Empirical Trials and Incidental Findings on the Path to Genomic Medicine

Robert C. Green, MD, MPH

Director, genomes2people
Research Program in Translational Genomics and Health Outcomes

Associate Director for Research,
Partners Center for Personalized Genetic Medicine
Division of Genetics, Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
Disclosures

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R01 HG006615 (Holm)   R21 HG00603 (Wang)
R01 CA154517 (Petersen/Koenig/Wolf)
The Path to Genomic Medicine
The Danger of Disclosure
Is Genetic Information Harmful?
APOE Genotypes in the General Population

- 3/3 (67%)
- 3/4 (20%)
- 2/3 (8%)
- 2/2 (1%)
- 4/4 (2%)
The REVEAL Study
NHGRI-funded (2000-2013)
REVEAL I

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, 2009
Mean Anxiety Scale Scores After Disclosure

Green et al., NEJM, 2009
Would Do Risk Assessment Again…

Green et al., NEJM, 2009
Willingness to Pay for AD Genetic Testing (reported after having obtained it)

Health Behavior Changes at 1 Year (Vitamins, Exercise, Medications)

Health Behavior Changes at 6 Weeks (Nutrition and Supplements)

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

Zick et al., Health Affairs, 2005
Taylor et al. Health Affairs, 2010
Dosing the Disclosure: Education and Counseling
352 Randomized

120 Assigned to **Extended Protocol**
- 112 Completed Pre-education Questionnaire
- 106 Participated in In-Person Education Session
- 101 Participated in Individual Counseling, 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 at:
- Six Weeks
- Six Months
- Twelve Months

REVEAL II

G2P
GENOMES to People
Condensed vs Extended Disclosure

Test-Related Distress among ε4-

Test-Related Distress among ε4+

Mean difference from EP on IES
CP worse \(-\)
CP better \(\uparrow\)

Protocol
- CP-GC
- CP-MD

Prespecified cutoff for non-inferiority
No difference

6 Weeks 6 Months 12 Months
Diluting the Disclosure: Adding an Incidental Result
During a genetic risk assessment for Alzheimer’s disease... what happens when one learns that APOE is also associated with heart disease?
REVEAL III

Phone Interview
\((n = 344)\)

Randomization
\((n = 291)\)

- \((n = 153)\) 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

AD Risk Assessment Disclosure
\((n = 138)\)

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

ɛ4 status: OR=2.5, p=0.010
AD+CVD Info: OR=2.2, p=0.039

- AD-Only Risk Info
- AD & CVD Risk Info

ɛ4-
8%
16%

ɛ4+
19%
33%
Test-Related Distress

Interaction: $\beta = -4.1$, $p = 0.03$

- **AD-Only Risk Info**
  - $\varepsilon 4-$: 2.4
  - $\varepsilon 4+$: 7.3

- **AD & CVD Risk Info**
  - $\varepsilon 4-$: 3.1
  - $\varepsilon 4+$: 4
Direct-to-Consumer Genetic Testing
A Naturalistic Experiment in Incidental Findings
Impact of Personal Genomics Testing Study (PGen Study)

(Green-Roberts, PIs)

23andMe

PATHWAY GENOMICS

G2P

NHGRI R01 HG005092
### Healthcare Utilization After DTC Testing

<table>
<thead>
<tr>
<th>Self-report at 6 months</th>
<th>Number (%) of N = 986</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussed results w/ PCP</td>
<td>256 (27.7%)</td>
</tr>
<tr>
<td>Discussed results w/ genetics specialist</td>
<td>25 (2.7%)</td>
</tr>
<tr>
<td>Results prompted me to make appt w/ medical professional</td>
<td></td>
</tr>
<tr>
<td>Already made appt</td>
<td>105 (10.8%)</td>
</tr>
<tr>
<td>Plan to make appt</td>
<td>100 (10.3%)</td>
</tr>
<tr>
<td>Had tests, exams, or procedures due to genetic info</td>
<td>104 (10.7%)</td>
</tr>
<tr>
<td>Genetic info will influence how I manage my health in future</td>
<td></td>
</tr>
<tr>
<td>Somewhat or Strongly Agree</td>
<td>567 (59.2%)</td>
</tr>
</tbody>
</table>
### Predictors of having Tests, Exams, or Procedures due to DTC Results

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (p-value) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaking w/doctor about tests, exams, or procedures due to genetic results</td>
<td>41.1 (p&lt;.001)</td>
</tr>
<tr>
<td>Perception of ‘many’ or ‘all’ results showing above average risk</td>
<td>9.0 (p=.032)</td>
</tr>
<tr>
<td>Better self-reported general health</td>
<td>2.4 (p&lt;.001)</td>
</tr>
<tr>
<td>Higher baseline anxiety</td>
<td>2.4 (p=.002)</td>
</tr>
<tr>
<td>Pre-test intention to discuss results w/PCP</td>
<td>1.8 (p=.008)</td>
</tr>
<tr>
<td>Pre-test intention to discuss results w/other medical professional</td>
<td>1.8 (p=.010)</td>
</tr>
</tbody>
</table>

* Controlling for Age, Sex, Race, Education, and Income
Using Whole Genome Sequencing In the Practice of Medicine
The MedSeq Project (U01 HG006500)
A Center for Sequencing Exploratory Research

Teams from:
- Brigham and Women’s Hospital/Harvard Medical School
- Baylor College of Medicine
- Duke University School of Medicine

Exploring the integration of whole genome sequencing into the practice of clinical medicine.
Exploring WGS in 2 Contexts

Patients with Disease

10 cardiologists & 100 of their patients with familial hypertrophic cardiomyopathy

Healthy Patients

10 primary care physicians & 100 of their generally healthy adult patients
Collect data on physician experience and clinical flow: Disclosure preferences, use of GRC, decision-making

Physician disclosure to patients
Decides on further work-up or treatment plan

Collect physician, patient, health and economic outcome variables
Baseline (prior to disclosure), 6 weeks, and 6 months post-disclosure

Medical Record Review

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**General Genomic Medicine**
Recruit and enroll 10 primary care physicians and 100 of their healthy middle-aged patients
Randomize physicians and patients

**Standard of Care & Family History**
Patients treated according to current standard of care guidelines and risk assessment based on family history

**Standard of Care, Family History & WGS**
Physician receives clinically meaningful information derived from WGS, with a specific cardiovascular focus

**Standard of Care, HCM Genetic Testing & Family History**
Patients treated according to current standard of care guidelines, genetic information by disease-specific testing and family history

**Standard of Care, HCM Genetic Testing, Family History & WGS**
Physician receives disease-specific interrogation of HCM-associated variants and non-HCM clinically meaningful risk variant interpretation derived from WGS

**Disease-Specific Genomic Medicine**
Recruit and enroll 10 cardiologists and 100 of their patients presenting with familial hypertrophic cardiomyopathy (HCM)
Randomize physicians and patients

**Genetics Resource Center**
Optional source for physician to seek guidance in interpretation.
SAMPLE – DO NOT USE FOR CLINICAL CARE

Name: John Doe
DOB: 01/23/45
Sex: Male
Race: Caucasian
Accession ID: 0123456789
Specimen: Blood, Peripheral
Received: 01/23/45
Family #: F12345
Referring physician: John Smith, M.D.
Referring facility: DoubleHelixHospital

GENERAL GENOME REPORT

RESULT SUMMARY
Sequencing of this individual’s genome was performed and covered 98.2% of all positions at 8X or higher, resulting in over 3.6 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details provided on subsequent pages.

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED
This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual’s lifetime.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1. Episodic ataxia type II (Autosomal Dominant)</td>
<td>Poor coordination and balance</td>
<td>CACNA1A p.Arg2156GlyfsX32</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>A2. Hypertrophic cardiomyopathy (Autosomal Dominant)</td>
<td>Progressive heart failure</td>
<td>MYBPC3 p.Thr146AsnfsX7</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>
# MedSeq General Genome Report

## B. CARRIER RISK: 3 VARIANTS IDENTIFIED
This test identified carrier status for 3 autosomal recessive disorder(s).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
<th>Carrier Phenotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1. Cystic fibrosis</td>
<td>Chronic lung and digestive disease</td>
<td>CFTR c.1585-1G&gt;A</td>
<td>Pathogenic</td>
<td>Infertility (moderate evidence)</td>
</tr>
<tr>
<td>B3. Usher syndrome type II</td>
<td>Hearing loss and retinitis pigmentosa</td>
<td>USH2Ap.Gly204ArgfsX12</td>
<td>Pathogenic</td>
<td>None reported</td>
</tr>
</tbody>
</table>

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual’s children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.

## C. PHARMACOGENOMIC ASSOCIATIONS
This test identified the following variant(s) associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require confirmation of the result.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1. Warfarin</td>
<td>Increased dose requirement</td>
</tr>
<tr>
<td>C2. Clopidogrel</td>
<td>Increased risk of bleeding, Decreased risk of cardiovascular events</td>
</tr>
<tr>
<td>C3. Digoxin</td>
<td>Chance of increased metabolism and decreased serum concentration of digoxin</td>
</tr>
<tr>
<td>C4. Hydrochlorothiazide</td>
<td>Increased effect on blood pressure</td>
</tr>
<tr>
<td>C5. Metformin</td>
<td>Increased effect on glucose tolerance</td>
</tr>
</tbody>
</table>
The Problem of Incidental Findings
What are Expert Choices for Return of Secondary (Incidental) Findings in Clinical Sequencing

Exploring concordance and discordance for return of incidental findings from clinical sequencing

Robert C. Green, MD, MPH\(^1,2\), Jonathan S. Berg, MD, PhD\(^3\), Gerard T. Berry, MD\(^4,5\), Leslie G. Biesecker, MD\(^6\), David P. Dimmock, MD\(^7\), James P. Evans, MD, PhD\(^3\), Wayne W. Grody, MD, PhD\(^8,10\), Madhuri R. Hegde, PhD\(^11\), Sarah Kalia, ScM\(^1\), Bruce R. Korf, MD, PhD\(^12\), Ian Krantz, MD\(^13\), Amy L. McGuire, JD, PhD\(^14\), David T. Miller, MD, PhD\(^4,15\), Michael F. Murray, MD\(^1,2\), Robert L. Nussbaum, MD\(^16\), Sharon E. Plon, MD, PhD\(^17,18\), Heidi L. Rehm, PhD\(^2,19\) and Howard J. Jacob, PhD\(^7,20\)
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. Genetics in Medicine, 2012
Incidental Findings:

What is the right analogy?

How can reports be generated and scaled?
ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH, Jonathan S. Berg, MD, PhD, Wayne W. Grody, MD, PhD, Sarah S. Kalia, ScM, CGC, Bruce R. Korf, MD, PhD, Christa L. Martin, PhD, FACMG, Amy McGuire, JD, PhD, Robert L. Nussbaum, MD, Julianne M. O’Daniel, MS, CGC, Kelly E. Ormond, MS, CGC, Heidi L. Rehm, PhD, FACMG, Michael S. Watson, MS, PhD, FACMG, Marc S. Williams, MD, FACMG, Leslie G. Biesecker, MD

American College of Medical Genetics and Genomics

Green, et al. Genetics in Medicine, in press
Principles: creating a list...

• Generate a **specific** list.

• Generate a **minimum** list of variants/conditions that laboratories should seek and report to ordering clinician.

• Known or Expected Pathogenic only.

• Revise the list at least annually.
Principles: creating a minimum list...

• High penetrance.

• Long asymptomatic period.

• Highly efficacious treatment available.

• Not part of newborn screening.
ACMG Recommendations
Divergence from Current Genetics Practice

• Systematically include positive findings in the report returned to clinicians for exome and genome sequencing.

• Return same findings regardless of the age of the patient.

Convergence with Current Medical Practice!
“…even though evidence is insufficient, the clinician must still provide advice, patients must make choices, and policymakers must establish policies”

US Preventive Services Task Force, 2009
Thank You !!!

Email: rcgreen@genetics.med.harvard.edu
Web: genomes2people.org
Twitter: genomes2people