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Facilitating Clinical Implementation of Pharmacogenomics

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Variability in drug response can be explained, in part, by genetic differences among patients. A clear role in drug toxicity and efficacy has been established for some gene-drug combinations, yet implementation of pharmacogenomic tests in clinical practice lags behind this knowledge. The evidence–adoption gap for many pharmacogenomic tests can be addressed in the short term through the development of consensus-based practice guidelines and clinician education.

For genetic variants associated with severe drug toxicities, there is a strong impetus for adoption. An example is the HLA-B*15:02 variant, associated with the potentially lethal Stevens-Johnson syndrome in Asian patients treated with carbamazepine.[1] Another example is the poor metabolizers of cytochrome p450 2D6 substrates that represent a range of risk when exposed to specific medications. The death of a child treated with fluoxetine illustrates the importance of identifying patients with impaired metabolism as well as the ethical dilemma of knowingly exposing patients with minimal metabolic capacity to substrates that require a specific enzyme for clearance.[2]

The adoption of testing for genetic variants that have a more modest effect on drug response or risk of adverse events has been more variable. In oncology, somatic mutation or expression tests for specific drug targets in tumors (eg, EGFR, ERBB2) can provide a clear indication for treatment efficacy, and rates of adoption have been relatively high. However, the current evidence for other pharmacogenomic tests for efficacy determination is less clear. For example, patients of European ancestry who carry the higher-activity allele of a serotonin transporter gene variant have a modest increased probability of responding to serotonin reuptake inhibitors.[3] The decision to use testing to increase the probability of a good response must be weighed against other issues, such as the efficacy and cost of

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Mrazek reported developing intellectual property that has been licensed by AssureRX Health and subsequently incorporated into physician decision support software and receiving research funding from AssureRX Health to create and maintain a bibliographic system designed to regularly monitor the scientific literature. Dr Mrazek also reported receiving royalties from the sale of a book on pharmacogenomics, and he reported that his institution has received medication from Forest Laboratories for an NIH-funded pharmacogenomic probe study. Dr Lerman reported serving as a consultant to Pfizer Inc on pharmacogenetic testing for smoking cessation treatment and receiving research funding from and consulting for AstraZeneca, Targacept, Pfizer, and GlaxoSmithKline, for work unrelated to this Commentary. Dr Lerman also reported receiving compensation for expert testimony.

alternative treatment options. Because the cost of testing is decreasing, cost is less likely to pose a barrier.

Evaluating Effectiveness

At the center of a debate on the clinical implementation of pharmacogenomics is the threshold of evidence required for use in practice. Consistent with the Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network,[4] the evidence threshold for implementation can be met by the existence of a strong biological rationale for a gene-drug combination, reproducible evidence linking genetic variation to drug response, and noninferiority compared with current prescribing practice.[5] Given the urgency to begin implementing highly predictive pharmacogenomic tests to reduce serious adverse drug effects, waiting for data from prospective randomized clinical trials (RCTs) may be depriving patients of safer and more effective medications. Moreover, because many of the genetic variants associated with severe toxicities are rare, prospective trials may not be practical. For more common variants with modest effects on efficacy, clinical utility may be difficult to demonstrate.

However, clinical adoption is influenced by the presence of regulatory recommendations and third-party payment, both of which require a higher threshold of evidence demonstrating improved clinical outcomes at an acceptable cost. This is particularly true for genetic-driven prescription of high-cost medications to patients for whom conventional therapies are predicted to fail. This need not impede clinical adoption of tests for which there is sufficient evidence to develop practice guidelines. Parallel integration of research into clinical practice settings in which initial adoption occurs would provide crucial data for improving clinical guidelines.

To generate the type and quality of evidence to influence policy decisions, alternate research models are needed. RCTs, the gold standard in medical research, may not provide answers to practical research questions needed to influence makers of health care decisions.[6] While RCTs can determine whether a pharmacogenomic test “works” under ideal circumstances, clinical and health policy decisions can be based on whether the test will improve health care outcomes under best-practice conditions, at an acceptable cost. However, best-practice conditions rarely follow the rigorous procedures for patient selection, testing, and treatment as performed in an RCT.

One approach to balance these issues and improve generalizability of research to practice is a pragmatic clinical trial (PCT).[6] In contrast to RCTs, with their strict eligibility criteria and delivery of protocol-driven therapies, PCTs are conducted in practice settings with diverse and comorbid patient populations. PCTs are more likely to use the standard or least expensive treatment as the comparator. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) compared atypical and typical anti-psychotics in a diverse sample of patients with schizophrenia enrolled at 57 clinical sites and used a global effectiveness outcome reflecting patient and clinician assessments.[7] PCTs are less experimentally rigorous by design and therefore will not replace traditional RCTs; however, once initial efficacy has been documented, a PCT could be part of the validation pathway for implementation of pharmacogenomic tests.

Health Care Challenges

The integration of genetic information into the medical record requires the development of more effective links between the actual reporting of a genotype and the clinical implications. The electronic health record provides potential solutions and efficiencies because genotypic reports can be organized in a single location within the record and linked to the primary

indications and implications of specific genetic variants. A special consideration for pharmacogenomic test results is that they be linked to the physician ordering system. This will help ensure that physicians are prompted regarding efficacy and safety considerations when ordering a specific medication and that they are trained to understand the implications of variant genotypes of predictive significance.

Given the rapid acceleration of the technology for identifying genetic variations, it is important to implement a consistent methodology to ascertain specific alleles and ensure the accuracy of results. With the anticipated adoption of gene sequencing technology in Clinical Laboratory Improvement Amendments–approved settings, the establishment of standardized methods for maintaining quality control will be necessary.

Despite calls for increased clinician education in genetics, levels of clinician-reported knowledge, confidence, and skill in genetics remain suboptimal.[8] Several initiatives to improve physicians' knowledge of genetics have been implemented, including the introduction of pharmacogenomics curricula during residency training.[9]

To facilitate the implementation of pharmacogenomic testing in practice, the development of clinical guidelines and other decision support tools is critical.[4] The Institute of Medicine has issued a report describing the development of clinical guidelines that stresses the importance of systematic scientific review of the evidence but also recognizes that a range of clinical evidence must be considered to facilitate the implementation of new technologies that provide clear benefit.[10]

Reimbursement for pharmacogenomic testing has been inconsistent, and the lack of certainty regarding payment represents a major barrier to utilization. A key issue in reimbursement is determining when pharmacogenomic testing is no longer investigative for a specific indication. As the cost of testing decreases and effectiveness becomes well documented, reimbursement would be more widely adopted.

Expectations for Implementation

The implementation of pharmacogenomic testing to protect patients from adverse drug effects will become common practice for an increasingly large number of gene-drug combinations. While testing for therapeutic efficacy can improve the overall health of patients, development of clinical guidelines, clinician education, and new models of effectiveness research may be required for widespread implementation.

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