Clinical utility

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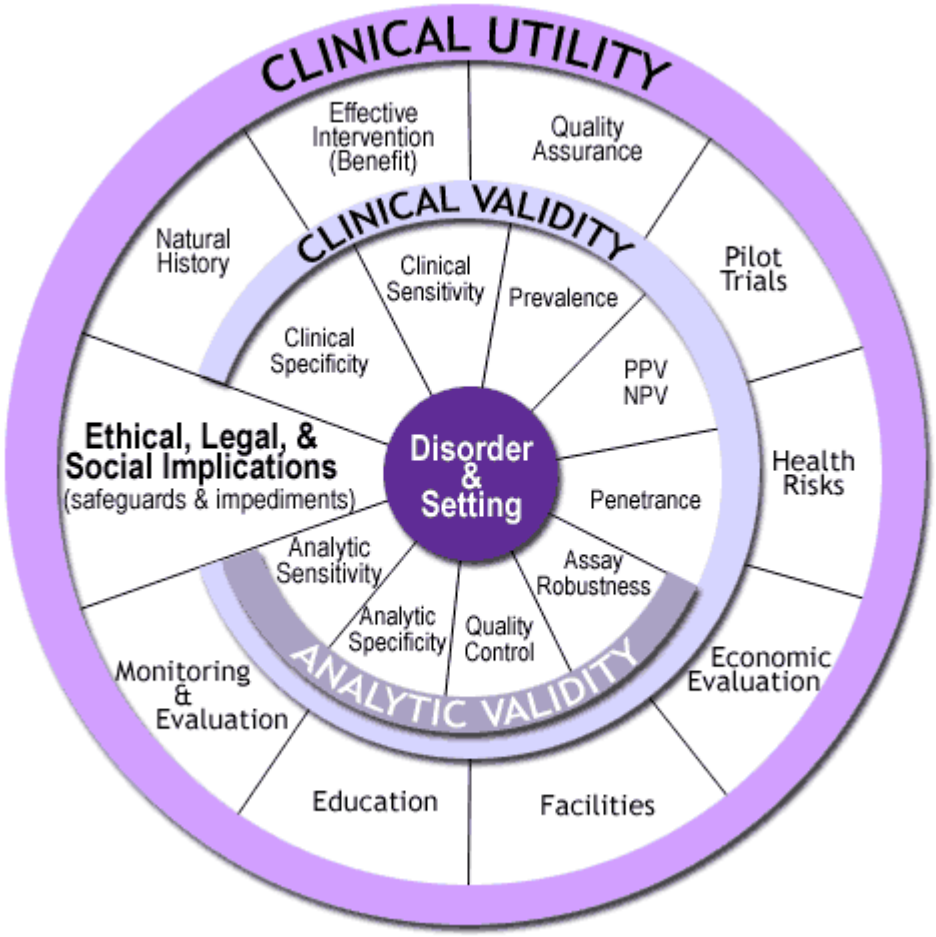
Clinical utility

- What is clinical utility?
- Should genetic tests be offered because they are available?
- Multifactorial disease testing: is it applicable?
- What about patient interests?
- Private vs public testing
- What parameters should be decided before a genetic test is offered?

- **A nalytical validity**
- **C linical validity**
- **C linical utility**
- **E thical, legal and social**

The guiding principle of the ACCE framework is that the evaluation of genetic tests should be an integrated approach including all domains.

- Clinical validity:
  - Accuracy of detection of presence or absence of phenotype/disease
- Clinical utility:
  - Likelihood of improved outcomes from use of “test”
- Evidence may not be easy to obtain for clinical utility – package of care not just an investigation



Centers for Disease Control and Prevention

In UK, national process for assessing genetic tests for NHS clinical service

A key concept –

a "genetic test" describes a test that detects

a particular genetic variant (or set of variants)

for a particular disease

in a particular population

for a particular purpose

Some of the questions used in considering genetic tests for clinical service in UK

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a) Diagnosis

Can a diagnosis be made for certain by any other method including clinical examination by an expert?
Will a molecular diagnosis remove the need to do other expensive or invasive tests?

b) Treatment

Will a specific molecular diagnosis affect treatment?

c) Prognosis and Management

Is there evidence in this disease that a specific molecular sub-type will affect prognosis and management to a significant extent? In other words - will the result significantly affect the lifestyle choices of the patient or the family?

d) Presymptomatic Diagnostic Screening

Will a positive molecular result accurately predict future disease and alter management?
Will a negative molecular result be definitive (ie: further tests do not need to be carried out)?

e) Genetic Risk Assessment

Will molecular diagnosis in the affected person reduce the needs for tests in the rest of the family?
Will molecular diagnosis resolve the mode of inheritance? (eg: HMSN)
Will molecular diagnosis provide a means of pre-natal diagnosis or carrier detection?
Will molecular diagnosis allow pre-symptomatic testing for other family members?

NHS

UK Genetic Testing Network

UKGTN Testing criteria for Infantile Spasm Syndrome X-linked

Details of patient and referrer

Name of Disease/test: Infantile Spasm Syndrome, X-linked / CDKL5 mutation search for infantile spasms / early-onset severe epilepsy in females

Referrals only will be accepted from one of the following:
(Please indicate with a tick which category refers to the referrer).

Referrer	Tick if this refers to you.
Clinical Geneticists	
Paediatric neurologists	

All criteria must be fulfilled for testing to be appropriate:

Criteria	Tick if this patient meets criteria
Criteria 1 seizures with onset in infancy (before 6 months)	
Criteria 2 marked developmental delay	
Criteria 3 female sex (the role of testing in males with similar features is being explored; potential referrals can be discussed)	
Criteria 4 Routine investigations have excluded other causes	

If the sample does not fulfil these criteria and you still feel that testing should be performed please contact ….

- Does this evaluative approach work for introducing new technologies?
- Yes – array CGH for mental retardation

Considerations in ordering a DNA test

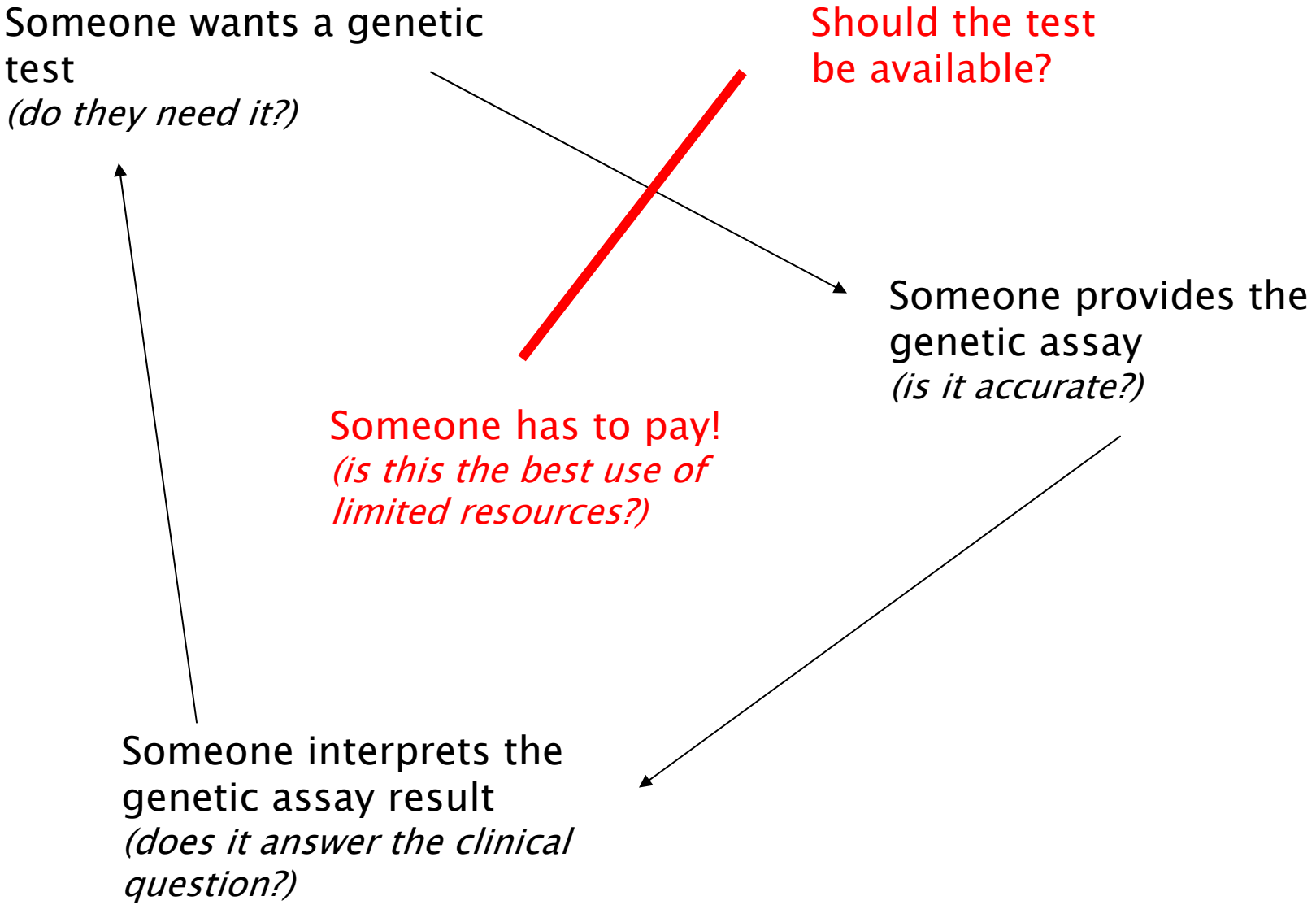
- Same test: different clinical utility in different clinical situations
    - Diagnosis
    - Treatment
    - Prognosis and Management
    - Genetic Risk assessment.
- Clinical judgment: DNA *vs* other testing
- Each test request on a case by case basis
- Priority under NHS funding for testing which directly affects clinical management

- Tests involving multiple alleles at multiple sites

- *Positive predictive value = penetrance* for a single allele – the probability of developing disease given a positive test.
- More complex with locus or allelic heterogeneity unless all alleles tested.
- Affects *clinical sensitivity* of the test and *its negative predictive value*.
- Therefore affects clinical utility particularly if offered on a whole population basis

- 5 SNPs (+ FH) and prostate cancer
- Odds ratio: 9.46

- Adding SNPs reduces prevalence of genotype
- “At risk” genotype <1% controls, <2% men with prostate cancer


Someone wants a genetic test
(do they need it?)
Should the test be available?
Someone provides the genetic assay
(is it accurate?)
Someone has to pay!
(is this the best use of limited resources?)
Someone interprets the genetic assay result
(does it answer the clinical question?)