The Spectrum of Clinical Utility for Inherited Conditions

Outline

• Introduction to clinical utility (CU): Why current definitions require updating
• Clinical utility challenges for inherited conditions
• Diagnosis, Prognosis, Pre-symptomatic /Prediction testing – examples of clinical utility for each category
• Redefining clinical utility for inherited conditions
• Conclusion: A more inclusive view of clinical utility
Definitions

• Analytic Validity: Ability of a test to accurately measure the analyte of interest
• Clinical Validity: Ability of a test to accurately classify a patient with respect to diagnostic, prognostic or predictive category
  – CFTR gene variants associated with cystic fibrosis
  – Also applies to variant classification – benign or pathogenic
• Clinical Utility: value or benefit assigned to a particular outcome or state; diagnostic information that contributes to the identification of a particular condition or disease; clinical utility can encompass prognosis and monitoring response to therapy as well as diagnosis.¹

¹. CLSI definition

Defining Clinical Utility

• Succinctly: The value/benefits of a test

• Today: Narrow definition is often applied
  – Determine drug and dose with demonstration of improved outcomes

• Need: Broaden to include other stakeholders
ACCE Framework

- Analytical validity
- Clinical Validity
- Clinical Utility
- Ethical, legal, social implications

An Expanded Model of Clinical Utility
Fry-Thornbury (Medical Imaging)

- Level 1: Technical efficacy – equivalent to analytic validity
- Level 2: Diagnostic accuracy efficacy – interpretation of the test result
- Level 3: Diagnostic thinking efficacy – how results change the clinician’s thinking; value of a negative test
- Level 4: Therapeutic efficacy – therapy, management, changed treatment of patient
- Level 5: Patient outcome efficacy – impact from a patient perspective; value to patient and the patient’s family
- Level 6: Societal efficacy – value to society
FEND Recommended: Stakeholders for Clinical Utility

Stakeholders for assessing clinical utility:

- **Clinician(s)** involved in the care of the patient
- **Patient/Family**: inherited genetic disorders are a family affair; increasingly engaged in payment for testing; patient utilities include long term care, end of life, reproductive, predictive, quality of life, functional status, patient satisfaction
- **Payers**: treatment, improved outcomes
- **Regulators**: analytical and clinical validity, and increasingly utility
- **Society**: Efficient use of healthcare/community resources; increasing focus on wellness/prevention

FEND Recommended: Inclusive, Definition of Clinical Utility

Ability of a test result to provide information to the patient, physician and payer, related to the care of the patient and his/her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions.
CU Challenges for Inherited Diseases

• Many inherited disorders are rare:
  – Approximately 4,600 known human genetic disorders
  – Insufficient patients for randomized control trials
  – Insufficient published data to develop evidence-based guidelines
  – Need to rely on medical professional’s experience

• But common as a group:
  – 100% of individuals have genetic variants that could affect drug response
  – 6% of babies are born with a genetic or partially genetic birth defect
  – 1 in 20 US individuals are carriers for either cystic fibrosis or spinal muscular atrophy

1. JAMA 286:2270, 200

CU for Inherited Disease - Additional Confounders

• Few targeted therapies for genetic disorders
  – CF: only for specific mutations
  – DMD: only for specific mutations
  – Ethical dilemmas of placebo v. treatment

• Other intervention and therapy benefits can be difficult to measure
  – Psychosocial well-being
  – Long-term care planning
  – Family impact
  – Reproductive planning
  – Off-setting co-morbidities

1. JAMA 286:2270, 200
Demonstrating CU has additional complexities for inherited disease

- Penetrance / variable expressivity;
  - e.g. Neurofibromatosis
- Pleiotropy – single gene influences multiple traits or conditions;
  - e.g. cystic fibrosis
- Clinical Overlap: pathogenic variants in multiple genes cause similar phenotypes;
  - e.g. more than 40 genes associated with autosomal dominant spinocerebellar ataxia
- Phenocopy – phenotype overlap due to environment that resembles the effect of inherited pathogenic variants;
  - e.g. epilepsy
- Polygenic traits: multiple genes contribute to the phenotype;
  - e.g. autism

CU Test Considerations for Inherited Diseases

- Same test for multiple clinical situations
- For example: CFTR gene mutation analysis may be used for diagnosis or carrier screening
  - The Methods Guide for Medical Test Reviews (AHRQ) asserts that the value of a test must be evaluated in the context of use
- One test for multiple conditions
  - Expanded carrier screening panels
  - Whole exome sequencing

Context: Symptomatic Individuals

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

Context: Asymptomatic Individual

• Predictive testing – predict future disease or drug response:
  – NIPS
  – Carrier screening
  – Pharmacogenetics
  – Newborn screening (State programs)
• Pre-symptomatic testing based on family history
  – Late onset neurological disease
• Known familial mutations
  – Test affected individuals for the benefit of family members
  – Test extended family for known familial mutations
Next Generation Sequencing

Implications for Clinical Utility in Inherited Conditions

Molecular Genetic Tests are Increasing in Complexity

- Single mutation
  - Factor V Leiden, Prothrombin
- Mutation panel
  - Cystic fibrosis, Galactosemia
- Gene sequencing
  - Hemophilia, Cystic fibrosis, etc.
- Gene and partial gene deletion/duplication
  - Duchenne/Becker muscular dystrophy
- Gene Panel (sequencing and deletion duplication)
  - Aortic dysfunction, hearing loss, etc.
- Exome/Genome
Single Gene vs Gene Panel vs Exome vs Genome

- 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
  - Exome/genome for combination of symptoms/family history consistent with genetic etiology, but remains undiagnosed

Diagnostic Utility of NGS Gene Panel Assays

- Overlapping phenotypes or genetically heterogeneous disorders:
  - Marfan Syndrome: most common (1:5000)
    - FBN1 is a large gene (66 exons)
    - Expensive and time consuming to sequence by Sanger
  - Loeys-Dietz Syndrome (LDS) and Ehlers-Danlos Syndrome (EDS) type IV are clinically related to Marfan Syndrome and difficult to distinguish clinically.
- Provide accurate diagnosis and identify co-morbidities
- Useful for patients
  - Eliminate repeated or non-essential medical evaluations
  - Eliminates time and cost of sequential sequencing of genes
- Useful for family members:
  - Mutation identification to prevent at-risk family members from complications
  - Reproductive planning
Diagnostic Yield of WES

- Multiple studies indicate good diagnostic yield for inherited disorders

- Yield varies by indication for testing and pre-selection of patients
  - 30% yield in the first set of pediatric cases that underwent WES at a mid-western children's hospital\(^1\)
  - 30% yield for patients on a diagnostic odyssey\(^2\)
  - 25.2% yield for primary pediatric population analysis\(^3\)

- Yield is higher with Trio analysis
  - 37% yield for trio analysis versus 21% for proband only at a large commercial lab\(^4\)

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4. *GIM.* 10.1038/gim.2014.154

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WES/WGS and Neurodevelopmental Disorders
WES/WGS and Neurodevelopmental Disorders

• Neurodevelopmental disorders\(^1\)
  – Affect more than 3% of children
  – Attributable to single-gene mutations at more than 1000 loci

• Diagnostic yield of WES/WGS in trios
  – 73% yield in acutely ill children
  – 40% yield in children with non-acute neurodevelopmental disorders

• Cost and benefit evaluation
  – The cost of prior negative tests in the non-acute patients was $19,100 per family
  – Sequencing cost-effective up to $7640 per family
  – A change in clinical care or impression of the pathophysiology was reported in 49% of families
  – Potential for earlier diagnosis: ~6.5 years


Examples of Clinical Utility

Inherited Disease

Expertise that advances patient care through education, innovation, and advocacy.
www.amp.org
Examples of CU for Inherited Genetic Disorders

• Diagnostic Thinking Efficacy (Diagnosis):
  – Rule out disease (differential diagnosis)
  – Stop diagnostic odyssey: prevent additional testing
  – Appropriate follow-up/monitoring/Intervention

• Therapeutic efficacy
  – Drug response

• Patient outcome efficacy
  – Patient management: improve outcomes
  – Prognostic: Determine aggressiveness of treatment
  – Predictive: pre-symptomatic, familial mutations, reproductive plans

• Societal efficacy:
  – Proper use of medical/community resources

Marfan syndrome

• Rule out disease – multiple disorders with overlapping presentations

• Disorder of connective tissue with a high degree of clinical variability
• Predisposition for aortic tear and rupture
• With proper management, life expectancy approximates the general population
Marfan syndrome
- Tall stature
- Arachnodactyly
- Hypermobile joints
- Scoliosis
- Aortic aneurysm
- Learning disability
- Positive family history, sudden death in a close relative

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

Ehler Danlos syndrome Type IV
- 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

Clinical Sensitivity of Gene Panel

- Aortopathy panel:
  - 17 genes
  - Each has clinical validity/utility separately
  - Clinical sensitivity: approximately 20%¹

- Mutation in FBN1 gene:

¹ Internal data from Dr. P Bayrak-Toydemir
Marfan syndrome Management

- Stop diagnostic odyssey: prevent additional testing
- Appropriate follow-up/monitoring/Intervention
  - Management of the patient:
    - Surgical stabilization of the spine for scoliosis
    - Surgical repair of the aorta or mitral valve
    - Medications that reduce hemodynamic stress on the aortic wall.
    - Annual ophthalmologic examination; periodic echocardiography
    - Avoid certain activities such as contact sports
    - Pregnancy management for women with Marfan syndrome
  - Evaluation of relatives at risk:
    - Echocardiography in relatives suspected of having Marfan syndrome
      or in apparent unaffected members if presentation subtle in index

Neurofibromatosis, type 1

- Disorder can be very variable: can be benefit from a definitive diagnosis by MDx
- Surveillance is important

- Patient management: Improve outcomes
  - Monitor for development of plexiform neurofibromas that can obstruct or become entangled around vital organs
  - Frequent monitoring for these tumors can ensure early detection and facilitate removal before they become life-threatening.
Hearing Loss/Deafness

- Prevalence 2-3 cases per 1,000 children
- 60% is genetic; more than 100 genes
- Comorbidities vary depending on condition; e.g:
  - Usher syndrome - night blindness and tunnel vision with age
  - Brachiootorenal syndrome – renal abnormalities
- Benefits can include:
  - identifying (or allaying concerns about) comorbidities
  - planning for future medical and educational needs
  - Family: estimations of recurrence risk
  - Psychosocial: plan for the birth of a deaf or hard-of-hearing chil
  - Relieving guilt and enhancing psychological well-being

Genetic Testing to Identify the Underlying Mutation(s)

- Drug response
  - Duchenne muscular dystrophy: drugs now available for patients with an exon 51 deletion
- Other therapies
  - Fragile X syndrome: Dramatic improvements in intellectual and adaptive functioning, as well as behavioral and emotional problems, can occur if intensive behavioral treatment is begun early in the child's life: demonstrated for autism, under investigation for FXS
Hereditary Breast Cancer Testing

- **Predictive: familial mutations**
  - Testing for BRCA1 and BRCA2 gene mutations is indicated (in unaffected women) when the family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2.
  - Certain ethnic groups have increased prevalence of mutations in BRCA1/BRCA2: Ashkenazi Jewish, Norwegian, Dutch, and Icelandic.

  - Any disorder with variable presentation where detecting of the familial mutation(s) will assist with detection, management, reproductive risk planning.

Hearing Loss/Deafness

- **Prognostic: Determine aggressiveness of treatment**
  - Individuals with genes preferentially expressed in the membranous labyrinth - good cochlear implant performance
    - **GJB2, SLC26A4, OTOF, LOXHD1, KCNQ1, CDH23, MYO7A, POU3F4, MYH9, TMC1, and COCH**
  - Individuals with genes preferentially expressed in the spiral ganglion - poor cochlear implant performance.
    - **TMPRSS3, CHD7, and DDP1/TIMM8a**
  - Cochlear with a large associated healthcare cost ($24,475 surgical cost and over $1,000,000 lifetime cost per patient). (2010; Cheng et al., 2000; Mohr et al., 2000)
Clinical Utility of Carrier Screening

- **Predictive: Reproductive plans**
  - During pregnancy
    - Reduced risk – reassurance, psychological well-being
    - Increased risk – test partner, if both partners are carriers:
      - Test pregnancy
        » Positive result
          - Discontinue pregnancy
          - Plan for an affected child
        » Negative result: Reassurance
  - Pre-conception carrier detection has more options: Donor (egg, sperm); Adoption; Preimplantation genetic diagnosis (PGD)
  - Implications for other family members when test positive

Carrier Screening by NGS

Cost-effectiveness study:
- 1,000,000 simulated couples representative of the U.S.
- 14 recessive disorders that are recommended for carrier screening by professional medical societies
- Predicted 1 in 686 couples in which both partners are carriers of the same disorder
- Carrier screening by NGS reduced incidence of affected cases by 61% (compared to no carrier screening)
- Lifetime treatment costs of the 14 recessive disorders were reduced by 66%
Carrier Screening: Tay-Sachs Disease

- Inheritance: autosomal recessive
- More common in certain ethnic backgrounds
  - Ashkenazi Jewish (1 in 30)
  - French Canadian
  - Cajun American
- Clinical features:
  - Exaggerated startle response
  - Loss of ability to hold up head or sit
  - Macular cherry-red spot
  - Death by age 5

Biochemical (enzyme) testing recommended by high risk carriers (ACOG/ACMG)

Carrier screening has reduced TSD by over 90% in the ultraorthodox Jewish community

## Carrier Screening: Tay-Sachs Disease

- Estimated cost to care for an affected child: $250,000
- Enzyme testing estimated cost: $130
- DNA testing estimated cost: $225
- Full gene sequencing cost: $1,700


## Diagnosis presymptomatic: Huntington disease

- **Predictive: Presymptomatic**
- Inheritance: autosomal dominant
  - True dominant
- Incidence: 1/20,000
- Gene: *HTT* also *IT15* (*Huntingtin*)
  - Exon 1 -(CAG)n
  - Normal: ≤26
  - Premutation: 27-35
  - Full mutation: 36-121
  - Juvenile: ≥60
- Anticipation – esp. male transmission
Diagnosis presymptomatic: Huntington disease

- Clinical features:
  - Manifests in early 40s
  - Chorea
  - Memory deficits
  - Personality changes
  - Death usually occurs 10-15 years after onset
- Simple definitive test
- Treatment: limited to symptoms
- Personal utility and family planning
- Long-term care and end of life planning

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
Therapeutic Efficacy: Clopidogrel

- inhibit blood clots in coronary artery disease, peripheral artery disease, and cerebrovascular disease.
  - It is also used, along with aspirin, for the prevention of thrombosis after placement of intracoronary stent
- Metabolized by cytochrome CYP2C19 to active form
  - $2\{-1\{(2\text{-chlorophenyl})\text{-2-methoxy-2-oxoethyl}\}\text{-4-sulfanyl-3-piperidinylidene}\}\text{acetic acid}
- FDA announced that clopidogrel cannot be taken with Prilosec (omeprazole) and Nexium (esomeprazole)
  - Inhibitors of 2C19

Therapeutic Efficacy: FDA changed Clopidogrel Label

- 12 March 2010
- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

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