Neurogenetics – Genetic Testing and Ethical Issues

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Objectives

1) To recognize the ethical issues to consider when obtaining consent for genetic testing

2) To develop an appreciation of molecular techniques utilized for diagnosis of neurogenetic disorders
Disclosure

• I have no conflicts of interest to disclose
Outline

• Ethical issues to consider when consenting patients for genetic testing
  ➢ Predictive testing
  ➢ Exome sequencing

• Establishing a diagnostic strategy (2 clinical scenarios)
  ➢ Selecting a lab / test
  ➢ Assessing the validity of a test
  ➢ Limitations/Challenges of different diagnostic strategies
Evolution of Genetic Tests
Ethical Issues – eg. HD

- Symptomatic vs predictive testing
- Depressive symptoms
- Timing of results
- Coping with results
- Effect on relationships
- Support
- Family planning
- Career decisions
- Insurance
Family History of HD
## Common Issues after Results

### Positive
- Unexpected reaction
- Meaning of repeat size
- Family planning issues
- When will I have HD?
- Telling family/friends
- Planning for the future

### Negative
- Unexpected reaction
- Survivor guilt
- Regrets over life choices
- Telling family/friends
- Planning for the future
Nothing is predictable in predictive testing

- Patient reactions may be unexpected
- Molecular testing results may be difficult to interpret
- The disease course itself may be unpredictable
Considerations in Reproductive Planning

- What will I do with the information?
- HD 30 years from now...
- Religious, ethical, moral issues
- Impact of my disease on my future children
- Timing of having family
- Choosing the best reproductive option for us
# Reproductive Options

<table>
<thead>
<tr>
<th>Choice grid</th>
<th>Prenatal Diagnosis</th>
<th>No Prenatal Diagnosis</th>
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</thead>
</table>
| Assisted Reproduction        | ICSI with IVF (PND to confirm ICSI result still recommended) | Sperm/egg donor  
                           |                                                           | Embryo adoption  
                           |                                                           | Adoption            |
| Natural Reproduction         | CVS  
                           | Amniocentesis                                            | Have a baby                                      |
Whole exome sequencing (WES) in clinical practice

80-85% of known disease causing variants (estimated)
Parent/patient motivation for WES

• Are these different from traditional genetic testing?
  – What is the diagnosis?
  – How did this happen?
  – Is there cure/treatment?
  – Is there prognostic information?
  – Who else is affected/at risk?

• Greater expectation for a diagnosis by WES among HCPs

• Promise of diagnosis can overshadow possible limitations of the test
Impact of WES/WGS in clinical practice

- WES: 25% dx rate 75% remain undiagnosed
- WGS: 30-35% dx rate 65-70% remain undiagnosed
  - Microarray 10-15% dx rate
Tailor information

Allow time for decision making

Manage expectations

Put test in context

Informed consent

Utility
Informed consent – an evolving concept

• Long-standing core competency for geneticists and genetic counselors

• Traditional informed consent has included specific details: contracting, procedures, possible risks (consanguinity, non-paternity), family hx assessment

• WES/WGS consent has expanded to include:
  – Focused genetic test result for a particular indication
  – Secondary/incidental findings - wide range of medically actionable and non-actionable conditions with varied penetrance, age of onset and symptoms
  – Possibility of reanalysis and updated or new variant results over time

• Uncertainty about type of results that will be returned, when and how they will be returned
  – Challenges specific to secondary findings
Elements of informed consent for exome sequencing

What is Exome sequencing

Types of results possible

Additional findings

Turn-around time & other logistics

Potential benefits & limitations

30-45 minutes

- Don’t expect all families to want WES
- Leave time to answer questions
- Parents may need more time to discuss
  - Who to test
  - Which results to return
- Insurance

Valid consent is...
- voluntary
- informed
- with capacity to make a decision
Types of possible results

- Primary diagnostic findings
- Secondary/additional findings
- Carrier status

- 25-35%
- 3-5%

Pathogenic, likely pathogenic, VUS, likely benign, benign
Secondary findings:
Lab and institution-dependent
ACMG 3-5%
Expanded list 13-14%
Typically includes risk of “treatable” disease but can also include neurodegenerative conditions
ACMG reportable list

- Hereditary breast and ovarian cancer
- Li–Fraumeni syndrome
- Peutz–Jeghers syndrome
- Lynch syndrome
- Familial adenomatous polyposis
- MYH-associated polyposis
- Juvenile polyposis
- Von Hippel–Lindau syndrome
- Multiple endocrine neoplasia type 1
- Multiple endocrine neoplasia type 2
- Familial medullary thyroid cancer
- PTEN hamartoma tumor syndrome
- Retinoblastoma
- Hereditary paraganglioma–pheochromocytoma syndrome
- Tuberous sclerosis complex
- WT1-related Wilms tumor
- Neurofibromatosis type 2
- Ehlers–Danlos syndrome, vascular type
- Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections
- Hypertrophic cardiomyopathy, dilated cardiomyopathy
- Catecholaminergic polymorphic ventricular tachycardia
- Arrhythmogenic right-ventricular cardiomyopathy
- Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome
- Familial hypercholesterolemia
- Wilson disease
- Ornithine transcarbamylase deficiency
- Malignant hyperthermia susceptibility
Challenges specific to disclosure of exome results

• Rare and ultra-rare diseases
  – Lack of communities of experts and management guidelines

• Atypical presentation of well-understood Mendelian disorders
  – “Affected”, “at risk”, “unaffected”
  – More counselling time and resources
  – Difficult to predict presentation in patient and other affected family members

• Partial diagnoses
  – Unexpected
  – Analysis is more difficult
Challenges – cont.

- Managing expectations
  - Not all pathogenic variants can be identified
  - No diagnostic variants = not genetic?
  - Who is being sequenced?
  - TAT, familial testing

- Different families have different responses to same result
  - Difficult to anticipate due to wide range of possible results

- Secondary/incidental/additional findings
  - Which ones and for whom?
  - Medical management in the context of more acute concerns
  - Lack of personal and family hx may affect choices
  - Time and resources required for interpretation, cascade testing and management
Establishing a diagnostic strategy

Choosing a multigene panel

• More genes is **not** always better!

  • More Variants of Uncertain Significance (VUSs)
  • Labs may include syndromic and nonsyndromic conditions associated with a disorder, and disorders where a given feature (e.g. epilepsy) is classically one of many others.

  – Targeted panels that include fewer genes may provide more robust analysis and coverage of the genes included, as they focus solely on the genes of interest
Establishing a diagnostic strategy
Selecting a test / lab

- Genetic Test Registry
- GeneTests
  - www.Genetests.org
- Orphanet
  - https://www.orpha.net/
Establishing a diagnostic strategy

What follow-up testing should I consider?

• Segregation studies
  • For an **Autosomal Recessive (AR)** condition:  
    – Del/dup vs parental testing
  • For an **Autosomal Dominant (AD)** or **X-Linked (XL)** condition:
    – Familial testing of relevant family member(s)
    – Interpretation of the inheritance of the variant can help clarify the likelihood of pathogenicity

• **Consider non genetic tests to interpret variants**
  – follow up studies are sometimes more informative than testing more genes
Reasons for Negative Exome Results

• A pathogenic variant may exist that the testing was not able to detect (e.g. an intronic variant)

• A pathogenic variant is present in a gene that was not tested or not yet discovered

• Clinical presentation may not be due to an underlying genetic cause (less likely)
Teaching Points

• Pre-test counselling is essential when considering genetic testing
• Communication between clinicians and the laboratory is crucial for optimal clinical utilization of genetic testing
• Genetic testing is not a substitute for careful clinical evaluation
Resources for Clinicians

- OMIM
- GeneReviews
- Genetic Testing Registry
- Orphanet
- Neurogenetics clinic at the Hospital for Sick Children