ECRIgene™
Genetic Test Resource

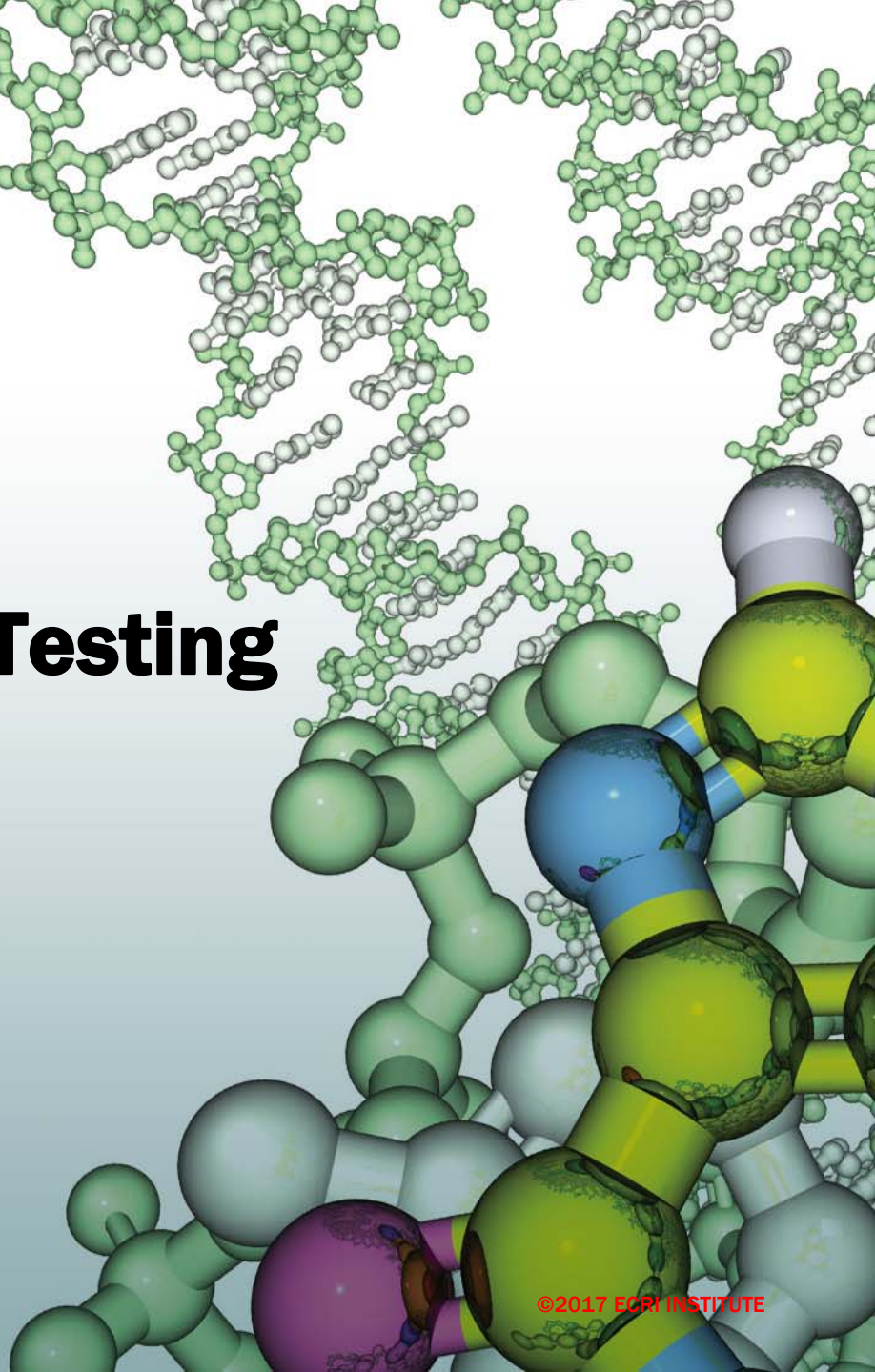
March 28, 2017

Precision Medicine: The Impact of Genetic Testing on Population Health

Population Health Colloquium
Thomas Jefferson University

Vivian H Coates
Vice President

ECRI Institute
The Discipline of Science. The Integrity of Independence.



Learning Objectives

- Summarize the current trends in genetic testing
- Explain how genetic tests are used in various clinical scenarios, particularly in personalized medicine
- Discuss how genetic testing is regulated and reimbursed in the United States
- Explain how genetic tests are assessed in terms of analytic and clinical validity, and clinical utility, including challenges and pitfalls

About ECRI Institute

- Nonprofit health services research organization
- 47 years of laboratory-based medical device evaluations
- 25 years conducting Health Technology assessment/forecasting/comparative-effectiveness research
- Worldwide clients number in the thousands
  - Hospitals and health systems
  - Private third-party payers
  - Government agencies (state and federal)
- For Agency for Healthcare Research and Quality (AHRQ)
  - ECRI Institute Evidence-based Practice Center since 1997
  - National Guideline Clearinghouse; National Quality Measures Clearinghouse
  - Healthcare Horizon Scanning System (2010 – 2015)
  - ECRIgene resource on genetic/genomic testing (2016)

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Integrity

- Neither ECRI nor any of its staff has a financial interest in the sale of any medical technology. ECRI and its staff are not permitted to accept royalties, gifts, finder's fees, grants, or commissions from the medical device or pharmaceutical industries and are not permitted to own stock in or undertake consulting work for such industries.
- Adhering to our conflict-of-interest rules—but also interacting with manufacturers and labs—are part of our culture

Genetic/Genomic Test Definition

- Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS): very broad definition (2008)
- A genetic or genomic test involves an analysis of human chromosomes, DNA, RNA, genes and/or gene products (eg, enzymes and other types of proteins) which is predominantly used to detect heritable or somatic mutations, genotypes or phenotypes related to disease and health.
- Will focus today on tests that detect mutations in tumors: cancer genomic tests

Personalized Medicine

- Customizing treatment for individual patients
  - Not a new concept
- Its effectiveness and safety depend on how well clinicians understand each person's unique characteristics
- The area has been rapidly evolving during the past several decades
  - Mainly due to the advance in genetic science and technologies
  - Genetic testing can provide crucial information to accurately predict risk of developing disease, disease progression and response to treatment

Example: Personalized Medicine Approach to Treating Non Small Cell Lung Cancer (NSCLC)

- The most common type of lung cancer
- Mutations in the EGFR gene are present in about 10 percent of NSCLC tumors
- The therascreen EGFR RGQ PCR Kit was approved by FDA as a companion diagnostic test
- EGFR mutation testing has been used routinely to select candidates for erlotinib or gefitinib
- Multigene panels can also include EGFR

Genetic Tests Present Huge Challenges

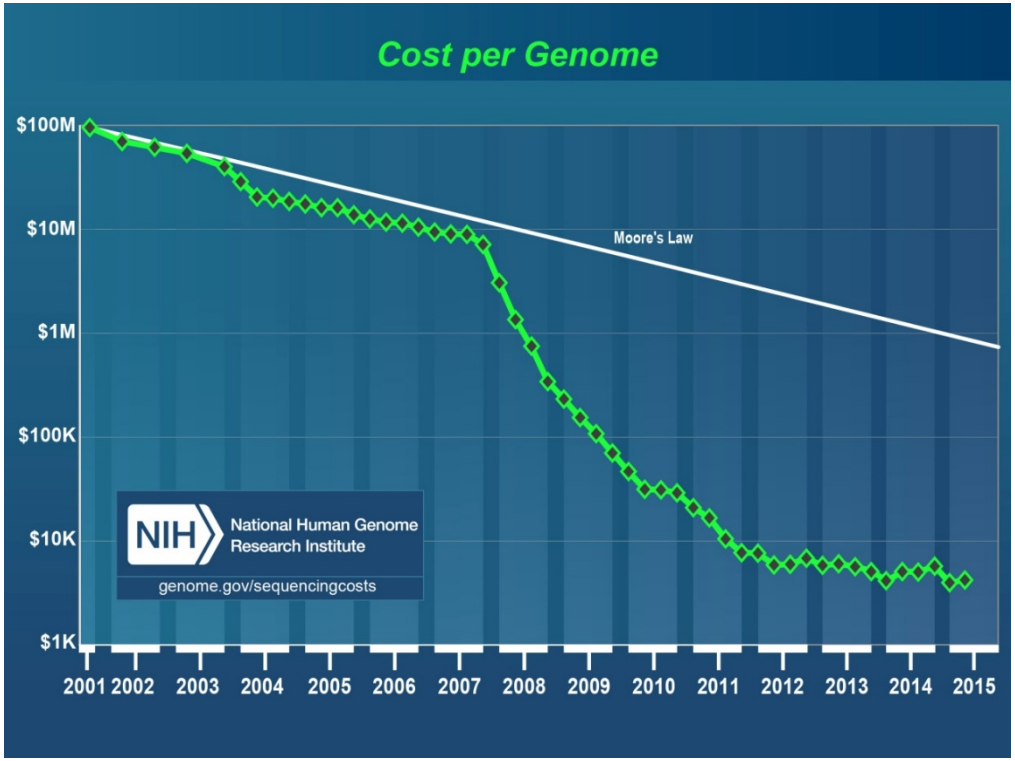
- ~$20 billion spent on genetic testing in 2015
- Increasing complexity of multigene test panels and underlying platforms
- Limited evidence
- Aggressive direct-to-consumer and provider marketing
- Concerns about ordering/interpretation/patient counseling
- Intensive time/resources needed to get answers you need

67,218 Tests
4,963 Disorders
5,946 Genes
707 Laboratories
1,083 Clinics
Source: GeneTests.org

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Whole genome/exome sequencing becomes increasingly available

- Cheaper
- Quicker
- Thanks to new technologies (e.g., NGS)



ECRI Institute
The Discipline of Science. The Integrity of Independence.

Managing Genetic Testing Manages Costs

Managing Genetic Tests Can Prevent Misorders, Avoid Costs, Stanford Study Shows

Mar 16, 2016 | Julia Karow

NEW YORK (GenomeWeb) – Active management of the use of complex genetic tests by doctors can help save hundreds of thousands of dollars in healthcare costs per year, according to researchers from Stanford University School of Medicine.

In a presentation at the American College of Medical Genetics and Genomics annual meeting in Tampa last week, David Stevenson, a medical geneticist at Stanford, showed that a genetic testing utilization service launched by Stanford University Medical Center a year ago helped cut the number of inappropriately ordered tests in half and saved about $250,000 in costs during the first year.

genomeweb

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Government Certification

- Federal
  - Clinical Laboratory Amendments Act of 1988 (CLIA) established quality standards for lab testing (administered by CMS)
  - Under CLIA, CMS accredits labs that produce Laboratory–Developed Tests (LDTs)
  - LDTs are performed only in the lab that developed the test
  - Does not look at evidence for clinical validity of a specific test
- State
  - 7 states also have certification programs: CA,FL, MA, MD, NY, PA, RI
  - NY has the most rigorous

FDA Regulatory Pathway

- FDA-cleared or approved test kits or systems (in vitro diagnostic tests = medical devices)
  - Historically, not actively regulated by FDA
  - Bar is higher for FDA-cleared tests than for LDTs
  - Can be licensed and performed in multiple labs
- FDA may increase oversight of LDTs: high-risk tests first
  - Risk stratification still being determined
  - Labs will have to get IDEs to start collecting clinical validity data, and then go through the PMA process
  - FDA already cracking down on labs marketing tests direct-to-consumer (23andMe, Pathway Genomics, DNA4Life etc)

FDA Cleared Genetic Tests

- Regulated as in vitro molecular diagnostic test kit
- Companion diagnostic: provides information that is essential for the safe and effective use of a corresponding drug or biological product
- Linked to a specific drug within its approved label
- Complementary diagnostic: diagnostics that are not required but provide significant information about use of a drug
- Complementary diagnostics associated more usually with a class of drugs, not confined to specific uses by FDA labeling

Companion Diagnostic Devices

- More than two dozen companion diagnostic devices have been approved or cleared by FDA; mostly, for cancer drugs
  - Herceptin (trastuzumab), Iressa (Gefitinib), Tarceva (Erlotinib), Mekinist (tramatenib); Tafinlar (dabrafenib), Erbitux (cetuximab); Vectibix (panitumumab), etc.
- Include molecular tests, cytogenetic tests, and immunohistochemical tests
- Genetic testing results may be considered with other clinical factors

Source: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

"... most laboratories that offer LDTs follow only the regulatory requirements of CLIA, which are intended to regulate the operations of laboratories, but are not specifically intended to regulate in vitro diagnostic devices."

- High false positive and/or false negative results
- Inflated claims of test accuracy by manufacturers
- Lack of validation data on test
- No clear evidence for association between test biomarker and disease, risk for disease, or disease prognosis (weak clinical validity)

"Despite the contention from some that 'CLIA is enough,' all of the tests described as problematic in this report were offered from laboratories following the minimum requirements of CLIA."

Potential for Harm

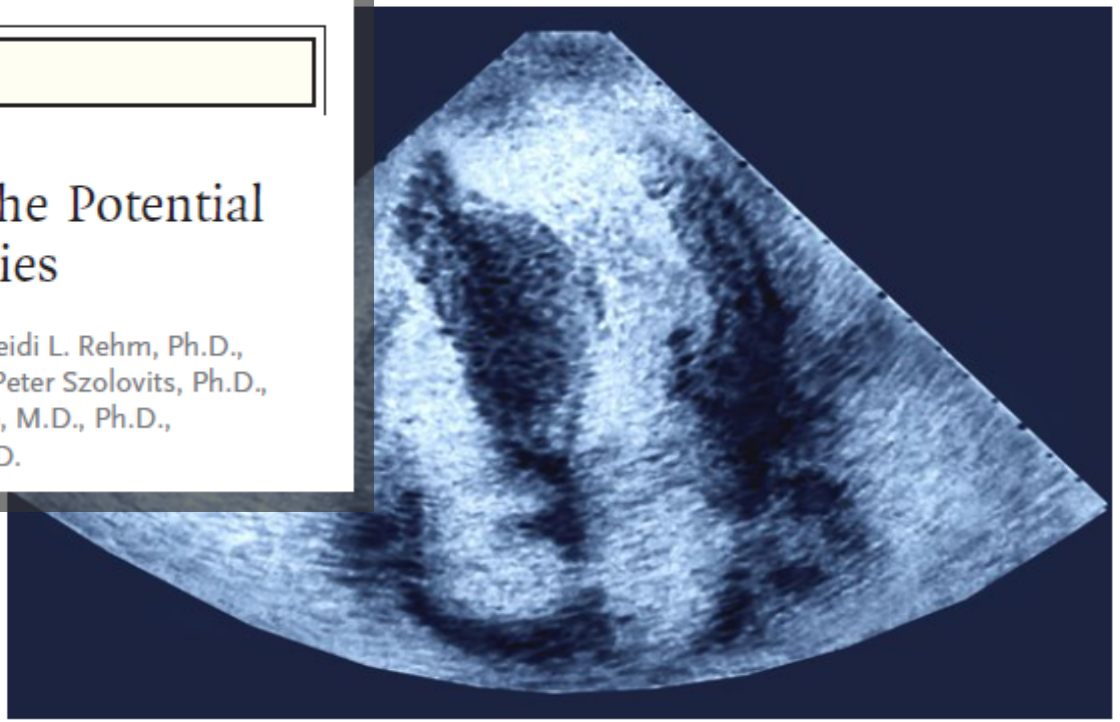
Genetic Tests for a Heart Disorder Mistakenly Find Blacks at Risk

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.



An ultrasound showing hypertrophy of the cardiac interventricular septum. Hypertrophic cardiomyopathy is a significant cause of sudden unexpected cardiac death.
BSIP / SCIENCE SOURCE

By DENISE GRADY
AUGUST 17, 2016

Genetic tests for an inherited heart disorder are more likely to have incorrect results in black Americans than in whites, according to a new study that is likely to have implications for other minorities and other diseases, including cancer.

ECRI Institute
The Discipline of Science. The Integrity of Independence.

What ECRI Hears

- Payers
  - "We don't know what we are paying for."
  - "We don't know whether any evidence underpins this test."
  - "Do we really need to pay for every gene in this panel?"
- Providers
  - "Our docs are ordering tests without understanding if it's the right test or if the results will be actionable."
  - "We don't know what the evidence is on this test."
  - "We don't really understand the results."
  - "We're under pressure. Payers are giving this a lot more scrutiny."
  - "This test gave me no valuable information to help my patient and insurance refused to pay for it."
- Labs/manufacturers
  - "What is ECRI telling payers and providers about our test."
  - "We need to understand how ECRI is identifying and evaluating evidence."

Challenges for Payers

- Making evidence-based coverage decisions - Lack of evidence showing clinical utility creates a major bottleneck for insurance reimbursement
- Sources for informing coverage decisions - but each has significant limitations and are only available for some genetic tests
- Professional guidelines - weigh heavily but are also limited in number
- FDA oversight - clearance is historically used as a starting point for test coverage, but most genetic tests are created and validated as laboratory-developed tests, which do not generally fall under FDA oversight
- Guidance on coverage decisions - other payers may be influential, particularly Medicare, but their decisions may not translate well to genetic tests for those under the age of 65

Assessing the Evidence Underlying Genetic Tests

- Analytic Validity (AV) - how accurately test detects whether a specific genetic variant is present or absent
  - Often a "black box"; we typically don't know the quality and consistency of laboratory assays over time
- Clinical Validity (CV) - how accurately the genetic information analyzed predicts the response to drug treatment
- Clinical Utility (CU) – degree to which test can improve patient outcomes
  - Can the test provide information about treatment or management that is helpful to consumers or patients?
- Poor analytic validity will typically compromise clinical validity and clinical utility, so we typically focus on evidence for clinical validity and clinical utility

We seek a "Chain of Evidence" leading from Analytic Validity to Clinical Utility

- Analytic validity → Clinical validity → Clinical Utility
  - Does the test detect the genetic variant accurately/reliably?
  - Does the test detect the disease/disorder accurately?
  - Does the test affect treatment decisions?
  - Does the treatment lead to improved health outcomes?
  - Are there any harms associated with the testing?

What are the Challenges in Assessing Evidence of Value, Especially for Clinical Utility?

Assessing Clinical Validity (CV)

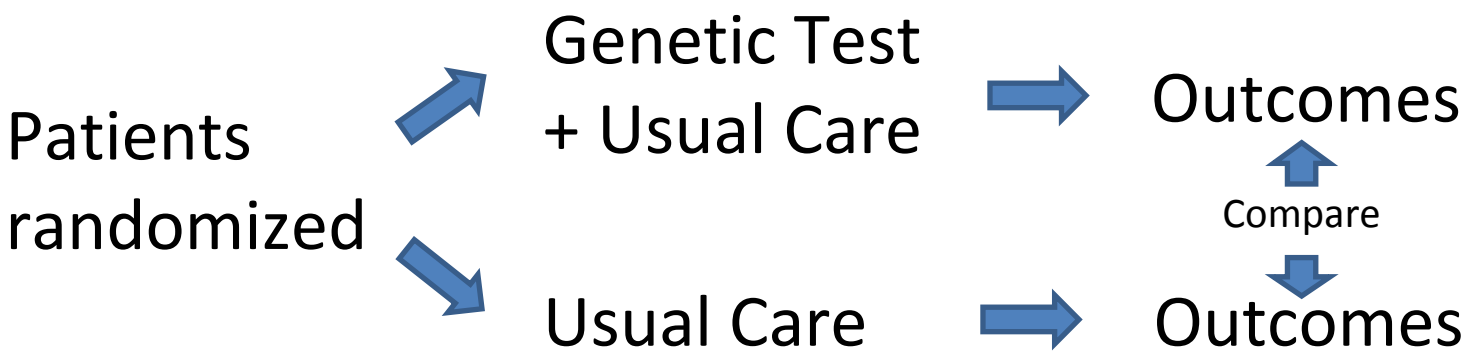
- Ideally need diagnostic accuracy studies: compare genetic test performance to GS test
- Diagnostic performance measures
  - Sensitivity
  - Specificity
- Clinical performance measures
  - Negative/Positive predictive values

Challenges in Assessing Analytic Validity (AV)

- Lack of transparency about the tests' technical detail
- Lack of published data
- Data may be about a previous version of the test
  - Does the evidence apply to the current version?
- Lack of assessment tools for rating the quality of analytic validity studies. Large diversity of studies.
- Analytic validity may vary across labs and over time
  - Changes in type/quality of reagents
  - Personnel changes in laboratories (rate of turnover in staff)
  - Standardization/certification procedures
  - Therefore, AV is often a "black box": we can only assess whether output is consistent, knowledge of inner workings is not available

Evidence for Clinical utility (CU)

- Clinical utility (the test's impact on health outcomes) is usually of ultimate interest in assessing GT technologies
- Ideal evidence is often a randomized controlled trial (RCT) comparing treatment with use of the GT to usual care (no GT)
- Reporting on patient-oriented health outcomes with sufficient follow-up



ECRI Institute
The Discipline of Science. The Integrity of Independence.

Questions/Challenges in Assessing Clinical Validity

- Is study size sufficient?
- Is the study population correctly matched to the test's intended purpose? (Is *spectrum bias* minimized?)
- Is there a substantial discrepancy between diagnostic performance metrics and predictive values? If so, will prevalence vary across different environments where test is employed?
- False negative/false positive rates. What is the clinical fate of these patients without use of the test?
- Manufacturers (mfrs) are not always clear about intended purpose of the test and/or the targeted patient population.

Challenges in Assessing Evidence for Clinical Utility (CU)

- Practical reasons for lack of direct evidence
  - Time, resources (many small companies with LKDTs have limited finances for conducting large, complex trials)
  - Difficulty in patient recruitment
  - Long follow-up may be required while there are constant changes and evolution in technologies
  - Sometimes CU follows logically from test validation and position in clinical pathway; additional evidence is not sought by mfrs
  - Some health outcomes (e.g., psychological distress) are rarely studied

Direct evidence for clinical utility is rarely available

- Clinical utility (the test's impact on health outcomes) is usually the ultimate interest of health technology assessment
- Ideal type of evidence: studies that compare use versus no use of the test, reporting on patient-oriented health outcomes with sufficient follow-up
- Practical reasons for lack of direct evidence
  - Difficulty in patient recruitment, constant changes in technologies, long follow-up required
- Some important outcomes relevant to predictive genetic tests are rarely studied
  - Psychological distress
  - Stigmatization or discrimination

Case Example: FoundationOne (Foundation Medicine, Inc.) Comprehensive Genomic Profiling Test for Guiding Targeted Therapy for Cancer

- FoundationOne
  - A genomic profiling test intended to help physicians make treatment decisions for patients with **all types of solid tumor cancers**
  - Uses next-generation sequencing
    - simultaneously examines the entire coding regions of 315 genes
    - select introns from 28 additional genes
  - Intended purpose: To identify molecular growth drivers of cancers and help oncologists match them with relevant targeted therapies

Is each included marker a good indicator for drug response?

- Markers were selected based on literature, according to Foundation Medicine
  - About 80 FoundationOne-relevant studies are provided on the company's website
- Some markers are considered well-established for guiding treatment decisions for certain cancers
  - e.g., *EGFR* mutations and *ALK* fusions for lung cancer (adenocarcinoma), *ERBB2* for breast cancer, KRAS mutations for colorectal cancer

The Main Challenge

- The test includes a very large number of genetic biomarkers
- Targeted to *all solid tumor cancers*
- *Clinical validity will not be available for all cancer types*
- Does FoundationOne affect patient outcomes (e.g., overall or progression-free survival)?

ECRI Evidence Report:

"This Product Brief is not intended to separately evaluate the clinical significance of each of the genes/introns included in FoundationOne for guiding cancer treatment. This Product Brief focuses primarily on evaluating the FoundationOne test's impact as a multigene panel on patient-oriented health outcomes. "

Does FoundationOne affect treatment decisions?

- Yes, for some markers/cancer types
  - Based on a small number of case series and single case reports
- But evidence is not available for all markers/cancer types
- It is questionable whether other markers included in the test carry the same clinical significance

Do treatment decisions based on FoundationOne results affect patient outcomes?

- FoundationOne is intended to identify actionable genomic alterations
  - Actionable genomic alterations—those for which there is available a U.S. Food and Drug Administration (FDA)-approved drug for the cancer or another cancer type or a registered clinical trial on a drug for the cancer
  - Most of the actionable genomic alterations are for guiding off-label use of targeted therapies, which may not necessarily improve health outcomes
- Limited reimbursement

What Evidence Do You Want?

"We don't know whether any evidence underpins this test." CMO at ECRI
Genetic Test Roundtable

- Simplify the Wild, Wild West of genetic testing
- Ample and good quality published evidence
  - Analytic Validity (test accuracy)
  - Clinical Validity (diagnostic accuracy)
  - Clinical Utility (impact on patient management and health outcomes)
- Ensuring appropriate access / reducing inappropriate utilization
- Efficient and evidence-based policy development/updating
- Education and outreach to provider networks

What "Evidence" Don't You Want?

- Unpublished data presented only as conference abstracts or posters
- Data summaries or unsubstantiated claims from lab and manufacturer websites with no independent validation of information
- Markov models and cost-effectiveness analyses based on hypothetical assumptions and inputs

Impact of Genetic Testing on Population Health

- Many examples where precision medicine has caused a paradigm shift in treatment and achieved superior health outcomes
- Challenges in developing a comprehensive genetic/genomic testing approach for population-based care
- Comparatively few biomarkers where a specific mutation is linked to risk for developing disease, or indicative of response to a targeted therapy
- Gaps in evidence exist: underlying science and data analytics must continue to evolve

Questions?

ECRI Institute
The Discipline of Science. The Integrity of Independence.