21st Century Research Risk: Where is the Tipping Point Now?

Agenda for 3rd Annual IRB Retreat

Wednesday, February 21, 2018

Morning Time	Presentation	Speaker	Afternoon Time
7:15 -8:00	Registration		12:15 -1:00
8:00- 8:10	Welcome & Housekeeping Information	Elizabeth Kipp-Campbell, PhD, CIP Director, Office for Human Research Ethics	1:00-1:10
8:10-8:30	State of the Office of Human Research Ethics	Elizabeth Kipp-Campbell, PhD, CIP Director, Office for Human Research Ethics	1:10-1:30
8:30-9:10	21st Century Research Risk: What Guidance does the Belmont Report Provide?	Robert J. Levine, MD Professor Emeritus of Medicine Chair, Executive Committee, Center for Bioethics Yale University	1:30 -2:10
9:10 – 9:40	Pregnant Women and Research: Tackling the Complexities of Inclusion	Anne Drapkin Lyerly, MD, MA Professor, Department of Social Medicine Research Professor, Department of Obstetrics/Gynecology Associate Director, Center for Bioethics University of North Carolina at Chapel Hill	2:10-2:40
9:40-10:10	Break	Break	2:40-3:10
10:10-10:40	Genetic Research: Routine or Risky for Human Research? What are the Red Flags IRBs should be Alert For?	Jonathan Berg, MD, PhD Department of Genetics UNC School of Medicine	3:10-3:40
10:40-11:30	Small Group Discussions of Vignettes	Elizabeth Kipp-Campbell, PhD, CIP Director, Office for Human Research Ethics	3:40-4:30

The Office of Human Research Ethics: An Update and Progress Report

February 21, 2018

Elizabeth Kipp Campbell, Ph.D., CIP
Director

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Topics of Discussion

1. Staffing of the OHRE
2. IRB Committees: Focus on recruitment
3. Educational Opportunities
4. Metrics of IRB Activity
5. 2017 Achievement Highlights
6. 2018 Opportunities and Challenges

Current OHRE Staffing

There are currently 20 staff members.

Internal hires of John Roberts and Mike Matamoros as Reliance Compliance Manager and Quality Assurance and Quality Improvement Manager, respectively.

Ongoing searches include: Deputy Director and Senior IRB Analyst.

There are currently 9 staff members who are certified as IRB Professionals (CIP).

Recruitment of IRB Committee Members

1. Increased turnover in the past year (partially 2-3 year cycle)
2. Significant proportion of our expertise is external
3. Continuing to add expertise across all committees
4. Continuing to seek MD participation through talks/ collaboration with the School of Medicine
5. Targeted focus on Nursing participation due to Magnet status
6. Added 20 new members in the past year, replacement and new expertise.

Educational Opportunities

The new Common Rule Rules!

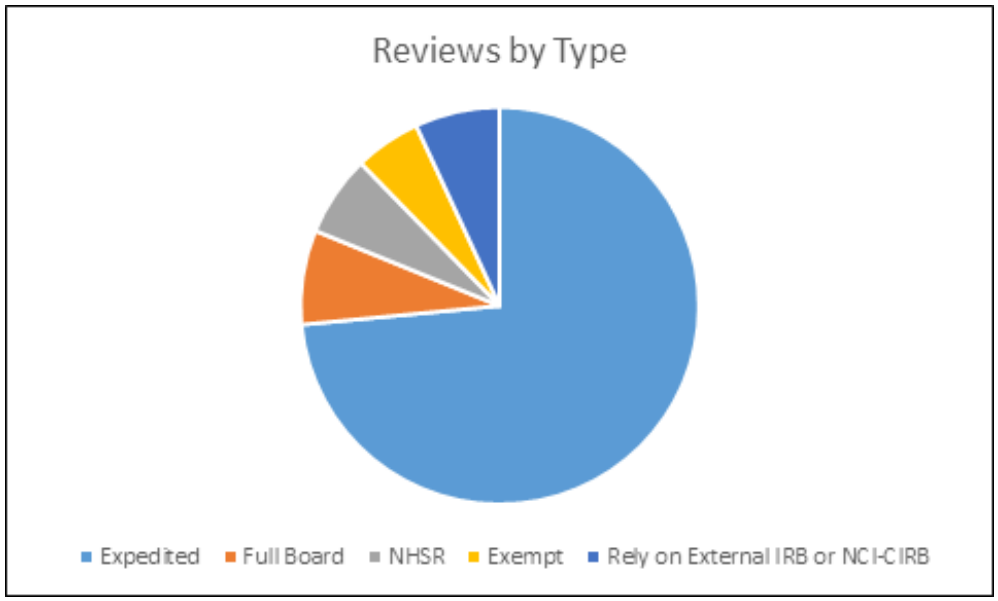
EROC taken down due to potential new Common Rule. Exploring two new interim options.

Sent 6 staff and chairs to the 2017 national Advancing Ethical Research (AER) Conference.

Participated in numerous Webinars from FDA, OHRP, PRIM&R, AAHRPP and others, many focused on Common Rule changes.

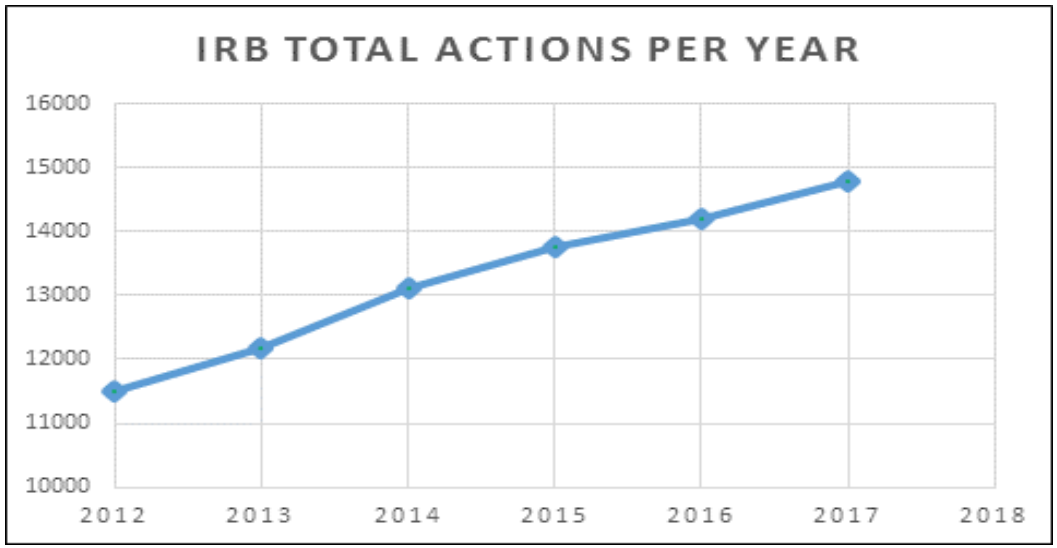
OHRE IRB Metrics

- The largest portion of reviews is Expedited, followed by Full Board, NHRS, and Exempt.
- Complexity overall, particularly of Full Board studies, continues to increase.



OHRE IRB Metrics

- Total volume continues to increase, averaging over 5% per year over the past 5 years.
- We have almost 6000 open studies and took nearly 15,000 actions this past year.



2017 Achievement Highlights

1. Successful AAHRPP Re-Accreditation!
2. Single IRB for multi-center, NIH-funded trials successfully implemented-UNC ahead of the curve.
3. Implemented annual evaluation process for IRB Chairs and members. Will add member review of Chairs (360) in 2018

2017 Achievement Highlights

4. Fully implemented “best practice” SOPs, including rollout of revised NSI Reporting and review.
5. IRB Virtual Pop-ups instituted for Network Entities.
6. Three Analysts earned their CIP certification this year.
7. New Common Rule ready.

2018 Opportunities and Challenges

- New Common Rule ?????
- Campus Communication and Education regarding New Common Rule
- Potential budget cuts/resource restriction
- Continued refinements related to NIH requirement for Single IRB of record

Robert J. (Bob) Levine, MD

Robert J. (Bob) Levine joined the faculty of Yale University in 1964 as Instructor in Medicine and Pharmacology and retired in 2016 as Professor Emeritus of Internal Medicine. He was Head of the Section of Clinical Pharmacology until 1973 when he changed the focus of his teaching and research to the field of medical ethics. He was Chairperson of the Institutional Review Board for 31 years ending in 2000.

In collaboration with Professor Margaret Farley he was the co-founder of the Yale University Center for Bioethics.

Bob is the author of multiple publications including the book, Ethics and Regulation of Clinical Research. He was also the founding editor of the journal, IRB: A Review of Human Subjects Research.

He has served several federal and international agencies involved in the development of policy for the protection of human subjects. Some examples: He was a ”special consultant” to the National Commission for the Protection of Human Subjects in which role he coauthored with Professor Tom Beauchamp the Belmont Report. He was chair of the committee that revised the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council of International Organizations of Medical Sciences (CIOMS), versions that were issued in 1993 and again in 2002. He was also chair of the World Medical Association’s committee that drafted the proposed revision of the Declaration of Helsinki that was issued in 2000.

21st Century Research Risk: What Guidance does the Belmont Report Provide?

– Robert J. Levine, MD
– Emeritus Professor of Medicine
– Center for Bioethics
– Yale University

- Chapel Hill, February 21, 2018

DOES THE BELMONT REPORT REQUIRE REVISION

- I will suggest:

- 1) that the *principles do not* need revision.

- 2) that the *definition of 'research'*, though still accurate, *may no longer be suitable* to define which activities require IRB review.

Recruited to IRB membership

- *Life is what happens to you while you're busy making other plans.*
- *John Lennon*

NATIONAL RESEARCH ACT: 1974

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Identify the ethical principles which should underlie the conduct of research involving human subjects.
  - Make recommendations for guidelines for "the protection of the rights and welfare of human research subjects".

ETHICAL PRINCIPLES

- Respect for persons
- Beneficence
  - Nonmaleficence
- Justice [distributive]

  - Historical order

NUREMBERG CODE: 1947

- Research done on ‘asocial’ persons

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should…yield…results for the good of society .
4. Avoid all unnecessary physical and mental suffering and injury.
6. Risk should never exceed…the humanitarian importance of the problem to be solved.

Looking further back

- Respect for Persons: Judeo-Christian
  Infinite worth of each human being
- Beneficence: Hippocratic Oath [Edelstein]:
  "Whatever houses I may visit, I will come for the benefit of the sick,"
- Non-Maleficence: Hippocratic Oath [Edelstein]: *"I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect."*

Looking further back[2]

- Justice: Aristotle: **justice** consists in what is lawful and fair, with fairness involving equitable distributions and the correction of what is inequitable.
- John Rawls: Justice as fairness.
  - A Theory of Justice 1971

Belmont [early draft]

- “Reliance on these three fundamental underlying principles is consonant with the major traditions of Western ethical, political and theological thought presented in the pluralistic society of the United States, as well as being compatible with the results of an experimentally based scientific analysis of human behavior….”

CARDIOPULMONARY RESUSCITATION-1960

- Before CPR when the heart stopped there were no options; this was death.
- 1958-60: Open cardiac massage.
  - A gruesome experience.
  - I performed many open procedures with no survivors.
- Revolutionized medical ethics discussions.

CARDIOPULMONARY RESUSCITATION[2]

- Justice issues
- On whom should it be performed:
  - Was withholding an injustice.
  - Was refusing suicide?
- Requesting a DNR order—living will
  - Extraordinary means (a concept from Roman Catholic moral philosophy).

CARDIOPULMONARY RESUSCITATION[3]

- Respect for persons
- Is research on resuscitation techniques without informed consent permissible?
- Is relatives' or guardian's permission required.
- What if relatives disagree?

CARDIOPULMONARY RESUSCITATION[4]

- Beneficence-Nonmaleficence
- Is this merely prolonging the process of dying?
  - Limited survival of hospitalized patients.
- Painful.
- Broken ribs, lacerated livers.

PUBLIC CONCERN WITH ETHICS OF RESEARCH

- Focus on beginnings and endings of life.
- We have considered one aspect of concern with the ending of life.
- Now let’s turn to the beginning.

ETHICAL PROBLEMS

- 1972 recombinant DNA
  - Moratorium Asilomar 1975
- Frozen embryos
- Blastomere biopsy
- Stem cell research
- Genetic engineering
  - Adding (recombinant) or “Knock-out” of genes or genetic material

National Commission-1974

- Imposed moratorium on fetal research.
  - Four months.
- The remainder of its work: Two years.
- Fetal research regulations issued 1975.
  - Lacked conceptual clarifications.
  - Required revision.
  - Three years before Belmont Report but had implicit references to the 3 basic principles.

1973 and 1974 Boston Cases

Kenneth Edelin: Charged with manslaughter for a legal abortion.

Leon Sabbath (Chief Resident OB/GYN @ BCH) et al: 1814 grave-robbing statute. Administered erythromycin and clindamycin, to mother about to have a ‘therapeutic abortion’ @ 24 weeks. Found both drugs crossed placental barrier.

Roe v. Wade-1973

- Right to Life organizations portrayed Roe v Wade opening flood gates for fetal research.
- Abortion providers, they asserted, were motivated to supply research material for fetal research.
- Fetal research was characterized as ‘material cooperation’ in an evil act.

CRISPR

- CRISPR: the closest I can get to imagining what ethical problems the future has in store for us. Presents ethical problems of the same order of magnitude as research on the fetus and recombinant DNA.
- Moratorium proposed.
- Dr. Jonathan Berg will probably cover this topic in the final presentation.

ETHICS OF REPRODUCTIVE TECHNOLOGIES

- The same fundamental principles apply.
- Respect For Persons is complicated by considering the point at which an entity that has the potential to develop into an independent human being becomes eligible to be treated with respect according to RFP. When should it acquire rights that should be protected by law? When does it become a member of the moral community?

ETHICS OF REPRODUCTIVE TECHNOLOGIES[2]

- Nonmaleficence is complicated by the fact that harmful genes introduced in the germ-cell line will be passed down through the generations.
- Justice: Considerations of justice may be complicated by the possibility of creating an elite class of superbabies.

ETHICS OF REPRODUCTIVE TECHNOLOGIES[3]

- The dividing line between human therapy and enhancement may be hard to define.
- The definition of “research” is still accurate but it may not continue to be suitable to distinguish which activities require review by an IRB.

CONCLUSION

- The Belmont principles do not need revision.
- The norms, regulations and procedures will require revision as we are faced, from time to time, with novel problems.
- Beware the appearance of ‘infinite malleability’.

THANK YOU

Anne Drapkin Lyerly, MD, MA

Anne Drapkin Lyerly, MD, MA is Professor of Social Medicine and Associate Director of the Center for Bioethics at the University of North Carolina, Chapel Hill. An obstetrician/gynecologist and bioethicist, she studies ethically complex issues in women's reproductive health. She co-founded the ***Second Wave Initiative***, an effort to ensure that the health interests of women are fairly represented in biomedical research and drug and device policies.

She is PI on the NIH-funded PHASES Project addressing the ethics of HIV research and pregnancy, and co-PI on a Wellcome Trust funded project to address the ethics research involving pregnant women in the context of Zika and public health emergencies. She has served on numerous national committees, including the *American College of Obstetricians and Gynecologists Committee on Ethics*, which she chaired; the National Institutes of Health Advisory Committee to the Director's Working Group on Stem Cell Research; and the March of Dimes National Bioethics Committee.

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

Pregnant Women and Research:
Tackling the Complexities of Inclusion

Anne Drapkin Lyerly, MD, MA

Professor, Department of Social Medicine

Associate Director, Center for Bioethics

University of North Carolina at Chapel Hill

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

NIH

Pregnancy Research Ethics
for Vaccines, Epidemics,
and New Technologies
PREVENT

wellcome

pregnancyethics.org

@pregnancyethics

Overview

- The problem of exclusion
- Toward responsible inclusion
- Addressing the complexities of inclusion
  - Informed consent
  - Risks and Benefits
  - Fair Access

The problem of exclusion

The first wave:
Women as research participants

- Early 1990s women noted to be underrepresented in research
  - Excluded from studies
  - Health concerns not investigated
- Alleged justifications
  - Women's physiologies complicate
  - Recruitment difficulties
  - Protection of women and fetuses

Dresser, *HCR* 1992

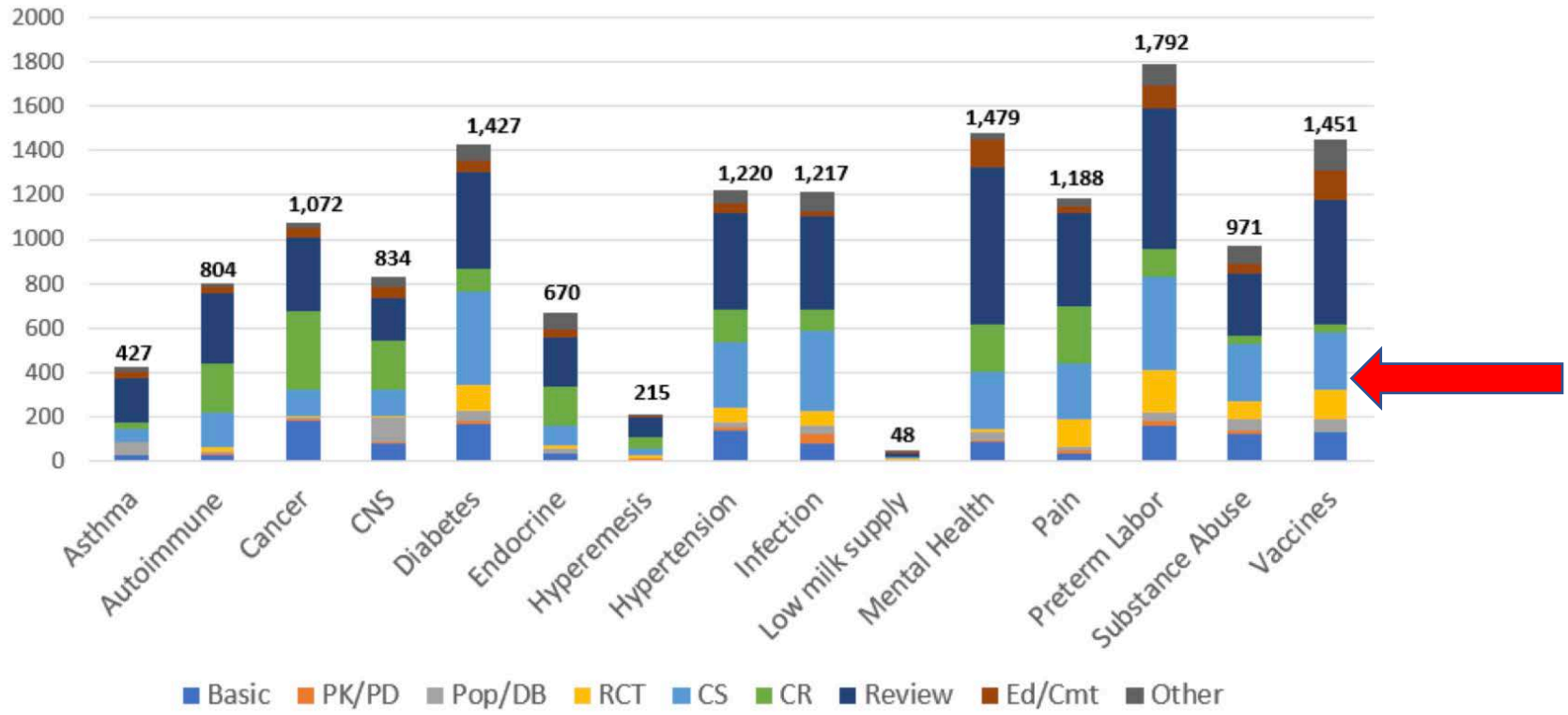
From protectionism to access

- 1993 NIH Revitalization Act
  - New requirements for inclusion of women and minorities in research
  - Justify exclusion on basis other than cost
- Women now majority of research participants (gaps remain)

➢Pregnant women: left behind

Pregnant women: "therapeutic orphans"

Figure 3: Number of Publications Related to Therapies for Pregnant and Lactating Women, by Category and Type, January 2006—August 2017



PRGLAC, 11/2017

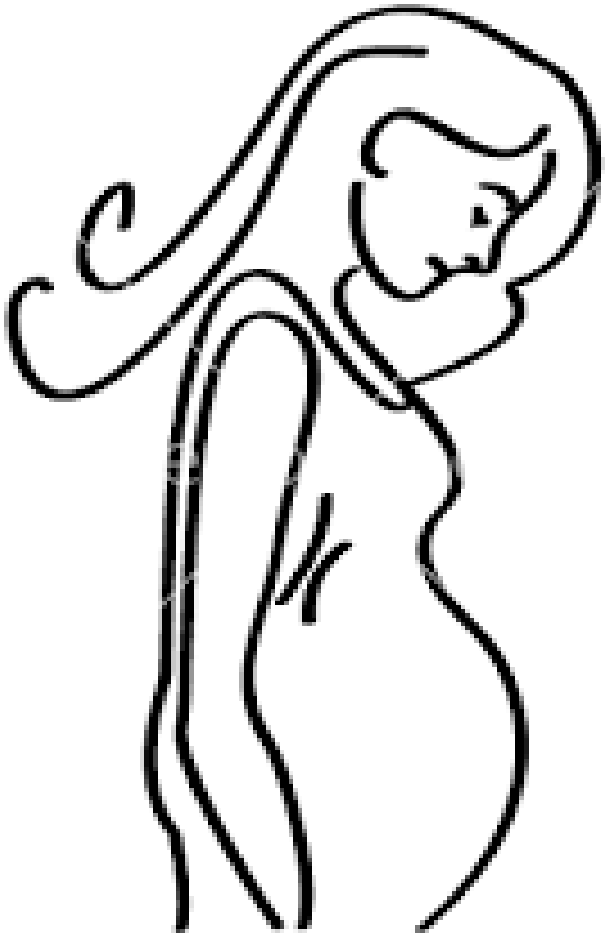
Key research gaps

- A substantial number of common and relatively rare but serious conditions are are ***largely unaddressed*** in the research literature.
- Placental transport (28 publications total)
- PK/PD research (1.3% of total pubs on pregnancy)
- Safety, including later emerging effects of medication
- Effects of untreated disease
- New drug development

Harms of exclusion

- Evidence gaps: safety of medication
  - 98% of drugs: undetermined risk
  - 27 years average for pregnancy safety determination
- Evidence gaps: dosing and toxicity
  - Scant PK/PD

Pregnant women are different



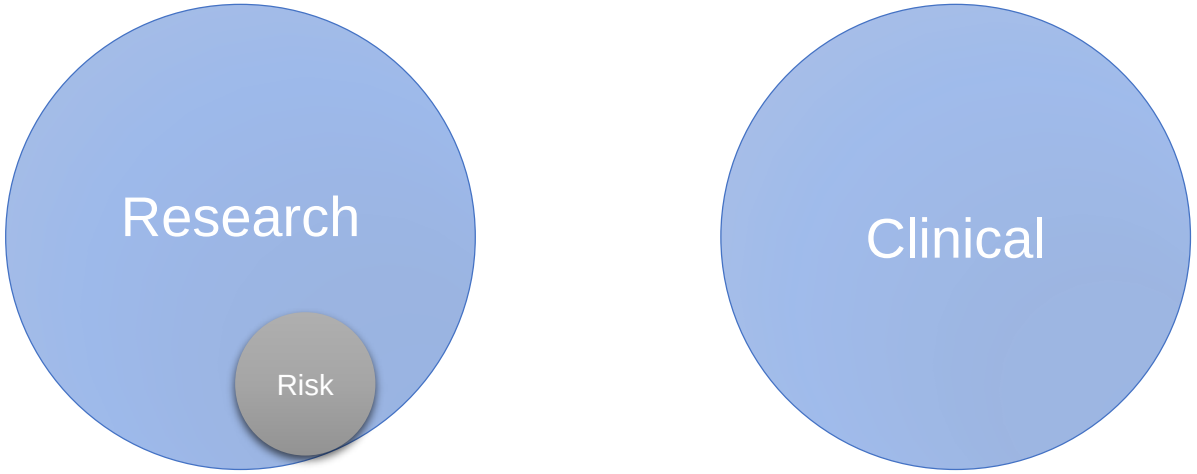
- ↑ cardiac output, plasma volume
- ↓ gastric emptying, intestinal transport
- ↑ renal excretion
- ↕ drug metabolism

Harms of exclusion

- Evidence gaps: safety of medication
  - 98% of drugs: undetermined risk
  - 27 years average for pregnancy safety determination
- Evidence gaps: dosing and toxicity
  - Scant PK/PD
- Reticence to use beneficial drugs
  - Diseases can be harmful, even teratogenic

- Disparities in access to PDB research

Risk shifting



Toward responsible inclusion

The Second Wave:

Pregnant women as research participants

TIME

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The Risks (and Rewards) of Pills and Pregnancy

We know little about drugs' effects on moms-to-be. How a group of advocates is trying to change that

mosaic

HOME ABOUT TOPICS SEARCH

welcome

Hard labour: the case for testing drugs on pregnant women

By Emily Anthes

24 NOV 2015

17 min

Sean Justice / Corbis; Tamiflu: Getty; Lipitor: Mel Evans / AI

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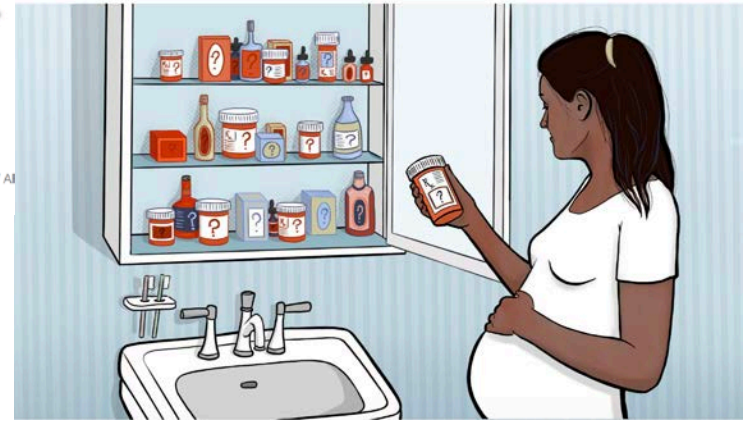
HEALTH

Pregnant women who need medications face a risky guessing game. A federal task force is now trying to help

By MEGAN THIELKING @meggophone / DECEMBER 5, 2017



The New York Times

Opinion

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION

EDITORIALS COLUMNISTS CONTRIBUTORS LETTERS THE PUBLIC E

OP-ED CONTRIBUTORS

A Custom Drug

By RUTH FADEN, ANNE DRAPKIN LYERLY and MAGGIE LITTLE
Published: May 9, 2009

TWITTER

PRGLAC

- Task Force on Research Specific to Pregnant and Lactating Women

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services regarding ***gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women****. PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary.*

No longer "vulnerable"

- **CIOMS 2016:** pregnant women must not be considered vulnerable simply because they are pregnant

- **45CFR46 2018*:** the final rule no longer includes pregnant women as examples of populations that are potentially vulnerable to coercion or undue influence

*not yet in effect

Addressing complexities of inclusion

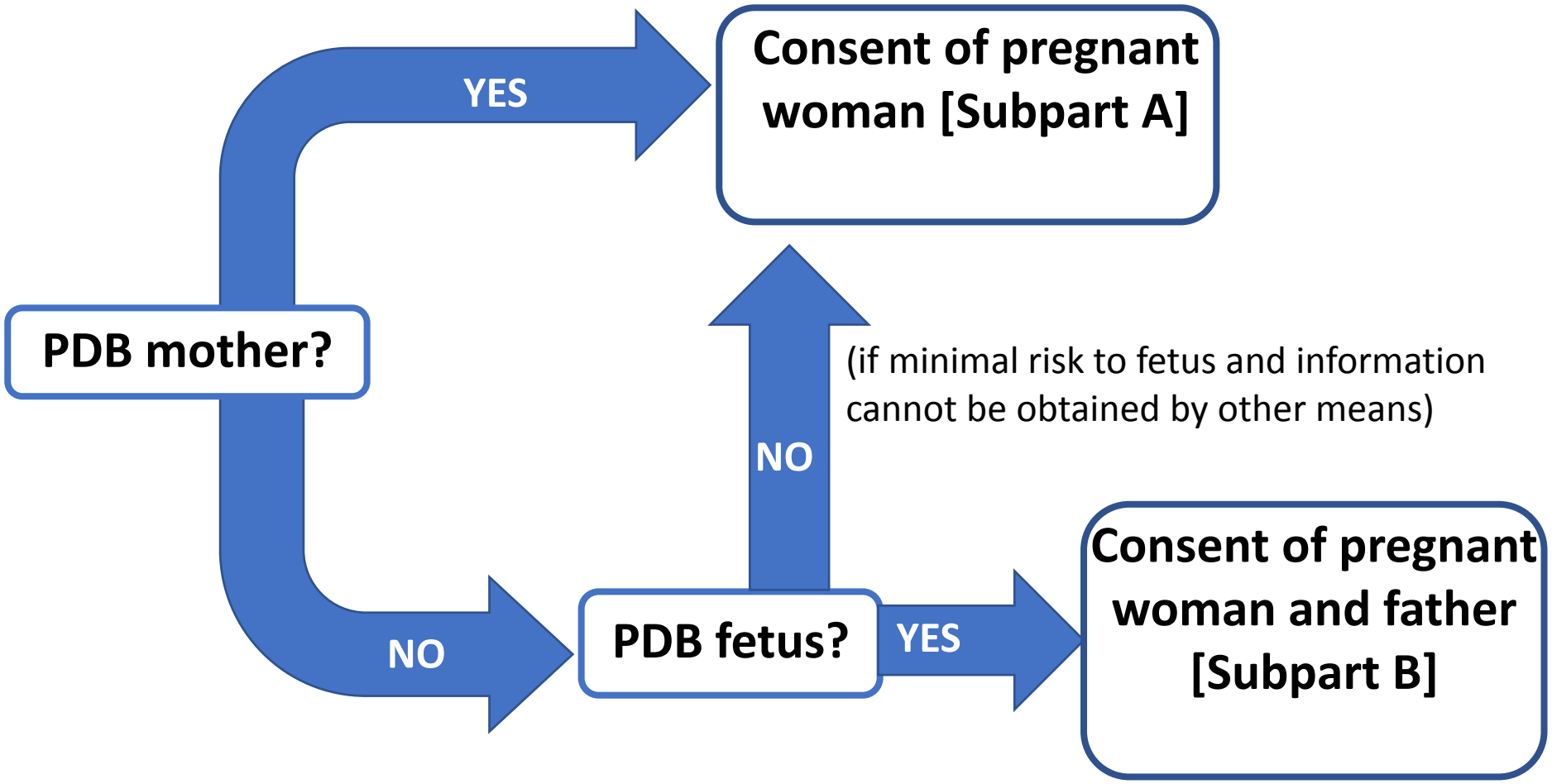
1. Informed Consent

- In many ways informed consent in pregnancy is similar to other contexts
  - Pregnancy does not interfere with capacity for informed decision-making

EXCEPT:

- Research in pregnancy takes place in context of profoundly limited evidence base
- Pregnancy may entail research involving an entity who cannot consent for itself (fetus)

HHS requirements – paternal consent



In favor of paternal consent

- [paternal consent in fetal-benefit research] is "most **respectful of the parents' joint interests** in their fetus's health."

  ➢Federal Register, November 2001

Objections to paternal consent

- **Potential barrier to research participation**
- **Doesn't respect pregnant women's autonomy**
- **Inconsistent with standards for clinical care**
  - e.g., cesarean, transfusion
- **May compromise privacy and safety of pregnant woman**
  - e.g., maternal HIV status
- **Maternal and fetal benefit not separable**
  - bodies, life trajectories intertwined
- **Fails to account for range of relationships**

Exceptions to PC requirement

45CFR46.204e

- father's consent need not be obtained if he is unable to consent because of **unavailability**, **incompetence**, or **temporary incapacity** or the **pregnancy resulted from rape or incest**.

A cross-cutting worry: gender dynamics

- *"It is somehow good… Because maybe the husband has refused you but you cling onto it. It can cause you certain problems… Maybe the marriage breaks down. Maybe he even rejects the baby saying it is not his."*

  Tafadzwa, 18

- *"You don't know, they coming out of abusive relationships—you don't know what kind of situation they're in now. So because you done sent them over there, because you want to consent you done caused a situation when that girl go home. So the rule is no good."*

  Aleesa, 23

Contrast with pediatric research

*where research holds PDB for offspring

TWO PARENTS

ONE PARENT

Another model for paternal involvement

- Some research involving pregnant women may be directed at the health of the fetus. In such cases, the **role of the woman remains the same: she is the decision-maker for any interventions that affect her**. This does not exclude the possibility of the woman **consulting with the father of the fetus, if she wishes**.

CIOMS, 2017

Mitigating considerations

- Interventions rarely offer prospect of benefit to fetus alone (interests, bodies intertwined)
- Interpretation of “reasonably available”

2. Risks and benefits

Prospect of direct benefit (PDB)?

Either
woman or fetus (or both)

Reasonable ratio of risk to benefit

e.g. Phase III efficacy trials

Neither
woman nor fetus

Fetal RRR capped at minimal risk

e.g. Phase I/II PK studies

Little, PRGLAC 2017

The "either" challenge: trade-off scenarios

Maternal risk/ fetal benefit	• Like other competent agents, a pregnant woman can altruistically volunteer to participate in clinical research with minimized risk and no PDB to her
Fetal risk/ Maternal benefit	• The decision to continue a pregnancy should not require a pregnant woman to forfeit rights to all important medical benefits
Fetal risk/ Future child benefit	• Pregnant women reasonably differ in the priority they place on avoiding fetal loss versus improving future child benefit

Little, Wikremsinhe, Lyerly, ACOG 2017

The "neither" challenge minimal risk standard

Vague

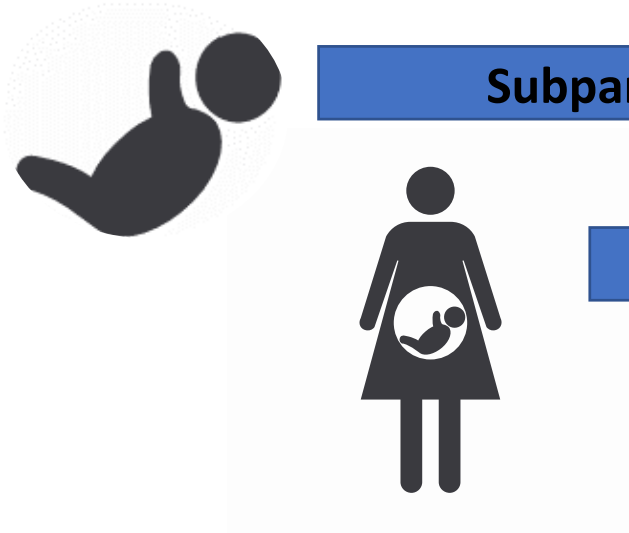
1. Whose daily risks?
2. Why daily risks?
3. Why risks of exam?
4. Diverging IRB interpretations

Dual function

1. Capping risk in compromised consent + no PDB
2. Justifying expedited review and informed consent waivers

Unintended chilling effect

- Example: pharmacokinetic studies (e.g., raltegravir)
- Solution: MIOMR for non-PDB research?



Subpart D: Minor increase over minimal risk

Subpart B: No such category

CIOMS 2016: "When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk."

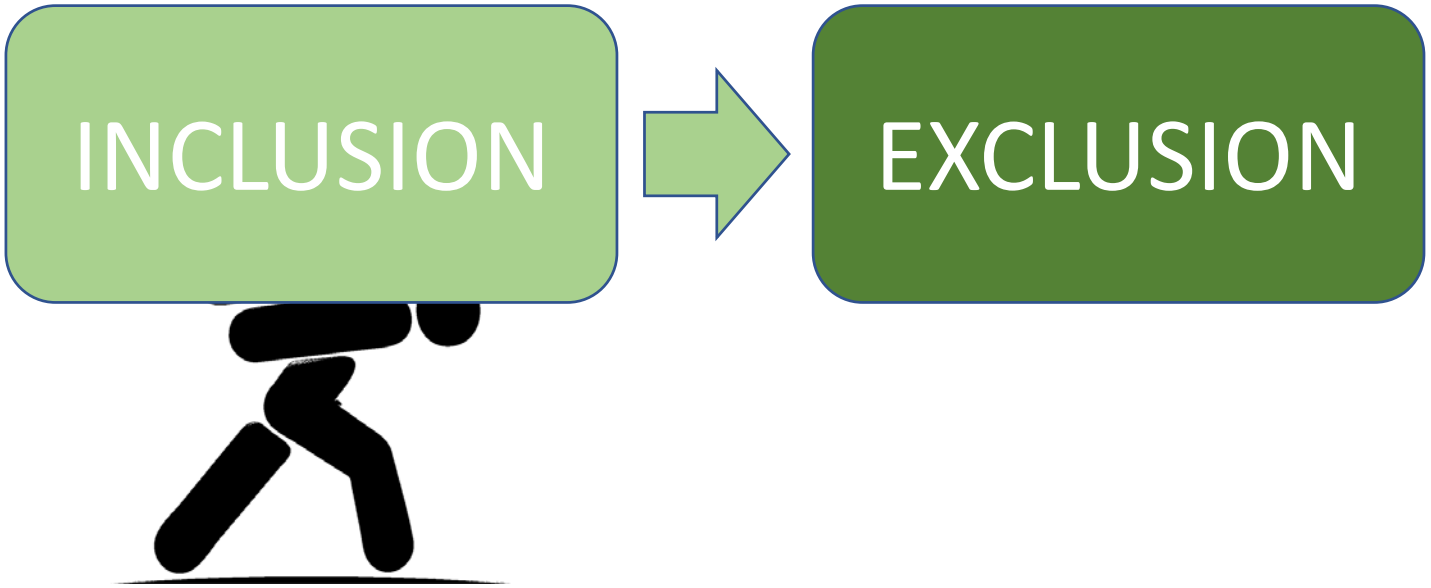
Fair access

- "Fair access requires that eligibility to enroll or continue in a trial depend on reasonable assessments of the potential benefits to participation related to the risks for the woman and her future offspring."
  - ZIKV Working Group, 2017

- What is the role of the IRB?

Burden of justification

- Shifting burden – require justifying *exclusion*



Acknowledgment

- Research reported in this presentation was supported by the National Institutes for Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI108368
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

BREAK

30 minutes

Jonathan S. Berg, M.D., Ph.D

Jonathan S. Berg, M.D., Ph.D., is an associate professor in the Department of Genetics at the University of North Carolina at Chapel Hill (UNC). He also has a clinical appointment in the Department of Medicine, Division of Hematology–Oncology and the Lineberger Comprehensive Cancer Center. Dr. Berg graduated from Emory University with a B.S. in biology and completed the M.D./Ph.D. program at UNC in the curriculum in neuroscience. He subsequently underwent residency training in clinical genetics at Baylor College of Medicine.

Dr. Berg is a practicing physician and translational researcher interested in the use of genetic tests in patients and their families. The recent revolution in genetic sequencing technology has led to an unprecedented opportunity to investigate the underlying etiology in families with suspected genetic conditions, and yet it raises potential pitfalls that must be addressed in order to translate these new technologies into the practice of clinical genomics.

Dr. Berg is co-principal investigator of NIH grants to investigate several aspects of genome-scale sequencing in clinical medicine: NCGENES, which examines the use of exome sequencing as a diagnostic test in patients with suspected genetic disorders; NC NEXUS, which asks whether sequencing could be used as a potential screening tool in healthy newborns; and ClinGen, which seeks to develop a publicly available database of clinically relevant genes and variants.

He is also an investigator in the UNC Center for Genomics and Society, a National Human Genome Research Institute funded Center for Excellence in Ethical, Legal, and Social Implications Research, which has examined the prospect of using genomics to improve the health of adults in the general public.

Dr. Berg is particularly interested in the range of “incidental,” or “secondary,” findings that are discovered during the course of genome-scale sequencing. This technology provides new avenues to identify presymptomatic individuals with rare but potentially preventable hereditary conditions as part of “precision medicine,” which in turn raises formidable questions about “who,” “what,” “when,” “where,” and “why” as we strive to implement genomic medicine.

Genetic Research: Routine or Risky?

Red flags for IRBs to be alert for, and considerations for human subjects protection

Jonathan S. Berg, MD/PhD

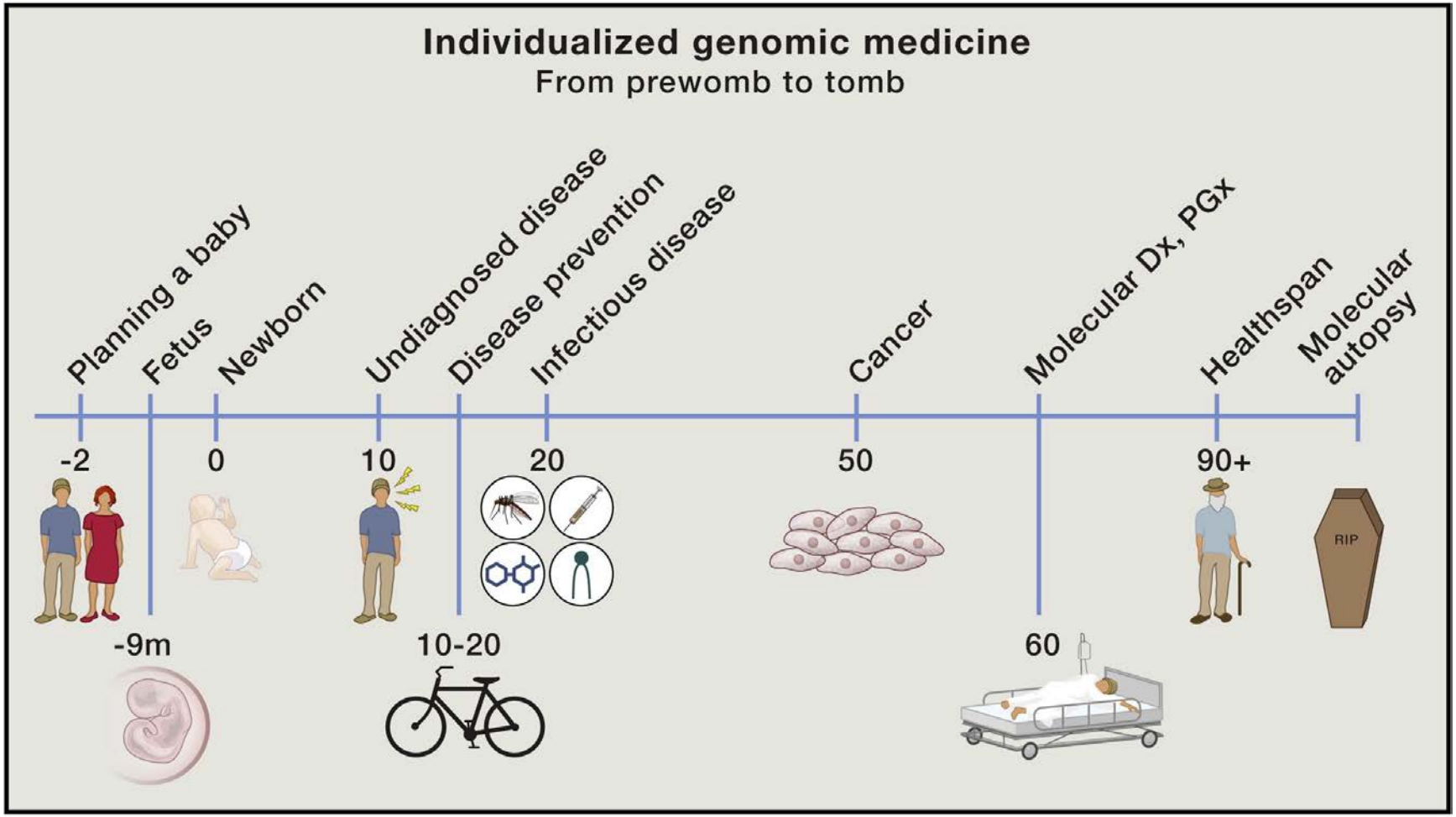
Department of Genetics

UNC Chapel Hill

Genetic Exceptionalism

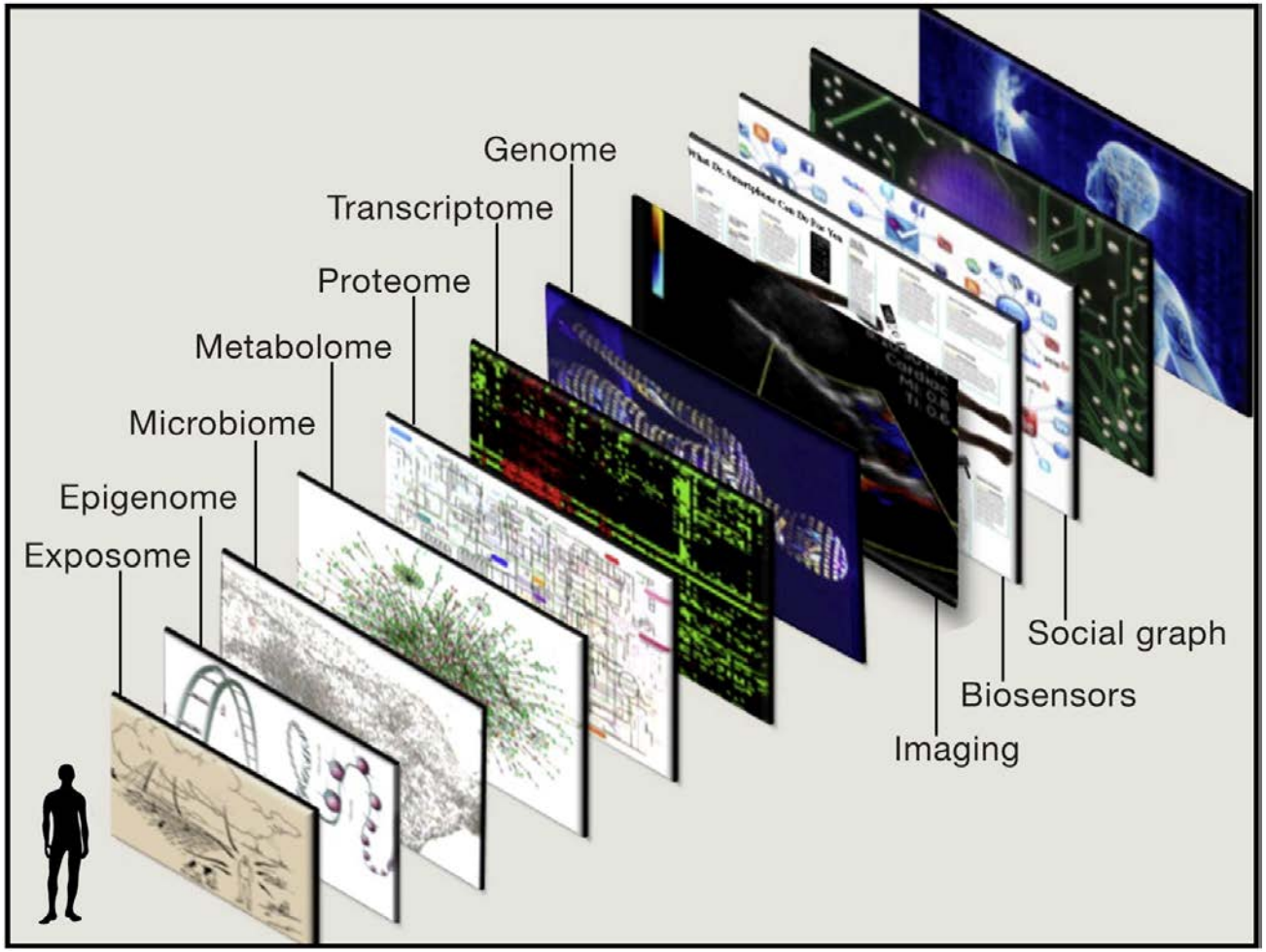
- Why are we concerned about genetic results?
  - Individual harm
    - Action/inaction based on genetic information
    - Discrimination (insurance, employment, etc.)
  - Group harm
    - Historic abuses of genetic information
- What is the information content in genetic information that is different than other data such as radiographic images?

Genomic data can be utilized across the lifespan



Topol, 2014 https://doi.org/10.1016/j.cell.2014.02.012

Are genomes different than any other types of predictive data?



Topol, 2014 https://doi.org/10.1016/j.cell.2014.02.012

Defined by regulatory bodies?

Ceiling
(maximum)

In between

Floor
(minimum)

Determined by respect for participants?

Big picture considerations

What genomic data will be generated and how clinically useful are they?

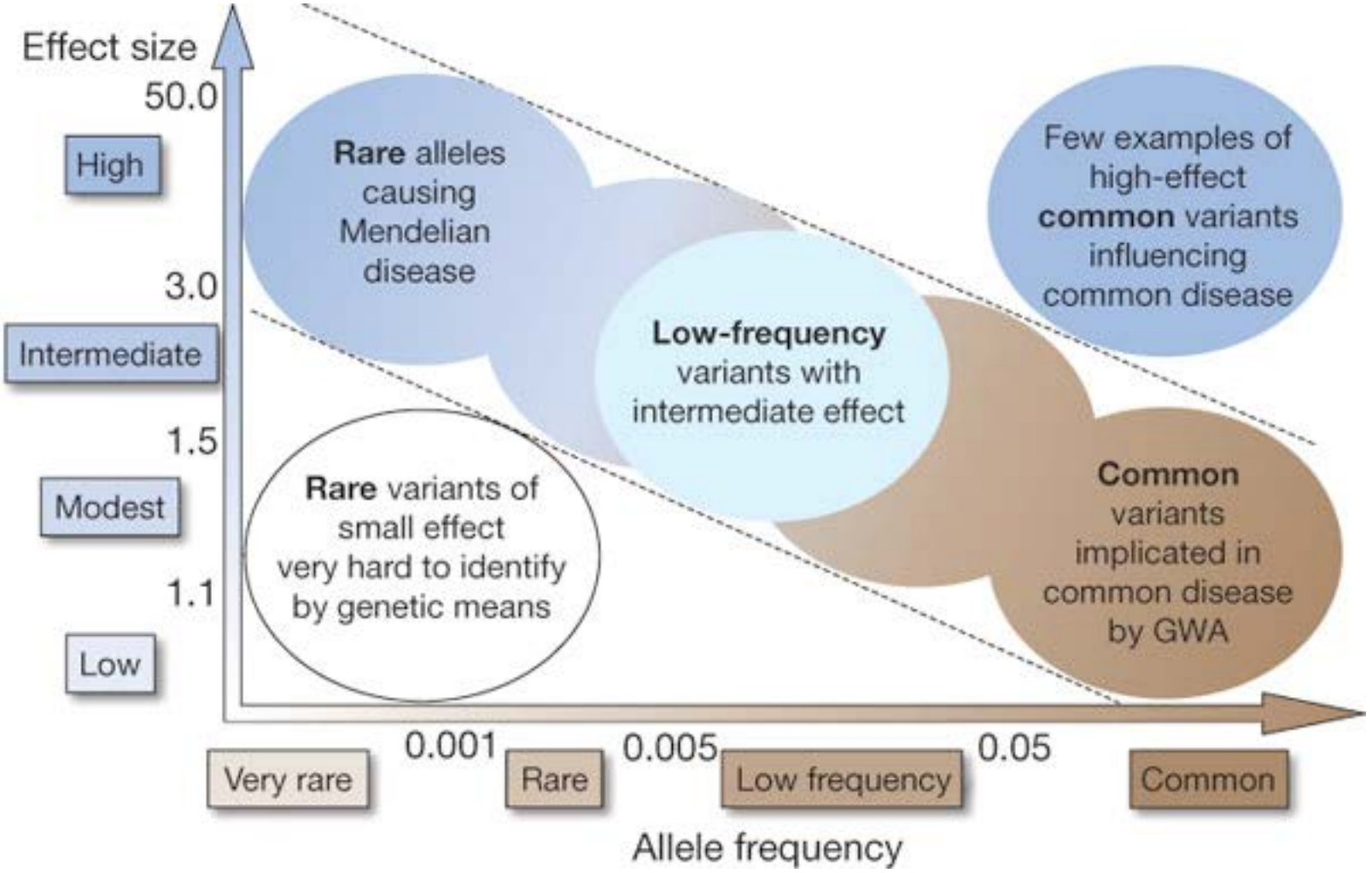
What will be done with the data and who will have access to it?

What are the obligations and responsibilities around returning results to participants?

Genomic data

- Target tissue source
  - Tumor
  - Germline (blood, saliva, other sources)
- Data type
  - Sequence variants (SNPs, rare variants)
  - mRNA expression (can include discovery of variants)
  - Epigenetics
- Extent of target
  - Focused analysis (PCR, Sanger sequencing)
  - Genome-scale analysis (microarrays, next-generation sequencing)

Range of genetic variation



Manolio et al. Nature 461, 747-753

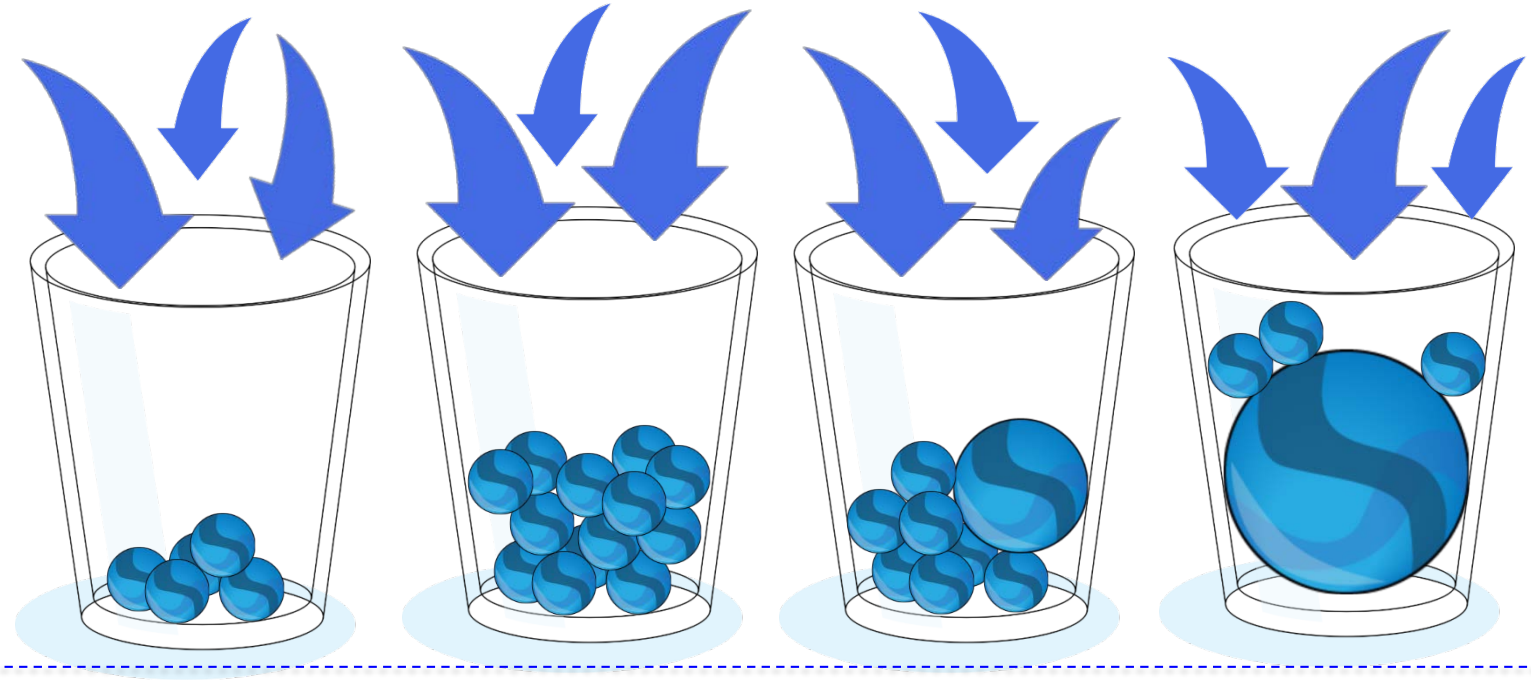
The spectrum of disease causation

Non-genetic influences

Chance Cosmic radiation Aging

Environment Toxins Carcinogens

Behavior Diet Exercise Smoking



Genetic influences (what you start your life with)

Common low risk alleles

Moderate risk (oligogenic) alleles

High risk (monogenic) alleles

Data sharing

- Genomic data is a hot commodity right now
  - Every NIH study wants to bank samples for future research (saliva, blood, cell lines, etc.)
  - This raises a huge potential for scientific discovery and should be facilitated
- Research participants should know what is being done with their samples and what will happen to the data
  - Especially when data will be deposited in public databases and/or shared with commercial interests

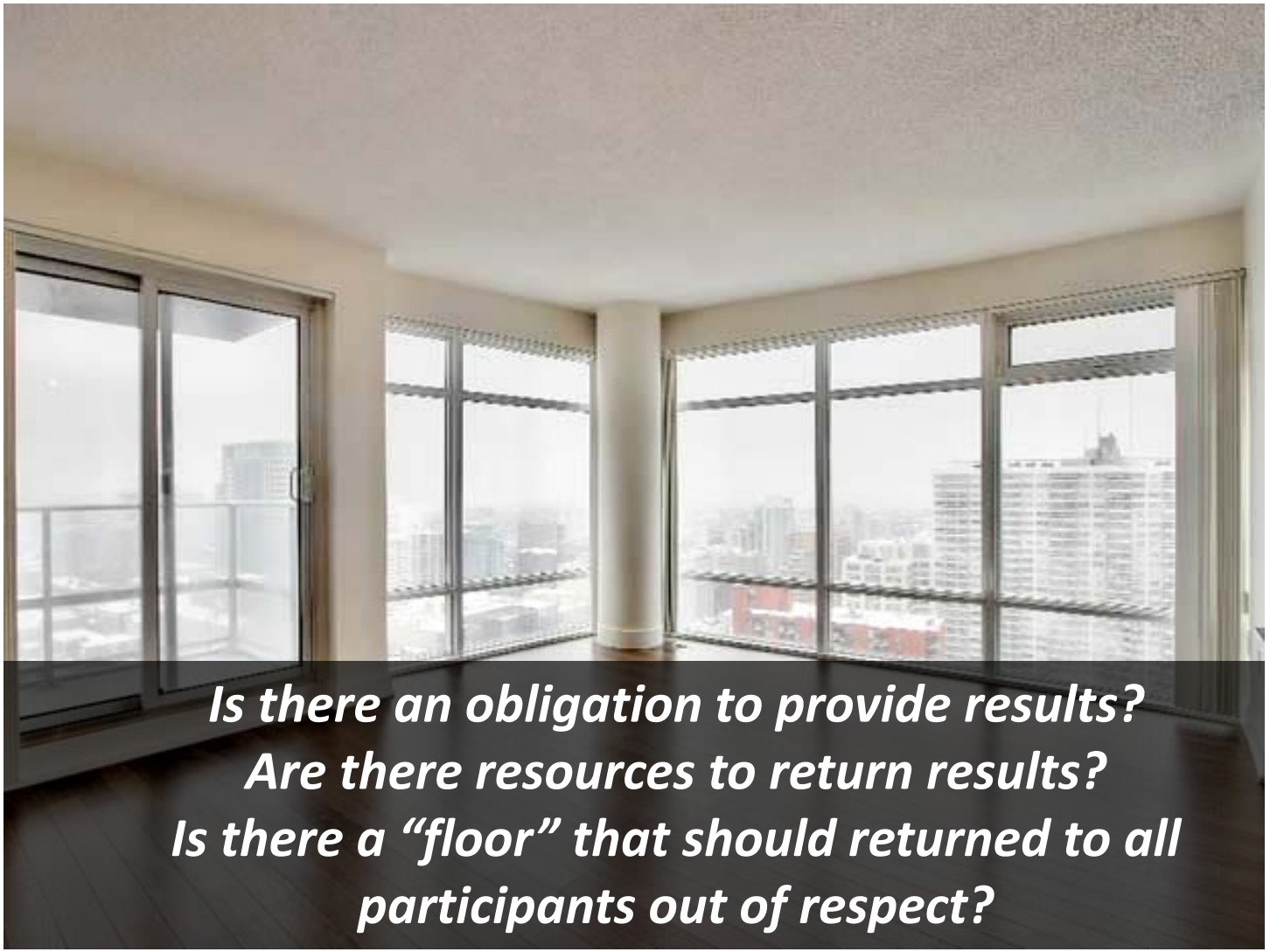
Return of results as participant engagement

- Growing sentiment (see “All of Us” cohort) for returning results as a way to engage and facilitate participation in research
- Puts enormous pressure on researchers across all domains of research, even those that might not be expert in genomics
  - And therefore pressure on IRBs to monitor and regulate what is being done

Should researchers provide results?

- Is disclosure of results to participants or clinicians part of the research question?
- Does the researcher have a direct clinical relationship with the research participants?
  - Possibly creating a sense of obligation on the part of the researcher
- If not, are the research participants potentially identifiable and/or somehow connected to UNC?
  - Possibly creating an obligation on the part of the institution
- To what extent would the costs of returning results interfere with scientific objectives?

Should researchers provide results?



If results are NOT being returned…

- Need to be clear about what data is being generated and explanation for why it will not be returned
- Should still have a contingency plan for “incidental findings” that rise to a significant threshold
- Future plans for systematic return of results would need to be addressed as an addendum

If results ARE being returned…

- Research team needs to articulate a clear plan
  - What results will qualify to be returned
  - How participants will be able to establish preferences
  - Qualifications of research team to conduct informed consent, clinical analysis, disclosure, and follow up

What results qualify to be returned?

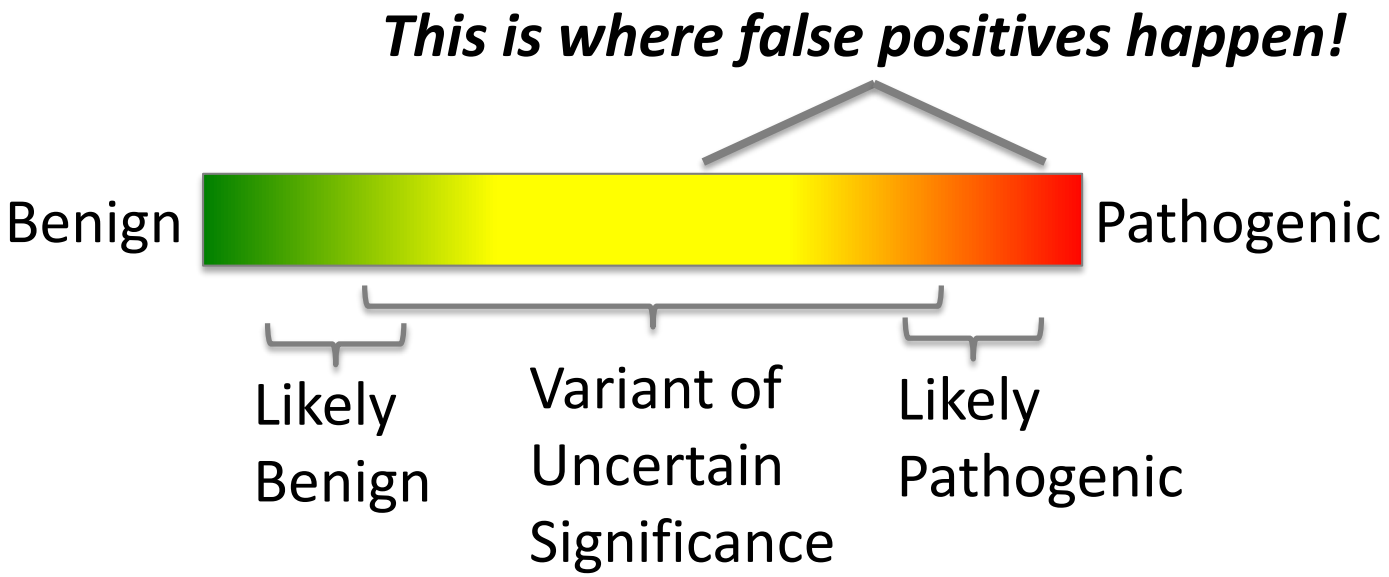
- Are the results potentially clinically relevant?
  - Diagnostic, prognostic, or predictive?
  - Clinical validity? Clinical actionability?
- Are the results clinically interpreted?
  - By whom? Using what criteria?

Types of clinically relevant results

- Mendelian
  - Diagnostic/Predictive, “Actionable” or not (~10%)
  - Carrier status (almost everyone has a small number)
- Pharmacogenomics
  - Everyone has alleles with varying level of importance
- Polygenic/multifactorial common disease risk
  - Can be calculated for a number of conditions but how useful are the predictions?
- Somatic
  - Drug targeting, prognosis, clinical trials eligibility

Mendelian conditions

- **Gene-disease pairs**
  - Need to ensure that results are clinically valid
- **Variants**
  - Interpreted with respect to a specific condition



Clinical Actionability

- Definition varies by person; best described as a continuum, not a binary state
  - Can be useful to define categories to enable preference setting
  - Our group evaluates five salient parameters for Mendelian disorders

Severity of outcome / Likelihood of outcome

Efficacy of interventions / Nature of interventions

Knowledge base

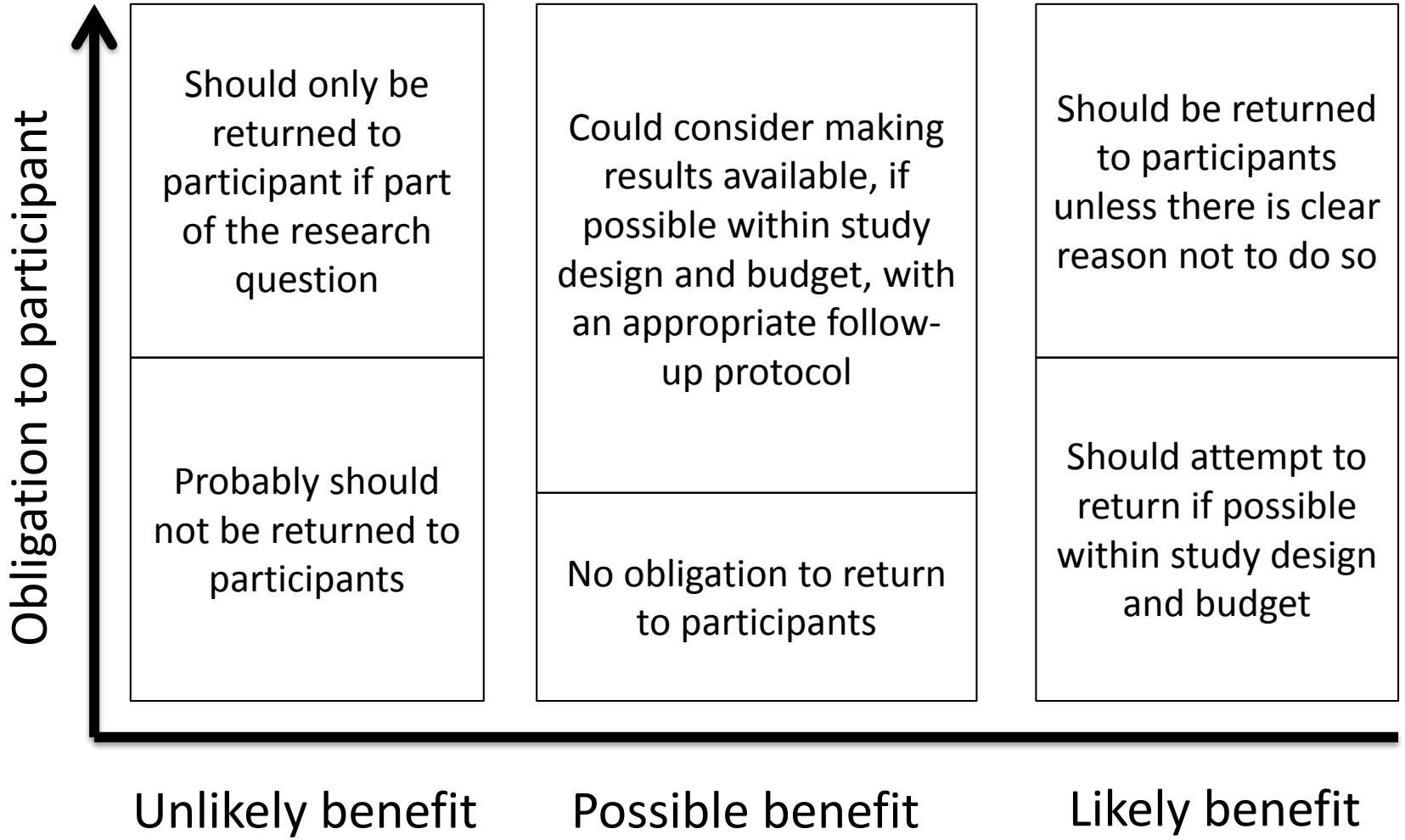
ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

- Consensus effort, loosely based on criteria that included "actionability"
- Initially 57 genes, then revised to 56 ("ACMG 56")
- Now recently updated to 59 (removed 1, added 4)
- Provides clinical labs with a standardized set of genes to analyze and return; patients can opt out
- Not defined for research, but frequently used

Clinical benefit vs. researcher obligation



Questions about return of results

- Who conducts consent and disclosure?
- What categories of results are offered?
- Is there a clear and valid plan for analysis?
- How does the participant decide what to learn? (or not to learn)
- Where will the results reside?
- Will there be follow up?

Consent and disclosure practices

- Genetic counseling
  - For consent? For participant preference setting? For return of results?
- CLIA confirmation
  - Perhaps commensurate with the type of information being provided?
  - Need to guard against misinformation
- Placement of results in the medical record
  - Necessary for clinically important results to be acted upon
  - Participants might prefer not to include some information

Should researchers provide results?

Should some form of "raw data" be provided to participants as form of engagement?
Is there a "ceiling" or limit on certain kinds of results in order to protect research participants?

Data formats and relative trade-offs

	PROs	CONs
Raw data	• The ultimate in “all of your data” • Greatest potential for re-use • Minimally influenced by analytic choices or governance decisions • Low cost to provide access	• Practically useless for most people • Potentially unlimited risk depending on what the participant does with their data

Data formats and relative trade-offs

	PROs	CONs
Processed variant calls	• Tangible “result” • Reasonably high potential value • Relatively inexpensive to provide access	• Still not very useful without further work • Analytic choices influence results • Requires participants to get information about clinical significance from someone else

Data formats and relative trade-offs

	PROs	CONs
Annotated variants	• Much richer information content • Automated generation • Relatively inexpensive to provide access	• Requires investment in data sources, annotation pipeline • High potential for misunderstanding by patients and clinicians

Data formats and relative trade-offs

	PROs	CONs
Interpreted variants	• Closest to clinical usefulness • Great benefit to small percentage of participants	• Very high cost of governance, oversight, clinical interpretation • Requires meaningful preference-setting engagement • Potential for confusion, overaction • Requires clear follow-up plan

The central paradox of result disclosure

- Clinically useful information, which researchers have more obligation to provide, creates greater burden on the research team to provide information in a responsible way

- The least burdensome form of results disclosure (providing raw data) is also the least useful to the participant and potentially the most risky

Responsible conduct of research

- The institution needs to have a consistent approach to how genetic information is handled in research
- Return of results, when appropriate, should be handled similarly across projects
- Does UNC need a standardized approach to genetic research results (consent, analysis, disclosure, and follow up)?
- Should there be formal stewardship of data to enable its use by participants in the future?

Standardization and innovation

Thanks!

Questions?

ClinGen Clinical Validity Framework

Definitive	Repeatedly demonstrated in research & clinical settings
Strong	Excess of pathogenic variants in cases vs. controls & supporting experimental data
Moderate	≥3 unrelated probands with pathogenic variants & supporting experimental data
Limited	<3 unrelated probands w/ pathogenic variants
No Evidence Reported	"Candidate" genes based on animal models or disease pathways, but no pathogenic variants reported
Conflicting Evidence Reported	
Disputed	Convincing evidence disputing a role for this gene in this disease has arisen
Refuted	Evidence refuting the role of the gene in the specified disease significantly outweighs any evidence supporting the role

Arrays versus Sequencing

- Array content is completely specified
  - Thus allowing explicit decisions about returnable content by design
  - But would fail to identify novel/private variants (lower clinical sensitivity)
- Sequencing can detect a greater range of possible variants
  - Raising the question of what to do about the return of novel/private variants
  - Greater chance for clinical misdiagnosis and harm

© American College of Medical Genetics and Genomics **ACMG STANDARDS AND GUIDELINES** | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

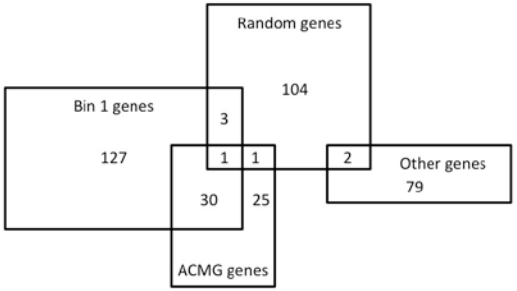
A semi-quantitative metric to define actionability and determine "Bin 1"

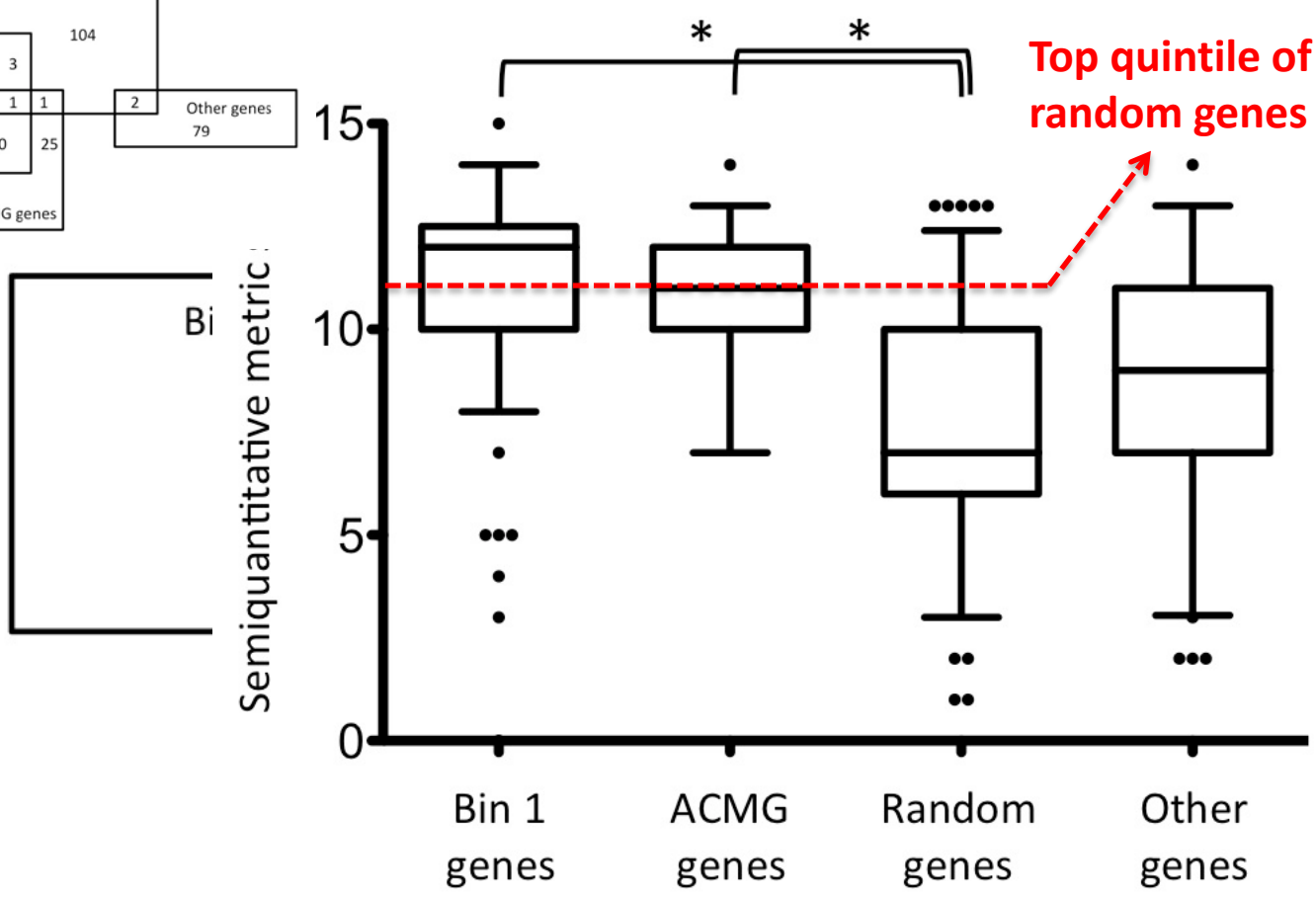
– Severity of disease	(0-3)
– Likelihood of a severe outcome	(0-3)
– Effectiveness of interventions	(0-3)
– Nature of interventions	(0-3)
– Knowledge base	(0-3)
	0-15

These elements can be used to generate a semi-quantitative "clinical actionability" score for every gene-phenotype pair

NCGenes

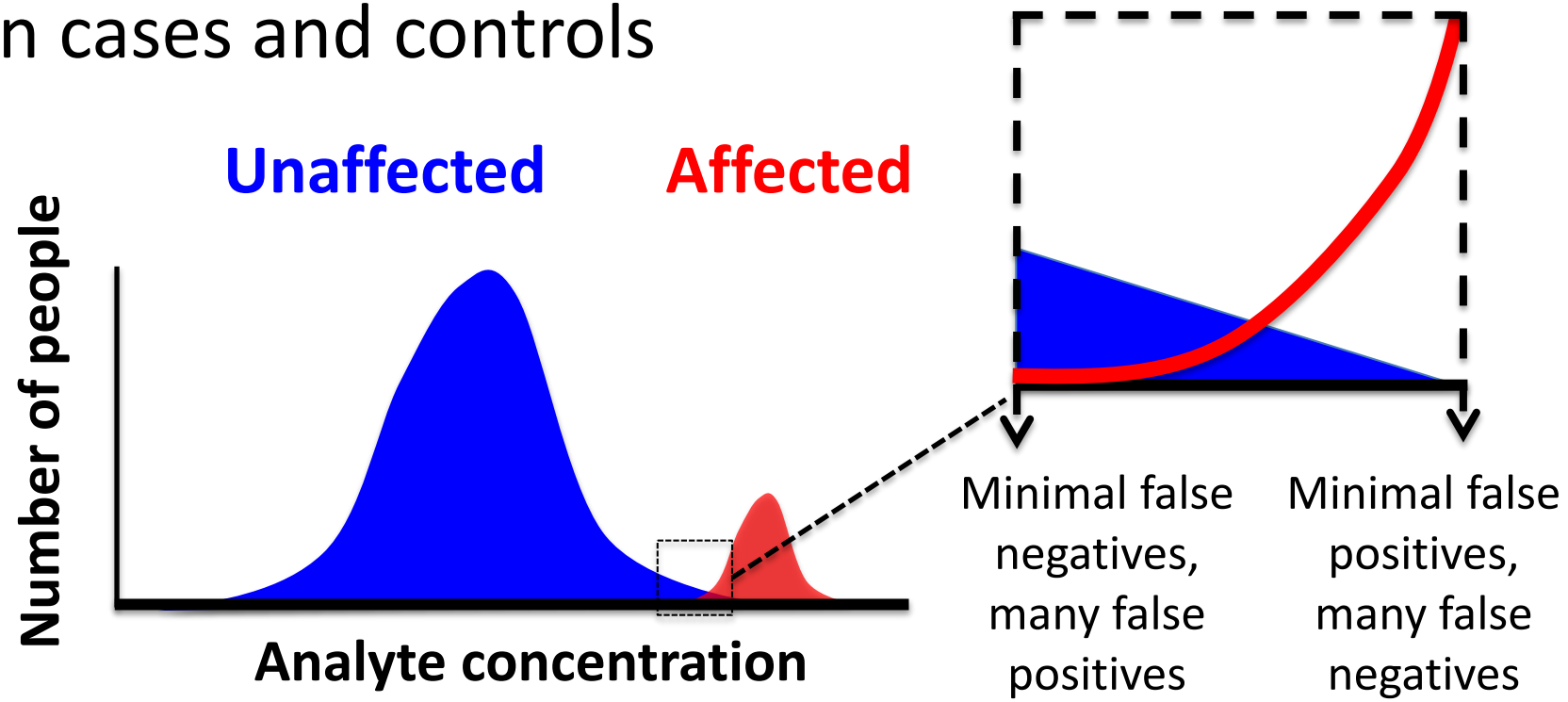
Application of the semi-quantitative metric in 372 gene-disease pairs





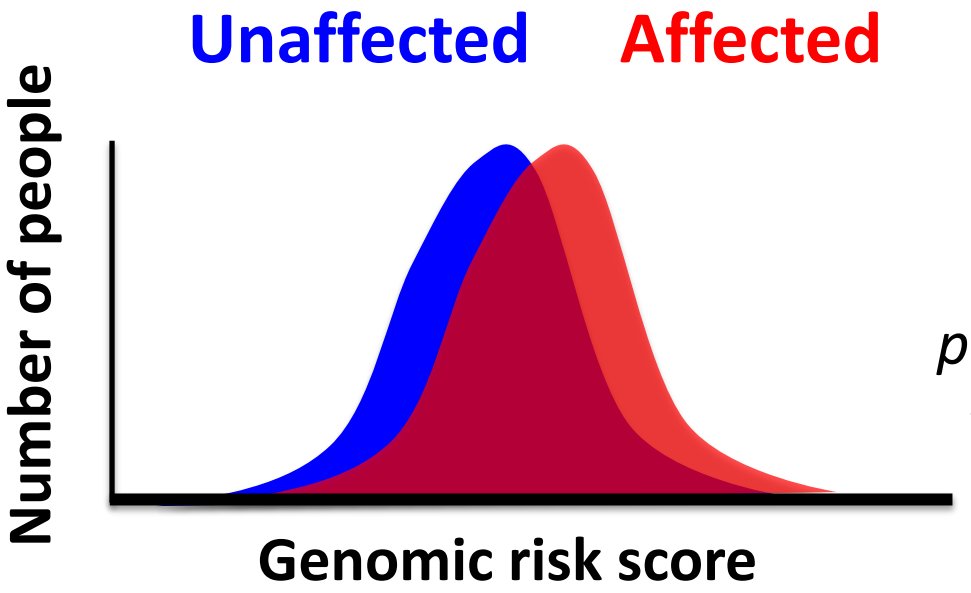
Test performance

Analyte tests can be calibrated based on profiles in cases and controls



Test performance

Genetic risk profiles can also be derived based on cases and controls



They just aren't anywhere near as predictive as they need to be for clinical use!

IRB Group Vignettes

A new intraoperative drug is being tested, designed to improve surgical outcomes. The majority of individuals undergoing this procedure are referred from long distances, thus potential participants are identified when they present to UNC on the day of surgery, and they approached by study staff to participate at that time.

- Are there informed consent issues in this situation, and if so, what can be done to mitigate them?

1

You are reviewing a renewal IRB application for a study that is investigating genetic differences in metabolizing enzymes. During the course of the study, several papers have been published, linking variations in one of the genes being studied to a high risk of developing colorectal cancer. Labs around the country have started offering genetic testing for this variant as a clinical service. Since it was not apparent that that the results would have clinical significance for the participants, the consent form did not include the possibility that study subjects would be contacted in the future or notified of results. The PI has contact information and it would be possible to reach them.

- When research produces unanticipated information of potential clinical or personal interest to study participants, should researchers share this information? What should IRB recommend in review of this renewal application?

2

A feasibility study of a new, non-significant risk device is being tested in men with enlarged prostates. The device is being tested as an alternative to surgical treatment of this condition. The Sponsor is covering all study costs except for use of the device, which is $10K. The PI plans to bill the insurance company for use of the device, and if not covered, the participant will be responsible for payment.

- Discuss the ethical and regulatory implications of this study, and ways to mitigate economic harm. Does this study violate justice principle of the Belmont Report?

3

You are reviewing a modification to an application studying the use of a mono-clonal antibody to treat recurrent and metastatic cancer, and in phase II studies it has shown to be of potential benefit when other approved drugs have failed. The study is comparing outcomes in participants given standard therapy versus standard therapy and this new drug, which is given in 3 doses over 9 weeks. The standard therapy is a single administration of a regimen that includes a known fetal teratogen, so pregnant women are excluded from enrollment on that basis. The modification includes a new IB for the study agent, which outlines newly identified fetal risk in mice. Pregnant mice exposed to this drug are at increased risk for early fetal loss. There is no definitive human data for or against human fetal safety. The PI intends to continue to exclude pregnant women from the study by confirming a negative pregnancy test at enrollment and encouraging contraception during the 9 weeks of study agent administration.

- Are additional protections necessary for women of child-bearing potential given the new IB information?

4

You are reviewing a modification to a previously approved Full Board study involving minors; the study subjects will engage in a photovoice project *"Through their eyes".* Subjects are children of racial minorities aged 10-17 and will photograph places, events, and things in their community representing marginalizing experiences or real/ perceived threats of harm and discuss the photos in a group setting with their parent or guardian present. The study currently carries a Child Finding 404 (minimal risk to subjects, permission of one parent required). This modification serves to add an additional procedure of exposing the children a second time to the gallery of photos and measuring the stress response by way of biophysical monitoring as an empirical validation for the qualitative data collected through focus groups.

- Are there potential harms to subjects? What might they be? In what ways might the modification alter the risk/benefit ration for subjects? What (if any) change to the child finding would be required?

5

Thank you for attending the 2018 IRB Retreat