NHGRI IDEs and Genomics Workshop: Risk Assessment Case Studies

June 10, 2016

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Panelists: Kellie Kelm (FDA), Jeffrey Seidman (FDA), and Anastasia Wise (NHGRI)

Protocol X

- 100 healthy newborns are enrolled in an NGS (WGS) screening study
- All pathogenic results are confirmed by Sanger sequencing in a CLIA-certified lab
- Results predicting non-medically actionable childhood-onset conditions will be reported to parents
- Results predicting medically-actionable adult-onset conditions also will be reported to parents
- Trio NGS conducted to ascertain if pathogenic variants are *de novo* or inherited
- Parents can consent to receive ACMG incidental findings for themselves
- A genetic counselor provides services before and after testing and also facilitates the return of results.

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Protocol X would likely be significant risk

Heightens Risk

- Healthy study population
- Return of results predicting disease
- Trio design

Lessens Risk?

- Sanger validation
- Returning incidental findings according to ACMG guidelines
- Genetic counseling

Protocol Y

- Phase III clinical trial: 500 patients with relapsed colorectal adenocarcinoma are randomized to standard treatment vs targeted therapy by NGS tumor sequencing
- Oncopanel analyses of both tumor & germline (blood) in a CLIA-certified laboratory
- Primary analysis: Tumors are analyzed for somatic variants that are targetable, based on literature search
- Secondary analysis: Germline variants known to predispose to inherited susceptibility to colon cancer
- Primary outcome: Participants with druggable somatic variants treated with therapeutic and survival time and/or recurrence will be compared to standard treatment
- Secondary outcome: Participants will receive molecular diagnostic reports of both the somatic and germline variants. Those with germline variants will be offered genetic counseling.

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Protocol Y would likely be nonsignificant risk

Heightens Risk

- Patients diverted from standard of care based on somatic variants
- Germline sequencing?

Lessens Risk?

- Patients have relapsed cancer
- Genetic counseling

Protocol Z

- Large 800,000 person nationwide cohort for a longitudinal study
- Cohort includes individuals recruited directly from healthcare provider networks
- Pharmacogenomics array and NGS exome sequencing in CLIA-certified lab
- Participants may download un-interpreted sequence data
- Incidental findings are reported according to ACMG guidelines
- Sequence data are deposited in EHRs and can be shared with providers upon participant's request
- De-identified, individual-level data are accessible to secondary investigators through a controlled-access process
- Secondary investigators may return individual-level results of their analyses to participants

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Protocol Z would likely be ???

Heightens Risk

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Lessens Risk?

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