PERSPECTIVE

Precision Medicine 2030

Michael Pacanowski[1,*] and Qi Liu[1]

"Precision medicine" conjures a sense that technologies will give prescribers high confidence in selecting the right drug at the right dose for individual patients. Some elements of this promise have been realized across the drug lifecycle, whereas others remain aspirational. We offer a reflection on advances in precision medicine and what is on the horizon.

REALIZING THE PROMISE OF PRECISION MEDICINE

Precision medicine, in the context of pharmacotherapy, typically relates to the use of predictive tools, such as biomarkers to select treatments, tailor dosing, or monitor response. The mainstays of precision medicine, which are now second nature, include therapeutic drug monitoring and managing drug therapy in the setting of organ dysfunction, interacting drugs, or other factors that influence concentrations and/or response. Technologies like genomic testing have given clinicians access to new tools, but these tools essentially serve the same function as traditional measures—to shift the probability of a certain outcome for a subgroup of patients through altered dosing or treatment. However, much hope and hype has surrounded the promise of modern precision medicine approaches, resulting in high expectations for predictive value and clinical utility. Despite healthy skepticism, the pace of translating new technologies to the clinic over the past decade has been impressive, most notably with respect to the broader use of next-generation sequencing technologies, availability of more US Food and Drug Administration (FDA)–authorized tests for novel biomarkers, and new treatments for monogenic diseases and various cancer subtypes.

Efforts to bring precision medicine principles to the clinic in the past 10 years faced challenges but ultimately established some boundaries for translation. Testing for pharmacogene variants, like CYP450 enzymes, might have been among the most immediate uses of modern genomic technologies in the clinic. However, evidence for pharmacogenetic interactions was often derived from observational studies or clinical pharmacokinetic data, which resulted in calls to demonstrate a *test's* impact on outcomes in controlled trials. This high standard was successfully accomplished for abacavir and HLA-B*5701 testing; such evidence indeed hastened the uptake of testing, and lack of such evidence hindered adoption of testing for other well-characterized gene–drug interactions (e.g., *CYP2C19* for clopidogrel). In contrast, prospective testing for *ostensibly* predictive biomarkers became routine in drug development, often because of a mechanistic link between the drug's pharmacology and the disease's molecular pathology. Building upon hormone receptor testing for breast cancer treatments, trastuzumab for HER2-positive breast cancer persisted as the archetype for contemporary targeted drug development long after its approval in 1998. It took several years for imatinib to increase the numerator of biomarker-based approvals. The paradigm seemed to shift a couple years later in 2008 with *post hoc* clinical trial findings that panitumumab and cetuximab were less effective for KRAS mutation-positive colorectal cancers. These findings prompted rapid adoption of KRAS testing in practice, but also drove extensive debate around the challenges of relying retrospective studies for regulatory decisions. All of these early cases served to clarify the basic evidentiary considerations for biomarker-based prescribing.

Over the ensuing years, the drug-diagnostic codevelopment pathway became well established and paved the way for continued innovation in clinical drug development. In the early 2010s, new treatments for certain patients with lung cancer (ALK-positive and EGFR mutation-positive tumors), melanoma (BRAF mutation-positive tumors), and breast and ovarian cancer (BRCA mutation-positive tumors) showed significant tumor responses or delayed disease progression in clinical trials and were approved along with companion *in vitro* diagnostic tests. More recently (over the past 3 years), approximately half of novel cancer drugs were initially approved for a subset of patients with a given tumor type. Cancer is now routinely thought of in a molecular context, and biomarker-centric (i.e., tissue agnostic) rather than histology-centric drug development approaches have been successfully pursued (e.g., pembrolizumab and larotrectinib). As biomarker testing has evolved, so too have the clinical trials and complex and innovative trial designs arose out of a need for

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. *Correspondence: Michael Pacanowski (michael.pacanowski@fda.hhs.gov)

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efficiency. Many basket and umbrella trials were planned and initiated to test multiple drugs or biomarkers under single protocol (e.g., Lung-MAP, iSPY-2).[1] The diversity of predictive biomarkers being investigated in clinical trials and covered by FDA-authorized companion or complementary diagnostics continues to increase.

Overall, the past decade was marked by significant growth in the development and use of targeted drugs and their respective *in vitro* diagnostic tests (**Figure 1**). The FDA has endorsed targeted development and sought to clarify regulatory expectations for diagnostics and clinical trial conduct. To the extent that precision medicine principles have tangibly impacted the drug development process, the regulatory framework, and the diagnostic workup of patients in the clinic, the promise of precision medicine has been realized in many ways.

GAPS AND OPPORTUNITIES TO ADVANCE PRECISION MEDICINE

Based on the advances to date, the next decade will likely bring many novel treatments and tools under the precision medicine umbrella (**Figure 2**). Many innovations that impact precision medicine are being brought into focus under the 21st Century Cures Act[2] and the 6th reauthorization of the Prescription Drug User Fee Act.[3] Consequently, the pathways to bring innovations to the clinic will continue to be a major focus in the coming years.

With regard to drugs, the portfolio of novel treatments has expanded. Microbiome, gene editing, and cell therapies are actively being investigated and evidence will continue to accumulate about their role in treating disease. In the nearer term, targeting RNA with synthetic oligonucleotides might be viewed as a novel platform that could yield many new drugs directed at the underlying molecular pathology of a disease. Products like nusinersen for spinal muscular atrophy and patisiran for hereditary transthyretin-mediated amyloidosis have demonstrated effects on the natural history of these severe and debilitating diseases. New oligonucleotide drugs can be created by altering the nucleotide composition, enabling products to be designed for individual patients—truly personalized medicines.

For typical small molecule and biologics, gaps remain. Genomic research has been able to uncover the molecular drivers of various cancers and created opportunities to evaluate drug effects in subsets of patients defined by molecular features. Unfortunately, predictive enrichment of clinical trials through the use of novel biomarkers remains uncommon outside of oncology. Although many common diseases are polygenic and result from environmental influences, genomic tools could enable better risk assessment, support enrichment, or stratification of clinical trials, or perhaps even disease interception. In addition, now that genome sequencing has become more common, research in large-scale genomic studies will potentially uncover new markers for disease susceptibility, which may be tractable targets for development of drugs with novel mechanisms of action (along the lines of PCSK9 mutations and the consequent inhibitors).

Regarding biomarkers, drug development programs have pushed beyond single analytes to predict therapeutic outcomes. For example, numerous mutations within a given gene may be targeted for development. Such programs have raised questions about the generalizability across different molecular alterations, prompting efforts to rely on experimental and mechanistic evidence in defining the target population.[4] More complex biomarkers, like

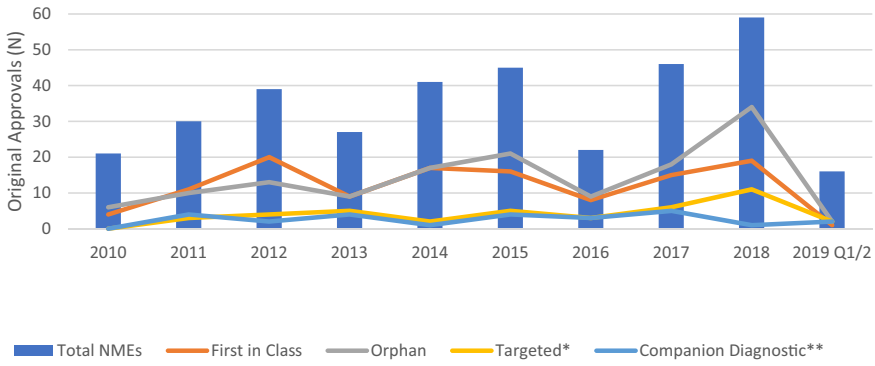

Figure 1 Trends over time in targeted drug development approvals are shown. *Targeted drugs for the purpose of this figure are new molecular entities (NMEs) for which the initially approved indication is restricted to a subset of patients who are identified through molecular testing. **Companion diagnostics reflect original premarket approvals or 510(k) authorizations.

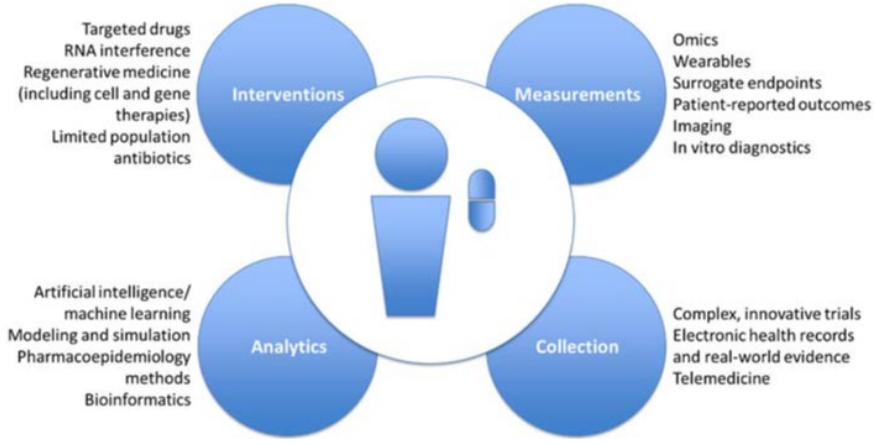

Figure 2 Emerging technologies in focus for the next decade. The 21st Century Cures and the sixth reauthorization of the Prescription Drug User Fee Act cover areas, including but not limited to targeted drugs for rare diseases, model-informed drug development, complex and innovative trial designs, qualification of biomarkers and other drug development tools, surrogate end point development, regenerative medicine advanced therapies, real-world evidence, patient-focused drug development, limited population antibiotic development, medical software, and breakthrough devices.

homologous recombination deficiency (e.g., for rucaparib) and specific gene signatures (e.g., for atezolizumab), have been evaluated in clinical trials, and mismatch repair deficiency or microsatellite stability formed the basis for a shift into tissue-agnostic drug development. Panels for tumor testing have obtained FDA clearance, and next-generation sequencing will continue to put more patient data in the hands of clinicians to guide therapeutic decision making. As these tests become less invasive (e.g., blood-based), it may become possible to monitor response to cancer treatments. Outside of cancer, genomic testing is now mainstream (e.g., for ancestry and other traits). More individuals are obtaining their own genomic information, and the FDA has cleared direct-to-consumer tests for various germline DNA traits, including pharmacogenetic interactions. Consequently, patients may be the driver for clinician access to genomic information, such as drug metabolizing enzyme gene variants, allowing broader uptake of precision-dosing strategies. The results of genomic tests continue to be reported in different ways and the test content and interpretation vary from institution to institution. Several efforts are underway to bring greater consistency in the practice of precision medicine (e.g., with respect to treatment recommendations, test validation and conduct, and interpretation).[5,6]

Regarding evidence generation and analytics, various approaches are emerging to complement the traditional clinical trial paradigm. Quantitative approaches, such as exposure–response analyses, population pharmacokinetics, and physiologically-based pharmacokinetic modeling, have become routine approaches to optimize dosing for special populations. Similarly, real-world evidence has been commonly used in the assessment of drug safety. It is increasingly being recognized that data generated from provider-patient encounters, as contained in electronic health records or administrative claims, can close knowledge gaps about outcomes in special populations to aid in dose optimization. In addition, resources for genome sequence data linked to health outcome data have grown exponentially, providing new opportunities to characterize variability in therapeutic benefits and safety.[7,8] These efforts will be further augmented by novel data sources like patient-reported outcomes captured through smartphones and physiologic data captured by wearables, or novel ways of analyzing existing data, as in the emerging fields of radiomics and radiogenomics. Enhanced data analytics (such as machine learning and artificial intelligence) could inform how to manage an individual patient (e.g., digital twin approaches) and be the basis for clinical decision support tools that aid prescribers in treatment and dose selection at the point of care. The FDA has taken steps to advance a new framework to promote development of digital tools that can help implementation of precision medicine.[9]

SUMMARY

The promise of precision medicine has been realized in certain therapeutic contexts through reduced times to market because of smaller trials with larger effect sizes and a higher probability of transitioning from phase I to market.[10] Medicine is inching closer to individualized decision making. Efforts to further enhance patient care continue to focus on improving precision in predicting outcomes, reducing the invasiveness and turnaround time of the diagnostic workup, demonstrating therapeutic benefits, and integrating complex data at the point of care. The regulatory authorities will continue to focus on ensuring the quality, safety, and efficacy of medical products while balancing the benefits and risks of innovations.

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CONFLICT OF INTEREST

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DISCLAIMER

This article reflects the views of the authors and should not be construed to represent the US Food and Drug Administration's policies.

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