

## EDITORIAL

# Translating Precision

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Precision medicine is based on a simple precept that deep information about an individual patient can be used to guide his or her healthcare. In the not-too-distant future, clinicians may have point-of-care access to an individual's entire genome, dense data captured from wearable devices, and informatics tools that aggregate data from clinical experience to allow for real-time decision support. The innovative technologies being developed in pursuit of precision medicine afford researchers and clinicians the opportunity to generate and consume information at an unprecedented scale. At the same time, the translational lifecycle from bench-to bedside is shortening. In this context, translational research has never been more integral and directly linked to patient care. As such, this issue of *Clinical and Translational Science* explores some essential themes in the field of precision medicine: reproducibility in research, modalities to experimentally validate markers of disease, and development considerations for the medical products used in practice.

### GETTING THE BASICS RIGHT

Credible discovery science is the foundation of precision medicine. Reproducing early research discoveries is the first step toward developing a medical product. Reflecting on the years of candidate gene research, hundreds if not thousands of publications were published and many reported conflicting findings. About a decade ago, high-throughput genomic techniques became more prevalent, and substantive gains were made in identifying genomic factors that were consistently associated with complex diseases and drug response. Progress in genomics may be attributed to a cultural shift whereby the scientific community emphasized replication, rigorous statistical methods, and experimental validation. Now, with the use of next-generation sequencing technologies and growing discussion of real-world evidence, the fundamental factors that will foster reproducibility need to be considered. The failure to confirm initial research findings, in at least some cases, could be attributed to preventable methodological missteps. From a funding agency vantage, McShane provides a thoughtful critique of many factors that investigators, journal editors, peer-reviewers, regulators, and other stakeholders alike must attend to in an effort to put quality science in the public domain: proper study design, robust assays, adequate sample sizes, careful

data management, rigorous statistical methods, and transparent reporting.<sup>1</sup>

### BUILDING CONFIDENCE

Assuming that rigorous methods are in place, validating a biomarker for a given clinical use often relies on the epidemiologic principles of causal inference (strength, cohesion, replication, effect size, statistical significance, and so on). Experimental genetic models provide the critical mechanistic basis for clinical action, whether used to establish a mutation as a disease-causing factor or to understand the influence of mutations on a drug's effectiveness. In fact, experimental models have been critical to defining the target population for targeted therapies for rare diseases and cancers. Deep sequencing of the human genome will undoubtedly identify many rare but clinically important variations. However, clinical studies will be limited in their ability to characterize the impact of rare or complex multifactorial signatures on clinical outcomes (e.g., because of sample size constraints). Alternative lines of evidence will play a greater role in informing clinical decision-making. With this in mind, Ipe *et al.* provide a very comprehensive overview of numerous technologies and resources that illuminate the functional relevance of genomic variations.<sup>2</sup>

### ADVANCING BIOMARKERS TO CLINICAL TESTS

The clinical or experimental validation of a biomarker alone does not make a clinical test. In order to successfully bring precision therapeutics to patients, reliable *in vitro* diagnostic tests have to be developed. The pharmaceutical industry has been a major driving force in evolving the diagnostic landscape over the past few years; the number of US Food and Drug Administration-authorized companion diagnostics continues to grow. While formal clearances/approvals of complementary diagnostic tests are limited to oncology, informative biomarker information has been incorporated in some recent drug approvals, such as the anti-interleukin(IL)5 drugs for eosinophilic asthma. All-comer development strategies coupled with diagnostic test co-development ensures that quality tests are broadly available, and provides prescribers with flexibility to individualize treatments in certain clinical contexts. Scheerens *et al.* expand

on many of these issues, offering a high-level overview of the diagnostics landscape from the pharmaceutical perspective, the burgeoning category of complementary diagnostic tests, and some of the strategic commercial considerations related to drug-diagnostic codevelopment.<sup>3</sup>

## TARGETED THERAPEUTICS

What follows from the drug and diagnostic development strategy is the decision about whether to restrict drug therapy to a certain patient population, which tends to be a function of therapeutic risks and benefits, and the extent to which the biomarker differentiates responses. In drug development, a biomarker-based strategy may be pursued to augment the drug's benefit-risk relationship, or streamline clinical development. Indeed, several tyrosine kinase inhibitors have now been developed and approved for patients with lung cancer whose tumors harbor epidermal growth factor mutations. For this class of drugs, the science has evolved over time, and new technologies have enabled more precise targeting of the drugs to patients based on mutation status rather than protein expression alone to enhance the benefit side of the equation. In addition, refinement of the target population may also occur after understanding risks and benefits in a broader population to optimize dosing (e.g., controlling concentrations) or exclude toxic responders, for example. Again, these maneuvers have the same net effect of shifting risks and benefits. Schuck *et al.* review the course of one particular tyrosine kinase inhibitor and other illustrative cases, providing insight into the regulatory perspective on the impact of biomarker-based patient selection strategies on therapeutic benefit/risk assessments.<sup>4</sup>

## CONTINUOUS REFINEMENT

Even when a particular biomarker has a clear functional basis and a well-understood impact on drug exposure or response, much may remain unknown about how best to use it in practice. For example, CYP2D6 and CYP2C19 variations that result in poor metabolism significantly influence the pharmacokinetics of amitriptyline—an old drug, and an old biomarker. However, population diversity is a major consideration in genomics research. Ensuring that pharmacogenetic interactions extend beyond the relatively homogeneous populations that are included in discovery efforts may be necessary to identify nuances that may limit generalizability to the diverse US patient population. On the heels of a recently updated guideline on the use of amitriptyline based on CYP2D6 and CYP2C19 genotype,<sup>5</sup> Ryu *et al.* offer additional insight on this well-described pharmacogenetic interaction in Korean patients.<sup>6</sup>

## SUMMARY

The US Precision Medicine Initiative, in tandem with the Innovative Medicines Initiative, and myriad other efforts described by Nimmesgern *et al.* of the European Commission, will contribute to a global database of knowledge about the role of various tools and technologies in precision medicine.<sup>7</sup> However, in their proposed taxonomy of “-omics,” Davis and Shanley provide a reminder that precision medicine is the sum of intrinsic and extrinsic factors, not just integration of the “endemic” factors that influence disease susceptibility, progression, and therapeutic response.<sup>8</sup> Human health is complex and the underlying science that facilitates prevention and management of disease is iterative. In the environment of precision medicine, the interplay between discovery, validation, and implementation may prove to be more dynamic than linear and result in incremental gains rather than tectonic shifts. However, quality discovery science begets validation, and validation begets effective intervention.

**Conflict of Interest.** The author declared no conflict of interest.

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