Returning Individual Results from Genomic Research: A Partial-Entrustment Account

Henry S. Richardson, JD, MPP, PhD,
Georgetown University

National Academy of Sciences
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Worrisome individual results: geneticists are not alone

- Pancreatic cancer encountered in a trial of a new virtual-colonoscopy procedure
- Probable brain tumor discovered by CT scan during an Indian trial of mannitol therapy for cerebral malaria
- HIV infection found during a study in Soweto of a new XDR-TB treatment protocol
- Ectopic pregnancy found in a Ugandan community study of the effect of STDs on the HIV-transmission rate

Worrisome individual results: Obligation to follow up? Why?

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The general duty of rescue

- If you can save someone from dire peril by making only a smallish sacrifice, you should do so.
- General: applies alike to everyone

Cf. Merritt, Taylor, & Mullany. 2010. "Ancillary Care in Community-Based Public Health Intervention Research," *American Journal of Public Health* 100: 211-16.

The duty of rescue does not go very far

- Will cover:
  - Simple warnings
  - Referrals (incl. "assisted referrals"?)
  - Simple therapeutic efforts (e.g., deworming)
- Will not cover
  - Logistically difficult warnings ← The typical genetic & genomic case
  - Paying for care
  - Complex or difficult therapeutic efforts

Some obligation to return findings despite difficulty. Why?

- Nascent consensus*:
  - Obligatory for researchers, including secondary researchers, to return some individual results
  - Permissible to return certain other findings
- What's the basis of this obligation?

* Wolf et al. 2008; Fabsitz et al. 2010; Presidential Commission 2013

Beyond rescue: The partial entrustment model

- Arose re "ancillary care":
  - Care that subjects need but is not required for sound science or study safety*
- "Partial": limited in scope & in strength
- Scope includes what comes to light via study procedures
  - And so includes IFs

*Richardson & Belsky *HCR* 2004; Belsky & Richardson *BMJ* 2004

Beyond rescue: The partial entrustment model

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  - Care and help that subjects need but is not required for sound science or study safety*
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Entrustment: from rights waived during informed consent

The partial-entrustment model's core argument

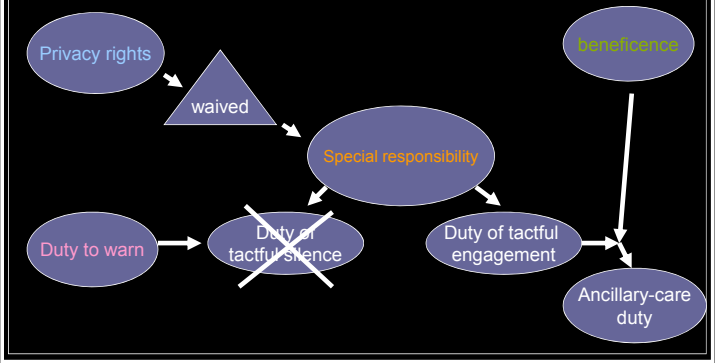
- Rights waivers → special permissions
- Accepting rights waivers → special responsibilities
- Scope of these responsibilities: tied to what's discovered in exercising the special permissions

WHY these special responsibilities? Privacy-based moral entanglement

R. L. Washington, "Make a Move"
www.arte10.com

- The old woman & the groceries
- Elements:
  - Helping
  - Accepting a privacy waiver
  - Getting in deeper
  - Duty to warn blocks silence

The nuts & bolts: How entanglement leads to partial entrustment



Follow-up obligation depends on the AC claim's strength

- *Difference* the care or help would make
- Degree of *dependence*
- Debt of *gratitude*, if any
- *Depth* (duration & intensity), or degree of intimacy, of the researcher-subject relationship
- *Cost* (in $ and personnel time)
  - Surgery for ectopic pregnancy in rural Uganda not supported

Ratcheting up rescue to get to an AC obligation to return results

- Suppose the duty of rescue calls upon each of us to expend $x of our own resources to save 1 life.
- Simplified expected-value assumption:
  - Suppose the probability of saving A's life is p (where $0 < p < 1$).
  - Then the duty of rescue calls on us to expend $px to save A's life.

Ratcheting up rescue, cont.

- Worrying apparent variants found: p = .01
- Quality-check the finding if cost < $(.01x)
  - If not, stop.
  - If quality-checked data not worrisome, stop.

Stages based on Jennifer J. Johnston, Ph.D. "Secondary Variants," NHGRI presentation Sept. 28, 2011

Ratcheting up rescue, cont.

- Worrying apparent variants found: p = .01
- Quality-check the finding if cost < $(.01x)
- Worrying apparent variants, still: p = .02
- Filter the variants if cost < $(.02x)
  - If not, stop
  - If the variants don't survive the filter, stop

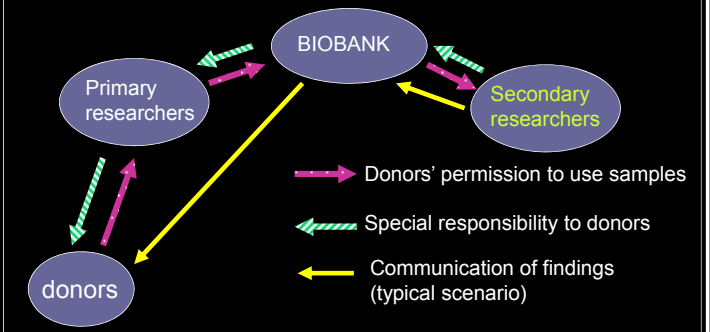
Ratcheting up rescue, cont.

- Worrying apparent variants found: p = .01
- Quality-check the finding if cost < $(.01x)
- Worrying apparent variants, still: p = .02
- Filter the variants if cost < $(.02x)
- Worrying variants, still, p. = .03
- Check pathogenicity if cost < $(.03x)
  - If not, stop
  - If pathogenicity score < 1, stop

Ratcheting up rescue, cont.

- Worrying apparent variants found: p = .01
- Worrying apparent variants, still: p = .02
- Worrying variants, still, p. = .03
- Check pathogenicity if cost < $(.03x)
- If pathogenicity score is 2-4, reeval. later
- If pathogenicity score = 5, duty of tactful silence overcome: report (AC duty kicks in)

Secondary researchers: The AC obligation travels with the permissions



Richardson & Cho *GIM* 2012

Conclusions

- The partial-entrustment model well explains why genetic & genomic researchers may have obligations to return certain individual results.
- These obligations go beyond easy rescue, yet remain limited in strength
  - Won't cover all cases of return of genetic findings (e.g., a case with some cost, but little difference to person's well-being)
  - Don't support a duty to hunt for findings, but will support a ratcheting up from rescue to AC obligation
- Planning for when & how to return individual results would ease the burden of fulfilling this obligation

Perelman School of Medicine
University of Pennsylvania

The case for a stringent approach to returning results

Steven Joffe, MD, MPH
Emanuel and Robert Hart Associate Professor
Department of Medical Ethics & Health Policy

Committee on National Statistics
National Academies of Sciences
Washington, DC
February 10, 2014

Preview

- Ought implies can
  - Ought researchers to offer to return of (some subset of) genomic results?
  - Can researchers actually carry out a policy of returning results?

Ought

Current guidelines

Individual genetic results *should* be offered to study participants in a timely manner if they meet *all* of the following criteria:

a. The finding has important health implications for the participant, and the associated risks are established and substantial
b. The finding is actionable
c. The test is analytically valid, and the disclosure plan complies with all applicable laws
d. The participant has opted to receive his or her individual genetic results

Circ Cardiovasc Genet 2010;3:574

Can investigators and subjects agree that findings will *not* be returned?

- Informed consent spells out terms of agreement between investigator & participant
  - quasi-contract
- Competent adults have wide latitude to set terms of their agreements

Can investigators and subjects agree that findings will *not* be returned?

- Not all terms of agreement are allowable
  - Some terms are *unconscionable*
  - Some terms are *expressly prohibited* by applicable regulations or laws
    - E.g., "No informed consent, whether oral or written, may include any exculpatory language through which the subject…is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence"

45 CFR 46.116

Can investigators and subjects agree that findings will *not* be returned?

- Would such an agreement be unconscionable?
  - agreement by subjects to accept a grave risk of serious harm might be
  - but we are talking about an agreement to forego some potential side benefit
- Is such an agreement expressly prohibited?
  - nothing in Common Rule or other laws/regs, at least at federal level, proscribes it

Can

Identifying pathogenic variants in an unselected population is challenging

- Johnston & colleagues analyzed exome sequence data from 572 participants in ClinSeq cohort
  - Sought to identify "likely pathogenic" and "definitely pathogenic" variants in 37 high-penetrance cancer-susceptibility genes
  - Participants selected for cardiovascular, not cancer, phenotypes

Am J Hum Genet 2012;91:97

Defining a "genetic result" requires a variant classification scheme

Table 3

Proposed Classification System for Sequence Variants Identified by Genetic Testing

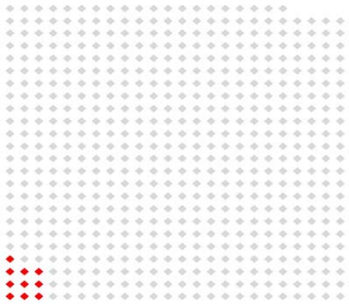
Class	Description	Probability of being Pathogenic*
5	Definitely Pathogenic	>0.99
4	Likely Pathogenic	0.95–0.99
3	Uncertain	0.05–0.949
2	Likely Not Pathogenic or of Little Clinical Significance	0.001–0.049
1	Not Pathogenic or of No Clinical Significance	<0.001

- These probabilities depend upon the *prior probability* that someone has a pathogenic variant
  - in the case of a secondary finding, this is very low

Human Mutation 29:1282, 2008

572 ClinSeq participants

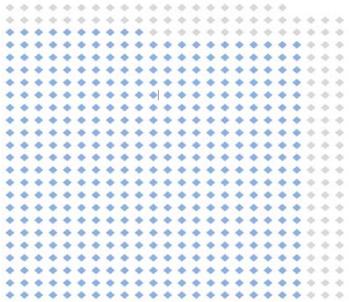
Numerator is manageable



* 10 definitely or likely pathogenic variants identified

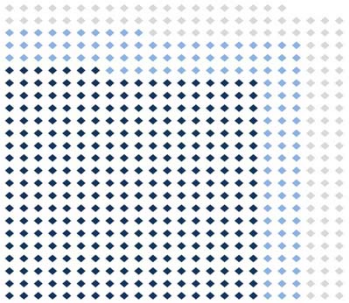
* MUTYH (familial adenomatous polyposis; N=4); BRCA1 (N=2); BRCA2 (N=3); SDHC (hereditary paraganglioma; N=1)

Denominator is probably not manageable



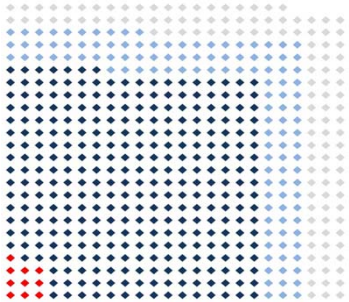
* 451 unique variants identified
  * limited to nonsynonymous, frameshift, nonsense or splice variants in 37 cancer genes

Denominator is probably not manageable



* 120 non-pathogenic variants eliminated on the basis of high population or cohort frequency or low data quality
  * leaving 331 variants required curation

Accuracy matters



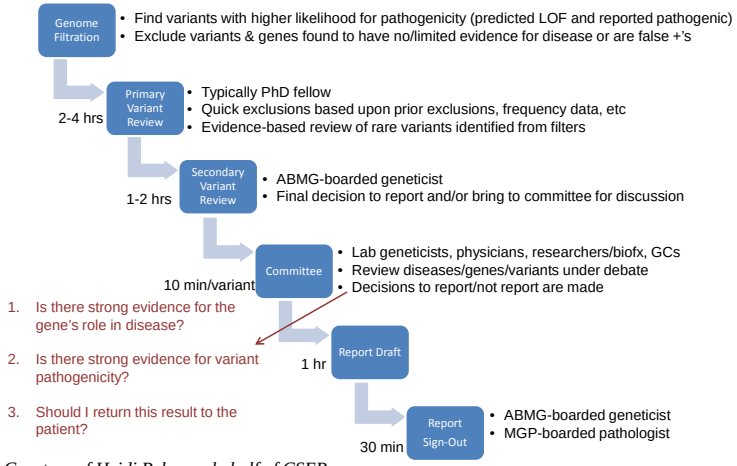
* Every blue dot is a setup for a false positive

False positives are a major threat

- Four main sources
  - Technical error in reading sequences
  - False-positive associations in the literature (e.g., due to multiple hypothesis testing)
  - Incorrect penetrance estimates
    - Esp because most data are based on variants from individuals with known phenotypes or family histories
  - Inaccurate annotation in reference databases

Genetics in Medicine 14:399, 2012

Gold-standard clinical genetics process



Courtesy of Heidi Rehm on behalf of CSER

Choices

1. No requirement for return
2. Require return, but accept lesser standard of interpretive validity than clinical genetics lab
   - Esp risk of false-positives
3. Expect research teams to achieve clinical-lab standard
4. Send every sample (or every screen-positive sample) to a clinical lab

Summary

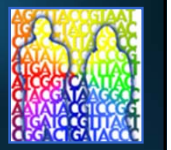
- Informed agreement between investigator and prospective subject that no results will be returned is ethically and legally permissible
- Unless list of returnable variants (not genes) is specified in advance, requirement to return secondary findings would either
  - be immensely costly,
  - or do more harm than good,
  - or both

Returning Genome-based Research Results: Public Accountability

Susan M. Wolf, JD
McKnight Presidential Professor of Law, Medicine & Public Policy
Faegre Baker Daniels Professor of Law
Professor of Medicine
Founding Chair, Consortium on Law and Values in Health, Environment & the Life Sciences
University of Minnesota

Overview

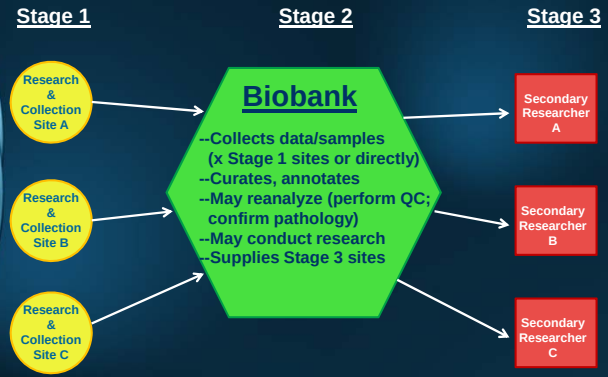
- Approaches to RoR/IFs in primary research & in clinical care don't adequately address research involving a biorespository or biobank
- BB research is characterized by 3 stages:
  - primary research & collection sites
  - biorepository or biobank
  - secondary (2ndary) analysis
- = a "biobank research system"
- BB research systems face issues of:
  - distributed duties, scope of return, time lapse, retrofitting
- As a publicly funded, pop.-wide study, NHANES can pioneer publicly accountable RoR/IF



GIM symposium & consensus paper

- Wolf et al. *Genet Med* 2012;14(4):361-384.
- On RoR/IFs in biobank research systems

Biobank Research System
(from *GIM* recommendations paper)



IFs & IRRs can arise at all 3 stages:

Stage 1—primary collection/research sites:

- ascertaining individual's eligibility to participate & collecting baseline info (eg, blood pressure)
- primary research on data/samples

Stage 2—biobank processing & research:

- processing of data/samples (eg, reconfirming cancer pathology and finding discrepant diagnosis)
- quality control (eg, finding chromosomal abnormality)
- biobank research in genetic/genomic OR phenotypic data (eg, in EHR)

Stage 3—2ndary research sites:

- analysis of data/samples by 2ndary researchers

Approaches to IFs/IRRs in biobank & 2ndary research

- **Conventional view**: return no IFs/IRRs, or BB & 2ndary researchers convey to primary researchers
- **Problems**: primary researcher funding expiration; inconsistency across BB sources; public demand
- **Question**: **Should BBs shoulder some responsibility to analyze IFs/IRRs & determine whether to return?**
- Should BBs -- or a trusted intermediary -- hold keycodes to reidentify participants, have ethics capacity to analyze IFs/IRRs, be funded to perform this function?
  - Debate at NCI Workshop (July 2010)
  - Comparative work at Brocher Workshop (Nov. 2013)

Ethical considerations re RoR/IFs in research involving biobanks:

- Withholding data from subjects makes them "passive purveyors of biomaterials and data," not research partners (Kohane et al. 2007)
- Researchers bear duty of reciprocity (Illes et al. 2006)
- Population-based research depends on public trust
- Recruiting a diverse population increases the need to ensure partnership
- Need means of stakeholder involvement & governance
- Ethics literature addresses BB responsibilities of stewardship & transparency
- Publically funded population projects have public duties

Starting place: governance

At the BB or Network:

- Committee on Incidental Findings (GENEVA)
- RoR Oversight Committee (eMERGE Network)
- UK Biobank Ethics & Governance Council (EGC)
- Informed Cohort Oversight Board (ICOB) (Coriell Personalized Medicine Collaborative; Kohane et al. 2007)
- Participant community engagement (eg, on ICOBs, EGC)

Recommendations for BB research systems—1 (of 4): (Wolf et al. *GIM* 2012)

- Core responsibilities: Biobanks should work with primary research/collection sites & 2ndary researchers so that BB research system responsibly manages IFs/IRRs; this requires planning, budget, coordination across Stages 1-3
- To allocate responsibilities across the BB research system, ID steps, "drive the CARR":
  - Clarifying criteria for "should return," "may return"
  - Analyzing a particular finding
  - Reidentifying the source individual
  - Recontacting the individual to offer the finding

Recommendations--2:

- To clarify criteria for return: BBs should have a multidisciplinary committee (eg, ICOB) to work w/IRB. Central advisory body may be useful.
- BB research system should return IFs/IRRs that:
  - are analytically valid, in compliance with law (eg, CLIA*)
  - reveal est'd & substantial risk of serious **health** condition
  - actionable (significant potential to alter onset, course, or tx)
  - return is consented to by source (at initial consent or after)
- BB research system may return more IFs/IRRs if:
  - reveal est'd & substantial risk of likely **health or reproductive** importance, or **personal** utility to source &
  - return is likely to provide net benefit

*Note continuing dispute re what CLIA requires.

Recommendations--3:

- Analyzing the finding: When IFs/IRRs arise in primary research, the primary researcher and institution will be responsible for handling.
- But when IFs/IRRs arise:
  - in collecting data/samples for BB
  - in BB quality control, processing, or research, or
  - in 2ndary research using BB data/samples,

  the biobank should bear primary responsibility for analyzing whether a particular IF/IRR should be offered back to the individual contributor.

Recommendations--4:

- Reidentification & recontact for return in a BB research system won't always be possible.
- When=possible, and only the primary researchers can reidentify (they alone hold key codes), they will need to reidentify.
- BBs should consider holding key codes or using a "trusted intermediary." Avoids relying entirely on the primary site for capacity to reidentify & for the time BB & 2ndary research are continuing.
- Still leaves Q of who recontacts. May best be handled by primary site.

Issues

- Retrofitting preexisting biobanks
  - Recontact & reconsent
- Dynamic consent processes
  - Tracking preferences over time
- Pediatric RoR/IFs
  - Reconsent at majority
- RoR/IFs to kin
  - Including after death of proband
- Collecting data on cost
- ACMG 2013 -- implications for research? →

ACMG 2013 (Green et al.): IFs in clinical genome sequencing

- Specifies "minimum list" of 56 more genes labs must analyze whenever they do sequencing for a different clinical reason
  - NO patient consent to analyze these specific genes
  - Patient who doesn't want IFs must decline sequencing
- Lab **must** report these to clinician
- Clinician reports these to patient
  - NO patient "right not to know"
    - "shared decision-making" isn't a right not to know
    - once IFs=in medical record, patients have access
- = opportunistic screening w/o adequate evidence base, as they acknowledge
- Issue: Some research projects are using this approach.

Reactions

- Rejects long-established patients' rights to refuse genetic tests & results
- Some patients may want the extra tests, but some will not— need to respect patient choice
- Unlike an x-ray or scan of a broken arm where the radiologist may report additional unexpected pathology in the scanned field:
  - ACMG says to hunt a predetermined list
  - hunting throughout the entire genome
  - including genes we've long asked consent to test for
- ACMG does not address research
- Presidential Commission (2013): parts ways on clinical
  - Researchers can reject or use hunt for IFs, with specific IC
  - Doesn't address person whose sole access is by research

Conclusion

- A publicly supported, population-wide study needs public support and trust
- Needs broad participation from a diverse population
- People should know they're participating, even if on a deidentified basis (cf. ANPRM, risk of re-ID)
- Address RoR/IF duties across the BB research system
- On scope of RoR/IF--public deliberation, transparency
  - Should offer (w/consent): hi health risk, actionable
  - May offer (w/consent): substantial risk of health, reproductive, or personal importance
- Cost relevant, but need rigorous evaluation
- NHANES can pioneer publicly accountable RoR/IF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