Return of genetic information in all its complexities: an erstwhile clinician’s view

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Disclosure Statement

I have no relevant personal/professional/financial relationship(s) with respect to this educational activity.
Comments for consideration and approach

- The nature of the result
- Importance of planning
- Adults
- Pediatrics
Don’t ask, do tell

From “Don’t ask, Don’t tell” to:

1. Decide what you need to “tell”  
   BUT: Say what you are going to tell
2. Decide what you don’t need to tell, but could
3. Decide what you will not tell  
   AND: Clearly describe both
Focus

- Not results from clinically-indicated tests
- Genomic results generated in the setting of research
- Reliability of results
  - Laboratory (and technology)
    - CLIA\textsuperscript{1} approved laboratory
      - CLIA\textsuperscript{1} v HIPAA\textsuperscript{2} regulations
      - Even in CLIA-approved laboratory, can have research result
    - Research laboratory: a continuum of reliability
  - Validity of result
- First, consider valid and reliable results

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

In 2013, ACMG published a minimum list of genes to be reported as incidental or secondary findings.

“The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality.”

Secondary Findings Maintenance Working Group (SFWG) established

Updated: 59 medically actionable genes recommended for return in clinical genomic sequencing
ACMG process for addition as actionable gene

- Semiquantitative metric, including
  - severity of disease/nature of the health threat
  - likelihood of the disease/health threat materializing (i.e., penetrance)
  - efficacy of specific intervention(s)
  - overall strength of the current knowledge base about the gene/condition.
  - acceptability of the proposed intervention based on its risks and benefits.

- SFWG review, ACMG Board approved

- ACMG: not to report unless part of ACMG 59
- And if part of ACMG 59, advice of mandatory return now revised to favor offering patients an opt-out of the analysis and return.
Paternalistic or Patient-Centric?

- Case: Huntington's Disease
  - fatal genetic disorder, triplet (CAD) repeat
  - triad of motor, cognitive, and psychiatric symptoms
  - symptoms appear ~30 to 50 years old
  - everyone who has the mutated HD gene will develop the disease
  - not medically actionable and not on the ACMG 59

- Of personal utility even if not medical utility
- As a physician, fiduciary relationship with a responsibility to help the patient and not only about medically actionable issues

https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/
And no international consensus

- ACMG: not to report unless part of ACMG 59
- CCMG (Canada): competent adult patients be offered the choice of whether or not they want to receive information regarding unsolicited findings prior to the test
- European Society of Human Genetics: “Patients' claims to a right not to know do not automatically over-ride professional responsibilities when the patient's own health or that of his or her close relatives are at stake.” That is, right not to know is not absolute (the right to provision of information supersedes this)
- Duty to inform may, in some cases, override the right not to know, even if the patient has previously declined receiving this information

When does the duty to inform override the RNTK?
Paternalistic or Patient-Centric

- Autosomal dominant
- HD allele size:
  - > 40 CAG repeats: 100% specific
  - < 26 CAG repeats never associated with HD phenotype
  - 27-35 CAG repeats rare and possibly mutable
  - 36-39 CAG repeats reported in both clinical affected and unaffected individuals

You make the call

And what do you say?
Great uncertainty:

- Results may not be reliable
  
  - Analytical Validity: the analytical specificity and sensitivity, accuracy and precision of the test. In the context of genetic testing, how well the test predicts the presence or absence of a particular gene or genetic change.
  
  - Interpretation of the result may not be known or is evolving

- Continuum, in research laboratories, of analytic validity
- Continuum, with genomic findings, of interpretation

<table>
<thead>
<tr>
<th></th>
<th>Validated</th>
<th>Not validated</th>
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<tbody>
<tr>
<td>Clinically actionable</td>
<td>Strong</td>
<td>Possible</td>
</tr>
<tr>
<td>Not clinically actionable</td>
<td>Possible</td>
<td>Weak</td>
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Assume research result has analytic validity

- Nevertheless complex: continuum of certainly of interpretation and of significance
- Planning in advance of the trial (or test) essential
  - Prospectively planned
  - Prospectively described
  - Informed consent clear
  - Need not determine at enrollment whether to know or not to know
  - Dynamic consent
- No duty to hunt. One and done. (although this too is evolving).
Important to communicate to participant

- Limitations of technology and of current study (and no intention to hunt)
- Limitations of current knowledge
- What will and will not be identified and communicated
- Whether and what participant can choose to or chose not to receive
  - If PI determines that some information will be obtained that is essential to communicate, then participant has the option not to participate if desires not to know
  - Not to participate should be a respected position
- Resources for information, further medical interventions, support should be considered in advance, if available
Potential reasons not to return individual results

- Potential to bias the study (relates to timing of return as well);
- Significance of the research result unknown;
- Known insignificance of the result;
- Lack of analytic validity
- Lack of medical actionability or personal utility of results.
- Administrative and/or financial burden too great and participant agrees to the conditions of the trial
  - (but beware of critical, clinically-actionable results)
A few true cases

- Non-paternity in familial genetic testing for determining donor in transplantation
- Research project to identify, by liquid biopsy, early cancer
- Newborn genetic sequencing
  - BRCA1
  - HD
Special issues in pediatrics

- To tell or not to tell
  - Parental decision and “right not to know”
  - Researcher (not parental) determination of RNTK and “Right to an Open Future”
  - Implications for biological parents and siblings
Questions?
Thank You!