An investigator’s experience with FDA oversight

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• NICHD and NHGRI funded 4 sites to explore genomic sequencing in newborns
  – Some included NICU or diagnosed conditions
  – Others included healthy newborns
  – Diverse study designs, wide-ranging plans for return of results
Brief overview of NC NEXUS

• Explores exome sequencing in newborn screening
  – 200 “known” affected infants and children
  – 200 “unknown” healthy newborns

• Studying parental decision-making about exome sequencing for their child, and whether to learn about non-medically actionable information
  – Carrier status, adult-onset medically actionable conditions, childhood-onset non-medically actionable conditions
FDA involvement in NSIGHT

• NSIGHT principal investigators received queries from the FDA shortly after announcement of the awards

  “We read with great interest of the recent grant that you were awarded by the NICHD for your clinical trial...”
  “(CIDR) ... is very interested in the science and clinical development of technologies that can be used for DNA sequencing.”
  “We would like to set up a brief teleconference ... to learn more about your study.”
Not the typical order of interaction

- Normally, the IRB oversees human subjects research and determines whether an IDE is necessary
  - Note that the FDA asserts statutory authority to overrule an IRB determination
- However, all four sites were asked to submit a “presubmission enquiry” to the FDA in order to make that judgment, before any IRB review
a.) Phases of FDA involvement in NSIGHT

- Pre-submission
- Risk determination
- IDE submission
- FDA oversight

b.) Timeline of FDA contact with NSIGHT research sites (colors denote site)

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- 9/3/13 Notice of Award

2013

- FDA contacts NSIGHT
- FDA/NSIGHT teleconference

2017

- IDE approved
- Annual report
- Supplement
- 5-day notices

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b.) Timeline of FDA involvement with NSIGHT research sites. Date is the FDA last contact with the site.

- CMH 5/8/2014
- BWH/BCH/BCM 2/23/2015
- UCSF 3/3/2015
- UNC 10/15/2017

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Source: L.V. Milko
Should this even apply to us?

• Research project with no plans to commercialize
• Mostly studying parental preferences and reactions to newborn exome sequencing, not extensively validating a clinical test
• False positives mitigated by Sanger sequencing, false negatives mitigated by usual NBS care
Risk determination

• The FDA determined that the NC NEXUS study posed a significant risk and required an IDE
  – Probably based on sequencing in healthy newborns and return of information beyond childhood onset conditions (ELSI concerns)
  – In particular, our plans to return carrier status and adult onset medically actionable conditions
a.) Phases of FDA involvement in NSIGHT

- **Pre-submission**
- **Risk determination**
- **IDE submission**
- **FDA oversight**

b.) Timeline of FDA contact with NSIGHT research sites (colors denote site)

- 2013: Notice of Award, Day 1
- 2017:

  - CMH: 5/8/2014
  - BWH/BCH/BCM: 2/23/2015
  - UCSF: 3/3/2015
  - UNC: 10/15/2017

Source: L.V. Milko
How does one apply for an IDE?

• Get help!
  – Institutional regulatory assistance
  – Mostly geared toward drug trials, some devices, but no experience with genetic diagnostics

• FDA did not provide any specific guidance or templates to follow
  – We kind of cobbled it together as we went along
What is our device?

• Exome sequencing with Sanger confirmation?
• Electronic decision aid, plus Exome sequencing with Sanger confirmation?
• Electronic decision aid, plus Exome sequencing with Sanger confirmation, plus longitudinal surveys to evaluate parental responses?
Analytic validation is a challenge

- Commercial saliva collection kits
- Automated DNA extraction in core facility
- Commercial exome library preparation kits
- High-throughput sequencing in core facility
- Standard bioinformatics pipelines
- Molecular analysis and CLIA confirmation
The IDE is about the entire study

• The device itself
• The population in which it is being used
• The return of results policy
• The potential for risk (not likelihood)
• No consideration of possible benefit
a.) Phases of FDA involvement in NSIGHT

- Pre-submission
- Risk determination
- IDE submission
- FDA oversight

b.) Timeline of FDA contact with NSIGHT research sites (colors denote site)

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- 2017
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Source: L.V. Milko

- Pre-IDE submissions and amendments requested by the FDA
- Significant Risk (SR) or Non-Significant Risk (NSR) determination
- FDA / NSIGHT site correspondence
- IDE submission (abbreviated and full)
- Site teleconference with FDA
- Internal site regulatory discussion
Conclusions

• FDA oversight is necessary to ensure that products reaching the marketplace are safe and appropriately validated

• However, it adds significant complexity to conducting academic research, beyond what a normal IRB protocol entails
  – Including reporting requirements and processes for making modifications to protocol

• Investigators considering translational research with return of results to participants should discuss risk with their IRBs!
Acknowledgments

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  – Especially Laura Milko

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