Presymptomatic genetic testing for adult onset neurological disorders

Dr Elisabeth Rosser
Consultant in Clinical Genetics
NE Thames Regional Genetics Service
Great Ormond St Hospital
• Basic genetics
• Principles of presymptomatic testing
• Practicalities of presymptomatic testing
Basic genetics
Genetic information

- Carried in genes – each have 2 copies of 20,000 genes
- Genes are on 23 pairs of chromosomes
Genetic dementias

• Dementia in OMIM – 344 genes
• HD – 1 gene (but at least 5 others that may overlap clinically)
• Late onset dementia – no one gene known
• Early onset Alzheimers – 3 genes known
• Many other genes for other forms of genetic dementias
• Many of those genes may have mutations anywhere in the gene
Inheritance of genetic dementias

Most are autosomal dominant
Autosomal Dominant

• Male and females affected in equal proportions
• All children of someone with condition have 50% chance of inheriting it
• A child of someone at 50% risk has ‘25% chance’ (either 50% or 0%)
Penetrance

• Fully penetrant – everyone with that genetic change will develop the condition

• Incomplete penetrance – having the genetic changes increases the risk to that individual but it is not inevitable that they will develop condition
Genetic testing

• **Diagnostic** - Individual has signs of disease, testing may show the underlying cause

• **Carrier** - Individual has genetic change which won’t affect them but may have implications for their children

• **Presymptomatic**

• **Prenatal** - Testing in pregnancy

• **Preimplantation** – combination of IVF and genetic testing
Presymptomatic testing
Pre-symptomatic genetic testing

• Testing of an asymptomatic individual to determine whether or not the person has inherited a disease-causing mutation for a specific monogenic disorder
Presymptomatic genetic testing

• First offered in 1987 for HD - linkage analysis
• Mutation analysis since 1993 for HD
• Usually done by clinical geneticists
• National and international guidelines but some practical differences in how tests are performed
• Many thousand tests done world-wide
• Most experience with HD but now possible for a range of other disorders including a range of dementias, MND and some familial cancer syndromes
HD experience

• Before gene found 90% of people at risk said they would have a test
HD experience

• Before gene found 90% of people at risk said they would have a test

• 10-15% of people have had test – consistent over time and different countries

• Uptake different for different disorders – higher for family cancers than dementias
Principles of presymptomatic genetic testing

• decision should be voluntary
• informed consent
• individual should have access to counselling of the highest quality
• testing should be offered within specialist units
Practicalities of presymptomatic genetic testing

Can only test if:

- Genetic change known in the family (gene and mutation)

or

- Disorder has the same genetic change in (nearly) all families

This is because it is impossible to interpret a ‘negative’ (ie no mutation found) result if the mutation in the family is not known or common
Testing Process (1)

• At least 2 appointments to discuss:
  – clinical features and inheritance
  – limitations of test
    • uninformative result
    • can’t predict when or how disease will manifest
    • penetrance, especially if reduced
  – process of testing and follow up
  – support groups
Testing Process (2)

– reasons for wanting test
– is now the right time?
– practical implications of positive result
– legal, social and emotional implications of results - positive and negative
– support during test - involving partner, family, GP
– who will be told of results – especially teenage / adult children
– plans around time of results
Testing Process (3)

- Physical examination (for some conditions)
- Consent
- Blood test
- Result usually 2 weeks
- Result given in person
- Follow up - all 1 month, thereafter as needed
Crucial questions

• Is the test the right decision?
• Is now the right time?
Decision making

Relieve uncertainty
Plan future
Avoid having affected / at risk children

No point planning future
Difficulty in making relationships
Worry about possible symptoms
Regret for previous decisions
Uncertainty remains – when/how
Change in family dynamics
Lose hope
No treatment
Presymptomatic genetic testing - Exclusions

- Coercion
- 3rd party requests
- Psychiatric illness
- Life events
- Children
Presymptomatic testing - Potential problems after test

- Suicide
- Depression
- Difficulty in adjusting to result
- Difficulty making relationships
- Worrying that it has started
- Regret
- Family breakdown
Presymptomatic testing - Potential problems after test

- Suicide
- Depression
- Difficulty in adjusting to result
- Difficulty making relationships
- Worrying that it has started
- Regret
- Family breakdown
Presymptomatic genetic testing - Alternatives

• Test not the only option
• Appointment for information
• Regular appointments and examinations / assessments
• Support groups
• Anxiety often increases around age that parent became symptomatic
Presymptomatic genetic testing - individuals at 25% risk

- Right of individual to have test overrides right of intervening at-risk parent
- Try to get applicant and parent to agree way forward
- In practice many applicants have no contact with parent or would not tell them the result
Clinician’s perspective

• 50% of people will get ‘good’ result
• Some people will have more problems than others (whatever the result)
• Use experience to identify those at higher risk of problems eg recent diagnosis in family, young age, affected siblings, previous mental health issues, results not as expected – take those more slowly
• Do no harm
Genetic testing

• Provides information – but information limited
• May alter management / treatment
• In most cases can’t give preventative treatment
• May allow reproductive choice
• May be a burden
Use with caution