The Personal Utility of Non-Actionable Genetic Information: The REVEAL Study

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RO1 HG 02213 (The REVEAL Study)
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# Financial Disclosures in the Past 5 Years

<table>
<thead>
<tr>
<th>Research Grants:</th>
<th>NIH, Myriad, Elan, Lilly</th>
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<tr>
<td>Speaking (compensated*):</td>
<td>Pfizer, Forest</td>
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<tr>
<td>Advisory (compensated*):</td>
<td>Schering-Plough, GlaxoSmithKline</td>
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<tr>
<td>Advisory (uncompensated):</td>
<td>23andMe, Navigenics, Myriad</td>
</tr>
<tr>
<td>Equity:</td>
<td>None</td>
</tr>
</tbody>
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*less than $5,000/year
Cumulative Risk of Dementia in First-Degree Relatives of Patients with AD

![Graph showing cumulative risk of dementia over age for relatives and spouses of white probands.](image-url)

Green et al., *JAMA*, 2002
Established Gene Markers for Alzheimer’s Disease

**Deterministic Mutations:**
- Amyloid Precursor Protein (APP)
- Presenilin-1 (PS-1)
- Presenilin-2 (PS-2)

**Susceptibility Polymorphism:**
- Apolipoprotein E (APOE)
There are six possible combinations of the APOE forms. These combinations are called genotype.
Why we should NOT do risk assessment for Alzheimer’s Disease with APOE…

• Psychological harm or discrimination may occur

• No treatment available to prevent AD

• Five (!) consensus conference recommendations
Why we should **EXPLORE** risk assessment for Alzheimer’s Disease using APOE…

- Define at-risk persons to enrich prevention trials
- Explore responsive or vulnerable sub-populations
- Respond to self-interested family members
- Develop clinical paradigms for the use of susceptibility markers in common disorders
The ACCE Model for Genetic Testing

- **Analytic Validity**
- **Clinical Validity**
- **Clinical Utility**
- **ELSI**
APOE and Alzheimer’s Disease
A Unique Model for Exploring
Clinical Utility and ELSI

• Excellent Analytic Validity
• Well documented Clinical Validity
• No treatments and (no market pressures!)
• Terrifying disease
• People still want to know their risk
The REVEAL Study

Is risk information beneficial or toxic?

Empirically measure the benefits and risks of genetic susceptibility testing…
How can we clearly communicate risk information based on genetics?
Estimating risk curves for first-degree relatives of patients with Alzheimer’s disease: The REVEAL study

L. Adrienne Cupples, PhD; Lindsay A. Farrer, PhD; A. Dessa Sadovnick, PhD; Norman Relkin, MD, PhD; Peter Whitehouse, MD, PhD; and Robert C. Green, MD, MPH
Risk of AD by APOE in Women

Cuples et al., Genetics in Medicine, 2004
Who wants to know?
Persons Agreeing to Participate in REVEAL

Systematically Ascertained: 24%
Self Referred: 64%

Roberts et al. Genetics in Medicine, 2004
Why do people want to know?
## Reasons Associated with Enrollment

<table>
<thead>
<tr>
<th>Strongly endorsed reason for seeking testing as predictor of study enrollment</th>
<th>Odds ratio</th>
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</thead>
<tbody>
<tr>
<td>To prepare family for AD</td>
<td>3.33</td>
</tr>
<tr>
<td>To arrange personal affairs</td>
<td>2.62</td>
</tr>
<tr>
<td>To arrange long-term care</td>
<td>2.52</td>
</tr>
<tr>
<td>To learn information for family planning</td>
<td>2.25</td>
</tr>
</tbody>
</table>

*Women strongly endorsed more reasons for seeking testing than men, \( p = .01 \)*

Roberts et al., *Alz Dis Rel Dementias*, 2003
REVEAL Questions

What happens to them when they find out?
REVEAL I: Randomized Clinical Trial

301 Participated in Informational Phone Interview

218 Participated in Education Session

183 Participated in Private Counseling and Blood Draw

162 Randomized

51 Assigned to Receive Risk Assessment Without Genotype Disclosure

111 Assigned to Receive Risk Assessment With Genotype Disclosure

Follow Up at:
 Six Weeks
 Six Months
 Twelve Months

Green et al., NEJM, in press
REVEAL I Study: Mean Anxiety Scale Score

Green et al., *NEJM*, in press
REVEAL I Study: Adjusted Impact of Event Scores

Green et al., *NEJM*, in press
Post-Disclosure Change to Depression Symptoms: 1 year

Green et al., *NEJM*, in press
Are they satisfied with the information?
Would Do Risk Assessment Again…

Green et al., NEJM, in press
Can they recall the information?
Recall of Disclosure Information
APOE Status (positive or negative)

Eckert et al., *Genet Med*, 2006
Recall of Risk Information: Lifetime Risk Figures within 5 Points

Eckert et al., *Genet Med*, 2006
REVEAL Questions

Does the information change their behavior (insurance purchasing)?
Insurance Changes 1 Year After APOE Disclosure

- **Health**: Control (5%), E4 Negative (0%), E4 Positive (15%)
- **Life**: Control (5%), E4 Negative (10%), E4 Positive (5%)
- **Disability**: Control (5%), E4 Negative (10%), E4 Positive (5%)
- **LTC**: Control (5%), E4 Negative (20%), E4 Positive (25%)

Does the information change their behavior (health behavior)?
Health Behavior Changes at 1 Year (Vitamins, Exercise, Medications)

APOE ε4+

APOE ε4-

Control

Health Behavior Changes at 6 Weeks (Nutrition and Supplements)

Vernarelli et al., in submission
How should we address ethnicity?
Risk of Dementia Among White and African American Relat Patients With Alzheimer

Differences Between African Americans and Whites in Their Perceptions of Alzheimer Disease

Yvonne G. Hipps, M.D., M.P.H.
Division of Genetic Medicine, Mayo Clinic, Rochester, Minn.
The Mayo Clinic Foundation, Rochester, Minn.

Comparision of Alzheimer’s disease risk factors in white and African American families

D.L. Bachman, MD; R.C. Green, MD, MPH; K.S. Benke, AR; L.A. Capples, PhD; and L.A. Farrer, PhD; for the MIRAGE Study Group

Alzheimer Disease and Associated Disorders
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Incorporating ethnicity into genetic risk assessment for Alzheimer’s disease: the REVEAL study experience

Kurt D. Christensen, MPH1, J. Scott Roberts, PhD1, Charmaine D. M. Royal, PhD2, Grace-Ann Fasyae, ScM, CGC3, Thomas Obisesan, MD, L. Adrienne Capples, PhD4,6, Peter J. Whitehouse, MD, PhD5,6, Melissa Barber Butson, ScM, CGC5, Erin Linnenbringer, MS, CGC6, Norman R. Relkin, MD, PhD6,7, Lindsay Farrer, PhD6,8,9, Robert Cook-Deegan, MD,7, and Robert C. Green, MD, MPH6,9

Differences Between African Americans and Whites in Their Attitudes Toward Genetic Testing for Alzheimer’s Disease

YVONNE G. HIPPS,1 J. SCOTT ROBERTS,2 LINDSAY A. FARRER,3 and ROBERT C. GREEN3
Are preparatory genetic counseling protocols necessary for safe disclosure?
REVEAL II

352 Randomized

120 Assigned to Extended Protocol
- 112 Completed Pre-education Questionnaire
- 106 Participated in in-person Education Session
- 101 Participated in Individual Counseling Session, Medical History & Blood Draw
- 93 Received Risk Assessment/APOE disclosure

232 Assigned to Condensed Protocol
- 217 Completed Pre-education Questionnaire & Medical History
- 210 Completed Education Brochure Sent by Mail
- 198 Participated in Question and Answer Session, Blood Draw
- 187 Received Risk Assessment/APOE disclosure

Follow-up:
- 6 Weeks
- 6 Months
- 12 Months
Stay Tuned for These Analyses from REVEAL

• What happens with telephone disclosure or on-line disclosure with minimal GC involvement?

• What happens when non-family members seek and receive genetic risk information

• What happens when participants receive risk information about a disease they did not expect to learn about (pleiotropy)?

• What happens when you combine genotype information and phenotype information (early memory loss) to offer individual more imminent risk information?
REVEAL Study Collaborators

Boston University
Robert C. Green, MD, MPH (PI)
Susan Hiraki, MS, CGC
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Kurt Christensen, MPH
Wendy Uhlmann, MD, CGC
Thank you!

Questions?