Return of Research Results
One Component of Transparency

October 1, 2016
P. Pearl O'Rourke, MD
Partners HealthCare
Boston, MA

Agenda

• Return of Research Results
  – General context
  – The difficult details
    • What
    • To whom
    • When
    • How

General context

• This is an old problem and relevant to any research result
• While NOT specific to genetics
  – The avalanche of genetic information focuses attention on this issue
• Numerous approaches and strong feelings for each
Limited

Return nothing – after all, it is research
Return valid, serious and actionable findings
  If included in the informed consent
Return valid, serious and actionable findings
  Regardless of the informed consent
Return all research findings
There is a ‘Duty to Hunt’

Expansive

And there is disagreement

Quality of the specimen and test

- How was the specimen obtained and maintained?
  - By whom; how labeled; environmental control
  - What was the quality assurance and control
    • Esp in secondary research and banks
- How was the sample identified?
  - Identifiable – then coded?
  - The re-identified and re-coded...etc?
    • Approx. 0.1% labeling errors in diagnostic labs
Quality of the specimen and test

- What was the chain of custody?
  - Note: secondary uses and banks
  - With every hand off comes potential error
- Who performed the test?
- Is the lab CLIA approved?

CLIA

- Clinical Laboratory Improvement Act of 1988
- For the regulation and quality assurance of human specimens within clinical laboratory environments

CLIA Research Exception

42 CFR 493.3(b)(2)
Exception. These rules do not apply to components or functions of research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.
CLIA Research Exception

42 CFR 493.3(b)(2)
Exception. These rules do not apply to components or functions of research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.

What if results are returned to an individual simply for interest/curiosity?
Seems CLIA would not apply?
Ya think?

CLIA

• Conservative (and increasingly applied) read is that the CLIA exception does NOT apply to return of research results – regardless of reason for returning.
  – Therefore, any research result that is returned to a participant must be performed in a CLIA lab

CLIA Meets HIPAA

• Inconsistent
• Joint HIPAA/CLIA Final Rule – 2014
  – Expanded designated record set to include “completed laboratory tests”
The Inconsistency

**HIPAA**
- Office of Civil Rights
- Individual right of access to PHI in a Designated Record Set (DSR)
- Can delay if appropriate: e.g., until end of the study

**CLIA**
- Centers for Medicare and Medicaid Services (CMS)
- Research labs without CLIA certification may NOT return results "for diagnosis, prevention or treatment of any disease of impairment of, or the assessment of the health of the individual patients."
- Many state laws prohibit direct return to patients

Your Dilemma

- Non-CLIA approved lab sits in a HIPAA covered entity
- Can you return results from this lab to the participant?
  - CLIA → NO
  - HIPAA → YOU MUST

Research result vs incidental finding

- True research result
  - Data intentionally obtained and needed for the research itself

- Incidental finding
  - Data obtained by chance without intention or calculation
    - Beyond that originally anticipated in the research protocol and are not related to the goals of the research
    - Beyond the information required to achieve the aims of the study
Research result or incidental finding

- Validity: analytic and clinical?
  - Yes: Reliable, repeatable, accurate measurement of a specific clinical ‘target’
  - No: Unknown reliability, repeatability or accuracy
- Utility?
  - Yes: Useful for decision-making
  - No: No known value

Examples

- Research study evaluating cardiac function using MRI imaging
  Finding: Decreased left ventricular function
  - Research finding or incidental finding?
  - Validity?
  - Utility?

Examples

- Research study evaluating cardiac function using MRI imaging
  Finding: Calcified lung nodule found on MRI
  - Research finding or incidental finding?
  - Validity?
  - Utility?
Examples

• Pharmacogenomic study of family members

Finding:
Mutation that was reportedly found in one person with a rare thyroid disease
  □ Research finding or incidental finding?
  □ Validity?
  □ Utility?

Examples

• Pharmacogenomic study of family members

Finding:
Mutation for decreased enzyme activity
  □ Research finding or incidental finding?
  □ Validity?
  □ Utility?

Examples

• Pharmacogenomic study of family members

Finding:
BrCa 1 mutation
  □ Research finding or incidental finding?
  □ Validity?
  □ Utility?
Examples

- Pharmacogenomic study of family members

Finding:

Non-paternity

- Research finding or incidental finding?
- Validity?
- Utility?

Challenges of Genetics

- Flood of information
- Validity and utility of specific genetic findings are often unknown or at the least controversial
  - How well can we assess at this point in time?
- In whole genome sequencing – is everything a research finding?
  - Hence no incidental findings?
- If you are sequencing the whole genome
  - Why not return the whole sequence and all findings?

<table>
<thead>
<tr>
<th>James Watson</th>
<th>Usher Syndrome</th>
<th>Cockayne Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular biologist and geneticist</td>
<td>Hearing loss, Visual impairment</td>
<td>Growth retardation, Impaired development of the CNS, Photosensitivity, Premature aging</td>
</tr>
<tr>
<td>B.S age 19, Co-founder of DNA structure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

James Watson
Molecular biologist and geneticist
B.S age 19
Co-founder of DNA structure

Genetics in Medicine
Advance Online Publication 9 Feb. 2012. doi: 10.1038/gim2011.68
Cautionary Tale Of Genetic Testing: You May Drop Dead! Oops, Never Mind

August 18, 2016
By Carey Goldberg
WBUR

Imprecise Medicine: Genetic Tests Lead To Misdiagnosis
August 17, 2016 by Larry Husten

- Some black Americans were wrongly told they had a high risk for hypertrophic cardiomyopathy. Precision medicine offers the promise of an accurate assessment of individual risk for serious conditions like hypertrophic cardiomyopathy (HCM). But a new report published in the New England Journal of Medicine, "which the authors describe as "a cautionary tale of broad relevance to genetic diagnosis," makes clear that the utility of genetic tests may be limited by the lack of diversity of people included in the underlying genetic databases used to assess risk.

Duty to Hunt

- Consider...
  - Study to evaluate the distal arm of chromosome 9 for association with pulmonary fibrosis
  - Methods: whole genome sequencing is done – less costly than focused sequencing.
Does the ‘Type’ of Research Matter?

• Consider: the same research finding…
  – Dr. Why, a clinician-investigator studying genetic basis of a specific disease
    • 20 subjects recruited from his clinic
  – Dr. Whatever’s multi-national biobank
    • Samples from over 500,000 individuals
What will be returned?

- If only limited information returned based on validity, seriousness, actionability
  - Who controls/operates the filter?
  - And under what authority?
  - Different for adults and children?
  - Do you use any external guidelines
    - E.g. ACMG?
- Will returned data be annotated or provided with interpretation?
  - How will the accuracy of the annotation be verified?

Return to whom?

- The adult participant
- The pediatric participant
- Family members
- Clinicians
The Adult Participant

- Can decide for themselves – and should be proactively informed in the informed consent form/process
- Should the result be disclosed to a clinician as well?

The Pediatric Participant

- 4 yo child enrolled in diabetes study that included whole genome sequencing
- Child found to be positive for:
  - Variant associated with Diabetes
  - Variant associated with Alzheimer’s Disease
  - BrCa 1 and 2

- What do you disclose to the parent?
  - Only those findings specifically relevant to the child’s health?
  - What about adult onset disorders?

The Pediatric Participant

- A 16 yo child enrolled in diabetes study that included whole genome sequencing
- Child found to be positive for:
  - Variant associated with Diabetes
  - Variant associated with Alzheimer’s Disease
  - BrCa 1 and 2

- The child wants nothing shared with the parents:
- What do you do?
The Pediatric Participant

- If a young child
  - Report to parents/guardians
  - Any obligation to child at the age of majority?
- If an older child
  - Report to the child?
  - Any obligation to report to parents/guardian?
    - If you do, does the child have to approve disclosure?

A Deceased Participant

- Study of pancreatic cancer: study included whole genome sequencing.
- Subject #14 who has since deceased, was positive for:
  - Variant associated with pancreatic cancer
  - Variant associated with melanoma
- Do you notify family members?
  - Which family members?
  - How do you identify and find the family members?
  - What if the proband did not want his family to know that he had pancreatic cancer and was in a study?

A Deceased Participant

- When to disclose to family?
  - Any family member?
  - Only ‘blood’ relatives?
  - Does the family know that their relative was in a research study?
  - Did the relative ever consider sharing results with family member?
When will it be returned?

- In real time as the data is generated
- At the end of the study
- In perpetuity
  - After all, data that is meaningless today may be incredibly important in three years… and vice versa
  - Is this even logistically possible?

Who will do the returning?

- The person who obtained the specimen
  - Participant may recognize this person
  - BUT - this person may have no clue re: the result
- The person who did the research
  - In best position to explain the result
  - BUT – may be an unknown to the participant
- A tissue bank representative?
  - Usually unknown to the participant
- Healthcare provider?
  - Usually not involved in the research
How will it be returned?

– Mode of communication
  • In person
  • Letter
  • Telephone call
  • Email
  • Interactive website

– Will there be a content expert for consultation?
– Will the individual be told to consult an MD?
– If an MD is consulted – will s/he know how to handle the results?

But it is not that simple…

– Participant preferences
  • Considering “old” consent forms/process
  • Proactive best practices

Existing Informed Consent Says…

– Nothing: Is silent re: return of results
– Really really important results may be returned
  • No details re: how, by whom, etc.
– Only aggregate results will be provided via a newsletter - no individual results will be returned
– Research results relevant to the specific research question will be returned
– All research results will be returned to subjects
  • Upon request
  • Without request
Existing Informed Consent

- Positively states what will happen
  - If you do not like it, do not participate
- Provides an option re: desire to receive research results
  - Opt-In
  - Opt-Out

Existing Informed Consent

- Individual checked the 'opt-out' box for return of research results

  - And then you find an 'oh wow!'
    - Did they really understand what they were opting in/out of?
    - Perhaps they should be recontacted with this new information to see if they may change their mind/s?

Proactive Informed Consent

- Should include basic information re:
  - Description of anticipated results and the possibility of incidental findings
  - Plans for returning research results and/or incidental findings
  - Plans for sharing with relatives
- Consider carefully…
  - Stating that no results will ever be returned
  - Giving options
The Headaches

- How to present the “burden of knowing”
  • Without being patronizing?
- How to avoid the pressure of ‘duty to receive’
  • Once offered – how difficult to decline?
- Difficulties of tiered consents and opt-out/ins
  • Logistics of tracking and respecting preferences
  • How often should participants update their preferences
- How to avoid therapeutic misconception

Sample consent form

- Research is not the same as clinical care and in general we do not plan to provide any information back to you. BUT – if we do find a result that could have an effect on your health, do you want us to contact you with this information?

The participant thinks…

- If it were so serious that they would go out of their way to contact me…it would be pretty bad
  • No way - I would want to know!
  • Absolutely - I would want to know!

- I have never been contacted!! No news is good news – correct?
Friday afternoon

• Just opened the mail

“Dear research participant
Remember the study you joined? Well, we found something in your blood test that may be important for your health – do you want to hear about it? Let us know…..”

And then there is…
The Harsh Truth

– Many people unable to recall
  • Details of the signed ICF
  • Ever signing an ICF
  • Ever being in research
– Daunting logistics
  • Large number of heterogeneous research protocols with heterogeneous research populations and no standard infrastructure and support

Return of Research Results and Incidental Findings
The Effect of Genetics

• ApoE and Alzheimer’s Disease
  – Ms. Green
    • Mother and 2 aunts with AD
    • Knowing her status is empowering
  – Mr. Blue
    • No family history
    • Knowing results has ‘ruined his life’
Return of Research Results and Incidental Findings

The Effect of Genetics

• You cannot stick the genie back into the bottle