Presymptomatic Testing for Huntington’s Disease

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Presenter Disclosures

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The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose or list
Symptomatic or Diagnostic Genetic Testing

• Genetic testing on someone who has symptoms of the disease in question
  – To clarify the genetic diagnosis
    • Disease subtypes
    • Predictive information about onset/course
  – To provide genetic information for other family members
  – For HD - to confirm clinical diagnosis
  – For possible changes to medical management (less common for neurological/dementia conditions)
Presymptomatic Genetic Testing

- If genetic testing has been done in a family for the disease and a mutation has been identified:
  - For at-risk individuals (no symptoms)
  - Genetic test should be available and adequately interpreted (or if not, full disclosure as to why not)
  - Patient wants information (empowerment)
  - Patient has reasonable likelihood of carrying the altered susceptibility gene
  - Curable vs. incurable genetic disease
  - Personal decision
Presymptomatic testing

• For a known mutation...
• Cannot prevent or predict for many adult onset conditions:
  – Onset of symptoms, age of onset, or disease progression
• Lots of factors to consider:
  – Psychological manifestations
  – Incomplete penetrance (ex: ALS)
  – No preventative treatment
  – Results could influence medical management
Timeline | Benchmarks in Huntington disease research


- George Huntington's paper is published.
- Mendel's work is rediscovered.
- Restriction fragment length polymorphisms (RFLPs) are first described.
- The HD gene is mapped to the short arm of chromosome 4 (REF: 15).
- The HD gene is isolated and a CAG repeat mutation is identified.
- The first mouse model for HD is described.
- Transcriptional dysregulation is first proposed.
- The first phase-III clinical trials for HD are published.

- Hoffman describes juvenile Huntington disease (HD).
- Purnell cites HD as autosomal dominant.
- The Venezuela project is initiated.
- Clone contigs of the candidate region are established.
- The Working Group on HD of the WFN/IHA publishes guidelines on counseling for predictive testing.
- Aggregates are described in mouse and patient brains.
- An inducible mouse model of HD is described.
- The first high-throughput screen is published.

WFN/IHA, World Federation of Neurology and the International Huntington Association.
Testing Process

- Test is done on a blood sample
- Must be ordered by a physician
- Genetic counseling is involved in the process
- Laboratory extracts DNA from white blood cells
- Test ‘counts’ the number of repeats in each gene copy
- Final result report gives two numbers

- > 18 years old
- Pretest counseling
  - Information about HD, current level of risk, options for testing, limitations/accuracy of test, outcomes
  - Ensure testing is desired for the patient and not to benefit other family members
  - Address impact of all results: +/-/uninformative: on future medical status, family members, career/financial planning, family planning
  - Advised to institute waiting period

- Neurologic examination
- Psychological/psychiatric screening
  - Provide those at risk with frequently needed services and identify people at risk for suicide
- Results disclosure
  - Must be done in person
- Post test follow-up
  - Monitor effects of result and provide support
A Multi-Step Process

- Provide post-test counseling and follow-up
- Disclose results
- Select and offer test
- Provide informed consent
- Provide pretest counseling
- Identify at-risk patients
Presymptomatic Testing Discussion

- What is your understanding of the condition?
- What do you think your risk of inheriting it is?
- What do you think your risk is for developing symptoms in the future?
- How is your <relative> handling the idea that he carries the gene mutation?
  - Has it changed the way he lives his life at all?
  - Do you feel that you treat him differently since you learned he has the condition?
  - Do other people know?
- What will you do with the information if you are found to have the mutation?
- If you are negative, how would it change your view? Survivor guilt for not inheriting the mutation, change the way you figured your life would turn out?
Presymptomatic Testing Discussion

• How do you see a positive result changing your life?
  – Would it affect whether you would be in a relationship with someone, get married, have children, save money, travel, job/career path taken?
  – If any would be affected, what if symptoms never get appear?
  – Would you look back on your life and have regrets for not doing these things figuring you would get symptoms?
  – If no children - donor egg? PGD?
  – If not saving money not expecting to live to old age, and then you do, then what?

• Timing of testing
  – Stressful time in life? (middle of divorce or break-up of relationship) at work, school, or good time in life such as right before or after marriage, or around the holidays?
Presymptomatic Testing Discussion

• Disclosure of results
  – Who will you tell about the results?
  – Will you tell them the same day you are given the results?
  – What will you do the day you get the results? Will you go back to work or take the day off?

• Relationships
  – Is your spouse supportive of your decision to be tested?
  – Is someone pushing you to have testing?
  – Have you discussed decisions affecting you as a couple that you might make differently depending on your test results?
  – Have you been fearful of your spouse leaving you when you show symptoms of the condition?
Presymptomatic Testing Discussion

• Children
  – Do you children know about the condition?
  – Will you tell them the results?
• Extended family
  – How do you perceive the results of the testing will impact your interactions with your siblings?
  – If you do not have the mutation, you may experience survivor guilt. How do you think you will cope with these feelings?
  – Who do you plan on telling the results to in your family?
• Friends
  – Are there people in your life that you feel you can talk to about your decision to be tested?
Reasons to Decline Presymptomatic Testing

• Psychiatric consequences from positive result
  – “I want to get tested but only if it’s negative.”
• Employment or insurance discrimination
  – GINA
• Interpersonal relationships/family dynamics
• People at 25% risk
Early predictive testing studies

• Schoenfeld et al. 1984 and Stern & Eldridge 1975 surveyed those at risk for HD and 73% and 77%, respectively said they would use a safe and reliable predictive test if one were available.
• In 1987 (after announcement of linkage analysis), five surveys were performed which suggested the number of at-risk individuals intending to take test was still high, 59-79%.
• Quaid et al (1989). n=349 at 50% risk. Only 65 (18%) contacted them for testing. 33 completed educational component: 21 requested testing; 12 did not request testing
• Lower than expected uptake of test of 5-24% for studies in the 1990s-early 2000
Behaviors of those undergoing predictive testing

• Those who have had prior exposure to severe HD and at 50% risk (compared to 25%) have longer waiting period to testing, but once were tested, were more likely to receive the results.
• Those who didn’t complete testing: younger, less experience with severe disease, at <25% risk, knew about risk for shorter time period
Brendan
Bridget
QUESTIONS?