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Genomic Medicine, Precision Medicine, Personalized Medicine: What's in a Name?

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Abstract

This issue of *Clinical Pharmacology & Therapeutics* is devoted to genomic medicine, and a reader may reasonably ask what we mean when we use those words. In the initial issue of the journal *Genomics* in 1987, McKusick and Ruddle pointed out that the descriptor "genome" had been coined in 1920 as a hybrid of "gene" and "chromosome," and that their new journal would focus on the "newly-developing discipline of mapping/sequencing (including analysis of the information)." A key milestone in the field was the generation of the first draft of a human genome in 2000, but this success really represents only one of many milestones in the journey from Mendel to MiSeq.

It is now clear in the field of genomic medicine that the ability to sequence nucleic acids is no longer an insurmountable financial or experimental barrier to advancing our understanding of the genetic underpinnings of variability in human physiology, disease susceptibility, or—of special interest to readers of this journal—drug response.[1] A consensus definition of genomic medicine is "using an individual patient's genotypic information in their clinical care".[2] In this issue of *CPT*, in addition to successes to date, Chisholm outlines challenges in implementing that vision,[3] and other authors offer commentaries on specific obstacles in developing and commercializing new lab tests,[4] in meeting educational imperatives from the lay population to health-care providers,[5] in developing methods to accumulate and curate information on the possible consequences of individual polymorphisms,[6] and in setting realistic patient expectations and meeting them.[7]

Acquiring and interpreting sequence variation data

A common vision is to couple DNA variant data in individual patients to their electronic medical records, thus enabling point-of-care decision support when a drug with an actionable pharmacogenomic variant is prescribed.[8] Although this seems appealing intuitively, this is very much a case of the devil being in the details: which variants are "actionable"? How are data on actionability obtained and validated? What does clinical decision support look like? Do health-care providers respond to genomically guided advice? What happens when they do? A specific example is provided by the Point/Counterpoint

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CONFLICT OF INTEREST
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presented by Rae[9] and Ratain and colleagues,[10] who debate the issue of decreased bioactivation of tamoxifen in patients with the *CYP2D6* poor-metabolizer phenotype. The decreased bioactivation is not disputed; instead, the questions are the extent to which this difference in biology drives clinical response to the drug and how to interpret available publications.

This particular controversy also highlights the obstacles in acquiring high-quality raw genotype data and translating those data to diplotypes that are, or are not, actionable. Addressing the latter question is the major mission of the Clinical Pharmacogenomics Implementation Consortium (CPIC)[11] that originated in the Pharmacogenomics Research Network (PGRN) and is published here in *CPT*; the CPIC is currently celebrating its second year with the publication of updates, including one on *CYP2C19* and clopidogrel.[12] Also in this issue, Shuldiner and colleagues describe the CPIC with respect to a variety of other experiences with pharmacogenomic implementation in the PGRN's Translational Pharmacogenetics Program.[13] Implementation efforts at individual institutions are then described by Farrugia and Weinshilboum at the Mayo Clinic Center for Individualized Medicine,[14] Gottesman *et al.* at Mount Sinai Medical Center,[15] and Evans *et al.* at St. Jude Children's Research Hospital.[16]

Where is the field headed?

The development of robust technologies to generate and understand sequence variation is already having an impact on health care. One extraordinarily exciting area is cancer biology, exemplified by the way in which the Philadelphia chromosome has moved from being a diagnostic marker for chronic myelogenous leukemia to the target for imatinib, a highly effective, well-tolerated therapy specific for the mutant sequence that the Philadelphia chromosome represents. Sequencing to identify driver mutations across the spectrum of cancers is offering spectacular new opportunities to understand the genesis of the disease and to develop new imatinib-like targeted therapies. Indeed, defining cancer by the organ in which it arises seems very "last-century"; cancers will now be defined by their molecular drivers and expected responses to targeted therapies. Evans and colleagues[16] and Nakamura and colleagues[17] outline strategies that take advantage of cancer cell profiling to point to new biomarkers for disease progression, better use of current drugs, and potential targets for new drug development.

Sequencing is now becoming routine in the investigation of emerging issues in infectious disease, from new epidemics to foodborne illnesses to the role of the microbiome. Sequencing has rapidly made the transition from a research tool to an indispensable clinical tool to identify the basis of Mendelian diseases previously inaccessible by traditional linkage analyses. The traditional tool of the family history is now being reinterpreted as a critical screening mechanism for important phenotypes, such as certain types of cancers or early heart disease that have increasingly well-defined genomic underpinnings with specific diagnostic and therapeutic implications: Lynch syndrome, Fabry disease, and subtypes of the long-QT syndrome are examples. The genome-wide-association study paradigm has identified common variants associated with complex traits, and sequencing is extending this understanding by generating an increasing catalogue of rare DNA variation—and most variation falls into this rare category[18]—that is enabling definition of the role of rare polymorphisms, sometimes associated with surprisingly large effect sizes. The ability to identify rare variants also carries with it challenges, such as sorting functional from bystander variants. As well, current next-generation approaches continue to pose challenges for analysis of some genes (including many cytochrome ones), with *CYP2D6* and the *HLA* locus of special interest to clinical pharmacologists.

Discovery is only now beginning

As discussed above, the application of sequencing technology to the bedside naturally creates challenges in the implementation realm, and these are being addressed in projects such as the CPIC, the Translational Pharmacogenetics Program, and the Electronic Medical Records and Genomics Consortium (eMERGE).[19] However, we must not lose sight of the fact that these technological advances carry with them unprecedented opportunities to address questions of fundamental scientific discovery. Determining the function of individual genomic variants and how they contribute to drug responses and other phenotypes is currently a major area of study. Analyzing multiple "omic" data sets—genomic, transcriptomic, proteomic, and others—and the way in which they interact is another promising approach. The ENCODE (Encyclopedia of DNA Elements) project's definition of function of noncoding regions of DNA represents an asset for investigating the likely impact of variation identified by association or sequencing studies. The cancer precedents suggest that we could be on the verge of redefining many common diseases by their genomic profiles and by their genetically predicted responses to drug therapy; pharmacogenomics thus holds the potential of repurposing existing drugs for genomically defined patient subsets as well as of identifying new drug targets. We look forward to reinterpreting human diversity using genomic variation within and across traditional "ancestries"; including large populations from around the globe in pharmacogenomic studies holds the potential of accelerating discovery of new functional variation contributing to disease susceptibility and drug responses.

Back to words

As this discussion highlights, the term "genomic medicine" has broader implications for scientific discovery and for implementation than we might have initially envisioned. Indeed, some have proposed that the data—starting with cancer—are so compelling that the phrase "precision medicine" should be adopted to describe the use of genomic variant data in caring for patients. To us, this seems premature at best. The idea that genomic sequence data can impact the way in which we care for patients is now beyond question. However, the health-care outcomes of an individual patient, including his or her responses to drug therapy, are not and are unlikely to ever be determined exclusively by genomic variation. Patients are more than collections of genomes and gene–environment interactions; they are individuals influenced by experience, culture, education, upbringing, and innumerable other factors. The term "precision medicine" carries an expectation of perfect outcomes that not only is unrealistic but runs the risk of overhyping the potential of the field to patients and their families. We prefer to continue and expand the use of "personalized medicine." The idea was nicely encapsulated by Sir William Osler when he said, " The good physician cares for the disease; the great physician cares for the patient."

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