Contrasting Clinician and Patient Perspectives on Variant Disclosure

Robert C. Green, MD, MPH, Director G2P - Translational Genomics & Health Outcomes
Associate Director, Partners Center for Personalized Genetic Medicine
Division of Genetics, Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Grants:</td>
<td>NIH</td>
</tr>
<tr>
<td>Speaking (compensated):</td>
<td>none</td>
</tr>
<tr>
<td>Advisory (compensated):</td>
<td>none</td>
</tr>
<tr>
<td>Advisory (uncompensated):</td>
<td>none</td>
</tr>
<tr>
<td>Research collaboration:</td>
<td>Pathway Genomics, 23andMe</td>
</tr>
<tr>
<td>Equity:</td>
<td>none</td>
</tr>
</tbody>
</table>
Key Collaborators at BWH / HMS

Heidi Rehm, Mike Murray, Scott Weiss, Sandy Aronson

Zak Kohane, Ingrid Holm, David Margulies

Kricket Seidman

George Church
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Incidental Findings in Genomic Medicine
What to look for? What to disclose?
Various Variants…

- Rare alleles causing Mendelian disease
- Few examples of high-effect common variants influencing common disease
- Low-frequency variants with intermediate effect
- Common variants implicated in common disease by GWA

McCarthy et al., *Nat Rev Gen*, 2008
Manolio et al., *Nature*, 2009
What do Patients/Consumers Want Disclosed?

It varies.....
1) Open access data
2) Examination to assure informed consent
4) Genome sequence and epigenome
5) Multi-traits
6) Cells available
7) IRB approval for 100,000 volunteers

16,000 volunteers
74 countries
2,418 scored 100% on entrance exam
1,056 medical records online
500 genomes in the pipeline
DTC Testing: A Consumer Driven Experiment in Incidental Findings

Invention of the Year

1. The Retail DNA Test
By Anita Hamilton

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin,
Impact of Personal Genomics Testing Study

“P-Gen”

Registration
2-10 days

Receipt of kit by customer

3+ days

Sample received by company

3-8 weeks

Test results available

Survey 1

Survey 2
(1-2 weeks)

Variable

Survey 3
(6 months)

New information made available

R01 HG005092 (Green-Roberts)
Can we even define “Clinical Actionability”? 

Probably not.....
Many Shades of “Actionable”

Narrow definition of clinical utility
* The information may help participants to treat or avoid disease

Broader definition of clinical utility
* The information may motivate participants to change their behavior
* Participants could learn more about the condition or gene
* Participants could monitor research and progress
* Participants could participate in other related research
* The information could be useful to participants in the future

Personal utility
* The knowledge could empower participants
* The information could give participants a feeling of control
* The information could benefit the participant’s family
* The information could make participants feel respected by the researchers
* The information could make participants feel more involved in the study
* The information could help participants plan or live more fully

Other reasons
* Results belong to the participant
* Participants want to know what the researchers learn about them
* Results are compensation for participating

Personal Communication, David Kaufman, 2011
There are six possible combinations of the APOE forms. These combinations are called genotype.
REVEAL Study: Persons Agreeing to Participate

Systematically Ascertained: 24%
Self Referred: 64%

Roberts et al. Genetics in Medicine, 2004
REVEAL Study: Would Do Risk Assessment Again…

### Table 3. Amount Willing to Pay for Alzheimer’s Disease Risk Assessment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Willing to pay &gt;$100 for testing (n=106)</th>
<th>Willing to pay ≤$100 for testing (n=150)</th>
<th>Adjusted (multivariable)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>56.9 ± 10.4</td>
<td>58.5 ± 10.5</td>
<td>1.011 (0.980, 1.043) 0.4864</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>68 (64.2%)</td>
<td>112 (74.7%)</td>
<td>0.702 (0.361, 1.363) 0.2956</td>
</tr>
<tr>
<td>Race (% African American)</td>
<td>13 (12.3%)</td>
<td>35 (23.3%)</td>
<td>0.959 (0.424, 2.170) 0.9203</td>
</tr>
<tr>
<td>Mean education, in years</td>
<td>16.6 ± 2.4</td>
<td>15.8 ± 2.5</td>
<td>1.076 (0.949, 1.219) 0.2533</td>
</tr>
<tr>
<td>Income (% ≥$50K)</td>
<td>89 (88.1%)</td>
<td>90 (64.8%)</td>
<td>2.969 (1.367, 6.450) 0.0060</td>
</tr>
<tr>
<td>APOE status (% ε4 positive)</td>
<td>47 (44.3%)</td>
<td>56 (37.3%)</td>
<td>1.119 (0.819, 1.524) 0.5709</td>
</tr>
<tr>
<td>Baseline Self-Perceived Risk</td>
<td>53.0 ± 22.3</td>
<td>49.1 ± 22.6</td>
<td>1.004 (0.990, 1.018) 0.5567</td>
</tr>
<tr>
<td>Increased desire to know future AD status</td>
<td>91 (86.7%)</td>
<td>98 (65.3%)</td>
<td>3.224 (1.516, 6.856) 0.0024</td>
</tr>
<tr>
<td>Increased concern about developing AD someday</td>
<td>75 (71.4%)</td>
<td>89 (59.3%)</td>
<td>1.324 (0.681, 2.575) 0.4079</td>
</tr>
</tbody>
</table>

\(^a\) Odds ratio (95% CI)
REVEAL Study: Health Behavior Changes at 1 Year (Vitamins, Exercise, Medications)

APOE ε4+  APOE ε4-  Control

REVEAL Study: Nutritional Changes and Supplement Use at 6 Weeks

Vernarelli et al., Am J Clin Nutr, 2010
REVEAL Study: Insurance Changes 1 Year After APOE Disclosure

Zick et al., *Health Affairs*, 2005
The REVEAL Study:
“I know what you told me, but this is what I think…”

Linnenbringer et al., *Genetics in Medicine*, 2010
**REVEAL Study: “Pros” of Disclosure**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Mean at baseline</th>
<th>Mean at 12 months</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>To seek information on preventative measures</td>
<td>4.26</td>
<td>3.75</td>
<td>-0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The need to make arrangements for my long-term care</td>
<td>3.67</td>
<td>3.31</td>
<td>-0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>To know more about my risk in case better treatments become available</td>
<td>4.26</td>
<td>3.91</td>
<td>-0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The desire to contribute to research on AD</td>
<td>4.11</td>
<td>3.86</td>
<td>-0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The desire to start doing things sooner than I had planned to</td>
<td>3.37</td>
<td>3.18</td>
<td>-0.19</td>
<td>0.018</td>
</tr>
<tr>
<td>To give information about my children’s possible risk of AD</td>
<td>3.01</td>
<td>2.82</td>
<td>-0.19</td>
<td>0.020</td>
</tr>
<tr>
<td>The need to arrange my personal affairs</td>
<td>3.69</td>
<td>3.56</td>
<td>-0.13</td>
<td>0.097</td>
</tr>
<tr>
<td>To confirm the feeling that I might already be developing AD</td>
<td>2.32</td>
<td>2.19</td>
<td>-0.13</td>
<td>0.099</td>
</tr>
<tr>
<td>To put my mind at ease if I found out I was not at risk for AD</td>
<td>3.53</td>
<td>3.45</td>
<td>-0.08</td>
<td>0.346</td>
</tr>
<tr>
<td>The need to prepare my family for my possible illness</td>
<td>3.43</td>
<td>3.38</td>
<td>-0.05</td>
<td>0.513</td>
</tr>
<tr>
<td>Curiosity</td>
<td>3.17</td>
<td>3.26</td>
<td>0.09</td>
<td>0.256</td>
</tr>
</tbody>
</table>

### REVEAL Study: “Cons” of Disclosure

<table>
<thead>
<tr>
<th>Cons</th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no way to cure or prevent AD</td>
<td>1.93</td>
<td>2.18</td>
<td>.25</td>
<td>0.007</td>
</tr>
<tr>
<td>The test does not give me a definite answer about whether I might get AD or not</td>
<td>2.13</td>
<td>2.30</td>
<td>.17</td>
<td>0.017</td>
</tr>
<tr>
<td>It could make me worry about my children’s risk of getting AD</td>
<td>1.81</td>
<td>1.79</td>
<td>-0.02</td>
<td>0.727</td>
</tr>
<tr>
<td>My family does not think it is a good idea for me</td>
<td>1.25</td>
<td>1.20</td>
<td>-0.05</td>
<td>0.350</td>
</tr>
<tr>
<td>It would be too upsetting to find out I’m at risk for AD</td>
<td>1.96</td>
<td>1.88</td>
<td>-0.08</td>
<td>0.289</td>
</tr>
<tr>
<td>The test results might upset my loved ones</td>
<td>2.10</td>
<td>1.97</td>
<td>-0.13</td>
<td>0.075</td>
</tr>
<tr>
<td>The test procedure would be too burdensome</td>
<td>1.37</td>
<td>1.24</td>
<td>-0.13</td>
<td>0.011</td>
</tr>
</tbody>
</table>

**Discrimination fears**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The results could affect my employment</td>
<td>1.60</td>
<td>1.85</td>
<td>0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>The results could affect my health insurance</td>
<td>2.37</td>
<td>2.48</td>
<td>0.11</td>
<td>0.184</td>
</tr>
<tr>
<td>The results could change how people look at or act toward me</td>
<td>1.78</td>
<td>1.88</td>
<td>0.10</td>
<td>0.153</td>
</tr>
</tbody>
</table>

REVEAL Study: Telling Others Your Results

- Family Member: 64%
- Spouse or Significant Other: 51%
- Friends: 35%
- Health Professional: 12%

REVEAL III

Phone Interview
(n = 344)

Randomization
(n = 291)

(n = 153)
Educational Brochure
Informed Consent
Q&A, Blood Draw

(n = 138)
Educational Brochure
Informed Consent
Q&A, Blood Draw

AD Risk Assessment Disclosure
(n = 138)

AD Risk Assessment + CVD Risk Disclosure
(n = 119)

Follow Up at:
Six Weeks
Six Months
Twelve Months
REVEAL Study: Rational Response to Incidental Findings - Exercise Change (6 weeks)

Green et al., presented at ACMG, 2011
Return of Incidental Genetic Findings
Children’s Hospital “Gene Partnership”

Kohane et al, Science, 2007
RC1 HG005491 (Holm), R01 HG006615 (Holm)
## Preference Setting

### Survey of 1126 Parents in a DNA Biobank

<table>
<thead>
<tr>
<th>Want ALL research results.</th>
<th>Parents' results</th>
<th>Childs' results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>78.6%</td>
<td>84.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Want to CHOOSE research results to receive</th>
<th>Parents' results</th>
<th>Childs' results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21.4%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Parent enrolling self</th>
<th>Parent enrolling child</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORE LIKELY</td>
<td>61.3%</td>
<td>68.8%</td>
</tr>
<tr>
<td>NO DIFFERENCE</td>
<td>35.0%</td>
<td>27.6%</td>
</tr>
<tr>
<td>LESS LIKELY</td>
<td>3.7%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>
Preference Setting
Survey of 1126 Parents in a DNA Biobank

Want all results

- Said "yes" to ALL categories of results
- Said "yes" to all DISEASE-related categories of results
- Well established
- NOT well established
- A LOT more likely to get disease
- A LITTLE more likely to get disease
- Treatable/preventable
- NOT treatable/preventable
- Severe (fatal or disabling)
- NOT severe (fatal or disabling)
- CHILDHOOD onset
- ADULT onset

Want to choose results

- 100.00%
- 50.00%
- 0.00%

RC1 HG005492 (Holm)
Survey of 1126 Parents in a DNA Biobank
The “Diagnostic Misconception”

Green et al, ASHG, 2011
RC1 HG005492 (Holm)
What do Clinicians Want Disclosed?

It varies.....
What do Clinicians Want Disclosed?

- Robert C. Green, MD, MPH
- Jonathan S. Berg, MD, PhD
- Leslie Biesecker, MD
- David Dimmock, MD
- James P. Evans, MD, PhD
- Wayne W. Grody, MD, PhD
- Madhuri Hegde, PhD
- Bruce R. Korf, MD, PhD
- Ian Krantz, PhD
- David Miller, MD, PhD
- Mike Murray, MD
- Robert Nussbaum, MD, PhD
- Sharon Plon, MD
- Heidi L. Rehm, PhD, FACMG
- Howard J. Jacob, PhD

...top 88 conditions from GeneTests, based on frequency ordered, adding breast/ovarian cancer, chromosomal abnormalities, CNVs and repeat expansions.... which variants discovered in the course of clinical whole genome sequencing should be returned to the referring physician...

Green et al., in submission
Concordance for Incidental Return of a Known Pathogenic Mutation (max = 99 conditions)

Green et al., in submission
Conditions/genes selected by all contributors for incidental return in adults

- Hereditary Breast and Ovarian Cancer
- Li-Fraumeni Syndrome
- Lynch Syndrome
- APC-Associated Polyposis
- MUTYH Polyposis
- Von Hippel-Lindau*
- MEN 1
- MEN 2
- PTEN Hamartoma Tumor Syndrome*
- Retinoblastoma*

- Gaucher Disease
- Phenylketonuria
- Galactosemia
- Homocystinuria
- Tyrosinemia Type 1
- Pompe Disease
- Wilson Disease
- GSD Type 1a
- Fabry Disease
- Familial Hypercholesterolemia
- Romano-Ward (Long QT)*

* Asterisk indicates condition/gene selected by all contributors for incidental return in children

Green et al., in submission
Concordance Patterns for Incidental Return – Adult Patient

* out of a total of 72 conditions/genes (excluding repeat expansion, chromosomal, and deletion conditions)

Green et al., in submission
Concordance Patterns for Incidental Return – Patient < 18

* out of a total of 72 conditions/genes (excluding repeat expansion, chromosomal, and deletion conditions)

Green et al., in submission