Physician Perspectives on *CYP2C19* Pharmacogenomic Active Clinical Decision Support

Adam Nishimura

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Committee:
Peter Tarczy-Hornoch
Brian Shirts
Beth Devine

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Abstract

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Adam Nishimura

Chair of the Supervisory Committee:
Peter Tarczy-Hornoch M.D., FACMI
Department of Biomedical Informatics and Medical Education, Department of Pediatrics,
Department of Computer Science and Engineering

Actionable pharmacogenomic (PGx) information is growing exponentially with lowering costs of sequencing technologies, yet the best means to disseminate such data to physicians remains unclear. One method involves alerts triggered when a physician prescribes a medication through a computerized physician order entry for a patient known to have a particular PGx variant. We sought to assess physician perspectives of a prototype alert built for patients with *CYP2C19* variants being prescribed clopidogrel through a computer-based simulation and 15-item online questionnaire assessing their perceptions of the alert's design, placement in workflow, and PGx content. A random sample of 55 physicians participated in the study. 89% of participants would modify their prescription based on the alert; only 4% would override the alert. 92% of the sample found the alerts helpful in choosing an appropriate medication. 75% of the physicians were unfamiliar with the PGx interaction of clopidogrel and *CYP2C19*. In conclusion, this sample of physicians felt that the PGx alert was useful, though many were unfamiliar with the specific drug-gene interaction. Future work should assess the alerts in real settings and identify appropriate educational resources to supplement the alerts.

The following components of this thesis were written concurrently with manuscripts intended for publication. Text within is intended to appear verbatim or in similar form in the following peer-reviewed journals:

-Pages 7 – 29: “Pragmatic and Ethical Challenges of Incorporating the Genome into the Electronic Medical Record” – *Current Genetic Medicine Review*

Text within is intended to appear verbatim or in similar form in other manuscripts listed below which are being submitted to peer-reviewed journals:

-Pages 47 – 50: “Implementation of Clinical Decision Support Alerts for Pharmacogenomic Incidental Findings from Whole Exome Sequencing.”

-Pages 50 –65: “Physician Perceptions of a Drug-Gene Alert for *CYP2C19* Variants and Clopidogrel Metabolism.”

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INTRODUCTION: Challenges of Genomic Clinical Decision Support

I. Background

The National Human Genome Research Institute (NHGRI) was established in 1997 by the National Institute of Health (NIH) to manage U.S. governmental funding of genetics research. It was largely responsible for the Human Genome Project's completion in 2003 and continues to serve as a significant force in the focus of the nation's genomic research agenda. Every five years the NHGRI issues a new strategic plan that determines its funding priorities. In 2011, the NHGRI's current director, Dr. Eric Green, released the institute's plan in a published manuscript titled *Charting a Course for Genomic Medicine: From Base Pairs to Bedside*.[1] The article highlighted the growing need for translational research in genetics to implement genetic sequencing data into improved healthcare. Translational science, in particular translational bioinformatics (TBI), seeks to unite biological data with patient care through a variety of innovative, systems-based approaches.[2] The strategic plan was accompanied by a reorganization of the NHGRI's funding divisions to reflect this need; the Division of Genomic Medicine was created to manage translational projects including the Electronic Medical Records and Genomics (eMERGE) network and Clinical Sequencing and Exploratory Research (CSER), both of which focus on the clinical application of genetic data. Currently, the shift in focus of the NHGRI is further evidenced by its budget proposal to Congress for 2015. The budget shows a 29.4% decrease in the request for funding of research on the structure of the genome and a 37% increase in requests for funds to support research on the use of genomes to improve the effectiveness of healthcare.[3]

The sea change at NHGRI is driven by a vision of genomic medicine's potential based on a growing numbers of reports of genome-driven diagnosis, treatment and management. In 2010, a team in Wisconsin used exome sequencing to diagnose a novel, refractory form of irritable bowel disease in a young boy, leading to successful treatment.[4] In approximately 25% of patients with rare Mendelian phenotypes, exome sequencing of patient-parent trios can lead to identification of underlying genomic defects.[5] In the field of oncology, the use of therapies targeted at tumors with certain genetic variants has become a mainstay of treatment such as with trastuzumab for HER2-positive breast cancer and imatinib for Philadelphia chromosome-positive ALL and CML. Pharmacogenomics extends beyond cancer therapies to common medications, and allows providers to assess a patient's likelihood for adverse reactions or poor metabolism prior to prescribing a regimen. For example, between 30-60% of patients may have a variant in the gene encoding *CYP2C19* that reduces the enzyme's ability to activate clopidogrel, an anti-platelet agent pro-drug that is commonly used after percutaneous coronary intervention to reduce stent thrombosis.[6] Though these examples of the diagnostic and therapeutic applications of genomics have generated excitement among many clinicians and health care institutions, they are disparate and often specialty-specific. As reflected by the NHGRI's strategic plan, there are issues of scalability that must be addressed in order for genomic medicine to become a part of comprehensive, standard patient care.

Perhaps the most pressing issue is the integration of a patient's genomic information into his or her electronic medical record (EMR).[7] Beginning in 2015, meaningful use regulations of the American Recovery and Reinvestment Act will penalize health care institutes that are not using EMRs for patient care.[8] Thus, the health record promises to be a pervasive element in any given individual's health care. Since a patient's record could potentially be used throughout her entire life and serve as a hub for the variety of providers she may see, the EMR has been deemed a potentially convenient place to store a patient's genomic data.[9] Furthermore, EMRs possess

clinical decision support (CDS) tools that may prove vital in disseminating genomic data to the most appropriate health care providers at the most opportune times.

However, the information present in gene sequences is distinct from other types of medical data and current EMR systems are not structured to handle it. A thorough understanding of the nature of genomic data is therefore an important step in determining how it could be integrated with the EMR.

II. The Nature of Genomic Sequencing Data

Biology of Genetics

The "central dogma" of molecular biology that has prevailed since the mid-20th century states that DNA is the fundamental source of a given individual's inherited characteristics, or phenotype. A person's DNA goes through self-replication to exist within each cell of the body, then serves as the precursor for two steps that ultimately form the proteins that are responsible for the chemical reactions in those cells. Deoxyribonucleic acid, or DNA, itself is composed of two strands of continuous nucleotides. Nucleotides are molecules with a ribose (5-carbon) sugar and base component; they are connected by high-energy phosphate-based bonds. There are four different bases: adenine, guanine, cytosine and thymine. These bases define a nucleotide and the order with which they occur in the DNA sequence results in the unique nature of each person's genetic make-up.

The first process in the central dogma is called transcription and involves the formation of RNA from DNA. RNA is similar to DNA in structure, but the thymine base is replaced with a base called uracil. RNA is also less structurally stable than DNA and is often seen as an intermediary product in a variety of processes. There are different forms of RNA, as well, such as tRNA, rRNA, and mRNA. mRNA is the intermediate for protein synthesis and is created from DNA

within the nucleus by an enzyme called RNA polymerase. RNA polymerase's activity is controlled by a number of regulatory factors in the DNA itself as well as from other regulatory proteins in the nucleus. Indeed, it is important to note that transcription does not convert the entirety of an individual's DNA into mRNA all at once, but rather in targeted, controlled sections.

Depending on the specific needs of the cell undergoing transcription, certain portions of the DNA will be locked off from the process through a number of mechanisms. DNA is normally stored in the nucleus in a form called heterochromatin, in which the strands of DNA are wrapped around polar molecules called histones. Heterochromatin is structurally stable, but is not available for transcription or replication. Regulated by the removal of methyl groups or addition of acetyl groups, certain portions of the DNA are released from histones to become euchromatin, a form that can be transcribed. Furthermore, a given length of DNA will have sections, called introns, which do not become proteins. Protein-coding segments are called exons and compose the strand of mRNA after a process called splicing, in which the introns are removed from the initial product of RNA polymerase. Ultimately, it is only the exons of euchromatin that will be transcribed into mRNA, which is then exported from the nucleus for the next step of the central dogma.

Translation is the process through which mRNA is converted to proteins. This step occurs within a cell's cytoplasm and is performed by proteins called ribosomes. Ribosomes read three mRNA bases at a time (called mRNA codons) and translate the code into any of the non-essential amino acids. The way that ribosomes match up mRNA codons to amino acids is referred to as the "genetic code" and has been identified by researchers to have several important characteristics: it is unambiguous, meaning one codon will produce one amino acid; redundant, because different codons can instruct for one amino acid; continuous, since the

sequence is read consecutively; and universal, because the code is mostly conserved throughout evolution. The resulting strand of amino acids then undergo post-translational modifications and complex folding processes to form active proteins. Proteins perform the majority of reactions within the cell and the body and are thus largely indicative of a given phenotype. While there are clearly many steps in the central dogma that are important for the final phenotype, the field of genomics is primarily concerned with the initial elements of DNA and its transcription.

Advances in genetic technologies and procedures in the latter half of the 20th century have allowed geneticists to study the human genome with increasing detail. Prior to completion of the Human Genome Project in 2003 and the advent of high-throughput technologies, most of the tools for genetic analysis in both research and clinical settings were limited to identification of large chromosomal aberrations. Such techniques allowed comparisons of phenotypes (pedigree analysis), comparisons of amounts of a specific gene in a cell (Southern blot), localization of gene abnormalities (Fluorescent In-Situ Hybridization), and observation of imbalances on a chromosomal level (karyotyping). These methods are useful for characterizing Mendelian traits in which a single gene mutation results in an altered phenotype, such sickle cell anemia; errors in DNA replication, such as Trisomy 21 (i.e., Down Syndrome); and structural variations, such as copy number variations (CNVs), inversions and translocations, that generally involve between 1,000 bases (1 KB) and several megabases. However, there are many more subtle variations that occur in any given individual's genome that cannot be detected without interpreting the actual sequence.

Changes in any of the nucleotides of the sequence are called single nucleotide polymorphism (SNPs) and have a variety of consequences for transcription. A genetic sequence that is identical to the human reference genome and results in normal functioning proteins creates what

researchers call the "wild type" phenotype. Changes to just one nucleotide within that sequence can have effects on the final phenotype resulting in disease, altered metabolism, or other characteristic changes. A SNP can result in a *nonsense* mutation causing early termination of transcription and non-functional proteins, such as truncation of the *CFTR* protein in cystic fibrosis. Other mutations include *missense* or *frameshifts* that may cause changes in amino acids and *silent* mutations, which do not alter the amino acid and have no phenotypic change from wild type. Even SNPs that result in nonsense, missense or frameshift mutations may have no phenotypic effect if they occur in introns, heterochromatin, or other non-protein coding regions of DNA. Further variability exists depending on whether the SNP exists on one strand, or allele, of DNA or both. Thus, identification of SNPs and their location in relation to genes is a key component of genomic analysis.

The Development of Genome Sequencing

The invention of gene sequencing technologies and techniques provided researchers the ability to rebuild a genetic sequence and examine the impact of variations on the level of a nucleotide. Sequencing technologies began in the 1970s with the Sanger chain-termination methods, which used di-deoxy synthetic nucleotides to stop transcription at identifiable spots. This technique was used for the latter quarter of the 20th century with additional elements to increase the speed and decrease the costs with which it was used. In 1995, it was used in "shotgun sequencing" to create the entire genome for the virus *Haemophilus influenza*. It was also the technique that was used to sequencing the first human genome.

However, it was not until 2000, in which "massively parallel signature sequencing" (MPSS) was invented that the era of *next-generation sequencing* (NGS) began. NGS involves the creation of myriad fragments of a genetic sequence that is then reassembled into a continuous sequence using computational algorithms. This high-throughput process allows for entire genomes to be

sequenced in Whole Genome Sequencing (WGS) as well as just the protein coding regions with Whole Exome Sequencing (WES). With NGS tools, both the costs and time requirements of sequencing the entire genome plummeted. According to the NHGRI, the cost of sequencing the human genome in 2002 was approximately $100,000,000; in 2012 that cost was closer to $8,000.[10] And, while the first human genome took 13 years to recreate, today a genome can be sequenced in under a day.

NGS has given scientists the ability to rapidly and affordably sequence an individual's genome, but it has also resulted in a tremendous amount of biological data requiring computational management. Any given individual's entire genome sequence is approximately 90 gigabytes of data and has about 3.5 million variants from the reference genome created by the Human Genome Project.[11] Furthermore, there are errors that occur in the sequencing process that must be identified and filtered. In addition to "cleaning up" the sequence data, there is an ample amount of energy required for assembly, trimming, and handling repetitive sequences. Bioinformatics has played an essential role in developing the software to make these processes semi-automated, but the availability of different tools used by different laboratories makes it important to label the sequence itself with meta-data about how it was created.

Despite the growing popularity of NGS technologies, older methods are still used to analyze parts of the genome. Thus, "genomic data" refers to a very broad swath of data that is generated from a variety of genetic tests with a number of different characteristics.

Genomic Data from Different Tests

Genomic data does not simply refer to entire genome sequences, but rather differs based on the type of test used. While whole genome sequencing (WGS) and whole exome sequencing (WES) may eventually become standard forms of clinical testing, most clinical genetic tests currently

rely on targeted testing of components of an individual's genome. Targeted tests could utilize NGS technology, but could also be performed with the older aforementioned techniques (e.g., FISH). These latter tests require *a priori* identification of the target gene or variant of interest, and are generally faster and less expensive than WGS/WES. In addition, targeted testing is sometimes necessary to detect certain variants that WGS/WES cannot easily distinguish. For example, WES technologies have difficulty analyzing copy number variations in the *CYP2D6* gene that produces drug-metabolizing liver enzymes.

WGS/WES tests may be done for specific purposes, such as identifying a hereditary pattern of a patient's colon cancer, but the test may also reveal additional variants with a phenotypic impact. These auxiliary results are called incidental findings (IF). A given health care institution must decide whether or not it will return IFs to patients, weighing the clinical importance of the finding with the potential confusion and/or stress it may cause. Given the large number of results that could potentially be returned to the patient, there is concern that incidental findings of lesser importance could distract the patient from results of greater impact. Some institutions allow patients prior to testing to opt out of receiving incidental findings; others have used a staged-release of results to allow patients to focus on the most important findings first.[12] For all findings, incidental or intentional, providers must weigh the validity of the sequencing results, the likelihood of pathogenicity, and the potential implications of returning a genomic result to a patient.

Another division of genomic data is based on the source of the tissue sample. Tissues for genomic analysis in one individual can be drawn from germ lines cells, somatic cells, or tumor cells, all of which are likely to have a different pattern of variation. In the realm of cancer genomics, genotyping of a patient's germ-line, or inherited, cells differ from the genotyping of his or her tumor cells. Neoplasms result from mutations in DNA, the genetic sequences of

tumor cells are likely to differ from other cells in the body. The sequence from a tumor may further vary depending on the part of the tumor from which the sample was drawn and whether the sample was taken in bulk or a single cell in circulation.[13] Heterogeneity extends beyond germ-line and tumor cells to the entirety of somatic tissues. As the cost of genotyping drops such that a given individual may have multiple tissues sequenced, a major question in representing the genome in the EMR may be, "Which genome?"

Finally, any of the aforementioned genomic technologies can be used for "reactive", "pre-emptive" or screening tests.[14] Reactive tests are requested by a clinician when he or she believes the test may impact a patient's diagnose or therapy, similar to other laboratory or imaging tests. Conversely, pre-emptive genotyping is done prior to the clinical event in which the genetic information may be useful. Reactive genotyping would include the order of a HLA*B5701 test for a patient diagnosed with HIV prior to initiation of abacavir to predict a hypersensitivity reaction; pre-emptive genotyping would involve a healthy patient having WES in a clinical trial and discovering the HLA*B5701 as an incidental finding. The pre-emptive data would only be of use if the patient is ever prescribed abacavir in the future. Pre-emptive genotyping can be further distinguished from screening, as positive results for the latter are generally immediately actionable. For example, genetic newborn screening tests, for conditions such as phenylketonuria (PKU), are intended for diseases in which early intervention can ameliorate negative consequences.[15] Results of a pre-emptive genetic test may not impact a patient for decades, or at all. The role of the EMR is especially important in the latter scenario. Furthermore, while it is essential for screening tests to have a high sensitivity, pre-emptive genotyping may be considered a diagnostic test, and thus relies on higher specificity.

Thus, genomic data can have numerous characteristics depending on how it is created, the source of tissue from where it's taken, the intention of the findings and the timing of the genetic

test. In addition, genomic data is a complicated type of data for medical use due to its new and evolving base of research and evidence for clinical relevance. Compound these aspects of genomic data with the fact that it has vast implications throughout an individual's entire life and it becomes clear why it is difficult to integrate into medical computing technologies – especially the EMR. Fortunately, the NHGRI has supported a number of major academic medical centers in research to better understand the possibilities of genome-EMR integration. A recent review of literature published by these centers provides a nuanced understanding of the barriers to integrating genomic data into the EMR and utilizing it through clinical decision support tools.

III. Current State of the Genome-EMR Literature

On-going Genome-EMR Integration Projects

The Electronic Medical Records and Genomics (eMERGE) network initially emphasized variant discovery, but in its second phase is primarily concerned with genome-EMR integration.[16] The NHGRI founded the network in 2007 to explore how data in the electronic medical record could be juxtaposed with large DNA repositories in GWAS studies to identify the phenotypic importance of novel variants. Nine healthcare institutions across the U.S. compose the network, with Vanderbilt serving as a lead coordinating center. *(Table 1)* While each eMERGE site has different diseases of interest which it is investigating, all of the sequencing readouts are collated into a central biorepository for collective use. In addition to this large-cohort approach to variant discovery, eMERGE sites all investigate ethical and legal issues of genomic medicine, with particular concern for privacy and community engagement. In 2011, eMERGE funding was renewed for a second phase in which member sites were challenged to incorporate their sequencing data into the EMR and clinical care.

The Clinical Sequencing and Exploratory Research (CSER) consortium was created in 2010 by the NHGRI to develop methods of incorporating sequencing data into clinical care and to study

the ethical, legal and social implications (ELSI) of the process.[17] It is a consortium of nine sequencing projects and nine ELSI-based projects at different health care institutions across the U.S. (*Table 1*), coordinated by a center at the University of Washington. Each project focuses on a different medical application of genomics. For example, Baylor College of Medicine studies the use of sequencing to provide targeted therapies for childhood solid tumors, while Brigham and Women's Hospital focuses on genomic medicine in primary care and cardiomyopathy. Regardless of its specific medical application, each site is concerned with the incorporation of the genome into the EMR.

Table 1. CSER and eMERGE sites

CSER Sites	CSER ELSI Sites	eMERGE sites
• Baylor College of Medicine • Brigham and Women's Hospital • Children's Hospital of Philadelphia • Dana-Farber Cancer Institute • University of North Carolina, Chapel Hill • University of Washington • Hudson-Alpha Institute for Biotechnology • Kaiser Foundation Research Institute • University of Michigan, Ann Arbor	• Cleveland Clinic • Columbia University • Children's Hospital Boston • Children's Mercy Bioethics Center • Johns Hopkins University • University of California, San Francisco • Vanderbilt University • University of Washington	• Children's Hospital of Pennsylvania • Cincinnati Children's Medical Center with Boston's Children's Hospital • Geisinger Health System • Group Health Cooperative with University of Washington • Marshfield Clinic • Mayo Clinic • Mount Sinai School of Medicine • Northwestern University • Vanderbilt University

Recent publications from CSER, eMERGE, academic centers aligned with the NHGRI's Pharmacogenomics Research Network (PGRN), or independently exploring genomic medicine, have laid the groundwork for the integration of genomics in the EMR. Among the eMERGE sites, Mayo Clinic,[18] Mount Sinai School of Medicine[19],[14] and Vanderbilt[20] have written about

their experiences of incorporating pharmacogenomics data into their EMR systems. Sites independent of eMERGE and CSER such as St. Jude Medical Center,[21,22] Harvard University,[23] the University of Chicago,[24] the University of Maryland,[25] and the NIH's care center have discussed similar ventures.[26] These publications share the process of connecting patient genomic data to the EMR and offer a framework for much of the following discussion.

Prototypic Flow from Gene to EMR

Based on the recent genome-EMR publications, a generalized prototypic workflow tracing the steps from genetic test to EMR-based clinical application can be extrapolated (*Figure 1*). The first step of genomic data generation is sequencing a tissue sample from the patient. The sample can be processed using various methods: Next-Generation Sequencing (NGS) technology, microarray, or Sanger sequencing. These methods have been described elsewhere and will not be discussed here.[5,11,27]

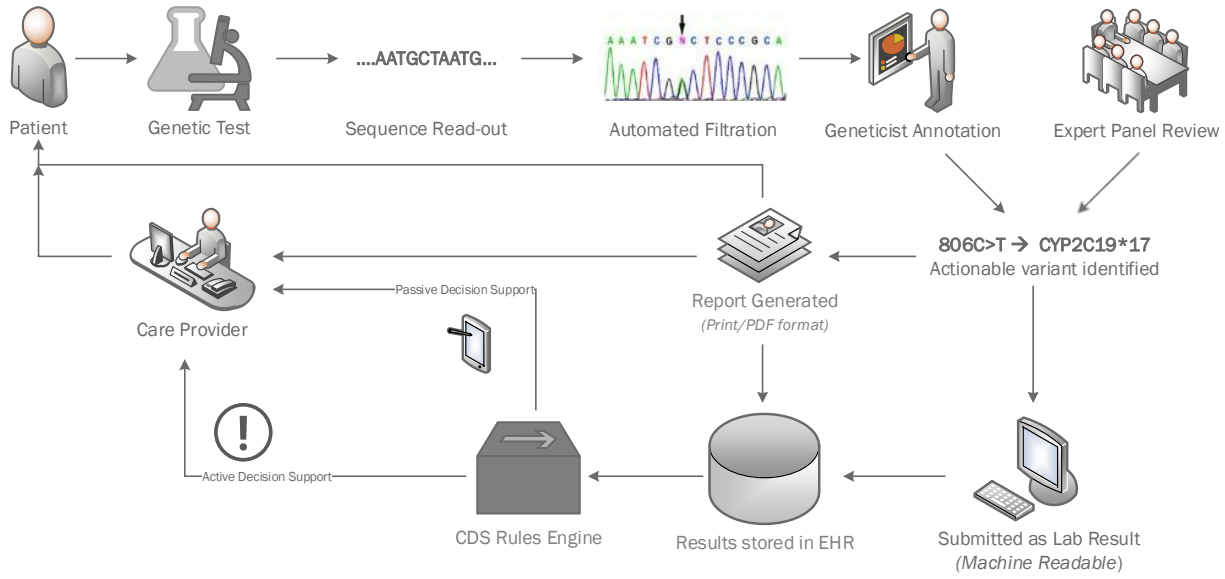

Figure 1. Prototypic Workflow of Genetic Testing to EHR Data

Any high throughput sequencing test will identify thousands of variants, genomic sites where the patient's sequence is different from the human genome reference sequence. Variants are identified and classified by pathogenicity in a process called annotation. Semi-automated bioinformatics tools allow the clinical laboratory geneticist to remove low-quality and common variants and flag variants with known pathogenicity. Annotation and prediction of phenotypic impact is a straightforward process if the variant is well classified, but if the variant is novel, a variant of unknown significance (VUS), or there is conflicting information from different sources, annotation may require extensive investigation by individuals or panels of experts. The results of genomic testing describing the variant and clinical significance are then disseminated to providers and, eventually, patients through a variety of means.

Representation Issues

Annotation

Once a genomic test is chosen and sequencing data is generated, institutions must determine which elements of the data are going to be stored. Currently, the parts of the genome that are most relevant to patient care are the variants that predispose an individual to a pathogenic or abnormal phenotype. While such variants are good candidates for inclusion in electronic records, accurately identifying, classifying and ranking the most actionable ones is by no means

straightforward. These processes are hindered by difficulties in annotation and a dearth of evidence supporting medical applications of genomics.

A consistent annotation pipeline helps identify the potential pathogenicity of variants, but the process is difficult due to a plethora of disconnected variant databases. Multiple databases of known variants exist, but each may carry different types of information, hindering any from serving as a fully comprehensive resource for annotation and the determination of a variant's clinical relevance.[28] Larger, popular databases used for annotation, such as HGMD,[29] are lacking in medically-applicable phenotypic information while newer clinically-oriented variant databases, such as GeneReviews and ClinVar, are currently limited in size. A survey of CSER sites found that institutions used a different databases for the annotation process.[30] The heterogeneity of resources increases the possibility that for any given variant, sites may reach inconsistent conclusions about pathogenicity and clinical implications. CSER and eMERGE leaders have long called for a well-curated, open-access, and clinically-relevant variant database to simplify and standardize the annotation process;[31] the NHGRI has responded accordingly by creating an RFP for the creation of such a database.[32] Another option would involve extensive sharing of information from the different databases. However, this solution would preclude fee-based services like HGMD and is currently hindered by problems in naming and identifying variants. Even if a variant is determined to have a high level of pathogenicity in the annotation process, institutions must still decide whether or not it requires clinical action.

Clinical Relevance

Currently, decisions about how a variant should be dealt with in the medical setting are determined by expert panels unique to different health care institutions. These panels often sift through the various forms of evidence and, as with the annotation process, their conclusions may be inconsistent between centers.[30] It is thus understandable that calls for a centralized

knowledgebase of clinical recommendations and strong guidelines tightly entwined with the variant databases have been made.[33] Some of the aforementioned variant databases, such as ClinVar or PharmGKB, have clinical guidelines for certain variants but health care institutions may be wary to rely solely on these for genomic recommendations. Accountability is a major issue, as hospitals and clinics may be concerned about liability for poor outcomes. Furthermore, characteristics of genomic tests make them subject to genetic exceptionalism, in which they are held to different standards than other medical tests.[34,35] The problem is exacerbated by the limited and fractured evidence base for many clinical genomic interventions.

A recent series of publications in the New England Journal of Medicine exemplified how the clinical relevance of genomic testing is a contentious issue. Three randomized control trials compared the impact of genotype-driven warfarin dosing on the time spent at an ideal INR. One showed mild improvements with intervention;[36] two showed no statistically significant differences between groups.[37,38] The publications prompted PharmGKB and CPIC to post an alert on their warfarin web guidelines and state that the papers were under evaluation for their impact on existing recommendations. However, as an editorial aptly noted, the studies were limited by controls having an unusually high frequency of INR testing, by focusing on short-term INR measurements, and by comparing complex, multivariate algorithms which only differed by the variable of genotype.[39] RCTs of pharmacogenomics, the author stated, must pay careful attention to choices of controls, interventions and outcomes. Nonetheless, the trials stimulated a discussion revealing the disparate opinions that exist regarding the use of genotyping to guide warfarin dosing.

Expert panels responsible for deeming a patient's variant clinically actionable must carefully sort through the literature before disseminating recommendations to their institution's providers through EMRs and clinical decision support. Shuldiner et al summarize the difficulty

in establishing a solid foundation of literature-based evidence for their creation of pharmacogenomics decision support for the anti-platelet agent, clopidogrel.[25] Smaller or non-randomized studies have given preliminary evidence in favor of genotype-driven anti-platelet management and guidelines offered by the Clinical Pharmacogenetics Implementation Consortium (CPIC), a project of PharmGKB and the PGRN, advocate altered therapies for poor clopidogrel metabolizers.[40] However, due to the low rate of adverse events currently associated with clopidogrel, powering an RCT to test the benefits of genotyping requires thousands of subjects and no trials to date have offered such evidence.[25] Thus, professional societies such as the American College of Cardiology are as of yet cautious about advocating routine genomic testing for anti-platelet therapy without a stronger evidence-base.[41] Such controversy is fueled by the limited clinical research that currently exists for most pharmacogenomics interventions.

For institutions implementing evidence-based medicine, clinical decisions are ideally informed by a strong base of statistically precise and scientifically valid research. However, the sheer number of genomic variants may preclude prospective randomized control trials (RCT) examining outcomes for each one.[42] While we can expect to see more RCTs and meta-analyses for common drugs such as clopidogrel and warfarin, it will be difficult to provide that level of evidence for the millions of variants that may impact patients' health – especially rare variants and variants of unknown significance (VUS). Proponents of genomic medicine have suggested that a larger-scale effort will require that alternative forms of evidence, such as non-inferiority comparisons, implementation research, or cost-effectiveness analysis.[43,44]

As resources to support the annotation processes become more consistent and additional research helps clarify issues of a variant's clinical relevance, the next question for institutions will be how to store such actionable variants.

Storage Issues

A given individual's entire genome sequence is approximately 90 gigabytes of data and has about 3.5 million variants.[11] Current EMR systems are not structured to carry that amount of information nor do they contain the software to analyze or manage the raw data in a meaningful way. Consequently, sequencing data is not stored directly in the records. Instead, many genomic-based lab results are currently captured in a semi-structured, free-text document written by geneticists or laboratory physicians.[30] These documents may be sent to a key care provider or stored into a patient's EMR as a PDF file. Unfortunately, they are not machine-readable and therefore cannot be used by EMRs to generate clinical decision support tools. Furthermore, the reports may not be readily visible to all the patient's providers, especially for care that is not temporally close to the genomic testing. Many institutions exploring genome-EMR integration leverage existing lab results systems to make parts of the genomic data machine-readable, but this solution poses some problems.

Identifiers

First, the consistency and interoperability of a discrete lab report depends on a standard variant identifier which may not exist. Currently, the variant naming standards established by the Human Genome Variation Society (HGVS) are considered the primary nomenclature required by most journals and publication sources. However, the so-called "traditional" nomenclature system is still used by certain labs and found in many earlier, important publications.[45] While some researchers have taken the approach of providing both naming formats, others may only use one of the two.[46] Even if the entire genomics community committed to the HGVS nomenclature, it is not without limitations. In particular, complex sequence changes involving translocations of varying lengths can result in an indecipherable name. The sheer intricacy of the genome may preclude a fully comprehensive naming system that would simultaneously

provide unique identifiers for every variant, thus IDs lacking descriptive information about the variants are likely necessary.

The variant identification systems in existence may be promising solutions, but are not yet consistent enough for complete integration of genomic databases. Reference SNP cluster Identifier (i.e., rsID) was created by the NHGRI's dbSNP database to catalog user-submitted variants. Different SNPs submitted by researchers are collated into a "cluster" if they exist at the same location in the genome. There are currently 4.5 million validated human SNP clusters identified with a unique rsID. Unfortunately, the identifier is not used for copy number variations. Additional variant nomenclature systems exist that are useful in specific contexts, such as pharmacogenomics, but unusable elsewhere. For example, the star-allele system for the P450 drug-metabolizing enzymes is a popular naming scheme, but only effective for genes encoding these enzymes. Without universal identifiers, the integration of data from different genomic resources remains a time-consuming process left to the annotator.

Without a consistent way to name and reference a patient's variant in the EMR, the storage and retrieval of genomic data becomes difficult. If an institution's laboratory uses an identifier for the variant in a lab result that does not match the identifier used in a different part of the EMR system, such as the rules engine used to generate clinical decision support, the discrete result will not be effective. Goldspiel et al note such difficulties in their system when the naming for an allele changed from HLAB5701 to HLAB57:01.[26] Even such minor discrepancies can have major impacts on clinical computing systems. One promising resource is the Sequence Ontology Genome Format Variation, an HL7 compatible ontology structured for variants applicable to genomic medicine.[47]

Another difficulty with discrete lab results is the choice in granularity that must be made, for which no best practices currently exist. For example, a patient has WES performed and is found to have a variant in the drug-metabolizing enzyme gene, *CYP2C19*. On the coarsest level of granularity, a discrete report could state in binary terms whether or not the patient is an abnormal *CYP2C19* metabolizer. However, an "abnormal" metabolizer could metabolize drugs too slowly (*CYP2C19*2* or **3*) or too quickly (*CYP2C19*17*), making a binary indicator insufficient. Instead, the report might state that the patient is a heterozygote for *CYP2C19*3/*2* variants or that the patient carries variants rs1295183 and rs1384513. While these latter formats have the benefit of granularity and the ability to represent the different impacts of specific variants, they are more challenging to maintain. Such granular lab results have the potential to drastically increase the number of defined elements in libraries of result definitions, rules engines, and interface engines. Though the granularity does not appear to drastically increase processing time for a rules engine,[48] it significantly amplifies the quantity of reports that must be curated, tested, and maintained.

Space

Regardless of how the discrete lab report nomenclature is structured, there is an additional choice in which variants will be captured and a resulting loss of data. The rest of the genomic data must then be stored elsewhere or abandoned completely. Yet, clinical genomics research is rapidly evolving; it is likely that some data filtered today as clinically-irrelevant may become relevant in the future.[49] An interdisciplinary group of experts at the workshop on "Integration of Genetic Test Results into Electronic Medical Records" convened by the National Heart Lung and Blood Institute stated as one of the desiderata of genome-EMR integration that raw genomic information be kept fully intact and accessible to avoid this problem.[50] Such an aspiration is not feasible using discrete reports alone for storage of the genome in the EMR. The workshop

experts suggested lossless compression of sequencing data to reduce file size. Alternatively, the genomic data could be stored in databases separate from the EMR that can be accessed as needed: Pulley et al discuss the "sequestration" of their raw sequencing data deemed irrelevant at the time of their study into a secure database.[20]

Given that an institution can determine which aspects of which genome to store and how it wants to store them, further questions arise in regards to how such information will be retrieved and utilized.

Ethical Issues

Return of Results

A major ethical concern raised by storage of data in the EMR is how it should be offered to patients. Given the complexities and implications of genomic test results, it is important that they be communicated to patients with sufficient educational support. Indeed, the American College of Medical Genetics and Genomics (ACMG) issued a recommendation in 2013 that patients be educated both before and after the testing.[51] Ideally, results would be returned with in-person explanation from a genetic counselor, supported by mixed-media educational tools. Yet, as the number of genomic tests increase, there will likely be a dearth of genetic counselors to facilitate such conversations and single visit discussions of all important results in an exome may become impossible. The task of explaining genomic test results would then fall to others. However, genetic counseling is a specialized skill that requires experience and practice. If all care providers may be responsible for returning results, genetic counseling would need to become a significant part of medical and nursing training. Providers would further need to learn their legal responsibilities to deal with both intended and incidental findings.[52]

Regardless of who ultimately returns the results, best practices will need to be established about when the results are given. For reactive genomic tests, it is reasonable to return the results as soon as they are available. However, for pre-emptive tests or incidental findings it may make more sense to inform the patient that he or she has the finding when it becomes clinically relevant. For instance, if a patient is found to have a variant in *TPMT* that alters his metabolism of thiopurine oncology medications, it may be more important to discuss the implications of the result if the patient needs such medications.

The return of results has special implications for pediatric populations. Long before next-generation sequencing, ethicists debated whether children should be given the results of genetic tests for adult-onset conditions. The prevailing argument stated that children have a moral right to an "open future", unburdened by knowledge of their imminent health status.[53] While the ACMG discourages screening children for adult-onset conditions, it has recently stated that incidental findings with "severe, actionable, pathogenic mutation" should be reported to children and their families.[54] The statement is supported by the ideas that such findings may be important for the health of the child's parents (e.g., BRCA mutation), which would ultimately help the child, and that incidental findings may not be accompanied by another indicator, such as hereditary risk, that would prompt the child to obtain testing upon reaching maturity. The statement remains controversial and has been deemed premature by experts who state the need for a broader conversation among stakeholders before any consensus is made.[55]

Privacy

One of the potential stressors patients may face upon the return of their results is a concern about who else in their lives should or could know about the findings. The social implications of genetic findings have long been an ethical topic of concern, as an individual's genetic pattern may reveal information about family members or communities. These issues remain true for

genomic testing and, in fact, may be more worrisome to patients as the scientific understanding of the genetic underpinnings of common disorders such as diabetes and heart disease improves. The Genetic Information Nondiscrimination Act (GINA) of 2008 prevents insurance agencies and employers from discriminating based on genetic information. However, the act does not seek to protect the privacy of genetic information. The privacy of genetic information in the EMR is protected under HIPAA legislation that covers all medical information; there are currently no national provisions for additional protection of genetic information, although several states have passed legislation specifically protecting genetic information.

Additionally, as previously stated, situations may arise in which a finding that was once deemed clinically-irrelevant is discovered to be pathogenic. Re-contacting patients raises a number of additional questions about what updates are worth informing the patient and whose responsibility it is to reach the patient.[56] As storage of genomic data in the EMR likely occurs soon after the tests are performed, protocol and systems will be needed to help providers deliver the information at the most appropriate times.

Informed Consent

Genomic information embedded in the EMR could serve as an important source of future research data, especially for institutions striving to become Rapidly-Learning Healthcare systems. However, use of that data should be approached with the utmost concern for patient privacy. New approaches to informed consent and de-identification must be developed to accommodate the potential for future use of digitally stored genetic data. The need for such approaches was highlighted by the legal battle of the Havapusai Native Americans. DNA samples in biobanks that were used for research purposes other than those to which they had consented. The research exposed information about the tribe that conflicted with its cultural beliefs as well as increased the risks of stigmatization about mental health issues. In order to

prevent similar occurrences, it will be important to ensure that patients are adequately informed about how their genomic data will be used or ensure robust de-identification of genetic data. Strategies for consenting patients to additional research, such as tiered consenting or presumed consent, may need to be implemented.[57]

Retrieval Issues

Targeted dissemination of clinically-relevant, patient-specific data to health care providers is a fundamental step of scalable genomic medicine and EMR-based clinical decision support (CDS) may be an important way to provide it.[58] CDS refers to information made available to health care providers at different points in care processes to strengthen their decision-making. While CDS can be provided in an analog format,[25] the EMR is commonly used to deliver it digitally. Certain forms of CDS have been shown to be an effective way to alter processes in care delivery, as well as to improve functional and clinical outcomes for a wide range of health care activities.[59] While there are many potential benefits to disseminating genomic data to providers through EMR-based decision support tools, the clinical decision support literature shows that these tools face challenges to successful implementation. At this point, an in-depth analysis of CDS is warranted given the complexity of these tools.

IV. Current State of the Clinical Decision Support Literature

Background

Clinical Decision Support is a broad term that applies to a variety of different techniques and technologies that have been used to help providers improve the quality of their care.[60] The concept can be broadly divided into *passive* and *active* decision support systems, the latter being automated and the former requiring access by the provider. Passive systems include information resources like lab reports scanned into the EHR, online reference systems such as

DynaMed or *UpToDate*, and, most broadly, the health record itself. Active systems include alerts that are triggered by certain provider actions in the EHR or by the interaction of certain elements in a patient's record. For example, if a patient has an allergy to penicillin, a passive CDS could be a note in the EHR's problem list, whereas an active CDS might entail a pop-up alert that appears when the provider attempts to provider penicillin through the Computerized Physician Order Entry (CPOE). While these are the most standard forms of CDS, the possibilities can be much more glamorous. For instance, the IBM computer *Watson* built with the *deepQA* knowledge-base was trained to help oncologists decide what the most appropriate chemotherapeutic regimen would be for a given patient.[61,62] Computer systems that can help solve complex problems like diagnosis and treatment plans, while perhaps more extravagant, are in fact some of the oldest forms of CDS.

CDS is one of the founding projects of the field of clinical informatics. During World War II, computers were being used in the early stages of artificial intelligence to create turrets that could respond to enemy planes.[63] The goal of using computers to replicate human activities continued in the academic sphere of computer science at universities including MIT, UC Berkeley, University of Minnesota and Stanford, after the war.[64] In the 1970s, Edward Shortliffe, a physician and computer scientist, published a seminal paper on his dissertation investigation of MYCIN, a computer-based knowledge-representation system that could help physicians with the complex task of choosing an antibiotic to treat microbial infections.[65] The MYCIN project, for many, represents the overlap of the artificial intelligence and medical communities and the birth of the field of clinical informatics.

CDS is an important facet of biomedical and health informatics because of its primary goal: to help care providers access, manage and use an increasingly large set of biomedical data. Biomedical data is unique in being timely, uncertain and actionable.[66] The data gathered by

researchers and clinicians is by nature temporal and incomplete, yet providers must still make decisions based on it. Another important facet of biomedical data is the rate at which it is growing. Indeed, the term *big data* has been adopted from other information-intensive industries to describe the massive amounts of biomedical data that are accruing thanks to advances in genomic analysis and the data-logging capabilities of EHRs.[67] On the clinic side, keeping track of new, relevant information is an extreme challenge for providers as the rate of clinically-relevant research rises. Thus, with continually changing nature of medical knowledge, tools such as CDS become important means of disseminating new information.

In general, the data used by CDS is wide-ranging and includes sources for concepts as well as rules to act on those concepts. For example, multiple comprehensive drug-drug interaction lists exist and each potential interaction can be considered an actionable concept for CDS. These concepts can be further categorized based on the severity of their results, the likelihood of their occurrence in a given population, and the alternate treatments to be offered instead. Ontologies and relational databases are both potential ways to store these concepts digitally, but they must be accessible by separate storehouses of rules. Rules specify how concepts should interact with actual data in the EHR/CPOE and must be customized to the environment in which they will ultimately act. The rules generally rely on a form of logic to specify *if* certain conditions exist *then* certain events should occur. Essentially, the CDS will draw on both databases/ontologies and rules to enact certain alerts or answers. Though this seems simple in theory, there are common barriers to creating CDS.

Pragmatic Challenges

The issues of standards are an important part of the evolution of CDS and serve as an example of the challenge of knowledge representation.[68] Standards for clinical terminology, such as ICD10 or HL7, are often used to structure the database or ontology of concepts from which CDS will be

generated. Thus, more functional and comprehensive standards allow for more customized and granular CDS opportunities. Certain CDS will attempt to draw on clinical guidelines for the rules database. Standardization of the clinical terminology improves the interoperability of a CDS tool. If the tool draws on a standard that is shared at another institution the tool can be adopted by the second institution. It should be noted that CDS for a given EHR/CPOE system may not be compatible with other systems.

In addition to standardizing clinical codes and program structures, CDS developers are also interested in standardization of guidelines. Since clinical guidelines are updated frequently, it would be ideal for the CDS system to have a way to draw from the guidelines in real-time and ensure that the support provided is in its most up to date form. To make guidelines machine readable, a standard syntax for guidelines would be necessary. Attempts at this have occurred in the past with GLIF,[69] but the support behind such standards have waned due to problems with unclear funding sources and discrepancies in needs between groups.

Finally, there is the challenge of integrating CDS systems into clinical workflow.[70] With MYCIN, it would take ample time for a physician to receive a diagnosis from the program, thus it would be difficult for the physician to use at the time she might need it most—with the patient at the point of care. The clinical workflow has developed over decades with paper records and clerical staff. As informatics attempts to replace these components with digital technologies, significant effort must be given to ensuring that the technologies don't distract providers from patients. Many providers and patients, too, are cautious about the creeping of technology into the clinical space as it poses further questions about privacy and accountability.

In the realm of clinical informatics, accountability largely comes into play in terms of who is responsible for the decisions made about or for a patient.[71] This is a particularly poignant issue

for CDS, as physicians may relinquish accountability to the information that has been propagated through support systems. On a superficial level, patients may develop a sense of unease if they discover that a computer, rather than the physician, has influenced their care. While clinicians and informaticists realize that the computer is merely aiding in a decision, there are valid concerns about where the information that the computer provides originates. The original ideal with "expert systems" – one of the original forms of CDS – was that expert clinicians would generate the rules for a CDS system. However, it has become clear that there are certain clinical topics without black and white answers.

Guidelines developed by professional societies offer recommendations, but even these may be in disagreement or influenced by conflicts of interest.[72] Furthermore, there have been some interesting data about information and knowledge attrition – even if the "right" guidelines are put in place, how long will they last? De Dombal, a British physician and informaticist who studied the use of CDS in acute abdominal ER management, identified this problem as early as the 1990s. In an editorial in the Archives of Internal Medicine, he discussed a study in which a CDS tool's performance "for the first few years exceeded that of even the best clinicians; but gradually deteriorated – until it was regularly exceeded by the clinicians performances."[73] He went on to postulate several explanations: perhaps the clinicians who "fed" data into the CDS "tired of their new toy"; or, maybe the updates that took place just became less stringent due to the data sources. While De Dombal hoped that CDS that could constantly and automatically source new knowledge might solve the mystery, the same problems still remain active sources of inquiry in the field today. If CDS systems are going to provide physicians with access to advice or information, informaticists face the challenge of sourcing the advice and deciding who—or what—will be responsible if the support system leads to problematic care.

Significant Literature

The inherent problems of CDS juxtaposed with its many hopefully possibilities has resulted in a sizeable amount of research on the subject. The historical development of CDS has been traced by Wright and Sittig, in a 2008 literature review that identified four different phases of CDS evolution.[74] The first phase of CDS development, as mentioned earlier in this paper, focused on standalone decision support systems such as MYCIN. Sittig and Wright identify the beginning of such systems even earlier with the 1959 paper by Robert Ledly and Lee Lusted regarding the use of Bayesian probability to help diagnose diseases with punch cards. Other seminal projects include Homer Warner's congenital heart defect diagnosis formula at University of Utah, Howard Bleichs acid-base disorder therapy system, de Dombals system for diagnosing gastric disorders, and systems following MYCIN such as INTERNIST and DXplain. The second phase of CDS development are systems that integrate into existing HIT structures. Examples include HELP, COMPAS, or the Veteran Administration's CPRS (Computerized Patient Record System). The third phase focuses on standards for improving CDS interoperability like Arden Syntax, GLIF and GELLO. Finally, the fourth phase includes service models such as SAGE (Shareable Active Guideline Environment) project or SEBASTIAN.

While Wright and Sittig's manuscript provides a historical overview of CDS technologies, a number of systematic reviews offer an overview of the types of research that have sought to study and improve CDS. Garg et al's 2005 systematic review in JAMA covered almost a hundred studies and found that overall, CDS improved the performance of health care practitioners.[75] In particular, active CDS – or CDS with automatic prompting – were more likely to improve practitioner performance. Unfortunately, the review identifies a potential source of publication bias as studies that focused on CDS systems created by the study authors were more likely to show successful outcomes. A more recent systematic review in the Annals of Internal Medicine

by Bright et al examined the literature up through 2011, gathering 148 randomized controlled trials. The review showed that CDS was overall successful in improving process outcomes for preventive services, ordering tests and prescribing therapies.[59] However, the authors note the lack of research on CDS impact on patient-centered outcomes, heterogeneity in research protocols, and the large potential for publication bias.

A number of researchers have offered useful perspectives on "home-grown" versions of CDS that have been developed at certain medical institutions. Unlike the proprietary vendor versions of CDS offered by companies like Epic or Cerner, institution-based CDS systems have been around for much longer and in many cases, have been relatively successful. Thomas Payne has written extensively about CPOE, order sets and alert fatigue based largely on studies performed with CPRS, the EHR/CDS system established at the VA hospitals.[76] Similarly, Rosenbloom has leveraged the experience of Vanderbilt's CPOE system, "WizOrder" to try and identify the "anatomy" of decision support systems.[77]

While many informatics researchers are eager to identify solutions to the existing shortcomings of CDS in order to reduce medical errors and improve quality of care, some have been more cautious about our expectations for the technology. A number of studies have asked the question, "Can CDS actually cause *new* types of medical errors?" Koppel et al. performed a qualitative and quantitative study at teaching hospitals between 2002 and 2004, interviewing a variety of hospital personnel and focus groups about CDS, in particular, CPOE, systems. They found over twenty elements of CPOE that could increase the risk of medication errors. Incoherent displays, ignored notices, inflexible ordering formats and functions that increase double-dosing were all frequently occurring phenomena at the participating hospitals.[78]

However, a number of editorials regarding the study identified that there were major flaws in the design of the CPOE system tested and that it lacked a development considerate of clinicial workflow.[79] Along these lines, Del Beccaro et al, at Seattle Children's Hospital, found that when considerable attention was given to design and implementation, a new CPOE system was not associated with increased mortality rates.[80] Another researcher, Joan Ash has similar research interests and later, in 2007, performed a telephone survey with her team to ask 176 hospitals about adverse consequences of CPOE use. Her team categorized eight types of consequences and found that 72% of respondents ranked them as "moderate to very important."[81] Ash and another collaborator on the paper, Dean Sittig, have also focused on the provider perspectives towards CDS and CPOE.

Ash's and Sittig's focus on the provider has initiated a movement towards studying the way that providers interact with the CDS technologies. Jan Horsky and his team at Partners Healthcare in Boston, shortly after the release of Koppel et al.'s 2005 article, published a commentary discussing the need for CDS researchers to pursue cognitive science and human-computer interaction (HCI). With the possibility that CDS may in fact *increase* medical errors, Horsky et al states that "a lack of attention to the principles of HCI in clinical software design is becoming a critical safety hazard."[82] Indeed, the use of cognitive analysis is likely to be an important methodology in future studies of CDS efficacy.

Sheehan et al recently published a report about a study they performed on physicians who ordered antibiotics in the neonatal ICU through a decision support system. Using a cognitive analysis technique called Theory of Action, developed by the engineer, Donald Norman, they attempted to identify what elements of the CDS system could cause unnecessary cognitive drain on the providers.[83] The importance of cognitive analysis was identified earlier by Patel et al in a JAMIA study from 2000, in which the team studied how use of a CPOE system actually

influenced the thinking and reasoning methods of the providers who used it. In their conclusion, they state that the importance of cognitive analysis and HCI in CDS is because "some of the most enduring effects of information technology may be both complex and unanticipated by both designers and evaluators of systems."[84]

As a subset of HCI, Dr. Horsky has also been involved with research to incorporate principles of User-Interface (UI) from engineering and industrial design. In a 2012 literature review, Horsky et al established a list of design recommendations for CPOE that emphasized issues like consistent terminology, unambiguous unit usage, concise language, visually distinct screens for confusable items, and clearly legible, sans serif fonts.[85]

Other approaches to improving CDS have looked towards fields outside of medical informatics for inspiration. Wu et al performed a systematic review of decision support tools outside of the health care realm as many other information-intensive industries have been much more successful with implementation.[86] Focusing largely on the literature for military, business management and law, they identified a number of lessons that could be applied to medical CDS development. For example, they found that decision support in these other fields offered its users a "big picture" systems-level view of an issue, whereas the literature for CDS in the medical field has spoken little about attempts to minimize tunnel-vision and myopia.

While the implementation of CDS has many challenges, the research of CDS faces its own limitations and problems. For instance, identification of a gold standard for CDS is fraught with difficulty. First, there are many gold standards that people have used depending on what they want to study: did the CDS provide the "right" answer? How often does the CDS get used or ignored? Do people like the CDS? While these are all reasonable questions, it is difficult to ascertain which is actually the most important in improving patient outcomes. Next, even when

the question of interest has been identified, gold standards can be elusive. Eta Berner discussed the shortcomings of a gold standards that have traditionally been used to study CDS efficacy.[87] In large part, the problems exist because the main tool we have to measure CDS against is the traditional physician workflow – which in itself is incredibly variable and individualized. Finally, there is a practical challenge in studying CDS systems that have already been implemented in an organization. In a given institution, the CDS system effectively alters the entirety of the workflow and eliminates any potential control group. Randomized control trials, cohort studies and even case control studies are difficult to perform in a real setting due to this problem. Unfortunately, the remaining study designs such as before-and-after analysis or simulation studies are generally perceived to be of lower quality and thus make it harder to infer the causal impact of CDS technologies.

Philosophical Challenges

In addition to research challenges, CDS brings up broader issues in the philosophy and sociology of technology studies. Experts in the study of technology have recognized the idea that tools and systems are not inert, valueless, inanimate objects. Any piece of technology that humans have developed to further their own aims is inherently embedded with particular concerns, values and consequences; CDS is no exception. Ash and Sittig have investigated the fact that CDS has consequences both intended and unintended.[81] The intended consequences are the ones for which CDS was ostensibly created: to improve health care. However, with all those expected consequences comes unintended, unforeseeable ones, for example, the issue of alert fatigue.

The consequences of a technology help reveal the values of its designers. It is easy to understand the conscious values of CDS's designers, such as a value of increased efficiency in the provision of care and a belief in evidence-based medicine. More challenging is to

understand the values that have led to unexpected consequences. It is not necessary to believe that there was a malevolence intended on behalf of CDS's creators. Rather, it is helpful to recognize that they carried unconscious and cultural values that were unknowingly embedded in the tool.

One value represented by CDS that has caused difficulties in the implementation of the tool is that of consistency, prized over physician autonomy. A common complaint of physicians where CDS is newly implemented is that, to them, the tools is created because they can't be trusted to do a good job on their own. Despite the evidence suggesting that outcomes can be improved with CDS and the mantra that CDS tools supplement, rather than replace physician knowledge, physician push-back is a major hindrance. Enforcing adoption of CDS has thus become a major socio-technical issue with the majority of responsibility lying in the hands of management. Ample articles have been written by the institutions that have been successful at propagating CDS throughout their systems and often involve the idea of finding a "physician champion" who other physicians respect and who will help advocate on behalf of the tool.

Another potential problem with technology is its ability to *alter its user* in unpredictable ways. Neil Postmen makes an even strong claim, that "technology changes the practice of medicine by redefining what doctors are, redirecting where they focus their attention, and re-conceptualizing how they view their patients and illnesses."[88] Evidence from HCI studies of CDS have been suggestive of such transformations as well. The aforementioned article by Patel et al. serves as an example, as the researchers found that physicians' use of digital CDS systems altered the way they reasoned through patient management. In some respects, the alterations of thought and behavior that happen with use of a tool like CDS may be good – it may increase the logic and rationality with which physicians approach clinical care. However, the negative impacts of that process occur when the change in practice induces a dependency on the technology. For

example, if a physician becomes reliant on reminders and alerts to help her reason through a case, we might be concerned that the tools have dulled her clinical reasoning skills. In such a mode of dependency, the physician is at risk of making mistakes if the tool fails (e.g., penicillin allergy in a human-readable but not machine-readable form in the EHR and the trigger fails to fire) or the entire communication system fails (e.g., loss of power to hospitals during hurricanes Katrina and Sandy).

Finally, Postman, has commented as well on how technologies are created to solve problems, but beget unique problems of their own that require additional technologies to solve.[88] The tautology ends up resulting in increased labor and increased technological specialization to sustain a technological fix without addressing the underlying problem. For example, CDS is a potential solution to the plethora of new biomedical data that physicians need to implement. However, it is also being offered as a solution to medical errors, as stated in the introduction. In this latter scenario, there are many unanswered questions regarding other possible problems leading to the errors: are residents sleep-deprived? Are incentives in place to ensure proper clinical management hand-offs? Is there a legal and social culture where physicians can admit to mistakes? If CDS is implemented without addressing the other underlying sociotechnical issues of medical errors, we should not expect it to solve the problem – indeed, we might prepare ourselves for new types of errors that the technology could create.

Summary

In sum, CDS has been offered as a theoretical solution to a number of problems in medicine and it has proven itself in a variety of settings to be effective. However, there have also been instances in which CDS has proven itself to be not just ineffective, but detrimental to clinical care. A large number of research questions in the field of informatics have been generated with

the goal of improving CDS and more will no doubt arise before the goal has been achieved. While many of these problems are currently technical (e.g., how to store and represent data), there is a growing concern about the psychological, social and organizational impacts of CDS. The technical problems are not insurmountable and, to some degree, the problems of implementing CDS will be ameliorated as more physicians are trained in an environment with CDS and as more institutions are required to have the technology to meet Meaningful Use criteria. However, the problems of CDS that will remain are going to be the ones that could easily be ignored or hidden "under the hood". Those problems will relate to whether or not we can fulfill the original ideals of CDS – to supplement, rather than replace physician knowledge – and to enhance, rather than detract, from humane, interactive patient-centered care. The looming questions will be, "Can CDS become an educational tool rather than a herding tool? Can we use it to improve our physicians as individuals instead of enforcing it as a crutch?"

V. Clinical Decision Support for Genomics

Genomic data could potentially take advantage of both passive and active forms of decision support. Indeed, in many of the on-going pharmacogenomics projects, a shotgun approach is being used to disseminate the data in as many forms as possible.[19] Existing examples of genomic CDS include static PDF reports, a line in the patient summary, a statement in the problem list, a genomics "tab" dedicating an entire page to such information, as well as drug-gene alerts triggered within a Computerized Physician Order Entry (CPOE) system.

Drug-gene alerts are an attractive form of pharmacogenomic CDS as they leverage existing drug-drug interaction rules engines and serve as a simple platform for "pre-emptive" genomics.[14] Because a pre-emptive genomic test may be separated from its clinical use by years, CDS solutions that ensure a provider is sufficiently notified at the appropriate time are required. As most EMR systems already have CPOE-based alerts, they are a quick and easy answer.

However, they are far from a silver bullet as they carry with them a number of challenges such as the threat of "alert fatigue".

The concept of alert fatigue has become an important field of study in the CDS literature and refers to the accidental override of significant alerts after becoming accustomed to overriding insignificant alerts.[89] Medication alerts are often ignored or bypassed, perhaps as much as 96% of the time.[90] In some cases, overriding alerts is appropriate, but occasionally it is to the detriment of the patient.[81] Key elements of effective alerts have been identified including high specificity, consistent design elements, appropriate visuals, supporting advice, and clinical relevance.[91] The major contribution of genomic medicine to clinical care is high specificity, as the associated tools could potentially be functional on a patient-by-patient basis. However, the research-base of best practices for genomic-CDS visual and educational content is limited.[92] And, as stated above, stable, evidence-based clinical relevance is still a major challenge for genomics. Furthermore, clinical relevance for decision support tools not only refers to available guidelines, but also to the tool's ability to accurately address the information needs of a specific clinical event between patient and provider.

Goldspiel et al highlight the difference between pre- and post-genomic testing alerts, exemplifying the need for alerts that are relevant to an institutions patient and provider populations.[26] Their CDS system includes alerts that fire when a provider prescribes the HIV medication, abacavir, for a patient. Pre-test alerts inform the provider of the risk for hypersensitivity reactions among patients with HLAB5701 variants and recommend genetic testing prior to initiation of treatment. The post-test alerts draw on a patient's genomic data to inform the provider that the patient *has* such a variant and that alternative treatment should be pursued. Providers overrode 100% of their pre-test abacavir alerts.[26] The authors note that HLA testing is routine and that all of the patients had received the tests elsewhere or were

already taking abacavir, thus making it reasonable for the providers to override. In this particular setting, using post-test alerts would likely prove more useful for the institution's providers and also reduce the total number of alerts to which they are subjected. The example highlights the need to consider both when and how an alert is intended to fire, which must be recognized for each specific drug-gene interaction of interest and each institution's particular patient population.

Given the potential negative effects of active CDS for genomic purposes, it is not unreasonable to look for passive or "semi-active" solutions that can also be rule-driven and patient-specific. O'donnell et al describe their passive CDS system as a provider portal that contains all of a patient's pharmacogenomic information and utilizes color-coded traffic light icons to signify different levels of priority.[24] One of the concerns with passive CDS is that they require extra actions from the provider and are unlikely to be utilized. Although O'donnell et al.'s portal was only piloted with six physicians, there was a high use rate (86%) based on the number of clinical encounters in which the portal was accessed.[24] Hoffman et al also describe the creation of a passive pharmacogenomics tab in their EMR system, which functions like a traditional lab results tab but with a "lifetime nature" to capture the temporal aspects.[22] Finally, many groups found the genomic drug information worthy of the patient's problem list. Indeed, Bell et al. even utilized the problem list entry as the discrete data for active CDS tools, bypassing issues of multiple lab results contributing to one phenotype (e.g., *CYP2C9* and *VKOR* both impacting warfarin metabolism).[21] Whether an institution chooses to use passive, active or both forms of CDS, the uptake and usage of the tools depends largely on provider buy-in.

Successful CDS require that providers trust the tools as a source of support and that they understand how the tools can improve their practices.[93] Engendering trust in genomic CDS tools is complicated by the fact that the knowledge generated by genomics will eventually exceed

the mental capacity of any individual physician. A single clinician will not have the time or ability to personally assess the clinical significance of each variant that could potentially be presented through decision support, thus, it will be difficult for them to evaluate the reasoning behind the tools. When a provider must abdicate her decisions to a computer, the "black box" effect can threaten her confidence in her actions. CDS developers can address this issue by stating the sources for decision support recommendations and offering the educational resources needed for personal investigation whenever possible. However, the choice of educational resources to provide remains a question. Genomic-CDS projects have sought to educate providers about their interventions prior to exposure,[19,26] upon the launch of a new drug-gene interaction through newsletters and presentations,[22] or within the CDS itself. Mayo Clinic, for example, provides education within the CDS by linking out to short summaries in the AskMayoExpert tool.[18] Offering such resources through active CDS ensures providers have educational resources at the point-of-care;[58] however, it has yet to be determined that alerts occur in the most opportune teachable moments for the complexities of genomics.

A final issue regarding genomic clinical decision support is deciding which providers will be alerted to the findings. It has been noted elsewhere that, despite the growing ability for automated annotation and development of comprehensive knowledge bases, the role of the care provider in interpreting and conveying genomic information remains of tantamount importance.[94] Thus, ensuring that the proper provider is given the responsibility of communicating genomic results with a patient is key. For certain pharmacogenomics findings, such as a predisposition to myopathies from statin drugs, it would be reasonable for a patient's primary care provider or cardiologist to know the information. However, the cardiologist is much more likely to have been exposed to issues of pharmacogenomics for this specific drug. Surveys suggest that genetic training for many primary care providers is limited.[95] Given the

need for successful genomic CDS tools to have supporting educational information, it is important to tailor the tools to the needs of the different types of physicians.[96]

Myriad elements go into the creation of effective CDS. As the issue of alert fatigue suggests, poorly designed and executed CDS is not only ineffective, but potentially harmful. While a sizeable pool of research has begun to reveal best practices for particular CDS uses, such as the prevention of drug-drug interactions,[97,98] it may not translate perfectly into genomic-based CDS. Indeed, there is currently no consensus on which forms of decision support are most necessary and appropriate for genomic data;[99] many of the early exploratory efforts of genome-EMR integration will hopefully provide evidence to establish genomic CDS best practices. The additional complexities of sequencing data will undoubtedly require CDS tools that are uniquely adapted for genomic medicine. Creative approaches to CDS will likely be required: the field of human-computer interaction has shed light on to the subtleties of CDS design that influence the tools cognitive impact on providers.[82,91] Further insight from traditionally non-medical fields may in the development of effective genomic CDS.[100]

VI. Physician Interactions with PGx CDS at UW

The existing clinical decision support literature reveals the difficulty in developing successful interventions. As discussed, an ample amount of attention must be paid towards the design of the CDS tool in terms of visual aesthetics, accurate and effective content, and appropriate timing within the clinical workflow. Indeed, the importance of these concerns is heightened when considering the potentially negative impact of a poorly-designed CDS intervention. While this remains true for both passive and active forms of decision support, active forms are perhaps more likely to engender negative consequences due to the growing threat of alert fatigue. Though these issues have been studied in other context, such as drug-drug interaction CDS, little research has been done in relation to pharmacogenomics (PGx). The growing importance

of PGx in clinical care and the impending necessity for methods of disseminating patient-specific PGx data to health care providers highlight the need for additional research in best practices for PGx CDS.

Research focusing on aspects of usability in PGx CDS has begun at the University of Washington. Devine et al. performed a multi-methods usability study of PGx alerts that were created in a prototype version of PowerChart® (Cerner Millenium®).[101] Though PowerChart® was not live at UW, the researchers were able to setup simulation labs in which study participants could interact with the CPOE and encounter the alerts in hypothetical cases. Indicators of usability were captured through a pre/post-survey as well as a heuristics-based analysis of a recorded "think-aloud" process. Seven cardiology and three oncology fellows were invited to participate in the study and a number of important results were generated. Qualitative results included suggestions for altering the user-interface, support for an "Infobutton" icon, as well as the recommendation of limiting content to guidelines and dosing recommendations. Survey results revealed that the participants found the PGx decision support useful.

Devine et al.'s study served as a foundational step in the design process of the UW PGx alerts. In 2013, work began in creating similar PGx alerts in the actual UW Cerner EMR system for patients in a clinical trial. In order to assess if the key usability and preference findings from the initial sample of fellows was replicable in a larger sample of UW physicians, we sought to perform a similar simulation and questionnaire that could be performed online.

METHODS

WES PGX CDS Implementation at UW

The survey is a sub-study of a larger PGX CDS implementation process currently underway at the University of Washington. In that process, active CDS alerts were created in the University of Washington (UW)vendor-based EMR system (Cerner®) for patients in the UW New EXome Technology (NEXT) Medicine study who had pharmacogenomic incidental findings (IF) found by Whole Exome Sequencing (WES).

The NEXT Medicine study is a part of the NHGRI's Clinical Sequencing and Exploratory Research (CSER) consortium. It is a randomized control trial in which patients with a personal and/or family history suspicious for hereditary colon cancer/polyps (CRCP) are randomized to receive usual care or usual care supplemented with WES. WES is performed as a send-out lab test at the Northwest Genomics Center (NWGC) in an established second-generation sequencing pipeline. NWGC uses Illumina HiSeq 2000 sequencing technology and variants to be returned are validated in a CLIA-approved laboratory. Variants are annotated with Genome Analyzer (GA) IIx. Initial read-outs are filtered by a medical geneticist. Remaining variants are prioritized for clinical relevance by a medical geneticist and genetic counselor based on allele frequency relative to disease frequency, *in silico* analyses, function (missense vs. truncation) and a review of published literature citing the variant. Incidental finding variants are classified and grouped into disease-risk information categories (high genetic risk vs. moderate genetic risk) through a committee-based framework. A pre-defined set of pharmacogenomics variants (Table 2) are highlighted for return and are confirmed by Sanger sequencing. One aim of the NEXT study is to integrate WES IFs into the EMR as a ground-breaking practice.

The NEXT Medicine Variant Subcommittee selected a subset of medications-genes pairs with pharmacogenomics implications that are considered clinically-actionable with a moderate to strong degree of literature-based evidence. Variants within these genes were chosen based on their ability to be captured through WES as well as their potential current and future relevance for NEXT Medicine study participants.

Table 2. Pharmacogenomic Genes and Variants used in NEXT Medicine

Gene	Variant(s)[a. b.]	Clinical Significance
CYP2C19	p.Pro227= (*2)	Clopidogrel, impaired responsiveness
	p.Trp212Stop (*3)	
	-806C>T (*17)	
CYP2C9	p.Arg144Cys (*2)	Warfarin sensitivity
	p.Ile359Leu (*3)	
VKORC1	-1639GA	
CYP4F2	p.Val433Met	
DPYD	IVS14 + 1G>A	5-fluorouracil toxicity; Dihydropyrimidine dehydrogenase deficiency
TPMT	c.6261G>A	6-mercaptopurine sensitivity; Azathioprine sensitivity
	p.Ala154Thr	
	p.Tyr240Cys	
	p.Ala80Pro	
UGT1A1	(TA)7 promoter insertion *homozygotes	Irinotecan sensitivity
SCLO1B1	p.Val174Ala	Statin induced myopathy
HFE *homozygotes OR compound heterozygotes	p.C282Y	HFE-Associated Hemochromatosis
	p. H63D	
F5 *homozygotes	Arg506Gln	Factor V Leiden Thrombophilia
RYR1	*31 established pathogenic mutations from European Malignant Hyperthermia Group	Malignant Hyperthermia Susceptibility

Discrete lab reports were created through the UW Department of Laboratory Medicine to capture the PGx IFs as results in the EMR. The IF lab results are structured as batteries of

paired tests with one result as binary indicators for the presence of abnormal gene activity and the paired result containing interpretive text about the specific variant and its clinical significance. Binary indicators were designed to describe general situations that could be flagged by the EMR; for example, a patient with a *CYP2C19* variant is documented as positive for "Abnormal *CYP2C19* function". Both text and binary results are stored within the lab results section of the EMR system and are machine-readable, allowing them to be utilized by decision support rules engines. In addition, all IFs in the entire exome for specific patient were reported in structured free-text documents that are stored as PDF files within the EMR. However, these documents are not machine-readable. Thus, results for pharmacogenetic variants were stored in the EMR in 3 different ways, embedded in PDF exome reports, as separate discrete laboratory results for each gene, and as binary machine-readable results.

University of Washington Information Technology Services built the decision support rules to trigger the PGx alerts. The alerts fire when a provider using the EMR's computer physician order entry (CPOE) system prescribes a medication with pharmacogenomics implications to a patient with abnormal gene activity stored as a discrete lab result. The rules were created in the Discern Expert® rules engine and leveraged pre-existing drug-drug interaction (DDI) rules. Alerts generated by the rules also resembled DDI alerts in color and design so providers would be familiar with the alerts' visuals. The content to be included in the alert was generated through an iterative process with the NEXT Variant Subcommittee and additional physicians from various specialties (e.g., laboratory medicine, pediatrics, and general internal medicine). Inclusion of a "Guidelines" button was based off prior PGx-CDS research at UW.[101] Based on a review of the CDS literature, content choices were focused on three goals: simple messages, clear actions and easy access to more information.[85] The resulting prototype thus included the following components: alert title; one sentence summary of drug-gene interaction; possible action; pharmacist contact information; lab result title; dosing calculator (if available); and

access to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines through a button.[102] The alert allowed for "Accept", "Modify" and "Override" actions on behalf of the provider.

Pilot Testing the Alerts: Simulation and Questionnaire

We sought to recruit 55 physicians from the University of Washington to participate in an online simulation and questionnaire. Inclusion criteria was that the provider was in the UW Physicians network or residency training program and had the ability to prescribe medications through the UW CPOE. A recruitment e-mail was sent to 457 attending physicians, fellows and residents that linked them to our online simulation and questionnaire. The link led directly to an online consent form. Providers that consented proceeded to the simulation portion of the study. In the simulation, a case scenario was presented in which the provider was responsible for prescribing anti-platelet therapy to a fictitious patient recovering from a stent placement procedure following a myocardial infarct (*Appendix A*). The providers were given a choice of therapies to choose from that were consistent with current American College of Cardiology guidelines for management of ST-elevation myocardial infarction.[103] After designating their therapy of choice, a new page was generated that displayed an image of the PGx alert for clopidogrel and the *CYP2C19* variant. Text stated that the patient had been a participant in a Whole Exome Sequencing study and had PGx incidental findings stored in his EMR as discrete lab reports. Providers were asked a series of questions about how they would respond to alert, then proceeded to the questionnaire portion of the study.

The questionnaire was a 15-item survey designed in the Catalyst WebQ® system to address three main topics: usefulness of the alert content, appropriateness of the alert in a clinical workflow, and quality of the alert's visual design. General structure of the questionnaire was adapted from other questionnaires in the literature that assessed clinical decision support tools.[101,104]

Questions were in a 5 point Likert-scale format (Strongly Disagree to Strongly Agree), True/False, and multiple choice format. There were no pre-specified objective answers to the questions; they were solely intended to assess subjective provider perspectives. Responses were stored in a secure, de-identified table within Catalyst. After completing the questionnaire, a provider's participation was recognized with an online gift certificate.

Physicians were sent a reminder e-mail if they did not respond within one week. Recruitment occurred between April 28th 2014 and May 28th 2014.

Data analysis was performed after the recruitment period closed. Data was downloaded from the Catalyst system into Microsoft Excel®. Qualitative responses were coded by the author for emerging themes. Descriptive statistics were performed using Excel or Stata 11®. Demographic data and Likert scale results for alert helpfulness were collapsed into binary outcomes (e.g., Strongly Agree and Agree both as Agree). Significance in the differences in responses to alert helpfulness based on age (<40, >40 years), level of training (Attending or not), and years in practice (<4, >4 years) were calculated with two-sample t-test. A two-sided P-value of 0.05 was considered to be statistically significant.

RESULTS

Demographics

A total of 55 physicians enrolled in the study and completed the simulation and questionnaire (12.0% recruitment rate; *Table 3*). The majority of study participants were between 30-39 years old, had less than four years of total medical practice, and had less than four years in practice at University of Washington. 58% of the participants were attending physicians. The most highly represented specialties were general internal medicine, anesthesiology, family medicine, and psychiatry specialties.

Table 3. Background Characteristics of Study Participants

Age (N = 55)			**Specialty (N = 54)**	
20-29	15%		General Internal Medicine	**24%**
30-39	**55%**		Anesthesiology	11%
40-49	16%		Family Medicine	7%
50-59	13%		Psychiatry	7%
≥60	1%		General Surgery	5%
Level of Training (N = 55)			Obstetrician/Gynecology	5%
Attending	**58%**		Ophthalmology	5%
Resident	29%		Pediatrics	5%
Fellow	13%		Cardiology	4%
Years in Practice (N = 55)			Emergency Medicine	4%
0-4	**55%**		Hematology/Oncology	4%
5-9	22%		Diagnostic Radiology	2%
10-14	9%		Gastroenterology	2%
15-19	2%		Infectious Disease	2%
20-24	7%		Neurology	2%
≥25	5%		Neurosurgery	2%
Years at Current Institution (N = 55)			Orthopaedic Surgery	2%
0-4	**73%**		Otolaryngology	2%
5-9	16%		Pulmonology	2%
≥10	11%		Rehabilitation Medicine	2%

Simulation Behaviors

Upon seeing the PGx alert, the majority of participants stated they would either cancel (40%) or modify (49%) their initial order for aspirin and clopidogrel (*Table 4*). Only 4% stated they would override the alert. 7% said they would perform an "Other" option (in a free-text response, these subjects wrote that the action would be to contact a pharmacist).

The majority of respondents said they would call the clinical pharmacist number provided in the alert, as well as click the guidelines button. After interacting with the alert 84% stated that they

would change their order to aspirin + prasugrel; 10% would change the dose of clopidogrel. Those who stated "Other" wrote that they would feel uncomfortable making a decision until speaking with the pharmacist or the rest of the patient's medical team.

Table 4. Simulation Responses Indicating Desired Behaviors

Action upon seeing alert (N = 55)	
Cancel Order	40%
Override Alert	4%
Modify Order	49%
Other (call pharmacist)	7%
Would use pharmacist number in alert (N = 55)	62%
Would use guidelines button in alert (N = 55)	65%
Would modify prescription to (N = 51)	
Aspirin + Clopidogrel, altered dose	10%
Aspirin + Ticagrelor	0%
Aspirin + Prasugrel	84%
Other (depends on team/pharmacist discussion)	6%

Respondents were asked to explain their choice of actions in a free-text response. Common themes included a desire for more information either about the patient or pharmacogenomic guidelines. A number of respondents also noted that their choice of actions would depend on the "flow of the day":

"My answer(s) above would largely depend on how busy I was with other clinical duties. I would either call the pharmacist to inquire about the need for alternate dosing or consider an alternate medication than clopidogrel."

"I would use another agent. I don't have time to do the other things"

One respondent that overrode the alert stated, "… I would not change my standard practice based on a computerized automatic alert alone." The comment suggests a reliance on other clinical knowledge. Similarly, another respondent felt that a decision depended on more than the alert's recommendation:

"Next step would be possible review of more information and definite discussion with attending/team, this is an important decision that should not be made alone on the day of discharge."

Questionnaire Responses

Visual Interface

87% of respondents agreed or strongly agreed that the text provided in the alert was helpful in the decision making process; the same percentage felt that the font, color and use of bullet points was appropriate, as well (*Figure 2-A*). The conciseness of our alert's text, with additional information available through external sources, was appreciated by some of the participants:

"[I] prefer availability of links to additional information in alerts without bogging down the alert with actual content or text of additional information."

""Make alert as simple as possible with [the] least amount of information that is needed."

80% agreed or strongly agreed that the guidelines button was a useful element, which was an interesting finding given that only 65% stated that they would use the button in the decision making process of the simulation. It is possible that, during the decision making process,

several participants did not recognize the purpose of the guidelines button, despite it being explained in text within the alert.

One participant requested that "there be some way to make different [alerts] stand out" from other one another in our CPOE system.

Appropriateness in Workflow

Overall, our sample of providers felt that the alert occurred at an appropriate point in the decision making process (91% agreed or strongly agreed; *Figure 2-B*). Similarly, most felt that they could easily resume their prescribing process (95% agreed or strongly agreed). One respondent strongly disagreed that the alert was properly placed in the workflow, but did not provide any specific comments as to why. However, another respondent commented on how the alert could be inconvenient if it impacted the prescription process for other concurrent medications:

"Most important of all, make sure delaying decision making about this one medication does NOT prevent you from being able to continue with rest of discharge medication reconciliation/prescribing."

Usefulness of Pharmacogenomics

While the majority of physicians felt that PGx data in general would be useful in their practice, a sizeable number were unsure (30%; *Figure 2-C*). One provider identified a potential use for CDS based on existing PGx testing in his/her practice:

"In [infectious disease], we already incorporate data of this nature in our practice, in that we test patients for certain HLA alleles that are associated with hypersensitivity to one of the HIV drugs, abacavir, if we are considering using this drug. There are no alerts, though. We

have to know this information and proactively order the HLA test before prescribing. We work closely with a clinical pharmacist but not all areas at UWMC can be staffed with a pharmacist, so I think these alerts would be fantastic! Alerts could also prompt clinicians to order important testing before prescribing, as with the abacavir example."

75% of our respondents were unfamiliar with the pharmacogenomic interaction of clopidogrel and *CYP2C19* variants. Though this large percentage could be expected due to the variety of specialties that participated, we found that the majority of providers in specialties that would likely be familiar with the specific drug-gene interaction were not familiar with it: cardiology (50%); internal medicine (64%); family medicine (75%); and general surgery (67%). Similarly, a large percentage (71%) of respondents were unsure about the level of evidence in the medical literature regarding clopiodgrel and *CYP2C19*.

Usefulness of the Alert

92% agreed or strongly agreed that the alert was helpful in choosing an appropriate medication in the case scenario (*Figure 2-D*); 92% also agreed or strongly agreed that the alert was applicable to the case patient's medical condition. Though the majority agreed or strongly agreed that the alert increased their confidence in their prescription choice, it was less strong than the other two usefulness items (77%). Some of the qualitative responses addressed the questions of usefulness directly:

"The usefulness of this type of alert is largely determined/limited by the volume and usefulness of other alerts…"

This respondent felt that the alert's usefulness depended on the broader ecosystem of alerts in the UW EMR system. Similarly, another respondent felt that the impact of the alert would depend on the type of provider:

"*Those who routinely prescribe medications with these type of support tools will be familiar with the data/controversies etc and will not benefit from the information. Those who prescribe less frequently will likely find the content very useful.*"

This was an issue that we identified a priori and performed three sub-group analyses to test. The results show that the perception of usefulness did not differ significantly by broad categories of age (P=0.4511), level of training (P=0.0912), or years in practice (P=0.6275).

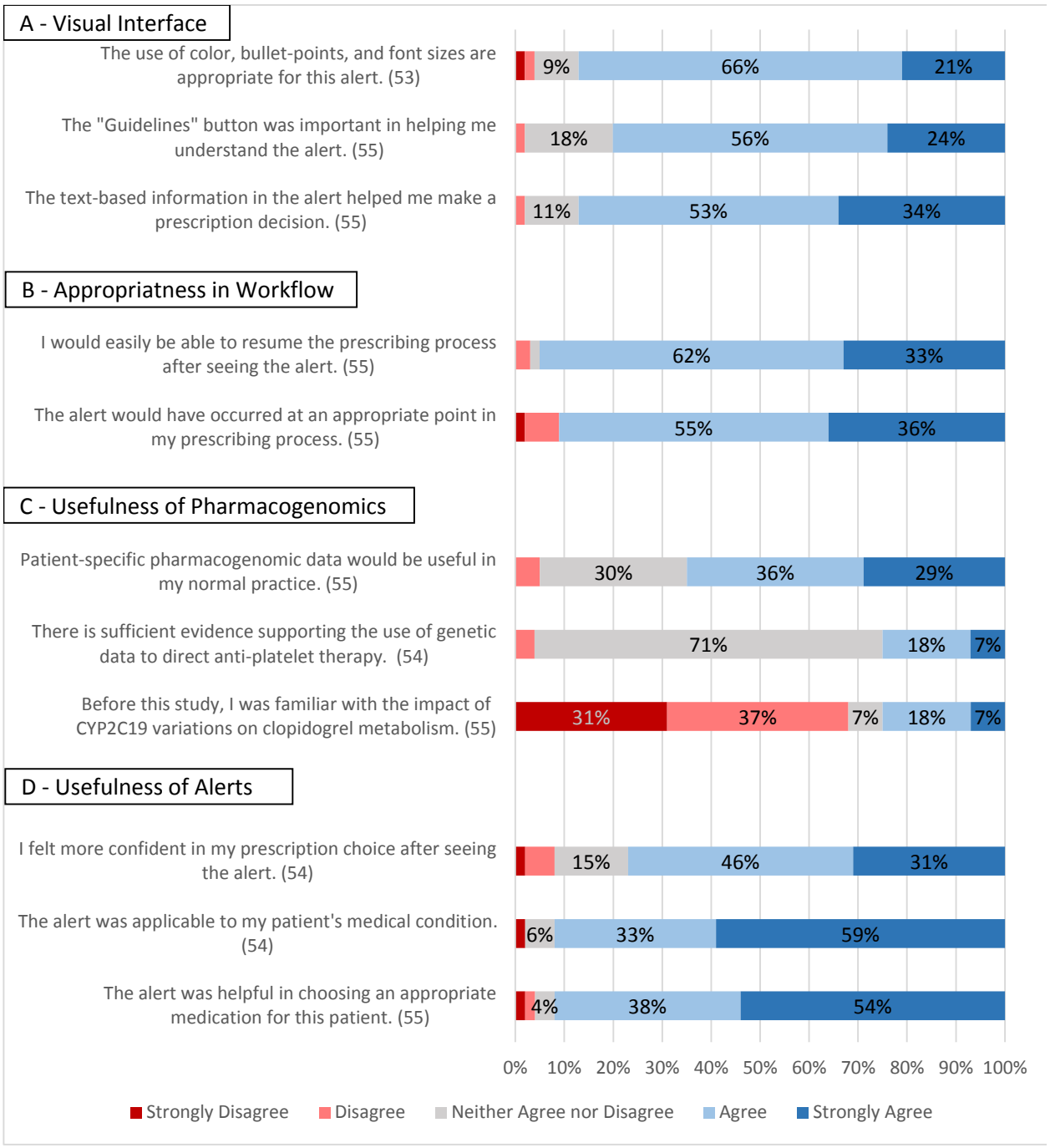

Figure 2. Results of Likert Scale Questionnaire Assessing Physician Perspectives

Block A shows most participants approve of interface design features and Block B shows they approved of the alerts place in the prescribing workflow. Block C shows that the majority were unfamiliar with the drug-gene interaction presented and were unsure about the evidence backing it. Block D shows that most participants felt the alerts were helpful and applicable to the simulation patient.

Modifications

When asked about potential modifications that could be made to the alerts, 80% of respondents preferred an option to allow drug/dose modification within the alert itself (*Table 5*). Though the majority also favored guideline text written in the alert, the consensus was less strong (67%). Most participants also stated that links to recommendation resources such as UpToDate® or Dynamed® should be included (60%), as well as a link to the patient's genetic lab report (52%). Conversely, most respondents did NOT want the patient's allele information (79%), calculators to help adjust dosing (62%), or links to additional guidelines (58%). There was ambivalence about linking to scientific literature through PubMed.

Table 5. Modifications

Would prefer to modify drug/dose within the alert (N = 55)	
Yes	80%
No	16%
No preference	4%
Would prefer guideline text within the alert (N = 55)	
Yes	67%
No	22%
No preference	11%
What additional information should be included	
Patient's allele information (N = 52)	21%
Links to patient's genetic lab report (N = 52)	52%
Links to PubMed articles (N = 52)	50%
Links to additional guidelines (N = 52)	42%
Links to UpToDate®, Dynamed® or similar resources (N = 52)	60%
Dosing calculators (N = 52)	38%
Other (N = 52)	6%

Participants were asked when the most appropriate time would be to learn more about the pharmacogenomics of clopidogrel and *CYP2C19* variants. 62% felt that learning more at the point of care, upon seeing the alert, would be appropriate. Smaller percentages of respondents felt that it would be better to learn before the prescribing process (33%), soon after the clinical encounter (22%), or on their own time in an unrelated setting (24%). One respondent stated in a free-text response that learning at a medical conference would be ideal.

DISCUSSION

The primary goal of our study was to determine if physicians found a pharmacogenomic (PGx) alert for *CYP2C19* variants to be useful. Broadly speaking, our results show that our sample of physicians felt this to be true. This reiterates the positive response that the participants in the prior study by Devine et al. had towards the PGx clinical decision support.[101] Furthermore, based on our participants' stated actions in the simulation, the alert would have an override rate of only 4%. Alert override rates in the CDS literature are generally much higher, between 52-96%.[105] Though the *CYP2C19* override rate is likely underestimated due the simulation-based nature of our study, it seems possible that the real rate would still be relatively low thanks to the high specificity of the alert, further indicating its usefulness. However, the terms "usefulness" and "helpfulness" are vague and rely on a number of other factors.

The usefulness of a decision support alert can be impacted by a variety of elements related to either the alert itself or the actual content it conveys. Alerts are essentially vessels for disseminating knowledge, but they can easily disrupt the message they are intended to communicate if they are poorly designed. For example, the visual and graphical interface of an alert can be distracting if poor color and font choices are utilized. We refined these elements of our alert based on recent research and the majority of our sample still felt that the alert visuals

were appropriate. We intentionally designed the alerts to be consistent with the drug-drug interaction (DDI) alerts with which our providers are familiar. However, several participants expressed the desire for the alerts to look distinct from existing alerts. These comments signify a concern about the role of an alert in the greater ecology of alerts that exist at a given institution.

The real medical environment also helps elicit the role of the alert in the clinical workflow. It is a well-established concept that decision support tools that hinder or disrupt a physician's normal workflow are less likely to be found useful.[81] Drug alerts triggered on prescription, in particular, may be potentially ill-placed. They often occur after a provider has considered medication options and discussed them with the patient, thus requiring the provider to backtrack and reformulate a new plan. Our alerts potentially have this flaw, yet the majority of our providers felt that the alert occurred at an appropriate point in their prescribing process. However, without exposing the participants to an alternate process, it is difficult to conclude the meaning of this finding. Another indicator of workflow was how well the prescribing process could be resumed. Again, most respondents were positive towards this characteristic of our alert. In addition, they strongly supported a feature of alerting prescriptions within the alert itself, which will likely improve usability and will be included in future iterations of the alert.

A final factor in the usefulness of an alert itself is the way it conveys the message. As stated, this text was intentionally simple and concise to avoid flooding the reader with information. We felt that making additional PGx information available through weblinks and guidelines was a good alternative to lengthy text descriptions. Indeed, the majority of participants felt that the guidelines button was an important feature in understanding the alert. When asked what additional resources would be useful, the majority felt that summary-based knowledge-bases such as UpToDate® would be useful. This finding is consistent with those of Devine et al., in

which participants expressed that access to such resources through an "Infobutton" was strongly supported.[101] Our participants also requested a link directly to the patient's pharmacogenomic lab results. While we had intended to include such a link, we are unfortunately unable to do so because of the restrictions of the vendor system used to generate the alerts. This fact highlights the limitations of leveraging DDI systems for the purposes of pharmacogenomics. Hopefully, future decision support engines in major vendor EMRs will include further genomic-specific capabilities.

Once we have verified that our physicians approve of the alert itself, we must consider the quality of the content it conveys in order to ensure that the alert as a whole is useful. Due to the novel nature of pharmacogenomic data, this step is especially important. One of the most striking results we found was that most of our respondents were unfamiliar with the pharmacogenomic interaction of clopidogrel and *CYP2C19* variants. While this finding may be due in part to the different specialties involved in the study, we found it to also to be true with the majority of physicians in specialties likely to be familiar with the interaction. Pharmacogenomics is by no means a standard part of clinical care, thus our alerts face the challenge of not only reminding physicians of PGx interactions, but rather introducing them to PGx. This poses significant challenges in the type of content to include, which is further complicated by the various opinions about PGx that exist in the medical literature.

The majority of our respondents were ambivalent or unsure about whether there was evidence to support genetically-guided anti-platelet therapy. Based on the existing literature, this is a fairly reasonable response. While our alerts are driven by Clinical Pharmacogenetics Implementation Consortium guidelines, the topic is far from settled in the medical literature. Outside of the community of genomic-enthusiasts, there is much uncertainty about pharmacogenomic care. For example, there is no question about the ability of genetic tests to

determine platelet reactivity and for alternative therapies to reduce thrombotic events. However, a recent article in the Journal of the American College of Cardiology highlights that the high number needed to treat of altered therapy juxtaposed with its increased risk of bleeding and higher costs makes the use of individualized therapy in low-risk PCI patients unclear.[41] RCTs and meta-analyses for such interventions do not exist, so a solid evidence-base is not available to help guide such decisions. Thus, the ambivalence our respondents showed is quite understandable.

While the majority of physicians felt that PGx data would be useful in their practice, a sizeable number were unsure (30%). This may be an extension of the lack of evidence behind many PGx interventions, as well as PGx presence in different specialties. Current PGx drugs are primarily in general medicine, cardiology, oncology, anesthesiology and psychiatry.

Strengths and Limitations

In combination with Devine et al.'s usability study, our study offers some of the earliest data about the best practices for designing and implementing PGx clinical decision support alerts. These results will be used to help UW refine its own PGx alert repertoire and could prove useful to many other institutions seeking to implement PGx CDS. We have also described a methodology for quickly and effectively obtaining physician input on clinical informatics interventions.

A major limitation of our study is its simulation-based nature. Alerts may need to be studied in real medical environments for accurate assessment. Furthermore, our sample size was not large enough to be considered representative of our entire physician population. However, while we cannot state that the sample is generalizable to all UW physicians, we can make use of the data in terms of honing our alert in a user-centered design process – similar to the way one might use

results from a focus group. A final limitation is that we only tested the alert for one drug-gene interaction. Though we did this intentionally for the sake of maximizing the input from our sample, we cannot be sure that the results are applicable to alerts for other PGx interactions. The ideal components of alerts that we have studied, such as text content choices, visual aesthetics, and supporting information may vary between alerts, acting as effect modifiers in the usability of the alert. For example, the amount of text most appropriate for a clopidogrel alert may differ from an alert for coumadin and *CYP2C9*. Thus, caution should be practiced in applying our results to PGx alerts as a whole.

Future Directions and Policy Implications

An additional project that is already underway is the study of PGx alerts in real medical environments. In that process we will also be studying the entire array of NEXT gene-drug interactions in order to define best practices beyond clopidogrel alerts. Future usability studies for PGx alerts would do well to continue exploring mixed-methods approaches to study the elements of Human-Computer Interaction.[106] In addition, research methodologies such as cluster randomized control trials and step-wedge designs that allow for the study of PGx alerts on patient-based clinical outcomes, like morbidity and mortality, should be utilized.

The findings of that UW has produced in regards PGx CDS usability could serve as initial steps towards a comprehensive guidelines for PGx CDS best practices. As meaningful use policies begin to require that health care institutions not only incorporate EMRs, but also effective CDS, into practice, it is essential to support the adoption of these technologies with sufficient guidance. The same can be said for the implementation of PGx testing. Thus, our results could begin to define the guiding principles for the intersection of these two novel fields.

CONCLUSION

Since the NHGRI's pivotal shift in focus of 2011 towards the use of genomic data in medical practice, a vast amount has been discovered about the process. The parallel growth of the EMR has situated it as an important facet in the bridging laboratory sequencing results to personalized patient care. Efforts by members of CSER, EMERGE, and other interested parties have provided a fruitful source of experiential knowledge about the integration of genomics and EMRs. In addition to the many anticipated benefits of genomic medicine, these projects have graciously shared the pitfalls and challenges they have encountered in the acquisition, representation and retrieval of genomic data. These challenges revolve around issues of shared knowledge resources, nomenclature and identification, data storage, clinical decision support and ethico-legal hurdles.

Pharmacogenomics is one form of genomic medicine that is beginning to impact clinical care. It is also a type of genomic medicine that could be disseminated through existing clinical decision support (CDS) tools. However, effective use of CDS is dependent on a variety of factors such as visual design, content choice, and appropriateness in workflow. Little research has explored these factors in the context of pharmacogenomics. We have reported findings from a study that we performed examining physician perspectives on pharmacogenomic clinical decision support alerts. We found that, among a sample of physicians from the University of Washington, many users felt that such tools could be useful in prescribing medications to patients. In addition, the majority of them supported the visual interface elements of our alerts and felt the alerts occurred at appropriate points in the prescribing process. Consistent with the pharmacogenomic literature, our study also showed that many physicians were unfamiliar with the *CYP2C19* and clopidogrel interactions and were ambivalent about the existing evidence base for interventions based on the interaction. The results of our study will hopefully serve as an

early step towards addressing one of the many challenges facing the integration of genomics into EMR systems.

We have attempted to outline these issues and provide concrete examples from the literature. We described certain issues in-depth at the expense of covering every challenge discussed in the literature. However, we recognize that these other aspects of genomic-CDS integration, such as the impact of epigenomics,[107] the just distribution of resources, and the influence of different EMR systems,[33] are of great concern and deserve attention. The field of genomic medicine is vast and requires a rigorous, multi-faceted and interdisciplinary approach of study. Yet, for researchers and institutions interested in pursuing the positive elements of the field, it is essential to maintain a comprehensive knowledge of both the positive and negative consequences for both patients and providers.

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Appendix A. Simulation and Questionnaire

Case Scenario

ID/CC: Mr. X is a 56 year old Korean male on your service who is in recovery following percutaneous coronary intervention with a drug-eluting stent for an ST-elevation myocardial infarction two days ago.

Current Status: The recovery has been uneventful and his current condition is stable. On physical exam he has a BP of 152/110, RR of 12, and normal O2 saturation. ECG shows inverted T waves, no new Q waves, no dysrhythmia, axis shift or conduction defects. On echo LVEF was 0.57. No recurrent ischemia, heart failure or hemodynamic compromise. There is no indication for future CABG.

Mr. X appears fatigued but in a pleasant mood.

Past Medical History: Mr. X has a history of hypertension and hypercholesterolemia. He has not suffered from gastric ulcers.

You inform Mr. X of his status and tell him that he will be discharged shortly. After providing him the appropriate patient education, you log into the Cerner CPOE to prescribe him anti-platelet therapy medications to be taken at home.

Question

Which of the following dual anti-platelet therapy regimens would you prescribe Mr. X?

Required.

Aspirin + Clopidogrel (Plavix)

Aspirin + Ticagrelor (Brilinta)

Asprin + Prasugrel (Effient)

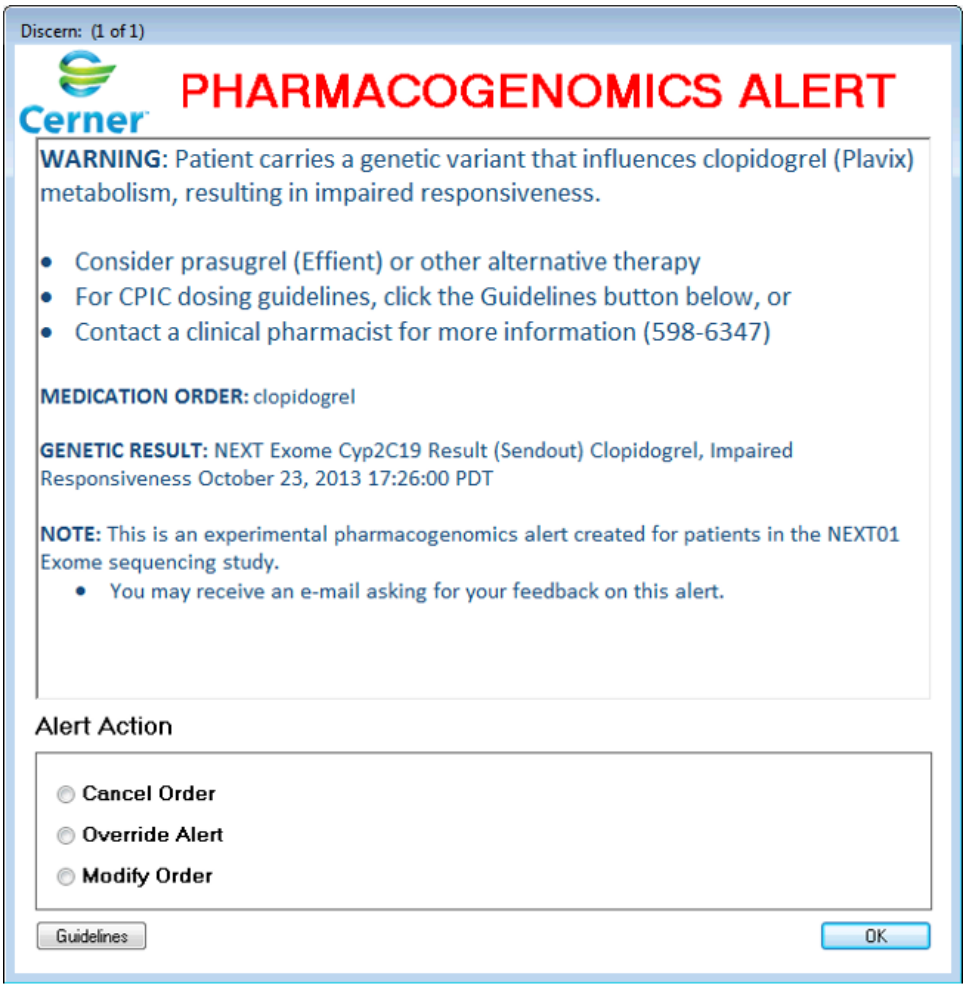
Other:

Simulation Questions

If you had ordered clopidogrel through the UW CPOE system, an alert would have appeared on the screen.

Mr. X has lab results in his electronic medical record created from genomic sequencing data he had performed as a part of a clinical trial. The sequencing revealed that Mr. X has a diminished ability to metabolize certain drugs.

Please read the alert and answer the following questions.



At this point, what action would you take?

Required.

- Cancel Order
- Override Alert
- Modify Order
- Other:

Would you call the clinical pharmacist number listed in the alert for more information?

- Yes
- No

Would you access more information from the "Guidelines" button?
The button would take you to the CPIC guidlines on PharmGKB.org

- Yes
- No

Briefly explain your choice of action(s) and elaborate your next steps in completing the prescription process for Mr. X's discharge. (Ex: I overrode the alert because...)

Limit response to 400 characters.

378 characters remaining

If you chose to modify the order, which of the following dual anti-platelet therapy regimens would you now prescribe Mr. X?

- Aspirin + Clopidogrel (Plavix), but different dose
- Aspirin + Ticagrelor (Brilinta)
- Asprin + Prasugrel (Effient)
- Other:

You have completed the simulation scenario. After providing background information, there are **15 questions to answer**.

Questionnaire

Alert Helpfulness

The alert was helpful in choosing an appropriate medication for this patient.

The alert was applicable to my patient's medical condition.

I felt more confident in my prescription choice after seeing the alert.

Pharmacogenomics Helpfulness

Before this study, I was familiar with the impact of *CYP2C19* variations on clopidogrel metabolism.

There is sufficient evidence supporting the use of genetic data to direct anti-platelet therapy.

Patient-specific pharmacogenomic data would be useful in my normal practice.

The Alert in Your Workflow

The alert would have occurred at an appropriate point in my prescribing process.

I would easily be able to resume the prescribing process after seeing the alert.

If you felt you needed to learn more about CYP2C19 variants and clopidogrel management, when would be the ideal time to do so?

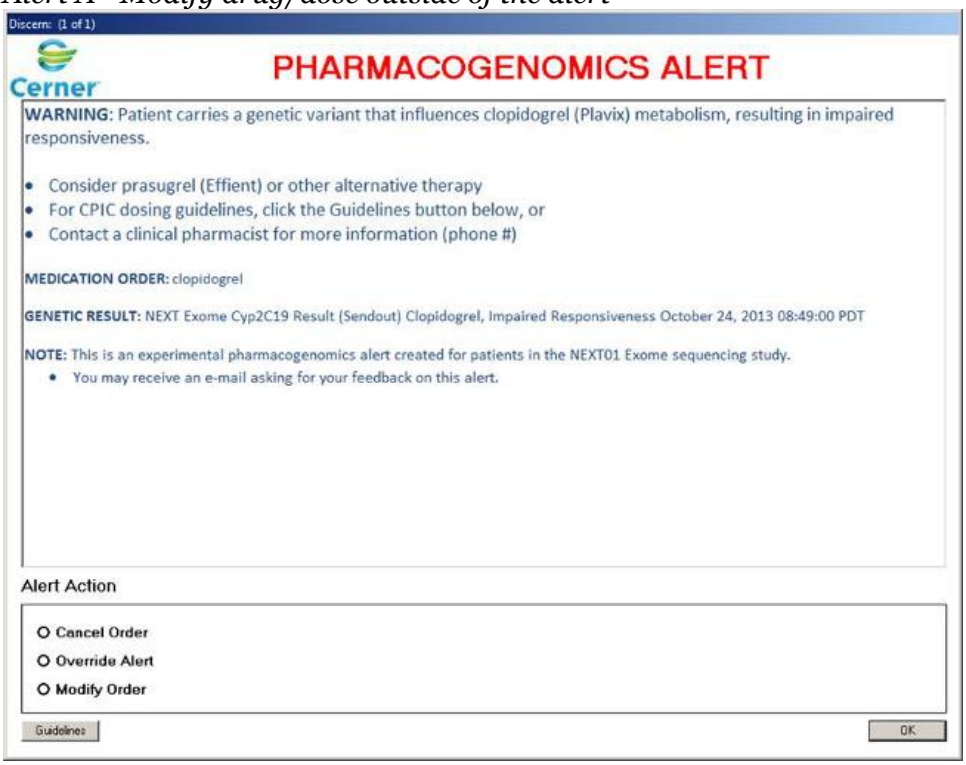
- ☐ Upon seeing the alert during the prescribing process
- ☐ Before the prescribing process begins
- ☐ Soon after the clinical encounter
- ☐ On my own time in an unrelated setting
- ☐ Other: _____

The alert you saw is a prototype alert being built for the UW EMR system. It is likely to change based on the results of this survey. Please provide your perspective on a modified alert with different functionality.

Modified alerts could allow you to change your choice of medication or dosing in the alert itself. The images below show how this would be different from what you saw in the scenario.

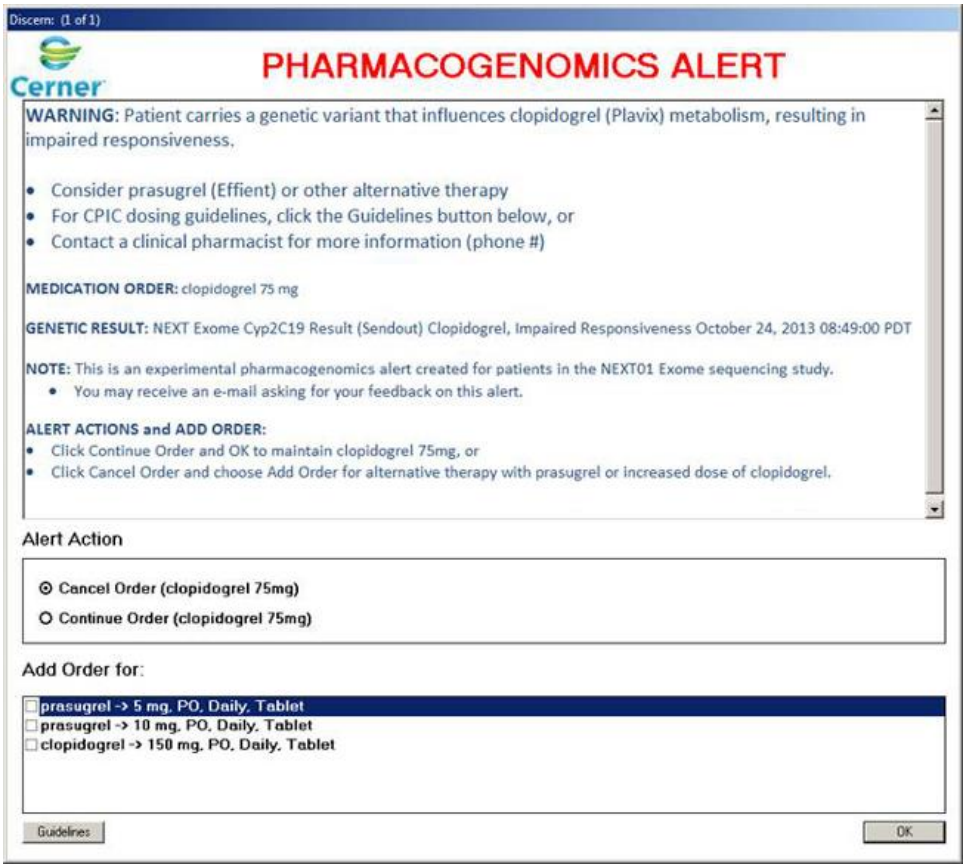
This is the original alert you saw:

Alert A - Modify drug/dose outside of the alert



An alternative format allows you to alter the prescription within the alert:

Alert B - Modify drug/dose within the alert



Some people might find this feature convenient, while some would find it confusing or distracting. Which type of alert would be more useful in your daily work routine?

- Alert A (original) - Modify drug/dose outside of alert
- Alert B (second) - Modify drug/dose within the alert
- No preference

Alert Contents

The text-based information in the alert helped me make a prescription decision.

The "Guidelines" button was important in helping me understand the alert.

The use of color, bullet-points, and font sizes are appropriate for this alert.

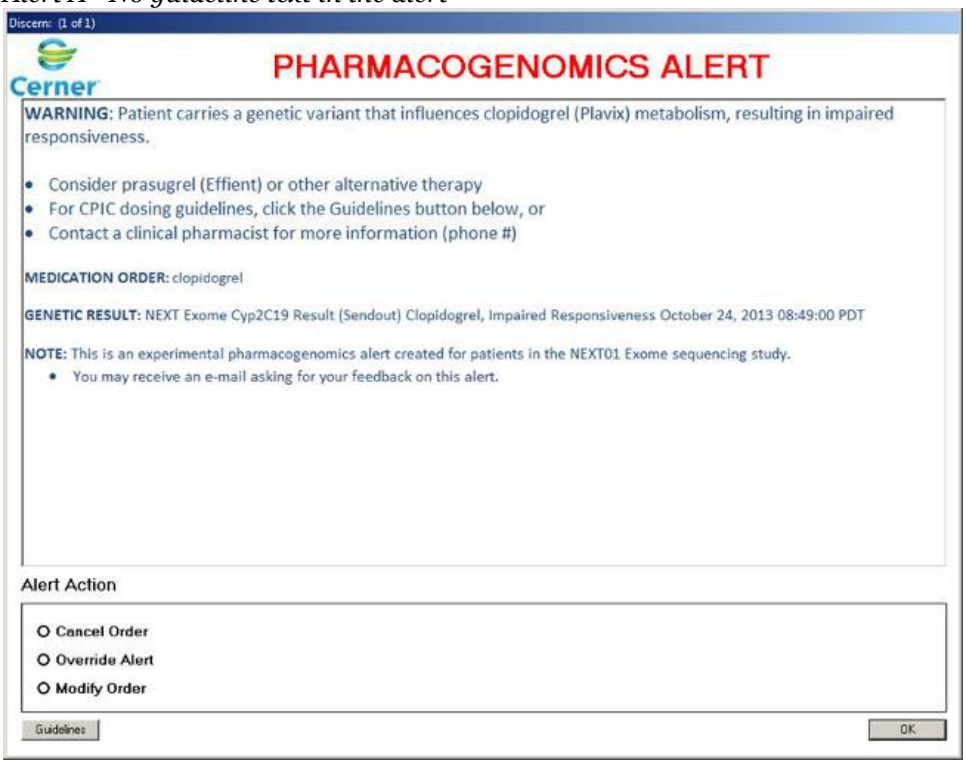
What additional information should be included in this pharmacogenomic alert?

- [ ] Patient's allele information
- [ ] Links to patient's genetic lab report
- [ ] Links to PubMed articles
- [ ] Links to additional guidelines
- [ ] Links to UpToDate, Dynamed or similar resources
- [ ] Dosing calculators
- [ ] Other:

For certain medications, the FDA and/or Clinical Pharmacogenetics Implementation Consortium (CPIC) provide alternative dosing suggestions depending on a patient's genetic variants. An example below shows how alerts would look without, and with the suggestions in the alert.

This is the original alert you saw:

Alert A - No guideline text in the alert



An alternative format might include the following. Notice that it includes additional guideline information in the text to help with prescribing drug choice and dosing decisions.

Alert B - Guideline text within the alert

Some providers would find the information helpful, while others would deem it unnecessary, irrelevant or untrustworthy. Which type of alert would be more useful in your daily work routine?

- Alert A (original) - No guideline text in the alert
- Alert B (second) - Guideline text within the alert
- No preference

You're all done! If you have any other comments regarding decision support pop-up alerts, pharmacogenomics, or this survey, please provide them below