Emily Doughty
BMI 258
Spring 2013
Final Report

The Future of Medicine: Challenges for Pharmacogenomics in the Clinic

Pharmacogenomics is a key first step towards personalized medicine by altering a patient's drug treatment based on his or her genetic variants. While there have been many promising results and utility both pre-clinical and clinical, there remain significant challenges that must be addressed before such data can be used effectively in the clinic. Such challenges can be broken into two primary components: utility of pharmacogenomics data and integration in the clinic. The utility of pharmacogenomics data is constrained due to lack of complete information for drug response, population-specific variants, and classical study design. For clinical integration, there are significant challenges regarding implementation in the clinic, cost-effectiveness of pharmacogenomics tests, reimbursement for genetic tests, and ethical and social concerns. These challenges must be fully addressed in order to incorporate pharmacogenomics information into the clinic as a common test before drug prescription.

Appropriate and safe drug treatment based on genetic variants requires complete information on these variants; however, there is a lack of complete genetic information for drugs for different diseases. There has been success for pharmacogenomics for cancer drugs such as Vemurafenib and Cetuximab, but cancer is not the only disease that affects patients today.(1) In fact, the variant information for drugs affecting chronic disease currently lags behind diseases caused by either a small number of genes or different cancers, which have been

extensively studied using targeted therapy. Chronic diseases are caused by both environmental and genetic variables, spread out over many genes. Such diseases also impact a large portion of the population over a longer period of time. Thus, a deficit in pharmacogenomics information for drugs affecting these diseases will create a hole in pharmacogenomics treatment if such treatment becomes common practice. Furthermore, some of the information that is available has been plagued with inconsistent replications (especially when evaluating drug-gene variants using a candidate gene approach), and thus hindering the use of such biomarkers in the clinical setting. One such example is clozapine which has had conflicting study results due to its complex pharmacological effects involving multiple different receptors in the central nervous system.(2) Such conflicting results in the literature set back the clinical utility for a given drug and its associated genetic variants. Finally, there is a lack of information regarding environmental effects on drug response, specifically the combined genetic and environmental effects.(2) All together, this lack of complete pharmacogenomics data impedes the use of genetic information in the clinical setting for drug prescription.

For actionable variants in the clinic, there must be information regarding population frequency and altered drug response. While this information is needed for clinical application, several current recommendations do not specify population information for the variants.(2) The widely used anticoagulant Warfarin is a classic pharmacogenomics example where variants in VKORC1 and CYP2C9 can alter the correct dosage required for a given patient. While variants in these genes are part of pharmacogenomics recommendations for warfarin, the variants used in

recommendations are not found in African, Chinese, and Japanese populations.(3) Thus, if a doctor orders tests for these variants in an African American patient, then the probability of finding such variants is highly unlikely. This does not mean there are not variants specific to non-European populations. For example, CYP2C9*8 is found in African Americans but is not listed on the pharmacogenomics recommendation for warfarin dosage in the clinic.(2) Such population-skewed information hinders clinical utility across multiple populations. Pharmacogenomics research and subsequent recommendations must fully incorporate population information, both nonspecific and specific population variants.

Pharmacogenomics study design can limit the utility of the resulting data based on the type of study. Common types of studies are randomized clinical trials, retrospective observational studies, DNA biobanks, and in-vitro studies, and each has their own set of limitations.(4) In a randomized clinical trial, study participants are randomly placed in different treatment groups under study, and then followed by the researchers in the exact same manner. A drawback to this type of study is that if a patient has an adverse reaction during the trial, the researchers will intervene and change the treatment course. This is done because it is unethical to deny a proven drug treatment to a patient; however, this will of course limit the amount of data about a specific drug effect. Another type of study is the retrospective observational study. This can be a case-control study where the participants are placed in cases and controls based on past types of drug response. These studies are limited by the participant's recollection of past events, which will be affected by memory. The researchers also must be careful about population

stratification when designing the study and interpreting results. An alternate type of retrospective study is to use data from DNA biobanks for a cohort found using electronic health records. This type of study does not rely on a patient's own recollection for past drug responses. Despite this advantage, the study is still limited by both the availability of individuals that fit the cohort description and the availability of useful data in the biobank for each patient in the cohort. Due to these limitations, creating a large enough cohort for a given study can be very challenging.

One way to eliminate the above problems with participant selection in study design is to conduct an in-vitro study. In these studies, different doses of a given drug treatment are applied to a cell line in order to measure gene expression and other cell characteristics. While these studies remove the ethical concerns of participant treatment and overall participant selection, the studies are hindered by tissue selection when the correct tissue for a given drug may not be available and thus the cell lines from the selected tissue may not express the enzymes required for a drug's pharmacokinetics. While all of these studies have clear limitations, they also have strengths such as strong informative power (randomized control studies), cost-effective (retrospective observational study, DNA biobanks, in-vitro studies), and well controlled between cases (in-vitro studies). Combined, the data from these studies have provided drug-variant associations that have proven useful in understanding drug response; however, as with any data, one must understand the studies that generated the data to understand the underlying limitations of the results.

Appropriate implementation is key in order to integrate pharmacogenomics data into the clinic. Such an implementation would require extensive knowledge of genetics by doctors and other medical personnel, clinical guidelines for pharmacogenomics-based therapies, and decision support for handling this data. A recent survey of 10,303 US physicians found that only 10.3% of respondents said they understood available pharmacogenomics tests and only 29% of respondents received pharmacogenomics training during either medical school or graduate school.(5) These responses highlight the current lack of knowledge and subsequent lack of confidence when physicians deal with pharmacogenomics data. So while there is a need for pharmacogenomics during medical school(6), this does not address the current deficiency in knowledge for acting physicians. Even if all physicians had intense training in this area during medical school, the total information for pharmacogenomics is too large and complex for a physician to simply memorize. For example, there may be multiple conditions that affect drug response including a combination of genetic and non-genetic conditions, and response can also be affected by additional drug-drug interactions.(2) Not only must physicians (and nurses, pharmacists, and other medical personnel) understand how variants and other variables affect drug response, they must also understand the nomenclature for such variants and how to interpret novel variants given known information.(7)

In order to address this lack of pharmacogenomics knowledge in hospitals, clear clinical guidelines and decision support systems are needed for a pharmacogenomics-based implementation in hospitals and clinics. Clear guidelines

would help physicians understand when and why to change a patient's drug treatment or possibly supplement treatment with another drug, and while guidelines have been created by several consortiums such as the Clinical Pharmacogenomics Implementation Consortium (CPIC) and the Pharmacogenomics Working Group of the Royal Dutch Association for the Advancement of Pharmacy, a complete set of guidelines is not currently available for physicians' use.(7) Along with these guidelines, decision support for pharmacogenomics is needed in order to aid physicians' and nurses' decisions about correct drug dosage and prescription based on genetic information. It is unreasonable for a physician to memorize databases of information, but decision support would provide a physician with access to this data and aid in appropriate patient care. This would also require electronic health record implementation and computerized physician order entry (CPOE) with pop-up alerts if a prescribed drug is significantly associated with a given patient's genetic variants. (2) In order to transition to pharmacogenomics-based drug therapy in the clinic, both hospitals and physicians must embrace these computerized systems.

In order for pharmacogenomics testing to become commonplace in the clinic, these tests and the analysis of the results must be cost-effective when compared to no testing. Ideally, the cost of the test would be less than the cost of treating the incorrect drug response (e.g., adverse drug reaction) and less than the cost of no drug response.(2) One approach for analyzing cost-effectiveness is to compare the relative costs and outcomes for different approaches (drug therapy based on genetic variants and drug therapy not based on genetic variants). Another type of cost-

effective analysis is to use a simulated patient cohort to find the difference in cost between treatments. Many variables may affect this cost-effectiveness for a given drug. For example, genetic testing for warfarin may be cost-effective for patients with European ancestry but not cost-effective for patients with African, Chinese, or Japanese ancestry. One factor that will not affect implementation cost is the cost of the genetic test itself.(7) With the cost of genotyping decreasing rapidly, the cost of the genetic test will not be a major roadblock for implementation; however, the cost of the analysis and interpretation of the data, and the cost of maintaining the computer systems for this data will affect cost-per-patient. One solution is to use a pre-emptive test so that the cost of the one genetic pre-emptive test is less than the cost of multiple tests over a patient's lifetime. Johnson et al. created a genotyping array using clinically actionable variants from the Pharmacogenomics Knowledgebase (PharmGKB). (8) This array contained 252 "pharmacogenetics SNPs" and did not include variants associated to disease risk. If such an array can be used once per patient, then the analysis per patient would also happen once. This of course assumes that the array will not updated regularly and that data is complete, neither of which is true (and should not be true for the array, at least for now). Currently, being able to definitively prove the cost-effectiveness of pharmacogenomics in the clinic remains a challenge.

Monetary reimbursement presents a challenge for pharmacogenomics implementation in the clinic due to reluctance of payers to reimburse the costs of these tests. This reluctance is due to either the lack of evidence for the test, the test not being deemed medically necessary due to lack of FDA classification, or lack of

cost-effective analysis. In fact even with the knowledge of warfarin variants and specific labeling, the Centers for Medicare and Medicaid Services decided to deny coverage for genetic tests in relation to warfarin dosage and decided to only pay when testing was required for clinical studies. (2) Also, Cohen et al. have shown that payers (for the most part) do not consider populations of interest and test cost as factors for reimbursement. (9) However, test cost should be a factor since the cost of a genetic test may be much cheaper than the cost of the medication, and yet payers for the most part disregard this information.(2) Finally, payers still want cost-efficiency tests but there are not many incentives for both pharmaceutical and diagnostic companies for such tests due to reduced revenue compared to the drugs and biomarkers. Based on the reluctance of payers, reimbursement proves to be a major challenge for pharmacogenomics implementation, especially in light of rising healthcare costs in the US.

Ethical and social concerns represent the last major roadblock for pharmacogenomics implementation in the clinic. There have been many concerns for genetic testing for disease risk including potential for job or insurance discrimination and whether or not to alert family members of a specific risk allele. While these concerns are still relevant for pharmacogenomics testing, they are not as critical as for genetic testing for disease risk.(1) Despite this, there is still the potential for pharmacogenomics testing to alert employers and payers of a patient's diseases, which can then lead to discrimination. Therefore in order to correctly implement pharmacogenomics testing, all potential privacy issues must first be addressed to protect a patient's identity and his or her conditions. Also depending

on the cost of the test and if a patient does not have insurance, there can be a gap in pharmacogenomics care between patients based on socioeconomic status. Thus, if a test is not covered by insurance or the patient does not have insurance, there will be a reduced quality of care relative to those that can afford the tests. Reduced cost of the test, coverage by insurance, and universal health care could alleviate these discrepancies between patients. Finally, there are concerns about lack of alternative treatments for a given drug that may have adverse effects or limited response linked to genetic variants. If there are no alternative treatments for such drugs, a physician has to decide if the effects without the drug are worse than the effects with the drug, and thus should prescribe a drug regardless of a patient's genetic variants.(2) Decision support systems and CPOEs can have overrides for built-in alerts to handle such scenarios. This will then pose an additional problem when physicians start overriding alerts too often, regardless of alternative treatments. This would be a misuse of the system and not beneficial for the patient. These social and economic concerns must first be addressed before pharmacogenomics can be applied without privacy or safety concerns.

Despite the challenges facing pharmacogenomics and its implementation in the clinic, there have been many success stories. The anticoagulant warfarin requires careful dosing in order to not over or under coagulate a patient. The common variants related to this dosing are well understood, at least for patients of European descent, and now there are genetic tests and recommendations for warfarin in the clinic. Abacavir is another drug that has had successful pharmacogenomics implementation. Abacavir is used to treat HIV, but

hypersensitivity occurs for 5-8% of individuals on the drug. This hypersensitivity is associated with HLA-B*57:01, and in 2008, the FDA issued a black box warning for abacavir, which strongly recommends that all patients be screened for this HLA-B variant before being given the drug.(4) Finally, St. Jude Children's Research Hospital has had success with pharmacogenomics implementations and has started using array-based genetic tests for pharmacogenomics variants.(7) Pharmacogenomics will be one of the first steps towards personalized medicine, and if the clinical challenges can be overcome efficiently, there is hope for a more substantial use of genetic information as a whole in the clinic.

References

1. Johnson JA. Pharmacogenetics in clinical practice: how far have we come and where are we going? Pharmacogenomics. 2013 May;14(7):835-43. PubMed PMID: 23651030.
2. Lam YW. Scientific challenges and implementation barriers to translation of pharmacogenomics in clinical practice. ISRN pharmacology. 2013;2013:641089. PubMed PMID: 23533802. Pubmed Central PMCID: 3603526.
3. Chan SL, Suo C, Chia KS, Teo YY. The population attributable fraction as a measure of the impact of warfarin pharmacogenetic testing. Pharmacogenomics. 2012 Aug;13(11):1247-56. PubMed PMID: 22920395.
4. Ritchie MD. The success of pharmacogenomics in moving genetic association studies from bench to bedside: study design and implementation of precision medicine in the post-GWAS era. Human genetics. 2012 Oct;131(10):1615-26. PubMed PMID: 22923055. Pubmed Central PMCID: 3432217.
5. Stanek EJ, Sanders CL, Taber KA, Khalid M, Patel A, Verbrugge RR, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clinical pharmacology and therapeutics. 2012 Mar;91(3):450-8. PubMed PMID: 22278335.
6. Nickola TJ, Green JS, Harralson AF, O'Brien TJ. The current and future state of pharmacogenomics medical education in the USA. Pharmacogenomics. 2012 Sep;13(12):1419-25. PubMed PMID: 22966890.
7. Crews KR, Hicks JK, Pui CH, Relling MV, Evans WE. Pharmacogenomics and individualized medicine: translating science into practice. Clinical pharmacology and therapeutics. 2012 Oct;92(4):467-75. PubMed PMID: 22948889. Pubmed Central PMCID: 3589526.
8. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing personalized medicine: development of a cost-effective customized

pharmacogenetics genotyping array. Clinical pharmacology and therapeutics. 2012 Oct;92(4):437-9. PubMed PMID: 22910441. Pubmed Central PMCID: 3454443.
9. Cohen J, Wilson A, Manzolillo K. Clinical and economic challenges facing pharmacogenomics. The pharmacogenomics journal. 2012 Jan 10. PubMed PMID: 22231566.