Healthcare Utilization, Economic an Value: Reaction

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Key Payer Questions

- How to evaluate the benefits and risks of tests that analyze many different genes and variants at one time?
  - What are valid study designs for assessing Clinical Utility?
  - How can they be assured that AV and CV are established? Across labs?
- When evaluating a test for a particular indication, why are more genes better?
  - Why WES or WGS rather than a targeted panel?
  - What is the value of adding additional genes?
- How can they support appropriate clinical integration?
  - With providers?
  - With patients?

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SPECIAL REPORT

Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk

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Advances in sequencing technology have made multigene testing, or "panel testing," a practical option when looking for genetic variants that may be associated with a risk of breast cancer. In June 2013, the U.S. Supreme Court[1] invalidated specific claims made by Myriad Genetics with respect to the patenting of the genomic DNA sequence of *BRCA1* and *BRCA2*. Other companies immediately began to offer panel tests for breast cancer genes that included *BRCA1* and *BRCA2*. The subsequent flourishing of gene-panel testing services (Table 1, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) has generated much interest both within the clinical genetics community and in the popular press.[2] These panels cover a total of more than 100 genes, and breast cancer is specifically mentioned as an indication for 21 of these genes. However, the fact that the technology is available does not necessarily mean that such tests are appropriate or desirable.

According to the framework proposed by the ACCE (established by the Centers for Disease Control and Prevention), genetic tests should be evaluated on the basis of the four criteria from which the name ACCE is derived: analytical validity, clinical validity, clinical utility, and ethical, legal, and social issues.[3] Analytical validity refers to the degree of accuracy with which a test detects the presence or absence of a mutation. Here, however, we focus on the key question of clinical validity: Are the variants the test is intended to identify associated with disease risk, and are these risks well quantified? The validity of the risk estimates is a key determinant of the clinical utility of panel testing, which in turn should inform decisions regarding the adoption of the testing in clinical practice. We do not consider in detail who should undergo testing, what level of risk is associated with any given variant that might be considered clinically useful, or how that risk might be managed. However, broadly similar guidelines for managing the care of women with a family history of breast cancer exist in several countries (Table 2). These guidelines are based on the stratification of patients according to levels of risk and provide guidance on the identification of women to whom screening (by means of mammography or magnetic resonance imaging), risk-reducing medication, and risk-reducing surgery should be offered. These recommendations could be modified to reflect the identification of risk variants through the use of gene-panel testing. Whatever the recommendations for the management of care, the underpinnings of the guidelines should be based on reliable estimates of the risk of cancer.

Before these guidelines are developed, the appropriateness of the tests themselves needs to be considered. The determination of analytical validity for laboratory-developed diagnostic tests falls under the remit of the Clinical Laboratory Improvement Amendments (CLIA) of 1988, but neither clinical validity nor clinical utility is part of the assessment process. Therefore, whereas new drugs without clinical utility will not be approved by the Food and Drug Administration (FDA), gene-panel tests can be adopted without

Coverage Challenges for Clinical Sequencing

Recent Past

- Personalized medicine tests (laboratory analysis of DNA, RNA, protein by any method) have had difficulty gaining coverage
  - Lack of evidence of clinical utility[1]
- With notable exceptions (e.g., predictive tests to guide drug therapy) there has been a fundamental failure in evidence generation to demonstrate clinical benefit. Possible reasons:
  - There is no benefit
  - Lack of incentives for researchers and test developers to conduct the necessary studies
  - The definition of benefit is too high of a bar and needs to change

Present

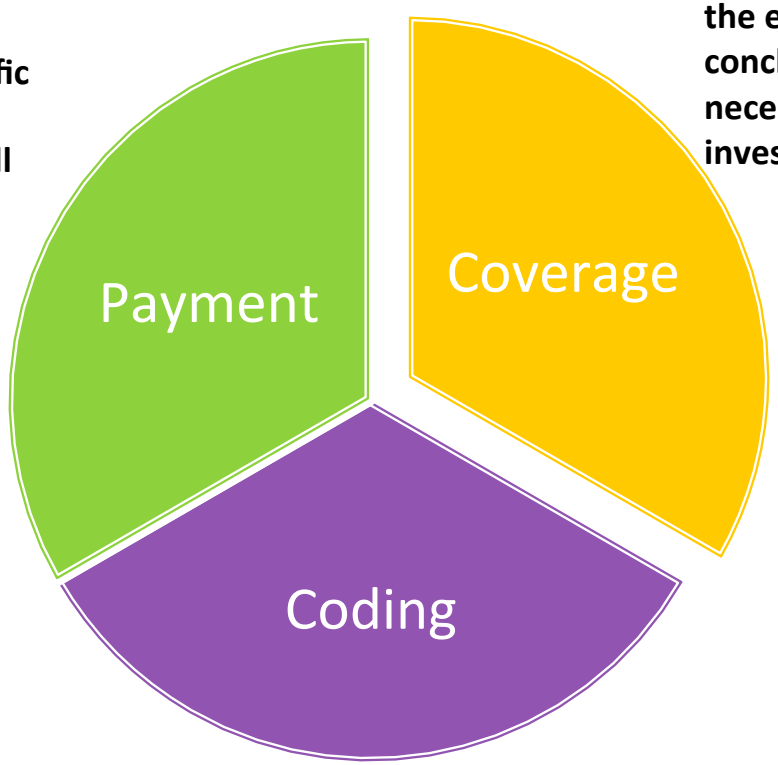
- Delphi study of barriers to clinical adoption, top coverage and reimbursement challenges[2]
  - Different payers have different evidentiary standards for assessing clinical utility, leading to inconsistent coverage & reimbursement policies
  - Some payers refuse to cover clinical sequencing because specific patient management decision to be informed by testing is unclear when the test is ordered
  - Inability of coverage and reimbursement frameworks to keep pace with the rate of sequencing-based genomic discovery
- Policy solutions are focused on multi-stakeholder groups developing standards
- Clinical sequencing-focused coverage policy registry funded by NHGRI[3] to study how payers make decisions
  - Are payers adapting their approach to gene panel coverage decision-making?

1. Hresko A & Haga SB. Insurance coverage policies for personalized medicine. J Pers Med 2012;2:201-16. 2. Supported by a grant (R01HG006460) from the National Human Genome Research Institute. 3. Payer Policy Registry (R01HG007063-S1)

The reimbursement framework

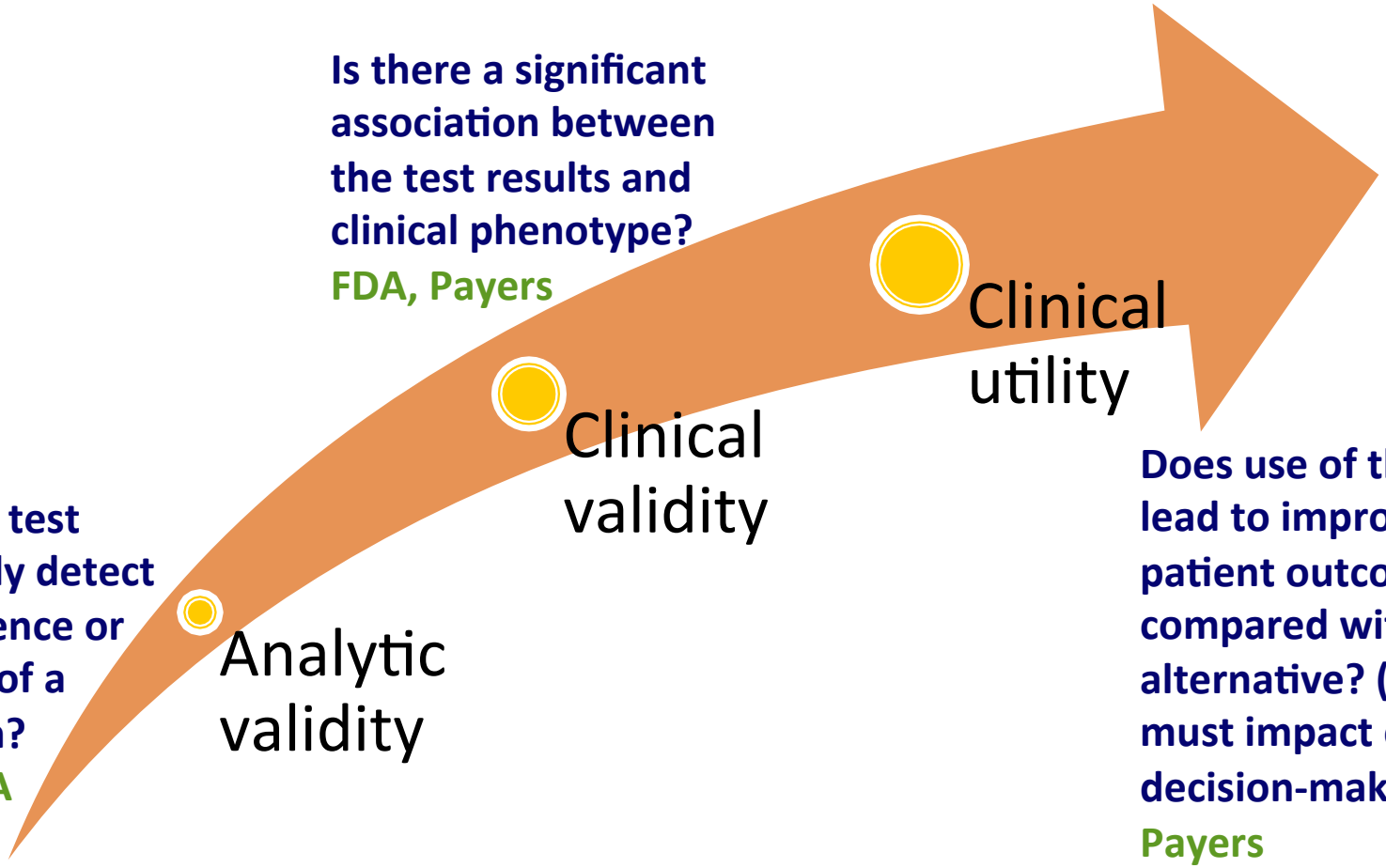
What is the specific payment amount that providers will receive?

Is the technology part of the defined benefit package? What is the evidence to support a conclusion regarding medically necessary vs. experimental/ investigational?



How will providers identify the service on claims forms?

Payer Assessment of New Tests



Clinical coverage criteria

The following criteria* are considered in evaluating a medical technology

- The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes
- The technology must improve net health outcome
- The technology must have final approval from the appropriate governmental regulatory bodies, when required
- The technology must be as beneficial as any established alternatives
- The improvement must be attainable outside investigational settings

Sources of evidence

- Studies from peer-reviewed literature
- Criteria developed by professional /specialty societies
- FDA labeling documentation
- Independent technology assessments
- Test developer sponsored publications
- Guidelines adopted by other health care organizations

*Criteria used by BCBCSA Tec and several national payers; applied to Dx tests of all types

Challenge 1 (what evidence do Payers need?)

Premise is that Clinical sequencing is ***Different***

Test features	Potential coverage issues[1,2]
Single test/multiple results	• Cannot assess efficiency of testing, or future utility as medically necessary • Complexity of bioinformatics requires separate assessment of validity
Varying levels of evidence supporting interpretation of results (some actionable, some suitable for research)	• Doesn't fit medically necessary vs. experimental definition • No precedent to evaluate integrative benefits
Methodological approaches for studies do not fit payers' evidentiary standards	• Lack of experience and skepticism re N-of-1, basket studies, *in silico* modeling, etc. • Recognition of infeasibility of conducting RCTs of CU for every variant, but published examples of alternative study designs are lacking
Limited amount of objective data for personalization of care is a major departure from SOC protocols	• Concerns re adoption and implementation of testing into clinical practice • Lack of education, IT infrastructure, guidelines, etc.

[1]Trosman J, et al. Challenges of coverage policy development for next-generation tumor sequencing panels: Experts and payers weigh in. JNCCN 2015;13:311-18.
[2] Deverka P & Dreyfus J. Clinical integration of next generation sequencing: coverage and reimbursement challenges. J Law Med Ethics 2014;42Suppl 1:22-41.

Response to Challenges: CSER

- Design CU studies for specific clinical applications
- Use a variety of approaches
  - Priority setting with Payer input (Advisory Board)
  - Broad view of CU across indications
    - Screening
    - Diagnosis
    - Treatment
  - Site-specific and consortium-wide comparative studies using common data collection tool
  - Policy models to frame research agenda and guide decision-making

Reaction

- Payer Engagement is critical
  - Research priority setting for NHGRI
    - Payers are currently involved elsewhere in developing
      - Evidence
      - Coverage evidentiary standards
- NHGRI should continue to develop infrastructure, methods, evidence for demonstrating CU, particularly for indications such as PGx, prenatal and disease risk prediction
  - Individual sites could adopt varying approaches to evaluating CU
  - Comparison of analytic approaches to inform the field re interpretation
  - Comparison of differing definitions of CU
- There is an ongoing need for federally funded studies of CU
  - Even if there were consistent payer evidence standards, there would still be major evidence gaps if we relied solely on test developers to conduct studies
- Need for rigorous cost-effectiveness studies
  - There is no cost-effectiveness without effectiveness
- Support translation of study results into practice and policy recommendations
  - Continue work of Cross-Consortium Collaborative Working Groups

Summary

- Important to understand how coverage decisions are made
  - Recognize the ways that clinical sequencing conflicts with
    - Concept of medical necessity
    - Single test/Single result coverage framework
- Design studies to include information that meets payer evidence needs
  - If RCTs are not feasible, what alternative study designs are valid and useful for decision-making?
  - Cost-effectiveness will become more important if clinical sequencing is to achieve it's disruptive potential
    - Community-based care
    - Diverse, hard-to-reach populations
  - Experts should be driving use of test, not the availability of technology
- Recognize that even with consistent evidence requirements for CU, there would still be variation in how payers make coverage decisions, as each insurer interprets evidence in their local context