Clinical Utility Overview

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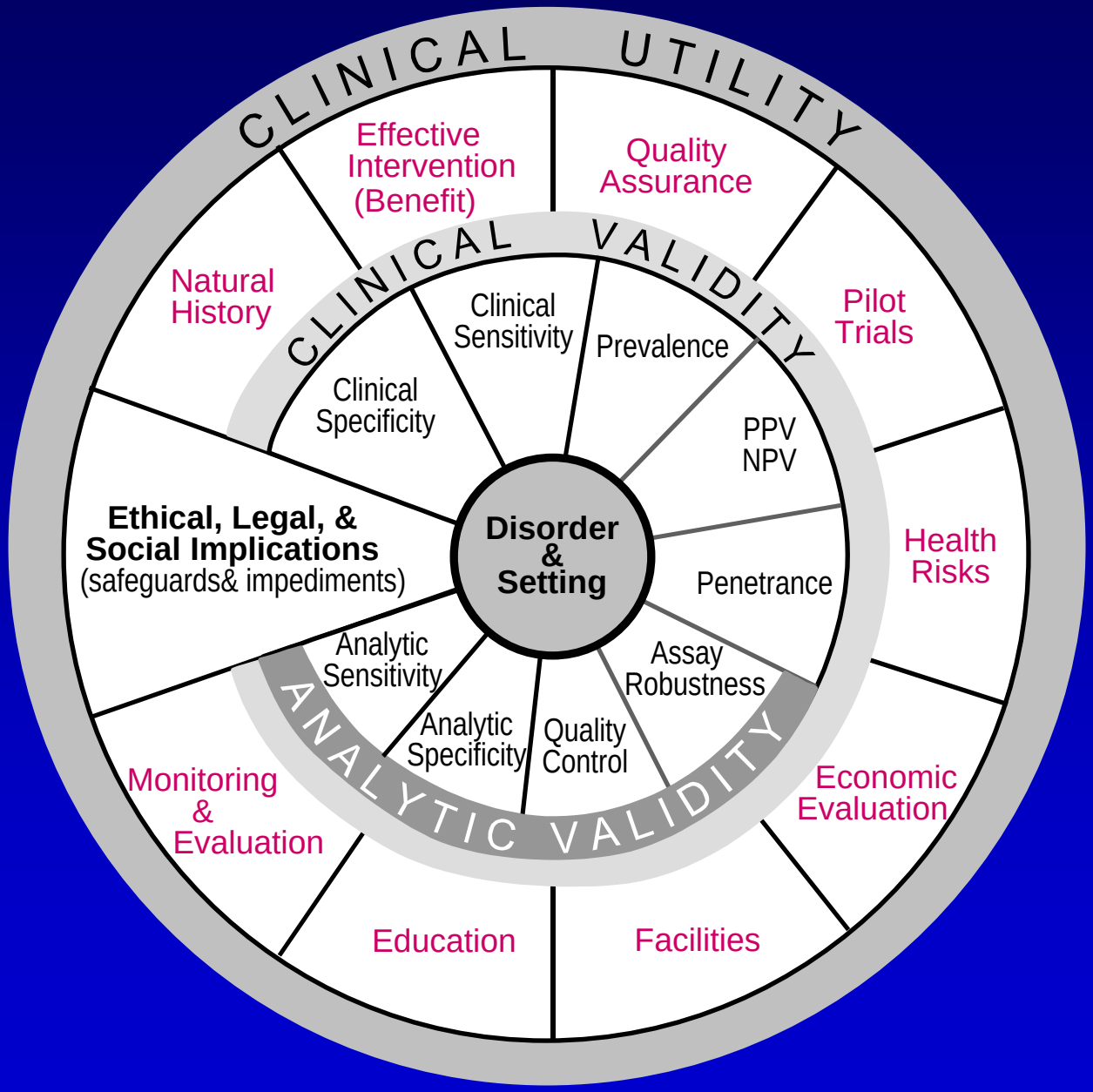
The ACCE Model System



Clinical Utility

- Defined as the elements that need to be considered by policy-makers to weigh the risks and benefits of introducing a genetic test into routine practice
- Assumes that the disorder/setting is well described, the test is analytically valid and that the clinical validity is known.
- Clinical utility presents information from diverse areas requiring wide-ranging expertise to complete

Natural History?

- The systematic account of natural phenomena
- Includes ages of onset, clinical findings, and associated morbidity / mortality

EXAMPLE: The natural history of hereditary hemochromatosis is not well described. In order for population-based testing for C282Y homozygotes to be considered, more information on natural history is required :

What proportion of C282Y homozygotes will develop liver disease, heart disease or diabetes?

What benefits could be derived from early intervention?

This ‘gap in knowledge’ has led to recommendations against population screening at this time

Impact of a Positive (or Negative) Test on Patient Care?

- The impact of a positive test might include additional testing, long-term follow-up, information provided to family members, and the offer of preventive/treatment actions
- Usually no action is taken after a negative test, but there may be social and behavioral impacts

Treatment after an initial venous thrombolytic event is the same, regardless of whether the factor V Leiden mutation is, or is not, present.

If a positive test results does not impact care, is testing warranted?

Diagnostic Tests Available?

- Usually, screening tests are followed by more expensive / invasive tests that establish a diagnosis (reducing false positives) or that determine the extent of disease

Often not true for genetic screening tests

- prenatal screening for CF is considered diagnostic
- women with a BRCA1/2 mutation have a ‘predisposition’ to breast/ovarian cancer
- individuals homozygous for C282Y might have biochemical or other tests to determine iron overload
- identifying an MLH1 mutation in a colon cancer patient is diagnostic for HNPCC

Effective Remedy, Acceptable Action or Other Measurable Benefit?

- For those with positive screening results, is an effective intervention available that has been shown to avoid morbidity / mortality associated with the disorder of interest?
- Is screening justified, if the only intervention is ‘risk-reducing’ behaviors that are recommended for everyone?

Evaluating the Health Outcomes from Newborn Screening for Cystic Fibrosis Scott Grosse

Family History as a Screening Tool for Public Health and Preventive Medicine. Paula Yoon

Quality Assurance in Place?

- Quality assurance is the program developed to ensure reproducible, high quality results in a timely fashion, which are clinically useful to patients and providers.
- A major goal is to minimize the human error that accounts for the majority of laboratory errors.
- The quality assurance program needs to address pre-analytic (consent, sample requisition), analytic (assay validation, proficiency testing) and post-analytic (reports, counseling) activities
- The quality assurance program should be subjected to qualified external oversight

Results of Pilot Trials?

- Obtain information for evidence-based policy-making:
  - rates at which health care providers offer the test
  - acceptance rates for both screening/diagnosis tests
  - the decision-making process
  - overall satisfaction with the screening process
  - analytic performance in a routine testing environment
  - verification of clinical performance
  - collection of real costs and benefits

One *CFTR* mutation (I148T) was included in the ACMG panel, but was never included in any of 13 pilot trials before being included in the ACMG panel.

Soon after large scale testing began, it was clear that I148T occurred about 100 times more often than expected. It is probably a polymorphism tightly linked to a real, but uncommon mutation.

Financial Costs of Testing? Economic Benefits of Testing?

- Computing costs requires the integration of information about analytic validity, clinical validity and several components of clinical utility with information about resource usage.
- Pilot trials provide information about uptake rates and real world costs

"Economics is not Accounting! The questions we should be asking are do we get value for our money and is this the best use of our resources."

Economic Evaluation of Screening for Hereditary Hemochromatosis Scott Grosse

Necessary Facilities?

- Facilities/personnel evaluation need to occur at three levels
  - pre-analytic - test offering, education, genetic counseling
  - analytic - number of laboratories, personnel with specialized skills
  - post-analytic - genetic counseling, clinical procedures, diagnostic testing

In 2002, the ACCE prenatal cystic fibrosis screening report estimated that the 30 to 40 labs would not be able to provide 1,000,000 tests without additional automation.

The number of tests is approaching one million. Since 2002, the number of labs participating in the ACMG / CAP MGL Survey for CF had risen from 40 to 81.

Validated Educational Materials Available?

- Effective provision of information requires timing (the 'teachable' moment) and appropriate materials
- SACGT suggests that provider materials include purpose, condition, laboratory test, analytic &clinical validity, contribution to health, and cost
- Patient information includes purpose, test performance, risks, limits and benefits, patient rights, who is tested, condition, counseling, interpretation, treatment and cost.

According to objective SAM (Suitability Assessment of Materials) criteria, the ACOG cystic fibrosis patient materials are rated 'Adequate' (reading level too high, no illustrations) and do not meet all of the content criteria.

ACOG cystic fibrosis provider materials do not include the estimates of clinical sensitivity.

Informed Consent Requirements?

- Routine ‘Genetic’ screening tests (e.g., *CF, HFE*) are unlikely to have the same level of education, counseling, and informed consent as presymptomatic tests (e.g., *BRCA1/2*)

Existing CLIA regulations do not require that labs document consent, but CLIAC recommends this

NCCLS Molecular Guidelines state that the primary care physician has responsibility

New York State regulations state that the laboratory should make a reasonable effort to document consent

Cancer Susceptibility: Investigation of a Direct-to-Consumer Marketing Campaign Melanie Myers

Methods for Long-Term Monitoring?

- Monitoring the screening programs can answer questions such as:
  - are providers and patients properly informed
  - are the expectations and pilot trial results being confirmed
  - are there problems integrating the testing into the health care delivery system?
  - is there a discernable impact on the disorder's prevalence / morbidity / mortality
  - is reimbursement a problem
  - are there ELSI that need to be addressed

Currently, no one is charged with the responsibility of collecting program performance information. Laboratories find it expensive, time-consuming and increasingly difficult (e.g., HIPAA) even though NYS, for example includes specific regulation to this effect.

Program Performance Evaluation?

- Program performance should include
  - who is responsible for collecting / evaluating data
  - what are the key measurements to be evaluated
  - how will the evaluation be funded
  - evaluation against pre-established goals

Although ACOG and ACMG have collaborated in setting prenatal cystic fibrosis screening, they do not address program evaluation.

Post-Implementation Data Collection and Monitoring Linda Bradley

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