Ethics & Omics

Return of Results in the Clinic & in Research

ELSI World Congress

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Return of Results

Genomics offers a useful lens through which to examine ROR

- Dilemmas involving ROR are not new and not confined to genomics
- But genomics has brought many of the issues to the fore due to:
  - New technology allowing broad, cheap genomic sequencing
  - Vast heterogeneity of results
  - Increasing clinical relevance
  - Probabilistic nature of results
  - Hyping of genomics by industry, academia & funders

Challenges to ROR

Multiple Dimensions of Heterogeneity

- Genomic results are heterogeneous in many ways:
  - Predictive value ranges from deterministic to very modest
  - Actionability
    - Ranges from highly actionable to utterly inactionable (
    - Knowledge Base varies dramatically
    - For the great majority of variants we know nothing about health effects
      - Indeed, most are meaningless and probably have no effects at all
  - Value of information to the individual varies
    - Some results many do not wish to know

Challenges to ROR

Value Heterogeneity

A few examples of really bad genetic diseases

- Alzheimer Disease
- Fatal Familial Insomnia
- Spinocerebellar Ataxia
- Huntington Disease
- CADASIL
- etc…

If you harbor a mutation that essentially guarantees you will develop a severe untreatable neurological disease in the next 10 years would you want to know?

- We have to figure out how to grapple with the profound variability in values among providers, researchers, research participants & patients
- In ways that allow us to fulfill our professional responsibilities

The Research Context Amplifies Heterogeneity

- Clinical testing (should) focus on seeking results that are highly predictive, actionable & for which we have a good knowledge base
  - *BRCA1/2*, Lynch Syndrome, FH
- The clinical focus is narrow – we (appropriately) do not routinely seek extraneous data
- This is not the case in research, where by definition we know much less and often seek maximal data

Challenges to ROR

Secondary (Incidental) Findings

- A long-standing issue in a variety of research contexts
  - 2000 subjects ages 46-97 receiving MRIs
    - 7% with infarcts, 1.8% with aneurysms
- 100% of those undergoing genome-scale sequencing will have secondary findings
  - Vast majority are not understood with regard to health significance
  - 2-3% will be “medically actionable”

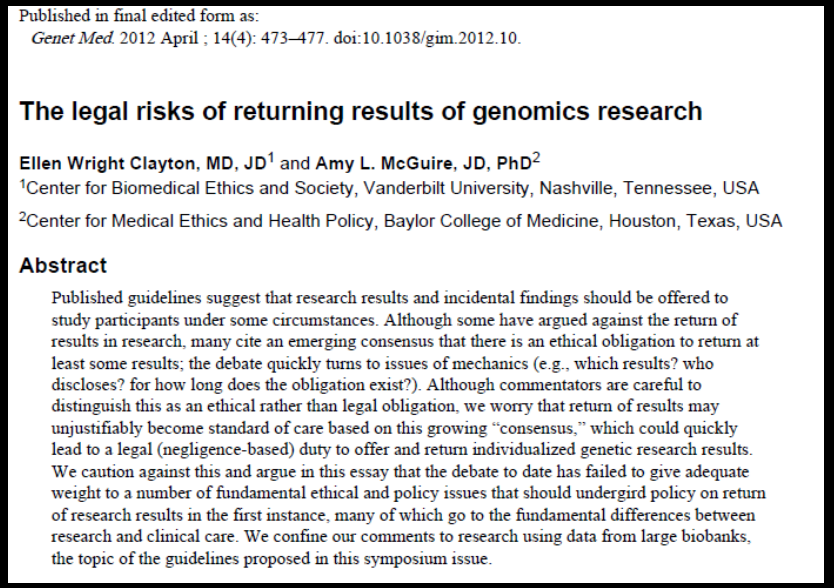
Table 1. Incidental Findings on 2000 MRI Scans.*

Finding	No. (%)
Asymptomatic brain infarct†	145 (7.2)
Lacunar infarct	112 (5.6)
Cortical infarct	41 (2.0)
Primary tumors, benign	31 (1.6)
Meningioma	18 (0.9)
Vestibular schwannoma	4 (0.2)
Intracranial lipoma‡	2 (0.1)
Trigeminal schwannoma	1 (<0.1)
Pituitary adenoma	6 (0.3)
Primary tumors, malignant§	1 (<0.1)
Other findings	
Aneurysm	35 (1.8)
Cavernous angioma	7 (0.4)
Metastases	1 (<0.1)
Subdural hematoma	1 (<0.1)
Arachnoid cyst¶	22 (1.1)
Type I Chiari malformation‖	18 (0.9)
Major-vessel stenosis**	9 (0.5)
Dermoid cyst of lateral orbital rim	1 (<0.1)
Fibrous dysplasia	1 (<0.1)

N Engl J Med 2007;357:1821-8.

Ethical & Legal Duties for ROR in Research

- Some argue that ROR in research sets a worrisome standard
  - Legally problematic
  - Inappropriately conflates clinical & research realms
  - Logistically unrealistic
- Many feel that *some* level of ROR in research is a duty



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The legal risks of returning results of genomics research

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Abstract

Published guidelines suggest that research results and incidental findings should be offered to study participants under some circumstances. Although some have argued against the return of results in research, many cite an emerging consensus that there is an ethical obligation to return at least some results; the debate quickly turns to issues of mechanics (e.g., which results? who discloses? for how long does the obligation exist?). Although commentators are careful to distinguish this as an ethical rather than legal obligation, we worry that return of results may unjustifiably become standard of care based on this growing "consensus," which could quickly lead to a legal (negligence-based) duty to offer and return individualized genetic research results. We caution against this and argue in this essay that the debate to date has failed to give adequate weight to a number of fundamental ethical and policy issues that should undergird policy on return of research results in the first instance, many of which go to the fundamental differences between research and clinical care. We confine our comments to research using data from large biobanks, the topic of the guidelines proposed in this symposium issue.

How do we formulate appropriate criteria for ROR?

Formulation of ROR Criteria

Some Possible (Bad) Criteria

- Some individuals may *want* all of their information
  - Turns research & the clinic into tools for satisfying personal curiosity
  - Undermines their appropriate roles
  - Leads to excess cost that society bears
- People *deserve* all of their information
  - They deserve results that are accurate & interpretable
  - Don't deserve extension of therapeutic misconception
- Broad ROR will increase research participation
  - Misses the point of research
  - Subjects should not induced by questionable "perks"
- Generating and/or returning a broad array of results will increase the "clinical relevance" of our field
  - We will be relevant when we demonstrate that our approaches and tools improve outcomes

Potential Harms from Poorly Conceived ROR Policies

Under reporting of results

- A small subset of genomic results portend a dramatic risk for preventable disease
  - e.g. mutation in a Lynch Syndrome gene
    - Very high risk of colon/uterine cancer
    - 1/500 in population carry Lynch mutation
    - Prevention well established
  - A few such genes exist in the human genome
    - Conferring high risk of breast cancer, aneurysms, cv, etc.
    - 0.5-1% of population carries such a mutation
    - Will be routinely uncovered in the course sequencing

Concern about harm from not reporting such results

Potential Harms from Poorly Conceived ROR Policies

Over reporting of results

- Confusion of subjects
  - Return of meaningless, uninterpretable results inappropriately legitimizes them & dilutes meaningful results
- Overt harm (even if testing itself is noninvasive)
  - Triggers cascade of inappropriate downstream tests & procedures
  - Prompts speculative consumption of drugs & supplements (with attendant side effects & costs)
- Harm from ROR that patients don't actually want
  - Little to be gained (and much to lose) from casual return of such information to ill informed subjects

Potential Harms from Poorly Conceived ROR Policies

Over reporting of results

- Damage to the research enterprise
  - The *raison d'êtr*e of research is communal good
    - Its primary intent is not to benefit the individual
  - In the All of Us cohort it might be best to start small with ROR confined to only the most clearly actionable and useful results about which we have a great deal of knowledge
    - One can always expand ROR later

The Clinical Setting Amplifies Harms of Overly Generous ROR

- Many more patients than research participants
- The “Medical Industrial Complex” is eagerly awaiting your results
  - Downstream impacts cause expense and risk, e.g.
    - PSA > prostatectomy
    - BRCA > mastectomy/screening
  - Generating & returning poorly understood data in the clinic begs for over interpretation & harm
- The sums of money involved are vastly greater
  - Much stronger perverse incentives and aggressive marketing
- Affects Society as a whole given the outsized role of Medicine

Perverse Drivers of Over-Testing and ROR in the Clinic

- Many forces drive inappropriate testing/sequencing/ROR
  - Marketing by industry
  - Boosterism by academia and funders
    - Such as selling “elective genomes” for which there is no medical indication and no evidence of benefit
- Determining the right role of the market
  - Good for development but an inappropriate way to drive the deployment of any complex medical test
- We all have a shared stake in appropriate use of medical modalities
  - We all pay for each other’s medical care

Kimberly Lovett Rockwell, MD, JD
Honigman Miller Schwartz & Cohn LLP, Bloomfield Hills, Michigan.

VIEWPOINT

Direct-to-Consumer Medical Testing in the Era of Value-Based Care

Medical Actionability

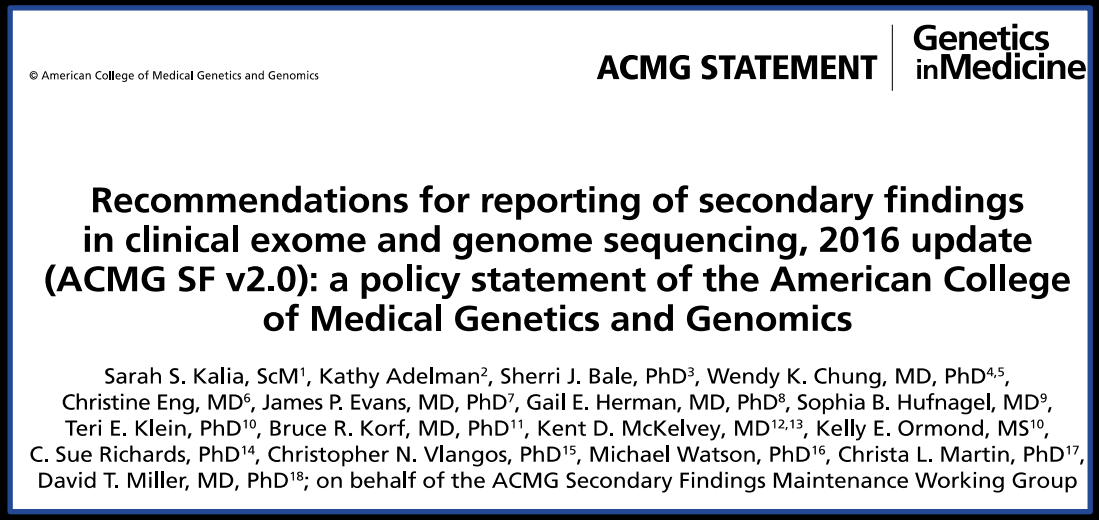
The most practical criterion to guide obligatory ROR

- Benefits participants and patients by returning truly important results
- Avoids ethical conundrums for researcher & guides clinician
- The devil is in the details

Determining Medical Actionability

- Too big of a job for each researcher or clinician so centralization makes sense
- Using evidence-informed criteria
- Guided by extant guidelines of professional organizations
- Must be iterative
- Other examples
  - Determining inclusion in NBS panels
    - A formalized aggregate of stakeholders & experts in a transparent process with defined criteria
  - ACMG, ClinGen efforts are attempting to provide guidance

Developing Such Guidance is Difficult



ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

- Generated in a non-systematic fashion
- Balancing fast-moving field and needs of providers/patients with thoughtful, systematic analysis is difficult
- Our knowledge base remains scant for many of these genes
- Major questions exist about the penetrance of pathogenic variants found in the screening context
- Treating them the same as variants discovered in a clinical context invites over-treatment and harm

Applying this list in the context of primary screening is worrisome

Cautions Regarding Secondary ROR

- What do we tell those who are positive?
  - Penetrance & health impacts likely inflated
  - What specific recommendations (with what confidence) should be made?
    - Need for further, more specific guidance to accompany each gene in the ACMG “list”
- We need to carefully study benefits, harms & costs of both primary and secondary genomic screening
- The formulation of / controversy around the ACMG “list” highlights the importance of *process* in formulating guidelines

What About Non-Actionable Findings?

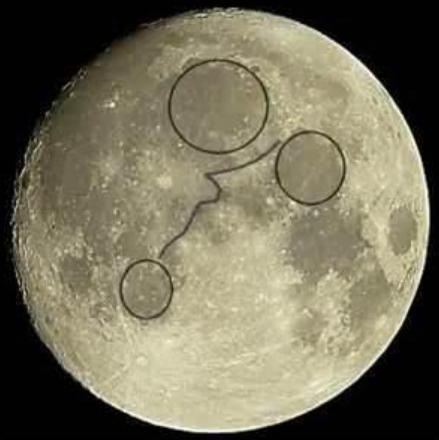
- Routine provision does not belong in clinical care, which is communally funded
- Reasonable to provide in research if relevant questions are being investigated
  - How badly to people actually want such results?
    - In NCGENES a majority (>80%) initially say they "want everything"
    - But <1/3 pursue any such findings (e.g. with a phone call)

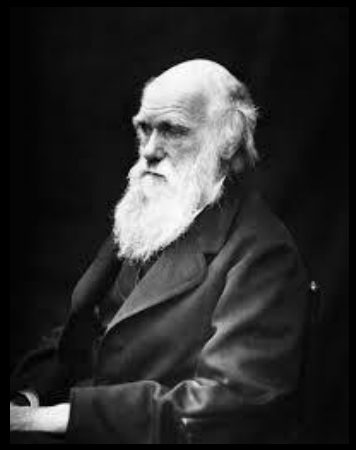
People "want" a lot of things…but they don't often want non-actionable findings enough to make a phone call

Broad Challenges to ROR

Interpreting & over-interpreting Results

- Serious decisions are made on the basis of result interpretation
- Calling a variant deleterious or benign leads to:
  - Years of invasive screening or RR surgery
    - Or forgoing such modalities when actually necessary
  - Decisions about family planning & abortion
- As humans we are evolutionarily predisposed to discern patterns
  - Even when not real
  - The genome is so big it *guarantees* amazing coincidences
- The bar for calling a mutation deleterious must be very high
- Not a problem unique to genetics – but amplified in the context of genomics





Challenges to ROR

Overpromising / Hubris

- Overly broad ROR/Sequencing “everyone”
  - Predicated upon low cost and the notion we can interpret results reliably in those without disease
  - Even if “free”, low cost is an illusion in Clinical Medicine
    - Misapplication of medical tests is very expensive b/o downstream impact
      - Financial costs to individuals & society
      - Morbidity/mortality to individuals (e.g. PSA screening)
  - Neither patients, participants nor healthcare systems are well served by returning large amounts of data we don’t understand
    - Begs for over interpretation & harm
- We must be guided by actual evidence of benefit

Challenges to ROR

Interpretation of Results is a Moving Target

- Family of Christian Millare suing Quest and Athena Diagnostics for wrongful death
- Seizure disorder & DD at ~5 months
- Clinical presentation c/w Dravet Syndrome
- *SCN1A* testing performed clinically; VUS reported
  - Plaintiffs:
    - At ROR in 2007 there were two publications linking this variant to Dravet Syndrome
    - Allege that if DS had been dxd, CM would not have received certain meds & would not have had fatal seizure
  - Quest counters:
    - They asked but didn't receive parental DNA to further investigate this variant
    - Testing in question occurred 9 years prior to filing of suit (CM died in 2008)
    - In 2015 the report was revised and VUS upgraded to deleterious (when plaintiffs requested the lab report)

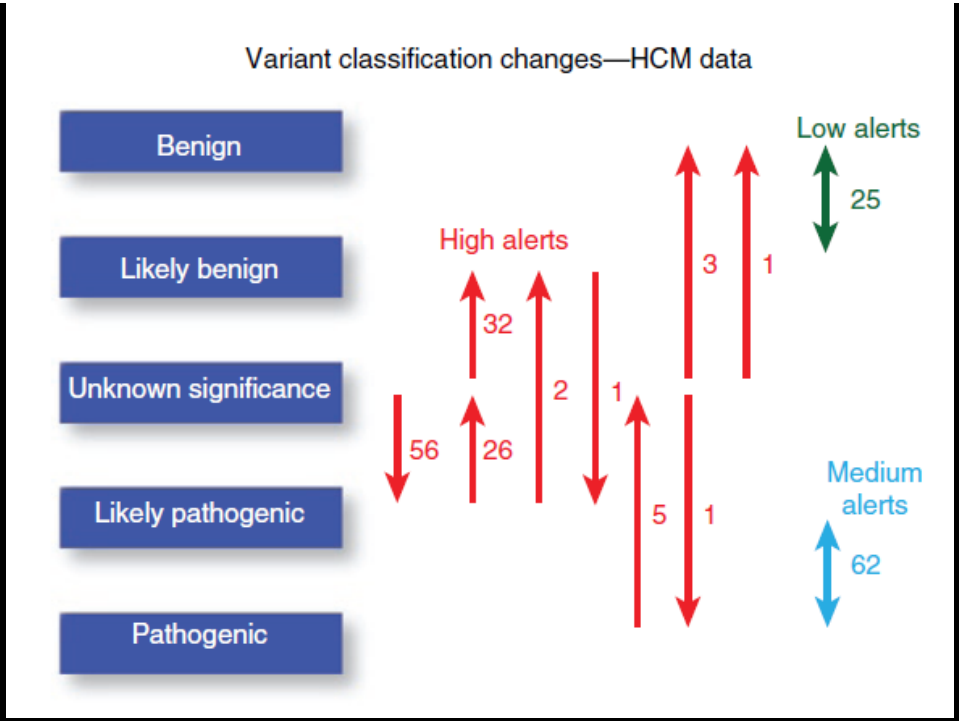
Challenges to ROR in Research

Changing Interpretations are Common

SPECIAL ARTICLE | Genetics inMedicine

Communicating new knowledge on previously reported genetic variants

Samuel J. Aronson, ALM, MA[1,2], Eugene H. Clark, BM[1,2], Matthew Varugheese, MS[1,2], Samantha Baxter, MS, CGC[3], Lawrence J. Babb, BS[1,2] and Heidi L. Rehm, PhD, FACMG[3,4]



~4% of cases per year received medium or high alerts

Slide/Data courtesy of Heidi Rehm

The Obligations of Ongoing ROR

- What threshold should be used for re-adjudicating variants?
- How does this responsibility differ between research and the clinical world?
- Who might be responsible for reanalysis?
    - The lab?
    - The provider?
    - The patient?
- No precedent in Medicine that mandates reinterpretation
- How often is reanalysis necessary?
- Whom to contact with revised results?
  - How to contact?
    - In context of fragmented healthcare system and mobile society
- What is the responsibility of the patient & family?
- Who pays?

Technology & Sharing to the Rescue?

J Am Med Inform Assoc 2013;0:1–5. Research and applications

A novel clinician interface to improve clinician access to up-to-date genetic results

Allison R Wilcox,[1,2] Pamela M Neri,[1] Lynn A Volk,[1] Lisa P Newmark,[1] Eugene H Clark,[3] Lawrence J Babb,[3] Matthew Varugheese,[3] Samuel J Aronson,[3] Heidi L Rehm,[4,5,6] David W Bates[1,4,6]

aci Applied Clinical Informatics 461

Evaluation: A Qualitative Pilot Study of Novel Information Technology Infrastructure to Communicate Genetic Variant Updates

Stephanie Klinkenberg-Ramirez[1]; Pamela M. Neri[1]; Lynn A. Volk[1]; Sara J. Samaha[1]; Lisa P. Newmark[1]; Stephanie Pollard[1]; Matthew Varugheese[2]; Samantha Baxter[3]; Samuel J. Aronson[2]; Heidi L. Rehm[3,4,5]; David W. Bates[1,4,5]

Journal of Biomedical Informatics

Usability of a novel clinician interface for genetic results

Pamela M. Neri [a,*], Stephanie E. Pollard [a], Lynn A. Volk [a], Lisa P. Newmark [b], Matthew Varugheese [c], Samantha Baxter [d], Samuel J. Aronson [c], Heidi L. Rehm [b,d,e], David W. Bates [a,b,e]

Journal of Biomedical Informatics 45 (2012) 950–957

Slide courtesy of Heidi Rehm

Sharing, Organizing & Making Data Accessible Are Necessary

The ClinGen Resource

- NHGRI-funded effort to create centralized resources of clinically annotated genes and variants to improve our understanding of genomic variation and optimize use in medicine and in research
- Focuses on:
  - Sharing genomic and phenotypic data
    - Not all labs are willing to do this
  - Standardizing interpretation
  - Application to diverse populations
  - Disseminating information widely

https://www.clinicalgenome.org/

Rehm et al. *NEJM* 372;23:2235 June 4, 2015

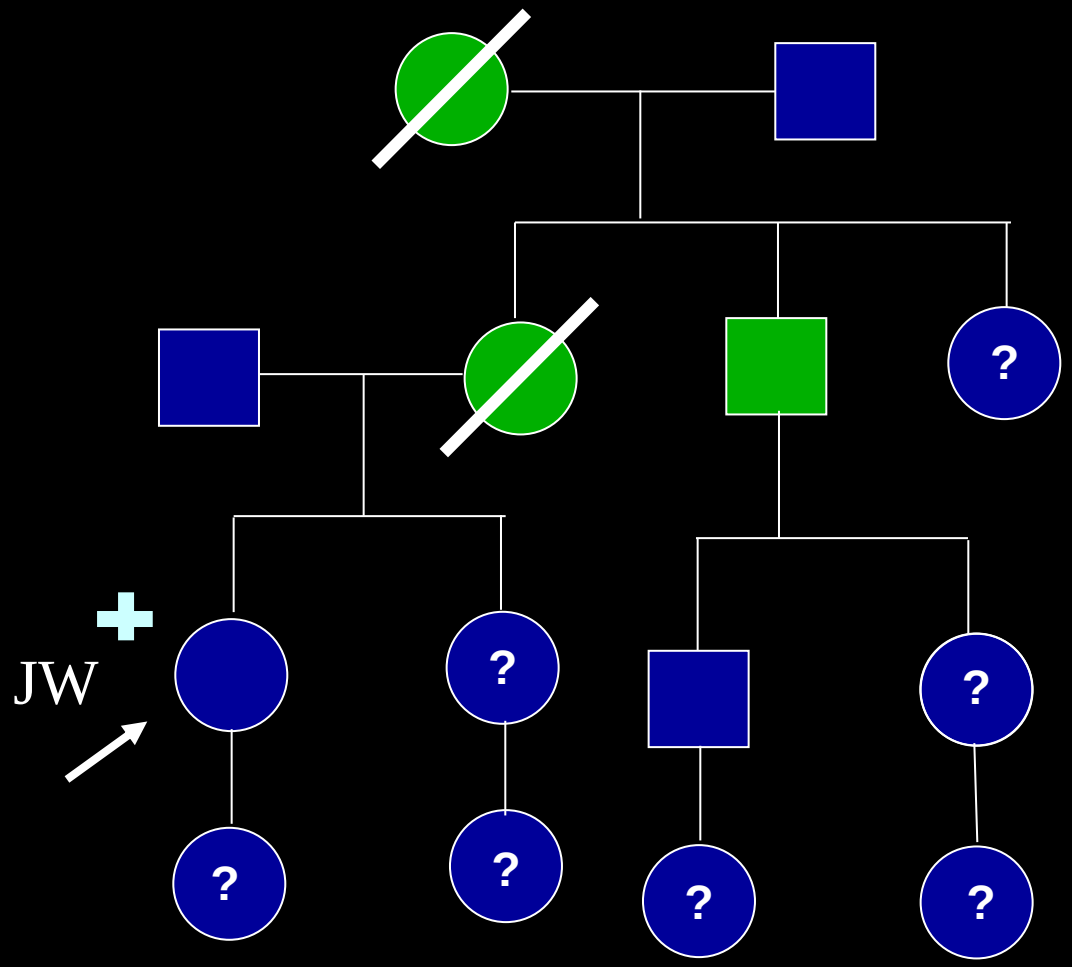
Obligations Differ Between the Clinical and Research Worlds

- In the clinical realm
  - Personal relationship with patient
  - Expectation of ongoing relationship
  - There is a stark “contractual” element in that relationship
    - And a body of law that helps define it
- The purposes of the two endeavors differ greatly
  - Group benefit/personal benefit
- The broad impact of policies differ
    - With clinical impact much greater

Obligations to the individual research participant and society are less than in the clinical world

Challenges to ROR

Results can have important impacts on others…especially in a genomic era



- Leave family communication up to participant?
  - Formalize facilitation?
- *Allow* contact by researchers (UK)?
- *Mandate* contact (STDs)?

Challenges to ROR

Group Harms

- Patients & participants can be harmed via results with implications for groups or one's identity within a group
  - Insurance discrimination b/o designation as "high risk"
    - GINA protection for employment and medical insurance
      - Under threat by HR 1313 introduced by Virginia Foxx of NC. Sigh.
    - No federal protections against adverse impact on Life Insurance, Disability Insurance, LTC Insurance
  - Social perceptions
    - Research on "traits" like alcoholism that vary among ancestral groups can be harmful to individuals and groups
  - Impact on self identity
    - Conflicts between self identity and information about ancestry derived from research results
  - Impact on group values and beliefs
    - Group origin stories can conflict with research results

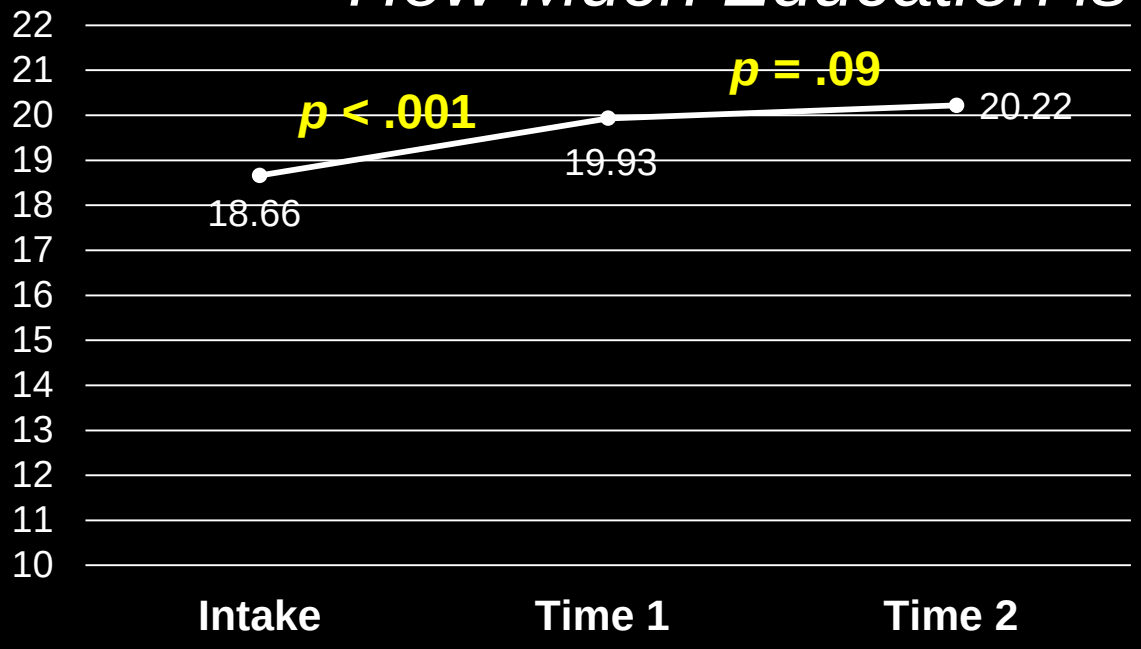
Challenges to ROR & Precision Medicine

Politics

- Genetics is disproportionately focused on prevention
  - Prevention is worthless if the population doesn't have access to it
- Ensuring access is a major challenge in the current political climate and imminent dismantling of the ACA
- We must all engage politically
  - With our representatives, regardless of party
  - Writing op-eds, letters to the editor
  - Running for office?

Challenges to ROR

How Much Education is Enough?



Courtesy of C. Rini

- ~30 minute NCGENES consent process (11 pages) increases knowledge
- Lower income, educational status and being single ~ lower levels of knowledge (but all gained after consent)
- How much education should we strive for?
  - "When I get an MRI on a patient I don't teach them about atomic spin vectors"

Strive for defined, clear – but narrow consent that focuses on the "big picture" outcomes

Consent, Trust & Partnership

- Clear, understandable, consent defining what will and will not be sought and returned
  - Anticipation must be proactive and methodical
  - Consent must be practical
    - If “too” lengthy or it becomes a burden to both parties and unintelligible
  - Primary focus should be on outcomes that matter to participants & patients
    - Not an effort to educate participants about the details of the field

The NCGENES Experience of ROR in Research

- Explicit communication about uncertainty & potential for future discovery helped moderate concerns about uncertainties
- Participants receiving negative and uncertain results viewed genomic researchers/clinicians as their best chance of finding a diagnosis
- Clinicians' and researchers' promise to "keep looking" for an answer constitutes a type of care and extends the clinical relationship with families

Trust

Slide adapted from Debra Skinner

"Informed Consent"

A misnomer?

- Ultimately, truly informed consent is impossible
  - Too much knowledge, power and value asymmetry between researchers (or clinicians) and participants (or patients)
  - No consent process can ever bridge that asymmetry
- *The indispensible factor is trust*
  - We have to be partners in the clinic & in research, which entails earning and keeping that trust through:
    - Transparent motives & appropriate setting of expectations
    - Being upfront about the likelihood of benefit to participants (small)
    - Ongoing communication with backup plans for contact
    - Being available to participants for questions and concerns
    - Active participation by researchers/clinicians and participants/patients
    - Minimizing the profit motive for provision of testing in the clinic
    - Empathy

NCGENES People

- **Project 1**

-Jim Evans
-Jonathan Berg
- Myra Roche
-Cécile Skrzynia
-Art Aylsworth
-Cindy Powell
-Jane Fan
-Yael Shiloh-Malawsky
-Bob Greenwood
-Muge Calikoglu
- Mike Tennison
- Tim Carey
- Laura Milko
-Julianne O'Daniel
-Brian Jensen
-Jennifer Brennan
-Kate Foreman
-Kristy Lee

- Hassan Alhosaini
- Allison O'Neal
- Angela Mayo
- Pam Reitnauer

Patients & Subjects

Project 2

- Kirk Wilhelmsen
- Karen Weck
- Phil Owen
- Chris Bizon
- Bradford Powell
- Jessica Booker
- Kristy Crooks
- Dylan Young
- Gloria Haskell
- Daniel Marchuk
- Mei Lu
- Manyu Li
- Piotr Mieczkowski
- Michael Adams
- Janae Simons
- Sai Balu
- Glenda Stone

Project 3

-Gail Henderson
-Chris Rini
-Debra Skinner
-Cynthia Khan
-Dan Nelson
-Sonia Guarda
-Elizabeth Moore
-Eric Juengst
-Martha King
-Kriste Kuczynski
-Gabe Lazaro
-Lacy Skinner
-Kelly Rasberry
-Michelle Brown
-Christina Leos
-Jenny Morgan
-Christian Tilley
-Sam Cykert

Thank You!

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