Title
Methods for Moving the Evaluation of Precision Medicine Into Practice and Policy

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Introduction to Themed Sections: Methods for Moving the Evaluation of Precision Medicine into Practice and Policy

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Introduction

Themed sections in *Value in Health* provide readers an opportunity to learn more about a contemporary issue in healthcare, research, or policy from several perspectives. This special themed section specifically focuses on methods for moving the evaluation of precision medicine into practice and policy. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle. This approach allows clinicians and researchers to predict more accurately which treatments and prevention strategies for a particular disease will work in which groups of people.

In this themed section, we focus specifically on next-generation sequencing (NGS) technologies, which are the fastest-growing type of precision medicine technology.[1] NGS includes panels that test multiple genes for a single indication, whole exome sequencing tests that evaluate the entire exome (coding regions of the genome), and whole genome sequencing tests that evaluate the entire genome.

This work leverages and continues our previous collection of articles on the topic published in *Value in Health*[2,3] and *Health Affairs*.[4] The previous work identified evaluation challenges (particularly focusing on economic evaluation), potential solutions, and the impact of the changing context within which NGS tests are evaluated and covered by payers. In this new set of articles, we move beyond the identification of challenges to address how these challenges can be overcome so that we can move evaluation into practice and policy. This work was developed in conjunction with a Global Economics and Evaluation of Genomics Clinical Sequencing Working Group comprised of experts on economics and NGS.[5]

The first article in this current collection, by Faulkner et al,[6] provides an overview of key issues involving the methods for moving the evaluation of precision medicine into practice and policy. The article, a report from ISPOR's Personalized Precision Medicine Special Interest Group, focuses specifically on what should be included in a value-assessment framework for precision medicine. This article describes the evolving paradigm of precision medicine using examples of current and evolving applications and key stakeholders' perspectives on the value of precision medicine in their respective domains, and defines the core factors that should be considered in a value-assessment framework for precision medicine.

A value-assessment framework provides a core structure for identifying and addressing methods for moving precision medicine into practice and policy. Thus the article by Faulkner et al[6] is relevant to all of the themed articles and provides a useful structure by which to consider all of the articles. Below are several assertions and recommendations by Faulkner et al[6] that are addressed by the other articles included in this theme.

First, the need for clarification on how to apply study designs, such as nonrandomized approaches and real-world evidence, is a topic addressed by Deverka et al,[7] whose article first describes the current landscape of how (and whether) payers use real-world evidence as part of their coverage decisions and then provides potential solutions for overcoming barriers. This article emerged from the observation that, despite an emphasis by researchers and other experts on the potential usefulness of real-world evidence for informing coverage decision making, payers have been relatively slower to adopt the use of real-world evidence in genetic test evaluations. Based on a scoping review, the authors identified evidence gaps for NGS and synthesized findings as solutions for improving the relevance and utility of real-world evidence for payer decision making. Potential solutions include the development of data and evidence review standards, payer engagement in a real-world study design, the use of incentives and partnerships to lower the barriers to real-world evidence generation, the education of payers and providers concerning use of real-world evidence and NGS, and frameworks for conducting outcomes-based contracting for NGS.

Second, linking stakeholder perspectives to value assessments is necessary, although we must recognize that each stakeholder will have different definitions of value and evidence requirements. This topic is addressed by Trosman et al,[8] whose article applies temporal analyses to better understand payer coverage policies. The article continues the payer perspective seen in the Deverka et al article[7] by examining the temporal trajectory of insurance coverage for next-generation tumor sequencing by private US payers, describing the characteristics of coverage adopters and

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non-adopters, and exploring adoption trends relative to the Centers for Medicare and Medicaid Services (CMS)'s National Coverage Determination (NCD) for NGS. Most research on insurance coverage for precision medicine in the United States has been cross-sectional, painting a coverage picture at a point in time. Temporal coverage assessment has been underexplored, but it reveals unique insights, including how long it takes a test to gain coverage, which payers adopt positive coverage earlier than others, and what events preceding coverage decisions may have had an impact. Using temporal versus cross-sectional analyses revealed important trends, such as the possible contribution of the CMS NCD to a faster pace of coverage adoption, the interdependence in coverage timing among Blue Cross Blue Shield Association plans, the impact of using a third-party policy on coverage timing, and the importance of small payers in early adoption. This study is a step toward systematic temporal research of coverage for precision medicine, which will inform economic and affordability assessments.

Third, the need for tighter alignment of evidence and reimbursement of testing and subsequent treatment/management is a topic addressed by Mackay et al.[9] This article tests a novel strategy for quantifying downstream healthcare utilization after genomic testing to more comprehensively and efficiently identify related services. The ubiquitous challenges of understanding how interventions influence follow-up medical care are magnified during genomic testing because few patients have received it to date and because the scope of information it provides is complex and often unexpected. The authors developed a "risk-based" approach with a trial of newborn genomic sequencing (BabySeq Project) where they defined primary conditions based on existing diagnoses and family histories of disease and defined secondary conditions based on unexpected findings. They then created patient-specific lists of services associated with managing primary and secondary conditions. Services were quantified based on medical record reviews, surveys, and telephone check-ins with parents. By focusing on services that genomic testing would most likely influence in the short-term, they reduced the number of services in the analyses by over 90% compared with analyses of all observed services. At the same time, our risk-based approach identified the same services that were ordered in response to unexpected genomic findings as an expert review and by confirming whether recommended services occurred. Data also showed that quantifying healthcare utilization with surveys and telephone check-ins alone would have missed the majority of attributable services. The strategy developed provides an improved approach for assessing the short-term impact of genomic testing and other interventions on healthcare utilization while conforming as much as possible to existing best-practice recommendations.

Lastly, the need for value assessment to evolve to accommodate the complexities of precision medicine is a topic addressed by Marshall et al.[10] This article provides a rationale for greater use of simulation models for economic evaluation in precision medicine because they enable patient-level analyses and capture the dynamics of interventions in complex systems specific to the context of healthcare service delivery. This article emerged from the observation that methods are needed that can handle the complexity of cascading decisions and the patient-specific heterogeneity that is reflected in the myriad of testing and treatment pathways for NGS. Traditional approaches (eg, Markov models) have limitations and other modeling techniques, such as simulation modeling (eg, discrete choice simulation), may be required to overcome these challenges. This article provides an overview of common simulation modeling methods and describes how these approaches can potentially address the specific challenges of economic evaluation in precision medicine. It presents several examples to illustrate how simulation modeling and optimization methods have been applied to capture individual care pathways in economic evaluations.

In conclusion, much progress has been made in developing and applying methods to evaluate precision medicine. Nevertheless, as noted in the article by Faulkner et al,[6] new tests such as minimally invasive liquid biopsies and emerging approaches such as artificial intelligence and machine learning platforms will continue to require the development and adaptation of methods used to assess the value of precision medicine. The collective efforts of a society like ISPOR can bring together the wide range of disciplines and stakeholders that will be needed to continue to evolve the methods and approaches used to assess precision medicine.

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