PGC Worldwide Lab Call Details

DATE: Friday, May 9th, 2014
PRESENTER: Paul S. Appelbaum, MD, Columbia University
TITLE: "Informed Consent for Return of Incidental/Secondary Findings In Genomic Research"
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
2400 AEST – Australia (Friday, May 9th into Saturday, May 10th, 2014)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
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- This conference line can handle up to 300 participants.

PASSCODE: 275 694 38 then #

Lines are Muted **NOW**

Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

Operators announce callers one at a time during question and answer sessions.

Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC Worldwide Lab

DATE: Friday, June 13, 2014
PRESENTER: To Be Announced
TITLE: To Be Announced
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
0000 AEST – Australia (Saturday, June 14th, 2014)
DURATION: 1 hour

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Informed Consent for Return of Incidental/Secondary Findings In Genomic Research

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Director, Center for ELSI Research on Psychiatric, Neurologic & Behavioral Genetics

Columbia University

Overview

- What are incidental/secondary findings and where do they come from?
- What should investigators do with incidental/secondary findings?
- What considerations enter into getting consent for return of incidental/secondary findings?

What Are "Incidental" Findings?

- Variants detected that are not related to the patient's indication for testing are called "incidental findings" or "secondary findings"
- Whole genome and exome sequencing (WGS/WES) have the potential to yield IFs because large portions of the genome are sequenced in addition to what might be regions of primary interest

What Can IFs Tell You?

- Predisposition to a disease condition in the future
  - Medically actionable (cancer, heart disease)
  - Not currently medically actionable but perhaps personally actionable (muscular dystrophy, neurodegenerative disease)
- Carrier status of a recessive condition
  - May have reproductive implications
- Pharmacogenetics: variants associated with drug response or toxicity

How Are IFs Found?

- IFs may be detected in the course of planned analyses ("true IFs")
  - Pleiotropic effects (e.g., GBA1 mutations causes Gaucher's disease if homozygous and increase risk of Parkinson's disease in carriers)
  - Genome-wide exploratory analyses may detect known pathogenic mutations
- IFs may be specifically sought ("secondary findings")
  - Analogous to ACMG recommendations for examining and reporting findings of actionable mutations in clinical sequencing

Not All Sequencing Studies Will Have IFs

- Targeted analyses can limit or avoid IFs by focusing only on findings of interest
  - E.g., only particular portions of the genome may be analyzed
- Reporting of specific findings can also be blocked
  - E.g., ApoE results in student self-sequencing projects
- Bottom line: not all sequencing studies will yield IFs—depends on methods used

What Should Investigators Do With Incidental/Secondary Findings?

- Arguments for returning IFs to participants
  - Beneficence: IFs can benefit health care, life-planning, reproductive planning
  - Autonomy: "I have the right to know what they found in my DNA."
  - Fairness: Ancillary-care obligations

What Should Investigators Do With Incidental/Secondary Findings?

- Arguments against returning IFs to participants
  - Beneficence: Many findings of uncertain import
  - Non-maleficence: People may be upset by receiving results
  - Fairness: Devoting resources to interpretation and counseling will undercut research effort

How to Balance Competing Considerations in Return of IFs?

- Studies of participants' preferences have found consistent interest in knowing about IFs, especially if clinically actionable
- Growing number of federal agencies, expert panels, and authors have recommended that at least some genomic IFs be made available to participants
- However, dissenting positions exist, especially within the research community, where concerns about the feasibility and cost of analyzing and returning IFs are often voiced—we wanted to hear more about this

Survey and Interviews of Researchers About Secondary Findings for Previously Enrolled Participants

- Survey of the practices and attitudes of 234 members of the US genetic research community in August-October, 2012
  - NIH RePORTER
  - 2011 ASHG program
  - 34.7% response rate
- Performed qualitative semi-structured interviews with 28 genomic researchers
  - 56% response rate

Genet Med. 2013; 15(11):888-895.
Genet Med. 2013 Sep 26. doi: 10.1038/gim.2013.140.

Characteristics of Researchers

Demographic characteristic	Percentage
Male	64.3%
Age	43.2 +/- 11.2
Race/ethnicity	
Asian	14.5%
Black or African American	0.4%
Hispanic	5.0%
Non-Hispanic White	73.0%
More than one race	1.7%
Unknown or not reported	5.4%
Education	
MD	19.1%
PhD	51.9%
MD PhD	13.3%
MS	7.9%
Other	7.9%

Genet Med. 2013; 15(11):888-895

Roles of Researchers and Their Research Studies

Researcher roles and characteristics	Number	Percentage
Role(s) of the researcher		
Obtaining informed consent	116	48.1%
Collection of clinical/phenotypic data and biospecimens	131	54.4%
Generating genomic data	164	68.0%
Analysis of genomic data	218	90.5%
Receives de-identified samples/data	194	80.5%
Provides clinical care	14	5.8%
Years of experience in human genetic research		
< 1 year	4	2.3%
1-5 years	54	30.5%
6-10 years	42	23.7%
11-20 years	48	27.1%
> 20 years	29	16.4%

Genet Med. 2013; 15(11):888-895

Roles of Researchers and Their Research Studies

Researcher roles and characteristics	Number	Percentage
Populations studied		
Adults	228	94.6%
Children	137	56.8%
Fetuses	20	8.3%
Adults lacking decision-making capacity	41	17.0%
Terminally ill	72	29.9%
Number of participants enrolled		
< =100	29	16.3%
101-500	29	16.3%
501-1000	20	11.2%
1001-5000	66	37.1%
5001-10,000	15	8.4%
> 10,000	19	10.7%

Genet Med. 2013; 15(11):888-895

Roles of Researchers and Their Research Studies

Researcher roles and characteristics	Number	Percentage
Genetic methods used		
Candidate gene resequencing	176	73.0%
CNV analysis	164	68.0%
GWAS	164	68.0%
WES	178	73.9%
WGS	132	54.8%
WES & WGS	112	46.5%
Plans to do WES/WGS	35	14.5%
Participants studied using WES or WGS		
< 10	25	12.3%
11-50	41	20.1%
51-100	32	15.7%
101-500	54	26.5%
501-1000	20	9.8%
> 1000	32	13.3%

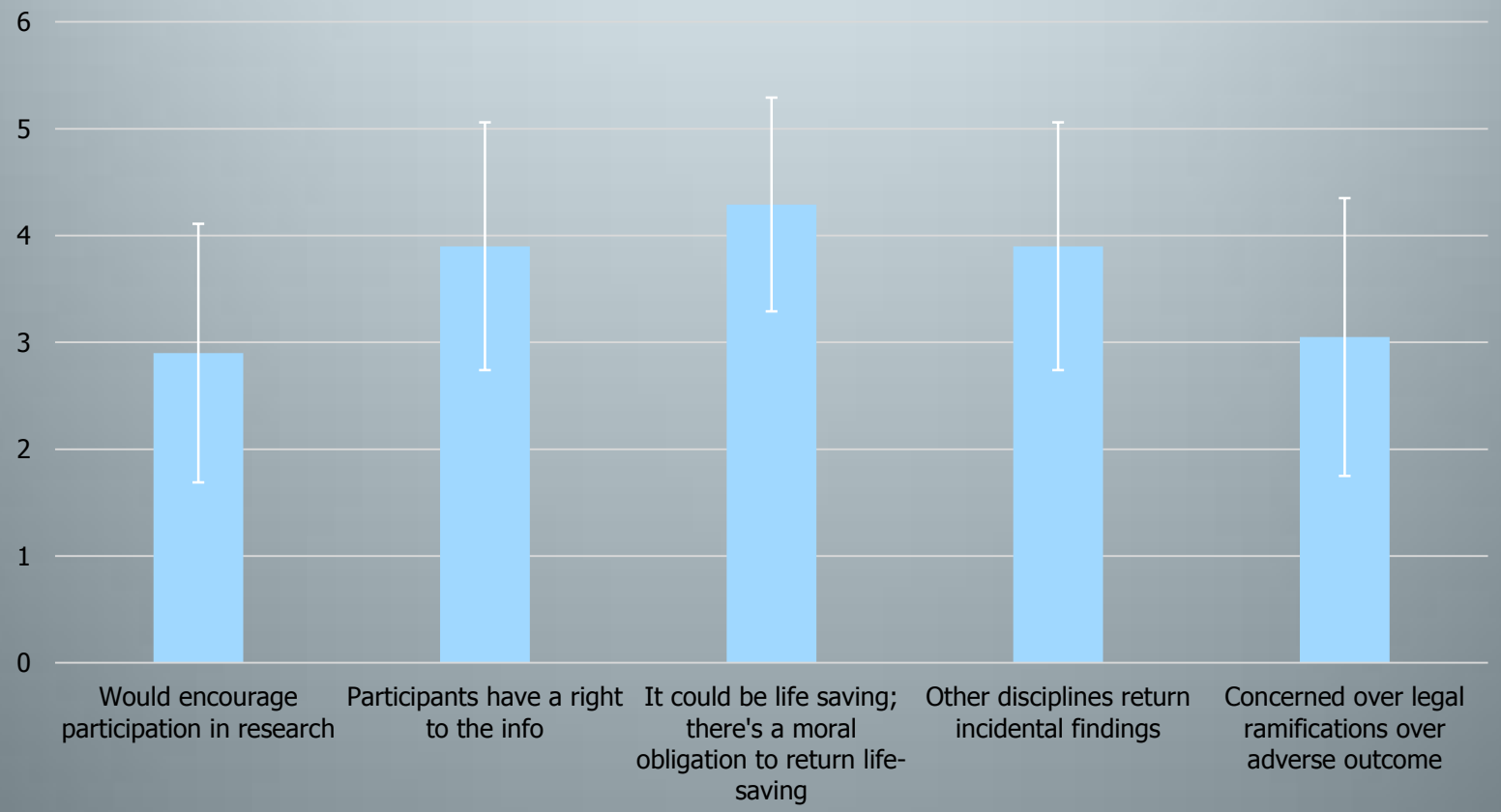
Genet Med. 2013; 15(11):888-895

Data Researchers Would Return to Participants of Different Ages

Kind of data	Adults	Children	Fetuses
High penetrance, with clinical intervention	95.0%		78.7%
Clinically actionable before adulthood		91.5%	
Clinically actionable only in adulthood		67.7%	
High penetrance, without clinical intervention	60.2%	48.5%	63.3%
Modest penetrance, with clinical intervention	79.3%		60.7%
Modest penetrance, without clinical intervention	40.7%	31.1%	32.7%
Reproductive implications for prospective parents	79.3%	58.3%	52.7%
Reproductive implications for the children of participants	65.6%		
Data on pharmacogenetic variants	54.4%	51.9%	40.7%
Potentially relevant, no clinical implications (ancestry)	21.2%	14.8%	
List of all variants from entire genome/exome	15.8%	14.0%	8.2%

Genet Med. 2013; 15(11):888-895

Importance of Each Reason for Returning Incidental Results



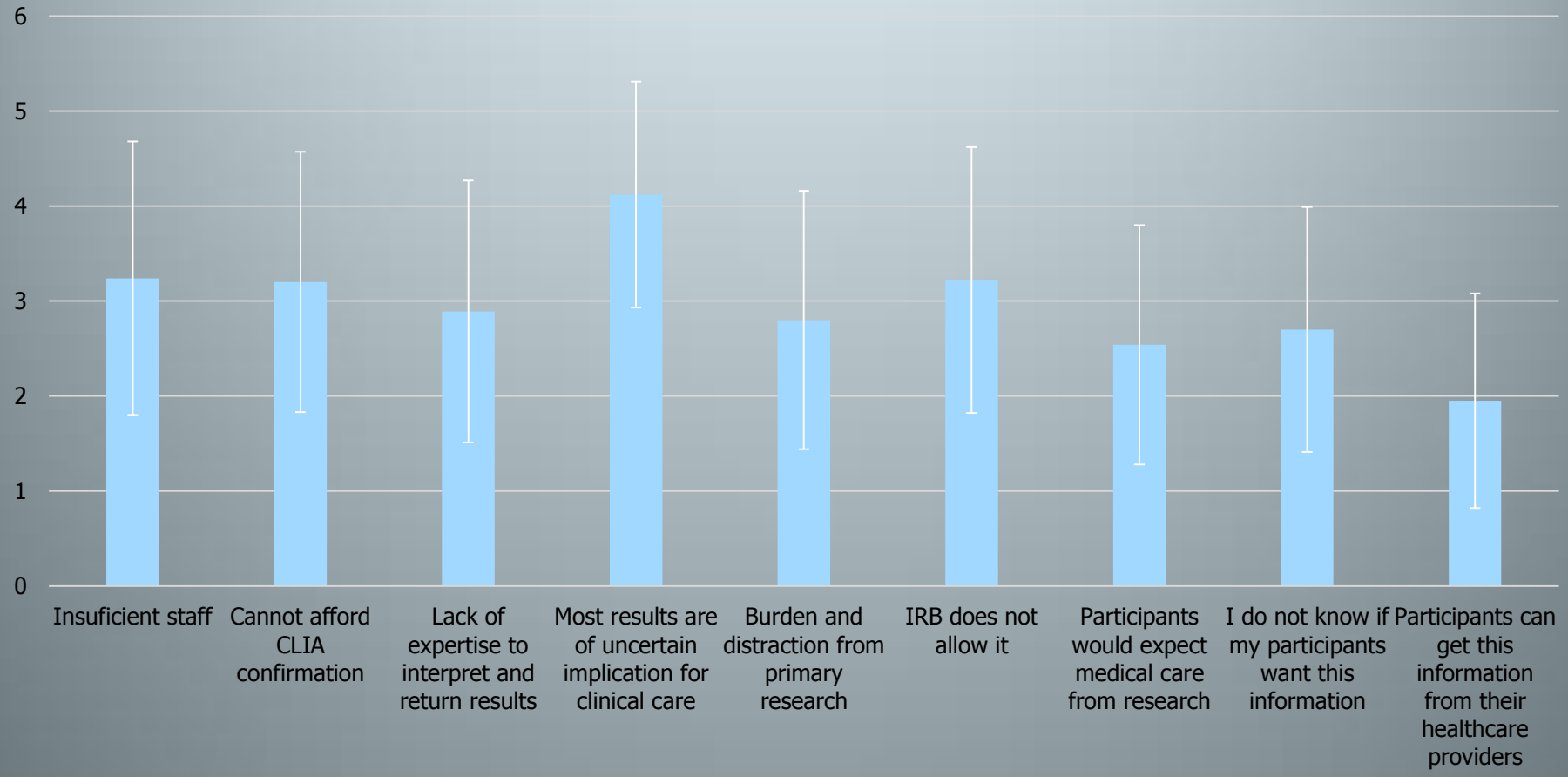
Genet Med. 2013; 15(11):888-895

Reasons to Return Incidental Findings

- To withhold such medically actionable information is morally uncomfortable.
- "Look, these are my patients. I'm going to tell them." (R-I 5)
- A person owns their own genome. If they want to know what their genome is… they have a right to know, period. The implications of the knowledge don't matter." (R-I 22)
- I think that returning of incidental results is often appreciated by research subjects as a way of demonstrating that the researchers care about the benefit to them and not just the benefit to the research. (R-S 001)

Genet Med. 2013; 15(11):888-895

Importance of Each Reason for Not Returning Incidental Results



Genet Med. 2013; 15(11):888-895

Reasons Not to Return Incidental Findings

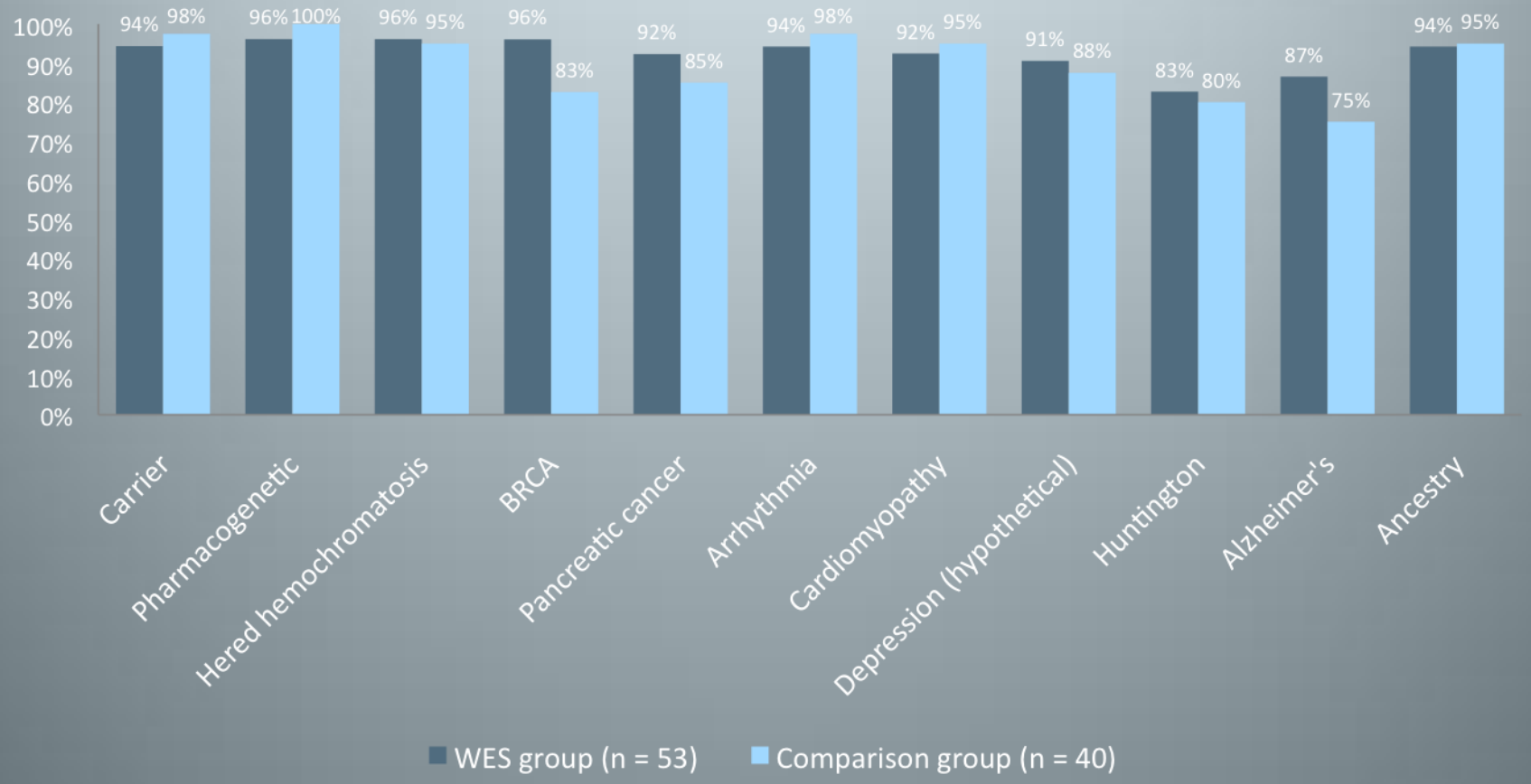
- "Seems [it] could open up liability even if we did nothing because it could be argued we should have done something. So there is safety in not being allowed to do anything." (R-S 118)
- "If we don't know what something means, we're doing more of a disservice than a service by telling patients…Our credo is 'do no harm.' Sometimes telling people something that you don't understand does harm. (R-I 17)
- "As researchers, we are not equipped to offer [to] return findings to patients. (R-S 182)
- "We just don't have the money to go back and re-test this, to re-analyze these sequences, to see if people have these variants… It comes down to cost."
- "Subjects should have the option of obtaining the results, but it can't be expected of a researcher (e.g., studying neurological disorders) to know the relevance of variants they found for cancer, etc." (R-S 106)
- "The number of potential IFs is essentially infinite. The amount of overhead for identifying and reporting incidental clinical findings would destroy the research enterprise in genetics." (R-I 28)
- "If we cut back deeply on the research, we won't get to that point in the future where everybody's genome will be sequenced, and become part of standard clinical care, rather than a research project." (R-I 18)

Genet Med. 2013; 15(11):888-895

Research Participants Generally Share the View that IFs Should be Offered

- We interviewed participants in WES studies and a comparison group after extensive informational process
- Detailed 30-minute video offering 12 clinical scenarios
- Written materials following with the video
- Followed by in person pre-test counseling with genetic counselor +/- clinical geneticist lasting 30-120 minutes

Participants' Preferences for Results



If IFs Will Be Returned, How Do We Approach Informed Consent?

- As part of survey of genomic investigators, we asked what information they thought should be shared with participants before they made a decision about return of IFs
- Also interviewed 20 research participants

What Benefits Should Be Disclosed?

Benefits	Researchers (n = 241)		Participants (n = 20)	
	%	Count	%	Count
A treatable disorder might be identified	94.5	225	95	19
Prophylactic measures may be available to prevent some disorders	84	200	95	19
Modern reproductive techniques (e.g., preimplantation genetic diagnosis) may allow carriers to have children with minimal risk of specific disorder	63.4	151	85	17
Knowing pharmacogenetic status can increase the likelihood of efficacy of some medications and reduce the chance of adverse reactions	67.6	161	90	18
Knowing one's propensity for developing particular conditions can help with life planning[b]	57.6	137		
Knowing whether they carry a disease mutation can relieve anxiety for some people[c]			85	17

IFs, incidental findings.

Genet. Med. 2013 doi:10.1038/gim.2013.145

What Risks Should Be Disclosed?

Risks	Researchers (*n* = 241)		Participants (*n* = 20)	
	%	Count	%	Count
The risk of false-positive findings[b]	94.5	225		
The risk of false-negative findings[b]	85.7	204		
The findings may be wrong[c]			90	18
Possible negative psychological responses	82.8	197	90	18
The danger of falsely concluding from a negative result that they are not susceptible to a disorder, e.g., because of limitations of the testing and existing knowledge	78.6	187	90	18
Possible confusion resulting from the ambiguity of the results	76.1	181	80	16
The possibility that the interpretation of the findings might be different in the future as more knowledge is acquired	85.7	204	90	18
The risk of stigma/discrimination (e.g., in insurance) if information about their test results becomes known	71.8	171	90	18
Possible need for further testing, counseling and follow-up, and the unavailability of funds from the study to pay for it	84.9	202	85	17
Risks to data security and confidentiality	53.4	127	85	17

IFs, incidental findings.

Genet. Med. 2013 doi:10.1038/gim.2013.145

What Else Should be Disclosed? – Family Issues

- Possible implications of IFs for participants' relatives - 92%
- Potential importance of participants sharing information with them – 92%
- Possible impact of findings on family relationships – 79%
- How IFs with implications for relatives will be handled if they become incompetent – 66%
- How IFs with implications for relatives will be handled if they die – 64%

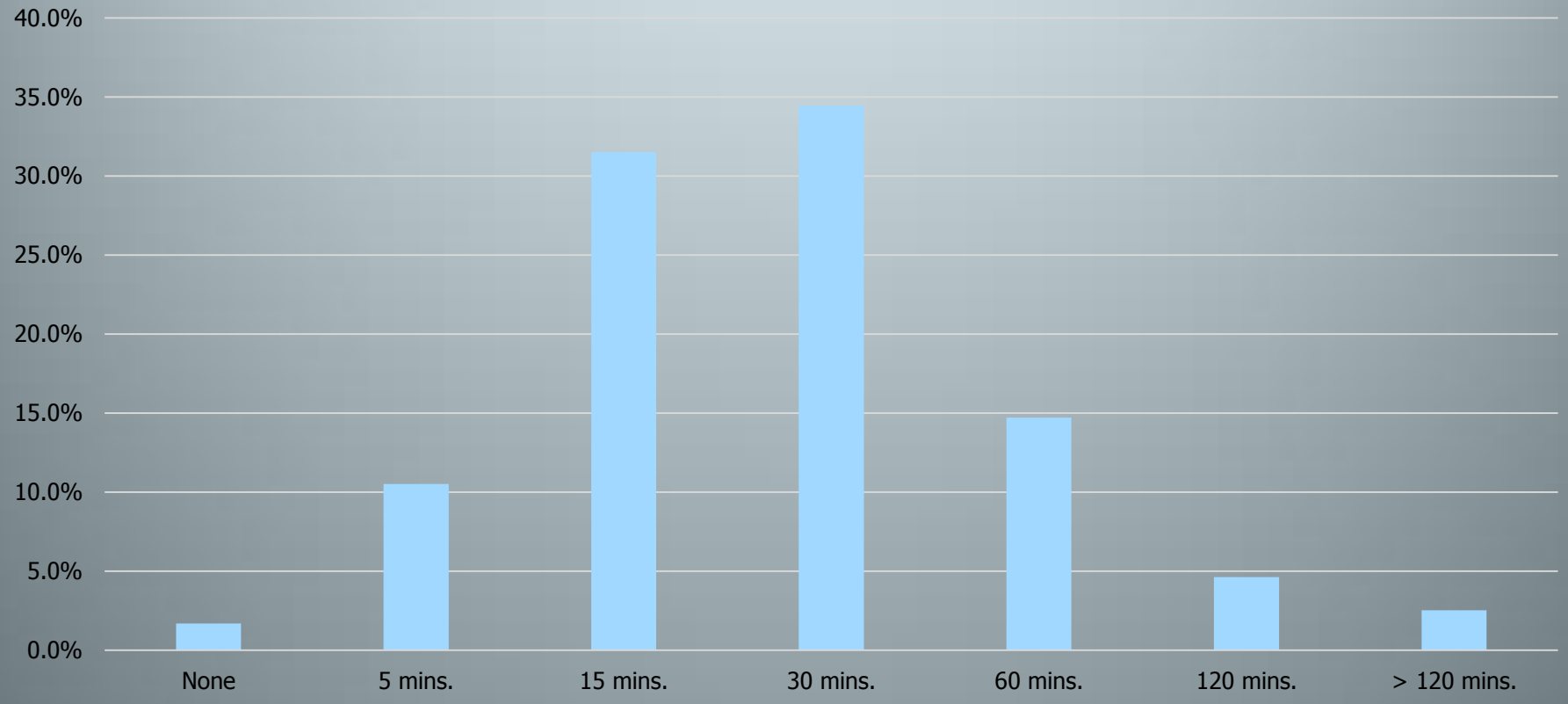
What Else Should Be Disclosed? – Other Issues

- Possibility of IFs from subsequent studies involving banked samples or archived data - 69%
- Data security procedures - 86%
- Penalties for researchers' failure to protect or properly use information - 47.9%
- Other issues mentioned
  - Paternity may be disproven
  - Incest may be discovered
  - If option exists to override participants' choices – 71%

What Other Decisions Should Participants Be Asked to Make?

- Obtaining consent for potential recontact – 78%
- Whether returned IFs are placed in their medical records – 76%

Reasonable Amount of Time for Informed Consent for Return of Incidental Findings



Genetics in Medicine: Accepted August 2013.

The Dilemma

- Standard approaches for obtaining informed consent are not likely to be effective at conveying all the information identified by our respondents as worth communicating—in the time available to do it

What's the Solution?

- Assuming that we maintain a commitment to participants making informed choices about receipt of IFs, innovative solutions are needed
- Based on survey responses, interviews, and literature review, we identified 4 leading models to consider
  - 1st model reflects traditional approach to consent, while the other 3 embody creative alternatives
  - Recognize that there are likely to be multiple permutations, including hybrid approaches that blur the boundaries between them, and other models may develop

Traditional Model

Traditional Consent: incorporate discussion of the issue into consent to participation in the underlying research

Potential Advantages

- Resembles traditional process, familiar to the research community
- Participant receives all IF information prior to deciding whether to participate
- Participant maintains choice about types of IFs to receive, or about opting out

Potential Disadvantages

- Adds time and information to lengthy and complex process
- Participant preferences may change after initial consent

Genet Med. : Accepted August 2013.

Staged Consent

Staged Consent: brief mention of incidental findings at the time of initial consent; more detailed consent when/if reportable results found

Potential Advantages

- Reduces time spent discussing IFs during initial consent; more detailed information provided later if IFs occur
- Participant makes decisions on IFs closer to the time of receipt, can consider current circumstances
- More detailed and specific information for participant
- Participant maintains choice about types of IFs to receive, or about opting out altogether

Potential Disadvantages

- Following-up and recontacting participants costly and burdensome
- Participant's decision to enroll made without full information about potential return of IFs
- Recontacting participant may reveal unwanted information about an IF, with negative impact on participant

Mandatory Return

Mandatory Return: Obtain consent to return of specific categories of IFs at the time of—and as a condition of—enrollment

Potential Advantages

- Simplifies consent at enrollment: participant receives information only on selected IFs, does not have to choose which findings to receive
- Researchers' obligations to return IFs clearly defined and limited to a pre-determined list
- Degree of choice maintained about whether to participate in the study

Potential Disadvantages

- Participant choice restricted—can't choose which findings to receive, and cannot refuse to accept designated findings
- Lack of participant choice may be disincentive to enroll in genomic research
- Efforts to follow-up and recontact participants could be costly and burdensome for researchers

Outsourced Model

Outsourcing: Refer participants to third parties for consent and return of incidental findings

Potential Advantages

- Researchers don't have to spend time explaining implications of IFs
- Costs associated with return of IFs avoided, including recontacting participants, hiring additional staff, etc.
- Participant spared immediate task of deciding which secondary findings to receive
- Researchers' obligations simplified: return each participant's raw data

Potential Disadvantages

- Though participant receives all genomic data, may not become aware of medically significant data
- Services for genomic interpretation and counseling not widely available at present
- May exacerbate health disparities, since further interpretive services may be costly and limited to wealthy participants

Which Model is "Right?"

- No perfect model—approach selected will depend on assessment of researchers' obligations and practicality
- Assessment depends in part on empirical data not yet available, e.g., which model leads to best informed decisions or reduces adverse consequences
- Balance likely to change over time, e.g., as identification of variants as pathogenic or not improves and becomes increasingly automated

Conclusions

- Many WGS/WES studies will generate some number of IFs of clinical or personal significance
- Evolving consensus suggests that at least some IFs should be offered to participants
- But the complexity of obtaining informed consent will push the field away from traditional model
- Which model of consent becomes dominant will depend on a mix of normative and practical considerations

Research Team

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- Erik Parens, PhD
- W. Nicholson Price, JD, PhD
- Cameron Waldman
- Josue Martinez

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Publications

- Klitzman R, Appelbaum PS, Fyer A, Martinez J, Buquez B, Wynn J, Waldman CR, Phelan J, Parens E, Chung WK. Researchers' views on return of incidental genomic research results: qualitative and quantitative findings. Genet Med 2013; 15(11):888-895.
- Klitzman RL, Buquez B, Appelbaum PS, Fyer AJ, Chung WK. Processes and factors involved in decisions regarding return of incidental genomic findings in research. Genet Med, published online 26 September 2013, doi:10.1038/gim.2013.140.

Publications

- Appelbaum PS, Waldman CR, Fyer A, Klitzman RL, Parens E, Martinez J, Price WN, Chung WK. Informed consent for return of incidental findings in genomic research. Genet Medicine, published online 24 October 2013, doi:10.1038/gim.2013.145.
- Appelbaum PS, Parens E, Waldman CR, Klitzman RL, Fyer A, Martinez J, Price N, Chung WK. Models of consent to return of incidental findings in genomic research. Hastings Cent Rep (in press).