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Implementation of a clinical research pharmacogenomics program at an academic medical center: role of the genetics healthcare professional

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“One of the major roadblocks to clinical implementation of pharmacogenomic testing is having the test results available in a timely fashion for clinical decision-making.”

Pharmacogenomic testing has been cited as one of the most tangible, clinically applicable advances currently available for personalized medicine; however, widespread utilization within the healthcare system remains limited [1]. Herein, we present our initial experiences providing pharmacogenomic testing and genomic counseling in the setting of a clinical research study within an academic medical center and offer suggestions for implementation using a team-based approach.

Challenges to consider when implementing a pharmacogenomics clinical service

One of the major roadblocks to clinical implementation of pharmacogenomic testing is having the test results available in a timely fashion for clinical decision-making [2,3]. The right drug for the right patient at the right time can only be administered if the pharmacogenomic information is available when the patient requires treatment. For example, having the *CYP2C19* genotype results for clopidogrel response at the bedside or easily accessible in the electronic medical record (EMR) prior to time-sensitive percutaneous coronary intervention would be optimal for drug therapy decision-making by the physician. This issue can, in part, be addressed through rapid point-of-care testing [4] or pre-emptive testing [3]. Pre-emptive testing refers to pharmacogenomic profiling that is

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completed prior to necessity of a medication with test results available pre-emptively in the EMR for the treating provider, although widespread availability of such testing remains a concern.

Another challenge is the potential for incidental findings. This is disease-risk information identified that is not related to the original motivation for testing [5]. Certain gene variants have pleiotropic effects, and in addition to being associated with differences in drug metabolism, are also associated with disease susceptibility. The incidental findings generated from a single pharmacogenomic test will be limited compared with multiplex analyses that include testing for a wide array of variants or whole exome and/or genome sequencing, which are now commercially available for both research and clinical purposes, where incidental results may become overwhelming. Of 34 drug response genes (184 SNPs) on the Illumina ADME Multiplex Panel, Westbrook *et al.* showed that 20 (58.8%) were associated with at least one disease and 14 (41.2%) with multiple diseases in two or more studies [6]. Some incidental findings may be clinically actionable, others are not. For example, variants in *CYP2D6* have been observed to be associated with risk for actionable diseases such as colorectal cancer and scleroderma, but also with Parkinson's disease and lung cancer [6]. Furthermore, significant differences for both race and ethnicity exist in genome-wide association studies, making global assumptions about genomic variants and potential disease risks for patients of different ancestries problematic [7]. Who will be responsible for sorting through potentially actionable genomic variants and providing the patient with this information?

Understanding drug metabolizer status and applying this information in the clinical setting places significant burden on the front-line healthcare provider, namely primary care professionals. Importantly, genetics and genomics are areas in which many practicing physicians feel least confident in their knowledge and many providers were trained before pharmacogenomic testing became technically feasible; only providers trained in the past decade or so may have learned about genomics in their curricula [8]. In an American Medical Association survey of approximately 10,000 physicians only 10% felt adequately informed about pharmacogenomic testing [9]. Haga *et al.* has queried primary care professionals regarding their perspective on pharmacogenomic testing and identified numerous concerns, including the ability to adequately interpret and communicate test results, among other considerations such as timing in ordering a test and insurance coverage [10,11]. As physicians become more frequently involved in ordering and interpreting genomic and pharmacogenomic tests, as well as being faced with the ever increasing likelihood of patients bringing multiplex genomic testing results to their office through use of direct-to-consumer testing [7], more widespread genomics education will be needed. Ongoing efforts to address these issues include educational resources and guidelines for clinicians on how to interpret pharmacogenomic test results [3,12–14]. Evidence-based, end-user friendly clinical decision support (CDS) tools embedded in the EMRs may also help alleviate some of these issues.

EMRs & concomitant clinical decision support

It has been stated that without the EMR, an attempt to provide genomic medicine and counseling may well be futile [15]. As part of a translational clinical demonstration project under the umbrella of the Pharmacogenomics Research Network (PGRN), we are working to incorporate pharmacogenomic results within CDS platforms based on discrete data elements (i.e., genomic variants). At Ohio State University Wexner Medical Center (OSUWMC) [13] and other PGRN sites, CDS tools will integrate information from the patient's EMR, such as medication orders, with genomic variant data to trigger 'best practice alerts' recommending for or against the use of specific medications and informing/reminding the healthcare team

of the availability of specialist resources and support (i.e., genetics providers and pharmacists). In a manner similar to drug allergy reminders in the EMR, knowledge could be automated into the system to reduce patient risk and maximize drug efficacy. Mobile applications to store and interpret individualized pharmacogenomic data have also recently been developed and could help bring this technology to larger groups of patients [16].

Provision of a clinical research pharmacogenomics service at an academic medical center: lessons learned thus far

At OSUWMC, in partnership with the Coriell Personalized Medicine Collaborative (CPMC), we have been providing patient research participants with Clinical Laboratory Improvement Amendments- approved pharmacogenomic testing results (*CYP2C9/VKORC1/CYP4F2; CYP2C19*) [13]. The CPMC study has an independent Pharmacogenomics Advisory Group who determines which drug–gene pair results are provided to participants. Detailed pharmacogenomic test reports are made available directly to participants via the CPMC web portal and a PDF file of each report is uploaded to the OSUWMC EMR for patient care purposes. The research process includes provision of genomic and pharmacogenomic education to physicians prior to patient recruitment, as well as preinformed consent education of study participants that includes discussion of the potential for incidental findings. Patients are randomized to receive either in-person genomic counseling, or not, so that the impact of genomic counseling on multiple outcomes can be measured.

“As physicians become more frequently involved in ordering and interpreting genomic and pharmacogenomic tests, as well as being faced with the ever increasing likelihood of patients bringing multiplex genomic testing results to their office through use of direct-to-consumer testing, more widespread genomics education will be needed.”

Our team has been involved in the provision of more than 50 genomic counseling sessions gaining ‘real world’ experience within the setting of an academic medical center. The process of genomic counseling includes reviewing the participant’s current medications, medical and family histories, lifestyle/environmental risk factors and review of their pharmacogenomic test results as well as multiple potentially actionable disease risk reports (e.g., Type 2 diabetes risk). Anecdotally, while contracting with research participants to set the counseling session agenda, we have observed that many participants are most interested in discussing their pharmacogenomic results, as they view these results as having the highest likelihood for clinical utility. There is not a ‘one-size-fitsall’ approach since the counseling provided is personalized to each participant’s specific pharmacogenomic test results and current medications. The counseling often includes education regarding their specific haplotype (e.g., *CYP2C9*1/*3*), metabolizer type, an explanation of the relevant medication(s) (e.g., warfarin) and the reasons it may be prescribed. Interestingly, because our subject population is specific to congestive heart failure and hypertension patients, many are taking, or have been prescribed in the past, one of the medications (clopidogrel or warfarin) impacted by their pharmacogenomic test results, again highlighting the utility of pre-emptive testing. After the session, a consultation summary is provided to the research participant and routed to the study physician through the EMR.

“Our team has been involved in the provision of more than 50 genomic counseling sessions gaining ‘real world’ experience within the setting of an academic medical center.”

Both benefits and limitations of this genomic counseling approach have been observed. The skill set of genetic counselors, including risk assessment, explanation and application of

genomic testing results and education of patients and providers, is well-suited for the delivery of genome-guided medicine [17]. Also, in a survey of genetic counselors, 52% indicated they would play ‘some’ role in the delivery of pharmacogenomic testing [18]. However, limitations do exist. First, on a logistical level, the allotment of genetic counselor and geneticist time and effort needs to be considered, with much dependent on whether a single targeted test versus a broader genomic testing platform is performed. It is likely that not every person that undergoes pharmacogenomic testing will require an individual counseling session. Since it is outside the scope of practice of the genetic counselor to prescribe medications, the delivery of a comprehensive pharmacogenomics service necessitates a team approach, including the prescribing physician and ideally the pharmacist [19]. Findings of a study exploring genetic counselors’ opinions regarding pharmacogenomics service delivery accentuate the potential role for genetic counselors, with most suggesting a clinical service delivery model where genetic counselors provide specialty expertise in conjunction with other healthcare professionals as part of a multidisciplinary team [20]. Another viable model might involve the genetic counselor and/or medical geneticist serving essentially as genomic consultants to the healthcare team for the delivery and support of clinical pharmacogenomics.

Conclusion

In summary, although challenges remain, it is our opinion that a unified team approach, including those with expertise in medicine, pharmacology, genetics and biomedical informatics, will facilitate the establishment of clinical pharmacogenomics programs in academic medical center environments.

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