Payer View: How Do We Assess Quality in the Age of Precision Medicine?

Lee N. Newcomer, MD

United Healthcare Oncology and Genetics, Minnetonka, MN

This spring I attended a hastily rescheduled wedding. The groom's father had metastatic colon cancer and he was not expected to live long enough to participate in the wedding on the originally scheduled date. The father wore white gloves because his hand desquamation was so intense that he was unable to touch others; he hugged his son with a stiff and awkward grip using only his forearms because his neuropathy was so painful. My friend had taken a targeted agent for an unusual genetic mutation. The drug was untested for the colon cancer that was invading his lung and liver. As a patient, he was well aware of the risks of his off-evidence treatment and he accepted them without complaint. His suffering, however, is being wasted. My friend was not in a clinical trial. His severe toxicities and his failure to respond will not inform the other patients who may someday confront his choices; his attending physician is the only person who can learn from the experience.

The experience of all patients needs to be used for learning. Personalized medicine—tailoring specific therapies to individual patients based on their genetic mutations—has immense potential, and its potential is increased exponentially if we learn quickly from the successes and failures of the early experiments. During this time of learning, medicine is facing impending resource constraints: if current trends continue, US households will be paying more than their average annual income for health care by about 2029.[1] The vignette shows how easy it is to squander the precious time, resources, and knowledge required to understand and use personalized medicine effectively. This editorial proposes the key strategies we need to assess and improve the quality of that care.

Precision medicine begins with genetic testing. Sequencing costs have been dropping precipitously, and conventional wisdom supports genome sequencing for about $1,000 soon. These rapid advances in technology have exceeded our knowledge about using them. Three elements are essential for the proper use of gene sequencing: (1) analytic validity standards, (2) clinical validity, and (3) clinical utility studies. Analytic validity ensures that each individual test is consistently producing the results it is intended to produce. There are no consensus standards for analytic validity in gene sequencing. Oncologists experienced a similar problem with the early testing for the human epidermal growth factor receptor 2 (*HER2*) gene; the analytic validity was insufficient, and inappropriate therapies were prescribed on the basis of an incorrect laboratory test.[2] Clinical validity is an equally necessary validation. Is the mutation being identified truly significant for the disease? It is tempting to label associations as causative or diagnostic rather than as hypothesis generating. The most important factor is the clinical utility—Does the test contribute to clinical decision making? The answer for the *HER2* gene in breast cancer

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is affirmative, but should a patient with sarcoma and *HER2* overexpression also be treated with trastuzumab? The answer requires a clinical trial. Sequencing may also add new clinical information unrelated to the treated disease that would affect clinical decisions.

Generating the data for these questions requires clinical studies that are expensive. It makes sense that test costs may rise to cover those expenses. Those costs, however, should be offset by the clinical value that a valid, accurate test can contribute to the therapeutic decision.

Decisions about the clinical decisions that arise from these tests demand the same level of evidence rather than inference. Even though there are dozens of personalized medicine programs active in the United States today, there are few studies that demonstrate the value of genetic-directed therapy as a general approach for cancer management. The French SHIVA (Molecularly Targeted Therapy Based on Tumor Molecular Profiling Versus Conventional Therapy for Advanced Cancer) study randomly assigned patients with metastatic disease to either standard of care selected by the attending physician or genetic-directed therapy selection.[3] The difference in survival between the groups was insignificant. Alternatively, Intermountain Healthcare reported a matched cohort trial with 36 patients in each arm that compared genetic-directed therapies to standard of care. They demonstrated a 10-week survival advantage, and treatment costs were similar in both groups.[4] The generalized strategy of genetic-directed therapy has yet to be proven.

There are good examples of trials to answer this question. The TAPUR (Testing the Use of Food and Drug Administration [FDA] Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer) trial, sponsored by ASCO, tested genetic mutation and targeted drug combinations in many tumors. That trial allowed any genetic test to identify the mutation; the issue regarding lack of standards described above may confound the trial, but it is commendable for providing access to all patients nationwide. Memorial Sloan Kettering Cancer Center has constructed a systemic program that screens for mutations, enrolls their patients in genetic mutation testing, and determines matching targeted drugs for all types of cancers. This program discovered a previously unknown signal for vemurafenib in the rare Erdheim-Chester disease or Langerhans cell histiocytosis; the response rate was 43% (95% CI, 18% to 71%), the median treatment duration was 5.9 months (range, 0.6 to 18.6 months), and no patients had disease progression during therapy—their systematic approach to all patients.[5] Without a basket mechanism to capture all genetic signals, this discovery would have not occurred.

The examples cited are good role models. In an ideal world, trials would have low enrollment barriers, encompass multiple clinics and pharmaceutical manufacturers, and have reliable data collection. My wish for a Moonshot Initiative goal is quite simple: enroll 100,000 patients in these types of trials during the next 3 years. Achieving that goal would validate the personalized medicine strategy and perhaps detect hundreds of new signals for future drug development.

Quality is simply a measurement of effectiveness. Creating standards for genetic testing, building systems to collect the data, and then conducting vast clinical trials is hard work. This is not a new challenge that is unique to the field of personalized medicine, but the scale of the work is much larger. Success for this project requires collaboration, and the early examples show that it is possible. One would hope that the vignette beginning this article will become the exception and that each life can be meaningful for others. JOP

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Corresponding author: Lee N. Newcomer, MD, United Healthcare Oncology and Genetics, Mail Route MN017-W700, 9700 Health Care Lane, Minnetonka, MN 55343; e-mail: lee_newcomer@uhc.com.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Lee N. Newcomer
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