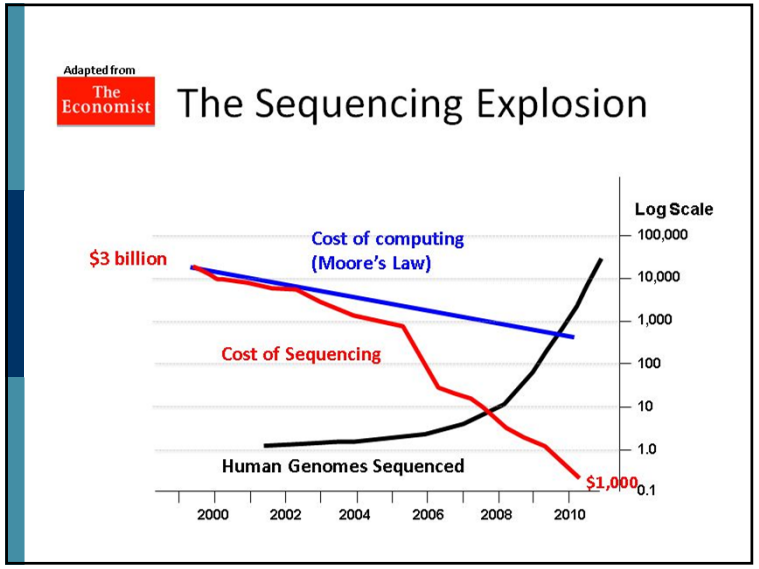
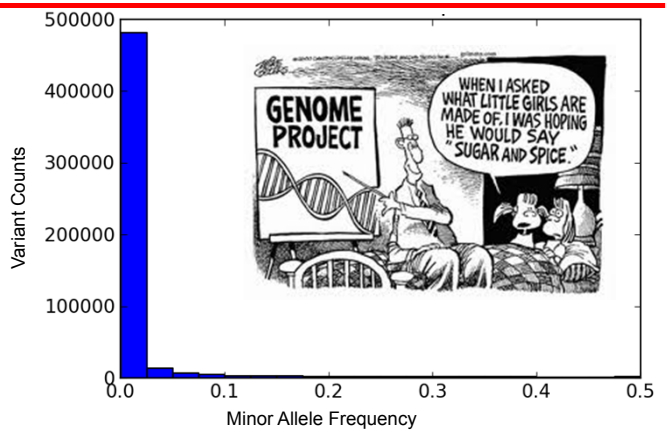
Overview

- Technology
  - Nextgen sequencing
- Utility
  - Clinical sequencing applications
    - Exome/genome
    - Panels
    - Interpretation / VUS
- Incidental findings
  - Expected frequency (1000 exomes)
- Return of results to research subjects consensus paper



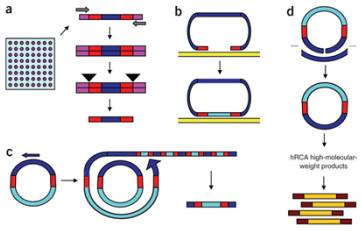
Rare variants are common



Nextgen Sequencing

Jay Shendure, UW Genome Sciences

Steve Henikoff, FHCRC

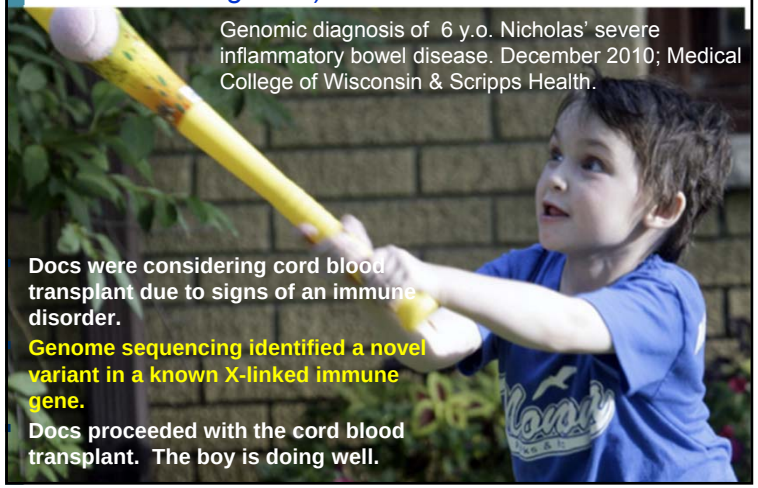


Porecca, et al. *Nature Methods* (2007)

Important terms and concepts

- Coverage (its not yet really a whole genome)
  - Cannot yet reliably determine trinucleotide repeats (HD)
  - Cannot easily distinguish homologous regions (CYP2D6)
  - Areas of “drop out”
- Capture (exome or panels)
- Read depth
- Accuracy for common variants
- Accuracy for rare variants
- Copy number variants (SNP arrays)
- Interpretation is hard
  - Often limited to coding regions
  - Variant frequency; Variants of uncertain significance

“The first child saved by DNA sequencing” (per Forbes Magazine)



Nextgen leads to gene panels

Some genes off target and great mosaic detection

Gene Dx

Bioreference Laboratory

OncoGene Dx: Comprehensive Cancer Panel - $4,530

APC	BRCA1	CHEK2	MRE11A	PALLD	SMAD4
ATM	BRCA2	EPCAM	MSH2	PMS2	STK11
AXIN2	BRIP1	FAM175A	MSH6	PTEN	TP53
BARD1	CDH1	FANCC	MUTYH	RAD50	VHL
BLM	CDK4	HOXB13	NBN	RAD51C	XRCC2
BMPR1A	CDKN2A	MLH1	PALB2	RAD51D	

Oregon Health & Sciences University
Retinal Dystrophy Panel

CEI Molecular Diagnostics Laboratory

www.ohsucasey.com/diagnostics

CASEY EYE INSTITUTE
Oregon Health & Science University

RETINAL DYSTROPH

ABCA4, ABHD12, ADAM9, AIPL
BBS3, BBS4, BBS5, BBS6, BBS
BBS15, BBS16, BBS17, BEST1
CACNA2D4, CACNA1F, CDH23,
CNGA1, CNGA3, CNGB1, CNGB3
EYS, FAM161A, FSCN2, GNA
GUCA1A, GUCA1B, GUCY2D, H
KCNJ13, KCNV2, KLHL7, LCA5,
NR2E3, NRL, NYX, OFD1, OPA1,
PDE6H, PDE6G, PDZD7, PITP
PRPF31, RAX2, RBP3, RD3, R
RLBP1, ROM1, RP1, RP1L1, R
SEMA4A, SLC24A1, SPATA7, TOPORS, TRPM1, TTC8/BBS8, TULP1, USH1C, USH1G, USH1J-CIB2, UNC119, USH2A, ZNF513

- Recent 60ish YO patient with RP; father affected
- Found 1 USH2A mutation and 1 CNV (array)
- AR disorder (pseudodominant) assoc. with deafness—would have taken a lot of genes to get there
- Patient now reports moderate to severe hearing loss recent onset

Panels lead to finding potentially pathogenic variants in unexpected genes

UW lab Coloseq and BROCA panels QA activity by Brian Shirts, MD, PhD

Note that many patients tested were known negative for BRCA1/2 or polyposis genes by previous testing.

Variant/gene	N	% SNVs	% of total patients
Expected in this patient	62	43.1	6
Unexpected, but consistent	52	36.1	5
Unexpected, not consistent	23	16.0	2
Unexpected, ? consistent	7	4.9	1

Trio sequencing to identify *de novos* *(ADHD)*

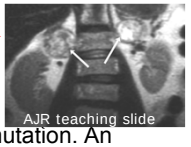
Table 1: Summary of *de novo* coding variants found in all three pilot sporadic ADHD trios.

Trio	gene	mutation	Gran-tham / GERP	Highest expression	gene function	disease reports/associations
A	*TRPM2*	*ARG707CYS*	180 / 4.2	Brain (cerebral cortex, thalamus, hippocampus, & midbrain;neurons, astrocytes & microglia)	Cation channel with enzymatic domains, regulated by ADP-ribose, activated by oxidative stress, confers susceptibility to cell death	Social disorder plus ADHD(gene deletion, single family);bipolar, amyotropic lateral sclerosis, and Parkinsonism-dementia
B	*WDR83*	*GLY127ARG*	125 / 4.5	Brain, testis	molecular scaffold of multimeric protein complexes, splicosome; regulates hypoxia inducible factor 1	None found
	PHLDA1	*GLN190 HIS*	24 / 2.7	Brain, pancreas	evolutionarily conserved, anti-apoptotic effects of insulin-like growth factor-1	None found
C	*MAL*	CNV deleting 5' end of gene	n/a	Brain, blood, kidney	myelin biogenesis or function, T cell differentiation	None found

Severe mutation: Grantham ≥50, GERP ≥3

Exomes and Genomes are underutilized: Could have been saved by a genome?

- < 35 year old man with diabetes, 1 month history of dyspnea. Presented to an outside hospital, treated for bronchitis, developed cardiogeneic shock, multiple organ failure, transferred to UW, died.
- Autopsy showed bilateral pheochromocytoma and a pancreatic neuroendocrine tumor.
- Cause of death: catecholamine cardiomyopathy.
- Autopsy genetic testing finds von Hippel Lindau mutation. An exome or genome would have made the diagnosis. A diagnosis prior to the cardiogenic shock would have been life-saving.


AJR teaching slide

How many actionable incidental findings will we see?

Dominant			X-Linked
ACTA2	*KCNE3*	*PTEN*	*DMD*
ACTC1	*KCNH2*	*RBM20*	*EMD*
ACVRL1	*KCNJ2*	*RET*	*GLA*
APC	*KCNQ1*	*RYR1*	*OTC*
BMPR1A	*KIT*	*RYR2*	
BRCA1	*LDLR*	*SCG5*	**Recessive**
BRCA2	*LMNA*	*SCN1B*	*ATP7B*
CACNA1C	*MEN1*	*SCN3B*	*BCHE*
CACNA1S	*MET*	*SCN5A*	*BLM*
CACNB2	*MLH1*	*SDHAF2*	*CASQ2*
	MLH3	*SDHB*	
HMBS	*PROC*	*TSC2*	*SLC37A4*
KCNE1	*PROS1*	*TTN*	*SLC7A9*
KCNE2	*PTCH1*	*VHL*	

Overlap with ACMG list in Green et al, 2013.

- They had our list.
- Adult relevant genes: we have all of theirs except *APOB, PCKS9 (cholesterol)*

=118 Total Genes

Lack of consensus on what to return:

Clinical Sequencing Exploratory Research (CSER projects): Would a pathogenic mutation be reported as a medically actionable incidental finding

	Sites [1]				
	BCM	CHOP	UNC	UW	
Gaucher disease (*GBA*) - Homozygosity in a child	Yes	Yes[2]	Yes	Yes	From Berg et al. Processes and preliminary outputs for identification of actionable genes…, GIM 2013
Gaucher disease (*GBA*) - Homozygosity in an adult	Yes	N/A	Yes	No	
CHEK2 1100delC heterozygosity	Yes	Yes	No	No	Increased breast cancer risk is modest and interventions not clear
Maturity Onset Diabetes of the young (*HNF1A*)	Yes	Yes[2]	No	Yes[3]	Presents in childhood and has clinical implications for treatment, but typically does not involve acute ketoacidosis
Long QT Syndrome - LQT1 (*KCNQ1*)	Yes	Yes[2]	Yes	Yes	Incomplete penetrance but chance for sudden cardiac death potentially preventable by implantable cardioverter-defibrillator
Long QT Syndrome - LQT12 (*GIRK4*)	Yes	Yes[2]	No	Yes	Extremely rare, concern about knowledge base regarding the phenotype

1000 Exome Variant Results by Ancestry Group

Classification	European ancestry	African ancestry
Pathogenic variants from HGMD	7/500	1/500
Likely pathogenic variants from HGMD	8/500	2/500
Disruptive pathogenic variants	0/500	1/500
Disruptive *likely* pathogenic variants	2/500	2/500
Total	17/500 (3.4%)	6/500 (1.2%)

Dorschner et al, AJHG 2013

1000 Exomes AV Conclusions

- 3.4% of European-ancestry and 1.2% of African-ancestry subjects had high penetrance actionable pathogenic or likely (>50%) pathogenic variants (adults)
- Deficit in African-descent samples
  - Incomplete literature vs. European population expansion
  - Health–care disparity?
- Mean review time of 23 minutes per unique variant
- HGMD misclassification of variants
  - Missing/weak data and compounding errors
  - No minor allele vs. disease frequency data considered
  - Nonstandard reporting makes informatic article extraction hard

VUS are a significant problem

- Male diagnosed with colon cancer at ~35 years old
  - Normal IHC
  - Parent with ≥5 adenomatous colon polyps
- Normal clinical test – Coloseq
  - 11 gene panel (*MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDH1, PETN, STK11, TP53)*

Exome finds VUS

- ***SDHB* c.299C>G, p.Ser100Cys**

SDHB Tumor Sites (high malignancy rate)	Penetrance
Skull base and neck paragangliomas	15%
Extra-adrenal abdominal or thoracic tumors	69%
Renal clear cell carcinoma and papillary thyroid carcinoma	?

  - *SDHB* known to be not associated with colon cancer
  - Novel VUS: ESP: 0%; Not in OMIM, NCBI, ClinGen, HGMD, LOVD
  - BAD: Grantham: 112, GERP: 6.17, polyPhen: 0.995
  - Pathogenic: Ser100**Phe**, Ser100**Pro,** Ser100**Glu** & p.Ser100**LeufsX4**
  - **What do we tell this patient?**

Research ROR of genomic findings

- What findings should be returned in research
- Motivated by increased genomics in research and by ACMG clinical recommendations
- Joint project of eMERGE and CSER
- Writing committee: Gail Jarvik, Laura Amendola, Jonathan Berg, Ellen Clayton, Sara Van Driest, Barabara Evans, Jim Evans, Malia Fullerton, Carlos Gallego, Nanibaa' Garrison, Stacy Gray, Ingrid Holm, Iftikhar Kullo, Lisa Lehmann, Cathy McCarty, Cynthia Prows, Heidi Rehm, Richard Sharp, Joseph Salama, Marc Williams, Susan Wolf, Wylie Burke; eMERGE ROR and CERC Committees, CSER Act-ROR Committee

Research ROR Principles

1. Research, even in a clinical setting, differs from clinical care in both its goals and its procedures; as a result, the minimal and maximal information returned in a research setting may differ from the standard of clinical practice.
2. Resources for research should be primarily directed at scientific discovery; thus, researchers do not have a duty to look for actionable genomic findings beyond those uncovered in the normal process of their investigations.
3. Research assessing the outcomes of a wide range of potential practices for returning genomic results is required for the ultimate formulation of best practices in both the research and clinical settings.
4. Analytically and clinically valid information of an important and actionable medical nature that is identified as part of the research process should be offered to a research subject.
5. Potential research participants or parents of minors should be provided proper informed consent that respects autonomy, including the right to refuse participation in research; participants should have the right to refuse any results that may be offered, unless return of these results is essential to the purpose of the study.

Research ROR Recommendations

1. At a minimum, researchers should offer genomic information deriving from their research studies that is valid, medically important and actionable, if discovered purposefully or by chance during the course of data analysis. Researchers are not obligated to search for actionable genomic variants to be returned beyond those identified in the course of their work.
   a. Given that there is no definitive "list" of medically actionable findings with respect to return of research results and that such a list would be context-dependent, those involved in genomics research should give thought to the types of findings that would represent the "floor" for return of results in their study, in consultation with local IRBs and funding agencies.
   b. This requirement to offer disclosure of results is limited to no longer than the term of funding to primary investigators who have identifiable participants, rather than secondary users of data, as outlined by Fabsitz et al[4].

Research ROR Recommendations

2. Participants should have the option to refuse research genomic test results, both related to the study purpose and to incidental findings, unless the study goals are related to the return of these data. When possible, this should be addressed at the time of consenting.
   a. When studies do not allow participants of any age to opt out of potentially receiving these data, this should be clearly addressed in the consent form.
   b. The consent process and form should clarify the circumstances in which a participant may be contacted in the future and explicitly ask whether the participant consents to future contact if new findings are found. Participants who are contacted regarding such results should have the right to decline receiving those results.
   c. Participation in research studies should be as non-coercive and self-directed for the participants as possible.
   d. Parents of pediatric participants should be offered the option of return or refusal of findings related to adult onset conditions.

Research ROR Recommendations

3. Researchers may be ethically and scientifically justified in returning all genomic information, in some format, and any level of information between the floor of actionable results and the ceiling of all genomic information.
   a. Special care should be taken when the benefits and harms of returning a particular type of genomic information are uncertain.
   b. Research studies intended to examine practices for the return of genomic information should include measurements of benefits and harms in the design of the study.

Research ROR

Recommendation 4:

4. Additional research projects that examine the potential benefits and harms of receiving genomic results and evaluate practices for returning genomic information are required to inform the increasing use of genomic sequencing in clinical research.

Remaining controversies/ opportunities for research:

1. CLIA
2. Method of return
3. Return of adult onset disorders in children

Thank you Team!

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Funded by NHGRI, NCI, and WA state (NWIGM): CSER and eMERGE consortia

Would a pathogenic mutation be reported as a medically actionable incidental finding

	Sites				Comments
	BCM	CHOP	UNC	UW	
CYP2C19 genotype (metabolism of Plavix and other drugs	Yes	No	No	No	
Malignant hyperthermia (*RYR1*)	Yes	Yes[2]	Yes	Yes	
Neurofibromatosis 1 (*NF1*)	Yes	Yes[2]	No	No	Management guidelines for children, but uncertain evidence for benefits when diagnosed incidentally, esp. in adults
Familial Mediterranean Fever (*MEFV*)	Yes	Yes[2]	Yes	No	Long diagnostic odyssey, effective treatment
Factor V Leiden (*F5*) - Homozygous	Yes	Yes[2]	No	Yes	For CHOP, whether or not categorized as "medically actionable" or "immediately medically actionable" depends on age and gender
Factor V Leiden (*F5*) - Heterozygous	No	No	No	No	Unclear clinical implications
Hemochromatosis (*HFE*) - Homozygous C282Y	Yes	Yes	Yes	Yes	Potentially severe long-term complications, completely preventable

Pathogenic actionable variants

Gene	Variant	Primary Associated Condition(s)	Inheritance	Ethnicity [2.]
BRCA1	p.1699Arg>Trp	Hereditary breast and ovarian cancer	AD	E (1)
BRCA1 [1.]	p.908Glu>stop	Hereditary breast and ovarian cancer	AD	E (1)
BRCA2 [1.]	p.1894Tyr>stop	Hereditary breast and ovarian cancer	AD	E (1)
LDLR	p.99Ser>stop	Familial hypercholesterolemia	AD	E (1)
MYBPC3	p.833Ala>Thr	Hypertrophic cardiomyopathy	AD	E (1)
MYBPC3	p.502Arg>Trp	Hypertrophic cardiomyopathy	AD	E (1)
PMS2	p.46Ser>Ile	Lynch syndrome	AD	E (1)
SERPINA1	p.Glu366Lys	Alpha 1 Antitrypsin deficiency (Z allele)	AR [3.]	A (1) }
SERPINA1	p.Arg285Cys	Alpha 1 Antitrypsin deficiency (S allele)	AR [3.]	A (1) }

1. Based on classification by Myriad Genetics Laboratory
2. E = European-descent; A = African American-descent
3. Found in the same individual

Likely pathogenic actionable variants

Gene	Variant	Primary Associated Condition(s)	Inheritance	Ancestry [2]
CACNB2	p.Ser142Phe	Brugada syndrome	AD	E (1)
CDH1	p.832Val>Met	Hereditary diffuse gastric cancer	AD	A (1)
DSG2	p.812Gly>Cys	Arrhythmogenic right ventricular cardiomyopathy	AD	E (1)
KCNQ1	p.600Thr>Met	Long QT syndrome	AD	A (1)
LDLR	p.606Ala>Ser	Familial hypercholesterolemia	AD	E (1)
MYBPC3	p.619Glu>Lys	Hypertrophic Cardiomyopathy	AD	E (2) [1]
MYBPC3	p.490Gly>Arg	Hypertrophic Cardiomyopathy	AD	E (1)
SCN5A	p.1303Thr>Met	Long QT syndrome	AD	E (1)
TNNT2	p.285Arg>Cys	Dilated and hypertrophic cardiomyopathy	AD	E (1)

1. One participant of Ashkenazi-ancestry
2. E = European-ancestry; A = African American-ancestry

Classification criteria (strict)

Pathogenic	Allele frequency of variant below cut off (1) AND Segregation in ≥2 unrelated families (3) OR Segregation in 1 family and identified in ≥ 3 unrelated affected individuals (4) OR Segregation in 1 family and ≥1 *de novo* event in trio (2) OR Protein truncation in where this event is known to cause disease
VUS - Likely pathogenic	Allele frequency of variant below cut off AND Identified in ≥3 unrelated individuals OR Segregation in 1 family OR ≥1 *de novo* event in trio

(1) Based on disease frequency and inheritance pattern, see text.
(2) Mutation identified as *de novo* dominant in an affected offspring of unaffecteds
(3) Defined as probability of consistent sharing in the family of ≤1/16
(4) Dependent on allele frequency

Classification criteria (strict)

VUS	**Allele frequency of variant below cut off** **AND** **Identified in <3 unrelated affected individuals** **OR** **No segregation studies** **OR** **No *de novo* events in a trio**
VUS Likely benign	**Allele frequency of variant WELL ABOVE cut off** **AND/OR** **Seen in combination with a known pathogenic mutation**

Ethical Frameworks for the Disclosure of Incidental Findings

Benjamin E. Berkman, JD, MPH
Office of the Clinical Director, NHGRI
and
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Disclaimer

- The following presentation does not reflect the official views of the NHGRI, NIH, or DHHS.

Roadmap

- State of the literature
- Two recent frameworks
  - President's Commission for the Study of Bioethical Issues
  - American College of Medical Genetics and Genomics
- Some relevant data
  - IRB views on reasons supporting an obligation to disclose IFs

State of the Literature

Lurking disagreements and controversial issues

- **On what principle (or principles) does an obligation to disclose rest?**
- Why can't we agree on a set of common definitions?
- How much does the research context matter?
- When is reconsent required?
- Do researchers have a duty to look for incidental findings?
- Is the right not to know absolute?
- How should clinical guidelines influence the research setting?

The problem

- There has been an active debate in the bioethics literature about whether there is an obligation for researchers to return incidental findings.
- While there seems to be an evolving majority view that there is some obligation, the contours of that obligation remain unclear.
- Arguably, this lack of clarity is at least partially due to the fact that there is no consensus about the principle(s) on which such an obligation might rest.

Guidelines and Frameworks

- NHLBI (2004/2009)
- Result-evaluation approach (Ravitsky and Wilfond)
- Net-benefit approach (Wolf et al.)
- Ancillary care framework (Richardson)
- President's Commission for the Study of Bioethical Issues (PCSBI)
- ACMG Recommendations

Why is there an obligation to disclose GIFs?

- **Beneficence:** the idea that researchers should have the welfare of the research participant as a goal.
- **Duty to rescue/warn:** obligation to warn participants if they are in significant, imminent danger.
- **Respect for persons/autonomy:** the recognition that all individuals have the right to make their own decisions.
- **Right to know:** research participants have an inherent right to obtain genetic information about themselves.

Why is there an obligation to disclose GIFs?

- **Reciprocity:** the idea that investigators owe participants something in exchange for their contribution to the research endeavor.
- **Doctor/Patient relationship:** participants should be treated like patients**,** and clinicians would disclose these results to their patients.
- **Professional responsibility** to inform their subjects
- **Justice/Fairness**

Why is there an obligation to disclise GIFs?

- **Legal liability:** fears about lawsuits if a participant later develops a condition that could have been prevented.
- **Public trust in research**
- **Institution's professional reputation**

Some arguments against an obligation to return incidental research findings

- Challenges to the notion that beneficence, respect for persons, reciprocity, justice are violated by lack of disclosure
- The purpose of research is not to benefit the individual research participant but rather to produce generalizable knowledge
- Risks associated with conflating research and clinical care
  - Therapeutic (diagnostic) misconception
- Resource limitations

President's Commission for the Study of Bioethical Issues

PCSBI - Taxonomy

Table 1.2: Bioethics Commission's Classification of Individualized Results of Medical Tests

TYPE OF RESULT DISCOVERED	DESCRIPTION	EXAMPLE
Primary Finding	Practitioner aims to discover A, and result is relevant to A	In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered
Incidental Finding: *Anticipatable*	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place	Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related[53]
Incidental Finding: *Unanticipatable*	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place	When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted[54]
Secondary Finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation	ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits[55]
Discovery Finding	Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results	A "wellness scan," a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body[56]

PCSBI - Principles

- Respect for Persons
  - Autonomy
  - Self-determination
  - "Freedom from limitations that prevent meaningful choice"
- Beneficence
  - "Ensure the wellbeing of others"
  - Duty to rescue/warn
  - Stronger when there is a professional relationship
  - Public beneficence

PCSBI - Principles

- Justice and Fairness
  - Equitable distribution of benefits and burdens
  - Assess claims about distribution of resources
  - Treat like cases alike
- Intellectual Freedom and Responsibility
  - Just because "something new can be done doesn't mean that it ought to be done"

PCSBI – Relevant Practical Considerations

- Relationship
- Expertise
- Participant preferences
- Features of the finding (e.g., clinical significance, actionability, etc.)
- Timing
- Feasibility of recontact
- Cost/burden

PCSBI - Recommendations

- During the informed consent process, describe the types of findings that might arise and whether or not such information will be disclosed
- Decide in advance how to honor participant preferences (i.e., their right not-to-know)
- Develop a plan to manage anticipatable and unanticipatable findings, subject to IRB approval
- If disclosure is very difficult or impossible (e.g., biobank research?) researchers must justify their plans for non-disclosure.
- No duty to look for secondary findings

American College of Medical Genetics and Genomics

ACMG

- Explicitly limited to the clinical context
  - Although there is an ongoing debate about the influence that clinical recommendations and guidelines should have in the research realm
- "Minimum list" of incidental findings to report from any clinical sequence
  - "unequivocally pathogenic mutations in genes where pathogenic variants lead to disease with very high probability and where evidence strongly supports the benefits of early intervention"
- Variants on the list should be actively sought by the laboratory
- Findings would be delivered to the ordering clinician, who could manage the information in the context of the patient's specific circumstances
- "Opportunistic Screening"

ACMG – No Right Not-to-Know

- Recommended not soliciting patient preferences about receiving incidental findings
  - Clinicians have a fiduciary duty to warn patients about high risk variants where an intervention is available
  - Beneficence > autonomy/respect for persons
  - Patients have the right to refuse sequencing if they don't want to learn about incidental findings

ACMG – Pediatric Issues

- Recommended disclosure of adult-onset conditions to pediatric patients
  - Breaks from standard view
  - Appealed to benefit to parents and other family members
    - Third-party beneficence > child's future autonomy
  - All variants on list should be returned to all patients, regardless of age

Data on IRB Views

Empirical literature

- A number of existing and ongoing studies on participant and investigator views
- Very little focus on the practicing research ethics community
  - How are IRBs actually thinking about and addressing this problem?
- Studies on IRB views that do exist have been framed in terms of GWAS, not WES/WGS
  - Mainly qualitative
  - Limited size

Goal

- First extensive national study of IRB professionals' understanding, experience, and beliefs surrounding incidental findings

Our Questions

- How are IRBs grappling with questions about incidental findings?
- What ethical principles do the research ethics community appeal to in support of an obligation to return incidental findings?
- To what extent do they recognize any limitations on a potential obligation?

Methods

- Online survey of 796 IRB members and IRB professionals (response rate: 35%)
- Participants recruited through PRIM&R
  - Contacted by mail
  - $5 pre-incentive
- Socio-demographic and attitudinal data
- Compared confidence intervals to test significance of difference between various groups

Sample Characteristics

Gender

female	74%

Education

< hs	0.1%
hs	0.4%
some college	6%
college	26%
masters	35%
doctorate	31%

Race

Caucasian	88%
African American	6%
Asian American	4%
American Indian	2%

Ethnicity

Hispanic/Latino	4%

Affiliated with IRB

Yes	92%

Time with IRB

<1 year	1%
1-2 years	9%
3-5 years	21%
6-10 years	32%
10+ years	36%

Role with IRB

chair or vice chair	15%
scientific member	8%
non-scientific member	5%
community member	2%
administrator	59%

Professional role

clinical	17%
scientific	43%

Experience with GIFs

Experience with GIFs

Yes	74%

Genomic knowledge

very confident	9%
somewhat confident	36%
slightly confident	35%
not at all confident	20%

Ethical knowledge

very confident	19%
somewhat confident	52%
slightly confident	22%
not at all confident	6%

Training for GIFs

a lot	5%
some	32%
a little	36%
none	27%

Preparedness for GIFs

very well prepared	8%
somewhat well prepared	39%
slightly well prepared	31%
not at all prepared	22%

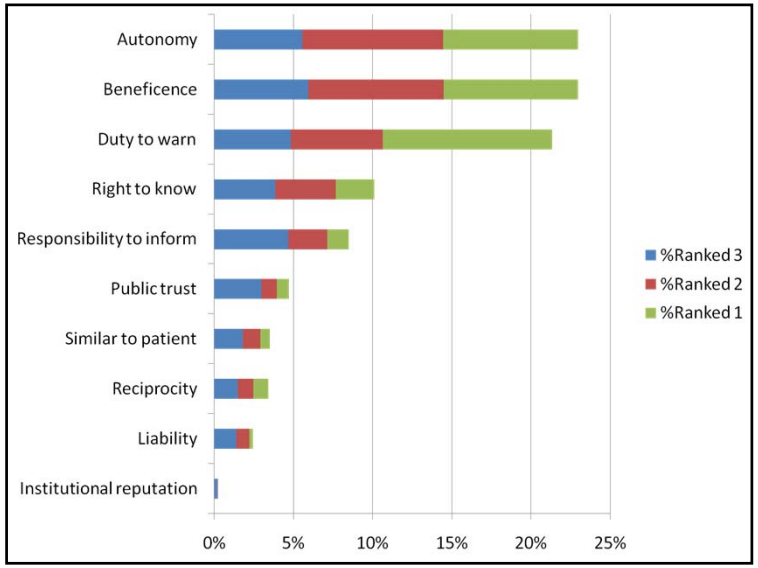
Initial Views on Whether There is an Obligation to Disclose GIFs

Do you believe that researchers have an obligation to disclose genetic incidental findings to participants?

Always	13%
Sometimes	65%
Rarely	13%
Never	2%
Don't know	7%

Ethical Reasoning

	Strongly agree or agree
Duty to warn	84%
Respect for autonomy	80%
Beneficence	79%
Professional responsibility	67%
Public trust in research	58%
Right to know	54%
Institutional reputation	36%
Legal liability	34%
Participants = patients	34%
Reciprocity	34%



Factors that can diminish an obligation to disclose GIFs

	Strongly agree or agree
Inadequate clinical or analytic validity	71%
Inadequately demonstrated clinical utility	66%
Lack of funding, resources or infrastructure	29%
Adverse psychological impact	23%
Participants won't understand	22%
Investigators ≠ clinicians	18%
Time and effort required	7%

#1 (validity) and #2 (utility) > #3, #4, #5, #6, #7 ($p<0.05$)

How do IRB professionals support an obligation to return GIFs?

- Conflict in the breadth of implied obligation
  - Duty to warn → only GIFs that represent significant risk of a serious disease
  - Beneficence → all potentially useful or relevant GIFs
  - Autonomy → all GIFs, allowing participants to decide for themselves which ones are most important

Limits on an obligation to return GIFs

- Most possible reasons for limiting an obligation were rejected
- Notably
  - Lack of resources to disclose GIFs (57% disagree)
  - Burden of additional time and effort required to disclose GIFs (86% disagree)
- Interestingly, both of these are often cited by commentators as significant obstacles to declaring a broad obligation to disclose, but support in the IRB community does not follow

Conclusion

- Ethical principles → contours of an obligation to disclose
- Arguably, there is still no consensus, although as thinking gets more concrete (e.g., PCSBI and ACMG) we will have increasingly productive starting points for debate
- In practice, IRBs seem to be tending towards principles that translate to broader disclosure obligations, with little sympathy for counter-arguments relating to burden on the scientific enterprise

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Questions

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