The IRB's Role in Risk Determinations for Genomic Research IDEs

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Disclaimer

- These views do not necessarily represent those of the Department of Bioethics, NHGRI, NIH, or the Department of Health and Human Services.

Roadmap

- The IRB's usual role in evaluating genomic sequencing as research procedure
  - Minimal vs. greater than minimal risk
- The IRB's role in evaluating genomic sequencing as medical device
  - Non-significant vs. significant risk

Risks of Genomic Research

- From breaches of confidentiality
- From disclosure of secondary findings
  - Stress, anxiety, self-image
  - Risky procedures (e.g., mastectomy)
- From uses that conflict with donors' fundamental values

Wendler and Rid (2015) *Trends Genet*

Risks of Genetic Research

- No reported cases of significant harm from genetic research
  - No reports of harms from confidentiality breach
  - Low frequency of adverse psychological outcomes
- Most genetic research qualifies as minimal risk
  - "Risks of daily life" standard
  - "Routine examinations" standard
  - "Charitable participation" standard

Wendler and Rid (2015) *Trends Genet*

Disclosure of Genomic Research Findings

- Increasing support for the return of some secondary genomic research findings
- "Identifying, validating, and communicating high-medical-impact variants from ES/GS research potentially provide substantial clinical benefit for participants."
- Which studies, which findings, how?

Darnell, Austin, Bluemke *et al* (2016) *AJHG*

The IRB's Role

- "[T]he IRB, in collaboration with the principal investigator (PI) of the study, is the appropriate body to determine which studies should return secondary genomic findings"
- Well-positioned to analyze:
  - Potential benefits and harms
  - Availability of resources

Darnell, Austin, Bluemke *et al* (2016) *AJHG*

Managing Risks of Disclosure

- Clinical validation of results
- Threshold for clinically relevant, actionable
  - Professional society lists
  - Expert committee review
- Counseling and consent
  - Ensure results are desired (pre-test)
  - Interpretation of results (post-test)
  - No pathogenic result identified ≠ no risk

FDA and Genomic Sequencing

- Entire test pipeline = device
  - Sequencing platform, analysis and informatics, interpretation of results for disclosure
- Categories:
  - IDE exempt (21 CFR 812 does not apply)
  - "Abbreviated" IDE (non-significant risk)
    - Labeling, monitoring, record keeping requirements
  - IDE (significant risk)
    - Application submitted to FDA

Significant Risk Device

- [*implants, support/sustain life*]
- 812.3(m)(3): For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 812.3(m)(4): Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Risks of Using Molecular Diagnostic Devices in Research

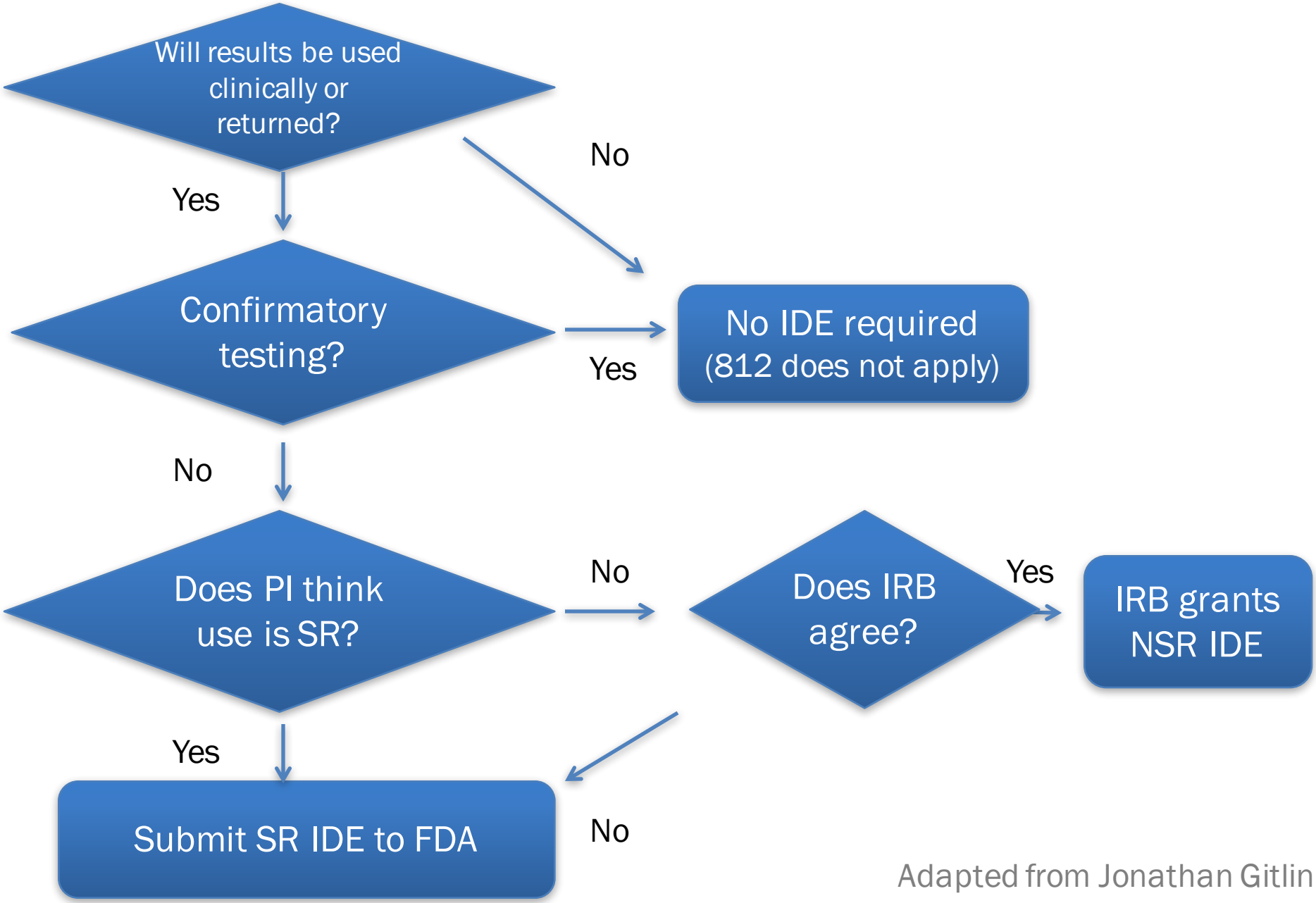
- Incorrect results
  - False negative: Not receiving a medically necessary treatment
  - False positive: Being exposed to a medically unwarranted intervention
- Relevance of use in healthy vs. sick participants

validation

genome.gov Points to Consider

Who Determines IDE Risk Level?

- Study sponsor/investigator
  - Primary responsibility
- IRB
  - Agreement or disagreement with sponsor/investigator
- FDA
  - Option of pre-submission review (can be concurrent with IRB review)
  - Can overrule IRB



Adapted from Jonathan Gitlin

Factors that Might Lead to NSR Determination by IRB

Case: *Process of disclosure of secondary genomic research findings with high PPV, low sensitivity for natural history studies of rare diseases*

- Use of gene list + expert advisory group
- Adequate plans for counseling, consent, reporting
  - To ensure understanding of "negative" findings
- Survey of understanding/impact of negative secondary findings report

Sample Consent Language

- “You could be falsely reassured by receiving no results from the study. This is not a complete genetic health assessment. If your doctor thinks you need a genetic test, you should get that test.”
- “You could feel reassured by learning you have no variants detected. Yet this may be due to our limited abilities, and variants may be present and escape our notice.”

Resources and References

- https://www.genome.gov/27561291/points-to-consider-in-assessing-when-an-investigational-device-exemption-ide-might-be-needed/
- http://ohsr.od.nih.gov/ohsr/public/SOP_15B_v4_2-24-16_508.pdf
- Wendler D and Rid A (2015) Genetic Research on Biospecimens Poses Minimal Risk, *Trends Genet* 31(1):11-15
- Darnell AJ, Austin H, Bluemke DA *et al.* (2016) A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research, *AJHG* 98(3):435-441

Thank you!