Genomic and Precision Medicine

Week 5: Clinical applications of genomics — Predictive Testing for Common, Complex Diseases

Jeanette McCarthy, MPH, PhD
Bryce Mendelsohn, MD, PhD
UCSF Medical Genetics
Predictive (predisposition) testing

Likelihood (chance) that a person without clinical signs and symptoms of disease will eventually develop it
Genetic tests for complex diseases

- Familial
  - Breast and ovarian cancer (HBOC) – BRCA1/2
  - Colorectal cancer (Lynch syndrome) – MMR genes
  - Hypercholesterolemia (FH) - LDLR/APOB
- Thrombophilia – F5
- Hemochromatosis – HFE
- Celiac disease - HLA
ACCE model

Framework for evaluating genomic tests

1997 U.S. Task force on genetic testing

Analytic validity

- How accurately and reliably the laboratory assay measures the genotype (sensitivity and specificity of lab test for mutation)

CLIA (Clinical Laboratory Improvement Amendments)

Qualifications of lab personnel
QC and testing procedures
Clinical validity

- How consistently and accurately the test detects or predicts the disease

<table>
<thead>
<tr>
<th>Truth</th>
<th>Disease</th>
<th>No disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>False Positive</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>False Negative</strong></td>
<td></td>
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<tr>
<td><strong>True Negative</strong></td>
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</table>

- Sensitivity
- Specificity
- PPV
- NPV
Important Test Metrics: Sensitivity and Specificity

Clinical Sensitivity
Among people with disease, how many test positive

Clinical Specificity
Among people without disease, how many test negative

Sensitivity and specificity are characteristics of the test
Positive Predictive Value (PPV)

Among those with a positive test
How many will develop disease (penetrance)

Characteristic of both test and population
E.g. BRCA1 mutations: ~60% chance of developing breast cancer by age 80

For constant sensitivity =95% and specificity =95%
Negative Predictive Value (NPV)

Among those with a negative test
How many will remain disease-free

- Characteristic of both test and population
- High NPV is good for ruling out disease
- e.g. HLA-DQ test has 100% NPV for celiac disease
Clinical utility

Does it improve health outcomes?

- Change in care to reduce or prevent disease, death, disability through use of efficacious treatment or intervention
- Does the test result in equivalent care, but faster results, at less cost, or less invasively?

Balance of benefits and risks

- Benefits/risks – to individual, families, society
- Benefits – includes disease reduction, reproductive planning; psychological
- Risks - psychological, social and economic
Outcomes of Genetic Testing in Adults with a History of Venous Thromboembolism

Evidence Reports/Technology Assessments, No. 180

Investigators: Jodi B Segal, MD, MPH, Daniel J Brotman, MD, Ashkan Emadi, MD, PhD, Alejandro J Necochea, MD, MPH, Lipika Samal, MD, Lisa M Wilson, MS, Matthew T Crim, MSc, MA, and Eric B Bass, MD, MPH.

Johns Hopkins University Evidence-based Practice Center

Rockville (MD): Agency for Healthcare Research and Quality (US); June 2009. Report No.: 09-E011

Structured Abstract

Objective: To address whether Factor V Leiden (FVL) testing alone, or in combination with prothrombin G20210A testing, leads to improved clinical outcomes in adults with a personal history of venous thromboembolism (VTE) or to improved clinical outcomes in adult family members of mutation-positive individuals.

Data sources: Searches of MEDLINE®, EMBASE®, The Cochrane Library, the Cumulative Index to Nursing & Allied Health Literature, and PsycInfo® through December 2008.
**Results:** We reviewed 7,777 titles and included 124 articles. No direct evidence addressed the primary objective. However, high-grade evidence supported the conclusion that tests for the detection of FVL and prothrombin G20210A have excellent analytic validity. Most clinical laboratories test for these mutations accurately. Heterozygosity [odds ratio (OR) =1.56 (95 percent confidence interval (CI) 1.14 to 2.12)] and homozygosity [OR=2.65 (95 percent C.I. 1.2 to 6.0)] for FVL in probands are predictive of recurrent VTE. Heterozygosity for FVL predicts VTE in family members [OR=3.5 (95 percent C.I. 2.5 to 5.0)] as well. Heterozygosity for prothrombin G20210A is predictive of recurrence in probands [OR=1.45 (95 percent C.I. 0.96-2.2)]. Evidence is insufficient about heterozygosity for prothrombin G20210A in family members and insufficient about homozygosity for prothrombin G20210A. A single study supported the hypothesis that clinicians might change management based on test results. There was high-grade evidence that anticoagulation reduces recurrent events in probands with FVL or prothrombin G20210A; however, there was low-grade evidence that the relative reduction with treatment is comparable to that seen in individuals without mutations. Moderate evidence supported the conclusion that neither harms nor benefits of testing have been demonstrated conclusively. Decision-analysis models suggest that testing may be cost-effective in select individuals.

**Conclusions:** There is no direct evidence that testing for these mutations leads to improved clinical outcomes in adults with a history of VTE or their adult family members. The literature supports the conclusion that while these assays have high analytic validity, the test results have variable clinical validity for predicting VTE in these populations and have only weak clinical utility.

Segal JB, et. al. Outcomes of Genetic Testing in Adults with a History of Venous Thromboembolism
Importance of evaluation frameworks

- ACCE not only framework
- Evidence-based, but evidence often sparse

Important for:
  - Insurance coverage decision
  - Clearance by FDA (when regulated)
  - Uptake by physicians

In absence of formal ‘reports’, healthcare providers should be comfortable evaluating the merits of genetic tests
Who is going to deliver personalized medicine?

Knowledge and skills
- What tests are available
- Validity and value of tests
- Practical issues (where to order, how to interpret)
- ELSI, communication of results

- Medical geneticists
- Genetic counselors
- Primary care providers/specialists
  - Physicians
  - Nurses
Cases scenarios
A patient with a family history of coronary artery disease came to you (the physician) with results from a genetic test. He said he tested positive for the 9p21 gene test and wanted to know what to do. Before you talk to the patient, you consult with a medical geneticist about these results.
Report: 9p21 testing for coronary artery disease (CAD)

Risk of CAD (%) for SNP rs10757278

My results
Average person

Your results
Based on your genotypes, you have a ~1.25-fold increased risk of coronary artery disease

9p21 testing was performed in a CLIA-certified and CAP-accredited laboratory.
This test has not been approved by the U.S. FDA.
9p21 associated SNP is not in a gene

- Rs10811661 could be in LD with causal variant in nearby gene (unlikely)
- Rs10811661 could affect regulation of a nearby gene (CDKN2A) ✓
- 88% of GWAS hits are intronic or intergenic
- Even in the absence of known function, a genetic marker may still have predictive power
Genetics may change overall risk profile

- Threshold for statin treatment
- Threshold for antihypertensives
- Threshold for aspirin

10 yr Absolute risk of CVD

- 30%
- 25%
- 20%
- 15%
- 10%
- 5%
- 1%

Person 1
- smoker
- diabetic
- Age>60

Person 2
- smoker
- Age>60
- Hi chol
- hyperten
- 9p21

Person 3
- hyperten
- Hi chol
Family history may be a better predictor of disease risk than genetic variants.

Diagnostic devices (testing kits)
- FDA’s office of In Vitro Diagnostics
- Analytical and clinical validity

Laboratory developed tests (most tests)
- Centers for medicare and medicaid services
- Analytical validity - CLIA regulations
Key concepts from Enactment 1

- A genetic test is not necessarily measuring the causal variant...but rather, a genetic marker that may be linked to the causal variant.
- Results of genetic test may have utility in motivating changes in risk factors or improve medication adherence.
- In some cases, family history remains a better predictor of disease than any specific genetic test.
- In the U.S. most genetic tests are considered laboratory developed tests (LDTs) and are currently not regulated by the FDA.
A patient comes to you (the physician) with a report from a DTC testing company showing that she is at increased risk of diabetes and wants you to help her interpret the report. Before you talk to the patient, you consult with a medical geneticist about these results.
T2DM genetic risk report

- Caucasian
- Female
- 40-50 yrs

Type 2 Diabetes

Jeanette: 25%
Average: 21%

This is the estimated lifetime incidence of Type 2 Diabetes for someone with Jeanette’s genotype compared to average.

Marker Effects

What does this chart show?
The chart shows the approximate effects of the selected person's genotype at the 11 reported markers. Higher, red bars indicate increased risk from the average, while lower, green bars indicate decreased risk from the average. The light gray bars show the maximum possible effects for the possible genotypes at the marker.

Mouse over individual bars to view additional information about each marker. Click on a bar to view detailed information about that marker below. You can read more about all markers in the technical report.
Odds ratios for 11 markers:

1.16  
0.89  
1.02  
1.20  
0.98  
1.04  
1.06  
1.06  
0.90  
1.03  
0.95  

1. Convert odds ratio to relative risk = 1.21

RR = OR/(1-P_0)+(P_0*OR), where P_0 is prevalence of disease (average risk)

2. Multiply together to get overall odds ratio = 1.27

3. Multiply relative risk by average risk to get my risk (1.21 * .21) = 25%

Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Jeanette: 25%</th>
<th>Average: 21%</th>
</tr>
</thead>
</table>

This is the estimated lifetime incidence of Type 2 Diabetes for someone with Jeanette's genotype compared to average.
Genes poorly explain T2DM risk

- Non-genetic (74%)
- Known genes (7%)
- Unexplained genetic (19%)

Heritability: 26%
Genes: 39
Factors that impact risk estimates from multiSNP panels

- Assumptions about average population risk of disease
- # of SNPs used to predict disease
- How SNP effects are combined

Table 1: Average population risks and number of SNPs used by 23andMe, deCODEme, and Navigenics in the prediction of risks for six multifactorial diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Average population risk (%)</th>
<th>Number of SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23andMe</td>
<td>deCODEme</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>6.5</td>
<td>8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27.2</td>
<td>25</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>0.53</td>
<td>0.5</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>17.8</td>
<td>16</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>25.7</td>
<td>25</td>
</tr>
</tbody>
</table>

SNPs, single nucleotide polymorphisms.
Comparison across DTC genetic testing results from different companies

Table 4: Agreement among the three companies in assigning individual consumers to the same risk category, according to the risk categories used by 23andMe

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Assigned to the same risk category by all three companies</th>
<th>Assigned to the same risk category by two companies</th>
<th>Assigned to different risk categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓↓↓</td>
<td>---</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>52.3</td>
<td>0.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>42.4</td>
<td>6.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>75.3</td>
<td>0.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>51.8</td>
<td>0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>15.6</td>
<td>4.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>22.2</td>
<td>7.8</td>
<td>14.7</td>
</tr>
</tbody>
</table>

23andMe categorizes disease risks as decreased (↓), elevated (↑), and typical (--) risks if the risks of disease are lower than 20% below the average population risk, higher than 20% above the average population risk, and in between, respectively. Values are percentages. For example, ↓↓↓ indicates the percentage of individuals that were at decreased risk according to all three companies, and ↑↓↓ indicates the percentage of individuals for which the three companies predicted risks in three different risk categories.

Perfect concordance across all 3 companies: 33-89%

Where to find objective information about tests

http://currents.plos.org/genomicatestests/

Also…

• Professional guidelines
• Technology assessments

EGAPP: Evaluation of genomic applications in practice and prevention

http://www.egappreviews.org/
EGAPP Recommendation Statement: The EGAPP Working Group (EWG) found insufficient evidence to recommend testing for predictive variants in 28 variants (listed in Table 1 of the recommendation) to assess risk for Type 2 Diabetes in the general population, based on studies in populations of northern European descent. The EWG found that the magnitude of net health benefit from use of any of these tests alone or in combination is close to zero. The EWG discourages clinical use unless further evidence supports improved clinical outcomes.
Key concepts from Enactment 2

- Multi-marker genetic risk panels should be interpreted with caution
- Genes identified to date poorly explain genetic underpinnings of complex diseases
- Several resources exist to find objective information/guidance on tests
- Genetic testing should not distract from modifiable risk factors (diet, lifestyle, medication)
- There are two sides to the controversy over direct-to-consumer testing
You have an older patient who is worried that he may be developing alzheimer disease since he has family history of dementia. You heard about a genetic test for APOE that may help predict risk of AD and was wondering whether it’s a good idea or not to have him tested. Before you talk to the patient, you consult with a medical geneticist.
GINA – U.S. Genetic Information Nondiscrimination Act of 2008

• Prevents health insurers from denying coverage or adjusting premiums based on an individual’s predisposition to a genetic condition

• Prohibits employers from discriminating on the basis of predictive genetic information

• Stops insurers and employers from enforcing mandatory genetic testing, maintains strict use and disclosure requirements of genetic test information, and imposes penalties against groups who violate these provisions
Personal utility

How valuable is the test for disease management

- Whether to do further diagnostic testing or ending the diagnostic odyssey
- Increased vigilance
- Lifestyle changes

How valuable is the test for other reasons

- Psychosocial effects (reassurance, acceptance, mental preparation)
- Family planning
Key concepts from Enactment 3

- GINA – what it does and doesn’t cover
- Personal utility is increasingly being recognized as rationale for genetic testing
- Where to find information about available tests
- Utility of targeted variant analysis versus sequencing entire coding region