ress, addressing institutional barriers to change, and integrating multiple teams' work. This group ensures that teams remain focused on organizational priorities and have the necessary resources, and it resolves conflicts that arise when multiple groups make demands on shared resources. The teams thus become part of a broader structure for clinical governance and form the core of performance-management and improvement efforts. At Intermountain, the permanent teams both redesign and manage care systems.

Finally, because any model of team-based redesign devolves authority and accountability away from top executives, transformers have invested in creating a widely understood set of unifying values and norms. Whether expressed in value statements, compacts, or credos, these standards help align staff behavior both with the organization's goals and among the professions working together to meet those goals, and they guide behavior when there's no clear decision rule.

An audio interview with Dr. Bohmer is available at NEJM.org

Many organizations find this approach challenging, and not only because it's slow or requires investment. It also risks requiring job cuts, or at least job changes. Most challenging, however, is the fundamental change it represents in an enterprise's governance. Clinician-led teams take control of patient-facing organizational subsystems and reform clinical protocols and operations, review performance data and make modifications, and may even have local financial control and responsibility. In effect, instead of taking their work context as a given, staff actively create the local system needed to provide the best possible care. This shift may be a bridge too far for some organizations, especially those facing reduced revenue or an urgent need for a turnaround.

Unfortunately, in the longer term, the prolonged hard work of repetitive, incremental, and often small-scale rebuilding of local operating systems probably cannot be avoided. Individual behavior change motivated by payment reform may be insufficient to generate the quality and efficiency gains needed in coming years. In their first year, the Pioneer Accountable Care Organizations have achieved only modest results.[4] However, organizations seeking transformation can ease the process by building the support system described above. The short-term investments that are required can be surprisingly small, because most organizations already have many of the requisite human assets. The most substantial hurdle, it seems, is the change in mindset.

Disclosure forms provided by the author are available at NEJM.org.

From the Nuffield Trust, London.

1. Imison C, Sonola L, Honeyman M, Ross S. The reconfiguration of clinical services. London: King's Fund, 2014.
2. Bohmer RMJ. Designing care: aligning the nature and management of health care. Boston: Harvard Business Press, June 2009.
3. James BC, Lazar JS. Health system use of clinical programs to build quality infrastructure. In: Nelson EC, Batalden PB, Lazar JS, eds. Practice-based learning and improvement: a clinical improvement action guide. Oakbrook Terrace, IL: Joint Commission Resources, 2007:95-108.
4. Schwartz AL, Chernew ME, Landon BE, McWilliams JM. Changes in low-value services in year 1 of the Medicare Pioneer Accountable Care Organization Program. JAMA Intern Med 2015;175:1815-25.

DOI: 10.1056/NEJMp1606458
Copyright © 2016 Massachusetts Medical Society.

Uncertainty in the Era of Precision Medicine

David J. Hunter, M.B., B.S., Sc.D.

A National Research Council report on "precision medicine" explains that the term "refers to the tailoring of medical treatment to the individual characteristics of each patient." The report goes on to say, "It should be emphasized that in 'precision medicine' the word 'precision' is being used in a colloquial sense, to mean both 'accurate' and 'precise.'"[1] In the colloquial sense, "precision" also implies a high degree of certainty of an outcome, as in "precision-guided missile" or "at what precise time will you arrive?" So will precision medicine usher in an age of diagnostic and prognostic certainty?

In fact, the opposite will probably result. The new tools for tailoring treatment will demand a greater tolerance of uncertainty and greater facility for calculating and interpreting probabilities than we have been used to as physicians and patients.

Oncology has been called "the clear choice for enhancing the near-term impact of precision medicine."[2] New tools extract information from cancer genomes that include both the mutations

The New England Journal of Medicine
Downloaded from nejm.org at SBBL on September 5, 2016. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.

that occur somatically (cancer genome sequencing) and the functional changes that result from both these mutations and epigenetic events (gene-expression alterations in tumors). For instance, by examining gene-expression changes in breast cancers, products such as Oncotype DX, MammaPrint, PAM50, and others contribute information about prognosis that is independent of traditional clinical predictors such as tumor size, grade, and nodal status. What is the process by which these new tools are incorporated into advice for patients about their therapeutic options?

In the case of the breast-cancer gene-expression products, key evidence on prognosis was obtained through existing studies in which tumor tissues had been preserved and could be used to develop the products and then test their prognostic utility.[3,4] Notably, these analyses provided evidence on the risk of tumor recurrence but no direct evidence regarding whether specific therapies were more or less effective within risk categories. However, women with stage I or II estrogen-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-negative breast cancer who were predicted by the gene-expression test to have a low risk of recurrence were advised that they might not need adjuvant chemotherapy. Some, but not all, subsequent retrospective nested case–control studies of randomized, clinical trials suggested that the benefit of adjuvant chemotherapy was absent or negligible in women categorized as having low recurrence risk.[5] Commendably, scientists involved in developing and marketing these tests have gone further to test, in prospective randomized trials, the effects of adjuvant chemotherapy stratified by predicted risk. The results of one such study are reported by Cardoso et al. in this issue of the *Journal* (pages 717–729).

In this study, women were classified according to clinical risk (C-high, C-low) and genomic risk (G-high, G-low). Among women classified as C-high but G-low who were not randomly assigned to receive adjuvant chemotherapy, 5-year survival without distant metastasis was 94.7%, with a 95% confidence interval of 92.5 to 96.2%; the lower bound of the confidence interval excluded a preset value of 92%, which the investigators interpret as evidence that women in this category "could forgo chemotherapy." However, among women in this group who were randomly assigned to receive adjuvant chemotherapy, 5-year survival without distant metastasis was 1.5 percentage points higher (a nonsignificant 22% reduction in distant metastases). Further complicating interpretation, the rate of disease-free survival with chemotherapy was a statistically significant 3 percentage points higher in the per-protocol population. In contrast to previous studies, the benefit of chemotherapy was equivocal in the group with low clinical risk and high genomic risk.

Thus, 9 years after the study began in 2007, with 6693 women enrolled and followed, of whom 2187 were randomly assigned to receive or not receive adjuvant chemotherapy, women at high clinical risk but low genomic risk are presented with a trade-off between the risk of recurrence and the toxic effects of treatment. As Hudis and Dickler point out in their editorial (pages 792–793), women of different ages may interpret this trade-off very differently. Contrary to the findings of some previous studies, women at low clinical but high genomic risk might not have much to gain from chemotherapy, although the confidence interval in this group includes both substantial benefit and harm.

What does such evidence tell us about precision medicine? The first thing to celebrate is that such studies are being performed. Arriving at the era of precision medicine does not mean that we can be so certain of molecular mechanisms that therapeutic decisions should not be subject to adequately powered trials. However, as in most medical practice, when the results are in, we are often likely to face far-from-certain answers.

It is also noteworthy that to make results interpretable, both statistically and clinically, a continuous variable (the genomic score derived from 70 separate gene-expression analyses) is dichotomized into "high" and "low" — in other words, precision is sacrificed for interpretability. A considerable tension exists between the splitting inherent in the idea of "tailoring . . . to the individual characteristics of each patient" and the lumping of tens, hundreds, or thousands of patients together in order to reach reproducible conclusions.

Finally, different gene-expression products may result in different risk categorizations, and they all should be improved as technology changes and the data mature, so that categorizations and advice may change over time. The derivation of the 70-gene signature was originally published 14 years ago.

The New England Journal of Medicine
Downloaded from nejm.org at SBBL on September 5, 2016. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.

In contrast to the talk of paradigm shifts in the age of precision medicine, there is something familiar and reassuring about the process of integrating these new tests into clinical algorithms. In this example, the new tests may be "-omic" and based on relatively new technologies, but they have been introduced through an established process of determining analytic validity (i.e., does the test reliably measure what it purports to measure?) and then clinical validity. Initial studies were interpreted by panels of experts, and the use of the tests was introduced into guidelines. Large-scale randomized trials such as this one are being performed to assess and refine clinical utility and thus refine the guidelines. The new tests are being compared with and tested in the context of previous decision tools, such as clinical prognostic indexes and immunohistochemistry results. The new tests add to, but do not replace, the information from these prior tools. This process is the usual one followed by clinical science, rather than a radical departure from proven models.

In the future, we are likely to face a potentially bewildering array of probabilities — estimates of disease risk based on inherited germline sequencing and, once a disease is diagnosed, of prognosis and therapeutic options guided by "-omic" and other analyses. Assessing and acting on these probabilities will require approaches to data presentation, risk quantification, and communication of uncertainty for which we are largely ill equipped and that we already struggle with. In most situations, the best advice will be far from obvious and will often rely on a preliminary estimate as the data mature. In parallel to developing the tools for "-omic" analyses, we urgently need to develop methods to help our patients absorb large amounts of complex information that will help them make choices among increasingly numerous options with increasingly numerous tradeoffs. These methods should also help our colleagues answer the age-old question, "What would you do, doctor?"

Disclosure forms provided by the author are available at NEJM.org.

From the Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston.

1. Committee on a Framework for Developing a New Taxonomy of Disease. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: National Academies Press, 2011.
2. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015; 372:793-5.
3. van de Vijver MJ, He YD, van 't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009.
4. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
5. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006; 24:3726-34.

DOI: 10.1056/NEJMp1608282
Copyright © 2016 Massachusetts Medical Society.

The Abyss

James D. Weisfeld-Adams, M.B., Ch.B.

I sat at the kitchen table at my in-laws' home in Florida, collating a list of everything I owned. My precise, microscopic handwriting suddenly resembled the scrawl of a 6-year-old. It was 2006, and we were preparing to ship all our belongings from England to New York, where I'd been accepted into a pediatrics residency program at a major teaching hospital. This move represented the culmination of years of preparation for living indefinitely overseas. We had arrived in Florida only 2 weeks earlier; for my wife, it was a homecoming after 4 years of living as a foreigner in Britain.

Now, suddenly, I couldn't write. I felt like an amputee retraining myself to write with my nondominant hand. My right hand had a peculiar tremor at rest, a vague heaviness waxed and waned in my right arm and leg, and my pupils were unmistakably asymmetric. Nagging uneasiness turned to panic. Being 27 years old and healthy, I hadn't arranged for additional health insurance to cover me before my new appointment, and without the convenience of affordable diagnostic testing options, I indulged in some free-form speculative self-diagnosis. My basic neuroanatomical knowledge suggested that the distribution — involvement of the arm and the leg on the same side — meant that there was a good chance that the problem

The New England Journal of Medicine
Downloaded from nejm.org at SBBL on September 5, 2016. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.