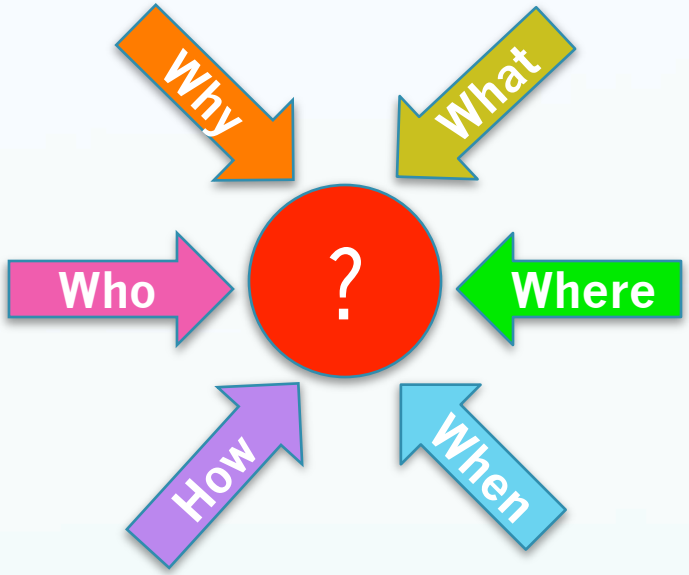
Returning Research Results



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Why return research results?

- Acceleration in the pace of genetic and genomic research
- Possible important implications for participants, patients, families – e.g. health, reproductive decisions
- Increasing discourse about investigators' ethical responsibility to offer participants access to research results
- Consistent with ethical principles of Beneficence and Respect for Persons, and Reciprocity

Bookman et al. 2006; Wolf et al. 2008; Fabsitz et al. 2010; Bredenoord et al. 2011; Tabor et al. 2011; Ravitsky & Wilfond 2006; Dressler 2009; NBAC 1999

What types of results might be generated?

Genetic Research Results

- Research focused narrowly on a few genes, targeted sequencing, or broadly on non-functional variants possibly linked to functional changes

- Incidental findings
  - Chromosomal rearrangements
  - Sex chromosome aneuploidy
  - Variants in candidate genes associated with other traits or diseases
  - Misattributed parentage

Genomic Research Results (esp. WES/GS)

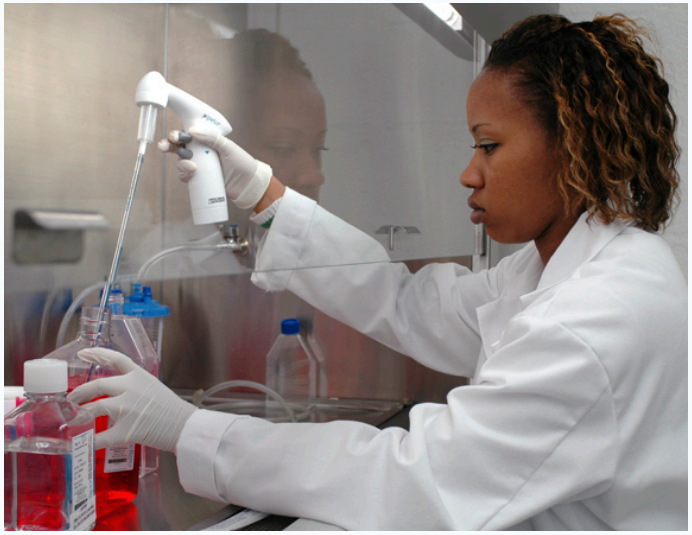
- Will identify a very large number of "functionally relevant" variants for each person
- Likely to produce more clinically useful and actionable results
- Known variants in genes for autosomal dominant diseases and traits
- Known genetic risk factors for complex diseases, pharmacogenomics response
- Unanticipated findings
  - Previously, no obligation to look because these findings were "incidental" to the content and purpose of original research
  - Now, major aim is to identify all variants in an exome/genome – minimizes the distinction between so called "incidental findings" and primary findings

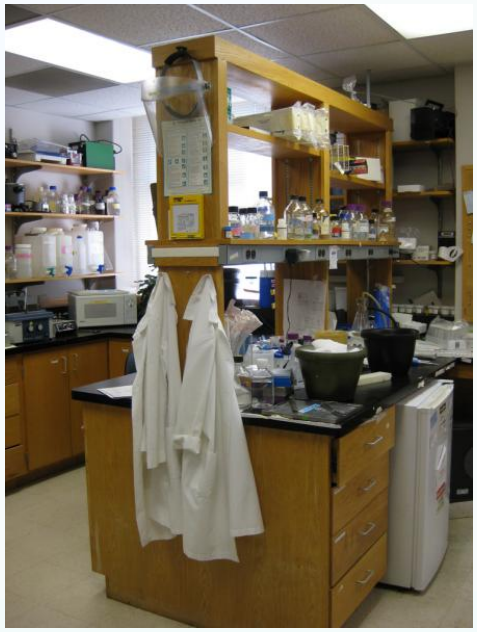
Tabor et al. 2011

Where might results be returned?

Basic Science Research

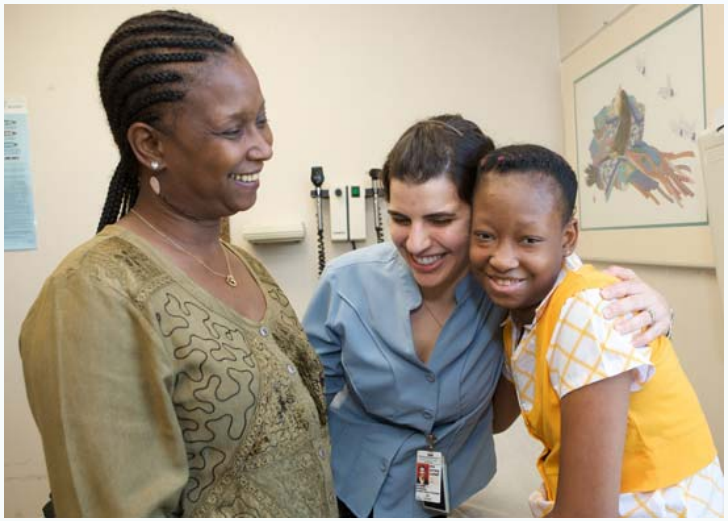
- Authorization of research labs to return results

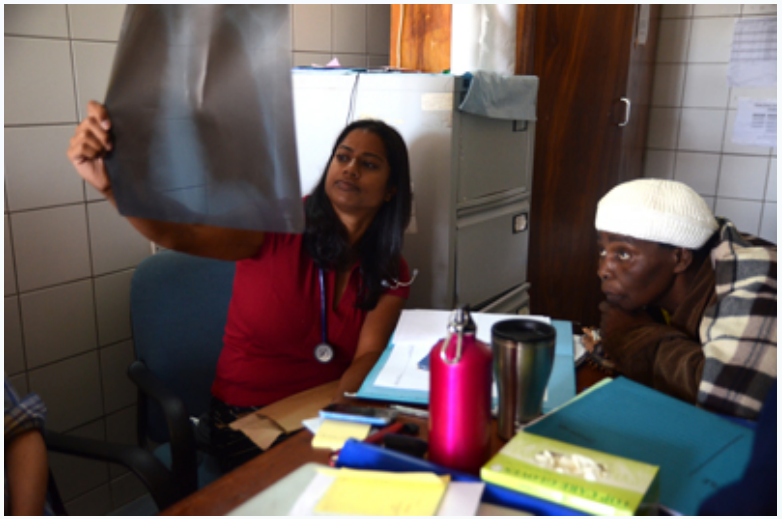




- Obligations and skills of researchers to evaluate, return, and explain different kinds of results
- Recontacting research participants (e.g. participants in biorepositories)

Clinical Research





- Clear communication of return of results process to participants as part of the informed consent process
- Blurring of the distinction between research and clinical care

When is it appropriate to return results?

- Clinical validity
  - The genetic variant being analyzed relates to the presence, absence or risk of a specific disease
- Clinical utility
  - Genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available
- Functional relevance
  - Known to be related to a function, but no clinical validity or utility

Berg et al. 2011; Beskow & Burke 2010

Proposed Binning System (Berg et al, 2011)

	Criteria:	*Clinical Utility*	*Clinical Validity*			*Unknown Clinical Implications*
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3 All other loci**
	Examples:	*BRCA1/2 MLH1, MSH2 FBN1 NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000
Alleles that would be reportable (YES) or not reportable (NO) in a clinical context						
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

N/A: not applicable; VUS: Variant of uncertain significance

[1] Reporting through decision making with an appropriate provider if elected by the patient.

[2] By definition, variants in genes with unknown implications could not be considered deleterious.

[3] By definition, SNPs or PGx variants will either be present or absent.

[4] Variants in genes with unknown clinical implications would not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.

How should results be returned?

Individual versus Aggregate Results

- Samples may be collected anonymously or pooled, limiting option of method of return
- Participants have expressed preference for individual research results
- Increased likelihood of participation in studies that returned individual research results compared to those that offered only summary reports
- Individual results may help build trust between participants and researchers

O' Daniel & Haga, 2011; Dixon-Woods et al. 2006; Berg et al. 2011; Schulz et al. 2003

In-person, Web Portal, etc.

- Limited public understanding of genetics
- Some participants prefer to receive results in-person
  - Increased cost and burden with this approach
- Novel tools are needed for participants to "revisit" their data and interpretations
- Online approach could create transparency, enable participants to stay informed of research progress, and increase engagement

O' Daniel & Haga 2011; Fernandez et al. 2007

Who are key players in the return of results process?

Deliverer(s) of Results

- Researcher, nurse, genetic counselor, participant's physician
- Participants more likely to choose to learn their results from their physician more than researcher *(O'Daniel & Haga 2011)*
- Large number of researchers did not consider returning results, and among those who did, most common factors considered - whether results were clinically useful, respect for participants *(Heaney et al 2010)*
- Delivery and follow-up require significant time & resources

Recipient(s) of Results

- Participants, families, populations, children
- Lack of receiving results can be a deterrent for research enrollment
- Participants see the potential familial benefit as an advantage of participating in research
- Accuracy of results, personal relevance, clinical utility more important than potential for discrimination
- Participants desire the option to decide what type of information they want to learn
- Generally, participants desire access to results, even if they are upsetting or not considered clinically valid or useful

O' Daniel & Haga 2011; Murphy et al. 2008; Wheeler et al. 2008; Fernandez et al. 2007; Schulz et al. 200; Biesecker 2012

U.S. Guidelines

Table 1. Summary of key U.S. guidelines on the return of genetic research results

	Disclosure policy	To whom information can be disclosed
National Bioethics Advisory Commission, 1999	Individual data only if valid, confirmed, have significant health implications, can treat or ameliorate	Research participant
Centers for Disease Control and Prevention, 2001	Aggregate and individual data only if likely to lead to evidence-based intervention	Research participant
RAND Corp., 2003	Aggregate data only	Public: via internet, newsletter, scientific meeting
National Heart, Lung, and Blood Institute (NHLBI), 2004	Individual data only if analytically valid, replicable, and significant; have severe health implications; can treat or prevent	Research participant
National Cancer Institute (NCI), 2007	Aggregate and individual data	Research participant, participant's health care provider, family
Public Responsibility in Medicine and Research, 2007	Individual data only if compelling rationale	Research participant[a]
National Institutes of Health Genome-Wide Association Studies, 2007	Individual data only in rare circumstances	Downstream users disclose to contributing investigator
National Human Genome Research Institute, 2008	Right to access individual data unless results are of unproven clinical validity and judged by IRB to be of no benefit to subjects	Research participant
NHLBI, 2010	Individual data only if analytically valid, replicable, and significant, have important health implications, can treat or prevent	Research participant
NCI, 2011	Aggregate and individual data if research participant has consented to receive research results and if results are analytically valid, clinically significant or serious, and clinically actionable	Research participant

Cassa et al. 2012

International Guidelines

- Approximately 15 international laws and guidelines
- Existing international norms are inconsistent
  - Use ambiguous terminology and conflate different concepts
- Spanish 2007 Law on Biomedical Research
  - Affirms participant's right "not to know" about incidental findings
  - Allows a close family member or representative to be informed of incidental findings if this will avoid a serious health problem for the participant or his/her biological relatives

Zawati & Knoppers 2012

International Guidelines

- WHO's European Partnership on Patients' Rights and Citizens' Empowerment's 2004 report:
  - Because "research includes matters of unknown future import, sometimes unexpected findings can be generated," and when "an immediate and clear benefit to identifiable individuals can be achieved…[which] will avert or minimize significant harm to the relevant individuals," such findings should be returned.

Zawati & Knoppers 2012

Summary

- Lack of consensus on many key aspects of the debate
- Decision-making process about returning results should be informed by:
  - Relationship of researchers with participants
  - Informed consent document
  - Resources available to analyze, confirm, and return results
- Researchers planning to return results need to make decisions about:
  - How to distinguish variants of known clinical utility, possible clinical utility, and unknown significance
  - What kinds of results to return, with input from participants
  - How to approach possible recontact of participants
  - Practical personal, institutional, and healthcare resources

Moving Forward

- Additional empirical research
  - Perspectives of various stakeholders
  - How recipients understand & utilize results over time
  - Assess psychological, social, and health outcomes
  - Assess impact on clinical care and costs
- Increased support/funding for empirical research and the development of relevant guidelines – local and global
- Development and dissemination of tools for managing the return of results as indicated