Genomic and Precision Medicine

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

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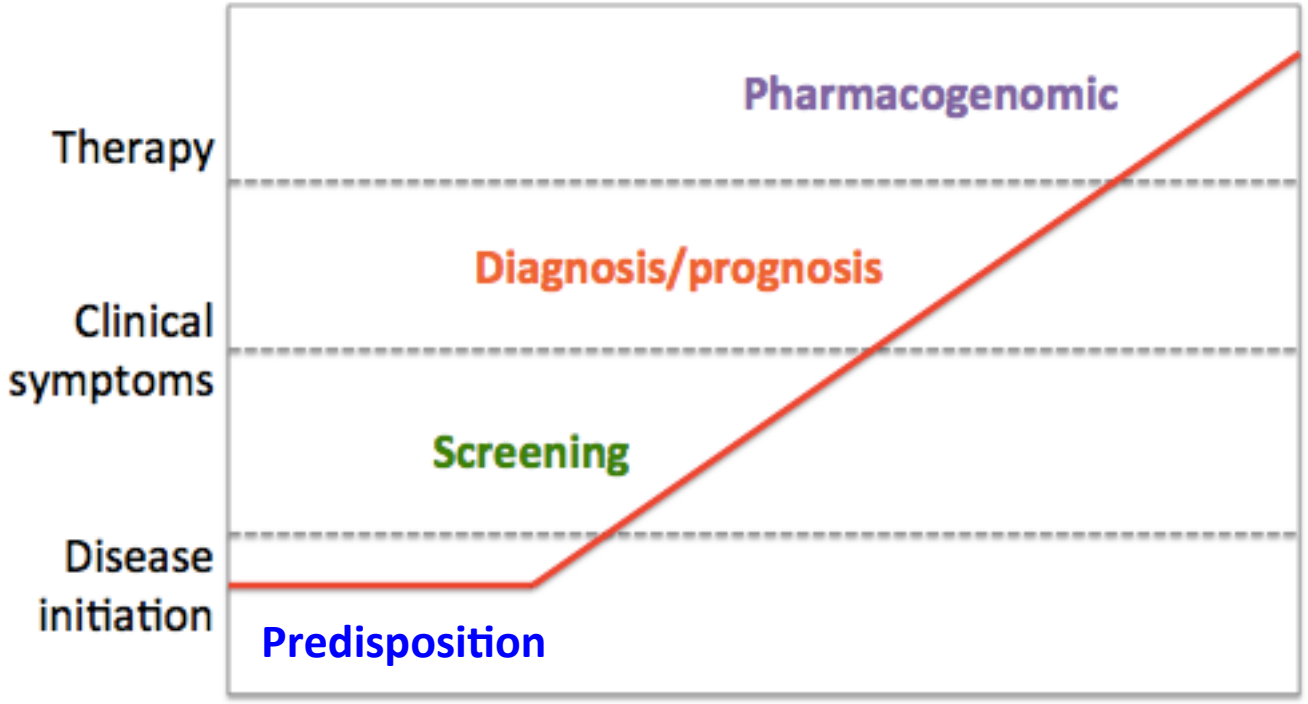
Predictive (predisposition) testing

Likelihood (chance) that a person without clinical signs and symptoms of disease will eventually develop it



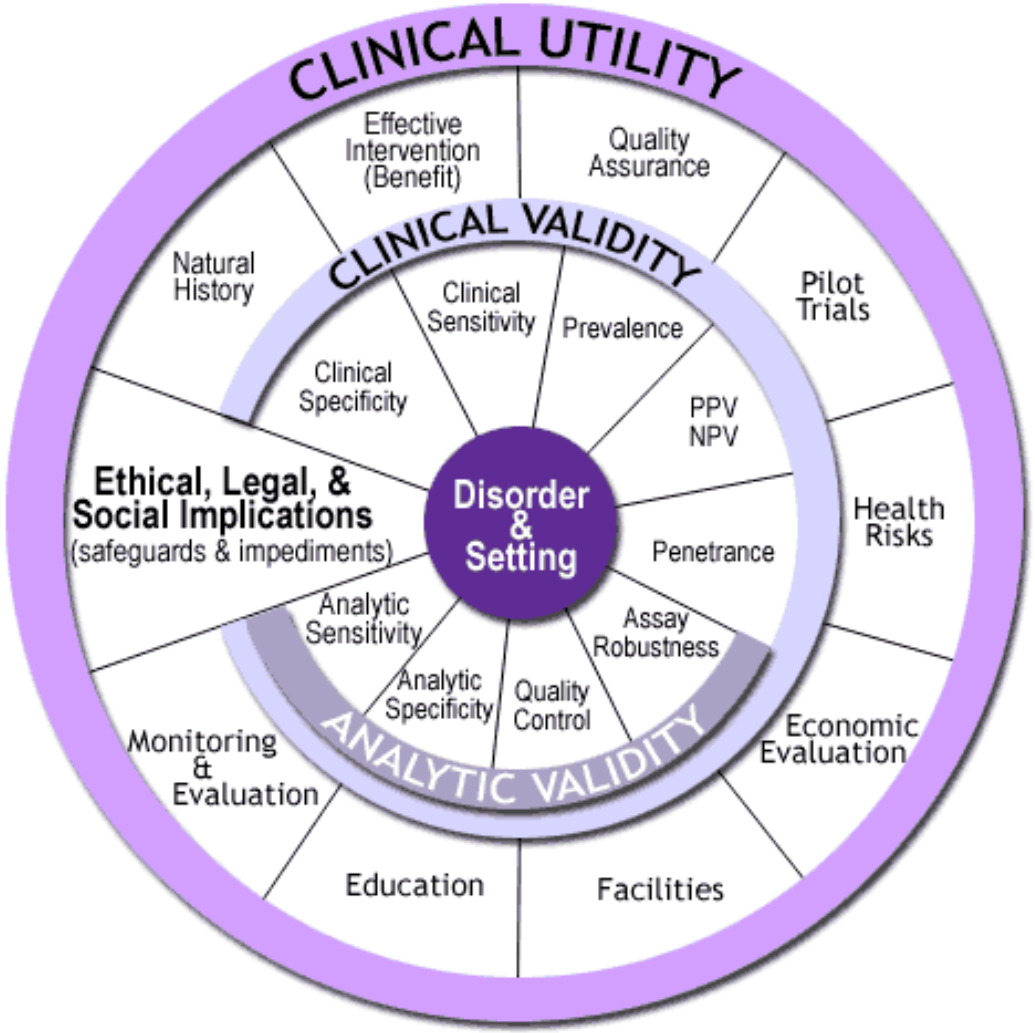
Genetic tests for complex diseases

- 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

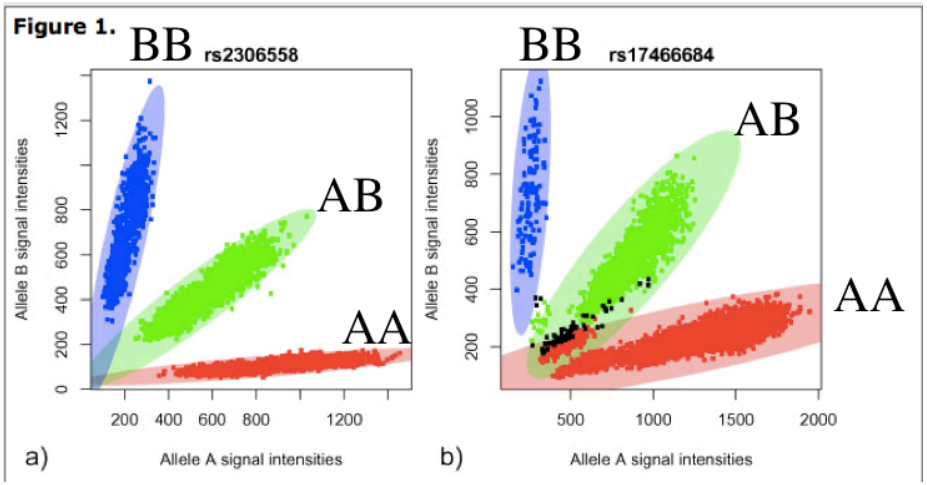
1997 U.S. Task force on genetic testing



ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing: http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm

Analytic validity

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

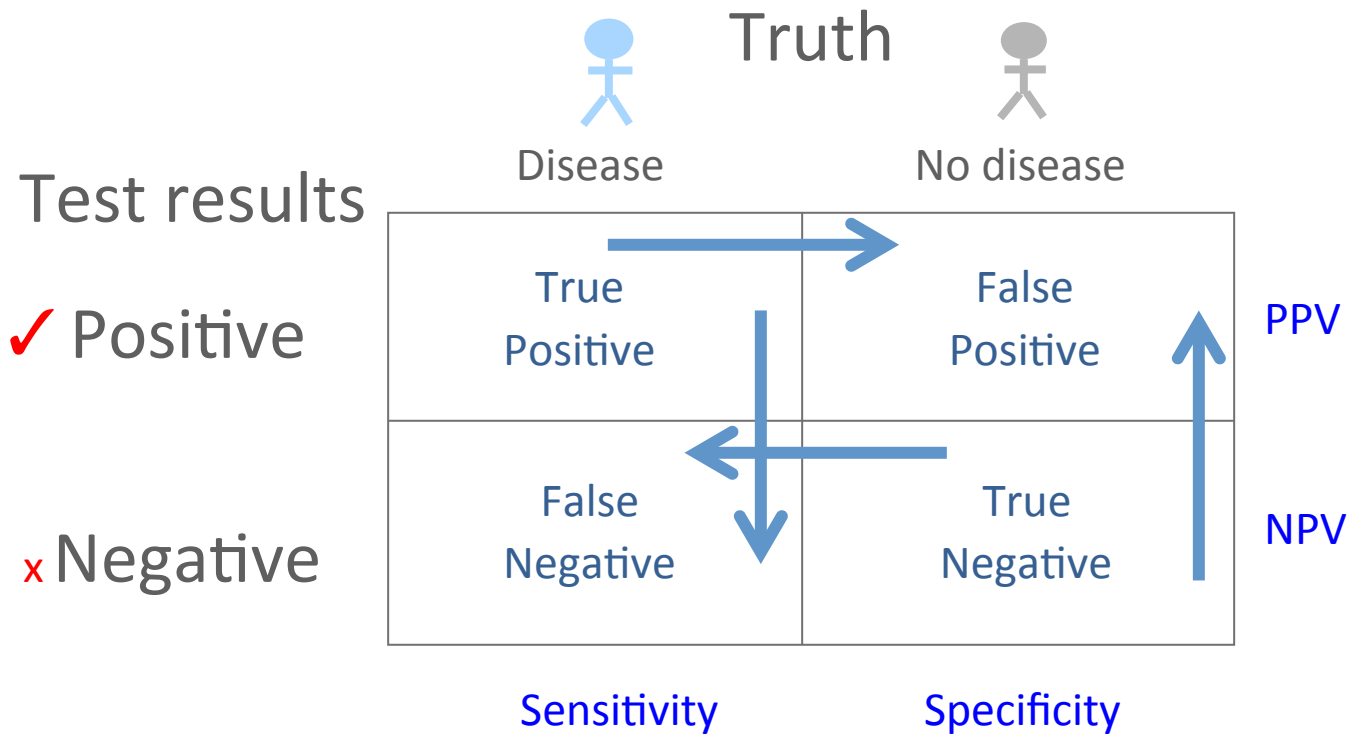


CLIA (Clinical Laboratory Improvement Amendments)

Qualifications of lab personnel
QC and testing procedures

Clinical validity

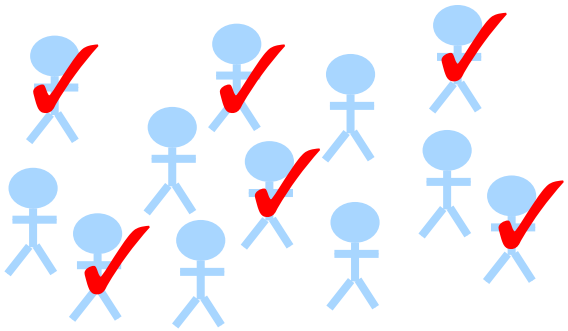
- How consistently and accurately the test detects or predicts the disease



Important Test Metrics: Sensitivity and Specificity

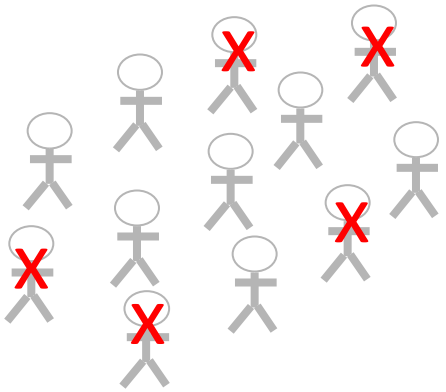
Clinical Sensitivity

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)

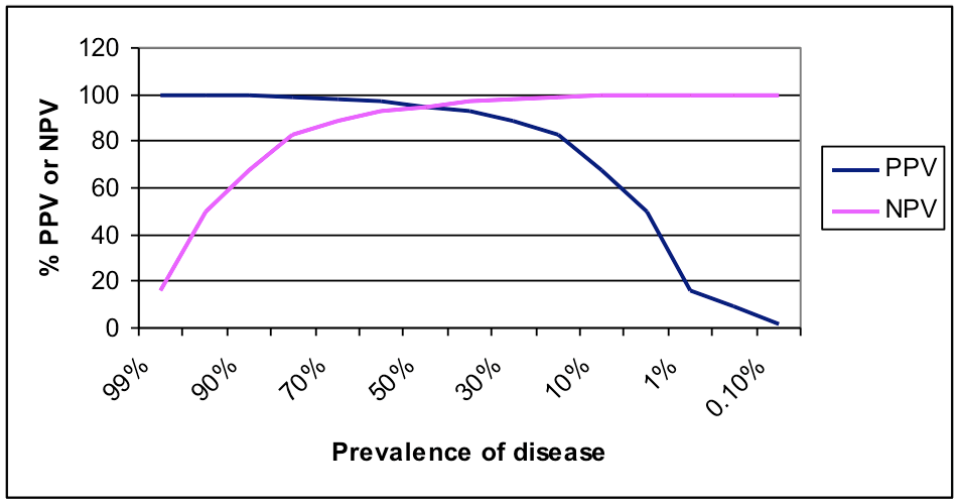
Among those with a positive test

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%



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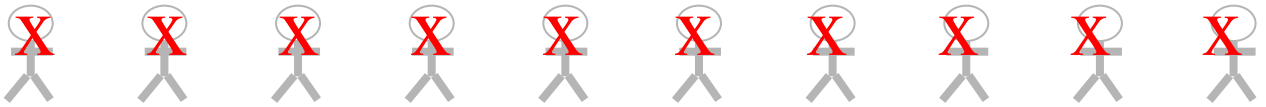
Negative Predictive Value (NPV)

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

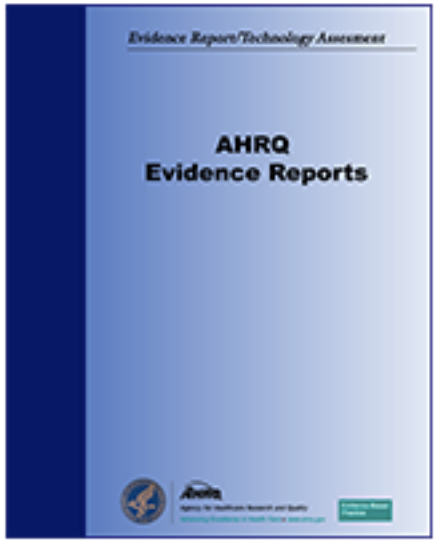
Does it improve health outcomes?

- 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

Application of ACCE framework



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.

Continued....

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 does homozygosity for FVL [OR=18 (95 percent C.I. 7.8 to 40)]. Heterozygosity for prothrombin G20210A is not 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. There was moderate evidence to support 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**
Evidence Reports/Technology Assessments, No. 180 http://www.ncbi.nlm.nih.gov/books/NBK44591/

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

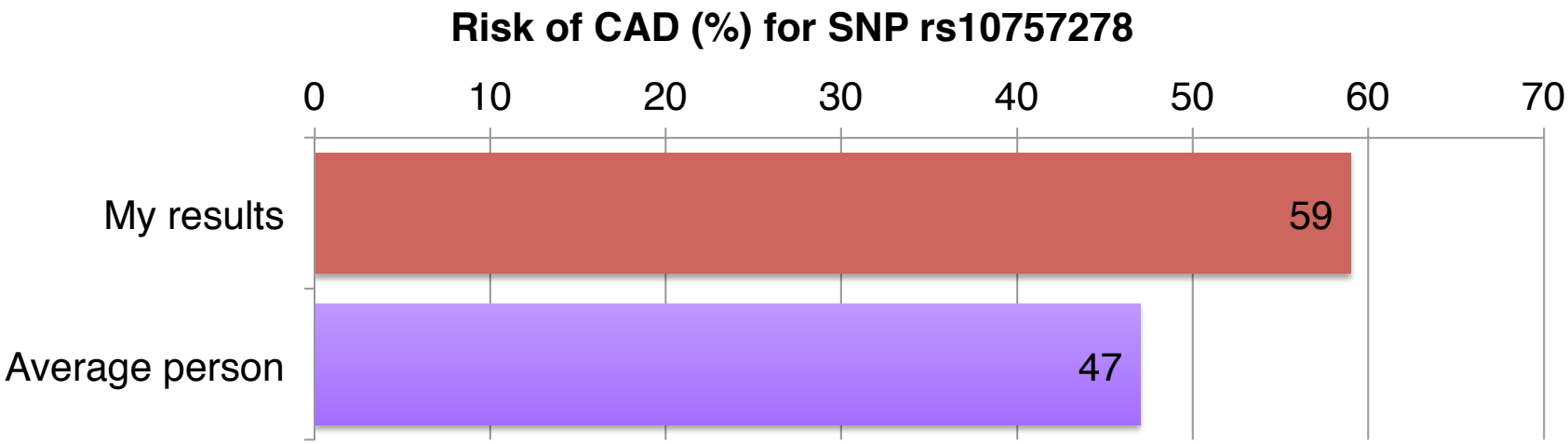
- Medical geneticists
- Genetic counselors
- Primary care providers/specialists
  - Physicians
  - Nurses

Cases scenarios

Enactment 1

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)



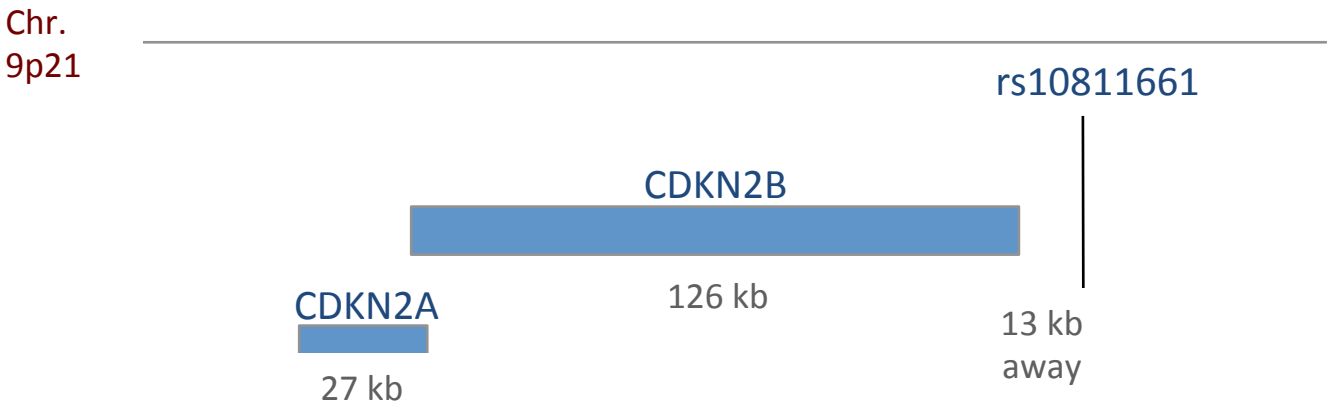
Your results

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.

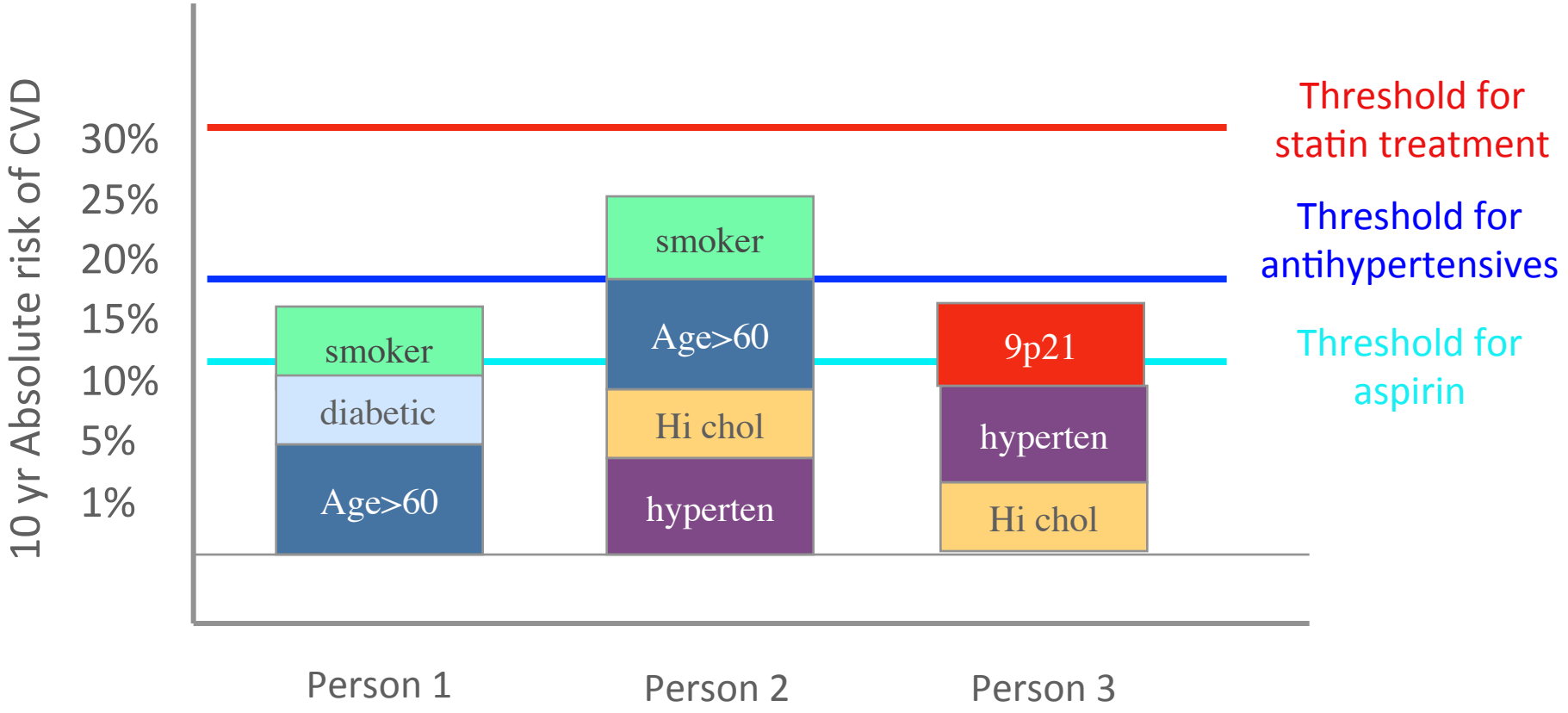
This test has not been approved by the U.S. FDA.

9p21 associated SNP is not in a gene

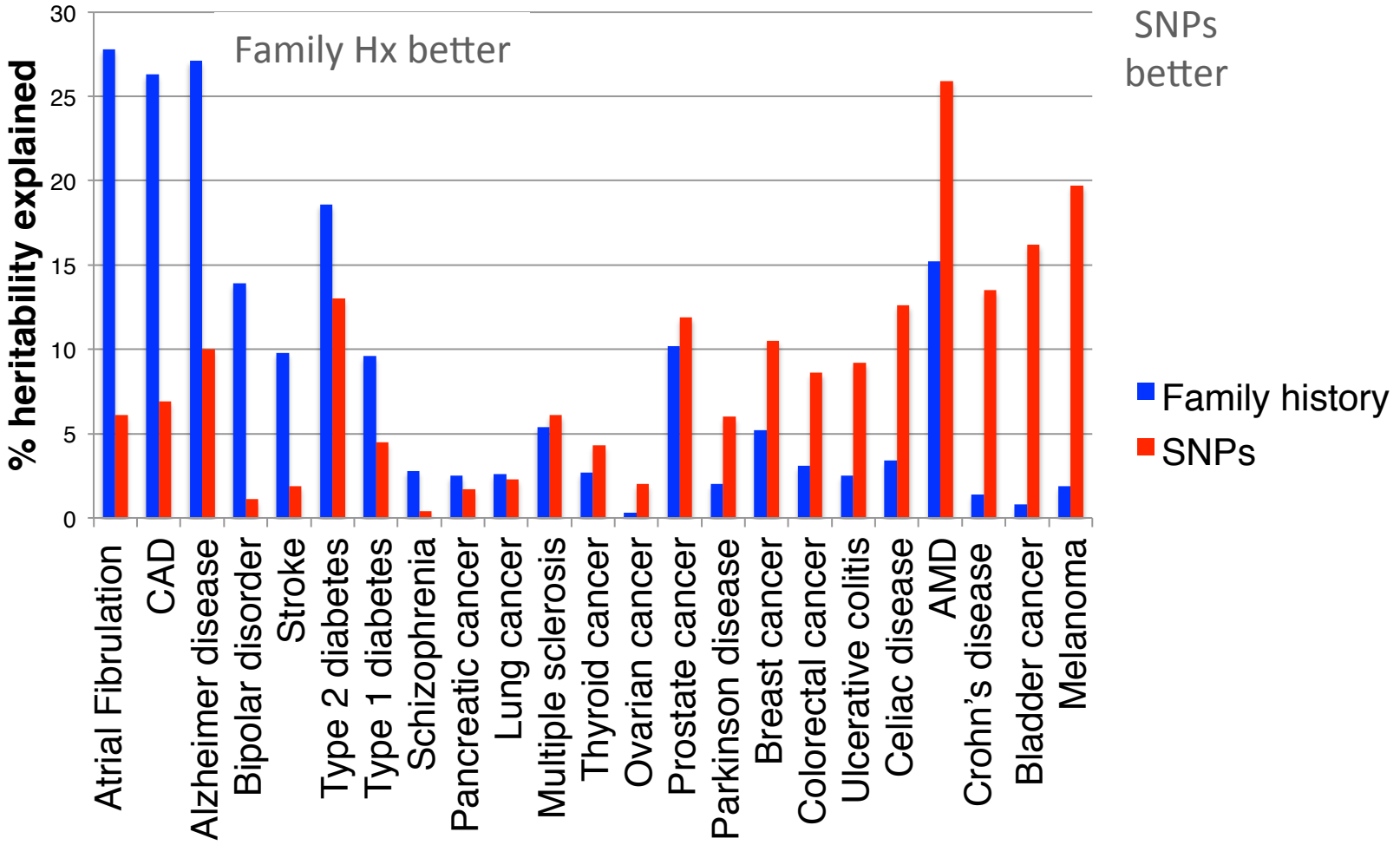


- Rs10811661 could be in LD with causal variant in nearby gene (unlikely)
- Rs10811661 could affect regulation of a nearby gene (CDKN2A) ✓
- 88% of GWAS hits are intronic or intergenic
- Even in the absence of known function, a genetic marker may still have predictive power

Genetics may change overall risk profile



Family history may be a better predictor of disease risk than genetic variants



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Do CB, et al. PLoS Genet 2012; 8(10): e1002973.

U.S. regulatory landscape for genetic testing

- 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.

Enactment 2

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

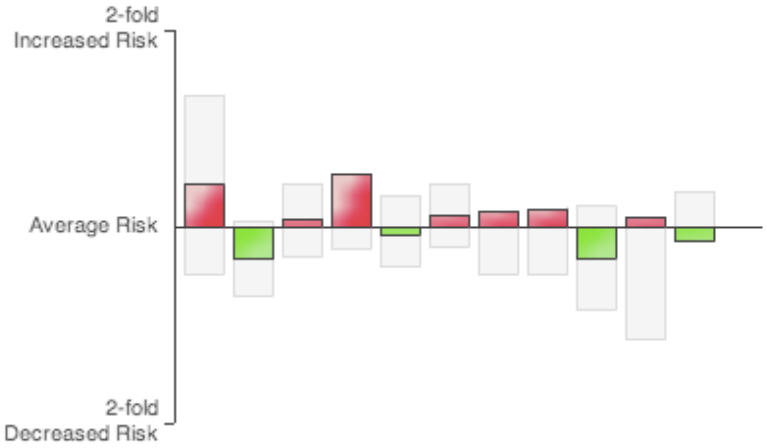
Type 2 Diabetes

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.

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Composite risk score

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

Multiply together to get overall odds ratio = 1.27

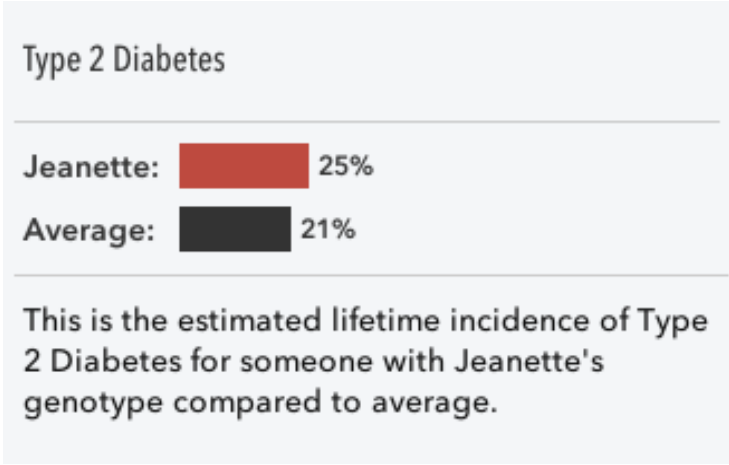
2

Convert odds ratio to relative risk = 1.21

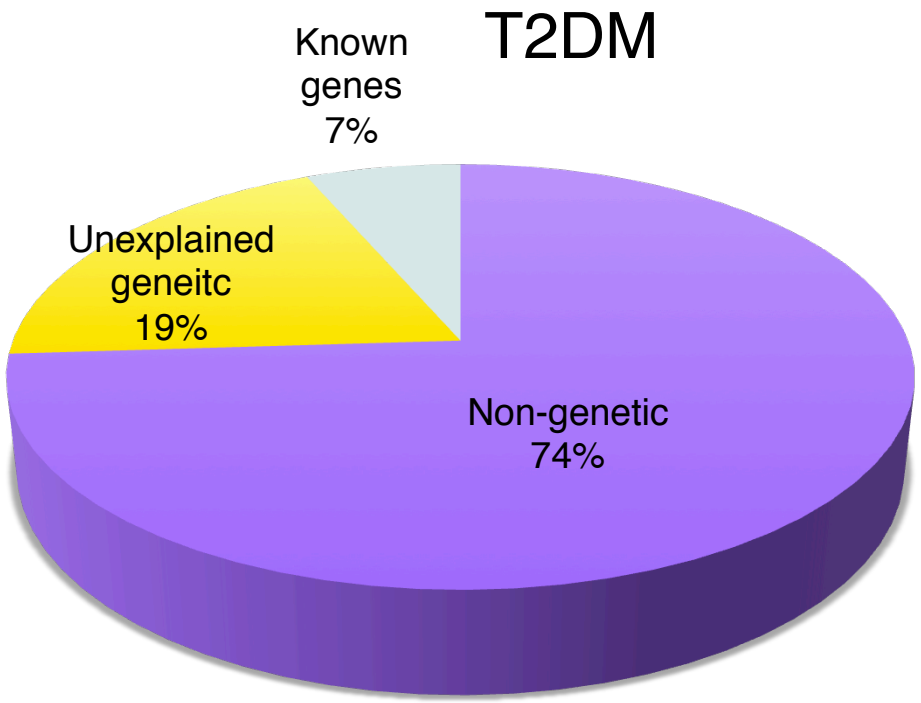
RR = OR/(1-P_0)+(P_0*OR), where is prevalence of disease (average risk)

3

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



Genes poorly explain T2DM risk



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

	Average population risk (%)			Number of SNPs		
Diseases	**23andMe**	**deCODEme**	**Navigenics**	**23andMe**	**deCODEme**	**Navigenics**
Age-related macular degeneration	6.5	8	3.1	3	6	6
Atrial fibrillation	27.2	25	26	2	6	2
Celiac disease	0.12	1	0.06	4	8	10
Crohn disease	0.53	0.5	0.58	12	30	27
Prostate cancer	17.8	16	17	12	26	9
Type 2 diabetes	25.7	25	25	11	21	18

SNPs, single nucleotide polymorphisms.

Kalf RR, et al. Genet Med. 2014 Jan;16(1):85-91.

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

	Assigned to the same risk category by all three companies			Assigned to the same risk category by two companies			Assigned to different risk categories
Diseases	↓↓↓	---	↑↑↑	↑↑- ↓↓-	--↑ --↓	↑↑↓ ↓↓↑	↑-↓
Age-related macular degeneration	52.3	0.5	15.2	6.1	6.0	12.5	7.4
Atrial fibrillation	42.4	6.7	16.7	27.3	5.7	1.2	0.0
Celiac disease	75.3	0.0	13.8	9.0	0.4	1.3	0.3
Crohn disease	51.8	0.2	3.5	13.8	3.7	19.9	7.2
Prostate cancer	15.6	4.5	13.5	29.4	21.7	6.5	9.0
Type 2 diabetes	22.2	7.8	14.7	24.1	23.1	3.2	5.0

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%

Kalf RR. Genet Med. 2014 Jan;16(1):85-91.

Where to find objective information about tests

PLOS | CURRENTS EVIDENCE ON GENOMIC TESTS

http://currents.plos.org/genomictests/

Also…

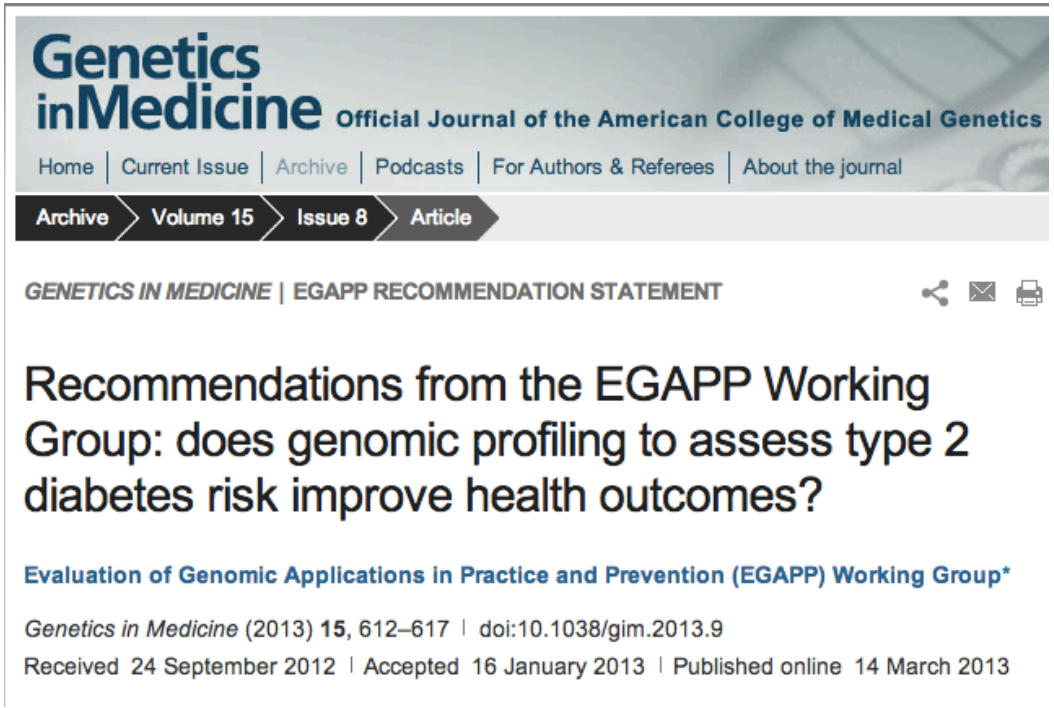
- Professional guidelines
- Technology assessments

EGAPP: Evaluation of genomic applications in practice and prevention

http://www.egappreviews.org/

T2DM multigene review from EGAPP

http://www.egappreviews.org/



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Archive > Volume 15 > Issue 8 > Article

GENETICS IN MEDICINE | EGAPP RECOMMENDATION STATEMENT

Recommendations from the EGAPP Working Group: does genomic profiling to assess type 2 diabetes risk improve health outcomes?

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

Genetics in Medicine (2013) **15**, 612–617 | doi:10.1038/gim.2013.9

Received 24 September 2012 | Accepted 16 January 2013 | Published online 14 March 2013

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

Enactment 3

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

President George W. Bush signs H.R. 493, the Genetic Information Nondiscrimination Act of 2008, Wednesday May 21, 2008, in the Oval Office. White House photo by Eric Draper.

- 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

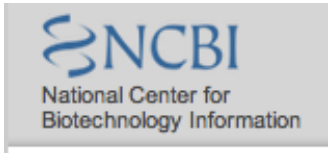
How valuable is the test for disease management

- 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 prepartion)
- Family planning

Genetic Testing Registry



Showing test for 1 condition

Enter text to filter the conditions

Select a condition reset

- Alzheimer disease, type 2
- Alzheimer disease, type 3
- Alzheimer disease, type 4
- Alzheimer's disease
- Amyloidogenic transthyretin amyloidosis
- Andersen Tawil syndrome

Compare labs

Test type reset

- [x] Clinical (9)

Test purpose

- [ ] Diagnosis (8)
- [ ] Mutation Confirmation (1)
- [ ] Pre-symptomatic (1)
- [ ] Screening (1)

Test method

Molecular Genetics (9)

- [ ] Sequence analysis of the entire coding region (5)
- [ ] Deletion/duplication analysis (1)
- [ ] Sequence analysis of select exons (2)
- [ ] Mutation scanning of select exons (1)
- [ ] Targeted variant analysis (3)

Test services

- [ ] Carrier testing (1)
- [ ] Prenatal testing (1)

Lab certification

Showing 1 to 9 of 9 tests for 1 condition in 6 labs

C Apolipoprotein E Gene Mutation

Methods: T Targeted variant analysis

Analytical Validity: Test was validated by testing at least 20 samples.

Lab: Immuno-Molecular Pathology University of Kentucky

Directors: C Jennings, MD, ABPath, FCAP, Lab Director

C Alzheimer: Apo-E, PSEN1, PSEN2, A2M and APP genes sequence analysis (select exons)

Methods: C Sequence analysis of the entire coding region

Analytical Validity: 99% sensitivity

Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases

Directors: Juan Lopez, PhD, Scientific Director

C Alzheimer: Apo-E, PSEN1, PSEN2, APP, A2M and MAPT genes sequence analysis (select exons)

Methods: C Sequence analysis of the entire coding region

Analytical Validity: 99% sensitivity

Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases

Directors: Juan Lopez, PhD, Scientific Director

C Alzheimer: MAPT, CLU, PICALM, CR1 genes screening

Methods: X Mutation scanning of select exons

Analytical Validity: 99% sensitivity

Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases

Directors: Juan Lopez, PhD, Scientific Director

C APOE: ApoE gene genotyping

Methods: C Sequence analysis of the entire coding region

Analytical Validity: 99% sensitivity

Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases

Directors: Juan Lopez, PhD, Scientific Director

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