Sequencing in large samples: Consent, data access, ability to recontact

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Where are the debates?

1) Consent models and access
   Informed consent vs. opt out vs. anonymous.
   Is recontact needed?
   What is appropriate consent language?
   Broad consent vs. narrow consent?
   Is all data broadly shared?

2) Recontact and Return of Results
   Value of recontact
   What is actionable?
   Can you ethically not return actionable data?
   Do you need to look for actionable data?
   Many people will want “all” data.
   Can subjects refuse to get actionable data?
   Do you give adult onset actionable findings to kids?
## Consent models for large cohorts

- **Full informed consent has advantages**

<table>
<thead>
<tr>
<th></th>
<th>Full informed consent</th>
<th>Anonymize, opt out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad data sharing</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Recontact</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Collect additional phenotypes</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Return results</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Incorporate genomics into care</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Identified subject with an HGMD pathogenic mutation in an arrhythmia gene
Recontact: The buff gene

Muscular
Strong
Shorter?
Normal lifespan
- Exome/genome variant server FABULOUS for allele frequencies
- But, I cannot find out of the people with my variant have the buff phenotype
- Likely NOT in their medical record; thus, I need recontact
Informed consent: study view

- Understand subject needs
- Explain data being generated, broad future studies
- Consent to **broad** study goals and data-sharing
- Consent to recontact
- Offer return of genetic results
  - Primary, if relevant
  - Incidental (Not secondary) Explain that our understanding of the genome is evolving
  - Address survivorship
Informed consent: subject view

- **Benefits (return dependent)**
  - Prevention or early diagnosis / treatment of disease
  - Pharmacogenetics to maximize safe and effective drug choices

- **Risks (return independent)**
  - Privacy (common rule may redefine genetic data as id)
  - False security

- **Risks (return dependent)**
  - Social / emotional risks
  - Life and long-term care insurance?
    - GINA law protects medical insurance
  - Incomplete penetrance
  - Misclassification of variant
  - Misinterpretation of VUS or benign
  - Cost of follow-up?
Subjects: “Glad you asked”

- Re-consent study invited first 400 mail consenters to participate in telephone interview
- 90% of participants said it was important that they were asked permission for data sharing
  - 69% rated it “very important”
  - 21% “somewhat important”

Ludman et al (2010) JERHRE
Trinidad et al (2011) Science 21; 331:287-8
## Acceptability of alternatives

<table>
<thead>
<tr>
<th>Subject Role/View</th>
<th>Completely unacceptable</th>
<th>Somewhat unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opt-out (Let us know if you don’t want your info shared)</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>Notification-only (We already shared it, fyi)</td>
<td>47%</td>
<td>20%</td>
</tr>
<tr>
<td>No consent, no notification</td>
<td>54%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Ludman et al (2010) *JERHRE*
What do people want?

- Public support for return of results
  - NYT’s Gina Kolada to weigh in
  - Many expect return even if consented to none
- Focus group participants are highly motivated and educated
- What do people that are less engaged want?
  - Best case?: Family study, last contact within 10 years, contact by mail only:
    - 1/234 decline of broad reconsent
    - 21 lost to follow-up
    - 212 signed and returned reconsent (91%)
Worst case reconsent success rate?
Veterans seen once, up to 20 years ago

<table>
<thead>
<tr>
<th></th>
<th>addendum returned and agreed to dbGaP posting</th>
<th>addendum returned and Declined dbGaP posting</th>
<th>Not interested per phone call</th>
<th>addendum not returned lost/ignored still working on following up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>872</td>
<td>79</td>
<td>124</td>
<td>655</td>
<td>1730</td>
</tr>
<tr>
<td>% of mailing group (n=1730)</td>
<td>872 (50%)</td>
<td>79 (5%)</td>
<td>124 (7%)</td>
<td>655 (38%)</td>
<td>1730 (100%)</td>
</tr>
<tr>
<td>% male</td>
<td>555 (64%)</td>
<td>42 (53%)</td>
<td>91 (73%)</td>
<td>420 (64%)</td>
<td>1108 (64%)</td>
</tr>
<tr>
<td>% WNHO</td>
<td>682 (78%)</td>
<td>57 (72%)</td>
<td>81 (65%)</td>
<td>438 (67%)</td>
<td>1258 (73%)</td>
</tr>
<tr>
<td>% Asian</td>
<td>102 (12%)</td>
<td>11 (14%)</td>
<td>14 (11%)</td>
<td>84 (13%)</td>
<td>211 (12%)</td>
</tr>
<tr>
<td>%BNHO</td>
<td>55 (6%)</td>
<td>3 (4%)</td>
<td>21 (17%)</td>
<td>91 (14%)</td>
<td>170 (10%)</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>20 (2%)</td>
<td>3 (4%)</td>
<td>4 (3%)</td>
<td>25 (4%)</td>
<td>52 (3%)</td>
</tr>
<tr>
<td>% Native American</td>
<td>13 (%2)</td>
<td>5 (6%)</td>
<td>4 (3%)</td>
<td>17 (3%)</td>
<td>39 (2%)</td>
</tr>
<tr>
<td>age range (mean)</td>
<td>37-97 (72)</td>
<td>54-87 (68)</td>
<td>56-93 (74)</td>
<td>29-95 (68)</td>
<td>29-97 (71)</td>
</tr>
<tr>
<td>% Vet</td>
<td>446 (51%)</td>
<td>39 (49%)</td>
<td>83 (67%)</td>
<td>360 (55%)</td>
<td>928 (54%)</td>
</tr>
<tr>
<td>declined both dbGap and Cell-lines</td>
<td>N/A</td>
<td>58 (83%) (n=70)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>% declined Cell-lines yes to dbGaP</td>
<td>3 (0.4%) (n=721)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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</table>
Return of results to kids and adults

- Should *consent* for ROR—never mandatory
  - Particularly relevant to incidental findings
  - World Med Assoc Helsinki: “right to self-determination”
  - Autonomy and Subsidiarity (do not take decisions away)

- Context dependence of actionable variants
  - Adults are past risk for pediatric onset conditions
  - Adult onset disease in a kids is a separate issue
    - Autonomy: Do not order tests for adult onset disease in kids
    - Differs when these are incidental findings of a genome test
    - Beneficence: seek the patients good
    - Justice: Rights of parent who transmitted the allele

- Return of incidental findings in an ill patient
  - May prefer not to have these during a critical illness
  - Consent to return to family in case of death
Data access

- Advocate broad data access
  - Demonstrated utility in eMERGE and ESP/EVS, among other projects
    - Many expect return even if consented to none
- Public is wary of commercial access and government control
- Exceptions? Minority populations, yet these data are most needed
- Impact of changes to common rule?
  - If genetic data is considered identifiable
Questions

- Who needs screening colonoscopy at
  - 40 years old?
  - 50 years old?
  - 60 years old?

- Can we predict who has celiac?

- Theme: Change medical system behavior
Conclusions

1. Consent
   a) Identified, recontactable subjects are optimal for the sequencing age
   b) Allow opt out of return of genomic results
   c) Consents should be shorter, but complete
   d) Consent language will evolve

2. Data access should be broad

3. Recontact and return of results
   a) Recontact increases utility
   b) Return of significant actionable findings
   c) Develop consensus on these
   d) We may not all agree on what is best
      What genes to return (and to whom)
      Pediatric return of adult onset
<table>
<thead>
<tr>
<th>Names</th>
<th>Institutions</th>
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<tbody>
<tr>
<td>Debbie Nickerson</td>
<td>NHGRI</td>
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<tr>
<td>Dave Veenstra</td>
<td>NHLBI</td>
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<tr>
<td>Wylie Burke</td>
<td>WA State Life</td>
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<td>Malia Fullerton</td>
<td>Sciences Discovery Fund</td>
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<tr>
<td>Peter Tarczy-Hornoch</td>
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<tr>
<td>Michael Dorschner</td>
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<td>Donald Patrick</td>
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<tr>
<td>Chris Nefcy</td>
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<tr>
<td>Peter Byers</td>
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<tr>
<td>Dean Regier</td>
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<tr>
<td>Fuki Hisama</td>
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<tr>
<td>Brian Browning</td>
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<tr>
<td>Patrick Heagerty</td>
<td></td>
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<tr>
<td>Robin Bennett</td>
<td></td>
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<tr>
<td>Barbara Evans, JD</td>
<td></td>
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<tr>
<td>James Evans</td>
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<tr>
<td>Clinical review committee</td>
<td></td>
</tr>
<tr>
<td>Martha Horike-Pyne</td>
<td></td>
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<tr>
<td>Laura Amendola</td>
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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}

**Purpose:** The aim of this study was to explore specific conditions and types of genetic variants that specialists in genetics recommend should be returned as incidental findings in clinical sequencing.

**Methods:** Sixteen specialists in clinical genetics and/or molecular medicine selected variants in 99 common conditions to return to the ordering physician if discovered incidentally through whole-genome sequencing. For most conditions, the specialists independently considered three molecular scenarios for both adults and minor children: a known pathogenic mutation, a truncating variant presumed pathogenic (where other truncating variants are known to be pathogenic), and a missense variant predicted *in silico* to be pathogenic.

**Results:** On average, for adults and children, respectively, each specialist selected 83.5 and 79.0 conditions or genes of 99 in the known pathogenic mutation categories, 57.0 and 53.5 of 72 in the truncating variant categories, and 33.4 and 29.7 of 72 in the missense variant categories. Concordance in favor of disclosure within the adult/known pathogenic mutation category was 100% for 21 conditions or genes and 80% or higher for 64 conditions or genes.

**Conclusion:** Specialists were highly concordant for the return of findings for 64 conditions or genes if discovered incidentally during whole-exome sequencing or whole-genome sequencing.

**Key Words:** incidental findings, whole-exome sequencing, whole-genome sequencing

PMID:22422049