Chapter 12
Use of Clinical Decision Support to Tailor Drug Therapy Based on Genomics

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Abstract Clinical decision support (CDS) has been an effective tool to improve prescribing to prevent errors, avoid adverse events, and optimize dosing. The imminent adoption of inexpensive panel assays to generate dense molecular data offers new opportunities to improve prescribing. Yet realizing the potential of such data to improve care faces many challenges to clinical informatics. These 'omic' data are large, are frequently stored and presented within non-computable narrative reports, require maintenance of an updated interpretation, and lack widespread representation standards for interoperability. In this chapter, we focus on using genomic data to guide drug therapy as a prototypic class of omic data with the greatest evidence base to support its clinical use in routine clinical care. We provide an overview of the challenges and opportunities of using genomic information within CDSS, the evidence for clinical utility, the emergence of genomic data standards, and examples of systems of pharmacogenomic prescribing. We conclude that the opportunities for genomic-guided therapy will likely increase over time. Clinical informatics development will be required to meet rapidly evolving needs, toward an outcome of improved patient care with the right drug at the right dose the first time, decreasing "idiopathic" adverse events.

Keywords Clinical decision support • Genomics • Pharmacogenomics • Electronic health records • Adverse drug events • Health level 7 • Pharmacology

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E.S. Berner (ed.), *Clinical Decision Support Systems*, Health Informatics,
DOI 10.1007/978-3-319-31913-1_12

One of the visions from the Human Genome Project was the ability to use genetic information to tailor therapeutic decisions for individuals. The scientific validity of this potential has been validated as numerous cases of common and rare genomic variations have been found to influence drug effects. Many prototypical rare "idiopathic" adverse drug events have been shown to have genetic influences, such as Stevens Johnson Syndrome with the antiepileptic carbamazepine [1] and drug induced liver injury with flucloxacillin [2]. The efficacy of other drugs has been shown to be influenced by genetic variation [3]. Other types of medications that are influenced by genetic variation are oncology medications [4]. Two types of genetic variation, termed germline and somatic, have been recognized as contributing to drug response. Germline variants are present since conception essentially in all cells and can affect an enzyme's activity, a receptor to which a drug binds, or alter the probability of an immune reaction to a drug. Somatic variations are mutations that have arisen after birth in a subpopulation of cells; typically they refer to neoplastic cells and allow a provider to target chemotherapy medications based on the specific genetic makeup of an individual's cancer. Accordingly, the US Food and Drug Administration (FDA) now includes genetic biomarker data (germline or somatic) in drug labels for 167 medications [4], some of which have acquired "Black Box" status.

Genomic data are just one type of high dimensionality data that could potentially be incorporated into clinical care for purposes of drug prescribing. Other types of 'omic' data being pursued in research settings include the proteome, transcriptome, microbiome, or even clinical phenome that could be considered; however, none of these have yet reached the necessary level of evidence to incorporate into actionable clinical testing. Genomic data also present many of the same challenges that are seen with using other forms of -omic testing (such as large scale and naming schema that may not make the actionability clear) were they to become clinically actionable. For these reasons, we focus this chapter on the use of genomic information in building Clinical decision support systems (CDSS), primarily in the context of drug prescribing.

Growth in available genomic testing and knowledge combined with reductions in costs have led to increasing availability of genetic testing and the possibility of integration of genomic information within the EHR. Indeed, during an interview in 2009, Dr. Francis Collins, current Director of the National Institutes of Health (NIH), remarked on the potential of the inevitability of pharmacogenomic-based prescribing with genomic information embedded in the EHR [5]. However, translating the basic science knowledge of genetic variation's influence on drug response into clinical action is not trivial. The nomenclature of genomic variants can be confusing, the data are high dimensional, and the knowledge base changes frequently. Thus, it is an ideal application for clinical decision support (CDS). In this chapter, we will review the evidence for incorporating genomic information into drug prescribing and some of the challenges and successes in doing so.

12.1 Opportunities for Integration of -Omic Technologies into CDSS

Until recently, use of genetic and genomic information to guide care has largely been relegated to esoteric situations driven by experts in the field. These include specialized genetic tests, often by clinical geneticists, to aid in diagnosis of suspected conditions or prenatal screening. Arguably, because genetics experts usually interpret the results, CDSS may not be needed for diagnostic support (e.g., does the patient have cystic fibrosis) or prenatal screening. The types of interpretation and patient education needed require experts to interpret and relay the information, and the breadth of possible results and integration with clinical knowledge would go beyond the capabilities of most CDSS for many genetic disorders.

One of the earliest uses of genetics to guide drug therapy involves testing of thiopurine methyltransferase (TPMT) activity during thoipurine (e.g., azathioprine) therapy for cancers and autoimmune therapies. Since this medication is ordered by a select few types of physicians, there has arguably been less of a need for CDS to guide what to do for individuals with altered TPMT activity. However, it is interesting to note that while this is a fairly widely-known pharmacogenomics trait and taught routinely in medical schools, TPMT activity or genotype testing is not always ordered routinely before prescribing azathioprine, which suggests a potential need for CDS to remind clinicians to order the appropriate tests.

Knowledge about genomic biomarkers affecting drug efficacy or influencing drug response has increased dramatically in the last decade. Specific evidence is discussed more in the next section.

12.2 How Is Genomic Decision Support Different from Other Types of CDS?

Use of genomic information has a number of unique challenges compared to typical use cases for CDS, such as for drug-drug interactions, dose or drug adjustment based on biologic factors such as body surface area, concomitant medications, or kidney function. One of the most common forms of variants is single nucleotide polymorphisms, or SNPs, which indicate variation (inserted, deletion, or variation) at a single base pair. SNPs are typically identified by their "rsID" (e.g., rs2359612). The National Center for Biotechnology Information's dbSNP lists nearly 150 million human SNPs in build 144, points in which variation has been detected amongst the three billion base pairs in the human genome [6]. Other variations include copy number variants (CNVs), larger insertions or deletions, and translocations. The latter are arguably less commonly studied and less comprehensively understood.

Importantly, most common genomic studies have surveyed SNPs. Because evolutionary history dictates that SNPs will statistically co-occur with other more complex genetic variation in similar lineages, larger insertions/deletions or CNVs are also marked by SNPs during genetic studies. This statistical co-occurrence within populations is called linkage disequilibrium, and occurs between two SNPs as well as between SNPs and more complete genetic alterations.

Dense genomic interrogation of hundreds of thousands of SNPs costs less than $100, and the cost of whole genome sequencing continues to fall faster than Moore's law, soon approaching the $1,000 genome [7]. Most of this genetic variation has little impact on disease or drug response; however the nomenclature is not straightforward for a provider to interpret. In contrast, providers are familiar with and can interpret the effects of decreasing kidney or liver function and interacting medications. The effects of genetic variants are not as self-evident, since they are named before their functionality is known. In addition to rsIDs, pharmacogenetic variants have typically also been identified by the "star" nomenclature. For example, *CYP2C19**2 indicated a specific allelic variant in *CYP2C19* which results in reduced activity of *CYP2C19*. The star-scheme, however, also includes non-SNP variation, such as CNVs, translocations, etc., unlike rsIDs. For both rsIDs and star-schema names, the effect of the variant (if any) on the enzyme's activity is not clear. For instance, *CYP2C19**2 decreases the *CYP2C19* activity, while *CYP2C19**17 increases the activity. In addition, variants discovered in one population may "tag" a causative variant but not be causative. For example, rs2359612 in *VKORC1* is highly predictive of warfarin sensitivity in individuals of European ancestry, but not in those of African ancestry, as it is only in linkage disequilibrium with the causative SNP [8]. Given each of these factors (and perhaps partially attributable to our early stage of use of genomic information to guide care), evidence can evolve rapidly, and a CDSS must be rapidly changeable and local institutions must be attuned to monitoring for changes in recommendations. For example, at Vanderbilt University Medical Center, in 2010 we started to use genetic information (*CYP2C19* variants) to identify individuals with decreased ability to metabolize clopidogrel. Evolving evidence caused us to revise our CDSS for clopidogrel based on *CYP2C19* variants five times within its first year of implementation. Table 12.1 presents some of the challenges and possible solutions to integration of genomic-guided therapy into practice.

12.3 State of the Evidence for Germline Pharmacogenomic Intervention

One of the barriers to clinical implementation of pharmacogenomics has been the lack of clear clinical care decisions that should be made based on genetic variant results. The two primary resources addressing this barrier for germline pharmacogenomic variants are the Food and Drug Administration (FDA) [4] and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [9]. Table 12.2 presents all

Table 12.1 Challenges and approaches to translating genome-directed drug therapy into practice

Challenges	Possible solutions
Most practitioners lack specialized knowledge of gene-drug relationships	Generate passive and active decision support modules with clear interpretation and easy-to-understand recommendations. Build decision support modules that intercept relevant drug orders. Use consistent drug sensitivity nomenclature
Order requisitions for individual drug-genotype pairings are confusing	Simultaneously test for all pertinent drug sensitivity genotypes in one test. Automatically prompt provider to order tests
Knowing whom to test can be confusing	Build algorithm to identify high-risk patients to test preemptively, and/or CDSS to identify those who need testing based on indications or prescriptions ordered
Results may not always include interpretation and actionable guidance	Both lab results and decision support need to include drug-specific recommendations as well as genotype results
EHR systems have varying capabilities and implementations	Build variety of passive (annotated lab results) and active (interruptive) decision support mechanisms Measure best way to provide recommendations and implement Plan-Do-Study-Act paradigms to adjust to best workflows
The clinical significance of drug-gene relationships constantly evolves	Periodically review and update CDSS. Utilize central resources for decision support where possible
Information to help explain testing and test results to patients is needed	Provide patient-friendly informational material in patient portals
Practitioners need succinct, quickly accessed education	Develop and link to personalized, detailed information and evidence from lab results and CDSS
Genetic consultations may be important due to unfamiliarity or rare variants	Provide centralized resources (e.g., MyCancerGenome.org, warfarindosing.org, links to Clinical Pharmacogenetics Consortium recommendations, MyDrugGenome.org, Molecular Tumor Board, Pharmacists)
Patient's clinical findings are essential to interpretation and guidance, but may not always be available	Integrate clinical data from EHR into clinical decision supported genotype-guided prescribing
Gaining an understanding of provider opinions and knowledge barriers is needed	Survey providers. Measure what content they view and how often they follow recommendations. Be responsive in design of CDS to emerging needs

sources of pharmacogenomic recommendations and a summary of existing recommendations as of the writing of this chapter. In general these guidelines evaluate two major criteria about the proposed recommendation: (1) the level of evidence supporting the recommendation and (2) the strength of the recommendation. The evidentiary criterion evaluates the strength of the literature surrounding the gene-drug interaction while the recommendation strength typically combines the level of supporting evidence as well as the potential harm from the interaction and the availability of alternate therapies.

Table 12.2 Summary of drug-gene guideline sources

Resource	Number of guidelines
Food and Drug Association http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm	158 Drug-variant pairs (105 germline, 42 somatic)
Clinical Pharmacogenetics Consortium (CPIC) https://www.pharmgkb.org/page/cpic	34 Drug-variant pairs (16 guidelines, 5 updates)
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) http://www.egappreviews.org/	1 Drug class-gene pair

The FDA issues pharmacogenomic guidance through affected drug product labels. The locations of these alerts indicate the type, severity of the interaction, and level of recommendation. The pharmacogenomic biomarkers in drug labeling cover genomic biomarkers that describe: (1) drug exposure and clinical response variability, (2) risk for adverse events, (3) genotype-specific dosing, (4) mechanisms of drug action, and/or (5) polymorphic drug targets and disposition genes. Importantly, FDA pharmacogenomic guidance includes both germline and somatic variation. The most serious warnings are presented as "black box" warnings where: (1) the adverse reaction is so severe that the genetic variant must be considered to properly assess the risk or benefit of the drug, (2) a serious adverse reaction can be reduced in frequency or severity based on use of the genetic variation, or (3) FDA approved the drug based on the pharmacogenomic restriction to ensure safe use. A recent study of the FDA Table of Pharmacogenomic Biomarkers reviewed the 158 drug-gene pairs present in the table as of June 2014. Of the 108 germline drug-gene pairs listed at that time, 6 were subject to black box warnings [10]. The study interpreted the FDA guidance as requiring genetic testing for nine germline drug-gene pairs and recommending genetic testing for a further four pairs. As of September 2015, the count had risen to a total of 167 drug-gene pairs, 111 of which included germline variants. Of these germline variants, eight had black box warnings.

Established in 2009 to address the lack of clear, curated guidelines for germline pharmacogenomic interventions, CPIC developed procedures to evaluate the levels of evidence needed to implement pharmacogenomic interventions [11]. Importantly, CPIC guidelines are based on the assumption that genetic test results are already available to the physician and the guidelines only provide guidance on how to interpret those results to improve drug therapy. Thus, unlike certain FDA recommendations, guidelines produced by CPIC do not address whether a patient should be tested for the gene-drug interaction. Drug-gene interactions are chosen by CPIC for guideline development based on surveys of CPIC members, availability of clinical testing for the indicated genotype, the potential for alternate treatments, and/or the severity of consequences of ignoring the interaction. Once written, drug-gene interaction recommendations are subject to ongoing updates (typically every 2 years) consisting of literature review of newly published data as well as possible guideline modifications. Guidelines and their updates have been published in the journal *ClinicalPharmacologyand Therapeutics*, and are posted to the NIH Genetic Testing

Registry, the AHRQ National Guideline Clearinghouse and the Pharmacogenomic Knowledge Base (PharmGKB) website (www.pharmgkb.org). In addition to these human readable guidelines, there are efforts to translate all recommendations into computer readable formats for easier integration into clinical systems.

12.4 Who, What, and When to Test

Clinical use of these markers can be considered in two broad contexts. The first is "reactive" – genotyping for specific variants is undertaken in individual subjects at the point of care, and then acted on when the results become available. This is the most common type of testing pursued in medicine, including not just genomic interrogation but any testing done in response to an individual's changing clinical status (presentation of a new symptom, family member diagnosed with a new disease, etc.). In the case of genetic testing for drug response, the reactive approach is to test an individual when they are about to be prescribed a drug with a pharmacogenomic variant known to affect a drug's effect, so a provider tests for the variant before or concomitant with prescribing the medication. Ideally the first therapy prescribed would be the correct one, taking into account the results of genetic testing. However, this is not feasible in the case of medications needed acutely, such as following a myocardial infarction or anticoagulation for a thromboembolic event, given that genetic information generally takes at least a few days to return. Thus, in reactive testing, providers have three options: (1) wait to prescribe the medication until genetic test results are available, delaying therapy; (2) prescribe a standard of care therapy (exposing some fraction of the population to increased risk of harm) and then revise as necessary once genetic test results are returned; or (3) avoid the therapy requiring genetic guidance and start with an alternate therapy that does not need genetic testing. While option 3 may seem ideal in many circumstances, it is important to remember that the initial therapy was chosen for a reason – it may be cheaper, have better efficacy, be better tolerated, or be generally more trusted by the provider or in the marketplace. In fact, as shown in Hong Kong, option 3 has been observed in practice, with negative outcomes. After requiring HLA testing to prevent Stevens Johnson Syndrome, or SJS, before prescribing carbamazepine for epilepsy, the prescription rates of alternative antiepileptic drugs increased. However, since the adverse reactions to the alternative medications could not be averted via genetic testing, the overall population rate of SJS did not decrease despite eliminating SJS from carbamazepine, as cases of SJS from other antiepileptic drugs increased significantly [12].

An alternative testing strategy is preemptive, in which dense genotypic information is routinely stored in advanced electronic health record (EHR) systems, allowing genotype-based advice to be delivered to providers prior to or during prescribing. Preemptive genotyping is analogous to a screening test. Screening tests in medicine are performed for a wide variety of conditions in medicine that have high morbidity

or mortality in the absence of early treatment. These conditions are effectively intervenable if diagnosed. When diagnostic screening tests perform well, they are cost-efficient and cause little harm. Examples of screening tests commonly performed in medicine include mammography for breast cancer, colonoscopy for colon cancer, and glucose testing for diabetes. These screening procedures have broadly established evidence bases and cost-effectiveness studies, unlike prospective pharmacogenomic testing. However, it can be argued that pharmacogenomic testing has little toxicity, costs relatively little [several hundred dollars for Clinical Laboratory Improvement Act (CLIA)-compliant testing], and may need to be performed only once for an individual, unlike many other screening tests.

An advantage of preemptive genetic testing is that the genetic information can be embedded in the individual's chart or EHR before such information is needed, so that the genotype-guided care can be the first therapy initiated, theoretically leading to better outcomes. This approach is dependent on the fact that one's genotype does not (generally) change over one's lifetime, such that once genotyped, that information can be used for many years. A disadvantage is that that genotypes needed for testing vary based on the drug one is to be prescribed. Fortunately, some pharmacogenomic variants influence multiple drugs, most commonly driven by cytochrome P450 and Human Leukocyte Antigen (HLA) variants. Thus, testing for a limited set of variants can cover many of the important variants determined by CPIC.

Another disadvantage of preemptive testing is the cost of testing. Schildcrout et al. studied 52,942 "medical home" patients (≥3 outpatient visits at Vanderbilt within 2 years) and found that 64.8 % were exposed to at least 1 of 57 medications with FDA pharmacogenomic guidance within 5 years, including 14 % having exposure to more than 4 of these medications over 5 years. Assuming reduction of risk of adverse events to baseline with alternative therapies, they estimated that, in this population over a 5-year period, implementation of pharmacogenomic testing could avert 383 serious adverse events such as myocardial infarction, warfarin-related bleeds, and myelosuppression [13].

12.5 Types of CDS Useful for Genomic Medicine

The three major types of CDS implementation methods include active, passive, and surveillance methods.

12.5.1 Passive Decision Support

Passive decision support amounts to providing education for providers and patients. Such efforts involve creation of human-readable documents and straightforward action steps for providers to follow when they prescribe medications where the

patients' response is influenced by genetic factors. This process can be very effective for medications prescribed by a select group of providers knowledgeable about the drug-genome interactions, such as the TMPT/thiopurine example above, or for genetic tests done for diagnostic support. Chemotherapeutics for cancer are another example, in which often a provider (or team of providers) orders a complex battery of tests, which increasingly includes somatic variants in the cancer, before deciding on a therapy plan. A human-readable interpretation (e.g., as a static, non-computable document) of genetic testing can effectively guide therapy for such cases.

12.5.2 Active Decision Support

Active decision support is a process that monitors provider activity and then actively advises the provider toward a path based on actionable information. It can be either synchronous or asynchronous. Synchronous CDS describes a workflow in which a clinician order, such as prescribing a medication, is monitored in real-time by rules embedded within the EHR, and clinician behavior is influenced when the rule is triggered. The most widely recognized approach is an alert window warning the user of a potentially risky order, such as an allergy or severe drug-drug interaction. Active decision support modules can contain both interpretation and advice (as would passive CDS) but active decision support has the added value of happening during the workflow and linking to actionable decisions, such as suggesting alternative therapies or doses. For genetic examples, this would involve taking into account the drug being prescribed, the genetic variants, and applying a rule to yield a recommendation. Since most examples in pharmacogenetics known to date involve genetic variants present in a minority of the population yielding increased risk of an ADE, most individuals would not need altering from typical therapies based on genetics. Thus, in many cases, active synchronous CDS may be invisible to the provider during the ordering process, and would only intervene on those individuals with the genetic variant.

Active CDS can also be deployed asynchronously, though this is less common. An example could be a system that evaluates for possible drug-drug interactions or gene-drug interactions in batch (e.g., once nightly) and delivers a clinical communication to a provider of a possible interaction. It can also suggest alternatives and would have the potential to provide a direct, actionable alternative suggestion. This model, however, may be desirable for lab results that are delivered after the medication is prescribed. Such decision support has been successfully applied when a medication that should take into account renal function has been prescribed. The CDS may suggest dosing changes when the lab results documenting an individual's kidney function are returned [14].

12.5.3 Surveillance Decision Support Mechanisms

In contrast to active decision support mechanisms, surveillance systems are designed to provide centrally-monitored "dashboards" for monitoring and managing something intervenable, such as drug dosing. One example of surveillance systems commonly used includes the anticoagulant warfarin, which can be implemented via a combination of human, workflow, and electronic means. In this chapter, we focus on electronic means for centralized decision support and surveillance of targeted drug-outcomes.

Surveillance systems have been used for germline genomic decision support at Vanderbilt University Medical Center [15]. Individuals with high-risk genotypes can be viewed as panels and their most recent medication lists searched for target medications to see if these individuals were still on these medications. These potential drug-genome interactions are reviewed by pharmacists, who contact each patient's provider for possible change in drug therapy according to genomic guidance. This type of CDS is important for individuals whose results are returned after an interacting medication is prescribed, especially so for tests ordered during acute events by non-primary providers (e.g., hospitalization for acute myocardial infarction for which *CYP2C19* testing was ordered to tailor antiplatelet therapy).

12.6 Standardized Representation of Genetic Variation

For genomic data to be actionable as inputs into a CDSS, they must be represented in computable forms in the EHR. Genotyping patients on a multiplexed panel generates a large set of potentially actionable genomic results that have persistent relevance over a patient's lifetime. Currently, systems that are using genomic CDS have typically represented their genomic results in the EHR in a variety of locally-developed, locally-computable formats [16–19]. Creating a portable version of results that can be shared across electronic medical records is a high priority for implementation of genomic medicine or any health analytics task that relies on uniform specification of genomic variation across EHRs. Standard representation of genetic results will also be important for broader adoption of genomic CDSS and to allow interaction of genomic data with a variety of systems.

Health Level Seven (HL7) has created a specification for genomic variation that leverages existing nomenclature standards for variant identification such as the HUGO Gene Nomenclature Committee (HGNC; http://www.genenames.org), Human Genome Variation Society (HGVS; http://www.hgvs.org), and the RefSeq ID (http://www.ncbi.nlm.nih.gov/refseq/). Additionally, it allows stipulation of brief coded interpretative phenotype text such as "poor metabolizer" using a controlled set of descriptors from the Logical Observation Identifiers Names and Codes (LOINC) vocabulary. The standard is focused on coding genetic test results from genotyping technologies where variants from a reference standard are defined as

opposed to raw sequence data. HL7 has released an implementation guide to generate messages on version 2.5.1 of the parent HL7 messaging standard. The clinical genomics standard is sufficiently robust to support interpretations at the allele (e.g., *CYP2C19**2) and gene (e.g., *CYP2C19*) level, and can describe in a single message a phenotype based on the combined impact of multiple gene effects. Such is the case with warfarin sensitivity, which is based on both *CYP2C9* and *VKORC1* variation. However, some common pharmacogene interpretation terms are not currently present in LOINC, such as the phenotypes of variants in *SLCO1B1*, which affect hepatic uptake of most statins and are known to be associated with simvastatin toxicity [20]. Additionally, momentum is building for newer standards to feature standard representations of genetic variation, such as the Fast Healthcare Interoperability Resource (FHIR) [21].

Direct support of clinical genomics standards from laboratory information systems and EHR vendors would accelerate the communication and interoperable use of interpreted genotype and sequencing results. Similar standards could be applied to family history and pedigree data as well. Currently, there are a number of systems that will structure family history/pedigree data in computable formats. The MyTree system, which is the focus of one of the grants in the Implementing Genomics in Practice (IGNITE) Network, [22] has been developed to be a consumer of FHIR information to receive EHR data in a standard format, though structured return of family history/pedigree data into the EHR has not yet been standardized.

12.7 CDS Knowledge Bases

Traditionally, clinical decision support content is developed by institutions or knowledge vendors and delivered by EHR vendors after undergoing extensive local customization. The scale and complexity of genomic medicine highlights the difficulty of recreating the rule set for every health system looking to implement across an enterprise. Several prior efforts within clinical decision support have aimed to publically standardize rule sets encouraging dissemination. A recent effort by two genomic medicine consortia, Electronic Medical Records and Genomics (eMERGE) and IGNITE, aims to collect local versions of genomic CDS and the design documents that were created during the course of implementation. The implementation 'artifacts' generated by consortia members have traditionally not been published or shared and include algorithms or logic, genotype to phenotype maps, optimizations of clinical workflow, design of clinician and physician facing user interfaces, and design or presentation of patient and provider communications.

A working version of the Clinical Decision Support Knowledge Base (CDS-KB, hosted at http://cdskb.org) has gathered a preliminary set of knowledge artifacts from academic medical centers and integrated health systems that have piloted genomic medicine programs. The site is supported through grants given by the National Human Genome Research Institute (NHGRI). The artifacts on the site are stored, indexed, and disseminated by the site. In addition, the site facilitates

exchanges and discussions between implementers across institutions and features a monthly educational webinar. While the majority of artifacts currently hosted represent a pharmacogenomics scenario given the accumulated years of experience within this domain, a few examples of CDS created for germline variation predicting disease state are included as well (such as *BRCA1* mutations and breast cancer or *APOL1* variants and kidney disease). The site is part of a larger effort being pursued by IGNITE and eMERGE to develop tools to help implement genomic medicine.

12.8 Examples of Genomic CDS in Practice

Pharmacogenomic testing to guide drug prescribing, often through use of complex CDS interfaces, has increased dramatically over the last 5 years. Sarkar identified genomic medicine clinical implementation efforts as one of the major recent informatics developments in his 2012 International Medical Informatics Association Yearbook Survey [23]. He noted only two clinical pharmacogenomics programs at that time: the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment (PREDICT) [17] and a similar effort targeted for the pediatric cancer population at St. Jude Children's Research Hospital [16]. Figure 12.1 shows

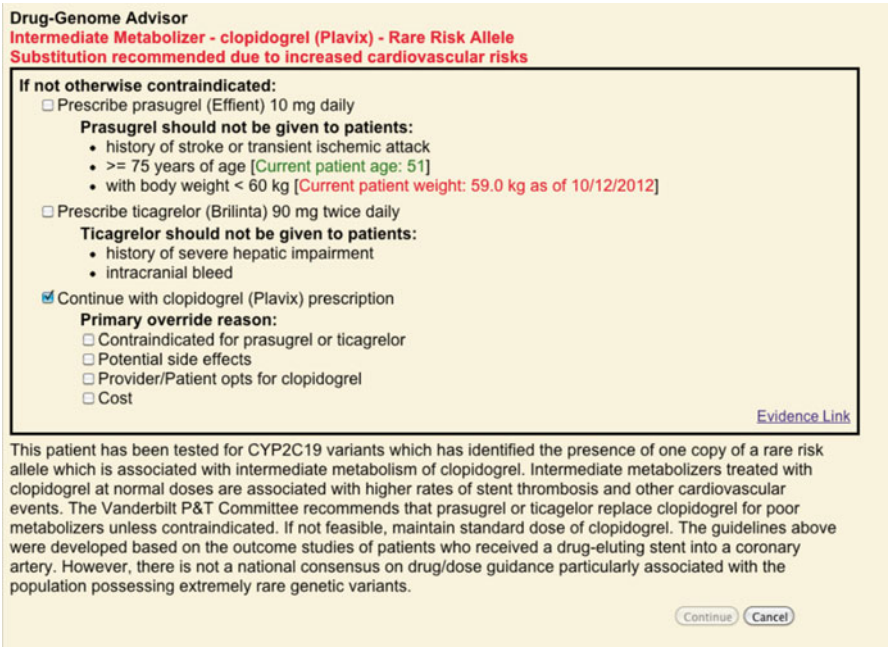

Fig. 12.1 Decision support for clopidogrel guidance as part of the Vanderbilt PREDICT program

a screenshot of a PREDICT CDS alert. Both of these efforts employed multiplexed genotyping assays to evaluate common pharmacokinetic and pharmacodynamic variants for germline variants affecting commonly prescribed drugs. To do so, both placed interpreted genetic results within the EHR in a structured format. A number of academic programs using genetic testing to guide care have since gotten underway. The University of Chicago is enrolling about 1,200 patients from 12 preselected physicians for prospective genetic testing [24]. Information on genetic variants is provided through a custom web interface that displays summarized phenotype information. The University of Florida/Shands Hospital's Personalized Medicine Program is testing individuals undergoing cardiac catheterization to genetically-guide clopidogrel prescribing [18]. They have since expanded to include other drug-genome interactions.

Each of the eMERGE Network sites developed systems to integrate genomic information within their EHR to guide prescribing. Specifically, the eMERGE-PGx project involved testing patients at pediatric and adult sites using a custom sequencing platform that investigated 84 pharmacogenes, with clinical validation and EHR implementation of select actionable variants. eMERGE sites have pursued a variety of genomic CDS implementation projects by leveraging either communicating with the EHR, infobutton technologies, or custom EHR solutions [25, 26]. In each of these solutions, a common theme of those with dense genomic information is a separate repository linked to the EHR, with actionable genomic information inserted into the EHR is computable formats (Fig. 12.2) [27, 28].

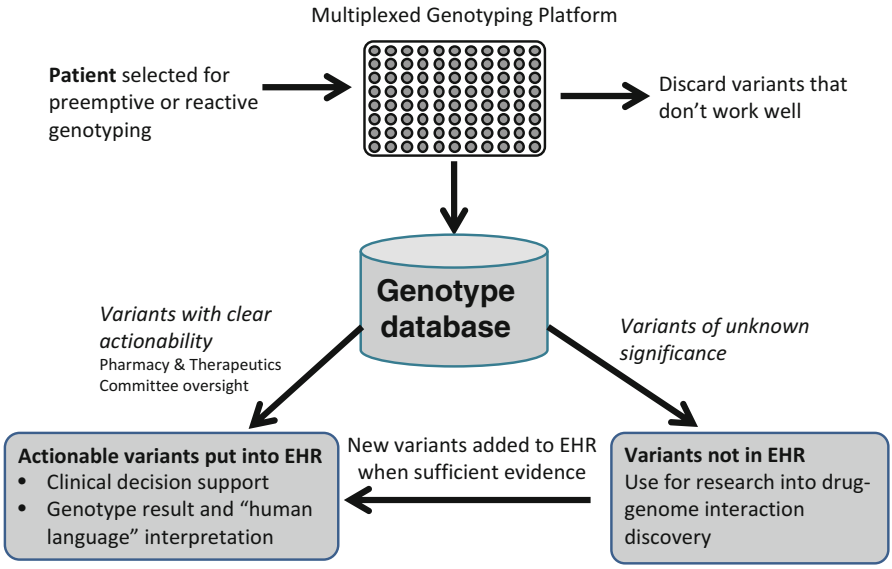

Fig. 12.2 Schematic for testing and storage of genetic variants in multiplexed testing (Adapted from Denny [27])

Although the use cases for somatic variation driving precision cancer care are becoming increasingly common, fewer systems have integrated somatic variant testing into CDSS. Typically, cancer genetic testing is performed by reference labs, which return results as documents containing non-computable information. One such example of computable variant information returned into the EHR is the Personalized Cancer Medicine Initiative [29] project, which includes structured somatic mutation testing with links to the MyCancerGenome website. The website serves as a central repository of cancer genetic variants, their interpretation, and relevant clinical trials. Thus, a provider looking at a given patient's cancer testing results can quickly discover the relevance of their genetic variants and can find out if there were open clinical trials for which the patient might be eligible. This report structure is a type of passive CDS. The authors are not aware of active CDSS that have been implemented based on somatic mutations.

In 2012, NHGRI funded the IGNITE network to integrate genomic information into EHRs and develop genomic clinical decision support at sites beyond large academic hospitals [22]. IGNITE consists of six member projects. Three of these projects are pursing pharmacogenomics, two others genome-based disease care, and another a computable family history module. Many of these sites are implementing genomic medicine across many sites. Duke University's Family History project is implementing within 28 primary care clinics across 5 different health systems. The Integrated, Individualized, and Intelligent Prescribing (I^3P) Network will be implementing germline and somatic pharmacogenomics in five different health systems. The Sanford Health System in the Dakotas, part of IGNITE, represents a large non-academic health system that has implemented genomic CDSS for a variety of medications (Fig. 12.3) [30].

12.9 Direct-to-Consumer Genetic Testing

Direct-to-consumer (DTC) genetic testing provides an avenue for patients to pursue genetic testing without requiring a doctor's order. Although initially there were several companies offering DTC genomic testing, 23andMe (Mountain View, CA) is the only major company still offering dense genomic testing to the public without requiring physician orders. 23andMe has currently tested more than one million individuals, and provides information to consumers on a consumer-friendly website that allows individuals to explore traits and ancestry information based on their genetic testing, which is performed on a high-density genotyping array performed in a CLIA laboratory. These personalized results initially also included health information, such as the individual's genetic risk for a number of diseases and some advice on pharmacogenomics, including warfarin sensitivity and clopidogrel efficacy. However, in November of 2013, the Food and Drug Administration ordered 23andMe to stop providing clinical guidance for genetic test results, citing "potential health consequences that could result from false positive or false negative assessments" [31]. As a result, 23andMe stopped providing disease risk and drug

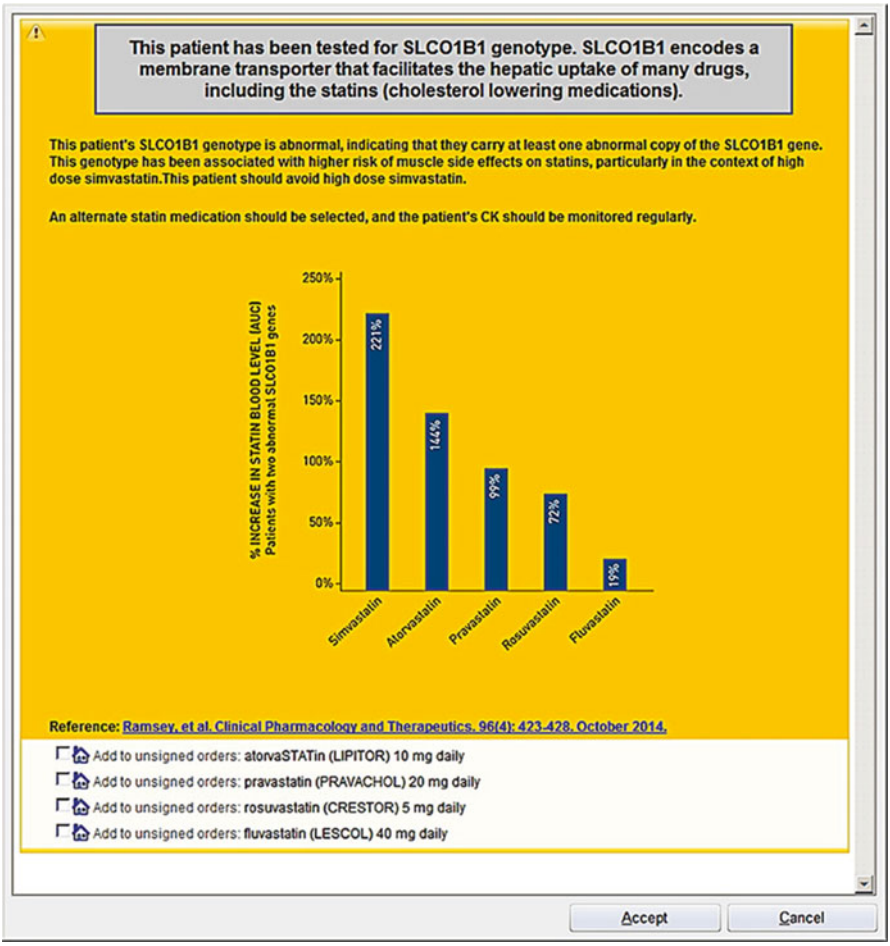

Fig. 12.3 Automated statin advisor implementing in an Epic environment. (Reprinted from Larson and Wilke [30], Copyright 2015, with permission from Elsevier)

response information to new enrollees, though such information remains available to prior enrollees at the time of this writing. In February 2015, 23andMe obtained FDA approval to release clinical information on Bloom syndrome carrier status, a rare Mendelian disease, as a first return to providing clinical data back to patients [32]. In addition, 23andMe offers the ability for customers to download, in bulk, their genome-wide genetic data, which include hundreds of thousands of variants. Thus, a particular savvy consumer (regardless of timing with respect to the FDA ruling) could go to 23andMe and download their genetic data and find and use the genetic data relevant to particular drugs (e.g., specific alleles at rs9923231 and warfarin sensitivity).

There is at least one published anecdote of DTC genetic testing being used to change care. Tenenbaum et al. described a model for how DTC genetic testing could be used to guide care with clinical input [33]. They reported the case of a woman with unremarkable personal and family history who learned through DTC testing about the presence of a prothrombin gene mutation, and as a result, underwent anticoagulation during pregnancy.

12.10 Conclusions

From the early days of clinical informatics to support order entry, CDS has been an important mechanism to effect change in provider behavior toward avoidance of medical errors, adherence to standards of care, and faster adoption of best practices. Researchers have leveraged CDS to not only enhance provider prescribing and monitoring, but also to engage multidisciplinary teams and to monitor a patient's changing conditions. Use of genomic information in CDS provides a new, but not altogether different, modality to enhance a provider's ability to prescribe the right drug at the right dose, at the first prescription. An exciting realization of pharmacogenomics is the shrinking of the domain of "idiopathic" reactions as some once unpredictable reactions become predictable. Much work remains to realize seamless genomic medicine through healthcare, but initial pilot projects are promising and provide guidance for broader implementation.

On January 20, 2015, President Obama announced a Precision Medicine Initiative (PMI), which has two major arms: precision cancer therapy and the creation of a natural, longitudinal cohort of more than one million individuals who will share their health data and biospecimens for research. One of the envisioned use cases for the PMI cohort initiative is study of pharmacogenomics and genetically-defined subtypes of disease, which may lead to targeted therapies, such as ivacaftor for the subset of cystic fibrosis patients with a particular CFTR mutation [34]. Individuals in the PMI cohort will receive genetic testing over time, which will include biomarkers of disease response (including but not limited to dense genomic investigation). A goal of the resource is that individuals will have access to their own data, and if they have genetic testing on relevant biomarkers, participants in the initiative could become advocates for use of their genomic data in prescribing. Similarly, the precision cancer therapy initiative will seek new knowledge for genomically-driven (as opposed to histologically-driven) cancer therapy. Both of these initiatives foreshadow a future with potential for dramatic growth in the opportunities for genomically-tailored care. Patients may catalyze the growth in use of these new classes of information, such as genetics, to guide their care. In order to achieve these goals, we will need adoption of EHRs capable of genomic decision support, agreed-upon standards for genomic representation, processes to maintain and update knowledge bases and CDSS, and report interpretations that are easily understood by both providers and patients.

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