Clinical utility

Peter Farndon
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?
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

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 (i.e.: 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? (e.g.: 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?
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).

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Tick if this refers to you.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Geneticists</td>
<td></td>
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<tr>
<td>Paediatric neurologists</td>
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All criteria must be fulfilled for testing to be appropriate:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if this patient meets criteria</th>
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<tbody>
<tr>
<td>Criteria 1 seizures with onset in infancy (before 6 months)</td>
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<tr>
<td>Criteria 2 marked developmental delay</td>
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<tr>
<td>Criteria 3 female sex (the role of testing in males with similar features is being explored, potential referrals can be discussed)</td>
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<tr>
<td>Criteria 4 Routine investigations have excluded other causes</td>
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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?)*

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?)*

Should the test be available?