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UNIVERSITY OF UTAH SCHOOL OF MEDICINE | Department of Pathology

ACCE and Genomic Testing

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Scope

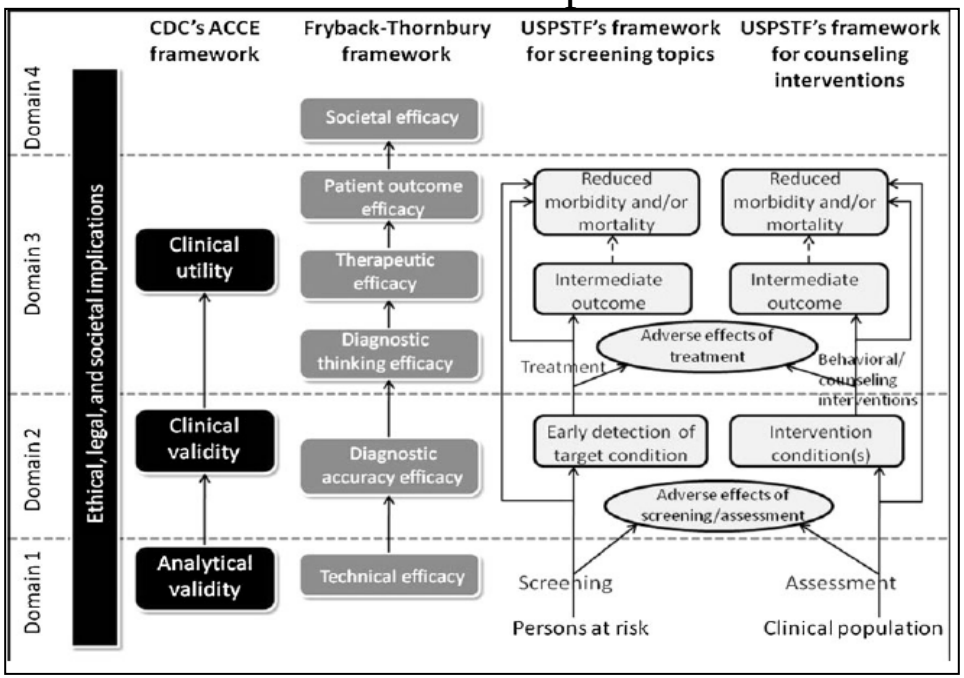
- Focus on molecular assays, attempting to fit models/definitions developed for clinical chemistry
- Disclaimer: My own opinions, considering BCBSA policy, but also looking towards the future

ACCE Framework

- **A**nalytical validity:
- **C**linical Validity
- **C**linical Utility
- **E**thical, legal, social implications

- Purposes for tests
  - Reduce morbidity/mortality
    - Provide information to manage patient/family members
    - Assist with reproductive decision-making

Framework Comparisons



Fryback GDG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991 11: 88
Matchar Chapter 1. Introduction to methods guide for medical test reviews. JGenIntmed 2012

BioMarkers vs Mutations

- Molecular Biomarkers (associated, relative risks)
  - Clinical trials to establish association
  - More likely to be proprietary
    - GWAS studies
    - Expression patterns
- Pathogenic variants (causative)
  - Mendelian disorders (germline)
  - Oncology (somatic variants)
    - Driver mutations, therapy – drug susceptibility, resistance variants

Analytical Validity

- Does the assay detect what is claimed that it detects?
  - Accuracy/ precision studies
    - Determines analytical sensitivity and specificity
  - Region interrogated defined
    - Targeted mutations
    - Gene sequencing
      - Targeted exons, Full gene sequencing (all exons, intron/exon boundaries, some known deep intronic or regulatory mutations
    - Deletion/duplication analysis
  - Performance affected by
    - Interfering substances (well known)
    - Rare, unknown variants at primer/probe sites, creating 2^{o} structure
    - Mosaicism, low mutation levels, limits of detection
  - Continuing evaluation: proficiency testing/alternative assessment

Clinical Validity

- Does the test correctly identify affected/unaffected individuals?
  - Does Analyte (gene) or Assay determine clinical validity?
    - Do mutations in a gene cause disease?
      - Linkage studies, functional analysis, case/control, cloned from known protein sequence
    - Depends on the region interrogated /defined phenotype
      - Clinical sensitivities (F8 example)
      - Not necessarily method dependent
  - PPV/NPV a measure of analytic or clinical validity or clinical utility?
    - How is it defined for single gene disorders?
      - Penetrance, mild vs severe mutations?
    - Dependent on population, indication for testing

Clinical Validity - Complications

- Inherited disease concepts
  - **Penetrance/expressivity**
  - Pleiotropy – single gene influences multiple traits
  - **Clinical Overlap:** pathogenic variants in multiple genes cause similar phenotypes
  - **Phenocop**y –phenotype overlap due to environment that resembles the effect of inherited pathogenic variants
    - Carefully define "phenotype", (BRCA Example)
  - Polygenic traits: multiple genes contribute to the phenotype
  - **Same test for diagnostic, predictive, carrier testing**
  - Interrogating regions (deep intronic, regulatory) of a gene or genes not well understood will produce more Variants of Uncertain Significance (VUS)
  - All genes on a panel to have established clinical validity
  - ClinGen project funded by NIH to examine disease categories

Modified ACCE (Fryback-Thornbury) for Clinical Utility

- Diagnostic Thinking Efficacy (Diagnosis):
  - Rule out disease (differential diagnosis)
  - Stop diagnostic odyssey: prevent additional testing
  - Appropriate follow-up/monitoring
- Therapeutic efficacy
  - Drug response
- Patient outcome efficacy
  - Patient management: improve outcomes
  - Prognostic: Determine aggressiveness of disease/treatment
  - Predictive: pre-symptomatic, familial mutations, reproductive
- Societal efficacy:
  - Proper use of medical/community resources

Reasons to Show Utility

- Aid clinicians in ordering, interpreting
- Demonstrate value of genomic medicine
- Reimbursement

Definition of Clinical Utility

- Utility for patient, clinician, payers, regulators, society
- Definition of Clinical Utility
  - Narrow: Determine drug and dose – improved outcomes demonstrated
  - For clinician/patient: diagnosis, treatment, management
    - Inherent utility of diagnostic testing
  - For patient/family: predictive testing, reproductive planning, long term care planning
  - For Payers: treatment, improved outcomes
  - For Regulators: analytical and clinical validity, expand to utility?
  - For Society: Efficient use of healthcare/community resources

Establishing Clinical Utility

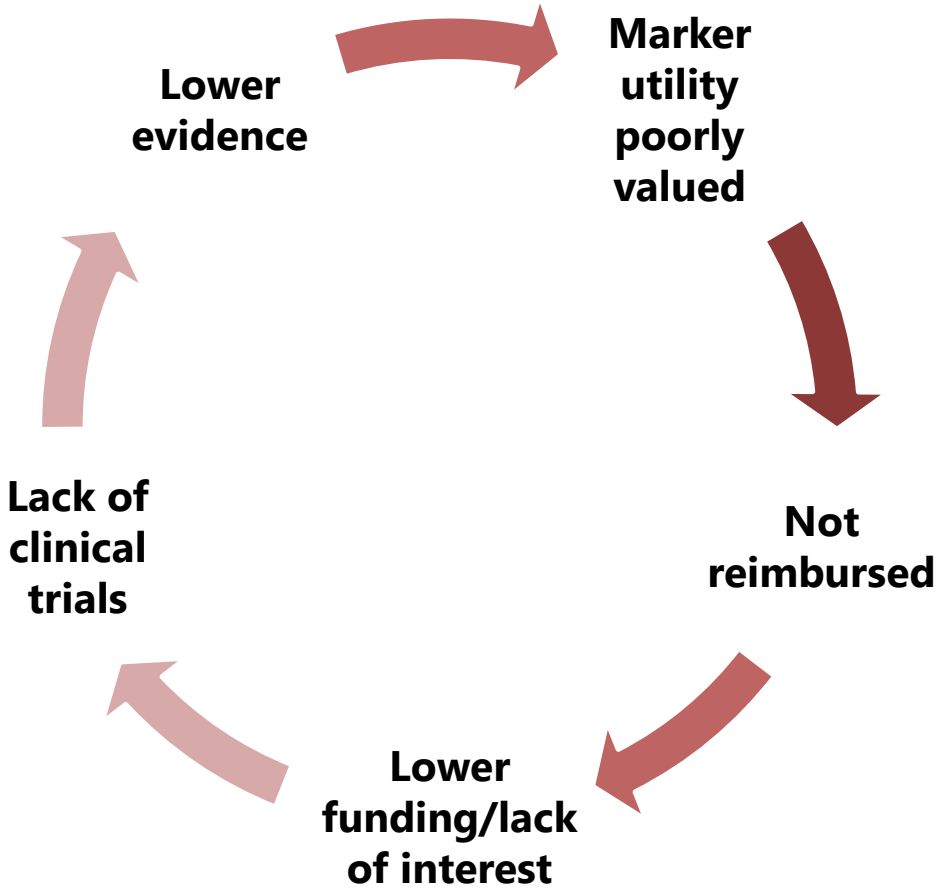
- Randomized prospective controlled studies
- Retrospective studies
  - Archived samples
- Issues with:
  - Rare inherited diseases
  - Rare mutations (somatic)
  - Long duration
  - Ethically valid?
  - Inconclusive results
    - Poorly designed
    - Insufficient numbers

EGAPP

- **E**valuation of **G**enomic **A**pplications in **P**ractice and **P**revention
- Common conclusion
  - Insufficient evidence
    - ...found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression.
    - In the absence of supporting evidence..., EGAPP discourages the use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed
- Taken as "Evidence Against"
  - SSRI studies extended to other uses
- Re-evaluate with continuing studies

http://www.egappreviews.org/

Circular Problem



Adapted from: Generating Evidence for Genomic Diagnostic Test Development: Workshop Summary: National Academy of Sciences. http://www.nap.edu/catalog.php?record_id=13133

Testing Symptomatic Individuals

- Diagnostic:
  - Explain the clinical symptoms
  - Understand disease course
- Prognostic:
  - Understand likely disease progression
  - Preventive management
- Therapeutic:
  - Determine most effective treatment/management

Asymptomatic Individual

- Predictive testing
- Family history
- Known familial mutations
  - Test affected individual for the benefit of family members
- Population screening
  - Newborn screening (State programs)

Testing Cancer Cells (Somatic)

- Diagnostic: identify genetic abnormalities causative of or resulting from disease
- Prognostic: determine aggressiveness of disease/treatment
- Predictive: determine therapy, resistance to therapy

Models

- Fully powered clinical studies not always feasible
  - Underpowered or partial data modeled for useful information?
- Require models for different scenarios? Types
  - Oncology
    - Chain of evidences (biological relationships/pathways)
    - Demonstrative usefulness in one or multiple cancer/specimen types?
    - Define “supportive” and “adequate” evidence
  - Inherited diseases
    - Approximately 4600 known medically relevant genes
      - Show each disease separately?
      - Another 20,000 in genome – how many will be shown to be medically relevant?
    - Compare to non-molecular diagnostic pathway/procedures
    - Diagnostic efficacy
- Same assay used for different purposes

Clinical Utility for Oncology

- "Driver" mutations essential for tumor progression
- "Passenger" mutations that might facilitate, but not essential for progression
- Prognosis
  - Help determine aggressiveness of treatment
- Predictive testing for therapy
  - Multiple tumor types – *BRAF* V600E
  - Histologically identical tumors- *KRAS2*

Selected Molecular Tests with Tier 1 cpt Oncology

CONDITION	DIAGNOSIS	MANAGEMENT	PROGNOSIS	PREDICTIVE
Acute myeloid leukemia	✓	✓	✓	✓
Stem cell transplant monitoring		✓	✓	✓
Chronic lymphocytic leukemia		✓	✓	✓
Chronic myelogenous leukemia	✓	✓	✓	✓
Colon Cancer		✓	✓	✓
Breast and ovarian cancer		✓	✓	✓
Non-small cell lung cancer		✓	✓	✓
Acute promyelocytic leukemia t(15;17)		✓	✓	✓
Gastrointestinal Stromal Tumors		✓	✓	✓
Melanoma		✓	✓	✓

Clinical Utility for Inherited Diseases

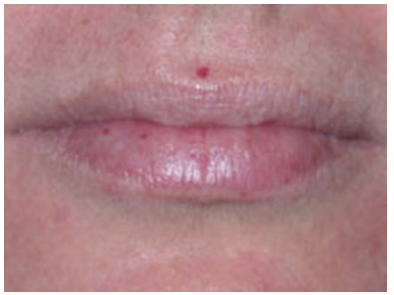
- Many are rare:
  - Approximately 4600 known human genetic disorders
  - Not feasible to show utility for each one
  - Aggregate by disease type, test method?
  - Still may have strong clinical validity/utility
    - lack cpt codes
  - Together, they are substantive
    - 100% of individuals have genetic variants that could affect drug response
    - *JAMA 286:2270, 2001*.

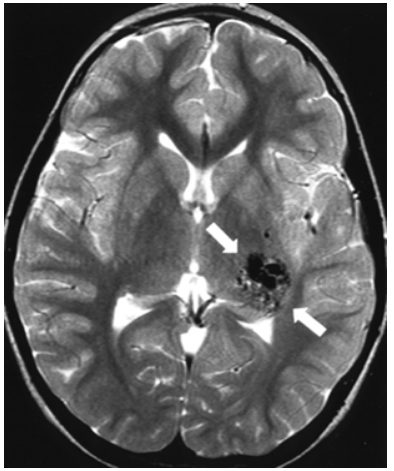
Selected Molecular Tests with Tier 1 cpt Genetics

CONDITION	DIAGNOSIS	MANAGEMENT	PROGNOSIS	PREDICTIVE
Alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease	✓	✓		✓
Alpha-1-antitrypsin deficiency	✓	✓	✓	✓
Ashkenazi Jewish:				
Bloom syndrome	✓	✓		✓
Canavan disease	✓	✓		✓
Tay-Sachs disease	✓	✓	✓	✓
Cardiomyopathies	✓		✓	✓
Cystic Fibrosis	✓			✓
Cytogenomic constitutional abnormalities (e.g. Kleinfelter, trisomy 21)	✓			✓
Familial adenomatosis polyposis (FAP)	✓		✓	✓
Fragile X	✓		✓	✓
Huntington Disease	✓		✓	✓
Hereditary breast and ovarian cancer	✓		✓	✓
Hereditary hemochromatosis	✓			Limited
Hereditary non-polyposis colorectal cancer, Lynch syndrome	✓		✓	✓
Long QT syndrome	✓		✓	✓
Marfan syndrome	✓	✓	✓	✓
Nonsyndromic hearing loss	✓	✓		✓
Rett syndrome	✓	✓		✓
Spinal Muscular Atrophy	✓	✓	✓	✓

Example: Hereditary Hemorrhagic Telangiectasia

- Appropriate use of health resources
  - Life threatening cerebral/pulmonary manifestations
    - Brain MRI with contrast:
    - Contrast echocardiogram:
      - 20% need F/U of chest CT, radiation exposure
  - Surveillance: every 5 years in affected individuals, or in unaffected individuals until approximately age 40 (unless ruled out by molecular testing)
  - Guidelines available
    - Faughnan J Med Genet 2011;48:73e87





Pictures courtesy of Whitney Wooderchak-Donahue

Single Gene vs Gene Panel

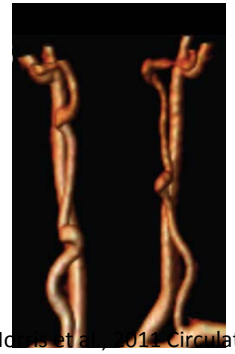
- ASHG:
  - "…, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient…."
    - Botkin JR et al. Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. ASHG 2015;97:6-21
- Use most focused assay available (as appropriate)
  - Single gene, if meets clinical criteria
  - Small gene panel improves diagnostic yield, if non-classic phenotype
  - Large gene panels - common symptoms for numerous diseases, in place of an exome?
  - Exome/genome for combination of symptoms/family history consistent with genetic etiology, but remains undiagnosed

Marfan syndrome

http://www.healthinplainenglish.com/health/cardiovascular/marfan_syndrome/index.htm

- Tall stature
- Arachnodactyly
- Hypermobile joints
- Scoliosis
- Aortic aneurysm
- Learning disability
- Positive family history, sudden death in a close relative

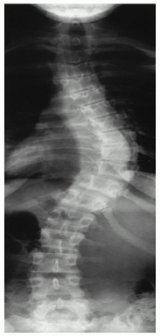
Loeys-Dietz Syndrome



Morris et al., 2011 Circulation

- Arterial tortuosity
- Hypertelorism
- Bifid (split) or broad uvula
- Aneurysms
- Scoliosis
- Positive family history, sudden death in a close relative

Ehler Danlos Syndrome Type IV



Cummings et al., 1998 JBJS

- Aneurysm
- Thin, translucent skin
- Extensive bruising
- Hypermobility
- Clubfoot
- Spontaneous pneumothorax or haemothorax
- Positive family history, sudden death in a close relative

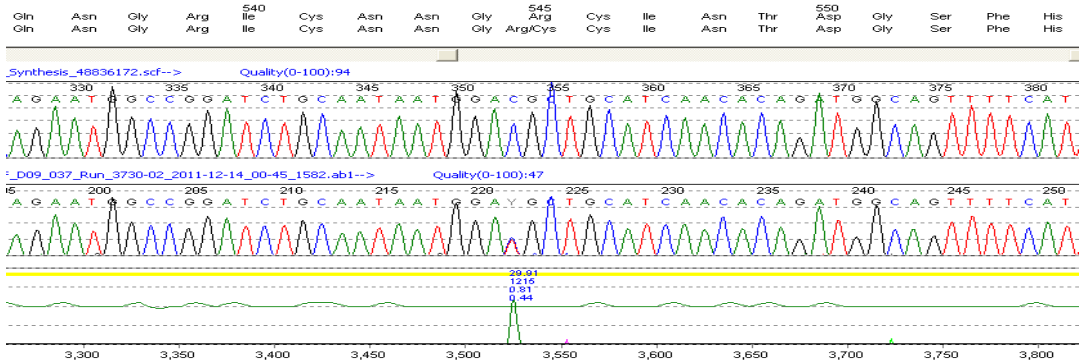
Arterial Tortuosity

- Tortuosity, elongation, and aneurysms of major arteries and the aorta
- Aortic stenosis, pulmonary artery or pulmonary valve
- Hypertelorism
- Hypermobile joints
- Arachnodactyly
- Scoliosis
- Hyperextensible skin
- Positive family history, sudden death in a close relative

Courtesy of Dr. P Bayrak-Toydemir

Marfan Single Gene Assay

- 66 exons
- Mutation positive (~10% positivity rate)
  - Includes known pathogenic and suspected pathogenic
  - 56%: diagnosis based on clinical phenotype
  - 44%: suspected diagnosis of Marfan disease
- ~4% Variants of uncertain clinical significance
  - 64%: suspected diagnosis of Marfan
  - 37%: diagnosis based on clinical phenotype



p. Arg545Cys

Clinical Sensitivity of Gene Panel

- Aortopathy panel:
  - 17 genes
  - Each has clinical validity/utility separately
  - Clinical sensitivity: approximately 20% (doubled)
    - Internal data from Dr. P Bayrak-Toydemir

Looking towards the Future: Exome Diagnostic Yield

- Overall
  - 25%
    - N Engl J Med 2013; 369:1502-1511
- Severe Intellectual Disability: 16%
    - N Engl J Med 2012; 367:1921-1929
- Neurological diseases: 64%
    - Brain. 2015 Feb;138(Pt 2):276-83.
- Retinal dystrophies: >50%
    - Am J Opthal online April 2015 doi:10.1016/j.ajo.2015.04.026

Levels of Evidence

- Multiple models needed
  - Randomized control studies
  - Retrospective
  - Adaptive clinical trials
  - Diagnostic yield
  - Observational data
  - Linkage
  - Functional studies
  - Biological relationships/pathways
  - Current care vs molecular diagnostic models
  - Professional organization practice guidelines

Thanks to:

- AMP's Committees
  - Professional Relations
    - FEND working group
  - Clinical Practice
  - Economic Affairs
- ARUP Molecular Genetics/Genomics

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