CLIA lab certification and CLIA test validation

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The Forefront of Genomics®

Current disclosures

- NIH/NHGRI research funding (intramural)
- As outside activities: Editor-in-Chief, American Journal of Medical Genetics; textbook/publishing royalties through Wiley, Inc.

My (relevant) background

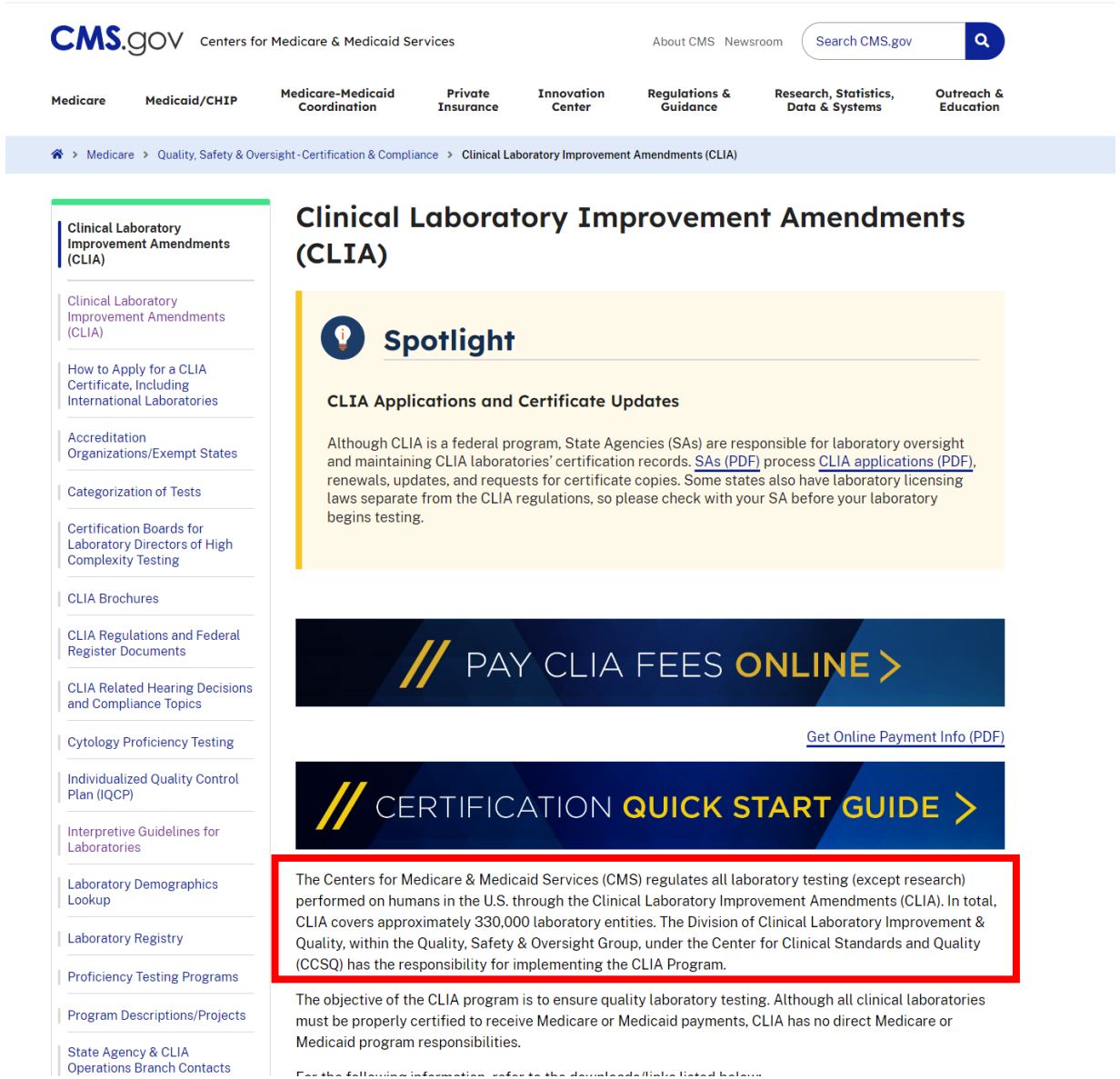
- Previously ran ~500-person CLIA/CAP-certified clinical genetics/genomics lab (which also conducted large-scale genomic research); ~100K samples/year (>200K tests/year), primarily exomes/genomes/large panels
- PI on several research studies involving WGS in healthy and affected individuals, involving an array of clinical and non-clinical analyses

Agenda

1. Certification and validation
2. Processes and examples

Certification and validation

CLIA: see https://www.cms.gov/regulations-and-guidance/legislation/clia



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Medicare > Quality, Safety & Oversight - Certification & Compliance > Clinical Laboratory Improvement Amendments (CLIA)

Clinical Laboratory Improvement Amendments (CLIA)

- Clinical Laboratory Improvement Amendments (CLIA)
- How to Apply for a CLIA Certificate, Including International Laboratories
- Accreditation Organizations/Exempt States
- Categorization of Tests
- Certification Boards for Laboratory Directors of High Complexity Testing
- CLIA Brochures
- CLIA Regulations and Federal Register Documents
- CLIA Related Hearing Decisions and Compliance Topics
- Cytology Proficiency Testing
- Individualized Quality Control Plan (IQCP)
- Interpretive Guidelines for Laboratories
- Laboratory Demographics Lookup
- Laboratory Registry
- Proficiency Testing Programs
- Program Descriptions/Projects
- State Agency & CLIA Operations Branch Contacts

Clinical Laboratory Improvement Amendments (CLIA)

Spotlight

CLIA Applications and Certificate Updates

Although CLIA is a federal program, State Agencies (SAs) are responsible for laboratory oversight and maintaining CLIA laboratories' certification records. SAs (PDF) process CLIA applications (PDF), renewals, updates, and requests for certificate copies. Some states also have laboratory licensing laws separate from the CLIA regulations, so please check with your SA before your laboratory begins testing.

PAY CLIA FEES ONLINE >

Get Online Payment Info (PDF)

CERTIFICATION QUICK START GUIDE >

The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). In total, CLIA covers approximately 330,000 laboratory entities. The Division of Clinical Laboratory Improvement & Quality, within the Quality, Safety & Oversight Group, under the Center for Clinical Standards and Quality (CCSQ) has the responsibility for implementing the CLIA Program.

The objective of the CLIA program is to ensure quality laboratory testing. Although all clinical laboratories must be properly certified to receive Medicare or Medicaid payments, CLIA has no direct Medicare or Medicaid program responsibilities.

For the following information, refer to the downloads/links listed below:

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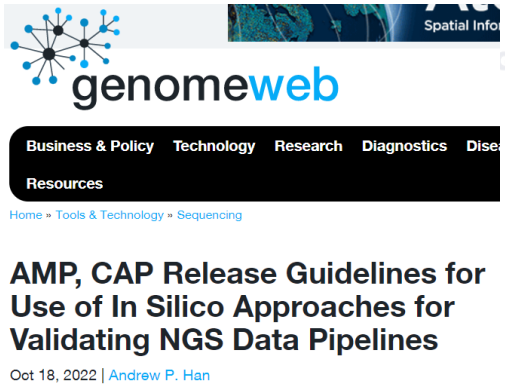
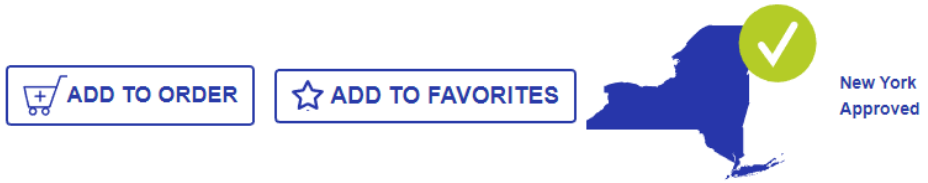
Some basic categories of "official" clinical lab certification in genetics/genomics

- CLIA (CMS, but involves FDA, CDC; various types of certification)
- CAP (peer-based inspection process)
- FDA (options for IDE research; specific assays; overarching approach continues to be discussed, and some major sequencers may proceed down this route)
- Some states require additional steps or can be exempt (eg, New York, Washington)



Licensing

Laboratories within the US are certified under the Clinical Laboratory Improvement Amendments (CLIA) and accredited by the College of American Pathologists (CAP). offers genetic testing in the US as well as internationally.



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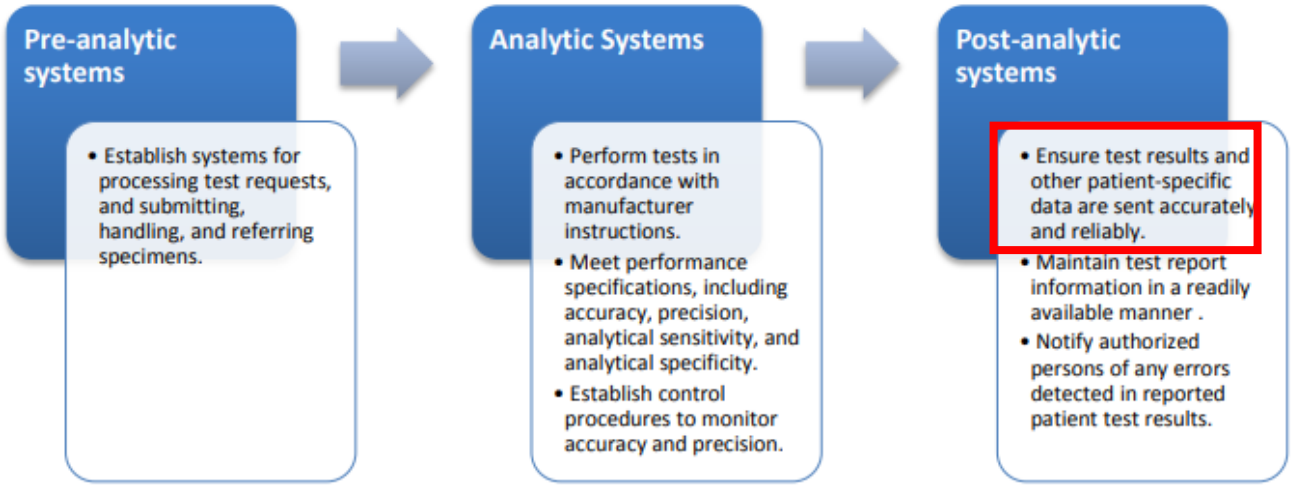
CLIA framework

- Required if **individual** results are returned (not related to whether patients are charged for results or if sequencing is done on a purely clinical or research basis)
- Focuses on **analytic** validity
- Test categories:
  - Waived tests - simple, no risk of harm
  - **Moderate/high complexity – includes genomics**
  - Specific specialty areas – includes cytogenetics

NIH NHGRI See: https://www.genome.gov/Pages/PolicyEthics/GeneticTesting/The_CLIA_Framework.pdf

Components

- Proficiency testing (PT) (non-specialty areas: biannual self-testing, PT exchange)
- Quality systems
- (FDA-related requirements)
- Personnel: Lab director, technical supervisor, clinical consultant, general supervisor
- CLIA inspections (biennial, usually w/ 2 weeks notice) – paperwork/documentation, procedure manuals, personnel interviews, real charts



https://www.genome.gov/Pages/PolicyEthics/GeneticTesting/The_CLIA_Framework.pdf

Reality at a mid-size genomics lab (~500 staff, ~100K samples/year)

- Lab director (for sign-off)
- QC director
- 3-4 staff on lab QC team
- 1 person for NY state requirements
- 1 person on "launch team"
- Integrated with other teams per requirements and by necessity (wet lab, bioinformatics, IT, individual clinical groups, legal/compliance, etc.)

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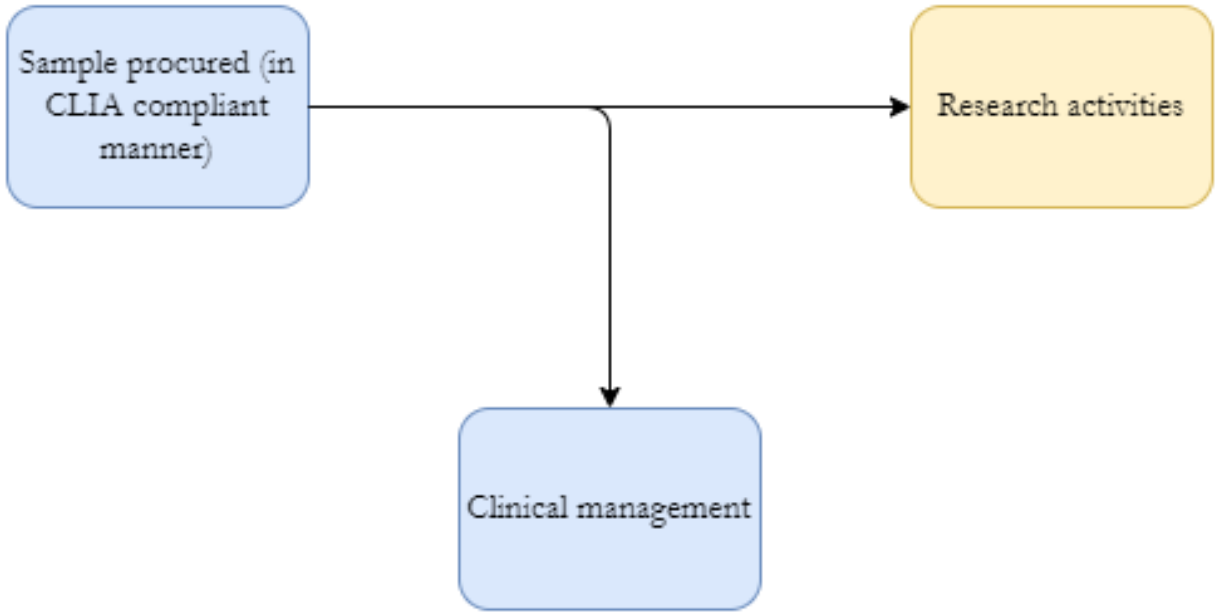
Processes and examples

Case study

- A research study plans to sequence the genomes of 10,000 people
- Consent includes possible receipt of individual, clinically relevant results from genome sequencing

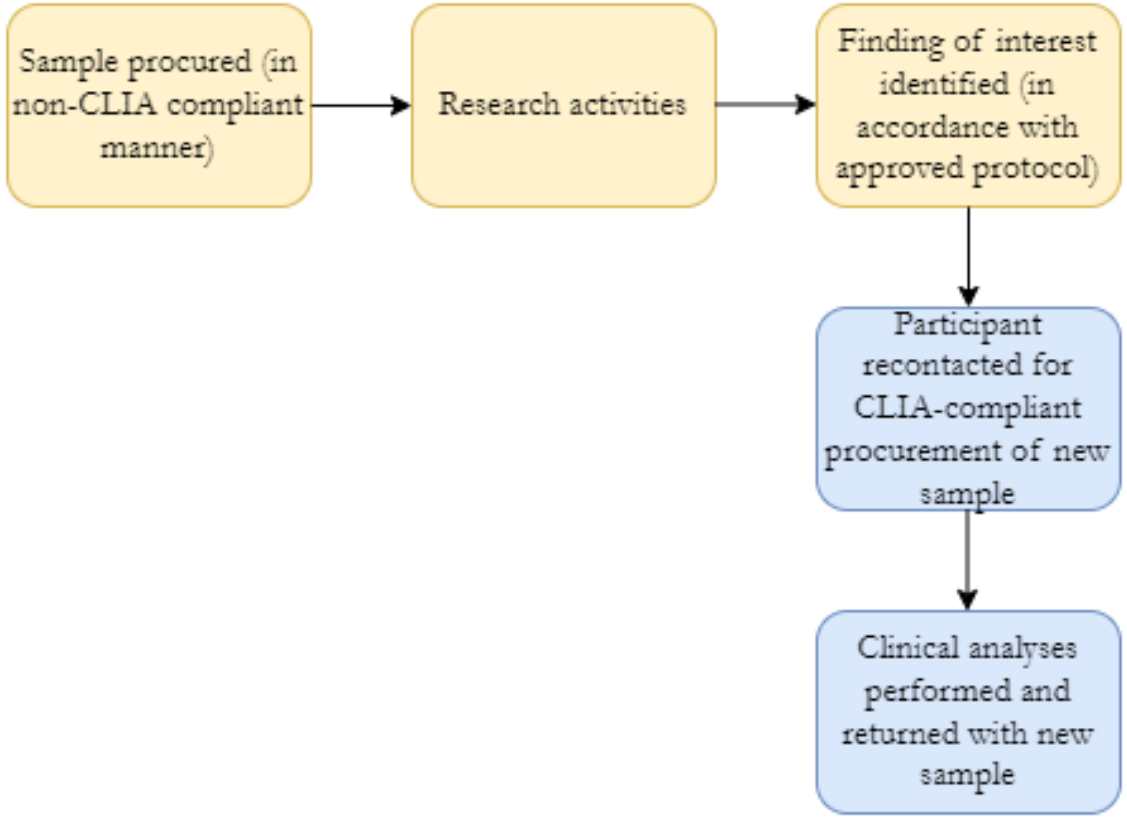
1. Pure CLIA (or similar) model

- **Everything** (e.g., DNA extraction, sequencing, orthogonal confirmation, etc.) handled in CLIA compliant manner from the outset
- Logistic frontloading
- Easier and more flexible downstream (e.g.,may obviate orthogonal confirmation in some situations), but may be difficult to set up and maintain
- Doesn't offer a path for many "historic" biobanks



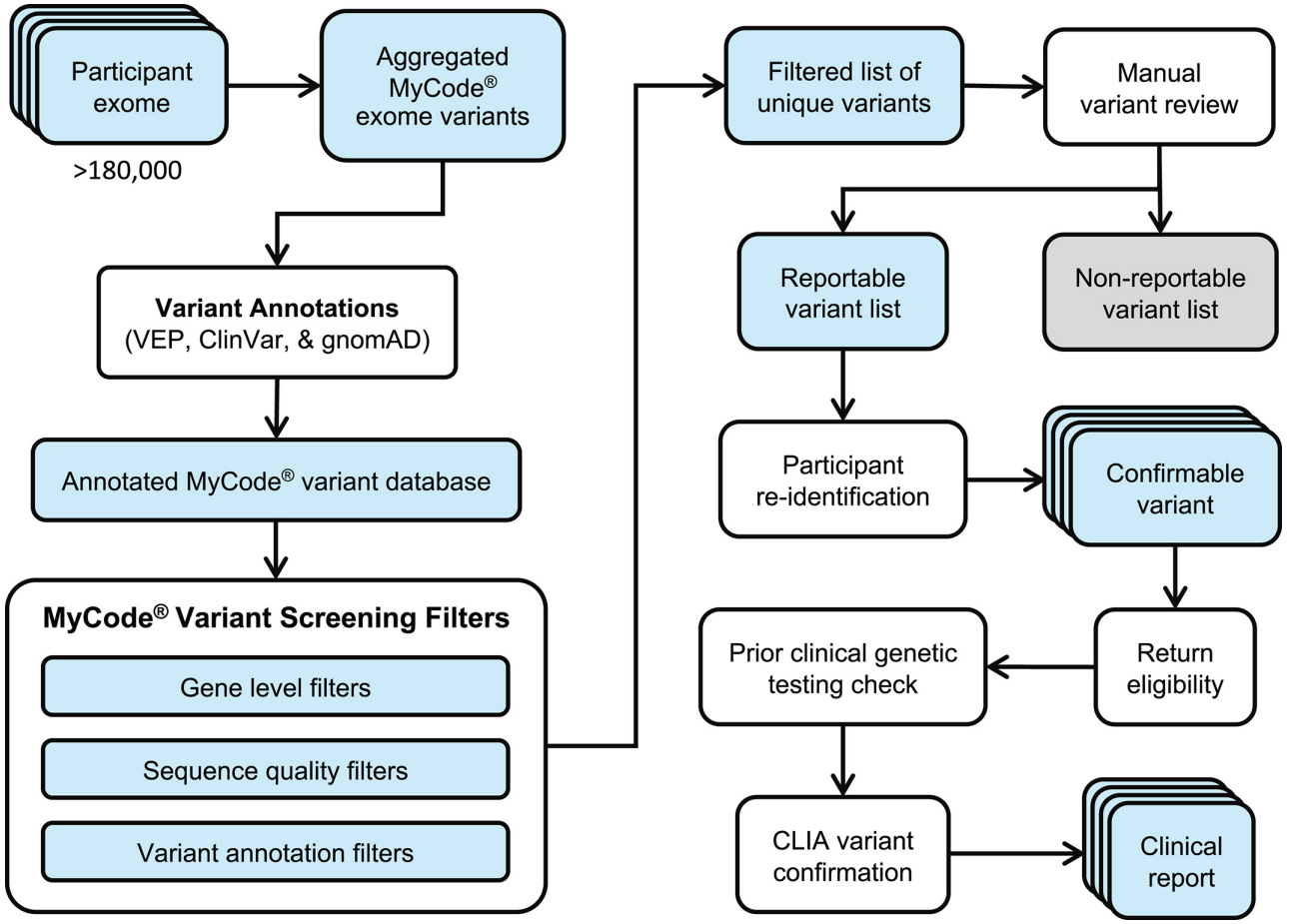
2. More frequent model (research → CLIA)

- Most common model
- Logistic backloading (doesn't require CLIA-compliant sample handling from the start)
- Recontact typically involves letting participant know there may be a finding of interest that requires technical validation, then collecting a **new sample for variant-specific, CLIA-based orthogonal confirmation**
- Requires ongoing communication



Example of hybrid approach

- Geisinger MyCode project
- Samples collected in CLIA-compliant manner (since 2015)
- Analyses done on research basis
- Data and CLIA-compliant samples shared with clinical lab for confirmation and reporting
- If samples had not been collected in CLIA-compliant manner, new samples could be obtained for confirmation/reporting



Kelly et al., AJMG part C 2021

A few lessons learned…

- Sometimes, **partnering** with a CLIA/etc.-certified "clinical lab" with lots of experience in this area (and data) can be helpful
  - Logistics of sample confirmation and regulatory management
  - Databases of variants for comparison
- Don't forget **non-SNVs**
  - Medically important, even if more challenging
  - Often requires different assays
- **Sample swaps!**
- Challenging participant-specific situations **will** arise: have an experienced advisory panel on hand!

Questions/Discussion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Performance establishment

CLIA performance specifications

- Accuracy
- Precision
- Analytical sensitivity and specificity
- Reportable range of results
- Reference intervals
- Any other required performance characteristics
- (No specific clinical validation requirements)
- (Reagent stability addressed through calibration, QC)

See: https://www.cdc.gov/labtraining/onelab/docs/6-30_EventSlideD.pdf

"Clinical" versus research

Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG STATEMENT

ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG)

David T. Miller[1,20], Kristy Lee[2,20], Wendy K. Chung[3], Adam S. Gordon[4], Gail E. Herman[5], Teri E. Klein[6], Douglas R. Stewart[7], Laura M. Amendola[8], Kathy Adelman[9], Sherri J. Bale[10], Michael H. Gollob[11], Steven M. Harrison[12], Ray E. Hershberger[13], Kent McKelvey[14], C. Sue Richards[15], Christopher N. Vlangos[16], Michael S. Watson[17], Christa Lese Martin[18] and ACMG Secondary Findings Working Group[19]*

Genetics in Medicine (2021) 23:1381–1390; https://doi.org/10.1038/s41436-021-01172-3

> Additionally, the recommendation to return SF only applies in the clinical setting. The decision to return SFs in a research setting is left to the research team and relevant local institutional review board (IRB).

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