These case studies were developed by NHGRI and DO NOT REPRESENT official guidance for FDA regulations.

IDE risk determinations will always depend on the specifics of the study. Risk determinations PRESENTED HERE have been made based solely on the information presented.

For more information please contact NHGRI’s Policy and Program Analysis Branch.
Protocol 1

- 100 healthy middle-aged adults
  - Randomized to family history or family history plus WGS
    - WGS results entered into participants’ EMR
- 100 cardiomyopathy patients
  - Randomized to family history or family history plus WGS
    - WGS results entered into participants’ EMR
- WGS conducted in a CLIA-certified laboratory.
- Following (actionable) results disclosure, participants surveyed for anxiety and depression. Follow up at 6 weeks and 6 months includes behavioral, economic, and health outcomes.
- Participants with elevated scores will be referred to a genetic counselor
Protocol 1

- 100 healthy middle-aged adults
  - Randomized to family history or family history plus WGS
    - WGS results entered into participants’ EMR
- 100 cardiomyopathy patients
  - Randomized to family history or family history plus WGS
    - WGS results entered into participants’ EMR
- WGS conducted in a CLIA-certified laboratory.
- Following results disclosure, participants surveyed for anxiety and depression.
- Follow-up at 6 weeks and 6 months includes behavioral, economic, and health outcomes.
- Participants with elevated scores will be referred to a genetic counselor.

In this protocol, the device may be all the physical components, reagents, and software that are operated under a single SOP to convert a patient’s sample into a result.
Protocol 1

- 100 healthy middle-aged adults
  - Randomized to family history or family history plus WGS
    - WGS results entered into participants’ EMR
- 100 cardiomyopathy patients
  - Randomized to family history or family history plus WGS
- WGS conducted in a CLIA-certified laboratory.
- Following results disclosure, participants surveyed for anxiety and depression.
- Follow up at 6 weeks and 6 months includes behavioral, economic, and health outcomes.
- Participants with elevated scores will be referred to a genetic counselor.

The inclusion of healthy volunteers who would not normally receive the test may increase the risk of the study.
Protocol 1

- 100 healthy middle-aged adults randomized to family history or family history plus WGS. WGS results entered into participants' EMR.

- 100 cardiomyopathy patients randomized to family history or family history plus WGS. WGS conducted in a CLIA-certified laboratory.

- Following results disclosure, participants surveyed for anxiety and depression. Follow up at 6 weeks and 6 months includes behavioral, economic, and health outcomes.

- Participants with elevated scores will be referred to a genetic counselor.

The risk to participants is mitigated somewhat thanks to appropriate counseling in cases where return of results results in increased stress or potentially inappropriate treatment decisions.
Protocol 1

100 healthy middle-aged adults
- Randomized to family history or family history plus WGS
  - WGS results entered into participants’ EMR
100 cardiomyopathy patients
- Randomized to family history or family history plus WGS
  - WGS results entered into participants’ EMR
WGS conducted in a CLIA-certified laboratory.
- Following results disclosure, participants surveyed for anxiety and depression. Follow up at 6 weeks and 6 months includes behavioral, economic, and health outcomes.
- Participants with elevated scores will be referred to a genetic counselor

This study would likely be significant risk.
Diabetic patients with high likelihood of monogenic diabetes

- Targeted Ion Torrent panel
- Pathogenic (for diabetes) mutations confirmed in CLIA-certified laboratory by FDA-approved immunoassay
- Only confirmed pathogenic sequencing results returned to physicians (no incidental findings)
- Pre- and post-test genetic counseling
Diabetic patients with high likelihood of monogenic diabetes
  - Targeted Ion Torrent panel
  - Pathogenic mutations confirmed in CLIA-certified laboratory by FDA-approved immunoassay
  - Only confirmed pathogenic sequencing results returned to physicians (no incidental findings)
  - Pre- and post-test genetic counseling

Here the device is the targeted Ion Torrent Panel.
Protocol 2

The use of an FDA-approved—and therefore “medically established”—diagnostic may make this study exempt, or nonsignificant risk at most.

(performing in a research laboratory)

- Pathogenic mutations confirmed in CLIA-certified laboratory by FDA-approved immunoassay
- Only confirmed pathogenic sequencing results returned to physicians (no incidental findings)
- Pre- and post-test genetic counseling
• Diabetic patients with high likelihood of monogenic diabetes

Restricting return of results to known, confirmed pathogenic findings would likely make this study nonsignificant risk.

- Only confirmed pathogenic sequencing results returned to physicians (no incidental findings)
- Pre- and post-test genetic counseling
Diabetic patients with high likelihood of monogenic diabetes

- Targeted Ion Torrent panel
- Pathogenic mutations confirmed in CLIA-certified laboratory by FDA-approved immunoassay
- Only confirmed pathogenic sequencing results returned to physicians (no incidental findings)
- Pre- and post-test genetic counseling

The risk to participants is mitigated somewhat by the inclusion of counseling.
Protocol 2

- Diabetic patients with high likelihood of monogenic diabetes
  - Targeted Ion Torrent panel
  - Pathogenic mutations confirmed in CLIA-certified laboratory by immunoassay
  - Only confirmed sequencing results returned to physicians (no incidental findings)
  - Pre- and post-test genetic counseling

This study would likely be exempt.
Protocol 3

- 6000 adults:
  - Subjects will be enrolled if they have ≥ 30% risk of receiving warfarin, clopidogrel, or statins, or documented adverse event to receiving warfarin, clopidogrel, or statins
  - 84 widely-accepted (PharmGKB) pharmacogenes will be sequenced on a research platform
  - Clinically actionable variants validated with Sanger sequencing in a CLIA-certified laboratory
  - Participants may consent to have clinically actionable variants returned.
  - No return of incidental findings
  - Data will be archived and used for future research, and to make treatment decisions through an existing clinical protocol
Protocol 3

- 6000 adults:
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The device here is the research platform and the panel of 84 pharmacogenes.
Protocol 3

- 6000 adults:
  - Subjects will be enrolled if they have ≥ 30% risk of receiving warfarin, clopidogrel, or statins, or documented adverse event to receiving warfarin, clopidogrel, or statins
  - 84 widely-accepted pharmacogenes will be sequenced on a research platform
  - Clinically actionable variants validated with Sanger sequencing in a CLIA-certified laboratory
  - Participants may consent to have clinically actionable variants returned.
  - No return of incidental findings

Data will be archived and used for future research, and to make treatment decisions through an existing clinical protocol.

Confining the study to variants with strong evidence of clinical validity mitigates risks to participants in this study.
Protocol 3

- 6000 adults:
  - Subjects will be enrolled if they have ≥ 30% risk of receiving warfarin, clopidogrel, or statins, or documented adverse event to receiving warfarin, clopidogrel, or statins
  - 84 widely-accepted pharmacogenes will be sequenced on a research platform
  - Clinically actionable variants validated with Sanger sequencing in a CLIA-certified laboratory
  - Participants may consent to have clinically actionable variants returned.
  - No return of incidental findings.

Confirming investigational device results with a “medically established” technique usually exempts a study from requiring an IDE.
Protocol 3

- Restricting return of results to known, confirmed pathogenic findings may make this study nonsignificant risk.
- Clinically actionable variants validated with Sanger sequencing in a CLIA-certified laboratory.
- Participants may consent to have clinically actionable variants returned.
- No return of incidental findings.
- Data will be archived and used for future research, and to make treatment decisions through an existing clinical protocol.
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  - Clinically actionable variants validated with Sanger sequencing in a CLIA-certified laboratory
  - Participants may consent to have clinically actionable variants returned.
  - No return of incidental findings
  - Data will be archived and used for future research, and to make treatment decisions through an existing clinical protocol

This study would likely be Nonsignificant risk or exempt.