Challenges and Opportunities in Expanding Genetic Testing in Vascular Surgery

Session: Diagnosis of Genetic Aortopathies
Friday, October 3, 2025

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Conflicts of interest

- None

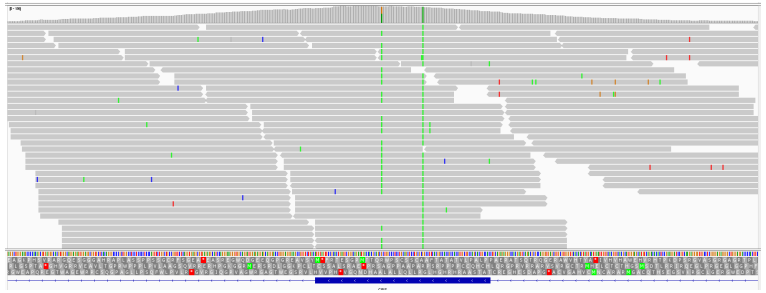
What happens when the sample enters the laboratory?

- Accessioning
- Extraction
- Sequencing
- Bioinformatics

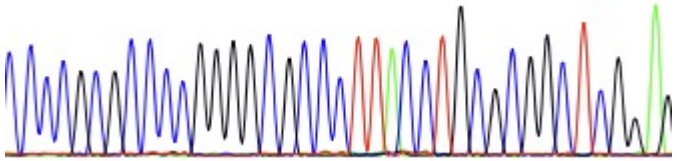
DRAGEN → Galaxy

What happens when the sample enters the laboratory?

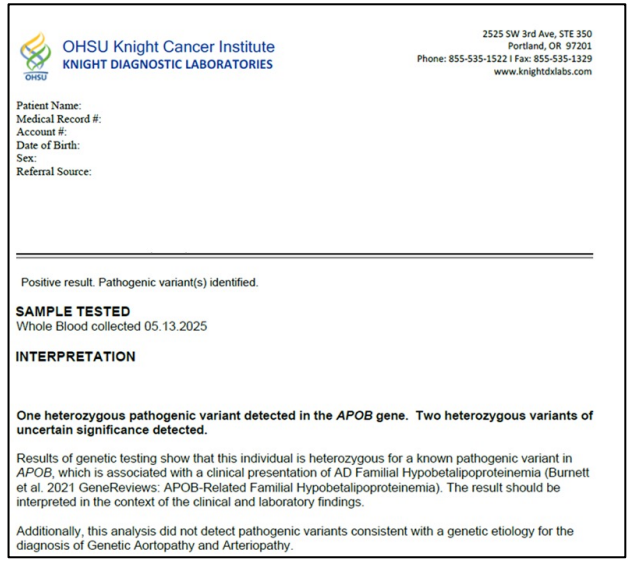
- Analysis



- Orthogonal confirmations



- Reporting



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Patient Name:
Medical Record #:
Account #:
Date of Birth:
Sex:
Referral Source:

Positive result. Pathogenic variant(s) identified.

SAMPLE TESTED
Whole Blood collected 05.13.2025

INTERPRETATION

One heterozygous pathogenic variant detected in the *APOB* gene. Two heterozygous variants of uncertain significance detected.

Results of genetic testing show that this individual is heterozygous for a known pathogenic variant in *APOB*, which is associated with a clinical presentation of AD Familial Hypobetalipoproteinemia (Burnett et al. 2021 GeneReviews: APOB-Related Familial Hypobetalipoproteinemia). The result should be interpreted in the context of the clinical and laboratory findings.

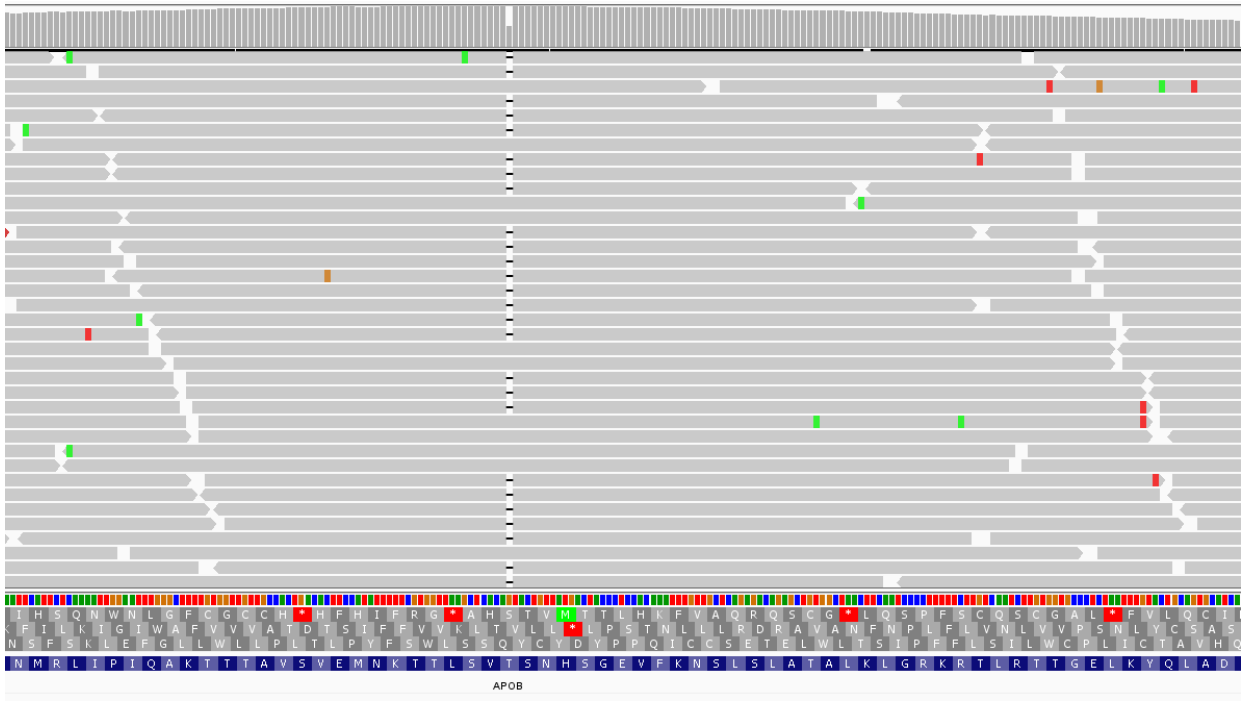
Additionally, this analysis did not detect pathogenic variants consistent with a genetic etiology for the diagnosis of Genetic Aortopathy and Arteriopathy.

Types of genetic tests

- Single gene
  - *FBN1*-related Marfan Syndrome
- Multi-gene panel
  - Disease specific: Genetic Aortopathy and Arteriopathy (84 genes)
- Whole exome sequencing
  - Interrogates ~20,000 genes (protein coding regions only)
- Whole genome sequencing
  - Interrogates the entire genome

Variant detection

- Single Nucleotide variants



- Copy Number Variants

Specimen types

- **Blood:** EDTA or ACD (Solution A or B):
- **Saliva**
- **Assisted Saliva**
- **Buccal Cells**
- **Skin Fibroblast**
- **DNA**

Challenges in Implementing Genetic Testing

Practical Challenges

- Insurance coverage and prior authorization barriers
- Turnaround times
  - urgent surgical cases vs genetic testing timelines

Challenges in Implementing Genetic Testing

Clinical Laboratory Challenges

- Incomplete penetrance and variable expressivity

- Limited ACMG/AMP/ClinGen guidelines for variant classification/interpretation as it relates to genetic aortopathies

Challenges in Implementing Genetic Testing

- Variants of uncertain significance (VUS): a genetic change that has insufficient or conflicting evidence supporting disease association.
  - VUSs differ in their likelihood of being pathogenic
  - Follow-up testing may be necessary
  - VUS classification can change over time
    - Biennial review of VUS

Challenges in Implementing Genetic Testing

- Incidental findings
  - may be reflected in quality metrics used for NGS testing

Where do I send testing?

Knight Diagnostic Laboratories

Molecular Genetics

Genetic Aortopathy and Arteriopathy Panel

Test Code:	1490
Department:	Molecular Genetics
Test Synonyms:	GAAP
CPT Code(s):	81410

Clinical Indications

- Aortic or arterial aneurysms and/or dissections at < 60 years.
- Clinical presentation consistent with Marfan syndrome, Loeys-Dietz Syndrome, or Vascular Ehlers-Danlos Syndrome or other genetic aortopathies.
- Positive family history for aneurysms and/or dissections.

Genetic Aortopathy and Arteriopathy Panel (84 genes)

ABCC6, ABL1, ACTA2, ADAMTS2, ADAMTS10, ADAMTS17, ADAMTSL4, ADAMTSL6 (THSD4), AEBP1, ALDH18A1, ATP6V0A2, ATP6V1A, ATP6V1E1, B3GALT6, B4GALT7, B3GAT3, BGN, CBS, CHST14, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A2, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2, DCHS1, DSE, DZIP1, EFEMP2/FBLN4, ELN, EMILIN1, ENPP1, FBLN5, FBN1, FBN2, FKBP14, FLCN, FLNA, FOXE3, GATA5, GGCX, HGD, HOXA1, KCNJ2, LOX, LTBP2, LTBP3, LTBP4, MED12, MFAP5, MYH11, MYLK, NKAP, NOTCH1, PLOD1, PLOD3, PRDM5, PRKG1, PYCR1, RIN2, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, SOX18, TAB2, TGFB1, TGFB2, TGFB3, TGFBR1, TGFBR2, THBS2, UPF3B, XYLT1, ZNF469

Opportunities for Vascular Surgery

- Expanding current understanding of the genetic contribution to these disorders
  - Broader use of next-generation sequencing (NGS) panels.

- WES in unexplained vascular disease.
  - Negative or inconclusive panel→ reflex to WES
  - New disease + gene phenotype

Opportunities for Vascular Surgery

- Early identification of high-risk patients
  - Genetic testing enables tailored surgical timing and surveillance.

- Family screening and preventive care
  - Extending impact beyond the index patient.

Opportunities for Vascular Surgery

- Interdisciplinary Collaboration
  - Genetics + vascular surgery + cardiology + radiology = comprehensive patient care
- Research and Innovation
  - Integrating genomic data into surgical outcomes
  - Tests are always evolving
    - New tests are developed to address the limitations of previous ones.

Take-Home Message

- Laboratory geneticists want to collaborate!
- Be aware of both the power and the pitfalls of genetic testing.
- Genetic testing is constantly evolving.

Thank you!

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