Genomics-based research results: to return or not to return?

Susan A. Berry, MD
Chair, IRB Executive Panel
University of Minnesota
Objectives

• Describe the nature of genomics results in a research setting
• Define risks associated with returning and withholding genomics research results
• Understand the differences between clinical and research genomics assessment
It’s always about the risks: impacts of genetic information

- Condition diagnosis
- Condition risk
- Possible health risks
- Unanticipated genetic relationships
- Impacts on other family members
And about the principles...

- **Beneficence**
  - Information of health impact
  - Minimize risk of information of questionable utility

- **Autonomy**
  - Individual must decide
  - (and what about children?)

- **Justice**
  - Results returned in informing fashion
  - Results returned validated
Some international guidelines

• UNESCO 1997
  Universal Declaration on the Human Genome and Human Rights
• Supplement 2003
  International Declaration on Human Genetic Data
  Assert the right of subjects to decide about return of results
  (provides no guidance about HOW!)
Important issues in return of genetic/genomic results (ROR)

- How specific is the result?
- How significant is the result?
- Did the subject know research was happening?
- Can the result be confirmed?
What kind of genetic information has been found?

- Is this the primary target of the research? (research results)
- Is this an incidental observation that may be anticipated from the performance of the research?
Perspective of participant (genetic research or not!)

- Without explicit statement, participant likely ASSUMES significant new information will be returned
- Conflating role of physician as caregiver and as researcher
- Silence may imply there was no significant information to reveal
- Generally subjects WANT results as a benefit (but may not know what they are bargaining for)
Why might genetic results be a special case?

- Results are complex
- Results are highly variable with regard to individual utility
- ROR is time-consuming and expensive
- Result utility may change with time
- Currently existing data for interpretation yields false positives due to:
  - Erroneous annotations
  - Sequencing error (99.9% accuracy = 1 M errors per genome)
  - Incorrect penetrance estimates
  - Multiple hypothesis testing (compounding)
What do potential participants want?

- Nearly all surveyed wanted at least some individual results back
- Priority on results that are well understood
- Less important
  - Magnitude of risk
  - Actionability of results
- Many believe researchers have obligation to return results
- Some want ALL but many accept limited results

Genet Med 2012; 14:451
Research? Clinical?

- When does research assessment become clinical?
- What makes a test clinically valid?
- What was the context of inclusion in research?

Continuum of relationship from individual patient → biobank contributor
IRBs must balance:

• **POSITIVE IMPACTS**
  Health impact
  Reproductive decision making
  Personal information
  Sense of contribution

• **NEGATIVE IMPACTS**
  Discrimination based on result
  Anxiety or worry from results
  Knowledge received that was not anticipated
What might an IRB consider re: ROR?

**Conscious consideration** of ROR

- Assess if a plan is in place for ROR
  - (may need two steps:
    - Consent at time of research initiation
    - Reconfirm at time of ROR)

- Evaluate the risks and benefits of ROR

- Evaluate the logistics of ROR
  - Confirmation of result in CLIA lab
  - Appropriate conveyance of result
  - Referral for care
Return of results: inquiring IRBs need to know

**PLAN AHEAD**

- Does the subject want to know:
  - Primary results of the research?
  - Secondary use results?
- Does the research result have a health impact?
- May new information emerge?
- What time frame?
Why NOT inform?

- Lack of relevance to the individual at hand
- Limited predictive value of the testing
- Potential misinterpretation of results by the recipient
- Absence of plan for good lab practice return (CLIA in US)
- Lack of feasibility
  - Anonymized dataset
  - Timing after research: “sunset”
ROR – emerging themes

• What criteria should ground an obligation/option to return?
  – Who should formulate?
  – Who should revise?
  – Return should be analytically valid and comply with applicable laws (CLIA, local)

• Contributor/research participant should have ideally consented to receipt of information
  – Issues exist when no earlier consent given
    • Refrain from return?
    • Only most important findings?
    • Contact for consent to return findings?
Wolf, et al.: Consensus recommendations for ROR

• Researcher *should* disclose
  – Genetic information revealing significant risk of a condition likely to be life-threatening
  – Genetic information that can be used to avoid or ameliorate a condition likely to be grave
  – Genetic information that can be used in reproductive decision-making to avoid above

• Researcher *may* disclose if possible net benefit
  – Genetic information revealing significant risk of a condition likely to be grave or serious, when that risk cannot be modified but a research participant is likely to deem that information important
  – Genetic information likely to be deemed important and can be used in reproductive decision-making

• Researcher should **NOT** disclose information offering unlikely net benefit including information whose likely health or reproductive importance cannot be ascertained

J Law Med Ethics 2008; 36:219
Core issues in biobanking ethics

- Consent and withdrawal
- Protection of privacy and confidentiality
- Ownership of data and samples
- Benefit sharing
- Commercialization
- Sharing of data and samples with other researchers

Should ROR also be a consideration? How feasible?
What about biobanks?

Suggested four core responsibilities for biobanks regarding information from both primary and secondary research activities
  – Clarify criteria for evaluating and creating roster of returnable findings
  – Analyze a new finding on that basis
  – Re-identify the contributor
  – Recontact to offer the finding
Deciding about ROR in a biobank

- Is the bank designed so re-identification can be done?
- What results fit actionable criteria?
- Who decides?
- How with this be maintained/revised?

Consider a ROR committee for biobanking if design includes any linkage to subjects
Biobanks: two ways only

• Design so that re-identification of contributors can occur
  – At primary collection site
  – At the biobank
  – Via a trusted intermediary

• Design so that NO links allowing any re-identification can be retained, hence no ROR
What about existing biobanks?

- Could consider re-contact of subjects generally in non-consented setting (e.g., letter or other general contact)
- If had consent, could consider re-contact those that consented if silent re ROR (similarly)
- If consent precluded return “may be difficult to argue for return” (Wolf, et al.)
- What, if any, resources exist for implementation if ROR is considered?
  - Reidentification
  - Confirmatory testing
  - Counseling

*Current biobanks would have significant challenges to implement ROR*
Deciphering Genetic Results

MMmmm
Good!
What kinds of genetic information might be returned?

• Single gene
  – Of known clinical significance
  – Of unknown significance
    • Predictably deleterious
    • Unlikely deleterious

• Condition-related polymorphisms
  – Weak association → Strong association

• Massively parallel sequencing data
  – Whole exome
  – Whole genome
The Human Genome

23 pairs of chromosomes made of 3 billion base pairs

Extragenic DNA
- Repetitive sequences
- Control regions
- Spacer DNA between genes
- Function largely unknown

- 70% of DNA
- 20,000-25,000 genes
- 30% of DNA
The DNA Double Helix

- Adenine (A)
- Thymine (T)
- Cytosine (C)
- Guanine (G)

- Sugar phosphate backbone
- Bases
- Base pair
Chromosomes, DNA, and Genes

Adapted from Understanding Gene Testing, NIH, 1995
Kinds of mutations: what alleles do

Quiet! I’ll speak for both of us!

I’ll have to be in charge now!

Dominant Allele  Normal Allele  Recessive Allele  Damaged Allele
Polymorphism

DNA sequence changes that do not alter protein function (common definition)
GWAS: Genome-wide association study

• “any study of genetic variation across the entire human genome that is designed to identify genetic association with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition”

(subject to density, linkage disequilibrium criteria that capture a large proportion of the common variation in the genome of the population under study with power to detect variants of modest effect)

NIH Policy Notice Number NOT-OD-07-088
ROR in GWAS: eMERGE Network
Genet Med 2012; 14:424

- 5 biorepositories convened an ROR committee
- Decided to return info about sex chromosome anomalies, homozygosity for fVL, mixed opinions about homozygosity for hemochromatosis
- Local considerations about return varied
Gene Structure

- RNA transcription start site
- Splice sites
- Stop site

Promoter

Exon 1 | Intron | Exon 2 | Intron | Exon 3

5' end

Exon 1 | Exon 2 | Exon 3

mRNA

3' end
Whole genome sequence

• Detects 3-4 million sequence differences compared to the reference
• 30-50 thousand differences will be in the protein-coding regions “exome”
“Whole” isn’t whole

- Genomic DNA (typically WBC) fragmented
- Attached to artificial sequences that allow DNA to attach to cDNAs on a solid matrix
- Random fragmentation process, so excess of sequencing done (typically 30X)
- Can interrogate genome or exome depending on what is fixed on matrix
- Evaluates only about 90% of the exome or genome
What can be learned?

One study (AJHG;2012 91:1)

- Study of 45-64 yo persons ascertained for arteriosclerosis risk
- All had family history recorded
- All had given consent for further interrogation of DNA for cancer risks
- Assessed for variations in sequence for 27 cancer syndromes
  - 37 genes
  - Adult-only cancers
The scope of the information

- 572 exomes
- 44.5 billion reads
- 3.84 trillion bp of sequence
- 1,921,814 variants
- 181,736 nonsynonymous, frameshift, nonsense, splicing
- 91.2% coverage (22.3-100%)
- 37 cancer genes only
- 454 nonsynonymous, frameshift, nonsense, splicing – with review 451
Parameters of ascertainment

- Seek variants highly likely to be causative
- “Filter” to minimize false positive (sacrifice sensitivity)
- Use sorting strategy to focus on nonsense, frameshift, splice site, nonsynonymous variant
- Classifications by likelihood and severity
Results

- Ten variants in highest probability classes
  - One variant in gene predisposing to paragangliomas
  - Identification of 7 probands in highest risk group with BRCA 1/2 mutations
    - Four met clear definition of “at risk” family by family history (2 knew of their family mutation)
    - Three did not
  - Two had AR gene predisposition to colon cancer
- 321 persons had variants of ambiguous pathogenicity
- HIGH burden of ambiguous variation
- Each alteration took substantial time to curate
"Whole" isn't whole
Return of results

- All “class 5” variants predicted to cause an autosomal dominant cancer syndrome confirmed in CLIA lab
- Results provided by clinical geneticist
- Participants with BRCA1/2 variants advised on cancer prevention and surveillance guidelines
- One subject with risk for paragangliomas-3 was advised about phenotype and its management
- Participants advised to share results with family
- Results with recessive carrier status for FAP2 NOT revealed (plan in place)
Summary

- Some genetic results from research studies should be returned
  - High impact and actionable
- Some results may be returned
  - With results meaningful to individuals and their families
- Some should NOT be returned
  - Ambiguous results; unconfirmable results
- Consent of subject/contributor REQUIRED.
- If returned, results must be conveyed in an informative fashion following applicable laws
And in children... for thought

- Results of high impact, early onset, and treatable should be returned even if parent did not want result? (surrogate should not deny access)
- Or, if participants DO get results child subjects should NOT receive if information is important but not actionable (plan in place to review at time of decision making?)