COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

Appropriateness: A Key to Enabling the Use of Genomics in Clinical Practice?

President Obama's Precision Medicine Initiative is poised to generate genome sequence data from 1 million Americans.[1] However, such data are not yet routinely used in clinical care. It is time to formulate strategies for clinical decision making and policy around genomic information. We argue that *appropriateness* can help bridge the evidence gaps that have opened between patients' genomes and their healthcare. The research methodology of appropriateness has been helpful for other emerging technologies, such as percutaneous coronary interventions,[2] and can guide clinical decision making as new evidence accumulates.

WHETHER TO TEST

There are still relatively few situations in which genetic or genomic testing is performed clinically. Many proposed applications—such as genome sequencing for childhood developmental delay or population *BRCA* screening for breast cancer risk—remain controversial because of their uncertain balance of risks and benefits. A key concept in genetic or genomic testing is *clinical utility,* but this has come to mean different things to different stakeholders. In one common model, clinical utility refers to the evidence that a test or intervention improves net clinical outcomes, generally defined as benefits weighed against harms.[3] In this model, clinical utility also includes actionability—evidence that providers would change clinical management on the basis of test results. Health insurers weigh clinical utility heavily in their coverage decisions about molecular testing, such as genome sequencing,[4,5] but many proposed applications of new genetic and genomic tests currently lack evidence that they improve patient outcomes. Clinical utility has thus come to mean *reimbursability* to clinicians and patients who are frustrated that the value they place on genomic information, including molecular diagnoses, may not align with payers' concept of clinical utility. In response, the American College of Medical Genetics and Genomics recently expanded its definition of the clinical utility of genetic and genomic testing to encompass clinical utility for individual patients, families, and society.[6] This redefinition reflects the value clinicians and patients place on testing, even when doing so may not change a patient's treatment or outcomes, if it helps to end a diagnostic odyssey, facilitate family planning, augment scientific knowledge, or achieve other benefits poorly captured by a stricter definition of clinical utility.

AFTER THE TEST

The clinical utility of genome sequencing is further complicated by the incidental detection of variants that have uncertain clinical significance. Sequencing can identify genetic variants that are associated with dozens of well studied conditions and are generally recognized as clinically meaningful.[7] However, analogous to advanced imaging, sequencing also uncovers thousands of other genetic variants, the majority of which have not been specifically studied and for which an evidence base may not exist. As individuals receive genomic results through clinical care or participation in research such as the Precision Medicine Initiative, clinicians will increasingly find themselves managing patients' genomic results without guidelines for how to do so. The potential risks of introducing this uncertain information to the clinical setting include a costly cascade of follow-up medical interventions, which may themselves cause patient harm. Although these risks remain largely theoretical, absent large follow-up studies of sequenced individuals, they might eliminate the clinical utility of sequencing by outweighing any potential health benefits.

REFRAMING CLINICAL UTILITY

Appropriateness may help mediate the disagreements about the clinical utility of genome sequencing and the management of uncertain results. This concept describes clinical management for which "the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, exclusive of

Funding: This work was supported by National Institutes of Health grant U01-HG006500. JLV is supported by Career Development Award IK2 CX001262 from the United States Department of Veterans Affairs Clinical Sciences Research and Development Service.

Conflict of Interest: None.

Authorship: All authors had access to the data and a role in writing the manuscript.

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0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2016.02.010

cost."[8] Appropriateness brings with it validated research methodologies to inform the current debates. It allows synthesis of published scientific evidence and expert review to identify management that is appropriate or inappropriate for specific clinical situations. This is particularly helpful for clinical contexts to which no empiric studies specifically apply. Using a metric called the disagreement index, this method also quantitatively identifies management of which experts disagree about its appropriateness.

Appropriateness could especially help genomic medicine. There is limited, but growing, evidence about the clinical impact of using genetic and genomic technologies in most patient populations. Some applications rest on a solid evidence base, including Lynch syndrome screening and HLA-B*57:01 testing before abacavir use. Others, however, remain controversial, such as pharmacogenetic testing for clopidogrel dosing and universal *BRCA* screening for breast cancer risk. For many of the proposed applications of genomic medicine, there is currently insufficient evidence for clinical utility as strictly defined by guidelines or policymakers. Moreover, because each patient's genotype is unique, there will never be empirical evidence to address every possible clinical question arising in genomic medicine. However, because all patients are unique for reasons other than genotype, this challenge is not particular to genomic medicine. Even for medical interventions supported by decades of experience and research, such as percutaneous coronary interventions, appropriateness methodologies have been used to aggregate both scientific evidence and expert opinion and extrapolate knowledge to clinical scenarios for which no specific evidence base exists. Clinical experts convene to review available literature and then apply clinical judgment in determining whether a certain intervention is appropriate for a certain context. This can be a highly effective approach for managing decision making in the face of uncertainty around the evidence in specific scenarios.

TOWARD APPROPRIATE GENOMIC MEDICINE

This methodology could also help advance the policy debate in genomics, a field with active research, a rapidly evolving evidence base, and a body of cutting-edge scientists with deep clinical expertise. A quantitative examination of appropriateness in genomic medicine could have at least 3 important outcomes. First, it will identify clinical contexts for which experts broadly agree that a specific genetic test or management strategy is appropriate. In the absence of high-grade randomized trial evidence, some policymakers state they would consider expert opinion in coverage decisions.[4] Agreement about a test's appropriateness among a diverse panel drawn from leading professional societies and clinical centers should be particularly compelling. It may also signal suitable targets for clinical decision support to be delivered within electronic health records to help providers. Second, this methodology will identify areas of genomic medicine deemed inappropriate. This is important because genomic medicine, like all other specialties, is practiced in an environment of constrained healthcare resources. The American College of Medical Genetics and Genomics recognized this in its recent participation in the American Board of Internal Medicine's Choosing Wisely campaign, identifying 5 wasteful genetic testing contexts.[9] Third, this method can identify specific genomic medicine contexts for which experts significantly disagree about appropriateness, which might represent high-priority areas for research.

It is important to note that neither clinical utility nor appropriateness implies *cost-effectiveness*. Indeed, expert panel members are asked to consider only the benefits and harms to patients, not costs, when assessing an intervention's appropriateness. However, a determination of an intervention's cost-effectiveness relies first on an assessment of its net benefit, which appropriateness seeks to define though scientific evidence and input from the experts who take care of patients.

If genome sequencing is to be increasingly used in clinical care, these issues must be addressed. The ongoing discussions about clinical utility in genomic medicine reflect a tension between optimizing patient care and getting value from limited healthcare resources. The concept of appropriateness can help identify a balance between these 2 worthy goals.

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References

1. Precision Medicine Initiative Working Group. The Precision Medicine Initiative Cohort Program — building a research foundation for 21st century medicine. Available at: www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf. Accessed February 4, 2016.
2. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection, and appropriateness of percutaneous coronary intervention. *JAMA*. 2015;314(19):2045-2053.
3. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med*. 2009;11(1):3-14.
4. Palmetto GBA. Molecular Diagnostic Program (MolDX): coverage, coding, and pricing standards and requirements. Version 3.0:1-11. Available at: http://palmettogba.com/Palmetto/moldx.Nsf/files/MolDX_Manual.pdf/$File/MolDX_Manual.pdf. Accessed February 4, 2016.
5. Deverka PA, Kaufman D, McGuire AL. Overcoming the reimbursement barriers for clinical sequencing. *JAMA*. 2014;312(18):1857-1858.

6. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2015;17(6):505-507.
7. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574.
8. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corporation; 2001.
9. American College of Medical Genetics and Genomics. *Choosing Wisely: Five Things Patients and Providers Should Question*. Philadelphia: American College of Medical Genetics and Genomics; 2015.