2D6* genotyping to guide treatment decisions with tamoxifen, others have argued against such an approach based on the conflicting literature. Clearly, a very high level of evidence should be required before withholding tamoxifen therapy in premenopausal breast cancer patients who are *CYP2D6* poor metabolizers, since alternative treatment with aromatase inhibitors is not an option in these patients.

By contrast, many of the current high-level pharmacogenetic examples are ones where the information is simply used to refine dosing (similar to serum creatinine in patients with renal impairment), or when used to withhold therapy there are good alternative treatments. Many of the CPIC examples highlighted in Table 2 fall into these categories. If the level of risk of using the pharmacogenetic information is low, then pharmacogenetic tests should be viewed like most other diagnostic or laboratory tests – simply a test that can be used to refine the clinical decisions about drug therapy for the patient.

Consistent with the view stated above is a three tier, risk tests proposed by Veenstra and colleagues [42]. It has become clear through the work of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group that for most genetic tests, there is insufficient evidence to recommend for or against genetic testing [43]. The challenge with such findings is that clinicians must still make decisions in the face of insufficient evidence. In this context Veenstra and colleagues proposed a three-tiered approach, specifically focusing on how to deal with examples judged to have insufficient evidence for or against testing. At the two ends are the examples where the evidence is sufficient to recommend for or to recommend against genetic testing. In the middle are those cases with insufficient evidence, in which case, the risk benefit profile is considered relative to the level of uncertainty in the evidence to make decisions about the appropriateness of genetic testing. This framework applies nicely to pharmacogenetic testing and as noted above, in many cases the risk benefit analysis is favorable (e.g., dosing based on genotype; altered therapy with good alternative treatments).

Over the coming years there is likely to be increasing clarity regarding the evidentiary standards for clinical implementation of pharmacogenetics. Until that time, there will be differences in opinion about when a pharmacogenetic test is ready for clinical use; and there will be different levels of adoption of these tests based on these differing opinions.

Ethical, legal & social implications as potential barriers—Finally, there are ethical, legal and social implications of genetic testing. It is widely believed that these issues are less important in pharmacogenetics, because in nearly all cases, actionable pharmacogenetic variants only influence drug response and not disease risk. There are challenging societal issues for disease genetics, such as discrimination in life, long-term care, disability

insurance, implications for family members who may carry the same risks, psychological effects from learning about genetic information and so on. However, these are viewed by many as less important for pharmacogenetics, where discrimination is unlikely based on predicted drug response, or individuals are unlikely to be psychologically affected based on information about possible drug response [44]. So while these issues are often raised, many believe the ethical, legal and social implications are less critical in pharmacogenetics, making it an easier place to start with clinical use of genetics to guide care decisions.

Conclusion

Since the completion of the HGP in 2001 there have been substantial advances in pharmacogenetics. These include examples of a number of drugs developed under a genetically targeted approach, though these are mostly for treatment of cancers. The value of genetically targeted approaches to drug discovery and development for drugs to treat common, complex diseases remains to be seen. Substantial advances in our understanding of the genetic determinants of drug response have also occurred, and as predicted by Francis Collins in 2001, we are moving toward more frequent use of pharmacogenetic data to guide drug therapy decisions. However, many barriers to broad clinical use of pharmacogenetics still exist, although increasing numbers of clinicians and investigators are seeking methods to overcome these barriers, leading to new data on implementation science.

Future perspective

It is anticipated that the next 5–10 years will define the importance of pharmacogenetics in the clinical setting. The last few years have seen the dawn of clinical implementation of pharmacogenetics into practice, but the examples to date remain relatively limited, and confined in many cases to a few academic medical centers. If pharmacogenetics is to have an important role as a tool in guiding drug therapy decisions, then substantial advances in clinical implementation are expected in the next 5–10 years. All signs point to continued advances, such that the projection of major clinical use of pharmacogenetic data in 2020 will occur. The next 5–10 years will also see the majority of cancer therapies developed around a genetically targeted approach. However, it is less likely that this approach will see major advances for the common, complex diseases. Rather, it is more likely that genetic data will help to identify useful drug targets, although such therapies will not be targeted to individuals with a specific genotype.

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Executive summary

Background

- The last decade has witnessed substantial advances in pharmacogenomics, including use of such data to drive drug discovery and development, an advancing knowledge base of genetic associations with drug response and movement toward clinical implementation of pharmacogenetics.

Genetic-guided drug discovery & development

- Targeted drug development based on genetic mutations has increased in the past decade, with therapies indicated in patients with specific genetic mutations.
- Genetically targeted drug development approach has predominantly been used in cancer; it seems unlikely that this approach will be as fruitful for drugs to treat common diseases.

Pharmacogenetics to guide drug therapy in the clinical setting

- Knowledge of the genetic contributors to variable drug response has exploded in recent years and for some drugs the knowledge base is sufficient to warrant use of genetic information to guide therapy in the clinical setting.
- Clinical implementation of pharmacogenetics is becoming increasingly common and numerous academic health centers are developing programs to identify barriers and challenges, and to facilitate such implementation.
- Barriers to clinical implementation of pharmacogenetics include pharmacogenetic test-related logistical barriers, knowledge barriers in pharmacogenetics and differences in opinion regarding the level of evidence required to utilize pharmacogenetic information clinically.

Table 1

Drugs approved by the US FDA with genetic indications.

Drug	Indication	Gene(s)
Cetuximab	$EGFR^+/KRAS^-$ metastatic colorectal cancer	*EGFR* and *KRAS*
Crizotinib	ALK^+ non-small-cell lung cancer	*ALK*
Denileukin diftitox	$CD25^+$ T-cell lymphoma (CD25 component of IL2-R)	*IL2R*
Everolimus	HER2-negative breast cancer	*ERBB2*
Ivacaftor	Cystic fibrosis with G551D mutation in *CFTR*	*CFTR*
Lapatinib	HER2 positive (hormone $receptor^+$) Metastatic breast cancer	*ERBB2*
Maraviroc	CCR5-tropic HIV infection	*CCR5*
Panitumumab	Metastatic colorectal cancer KRAS negative	*KRAS*
Pertuzumab	$HER2^+$ metastatic breast cancer	*ERBB2*
Trastuzumab	$HER2^+$ overexpressing breast cancer	*ERBB2*
Vemurafenib	Metastatic melanoma with *BRAF* V600E mutation	*BRAF*

Table 2

Summary of Clinical Pharmacogenetics Implementation Consortium guidelines.

Drug(s)	Gene(s)	CPIC recommendations	Ref.
Azathioprine, 6-mercaptopurine and thioguanine	*TPMT*	Dosing recommendations based on *TPMT* genotype	[9]
Clopidogrel	*CYP2C19*	Recommendations for alternative treatment based on *CYP2C19* genotype in post-percutaneous coronary intervention patients being considered for clopidogrel	[10]
Warfarin	*VKORC1/CYP2C9*	Recommendations for use of pharmacogenetic algorithms that incorporate *VKORC1* and *CYP2C9* genotype with clinical factors for warfarin dose prediction	[11]
Codeine	*CYP2D6*	Recommendation to avoid codeine in individuals with ultrarapid or poor metabolizer phenotype predicted based on *CYP2D6* genotype	[12]
Abacavir	*HLA-B*	Recommendation to avoid abacavir in individuals positive for *HLA-B*57:01* genotype	[13]
Simvastatin	*SLCO1B1*	Guidance for simvastatin use or dosing based on *SLCO1B1* genotype	[14]
Allopurinol	*HLA-B*	Recommendation to avoid allopurinol in individuals positive for *HLA-B*58:01* genotype	[15]
Tricyclic antidepressants	*CYP2D6/CYP2C19*	Dosing recommendations for tricyclic antidepressants based on *CYP2D6* and *CYP2C19* genotype	[16]

See [102] for update on published and in progress CPIC guidelines.

CPIC: Clinical Pharmacogenetics Implementation Consortium.