ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Incorporating Preemptive Pharmacogenomic Testing Into the Clinical Setting

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H&O What is preemptive pharmacogenomic testing?

PO Preemptive pharmacogenomic testing refers to germline genetic testing that is performed before administration of a certain drug to predict a patient's susceptibility, response, and risk of toxicities. An example is use of broad testing for relevant genetic markers that are known to be clinically actionable, even before the patient receives a prescription for a certain medication. The idea behind preemptive testing is to perform one test that can inform a lifetime of prescribing. Germline genetics do not change; they are inherited at birth. I prefer the term *pharmacogenomic* vs *pharmacogenetic* because the idea is for the test to be panel-based rather than administered for a certain gene and single drug at a time. Many clinicians believe that reactive testing is performed too late. In many clinical scenarios, there is no time for a clinician to receive results from testing before selecting a certain treatment from among multiple options. A patient in pain is a good example. It is not tenable for a patient in pain to wait days or weeks for a prescription.

H&O What are the goals of preemptive pharmacogenomic testing?

PO The goals of pharmacogenomic testing, in general, are to reduce adverse events and improve therapeutic response. Pharmacogenomic testing can identify populations or patients who might be genetically susceptible to developing toxicity or unacceptable serious adverse reactions. Testing can enable selection of the right drug the first time, rather than relying on trial and error.

As I mentioned, preemptive pharmacogenomic testing would incorporate panel-based approaches that inform more than one medication at a time. Insurance companies have traditionally been resistant to the idea of panel-based pharmacogenomic testing. The laboratory structure was developed around the idea of testing for one specific medication using one gene at a time, rather than a panel. There are other models in addition to panel-based testing. Preemptive testing can be performed in populations that are likely to receive at least one actionable medication. For example, in the oncology setting, a preemptive pharmacogenomic test could be administered to patients who are likely to start a specific type of chemotherapy. This type of preemptive model might be more achievable in the near term because of the reluctance of laboratories and payors to consider panel-based tests. With this model, it will be necessary to identify which patient groups are likely to benefit from such drug-specific preemptive testing.

H&O How have you implemented testing at the University of Chicago?

PO We implemented a preemptive pharmacogenomic test program under a hybrid research/clinical umbrella. The original program was known as the 1200 Patients Project. All of the tests in our programs are performed in a clinical laboratory accredited by the Clinical Laboratory

Improvement Acts (CLIA) and the College of American Pathologists (CAP) so that the genotype results can be used in clinical practice. In our first iteration of the project (the 1200 Patients Project), we targeted populations that are highly likely to benefit from these types of genotype tests, such as patients receiving multiple medications or treatments that are clinically actionable. The program included cancer populations that are likely to receive clinically actionable medications.

We took a broad approach when this program was first initiated in our outpatient clinics. We included 8 different subspecialties: primary care, oncology, cardiology, nephrology, gastroenterology, executive health, hepatology, and pulmonology. We first asked providers if we could enroll patients in their clinics. We then contacted patients to obtain DNA samples. We performed preemptive pharmacogenomic testing on patients who agreed. The results were forwarded to the treating physicians, who were free to use them to guide treatment decisions. This approach provided a natural experiment that allowed us to monitor how often physicians used the information provided by pharmacogenomic testing to inform treatment selection or modify dosing, as well as how often results were communicated to the patient as part of the conversation regarding the management plan. The program also allowed us to assess how often patients were treated with potentially safer medications based on the availability of results from preemptive pharmacogenomic testing.

H&O What was learned?

PO Our analysis showed that clinical integration of genomic medicine enhanced decisions regarding prescriptions. Patients were interested in learning the results of genomic testing, and physicians routinely applied the information to clinical care. The use of pharmacogenomic information when prescribing increased patient-provider communications, the patient's recall of the medication, and the provider's understanding of genomics. Throughout the entire study, no high-risk medications were prescribed after physicians consulted a clinical decision support tool that categorized risk according to pharmacogenetic results.

H&O How has this strategy evolved?

PO We have now implemented this program in our inpatient hospitalist medicine section through a consortium known as ACCOuNT (African American Cardiovascular Pharmacogenetic Consortium; NCT03225820). With the consent of the section leadership, we invite patients to join the program upon admission to hospitalist services. This study is unique in that it is specifically examining the potential utility of delivering pharmacogenomic information to inform decision-making for the inpatient care of self-identified African Americans. Patients who agree have a sample collected during their hospitalization. The pharmacogenomic test is performed. Currently, the turnaround time for the results is not usually quick enough to inform the current admission. We have learned, however, that many patients have frequent repeat admissions to the hospital. The results are then available for any subsequent admissions. This is a longitudinal project spanning many months or even years that can inform treatment for these patients, who may be receiving many new medications for each admission. These patients are at risk for pharmacogenomic interactions. We are currently studying how pharmacogenomic testing can impact their management.

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We have another project, known as the ImPreSS trial (Implementation of Point-of-Care Pharmacogenomic Decision Support in Perioperative Care), which is ongoing in the operative setting (NCT03729180). We have engaged the leadership of the department of anesthesia and critical care. We administer preemptive pharmacogenomic testing during a patient's preoperative visit to the anesthesia perioperative medicine clinic. The test results can be used to optimize the medication list before the anesthesia day/procedure day, and to specifically develop tailored plans for sedation or pain management. Test results are available within 10 days of DNA collection, for use by the anesthesiologist on the day of the procedure. We have observed that anesthesiologists are using pharmacogenomic information to tailor anesthesia care plans. The pharmacogenomic information is also available to guide any type of postoperative care, whether the patient is admitted to the hospital or the intensive care unit. We are studying how results from pharmacogenomic testing might influence prescribing in these settings.

H&O Are you initiating any other studies?

PO We are currently preparing to launch a cancer-specific trial that will focus on patients with breast cancer,

gastrointestinal cancers, and head and neck cancers. These patients are frequently treated with fluorouracil and irinotecan, which can cause well-known toxicities in those with certain polymorphisms. We will offer enrollment and preemptive pharmacogenomic testing to patients before they initiate chemotherapy. We will evaluate how test results can be used to inform dosing and reduce serious adverse events in these patient populations. This study will be part of a randomized trial.

H&O Are there any barriers to the use of preemptive pharmacogenomic testing?

PO There are many barriers in clinical practice. To begin, most hospitals and health systems lack the ability to perform in-house pharmacogenomic test assays, even for variants considered actionable by consensus groups. If these tests are ordered at all, they must be sent out for processing. At the University of Chicago, we recognized that the use of in-house assays would be essential to the implementation of a pharmacogenomic testing program on any meaningful scale. We set up our own in-house pharmacogenomic assays, which are validated in the CLIA and CAP settings. All of our testing is performed in-house. I am not suggesting that every institution should follow this approach, but it is a practicable way to implement widespread testing.

The second major hurdle is the necessity to obtain results from pharmacogenomic testing in a useful timeframe. Preemptive testing addresses this concern. If test results are already available, then there is no need to wait when a patient needs a new, unanticipated prescription.

Support for clinical decision-making must accompany the pharmacogenomic test results. It became apparent early on that we cannot simply forward the genotype test results to clinicians and expect them to know how to apply the information. Most providers were trained before the first human genome was sequenced, and they are learning about the clinical application of pharmacogenetics in real time. We have built into the electronic medical record prompts that direct a clinician to pharmacogenomic information when a certain medication is being prescribed. There are clinical workflow processes that must be established, including the judicious use of best practice alerts, in order to ensure that implementation is impactful.

Reimbursement is a major barrier to pharmacogenomic testing, especially preemptive testing. Unfortunately, widespread reimbursement is lacking for most pharmacogenomic tests. Only a few pharmacogenomic testing indications are reimbursed by Medicare and Medicaid or by third-party payors and private insurers. In our program at the University of Chicago, we do not currently bill for the pharmacogenomic tests that we order. The tests are supported through our institution, our Center for Personalized Therapeutics, grants from the National Institutes of Health, and philanthropic contributions. This support has allowed us to genotype thousands of patients. However, this model is not sustainable for clinical care in the future. Therefore, reimbursement for pharmacogenomics will need to change if implementation of testing is to occur on a wide scale for most drugs that could have relevance.

H&O Do you have any recommendations on how institutions can implement a pharmacogenomic testing program?

PO The barriers that I mentioned above must be addressed. However, the most important aspect is leadership support. Unless there is high-level, institutional support for this type of program, it is unlikely to succeed. It is also necessary to assemble a team of investigators who are experts in the field of pharmacogenomics.

H&O How can physicians use information from preemptive pharmacogenomic testing in oncology/hematology?

PO One older example is testing of the thiopurine S-methyltransferase (*TPMT*) gene to guide leukemia treatment. This strategy has been in place for many decades and is well-established. Two additional examples that I mentioned above are fluorouracil and irinotecan. Labeling of irinotecan by the US Food and Drug Administration includes dosing precautions for patients with the uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) polymorphism. Unfortunately, these precautions are not routinely used to guide prescribing, at least in a preemptive manner. A more recent example is the use of 5-fluorouracil and capecitabine in patients with a variant of the gene encoding dihydropyrimidine dehydrogenase (*DPYD*). Fluoropyrimidines are one of the most widely used cancer therapies. In Europe, there is a mounting consensus that it is unethical to prescribe a fluoropyrimidine without knowing the patient's *DPYD* genotype or dihydropyrimidine dehydrogenase (DPD) status. In the United States, this approach is not yet the accepted standard. Guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network do not yet endorse routine preemptive screening before the use of a fluoropyrimidine. This area deserves active research to better understand the role of this genetic alteration, the potential impact on providers and patients, and how pharmacogenomic testing can be used to manage treatment.

H&O Is germline genomic testing common in the oncology setting?

PO Currently, the patient's germline genome is almost completely ignored in oncology. Oncologists are focused on somatic testing as part of the standard of care. Somatic results can change over time or with different clones, as mutations are acquired throughout disease progression. Germline testing provides a different model, but one that is similar to somatic testing. Oncologists should be primed for germline pharmacogenomic testing. It is not clear why somatic testing is commonplace, whereas germline testing is rare. Our research aims to address this translational gap.

Disclosure

Dr O'Donnell serves as a member of the Data Safety Monitoring Committee for the NIH/NHGRI Implementing Genomics in Practice (IGNITE II) Networks.

Suggested Readings

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