We've methodically performed secondary research.

SO RELAX,
we have the answer.

Genetic Testing

ROSE Conference

September 14, 2017
Overall Learning Purpose/Goal

This presentation will examine the hype around genetic testing and help guide attendees through the copious amount of information to identify what is key to understanding genetic tests and ultimately identifying which tests improve patient healthcare and outcomes.
Learning Objectives

At the conclusion of this activity, participants will be able to:

• Understand the current regulatory landscape
• Identify key criteria when assessing tests that look at somatic variants
• Understand germline genetic testing and why standard definitions of clinical utility may not be appropriate
• Explore the future of molecular diagnostics
Navigating the Hype of Genetic Testing

Renee Balliet, PhD, MBA
Product Manager, Genetic Solutions
Genetic Testing Overview
Genetic Testing in the Clinical Setting

- **Prenatal Screening** for genetic disorders
- **Newborn Screening** for inherited conditions
- **Risk Assessment**: Identify increased risk for disease
- **Diagnostic Testing**: To confirm a diagnosis when patient has signs or symptoms of disease
- **Prognostic Testing**: Predict course of disease
- **Tumor Genotyping**: Predict response to therapy and prognosis
- **Companion Diagnostics**: Diagnostic test for mutation paired with targeted therapy to treat the condition (oncology, cystic fibrosis, familial hypercholesterolemia...)
- **Pharmacogenomics**: How genetic makeup affects response to drugs
Genetic Test Technologies

Conventional Genetic Tests

Karyotyping
• Looks at the number and appearance of chromosomes and is ordered for certain conditions such as Down’s syndrome, Trisomy 18, Trisomy 13, ambiguous genitalia.

Chromosome Microarray (arrayCGH)
• Detects genetic abnormalities on all chromosomes simultaneously, including deletions and duplications. More sensitive than conventional karyotype for genetic evaluation of infants and children with unexplained intellectual disability, congenital anomalies, or autism spectrum disorder.

Single gene/variant sequencing or genotyping
• Sanger sequencing, Sequenom, PCR
• May be useful when a gene is suspected to cause a patient’s condition or to confirm a known family variant in a patient.

NGS-Based Genetic Tests

Next-Generation Sequencing (NGS)
• High throughput sequencing technologies that support more rapid and less expensive DNA sequencing.
• Can evaluate multiple variants at the same time.
• May be useful when no genetic basis for a phenotype is suspected or when multiple genetic variants could be responsible for a patient’s condition.

Whole Exome Sequencing
• Defines the DNA sequence of the protein-coding region (exons) of the genome.
• Represents ~1% of the human genome.

Whole Genome Sequencing
• Defines the DNA sequence of the entire genome.
• May not include the mitochondrial genome.
Federal Regulation and Oversight of Genetic Tests
Regulatory Landscape: FDA

• FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.

• FDA classifies each test based on the complexity of the test method.

• FDA defines a Laboratory Developed Test (LDT) as an *in vitro* diagnostic test that is manufactured by and used *within a single laboratory*; LDTs are high complexity.

• LDTs are subject to regulatory oversight by the FDA but *do not* go through premarket notification or premarket approval (enforcement discretion).

Regulatory Landscape: CLIA

• CLIA program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results.

• Accredited labs can develop their own in-house LDTs, including those using NGS.

• Test complexity (FDA assigned) informs CLIA laboratory requirements.

• Labs must establish the analytic validity of a test—the ability to report the presence or absence of a particular gene or genetic change—but clinical validity and clinical utility are NOT assessed!

• CLIA accreditation is specific to the lab and the analytic validation is not valid outside the lab that did the analysis.

Differences Between FDA and CLIA Regulation

• Regulates medical devices (including genetic tests)
• Reviews tests PRIOR to marketing
• Clinical validity is assessed in premarket approval (PMA)

• Regulates laboratories
• Review of analytical validity may occur AFTER testing begins
• Clinical validity NOT assessed
When CLIA Isn’t Enough: Discordant Results in Direct-to-Consumer Testing

Kira Peikoff, 28, had her DNA tested by three direct-to-consumer companies, and the results didn't agree.

By KIRA PEIKOFF
Published: December 30, 2013
When CLIA Isn’t Enough: Discordant Results in Direct-to-Consumer Testing

Pathway Genomics found that Kira Peikoff had an average genetic risk of psoriasis, top, while 23andMe assessed it as higher than average, and Genetic Testing Laboratories as low risk based on proprietary risk algorithms with different genetic variants.
Implications of Genetic Testing

• Test results may impact family members.

• Secondary findings: Unexpected finding unrelated to the reason for doing the test? Should they be reported?
  • American College of Genetics and Genomics recommends reporting findings that could lead to serious health conditions such as:
    • Inherited cancer syndromes
    • Disorders associated with sudden cardiac arrest
    • Susceptibility to anesthesia complications
  • Reported secondary findings may become part of medical record and may be reviewed when applying for life or disability insurance. Laws prohibit health insurance companies and employers from discrimination based on genetic test results.

• Genetic testing may reveal information about family relationships e.g., non-paternity.

• Insurance may not cover costs of testing.

http://www.nature.com/gim/journal/v19/n2/abs/gim2016190a.html
Direct to Consumer: 23andMe

- 23andMe is a direct-to-consumer DNA personal genome service (PGS) that provided a variety of health information to their clients.

- **All laboratory testing for 23andMe is performed in a CLIA-certified laboratory.**
Direct to Consumer: 23andMe

- November 2013 FDA letter
- 23andMe in violation of FD&C Act
  - Marketing a medical device without FDA clearance
- 23andMe ordered to “immediately discontinue marketing the PGS [Saliva Collection Kit and Personal Genome Service] until ...it receives FDA marketing authorization for the device”
- FDA does “not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses” and noted concern “about the public health consequences of inaccurate results from the PGS device”
- FDA noted particular concern about how consumers might use test results about breast cancer mutations and genotypes impacting drug response
Direct to Consumer: 23andMe

• After FDA warning letter, 23andMe stopped marketing its PGS (only ancestry information and raw data could be obtained)

• 23andMe worked with FDA to resolve outstanding issues

• February 2015: 23andMe’s Bloom Syndrome carrier test obtained FDA clearance
  • October 2015: FDA classified carrier screening tests as class II with special controls and intends to exempt these devices from FDA premarket review
April 6, 2017, FDA approved marketing of 23andMe Personal Genome Service Genetic Health Risk (GHR) tests for 10 diseases or conditions.

- Parkinson’s disease, a nervous system disorder impacting movement
- Late-onset Alzheimer’s disease, a progressive brain disorder that destroys memory and thinking skills
- Celiac disease, a disorder resulting in the inability to digest gluten
- Alpha-1 antitrypsin deficiency, a disorder that raises the risk of lung and liver disease
- Early-onset primary dystonia, a movement disorder involving involuntary muscle contractions and other uncontrolled movements
- Factor XI deficiency, a blood clotting disorder
- Gaucher disease type 1, an organ and tissue disorder
- Glucose-6-phosphate dehydrogenase deficiency, also known as G6PD, a red blood cell condition
- Hereditary hemochromatosis, an iron overload disorder
- Hereditary thrombophilia, a blood clot disorder

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm
FDA Exemptions

On July 11, 2017, the FDA announced **Exemptions from Premarket Notification: Class II Devices**. The list, which includes more than 1,000 class II devices, includes genomic platforms and tools:

- High throughput DNA sequence analyzer
- DNA genetic analyzer
- Mass spectrometer for clinical multiplex test systems
- Real-time nucleic acid amplification system
- Complete gene expression profiling accessory reagents
- Quality control DNA materials

Evolving Regulatory Landscape: LDTs

• **October 2014: 2 draft guidance documents**
  - Notification and Device Reporting for LDTs:
    - Enforce certain device requirements and reporting of safety issues for LDTs and manufacturer requirements for labs that manufacture LDTs
  - Framework for Regulatory Oversight of LDTs
    - Develop a risk-based approach to oversight

• **July 2016: 4 draft guidance documents**
  - Use of real-world evidence (RWE) to support regulatory decision-making for medical devices
  - Use of Public Human Genetic Variant Databases to Support Clinical Validity for NGS-based IVDs
  - Principles for Co-development of an In Vitro Companion Diagnostic (CDx) device with a therapeutic product
  - Standards for Next Generation Sequencing (NGS)-based IVDs for Germline Disease Diagnosis

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm

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Evolving Regulatory Landscape: LDTs

• January 2017: Discussion Paper on Laboratory Developed Tests
  “Growing consensus that additional oversight of LDTs is necessary”
  • A risk-based approach to oversight
  • Independent premarket review for certain tests and for some modified tests
  • A focus on analytical validity and clinical validity as the basis for test approval
  • Risk classification activities
  • Adverse event reporting
  • Exemption of certain categories of tests from premarket review
  • A robust laboratory quality system
  • “Grandfathering” for tests available prior to a specific date
Rapid Growth of Genomic Testing


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Rapid Growth of Genomic Testing

- **68,000+ Tests**
- **68,229** Tests
- **5,036** Disorders
- **6,042** Genes
- **714** Laboratories
- **1,083** Clinics

Updated July 19, 2017

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm
https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
Cost per Genome

Cost in late 2015 ~$1000
Illumina has the goal of $100 genome
Helix launched $80 exome

*Cost of sequencing does not include cost of analysis.

https://www.genome.gov/sequencingcosts/

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Current Genomic Diagnostic Environment

- Minimal regulation and oversight
- Continuously changing or updating of tests
- One indication, 100s of genetic tests
- Multiple technologies used for one test
- “Designer” gene panels
- Whole Exome/Genome Sequencing
- Direct-to-physician and client marketing
- Nonspecific CPT codes
- Inconsistent costs
Making Sense of Genetic Tests
Recently Proposed Method

• Clinical applications of genetic/genomic testing are potentially important but, as others have observed, “the current knowledge base . . . to turn the promise of genomic medicine into reality is severely limited.”(1)

• The National Academies of Sciences, Engineering, and Medicine report titled “An Evidence Framework for Genetic Testing” included framework for decision-making regarding the use of genetic tests in clinical care.
  • 7 evaluation steps, including definition of the genetic test scenario, conducting evidence reviews, and completing a structured and transparent decision process with routine updating and review of new evidence.(2)

Germline vs Somatic Variants

**Germline**
Can be passed on to other family members.

**Somatic**
Not passed on to other family members.
Example: Tumor profile
Genetic Testing in the Clinical Setting

Germline
- Prenatal Screening for genetic disorders
- Newborn Screening for inherited conditions
- Risk Assessment: Identify increased risk for disease

Somatic
- Tumor Genotyping: Predict response to therapy and prognosis

Germline/Somatic
- Diagnostic Testing: To confirm diagnosis when patient has signs or symptoms of disease
- Prognostic Testing: Predict course of disease
- Pharmacogenomics: How genetic makeup affects response to drugs
- Paired Diagnostics: Diagnostic test for mutation paired with targeted therapy to treat the condition (oncology, cystic fibrosis, familial hypercholesterolemia…)

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Somatic Variants

• Specific to patient’s tissue
• Somatic: Can look at DNA, RNA, miRNA, methylation, protein, etc.
  • Biomarkers, tumor profile, precision/personalized medicine
• Can change (time, treatment)
Somatic Variants Example: GPS Cancer (NantHealth)

• Goal:
  Help guide personalized treatment options, including approved drugs and active clinical trials that correspond to the molecular composition of a patient’s individualized tumor in solid tumor cancer patients.

• Techniques:
  • Whole-genome DNA sequencing
  • Whole-transcriptome sequencing (RNA)
  • Quantitative proteomics analysis (protein)

• What’s being reported to physicians:
  • DNA and RNA alterations and protein levels
  • FDA-approved therapies with potential clinical benefit and/or potential tumor-resistant therapies
  • Active clinical trial therapies that may have clinical benefit

http://www.gpscancer.com/overview/
# Approaches to Assess Somatic Variants

## Analytical Validity

*accurately detect whether variant is present or absent*

- Should it show for each method used or for entire process?
- Should it be shown for each biomarker? For each tissue?
- Can they reference general techniques for their test?

## Clinical Validity

*variant tested is associated with phenotype or outcome*

- Should it be shown for each biomarker? For each tissue?
- What time points? (before/after treatment)

## Clinical Utility

*information about diagnosis, treatment, or management of a disease that will be useful for the physician or the patient*

- Does it change physician’s course of action?
- Does it improve outcome?
Somatic Variants Example: GPS Cancer (NantHealth)

• Laboratory lists 55 peer-reviewed publications in support of test
• Cost of test: $34,000
• Closer look:
  • None of the 55 studies support GPS Cancer assay and process specifically.
  • Proprietary/not available bioinformatics are used to determine aberrant biomarkers and how the information is translated into therapy prediction.
  • No studies support this assay, process, and reporting improves patient outcomes.

http://www.gpscancer.com/overview/
Guidelines for Validation of Next-Generation Sequencing–Based Oncology Panels

Goal: To establish analytical validation best practice guidelines for NGS gene panel testing of somatic variants

• Recommendations address NGS test development, optimization, and validation, including:
  • Panel content selection and rationale for optimization and familiarization phase conducted before test validation
  • Utilization of reference cell lines and reference materials for evaluation of assay performance
  • Determining positive percentage agreement and positive predictive value for each variant type
  • Requirements for minimal depth of coverage and minimum number of samples that should be used to establish test performance characteristics
Tests that Look at Somatic Variants

• Look at what the laboratory is claiming.
• Is their support for the use of the entire assay process or just portions?
• Does the specific test show clinical utility?
Germline Variants

- DNA
- Consistent throughout cells (excluding mosaicism)*
- Does not change over time*
- Passed on to offspring, thus can impact entire families and populations

* Unless somatic changes occurred.
# Challenges to Assess Germline Variants

## Analytical Validity

- **accurately detect whether variant is present or absent?**
  - Most laboratories, if they provide any information about the test
  - May list what method(s) used
  - Methodology details typically not provided
  - May list gene(s) examined
  - Typically do not list specifics about variants (SNP, CNV, del/dup)
  - May provide internal sensitivity and specificity
  - Do not publish on the analytical validity and cite general literature

## Clinical Validity

- **variant tested is associated with phenotype or outcome**
  - Laboratories and manufacturer's do not/cannot (need large number for enough power) publish on clinical validity and thus reference the literature (even FDA recognizes and encourages use of databases)
  - Shift from publications to database
  - Clinical validity is very complex
    - Allele frequency
    - Populations
    - VUS
    - Power to observe effect
    - Variable expressivity
    - Incomplete penetrance
    - Environmental factors ("increase risk")
    - Rare variants

## Clinical Utility

- **is genetic testing clinically useful**
  - Need a broader definition
  - Impact of genetic testing may depend on the perspective (payer, provider, health system, patient, family)
  - Can be difficult to measure/assess
  - Study designs likely to be different than for other medical devices (few/no RCTs)
  - May see only case reports or small sample sizes for rare disorders

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Approaches to Assess Germline Variants

Clinical Utility

*genetic testing is clinically useful*

- Need a broader definition
- Impact of genetic testing may depend on the perspective (payer, provider, health system, patient, family)
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Assistance for Genetic Testing

• Many centers recommend meeting with a genetic counselor before and after some genetic tests.

• Genetic counselors:
  • Help patients and family understand the test, the possible outcomes, impact on family members and possibility of secondary findings.
  • Help families decide if they want to know about secondary findings.
  • Guide patients and families through the medical consent process.
  • Assist in preparing documents for insurance prior authorization.
  • Meet with patients and families to review test results.

• Financial counselors:
  • Review individual benefit coverage with patients, including any out-of-pocket costs for testing.
Drivers for Genetic Testing

- Technology
- Big Data
- ELSI
- Medical Needs
- Special Interests
- Cost
Future

• Without a strong outcry, regulation will remain lax.
• Germline test cost will continue to come down in price.
  • Increase in testing
  • Everyone who wants, will have exome/genome sequenced
• Somatic testing will continue to assess multiple biomarkers and personal information with complex computations to derive recommendations.
• Question will not be IF genetic testing is needed, but rather what to do with the information.
Thank you

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Questions?