Consent at the Crossroads

A Discussion with COGR
February 25, 2016

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Conflicts of Interest

- I have no financial relationships that might create a COI for this presentation

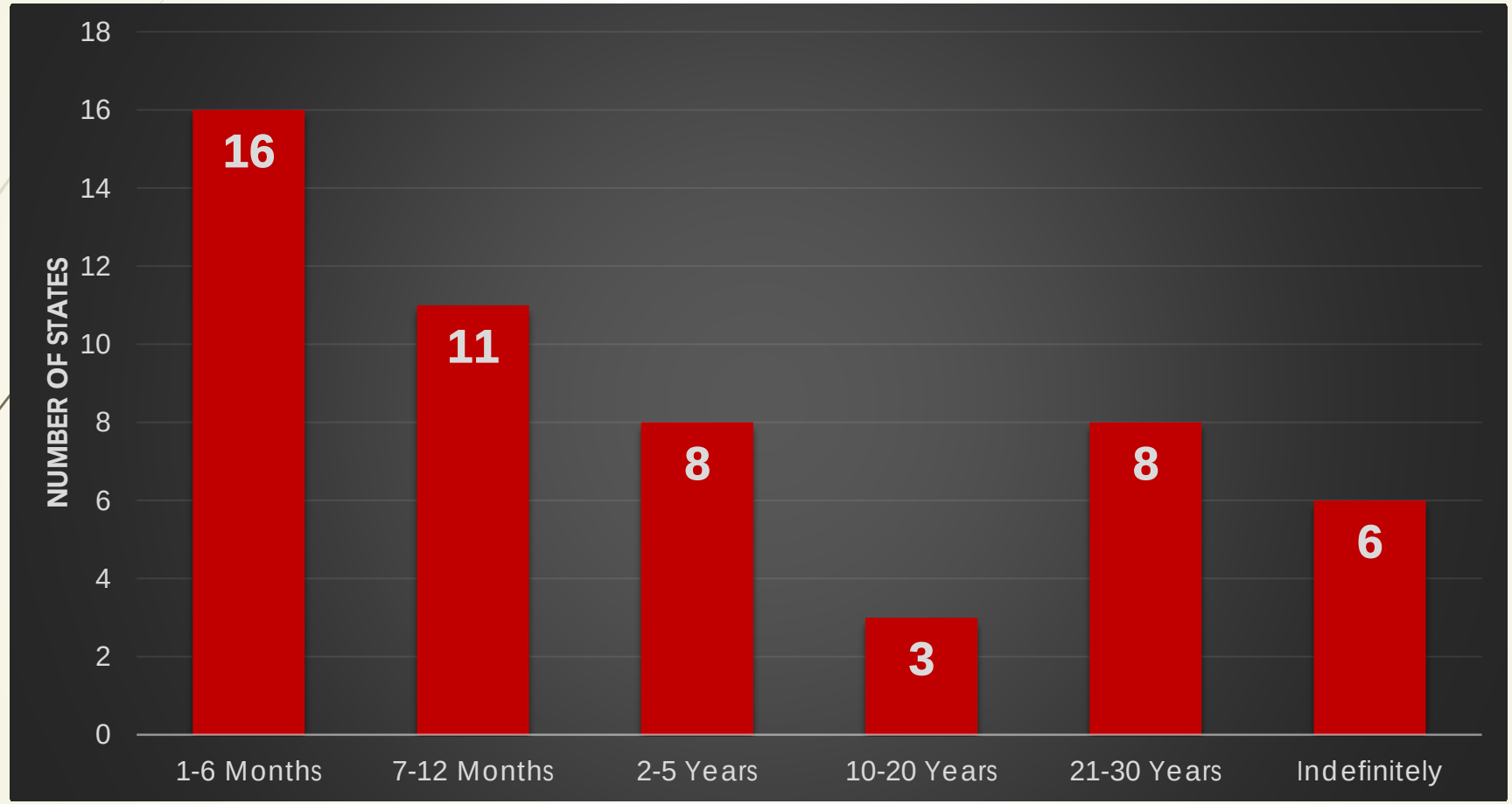
Objectives

- Review the federal regulations and proposed changes regarding informed consent, specifically secondary research uses of clinical biospecimens
- Highlight the challenges with informed consent
- Discuss an approach to transparency and choice regarding biospecimens and consent in other contexts

One Context

- Is it ethically appropriate for state health departments to save residual bloodspots after newborn screening for biomedical research?
- How much should parents know about this practice?
- Should parents be asked their permission?

Dried Blood Spot Retention Time



From: NewSTEPS, Sontag, August 2015

Bloodspot Retention and Use

- Lawsuits in two states: Minnesota (2009) and Texas (2009)
  - Minnesota suit based on state genetic privacy law
  - Texas suit based on constitutional claims regarding illegal search and seizure
- Reflects public dissatisfaction with current approaches

Federal Policy Change

- *Newborn Screening Saves Lives Reauthorization Act of 2014* (Public Law No: 113-240)
  - **TEXT OF SEC. 12. INFORMED CONSENT FOR NEWBORN SCREENING RESEARCH.**
  - *(a) IN GENERAL.—Research on newborn dried blood spots shall be considered research carried out on human subjects meeting the definition of section 46.102(f)(2) of title 45, Code of Federal Regulations, for purposes of Federally funded research conducted pursuant to the Public Health Service Act until such time as updates to the Federal Policy for the Protection of Human Subjects (the Common Rule) are promulgated pursuant to subsection (c). For purposes of this subsection, sections 46.116(c) and 46.116(d) of title 45, Code of Federal Regulations, shall not apply.*

Newborn Screening Saves Lives Reauthorization Act

- Interpretation
  - Research with newborn screening dried bloodspots is humans subjects research whether or not they are de-identified
  - Waiver of parental consent for research use is not permissible
  - This law will be superseded by anticipated changes in the Common Rule

NBS Saves Lives Act

- New consent provisions difficult to implement because no consent for NBS
- Post partum period is short, hectic, and with many clinical priorities
- Consent process likely to result in a substantial decrease in available DBS for research

NBS Saves Lives Act

- Targeted intrusion of Congress into the broad domain of human subjects protections
- Focused on one domain (NBS) but potentially applicable to a broad range of secondary research with biospecimens
- Suggests serious disagreement with current regulatory approach
  - Are we at a crossroad for consent?

Federal Notice of Proposed Rulemaking (NPRM) for Human Subjects Regulations

- NPRM proposed to extend the definition of "human subject" to biospecimens whether or not they are identifiable
- Broad consent from individuals would be necessary before biospecimens could be used for research
  - Criteria for waiver of consent would be limited

COGR Comments on NPRM

- "COGR strongly opposes the proposal to expand the definition of a "human subject" to cover research with non-identified biospecimens as proposed at .102(e)(1) and to require informed consent for research involving biospecimens in all but a limited number of circumstances. We believe non-identifiable biospecimens should remain excluded from the regulations and not subject to consent."

COGR Board of Directors, December 8, 2015

Biospecimen-based research

- Ethical and regulatory issues arise because
  - Research with biospecimens is removed in time and place from the source individual
  - Public sensitivities about the personal nature of biospecimens (“Its part of me.”)
  - High scientific yield
  - Low risk

Biospecimen-based research

- Controversies focus on secondary uses of biospecimens obtained for other purposes
  - Secondary uses of clinical specimens for which no consent is obtained for research
  - Secondary uses of research specimens for which secondary uses cannot be predicted

Risks Associated with Biospecimen Research

- Essentially none: No instances of welfare harms from biospecimen research
- Instances of "dignitary harms"
  - Havasupai Tribal case
  - The Moore Case
  - Henrietta Lacks case
  - Newborn screening lawsuits

Federal Regulations Governing Biospecimens

- If biospecimens are not readily identifiable to the investigator, the research is not considered human subjects research and falls outside the regulations
  - HIPAA may apply in covered entities unless de-identified by HIPAA standards
- Identifiable specimens: consent can often be waived if an IRB determines that the criteria are met
- Consent can be simplified/altered if research meets the waiver criteria

Waiver/Alteration Criteria (45CFR46.116(d)

- Minimal risk research
- Will not adversely affect the rights or welfare of subjects
- Not practicable to obtain consent
- When appropriate, subjects given pertinent information after participation

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Public Attitudes about Consent

- Hull et al **Patients' views on identifiability of samples and informed consent for genetic research** Am J Bioeth. 2008 Oct;8(10):62-70
  - 1395 adult patients in 5 academic medical centers across the country
  - Hypothetical issues survey
  - 86% would permit use if anonymous, 84% if de-identified
  - 71% wanted to be informed about research use of clinical samples even when de-identified
  - Of those who wanted to be informed about research uses, 57% would require permission before use
    - The remainder were satisfied with notification

Public Attitudes

- Kaufman et al **Preferences for opt-in and opt-out enrollment and consent models in biobank research: a national survey of Veterans Administration patients**. Genet Med. 2012
  - 451 veterans in online survey with hypothetical choices
  - 80% willing to participate in biobank with an opt-in approach
  - 69% willing to participate with an opt-out approach

Public Attitudes

- Botkin et al **Public attitudes regarding the use of residual newborn screening specimens for research** Pediatrics 2012 Feb;129(2):231-8
  - 3855 adult respondents in national survey
  - 81.5% supportive of retention and research use of residual dried bloodspots
  - 62% of respondents would want parental permission for secondary use of specimens (opt-in) compared to 38% for a notification and opt-out

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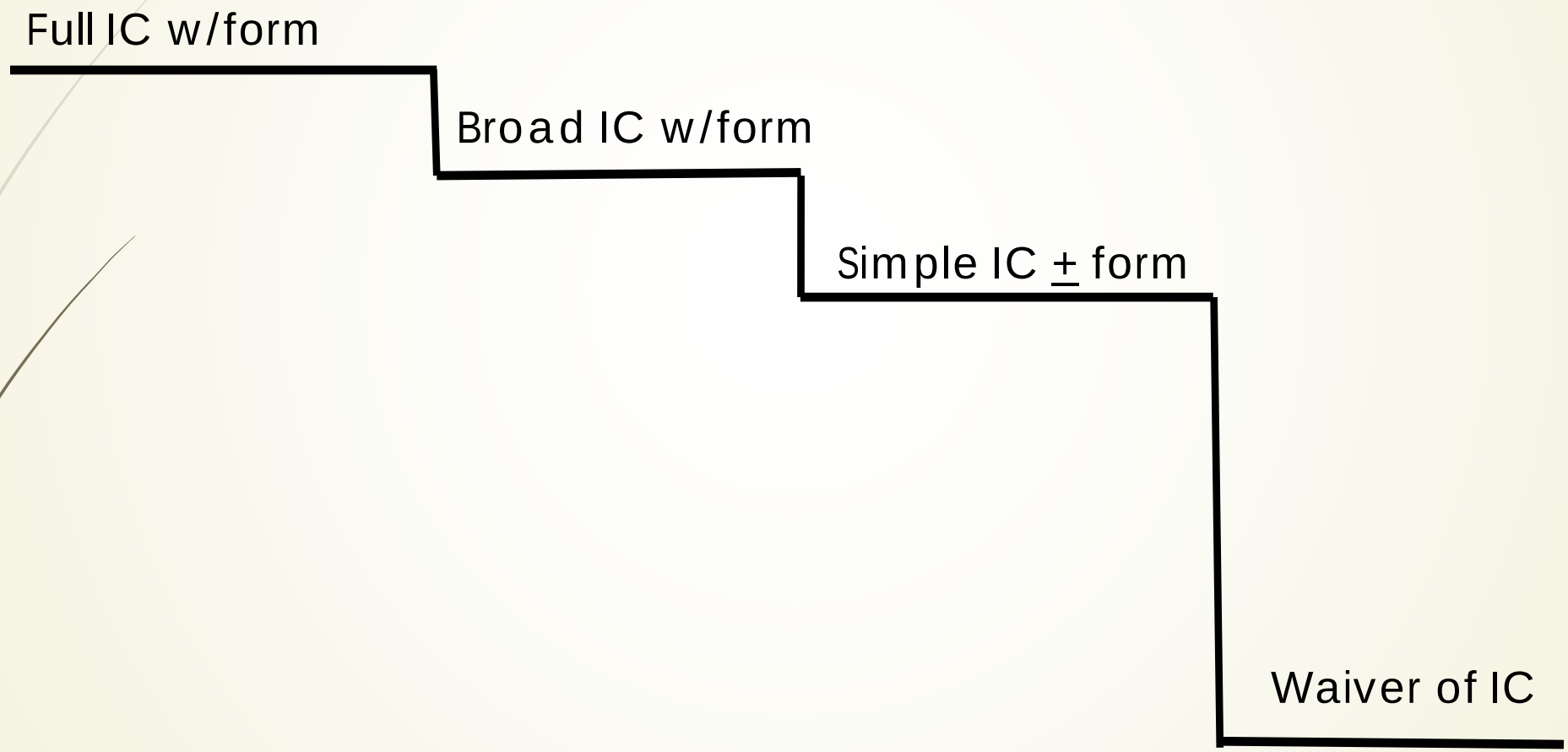
Public Attitudes

- Bhimarao CN, Rothwell E, Hart K, Latimer S, Schiffman JD, Botkin JR. **Attitudes of parents of children with serious health conditions regarding the use of residual newborn screening specimens for research**. Public Health Genomics. 2014;17(3):141-8.
  - 27 parents of a child with leukemia
  - 22 parents of a child with PKU
  - 1927 members of the general public
  - Results:
    - Parents of children with a serious health condition had higher levels of support than the general public toward the use of residual dried blood spots
    - Groups had similar attitudes regarding opt-in vs opt-out approach to parental permission (opt-in> opt-out)

Summary of the Literature

- The majority of individuals support the secondary use of clinical biospecimens for research use
- People want to know about this practice
  - Some want to be informed about *each* use
- People want a choice about whether their biospecimens are used
  - Opt-in > opt-out

Consent Levels



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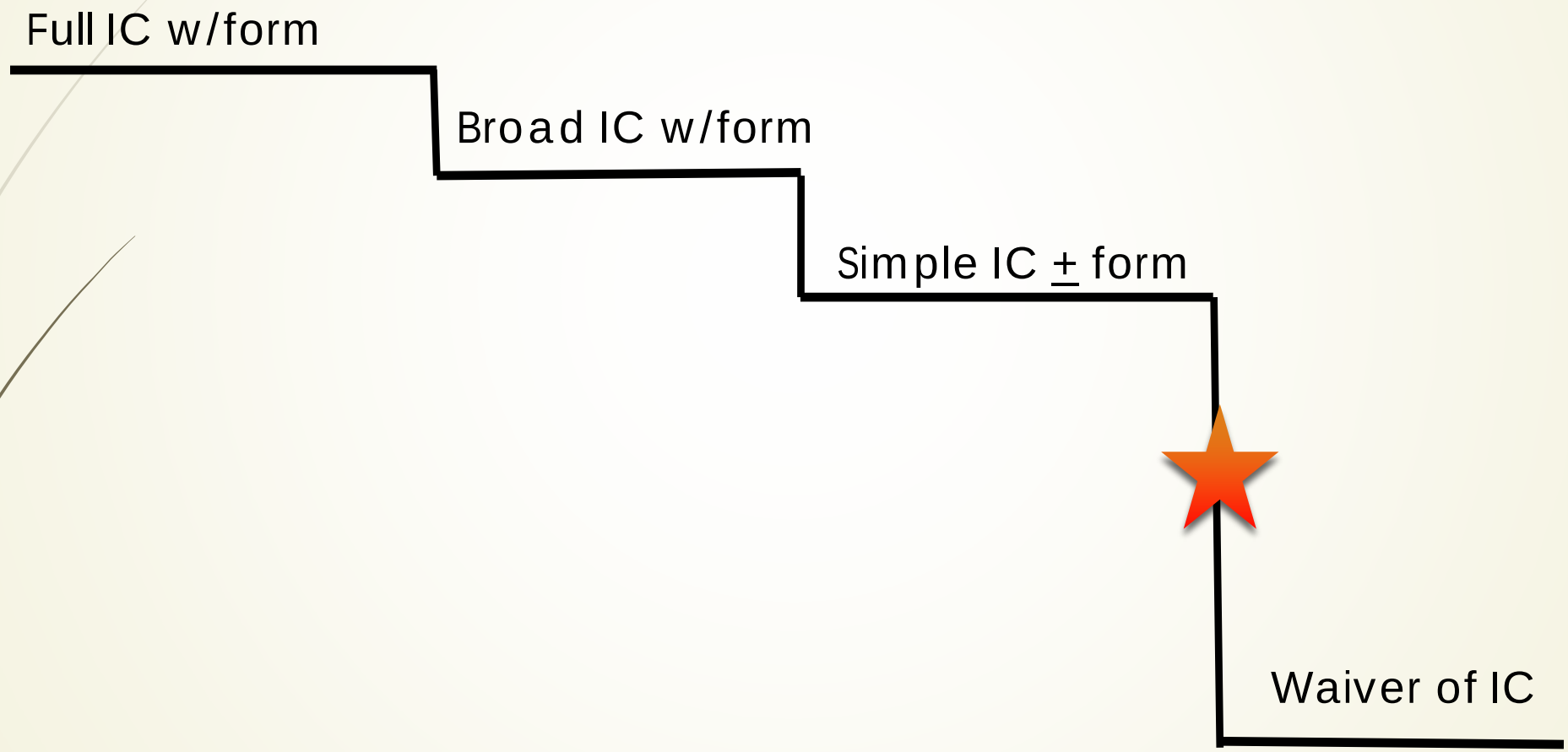

Informed Consent Challenges

- Process and content of informed consent in 45CFR46 are not evidence-based
  - They do not reflect the content or priority of what people want to know in context

Informed Consent Challenges

- Comprehension
  - Content is intrinsically difficult for populations with:
    - Low scientific literacy
    - Lack of familiarity
    - Highly variable literacy
    - Highly variable numeracy
  - Content is difficult for investigators
  - Forms are crafted with limited attention to comprehension
    - Long, high reading levels, dense, limited use of graphics

Informed Consent Challenges

- Comprehension (cont)
  - Psychological orientation of patients fosters misconceptions
    - "Therapeutic misconception"
  - Few incentives for any of the stakeholders to improve comprehension of the IC form and process
    - Sponsors, investigators, IRBs: all gain benefits or avoid burdens through high complexity

Comprehension

- Despite extensive evidence that research participants often have a very limited understanding of key elements of research protocols:

PEOPLE CONSENT TO PARTICIPATE IN RESEARCH ANYHOW!

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Aiding Comprehension

- No magic!
  - Revising forms for simplicity, processability, and graphical presentations shows some efficacy
  - Use of multimedia tools is promising
  - “Teach back” and one-on-one time are promising
  - Therapeutic misconception remains a serious concern without adequate remedies
  - TRUST is a much greater factor in decisions to participate than is the nature of the disclosure

Aiding Comprehension

- Improving comprehension is likely to entail increased personal engagement between investigators and potential participants
- To what extent is this justified in the research context if
  - Consent levels are high for biobanking?
  - Risk levels are very low?

Aiding Comprehension

- What should be the nature of informed consent in the clinical context for secondary biospecimen research given:
  - A substantial commitment of time for meaningful dialogue
  - A need for knowledgeable staff to obtain IC
  - The low priority of secondary research opportunities during clinical encounters
  - The need for large investments in tracking databases
  - The lack of risk

NPRM Proposals Regarding Informed Consent

- *"The information must be presented in sufficient detail relating to the specific research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or representative's understanding of the reasons why one might or might not want to participate."* *(emphasis added)*
  - Will enable OHRP to require elements to promote and assess comprehension
  - SACHRP supports this language

Informed Consent

- Foundational principle in research ethics
  - First principle in the Nuremburg Code
  - Primary element in “Respect for Persons” in the Belmont Report
- Founded on the notion of “autonomous authorization” (Faden and Beauchamp 1986)
  - Intentional
  - With understanding
  - Without controlling influence

Informed Consent

- What if “autonomous authorization” is not a realistic goal?
  - Can we define more limited goals that permit research when fully autonomous authorization cannot be achieved?
  - Are there different ways to think about the obligations to sources of biospecimens?

The "Fair Transaction Model" of Informed Consent

- Franklin Miller & Alan Wertheimer. "The Ethical Challenges of Human Research" Oxford Press 2012
  - *"The criteria for assessing the validity of consent transactions should be based on fair terms of cooperation for the respective parties that reflect the context of the activity for which consent is given."*
    - Fairness is relevant to both the participant and the research team

The "Fair Transaction Model" of Informed Consent

- Franklin Miller & Alan Wertheimer. "The Ethical Challenges of Human Research" Oxford Press 2012
  - *"What fairness entails will vary reasonably depending on the risk-benefit profiles presented by different clinical trials."*
    - High-risk trials require a high level of autonomous authorization
  - The example of signing forms for mortgages, car rentals, software purchases, etc.
    - The validity of these consent agreements is heavily dependent on institutional protections that can justify such agreements in the face of limited understanding

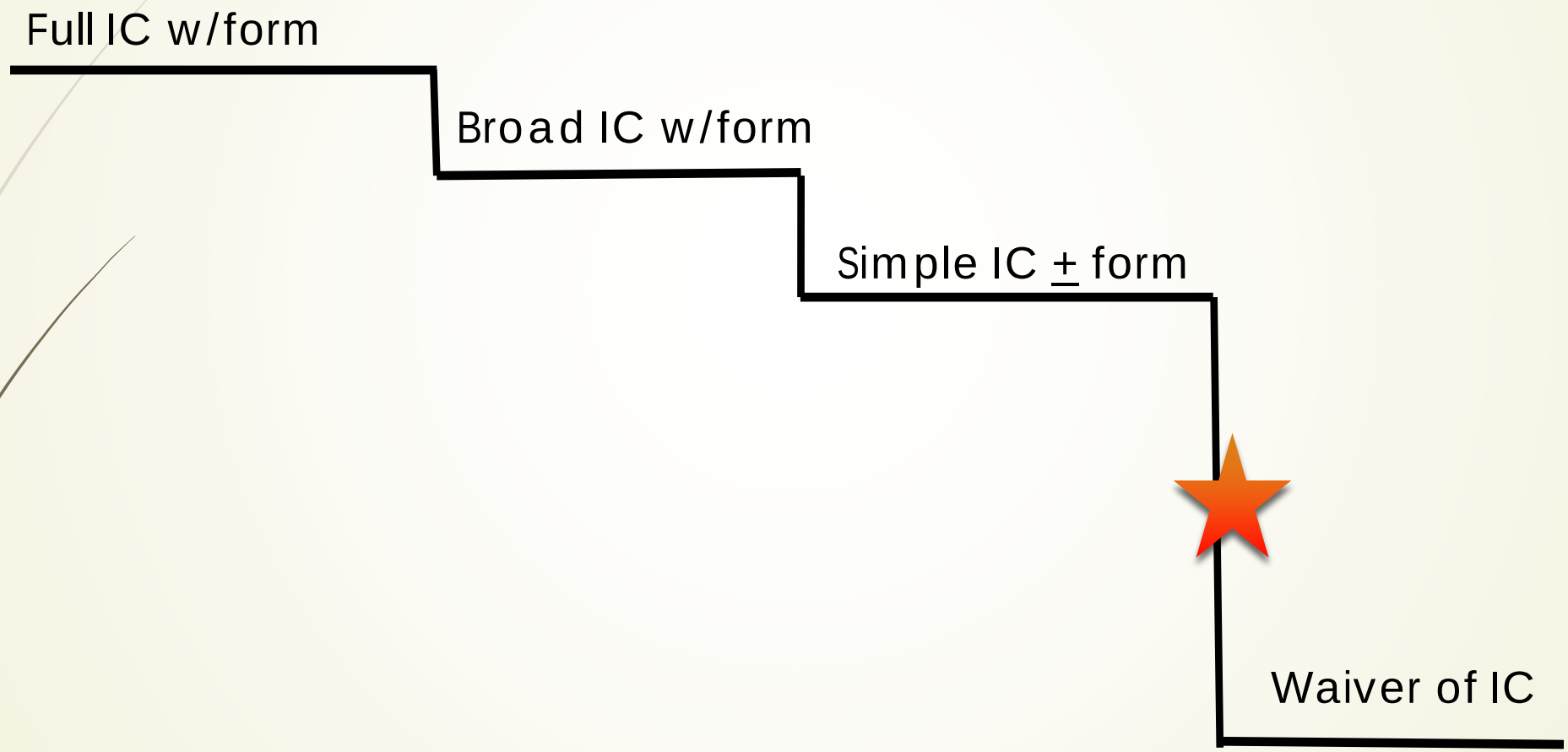
The Fair Transaction Model

- Seems to allow a limited disclosure of information when risk are low and institutional protections are in place for the participant
- Seems to allow a limited or no assessment of whether comprehension has been achieved when risks are low and institutional protections are in place
- Uncertain whether this model permits research when a lack of comprehension, or misconceptions, are identified

The Fair Transaction Model with Biospecimen Research

- Secondary research with biospecimens is extremely low risk/low burden for sources
  - Strong institutional structures in place to protect sources
- Such research has high scientific value
- A highly burdensome systems to attempt to obtain fully autonomous authorization for secondary uses is not "fair" to the research enterprise
- A modest level of authorization is acceptable
- No assessment of comprehension is acceptable
- BUT: A complete lack of transparency is not acceptable

Consent Levels



SACHRP Proposal on the NPRM

- Proposal relevant to secondary research uses of clinical biospecimens
- **Notice with opt-out**
  - "SACHRP recommends that the requirement for broad consent under §_.104(f) be replaced with a requirement for provision of notice of research practices, with an opt-out mechanism for those individuals who desire not to allow their biospecimens or identified data to be used for future research. Such a notice and opportunity to opt out do not constitute informed consent, but are more informative and respectful than current regulatory requirements and avoid many of the problems associated with a "broad consent."
  - "SACHRP recommends that guidance suggest that no signature be required to acknowledge the provision or receipt of notice of research practices."
  - "SACHRP recommends that the guidance to be promulgated by HHS advance the notion of a robust system whereby individuals are made aware of their options, have an opportunity to ask questions and get answers, and be able to exercise readily their opt out rights."
  - Institutional tracking of those who opt-out; no waiver of opt-out available

SACHRP Proposals on the NPRM

- "SACHRP believes that the most appropriate and effective method of preventing and deterring unauthorized re-identification of subject data and biospecimens lies in regulatory, administrative, civil, and criminal penalties against investigators and entities that would seek to re-identify any de-identified biospecimens and data that have been distributed for research uses."

Notice and Opt-out

- Promotes transparency and choice
- BUT: ethical justification contingent on robust efforts with the notification effort and the facilitation of choice
  - The weakness of a notice and opt-out approach is perfunctory efforts to provide notice and/or high hurdles to effective choice
- This approach is appropriately calibrated to the degree of risk and challenges compared to a more robust system of achieve autonomous authorization

Public Attitudes

- Botkin et al. **Public attitudes regarding the use of electronic health information and residual clinical tissues for research** J Community Genet. 2014 Jul; 5(3): 205–213
  - 12 focus groups (131 participants) in Utah, Washington, Arizona and Minnesota
  - Participants informed of current practices regarding the secondary research uses of clinical records and residual biospecimens
  - Informed that the University was considering a information and opt-out approach and asked whether this was acceptable
  - The large majority of participants supported the proposed approach

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Notice and Opt-out

- Botkin JR Waiving goodbye to waivers of consent. Hastings Center Report 2015 Nov (45)6:backcover
- Botkin JR. Crushing consent under the weight of expectations. Am J Bioethics 15(9): 1–3, 2015
- Rothwell E, Anderson RA, Swoboda KJ, Stark L, Botkin JR. Public attitudes regarding a pilot study of newborn screening for spinal muscular atrophy. Am J Med Genet A. 2013 Apr;161A(4):679-86.
- Botkin JR, Huckaby-Lewis M, Watson MS, Swoboda KJ, Anderson R, Bonhomme N, Brosco JP, Comeauy AM, Goldenberg A, Goldman E, Therrell B, Levy-Fisch, Tarini B, Wilfond B. Parental permission for pilot newborn screening research: Guidelines of the NBSTRN. Pediatrics 2014;133:e410-e417. (Newborn Screening Translational Research Network)

Consent at a Crossroads

- Several options to move forward (not mutually exclusive)
  - Redouble efforts to improve comprehension (audio-visuals, more personal engagement, teach back, others?) for some contexts
    - Essential for higher risk research protocols
  - Define minimum levels of comprehension for research protocols that pose different levels of risk
  - Better define when simply providing information and *opportunities* for comprehension are sufficient
    - Risks are low and institutional safeguards are in place
    - Transparency is key

Conclusions

- Consent with biospecimens represents a challenging conflict in values: respect for autonomous decision-making and the promotion of valuable research
- Debate is relevant to other research contexts that are removed from the "bedside"
  - "Big data"
  - Cluster randomized trials
- Notice and opt-out may be appropriate when risks are low and institutional safeguards are in place
- Innovative ideas are necessary to develop new approaches and safeguards for these domains of research

Thank You!