Incidental Findings in the Era of Large Scale Biobanking and Genomic Discovery

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What is a Biobank?

• Collect and store biospecimens
  – Can include any kind of tissue or body fluid donated by an individual: tumor biopsies, blood, urine, etc.
• May perform sample analysis
• Make specimens and data available to researchers
Biobank Diversity

- National survey of US Biobanks in 2012
  - Biobank = organization that acquires & stores human specimens & associated data for future use
  - Representatives of 636 biobanks with online presence contacted
  - 456 respondents (72% response rate) for online survey

- Results:
  - 59% established recently (since 2001), but 17% have been operating for >20 years
  - Size varies greatly (# samples stored or # individuals contributing): <500 to >500,000

Henderson et al. Genome Medicine 2013, 5:3
US Biobank Survey - Results

- Most biobanks (87%) store more than one type of specimen
- Most frequent combination: whole blood, plasma, and solid tissues
- Most biobanks with only one type store solid tissue

<table>
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<tr>
<th>Percentage of biobanks storing specimens of this type</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Serum or plasma</td>
<td>349</td>
<td>77</td>
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<tr>
<td>Solid tissue specimens, including paraffin-embedded, frozen, or other</td>
<td>315</td>
<td>69</td>
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<tr>
<td>Whole blood</td>
<td>251</td>
<td>55</td>
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<tr>
<td>Peripheral blood cells or bone marrow</td>
<td>222</td>
<td>49</td>
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<tr>
<td>Cell lines</td>
<td>162</td>
<td>36</td>
</tr>
<tr>
<td>Saliva or buccal cells</td>
<td>155</td>
<td>34</td>
</tr>
<tr>
<td>Urine or stool</td>
<td>138</td>
<td>30</td>
</tr>
<tr>
<td>Cerebral spinal fluid</td>
<td>85</td>
<td>19</td>
</tr>
<tr>
<td>Cord blood or cord blood derivatives</td>
<td>51</td>
<td>11</td>
</tr>
<tr>
<td>Other biological specimens</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Pathological body fluids</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Hair/toenails</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

Henderson et al. Genome Medicine 2013, 5:3
US Biobank Survey - Results

• Specimen source:
  – 75% directly from individuals donating them
  – 57% residual specimens acquired from clinical care in hospitals, clinical labs, or pathology departments

• Specimen contributors:
  – 76% individuals with particular disease/type of disease
  – 76% patients from specific hospital(s) or clinic(s)
  – 40% participants in a cohort study
  – 39% participants in clinical trials
  – 27% individuals from specific geographic area

Henderson et al. Genome Medicine 2013, 5:3
Basic Biobank Model

- May or may not involve Human Subjects, IRB review
- May or may not involve informed consent, or even notification
- May or may not require HIPAA compliance
- May be state/local laws, institutional requirements

Adapted from Marianna Bledsoe
Biobank Model – Distributing for Secondary Use

- Design and function generally different from project specific biobanks
- Optimized to serve large numbers of investigators. Typically includes an application process and results in de-identified (or coded) specimen/data set
Biobanks not “one size fits all”

• Policies should not be “one size fits all” either
• Practical considerations for potential individual result return:
  – Pre-existing samples or prospectively collected?
    • Some collections predate informed consent; others are used for research under waivers of consent; many (most?) consents didn’t foresee current state
  – Are there links to subject identifiers?
    • Feasibility of recontact? How enduring is contact information?
  – Level of rigor around sample tracking & labeling

Slide adapted from Marianna Bledsoe
Focus on Prospective Enrollment

• Prospective collections, with prospective enrollment, are best suited to allow for responsible return of individual results
  – Biobanks can develop plans and policies anticipating this
  – Modern communication methods offer better prospects for long-term follow up

• Informed consent
  – Should be clear whether research results will be returned, and if so, under what situations (difficult)
  – Participants should have the option not to receive results at the time of original consent & beyond
Participant Perspectives

• Many studies have reported significant participant interest in receiving individual results from research*
  – Especially “medically actionable” results
  – Also interest in non-actionable results
  – *Unclear if limitations or resource requirements are fully understood

• Most likely common option: return of medically actionable results
  – Preferred by researchers and other professionals
Spectrum of Biobanks Supporting Large-Scale Research

Goal: half million participants for cohort study

Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH)
Goal: 500,000 KP members from N. & S. California

Provides participant reports with genetic & non-genetic risk for disease
GWAS Era

- Genome-wide Association Studies (GWAS) – analyze hundreds of thousands of SNPs for association with disease in thousands of individuals
- Used to study common, complex disease
- Many statistically significant findings
- Few SNPs of likely clinical relevance
- 2007 - 2012

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip...
Published Genome-Wide Associations through 12/2012
Published GWA at p≤5×10^{-8} for 17 trait categories
What are Incidental Findings?

- Incidental Findings/Secondary Findings – Results that are not related to an individual’s reason for testing or primary focus of research study

- Many biobanks support broad health research – isn’t everything “incidental”? 
Few clinically relevant IF possibilities from GWAS

• Analyzed 18 commercially available SNP arrays for variants with CLIA tests available (Johnson et al., Genet Med 2010, 12:6)
  – ID’d gene variants in: APOE, F5, HFE, CYP21A2, MEFV, SPINX1, BTD, GALT, G6PD

• Electronic Medical Records and Genomics (eMERGE) Network experience (Fullerton et al., Genet Med 2012)
  – GWAS on ~19,000 samples for primary & secondary phenotypes
  – Incidental discovery of Sex Chromosome Abnormalities from GWAS Quality Control
  – Mendelian conditions: Factor V Leiden & Hemochromatosis
GWAS to NGS

- New technology allows for millions of sequencing reactions to be performed at once
- Computer algorithms are used to assemble sequence date
- Whole exome seq. (WES) more common than whole genome seq. (WGS)
Sequencing a genome is simple - Finding a cause of disease is not

MUSINGS

The $1,000 genome, the $100,000 analysis?

Elaine R Mardis®

Moorthie et al. Genet Med 2013, 15:3, Figure 1
Return of Research Results

• Many groups have deliberated and issued recommendations (NBAC, NHLBI, etc)
• Discussions about return of research results from biobanks are more recent (NCI, ISBER, Genetics in Medicine Special Issue 14:4, 2012)
• Key issues/considerations
  – Clinical care vs. research obligations
  – Participant wishes (autonomy)
  – Ethical, legal, practical, regulatory, etc.
Disclosing Results from Genetic Research

- Sharing aggregate results (e.g. study progress) is respectful of donors/participants
  - Majority of participants want to know about research
- Returning individual genetic research results
  1. Clinically relevant results with significant medical impact (focus area of research)
  2. Incidental/Secondary Findings discovered during the course of research
Aggregate Results

• Various groups have suggested that summary results of research should be provided to biobank participants
  – Options: newsletter, website, other outreach

• Rationale:
  – Demonstrate respect and reciprocity
  – Provide ongoing information after broad consent
  – Provide education about the research process
  – Build trust in research enterprise
Offering Aggregate Results to Participants in Genomic Research

Key recommendations:

• Researchers should communicate clearly with participants & public about research conducted & its outcomes
  – Language should identify major findings & study limitations

• Moving forward, plans for return of aggregate results should be described in grant applications & IRB protocols and should be disclosed at the time of consent

• Return of aggregate results should not be used as a way to avoid an obligation to offer individual findings

Managing incidental findings and research results in genomic research involving biobanks and archived data sets

Susan M. Wolf, JD1, Brittney N. Crock, JD1, Brian Van Ness, PhD1, Frances Lawrenz, PhD1, Jeffrey P. Kahn, PhD, MPH2, Laura M. Beskow, PhD, MPH3, Mildred K. Cho, PhD4, Michael F. Christman, PhD5, Robert C. Green, MD, MPH6,7, Ralph Hall, JD1; Judy Illes, PhD8, Moira Keane, MA1, Bartha M. Knoppers, JD, PhD9, Barbara A. Koenig, PhD10, Isaac S. Kohane, MD, PhD7, Bonnie LeRoy, MS1, Karen J. Maschke, PhD11, William McGeeveran, JD1, Pilar Ossorio, PhD, JD12, Lisa S. Parker, PhD13, Gloria M. Petersen, PhD14, Henry S. Richardson, JD, MPP, PhD15, Joan A. Scott, MS16, Sharon F. Terry, MA17, Benjamin S. Wilfond, MD18 and Wendy A. Wolf, PhD19

• 10 recommendations for biobanks, as the central element of a “biobank research system”
• Different implications for new vs. pre-existing biobanks
• Outlines shared responsibility for return of IFs between investigators & biobank, but shifts towards biobank

Wolf et al., Genet Med 2012, 14(4)
Key Recommendations

• Biobank research system includes primary researcher, biobank, and secondary researcher – each have a role in management of IFs. The biobank, as the central hub, should ensure that the system meets these responsibilities (#1)

• When reidentification of participants is possible within the overall biobank system, the biobank should work to create a responsible approach to return IFs (#2)

• Biobanks should work with researchers to: develop criteria to evaluate results & develop a “to return” list (#4); analyze results to determine whether they should be returned (#5)

• Reidentification by primary researcher and/or biobank (#6)

• Recontact managed by primary researcher (#7)

Wolf et al., Genet Med 2012, 14(4)
Debate

Return of research results from genomic biobanks: cost matters *

Marianna J. Bledsoe, MA, Ellen Wright Clayton, MD, JD, Amy L. McGuire, JD, PhD, William E. Grizzle, MD, PhD, P. Pearl O’Rourke, MD and Nikolajs Zeps BSc (Hons), PhD

Secondary variants and human subjects research *

To the Editor: In the article titled “Return of Research Results from Genomic Biobanks: Cost Matters,” Bledsoe

Return of results in genomic biobank research: ethics matters *

To the Editor: In “Return of Results from Genomic Biobanks: Cost Matters,” Bledsoe et al.1 offer critique of a 26-author

*Bledsoe et al., Genet Med 2013, 15(2) Commentary
Responses: *LG Biesecker and *SM Wolf
Debate Continued

- Data are needed on the actual benefits, risks and burden of returning individual research results
- “Care must be taken so that the return of individual findings generated in research does not get ahead of what is acceptable for return in clinical care.”

Bledsoe et al., Genet Med 2013, 15(2)
Disclosing individual genetic research results

• Any consensus?
  – Some agree that researchers have an ethical responsibility to offer clinically actionable findings to research participants that want them
    • Respect for persons
    • Duty to rescue
  – Others disagree
    • Research donation is altruistic
    • Promotes therapeutic misconception
    • Potential harms if data returned is incorrect/not validated
Example: eMERGE

• NHGRI-funded consortium formed to assess the value of EMR-coupled biobanks for large scale genomic research

• GWAS on ~19,000 samples for 5 primary & numerous secondary phenotypes

• Incidental discoveries
  – Sex Chromosome Abnormalities from GWAS QC
  – Mendelian conditions: Factor V Leiden & Hemochromatosis

Fullerton et al., Genet Med 2012, 14(4)
## eMERGE Network

<table>
<thead>
<tr>
<th>Institution</th>
<th>Biorepository Population</th>
<th>Ongoing Participant Interactions</th>
<th>Current/Expected Size</th>
<th>Age Range/ Mean Age</th>
<th>Consent for RoR?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group Health Cooperative</strong> (Seattle, WA)</td>
<td>Disease-specific: Alzheimer’s disease patient registry &amp; Adult Changes in Thought Study</td>
<td>Yes</td>
<td>~4,000 &gt;96% Eur. Amer.</td>
<td>40 – 90+ (over 65)</td>
<td>Yes</td>
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<tr>
<td><strong>Marshfield Clinic</strong> (Marshfield, WI)</td>
<td>Population: Personalized Medicine Research Project</td>
<td>No</td>
<td>20,000/ 21,000 98% Eur. Amer.</td>
<td>18 – 90+ (48)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Mayo Clinic</strong> (Rochester, MN)</td>
<td>Disease specific: Mayo Clinic Non-Invasive Vascular Laboratory</td>
<td>Yes</td>
<td>750 ea. PAD &amp; controls &gt;96% Eur. Amer.</td>
<td>20 – 90+ 17 – 90+</td>
<td>Yes</td>
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<tr>
<td><strong>Northwestern University</strong> (Chicago, IL)</td>
<td>Population: NUgene Project</td>
<td>No</td>
<td>8,500/ 20,000 12% AA 8% Hispanic</td>
<td>18 – 90+ (50)</td>
<td>No</td>
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<tr>
<td><strong>Vanderbilt University</strong> (Nashville, TN)</td>
<td>Population: BioVU</td>
<td>No</td>
<td>75,000+/ 200,000 13% AA</td>
<td>18 – 90+ (52)</td>
<td>N/A</td>
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eMERGE C&CC Return of Results WG Recommendations

• Return of aggregate study findings to study participants encouraged

• *Routine* return of individual research results discouraged

• Recommended establishment of Oversight Committee to deliberate *limited return* of “clinically actionable” incidental and/or individual research results
  – “Actionable” = result with potential to change medical care
  – OC recommendations advisory, not binding, and subject to local IRB oversight and approval

http://www.gwas.net
eMERGE RoR Oversight Committee Recommendations

• Charge:
  – Criteria for defining a “clinically actionable” result of direct benefit
  – Considerations surrounding the return of non-CLIA certified research findings
  – Appropriate methods for return, including when, to whom, and with what support for follow-up (including ways to avoid delivering unanticipated or unwanted information)

• Determinations:
  – Turner Syndrome (45, X) – Pot clinical benefit; merits consideration
  – Klinefelter syndrome (47, XXY): Pot clinical benefit; merits consideration
  – Factor V Leiden (R506Q, rs6025): Clinical benefits uncertain for heterozygotes: consider return for homozygotes
  – HFE hemochromatosis (C282Y, rs1800562): Clinical benefits uncertain due to low penetrance; consider return to male homozygotes
Conclusions

• Unclear whether any eMERGE findings will be returned
  – Dealing with specific examples is clarifying
  – Value in documenting and sharing deliberative experience

• GWAS case “easy” yet consensus is difficult to reach
  – Within RoR Oversight Committee
  – Hand-off to individual institutions for local decision-making

• Individual context is important
Apply this to NGS results

- eMERGE deliberations involved 4 cases and 80 participants (0.4% of the genotyped population)
- Recent study* of 1,000 exomes estimates high-penetrance actionable pathogenic or likely pathogenic findings at 1.2% – 3.4% depending on ancestry
  - Based on our current knowledge

*Dorschner et al., AJHG 2013, 93.
Offering Individual Genetic Research Results: Context Matters

Laura M. Beskow¹,²* and Wylie Burke³,⁴
Published 30 June 2010; Volume 2 Issue 38 38cm20

The disclosure of individual genetic research results may be the subject of vigorous debate and public comment. However, it is important to consider that research conducted under these circumstances has not been done with an ancillary care framework. In this context, the focus of research is not on individual patients, but on the larger population with similar genetic characteristics. The goal is to develop a better understanding of the disease process and to improve patient care. In these circumstances, researchers may have access to information that was not collected specifically for research, such as family history or de-identified medical records. The importance of this information should be considered when evaluating the potential benefits and risks of sharing it.

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<tr>
<th>Table 1. Examples of strength of claims for ancillary obligations in different research contexts.</th>
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<td><strong>Strong</strong></td>
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<td><strong>Moderate</strong></td>
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<tr>
<td><strong>Weak</strong></td>
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Science Translational Medicine, 30 June 2010, Vol 2, Issue 38
Summary

• Biobanks are diverse in their design, scope, operations, and nature of research they support
  – Policy development should recognize, and allow for, this variability
• Biobanks with prospective enrollment are best suited to allow for responsible return of individual results and should develop plans addressing IFs from genetic research
• Policies should be based on empiric data – collection underway
• Adoption of WES/WGS technology will intensify the need to address IFs in a scalable way
Acknowledgements

• Marianna Bledsoe
• Sarah Savage
• eMERGE collaborators
  – Consent & Community Consultation (CCC) WG
  – Return of Results Oversight Committee
  – Consent, Education, Regulation & Consultation (CERC) WG
  – Return of Results WG

eMERGE Network – phase 1
• NHGRI
• Group Health/University of Washington
• Marshfield Clinic
• Mayo Clinic
• Northwestern University
• Vanderbilt University