

Genomic and Precision Medicine

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



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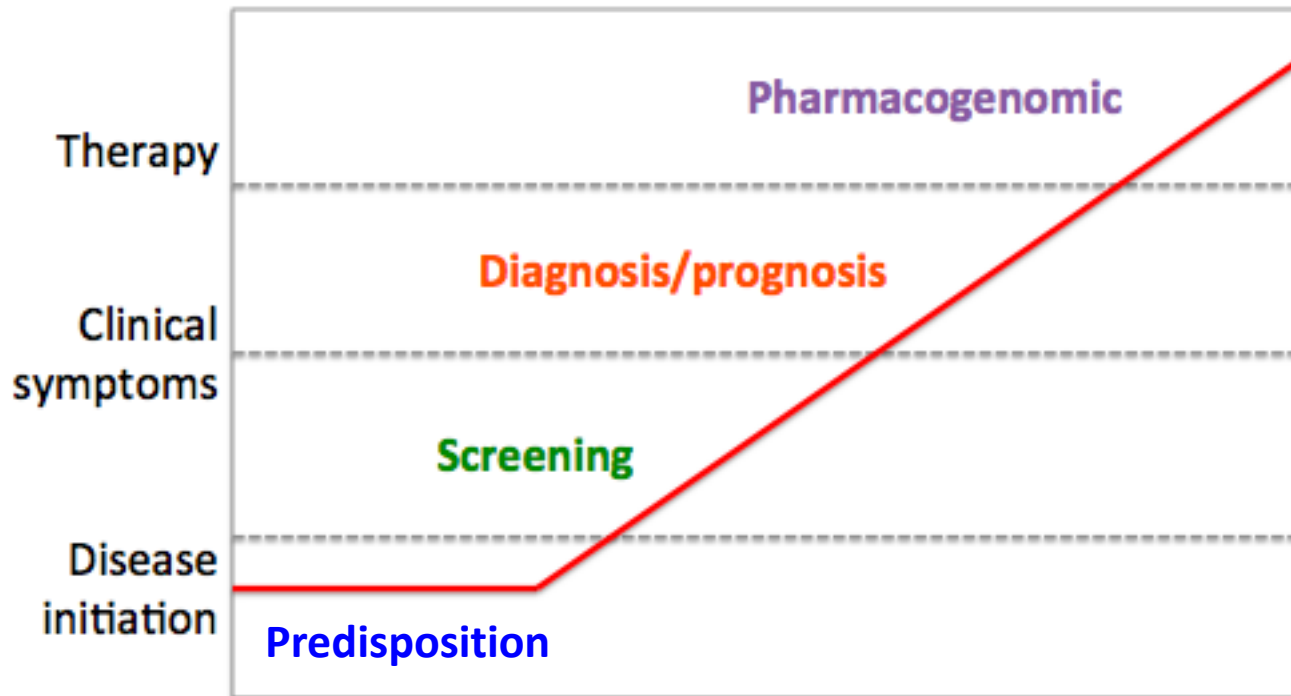


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Predictive (predisposition) testing

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

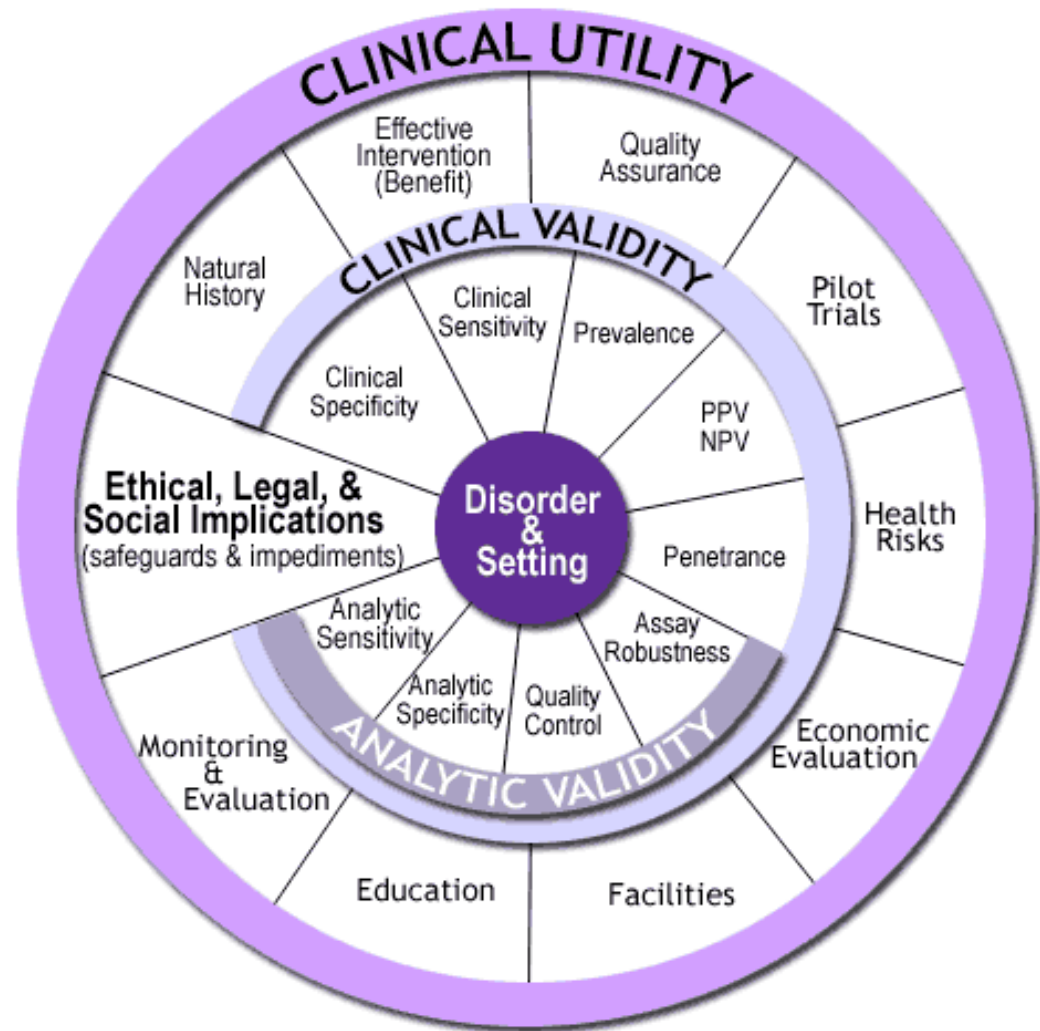
- Hemochromatosis – HFE

- Celiac disease - HLA

ACCE model

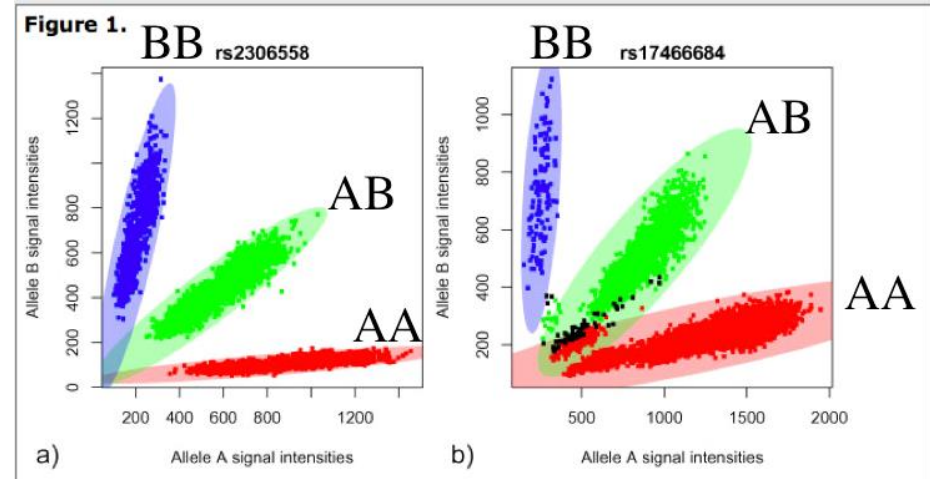
Framework for
evaluating genomic
tests

1997 U.S. Task force on
genetic testing



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)

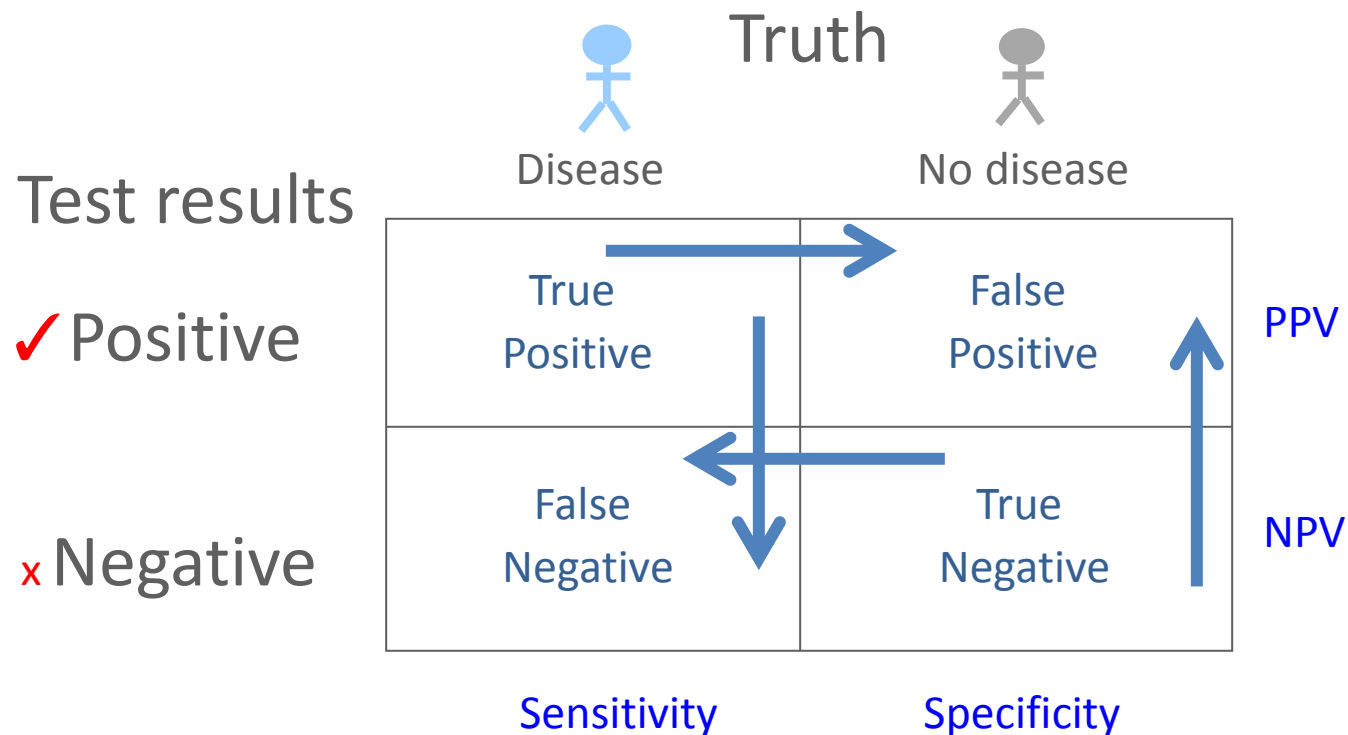


Qualifications of lab personnel
QC and testing procedures



Clinical validity

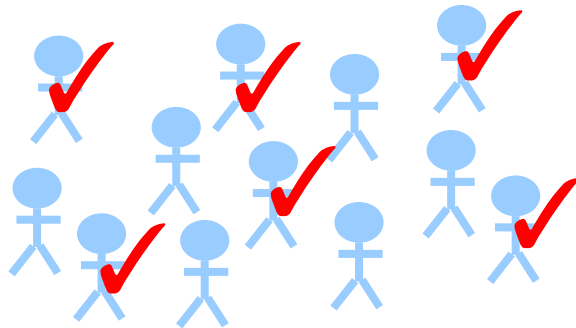
- How consistently and accurately the test detects or predicts the disease



Important Test Metrics: Sensitivity and Specificity

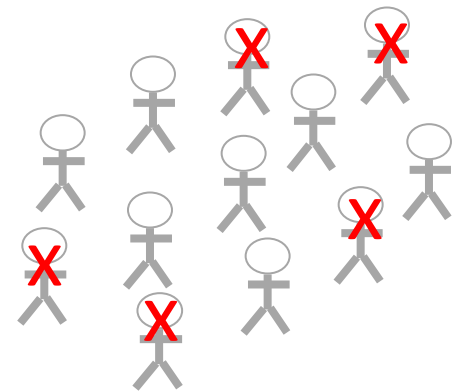
Clinical Sensitivity

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)



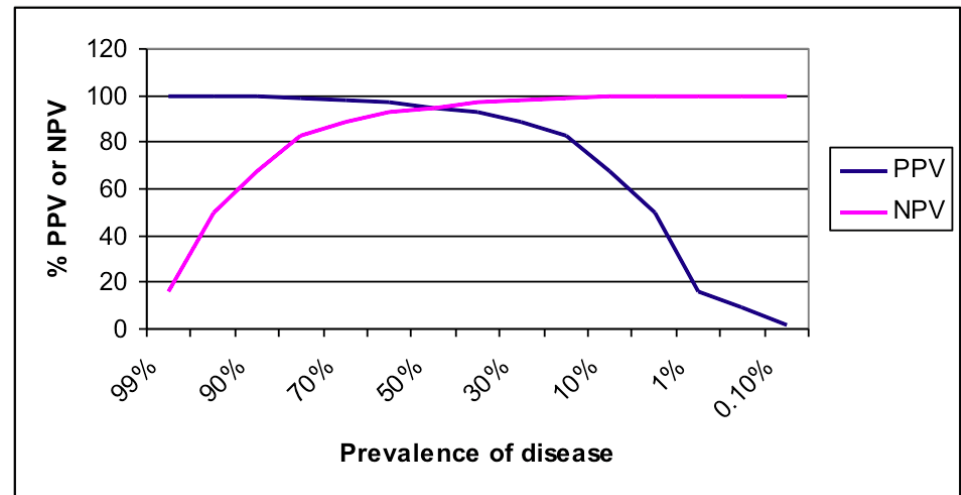
Among those with a positive test

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%



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?

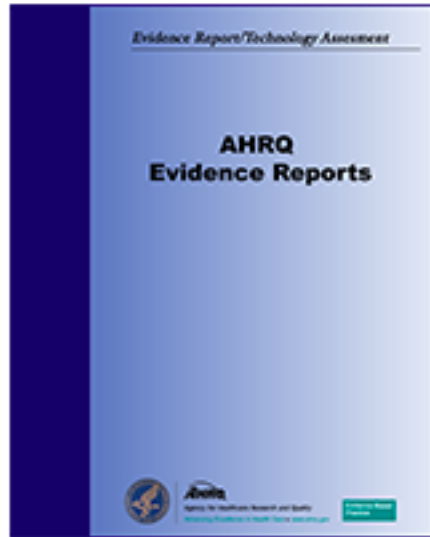
- Change in care to reduce or prevent disease, death, disability through use of efficacious treatment or intervention
- Does the test result in equivalent care, but faster results, at less cost, or less invasively?

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

Cases scenarios