



Welcome to FDN Session 164

“Discovering Molecular Mechanisms of Genetic Disorders with NCBI Resources”

Today's materials: <https://bit.ly/2024foundations-molecularpathology>



National Library of Medicine
National Center for Biotechnology Information

Workshop Materials

<https://bit.ly/2024foundations-molecularpathology>

A website with ALL of the information for today and for you to refer to throughout med school.



The screenshot shows the NIH website interface. At the top, the NIH logo and 'National Library of Medicine' are on the left, and a search bar labeled 'Search NLM' is on the right. Below the header are navigation tabs: 'PRODUCTS AND SERVICES', 'RESOURCES FOR YOU', 'EXPLORE NLM', and 'GRANTS AND RESEARCH'. The main content area features a sidebar on the left with a red border containing a table of contents: 'Session Information', 'Introduction', 'Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups', 'Group Cases: Marco, Alexei, James & Bo', 'Lightning Round: Speedy variant/phenotype research!', 'Conclusion', 'A Guided Case for Self-assessment: Leslie', and 'Independent Practice Cases for Self-assessment: Jeff, Jonathan, David'. The main content area has a title 'GWU Medical School Foundations of Medicine Block Session 164' with social media share icons (Twitter, Facebook, LinkedIn, Pinterest). Below the title is the subtitle 'Molecular Pathology Case Studies' and a sub-header 'Connecting the dots between genetics, molecular biology and biochemistry in real patients.' The text describes the integration of molecular science and genetic analysis in precision medicine. A blue button with a right-pointing arrow asks 'How should I prepare for this session?'. Below this is the section 'In Session 164:' followed by a bulleted list of session topics.

NIH National Library of Medicine

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Home

Session Information

Introduction

Clinical Genetics/Genomics
Toolkit: Research tips for patient work-ups

Group Cases: Marco, Alexei, James & Bo

Lightning Round: Speedy variant/phenotype research!

Conclusion

A Guided Case for Self-assessment: Leslie

Independent Practice Cases for Self-assessment: Jeff, Jonathan, David

Share X f in p

GWU Medical School Foundations of Medicine Block Session 164

Molecular Pathology Case Studies

Connecting the dots between genetics, molecular biology and biochemistry in real patients.

With recent advances in the integration of various disciplines of molecular science and technological developments in genetic analysis, it is now possible to implement truly "personalized" medicine. The growing adoption of "Precision Medicine" involves the full understanding of a patient, including their own specific molecular pathology and disease etiology, which can help to establish an accurate diagnosis and to select an effective therapy.

NCBI has long had online resources for biologists to explore what is known about a biological molecule including its structure and function and has recently developed clinically-focused resources enabling scientists and clinicians to integrate known molecular biological information with clinically-relevant genetic variations.

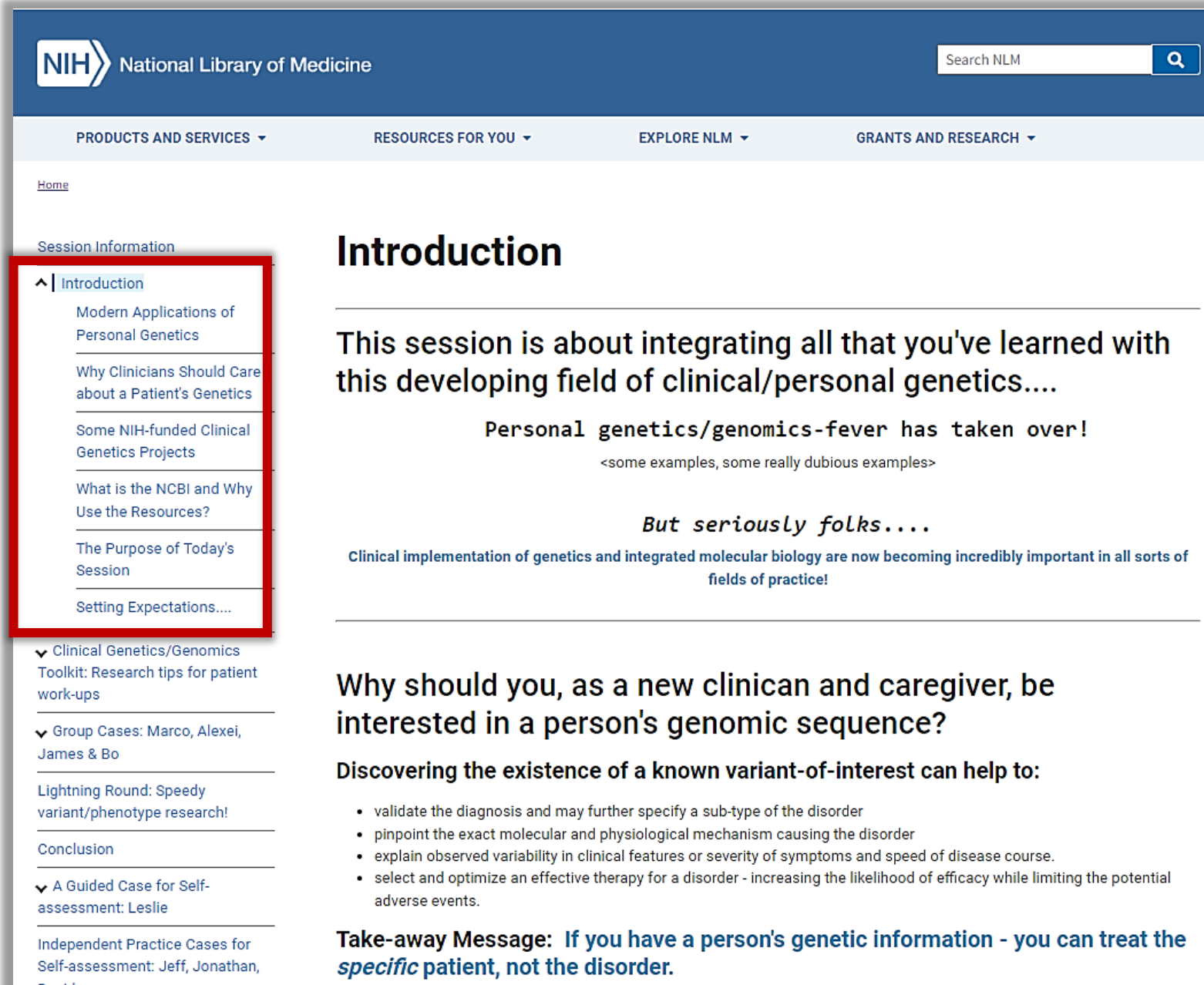
► [How should I prepare for this session?](#)

In Session 164:

- We will discuss the state of clinical practice with regard to the application of precision medicine principles.
- We will work together through a cluster of similar-sounding patient cases and discover the underlying cause of pathology in each of these real patients.
- By looking at the patient's diverse molecular mechanisms, we will explore how knowing the pathology of a patient's genetic disorder could be useful for precision diagnosis, explain the clinical presentation, and may be helpful in customizing the case management plan.
- I have provided you with some practice cases for you to work on.

Introduction

Some background information & setting up today's activity!



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PRODUCTS AND SERVICES ▾ RESOURCES FOR YOU ▾ EXPLORE NLM ▾ GRANTS AND RESEARCH ▾

[Home](#)

Session Information

- Introduction**
- Modern Applications of Personal Genetics
- Why Clinicians Should Care about a Patient's Genetics
- Some NIH-funded Clinical Genetics Projects
- What is the NCBI and Why Use the Resources?
- The Purpose of Today's Session
- Setting Expectations....

▾ Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups

▾ Group Cases: Marco, Alexei, James & Bo

Lightning Round: Speedy variant/phenotype research!

Conclusion

▾ A Guided Case for Self-assessment: Leslie

Independent Practice Cases for Self-assessment: Jeff, Jonathan, David

Introduction

This session is about integrating all that you've learned with this developing field of clinical/personal genetics....

Personal genetics/genomics-fever has taken over!
<some examples, some really dubious examples>

But seriously folks....

Clinical implementation of genetics and integrated molecular biology are now becoming incredibly important in all sorts of fields of practice!

Why should you, as a new clinician and caregiver, be interested in a person's genomic sequence?

Discovering the existence of a known variant-of-interest can help to:

- validate the diagnosis and may further specify a sub-type of the disorder
- pinpoint the exact molecular and physiological mechanism causing the disorder
- explain observed variability in clinical features or severity of symptoms and speed of disease course.
- select and optimize an effective therapy for a disorder - increasing the likelihood of efficacy while limiting the potential adverse events.

Take-away Message: If you have a person's genetic information - you can treat the *specific* patient, not the disorder.

Personal Genetics/Genomics fever
has taken over!

Wait! What?

Wide-spread application of genetic/genomic information started out with human migration & ancestry,

Already Have An Account? [Sign In >](#)

THE GENOGRAPHIC PROJECT

About News Buy The Kit Research

The Human Story

Join the project to learn about your story

Since its launch in 2005, National Geographic's Genographic Project has used advanced DNA analysis and worked with indigenous communities to help answer fundamental questions about where humans originated and how we came to populate the Earth. Now, cutting-edge technology is enabling us to shine a powerful *new* light on our collective past. By participating in the latest phase of this real-time scientific project, you can learn more about yourself than you ever thought possible.

Geno 2.0 Next Generation

Eleven years ago we launched the Genographic Project. More than 100,000 people have participated, learning about their haplogroups and their personal history. Our revolutionary Geno 2.0 Next Generation test has been enhanced to include the latest to date ancestry available through our partner Helix.

[Buy the kit >](#)

834,322 PARTICIPANTS IN THE GENO 2.0 PROJECT

ancestry FAMILY TREES SEARCH DNA HELP EXTRAS SUBSCRIBE SIGN IN >

AncestryDNA® ethnicity estimates are now more precise than ever.

We've applied our latest cutting-edge science to AncestryDNA® ethnicity results. Take a look at your updated results and get a more precise picture of just where your ancestors came from.

[Learn more](#)

have
ng new.

ns to the most
ther DNA test
experience.

ude

46% Mali
23% Ireland
21% England & Northwestern Europe
4% France
4% Ivory Coast & Ghana
2% Germanic Europe

3rd Cousin

FamilyTreeDNA DNA Tests Upload DNA Data Shop Sign In Help

Overview Map Your Origins Family Matches Ancient Origins FAQ ONLY \$59 USD [ORDER NOW](#)

PUT YOURSELF ON THE MAP

Discover Ethnic Percentages

Uncover your heritage with myOrigins, our unique visual mapping tool that provides a detailed ethnic and geographic breakdown of where your ancestors came from.

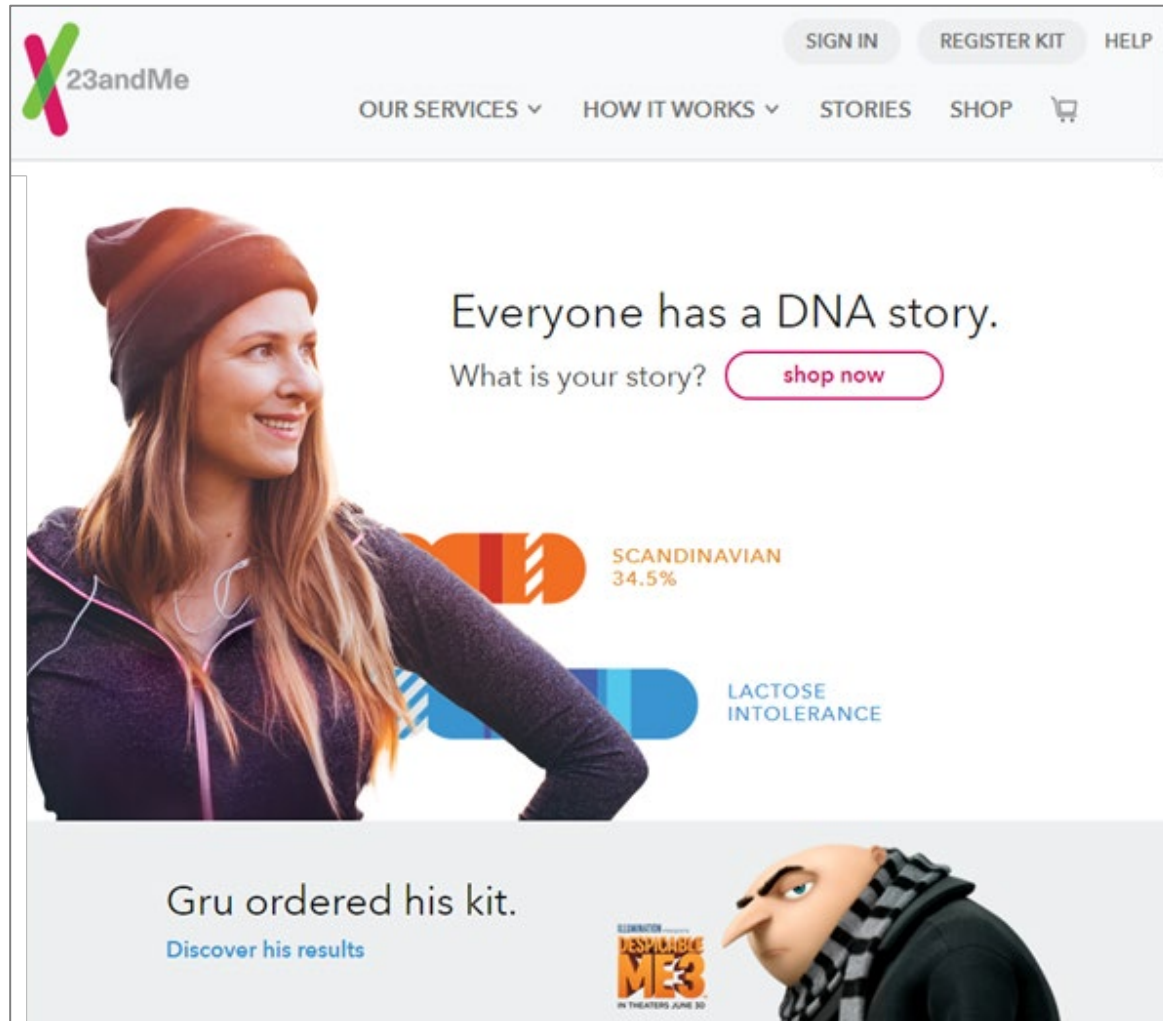
Your heat map reflects your personal genetic ancestry, and may also reveal related population clusters that mixed with others in ancient times.

- ✓ Updated to include 60+ new populations.
- ✓ Map your ethnic and geographic background.
- ✓ Gain insight into your ancestral origins.
- ✓ Confirm family history and traditions.

60+ NEW POPULATIONS

Africa	81%
West Africa	30%
• Ghana, Togo & Benin	30%
• Nigeria	19%
• Guinea & Sierra Leone	12%
Central Africa	11%
• Atlantic Equatorial Africa	11%
• Southern Congo Basin	4%
Europe	19%
West Europe	11%
• Central Europe	11%
• Scandinavia	8%

and from there, family history & phenotypes,



23andMe

SIGN IN REGISTER KIT HELP

OUR SERVICES ▾ HOW IT WORKS ▾ STORIES SHOP

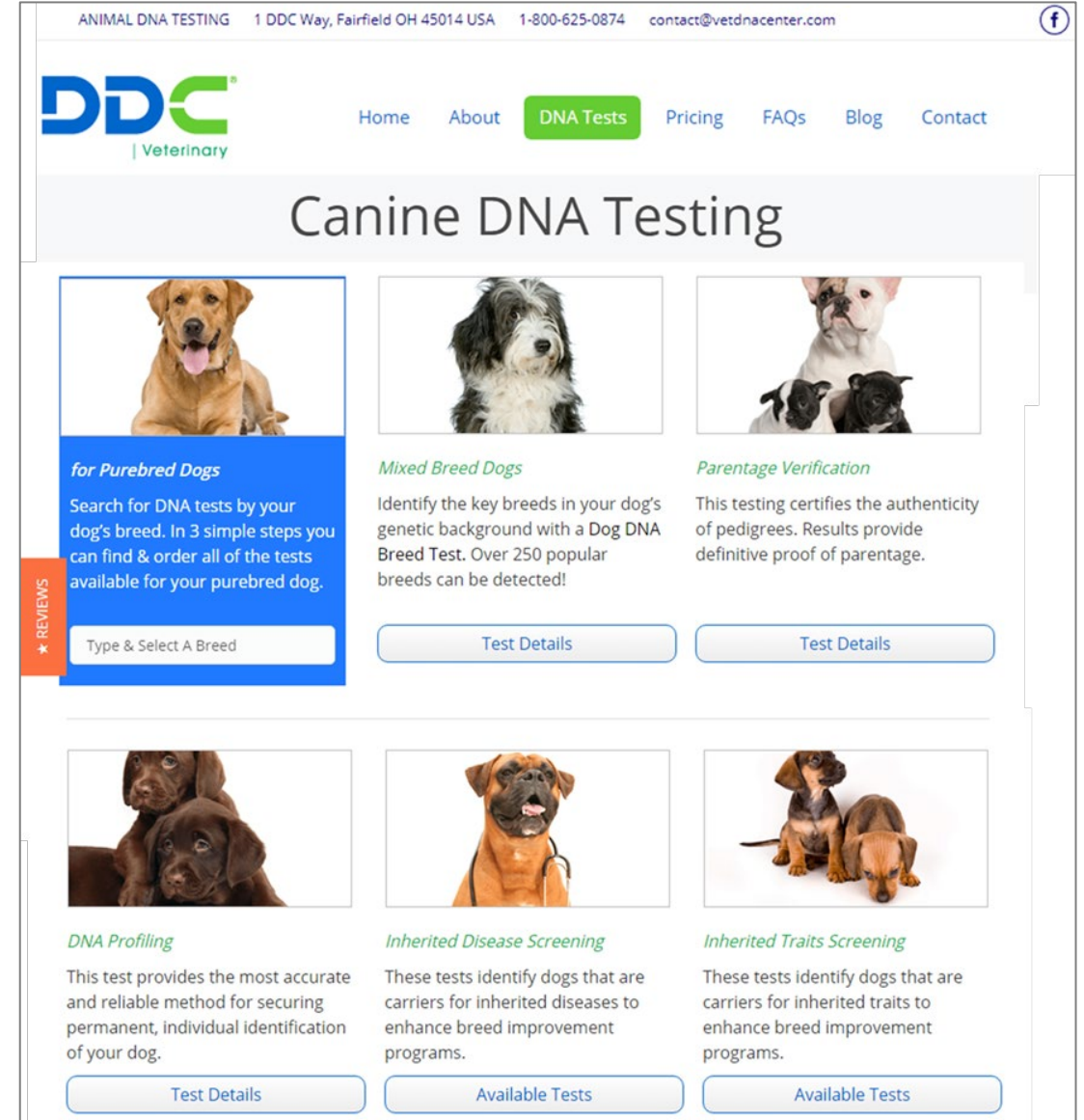
Everyone has a DNA story.
What is your story? [shop now](#)

SCANDINAVIAN 34.5%

LACTOSE INTOLERANCE

Gru ordered his kit.
[Discover his results](#)

ILLUSTRATION BY JIM LEE
DESPIRABLE ME 3
IN THEATERS JUNE 30




ANIMAL DNA TESTING 1 DDC Way, Fairfield OH 45014 USA 1-800-625-0874 contact@vetdnacenter.com

DDC Veterinary

Home About **DNA Tests** Pricing FAQs Blog Contact


Canine DNA Testing



for Purebred Dogs
Search for DNA tests by your dog's breed. In 3 simple steps you can find & order all of the tests available for your purebred dog.


★ REVIEWS

Type & Select A Breed




Mixed Breed Dogs
Identify the key breeds in your dog's genetic background with a Dog DNA Breed Test. Over 250 popular breeds can be detected!

Test Details




Parentage Verification
This testing certifies the authenticity of pedigrees. Results provide definitive proof of parentage.

Test Details




DNA Profiling
This test provides the most accurate and reliable method for securing permanent, individual identification of your dog.

Test Details



Inherited Disease Screening
These tests identify dogs that are carriers for inherited diseases to enhance breed improvement programs.

Available Tests



Inherited Traits Screening
These tests identify dogs that are carriers for inherited traits to enhance breed improvement programs.

Available Tests

what type of diet and/or what you should eat,

Helix
Home Population Health Research Account Search

How it works Register kit

Helix
We are a personal genomics company with a simple but powerful mission: empower every person to improve their life through DNA.
January 10, 2019

Start with proven weight loss principles

Lose It! is the weight loss tool that has helped its members shed **pounds** with proven techniques like calorie tracking, goal management, and food logging—including support for many popular fitness trackers. Can it be so tricky if you don't have the nutritional labels handy for everything you eat, but Lose It!'s ever-growing database of over 6 million foods makes it as simple as a tap or two.

embodyDNA

Hello, Charlie

Welcome to embodyDNA!

We've analyzed several important genetic markers in your DNA related to health and weight loss. Below you'll find helpful information on what we discovered, and how to make the best choice for your body.

DNA Powered Guidance

- Macronutrient Goals
- Food Suggestions

Personal DNA Reports

- Weight Loss
- Nutrition
- Fitness

Food Suggestions

Your Suggested Foods

- Bran Flakes Cereal
- Whole Milk
- Bison
- Soy Milk
- Clams
- Edamame
- Pork Loin
- Lentils
- Shrimp

Saturated Fat

Saturated Fat

Charlie, your genes suggest that the amount of saturated fat in your diet is not likely to impact your BMI.

Recommendation: Pay close attention to your calorie budget and keep saturated fat to <math><6\%</math> of total calories.

Even though you don't carry a risk factor for increased BMI due to saturated fat intake, you may still want to pay attention to your saturated fat intake to stay within the American Heart Association's guidelines.

It's estimated that 94.4% of the world's population shares this trait.

With embodyDNA, you'll go beyond basic calorie counting—you'll get real advice on how to fine-tune your diet based on your unique genetic profile. See which foods are recommended, which types of foods you may want to avoid, and how you can optimize your weight loss strategy to match your DNA. Lose It! is with you every step of the way.

Helix
Shop How it works Register kit Account

Women's Wellness

No two women are alike. But you knew that! What you might not know is whether you get a little extra help from a low-fat diet. Or why you've always struggled to fall asleep at night. That's where we come in. With Women's Wellness by Helix, you can discover a selection of genetic traits that shed light on who you are and how your body likely works—all designed to help you lead a more empowered life.

Created by women, for women, Women's Wellness offers insights that touch every part of your day-to-day. Learn how DNA may influence your skin type, your sleep habits, how your body responds to certain nutrients, and so much more.

Insights

- Caffeine Metabolism**
More caffeine, please!
- Sleep Duration**
Longer
- Bone Density**
May be typical

Exercise Impact on Weight

Let's get moving

We all know being active is important—especially when so many of us sit at a desk most of the day. But for some women, physical activity may provide even more benefit. In some cases, a specific genetic factor may predispose women to weigh less if they are more physically active.

Understanding your result

To determine whether you might see added benefit from being active, we look at the specific genetic factor called rs9939609. Your result is based on the letters, or bases, you have there.

Your result

You may benefit more from physical activity

This means you may weigh less if you engage in physical activity.



Order a Test ▾

Bundles ▾

About ▾

Local COVID-19 Testing

Account

Register a Kit



Home Health Tests

Proactive Health

Family + Ancestry

Personalized Medicine

Substance

DNA Artwork

Personalized Medicine



Pain Management

PGx Test

- Reduce trial and error to 40+ medications
- Dosage recommendations
- Suggest alternatives to high-risk medications



Cardiovascular Health

PGx Test

- Eliminate trial and error for 30+ medications
- Dosage recommendations
- Suggest alternatives to high-risk medications.



Mental Health

PGx Test

- Eliminate trial and error to 90+ medications
- Dosage recommendations
- Find alternatives to high-risk medications



Comprehensive

PGx Test

- Eliminate trial and error for 150+ medications
- Dosage recommendations
- Find alternatives to high-risk medications

Proactive Health



Nutrition

DNA Test

- Optimal diet for weight loss
- Food reactions and nutritional needs
- Healthy eating behaviors



Fitness

DNA Test

- Optimal exercise for weight loss
- Muscle strength and growth
- Injury risk and recovery time



Skin

DNA Test

- Anti-aging and nutritional needs
- Predispositions to skin health risks
- Solutions for problematic skin



Personality

DNA Test

- Character insights
- Mood, behavior, and persona
- Mind-body connection

Substance



Cannabis

DNA Test

- Discover your CBD and THC metabolism
- Potential side effects from cannabis use
- Dosing and product selection guidelines

DNA Artwork



DNA Portrait

\$199

[View](#)

and from there health, nutrition, personality, family relationships, response to cannabis & DNA Artwork!

Family + Ancestry



Ancestry

DNA Test

- Maternal and paternal haplogroups
- Ancestral migration patterns
- Ethnic composition



Paternity

DNA Test

- Reliable paternity confirmation
- Fully confidential results
- Simple and easy cheek swab



Siblingship

DNA Test

- Confirmation of familial relationships
- Fully confidential results
- Easy to read report

what sport/position you should play,

DNAfit New
Our Products ▾ Your Goals ▾ 23andMe Users Why DNAfit COVID-19 More ☰

Build the body you always wanted

Health Fit, our simple, at home DNA test teaches you how to make your workouts work for you, by understanding your response to power and endurance-based activities.

Personalised diet and training plans, based on your unique genetic results, allow you to leverage your body's strengths for superior results. Whether you want to tone your muscles or bulk up, DNAfit let's you discover how your genetics affect your exercise response.

Diet **Nutrients** **Fitness** **Stress**

Your tools:

SOCCER GENOMICS

DNA extraction
Our home-based buccal swab kit is the right way for you to send your DNA to our lab.

Sequencing
Our labs are CLIA-certified and CAP-accredited in order to process all buccal samples.

Soccer Genes - SNP
The analyzed genes are those that have direct relation with the skills required of a soccer player needs.

DISCOVER YOUR SOCCER GENETIC BLUEPRINT

Welcome to your specific player DNA

Unique Genetic Soccer Report.

Based on age and gender our multidisciplinary team employs a rigorous process in generating the soccer report, which provides insight into the development of a personalized training program designed to maximize overall performance.

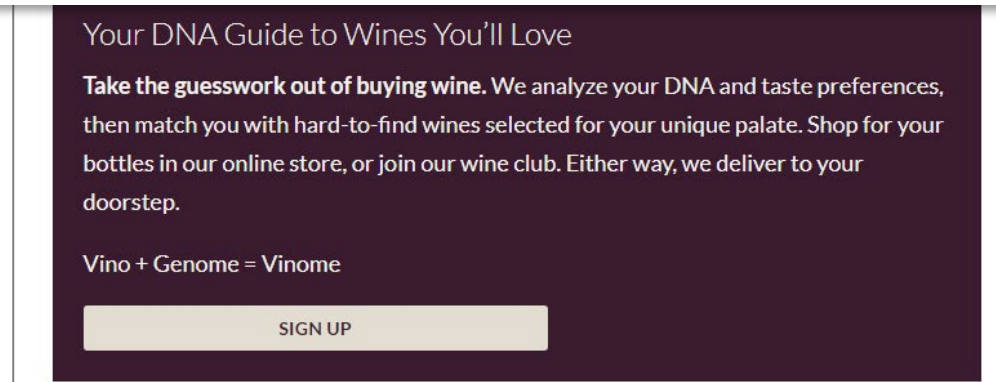
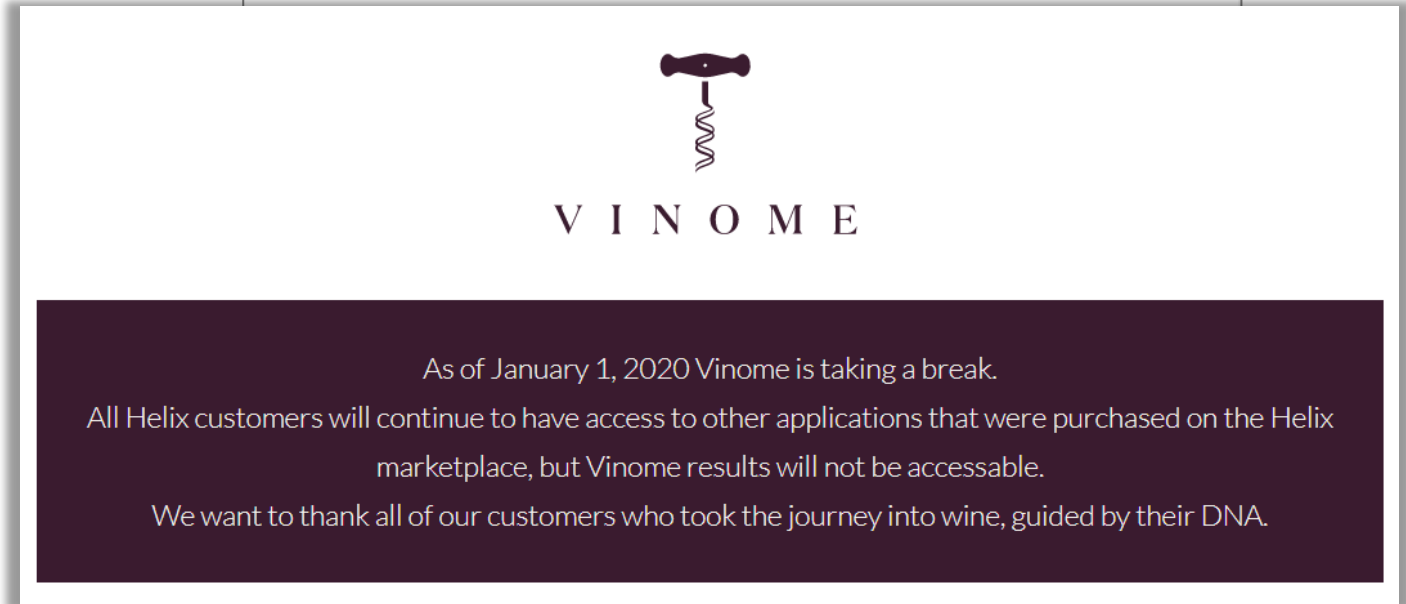
- ✓ SPEED
- ✓ ENDURANCE
- ✓ STRENGTH
- ✓ FLEXIBILITY MOBILITY
- ✓ RISK OF INJURY
- ✓ NUTRITION
- ✓ TRAINING GUIDE

No payments + no interest if paid in full in 6 months on purchases of \$99+.
Check out with PayPal and choose PayPal Credit.

Subject to credit approval. See terms. US customers only.

PayPal CREDIT

what wine
you should buy....



Have you.....

- Thought about taking a genetic test, but have not
- Taken a direct-to-consumer genealogical/ancestry DNA test
- Taken a direct-to-consumer genetic test with health-related information
- Seen a genetic test for a patient
- Seen a case management plan changed based on a genetic test result
- Given your dog a genetic test

But seriously, folks....

Using Genetic/Genomics to assist in
High-Definition Diagnosis &
Precision Treatment Selection



High
Definition &
Precision?

An outline of a history of medical practice

- The Art of Medicine
- The Science of Medicine
- Evidence-based Clinical Practice

"Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values."
- "Personalized" Medicine

[AMA – all patient-care should be "personalized"]
- "Precision" Medicine

"Precision medicine is an emerging approach for disease diagnosis treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."
- *and now?*

.....Molecular Medicine, Genomic Medicine, High-Definition Medicine....

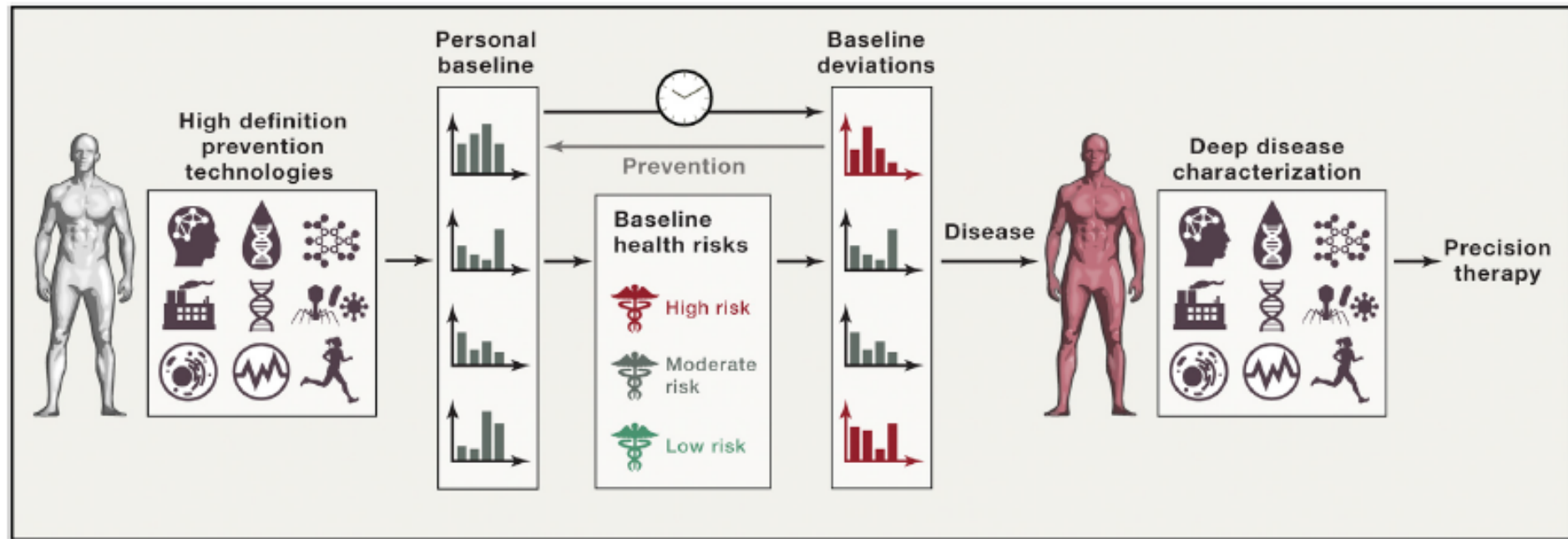


HIGH-DEFINITION MEDICINE?

Establish an Individual's **Baseline** of Health

Create a Personalized "**Prevention**" Strategy

Perform **High-Definition Diagnosis** & Select **High-Precision Treatment**



"High-Definition Medicine." Torkamani A, Andersen KG, Steinhubl SR, and EJ Topol.
Cell. 24 August 2017 170(5), 828–843.

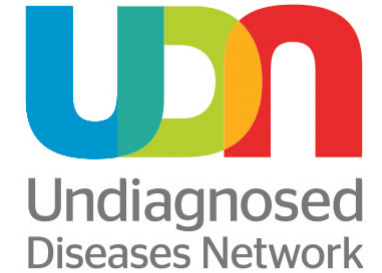
“Precision” Medicine – NIH funded research projects for disease characterization and to improve diagnoses & treatments



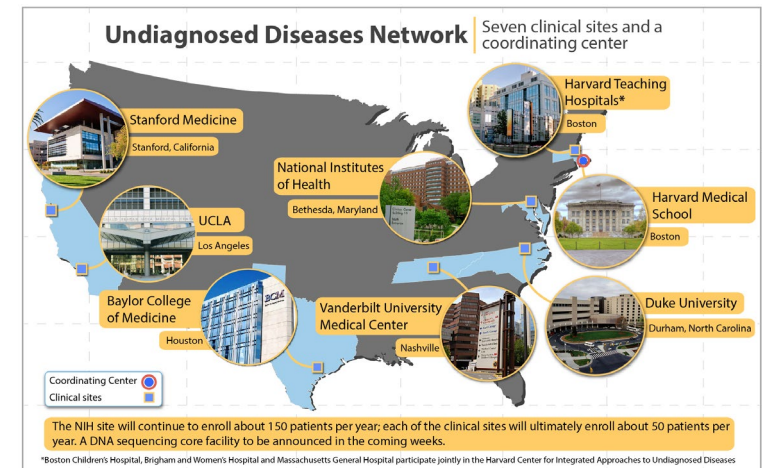
NATIONAL CANCER INSTITUTE
PRECISION MEDICINE
IN CANCER TREATMENT

Discovering unique therapies that treat an individual's cancer based on the specific genetic abnormalities of that person's tumor.

The graphic contains three rows of icons. Each row starts with a group of human silhouettes in various colors (blue, green, orange) with a small colored star on their chest. To the right of each group is a blue DNA double helix with a small colored star on it. To the right of each DNA helix is a medicine bottle in a different color (purple, green, orange) with a small colored star on its label.



Solving medical mysteries through team science.



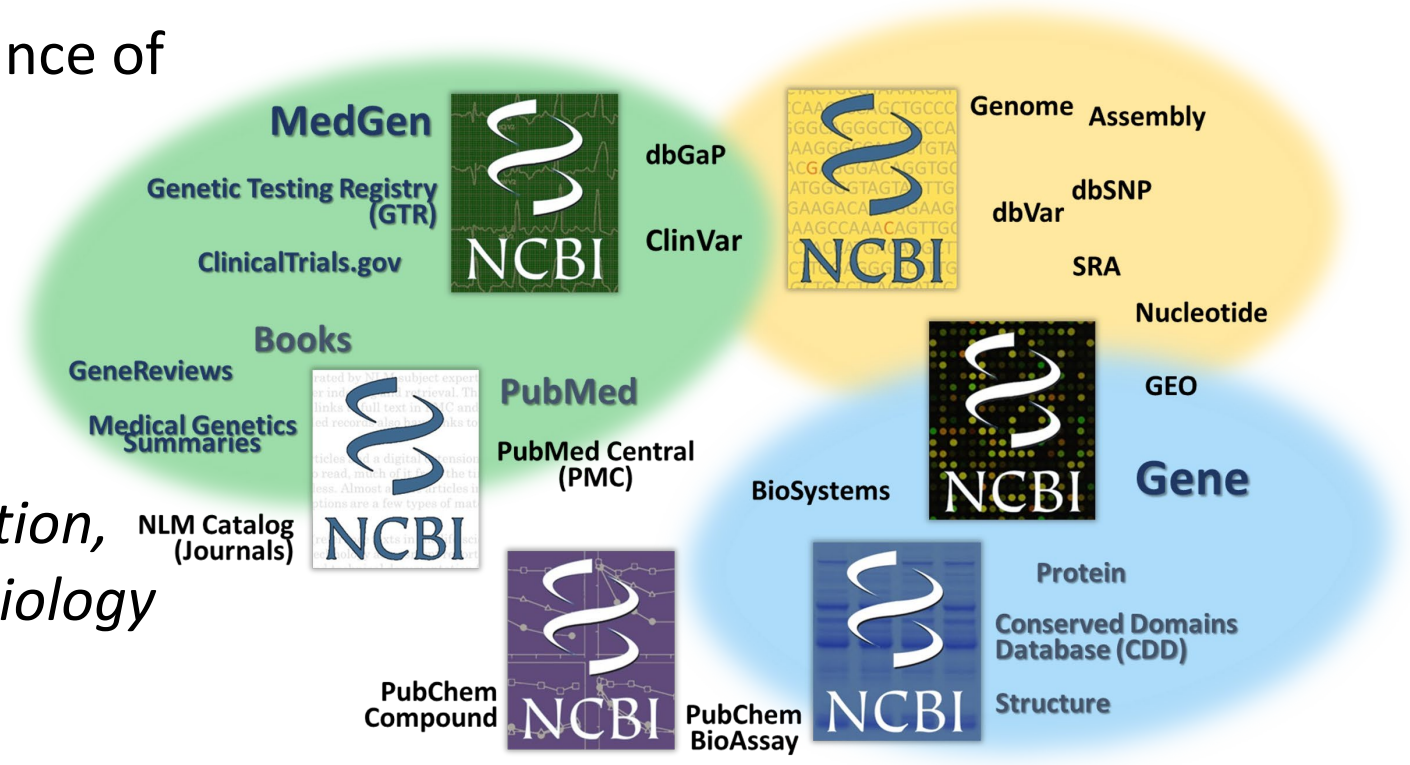
WHY “NCBI”?



National Center for Biotechnology Information
A Division of the U.S. National Library of Medicine

We are a “center” within the NLM responsible for creation, curation and maintenance of medical and scientific databases *and other things...*

We receive, create, archive & make available biomedical information, as well as perform computational biology & IT systems research....



we aspire to help make sense of all that information!

FOUNDATIONS SESSION 164

Molecular Pathology Case Studies:

Connecting the dots between

- *Genetics*
- *Molecular biology*
- *Biochemistry*

in real patients!

With recent advances in the integration of various disciplines of molecular science and technological developments in genetic analysis, it is now possible to implement truly “personalized” medicine. The growing adoption of “Precision Medicine” involves the full understanding of a patient, including their own specific molecular pathology and disease etiology, which can help to establish an accurate diagnosis and to select an effective therapy.

NCBI has long had online resources for biologists to explore what is known about a biological molecule including its structure and function and has recently developed clinically-focused resources enabling scientists and clinicians to integrate known molecular biological information with clinically-relevant genetic variations.

Today:

- We will discuss the application of precision medicine principles in the clinic.
- We will work together through a cluster of similar-sounding patient cases and discover the underlying cause of pathology in each of these real patients.
- By looking at the diverse molecular mechanisms seen in these patients, we will:
 - explore how knowing the pathology of a patient's genetic disorder can facilitate a “precision diagnosis”
 - explain the clinical presentation
 - and can be helpful in customizing the case management plan.
- There are some additional cases for you to work on for practice & self-assessment.

**This session was designed to help you
review the major concepts you've been learning**

& to give you experience in integrating all of them in real-world patient case studies!

SETTING EXPECTATIONS

What we will cover

- NCBI's web-based **resources** that may be helpful to learn about human genetic disorders/conditions, genetic variations, genes and gene products.
- **Examples** of how you can use these resources from real clinical cases to explore and understand the underlying molecular pathology.

What we will *not* cover

- basic genetics or genetic principles - although we *will* use your knowledge about these in our discussions.
- high-throughput variant analysis - but you may find some helpful resources in the provided reference materials.
- resources for *all* human disorders, today we are focusing on simple genetic disorders. (for example, we will not discuss polygenic disorders such as most cancers or variants in disease-causing pathogens)
- Today's workshop is about *finding helpful information* you can use in your research.
We will not discuss best practices for implementation of genetic information in the clinic or production of diagnostic or therapeutic products.

Disclaimer

- ⇒ We cannot make recommendations on what you should do.
We provide resources, data and information that you can use as part of your work.

Let's get this out of the way – *“How am I going to be tested on this?”*

You are going to be tested on this in several ways:

Next week's exam

- You will **not** have to run through a whole case study.
- You will **not** be tested on the specifics of each of these cases.
- **You will need to be able to answer questions based on *application* of genetics/molbiol/biochem in patient cases:**
 - When is genetic testing something to consider and how does it fit within clinical cases?
 - Why is it helpful to integrate molecular sciences for decisions about patient care & case management?
 - How are problems at the molecular level (integrated molecular pathology) related to health?
 - Where can you find high-quality biological information *when you need it?*

USMLE Step 1

- Integration of molecular sciences information will help you answer case study-driven questions.

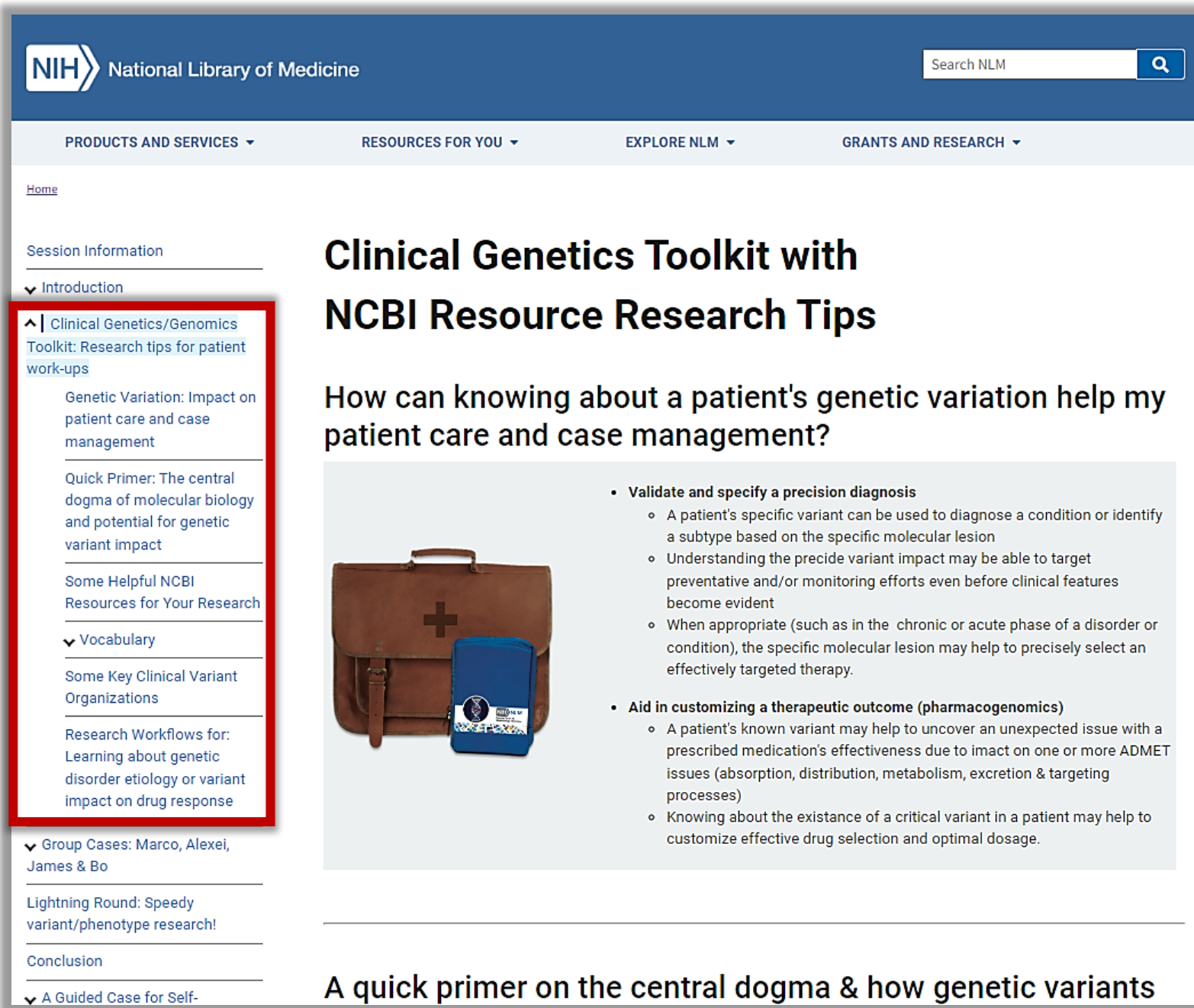
Your CAREER!

- Keep up with science, technology with an increasingly-specific focus on individual patient's cases
- Resident Preceptors, Attending Physicians, etc. – will all be asking you questions.....
- Patients & Parents increasingly wanting to know “why?” Be able to fully explain things!

Clinical Genetics Toolkit

- a reference source -

A reference for you with
information about clinical
variations for now & later
when you need it!



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[Home](#)

Session Information

▾ Introduction

▾ Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups

- Genetic Variation: Impact on patient care and case management
- Quick Primer: The central dogma of molecular biology and potential for genetic variant impact
- Some Helpful NCBI Resources for Your Research
- ▾ Vocabulary
- Some Key Clinical Variant Organizations
- Research Workflows for: Learning about genetic disorder etiology or variant impact on drug response

▾ Group Cases: Marco, Alexei, James & Bo

Lightning Round: Speedy variant/phenotype research!


Conclusion

▾ A Guided Case for Self-

Clinical Genetics Toolkit with NCBI Resource Research Tips

How can knowing about a patient's genetic variation help my patient care and case management?

- **Validate and specify a precision diagnosis**
 - A patient's specific variant can be used to diagnose a condition or identify a subtype based on the specific molecular lesion
 - Understanding the precise variant impact may be able to target preventative and/or monitoring efforts even before clinical features become evident
 - When appropriate (such as in the chronic or acute phase of a disorder or condition), the specific molecular lesion may help to precisely select an effectively targeted therapy.
- **Aid in customizing a therapeutic outcome (pharmacogenomics)**
 - A patient's known variant may help to uncover an unexpected issue with a prescribed medication's effectiveness due to impact on one or more ADMET issues (absorption, distribution, metabolism, excretion & targeting processes)
 - Knowing about the existence of a critical variant in a patient may help to customize effective drug selection and optimal dosage.



A quick primer on the central dogma & how genetic variants

The Workflow

- a guided workflow -







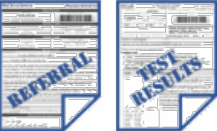
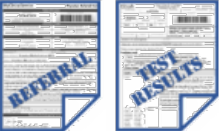
Time to practice a patient case workup with some guidance!

And we'll compare case workup information for four boys with similar-sounding issues.

The screenshot shows the NIH National Library of Medicine website. At the top, there is a search bar and navigation menus for 'PRODUCTS AND SERVICES', 'RESOURCES FOR YOU', 'EXPLORE NLM', and 'GRANTS AND RESEARCH'. The main content area is titled 'Group Cases' and features four columns, each representing a boy: Marco, Alexei, James, and Bo. Each column contains a photo of the boy and two document icons labeled 'REFERRAL' and 'TEST RESULTS'. Below the photos, there is a text box that reads: 'A Case Workup worksheet for use to keep track of your patient's information. OR, if you prefer, here is a Group Case Workup worksheet to track them all at in one place.' At the bottom, there is a section titled 'What do you know about your patient's phenotype? (Researching the Referral)' with a paragraph of text starting with 'In this scenario, each of four boys was referred to the genetics clinic because their preliminary diagnoses suggested they...'. On the left side of the screenshot, there is a sidebar menu with a red border around the 'Group Cases: Marco, Alexei, James & Bo' section. The sidebar menu includes: 'Home', 'Session Information', 'Introduction', 'Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups', 'Group Cases: Marco, Alexei, James & Bo' (highlighted), 'Welcome to Your Patient!', 'Researching the Referral', 'Finding a Genetic Test and Understanding the Results', 'Learning about the Genetic Variant', 'Learning about the Impacted Gene', 'Mapping the Genetic Variant through the Central Dogma', 'Understanding the Potential Impact of the Genetic Variant', and 'Take-away Message'.

Optional Worksheet: *a WordDoc to fill out*

Group Cases

 Marco	 Alexei	 James	 Bo
			

A **Case Workup worksheet** for use to keep track of *your* patient's information.

OR, if you prefer, here is a **Group Case Workup worksheet** to track them all at in one place.







Today, you are going to work with one of these boys!

Your Patient's Info	NOTES
Phenotype	
Preliminary Diagnosis	
Genetic Variation(s)	
Laboratory Assertion(s)	
Variant Information: <ul style="list-style-type: none">• Asserted interpretation listed in ClinVar• HGVS names from ClinVar• Is population data available in dbSNP?	
Gene Information in NCBI Gene: <ul style="list-style-type: none">• Symbol and Name• Gene Summary • Tissue Expression information • Gene Ontology information	
Ultimate Impacted Biomolecule based on: <ul style="list-style-type: none">• GDV to view the chromosome and gene region• RefSeqGene Graphics view of gene region and transcript(s)• RefSeq Protein Graphics view of protein and domains• CDD or iCn3D to view a structure, as needed	
Proposed Molecular Mechanism of Variant Impact	
How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	

	Marco	Alexei	James	Bo				
Phenotype (including severity)	Referral	Test Result	Referral	Test Result	Referral	Test Result	Referral	Test Result
Preliminary Diagnosis								
Genetic Variation(s)								
Laboratory Assertion(s)								
Variant Information: <ul style="list-style-type: none">• Asserted interpretation listed in ClinVar• HGVS names from ClinVar• Is population data available in dbSNP?								
Gene Information in NCBI Gene: <ul style="list-style-type: none">• Symbol and Name• Gene Summary• Tissue Expression information• Gene Ontology information								


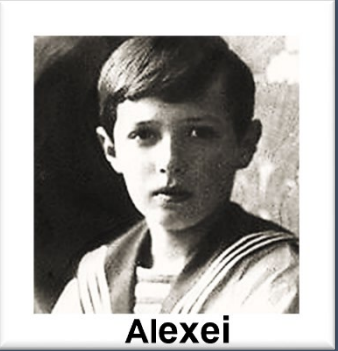


Researching the Referral

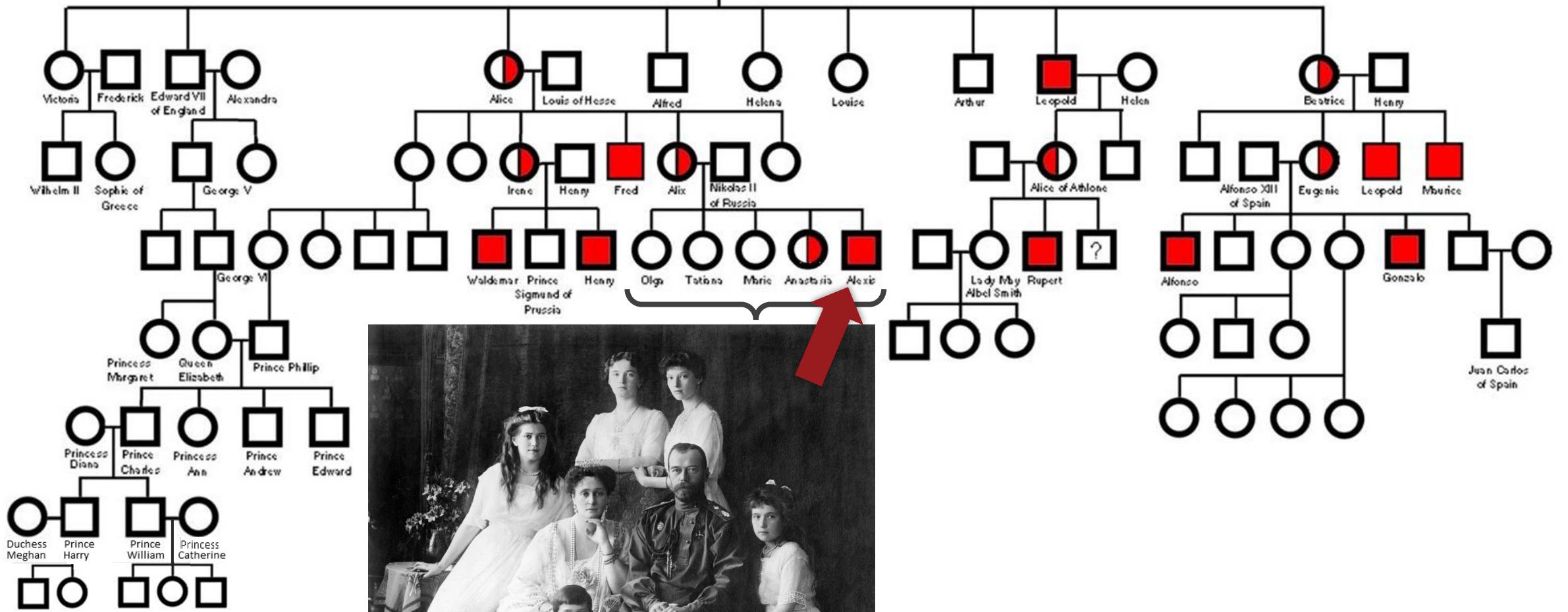
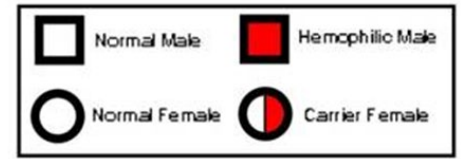
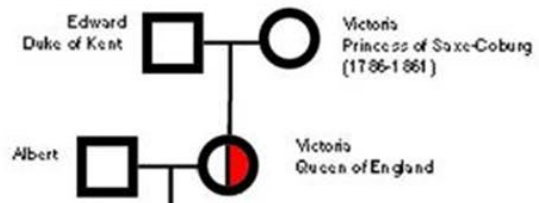
Read the **Referral** – *and take notes!*

	 Marco	 Alexei	 James	 Bo
Phenotype (including severity)				
Preliminary Diagnosis				

If you want to learn more about this disorder.....Search in **MedGen!**

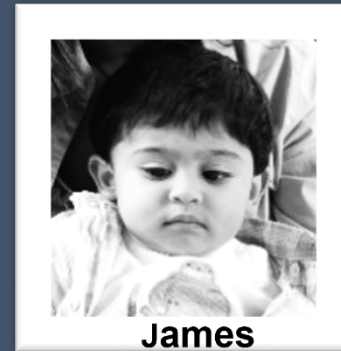
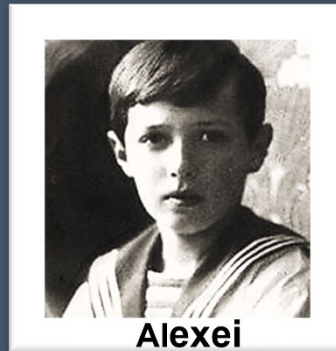
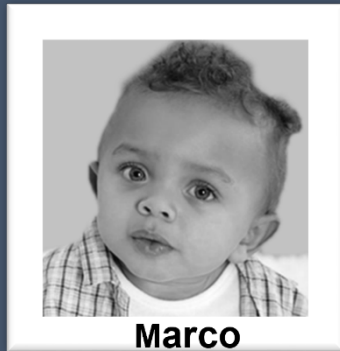
Read the **Referral** – *and take notes!*

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Phenotype (including severity)	<p>significant bruising and severe pain after his first soccer practice</p> <p>previous episodes of scratches causing prolonged bleeding</p> <p>family history: a male cousin was known to have hemophilia.</p>	<p>severe hematoma on thigh after bumping into a boat's oarlock.</p> <p>long history of recurrent episodes of illness (bruises, bleeding episodes, and long painful recoveries) since shortly after birth</p> <p>Family history:</p> <ul style="list-style-type: none"> rumors of bleeding issues in many cousins of the maternal family. 	<p>relentless nosebleed caused by "bumping into a coffee table"</p> <p>visible bruising on his knees and palms since he began crawling at 6 months</p> <p>Family history:</p> <ul style="list-style-type: none"> Mother required a blood transfusion after natural childbirth Maternal uncle died at the age of 6 years old from a "brain bleed" after a fall. 	<p>profuse bleeding laceration on left index finger</p> <p>previous episodes of prolonged bleeding which hadn't "risen to the level of an ER visit but were concerning."</p> <p>Family history:</p> <ul style="list-style-type: none"> No "genetic" family history is available as Bo was adopted from China at the age of 3 years old
Preliminary Diagnosis	<p>Hemophilia <i>(sub-type not determined yet)</i></p>	<p>Hemophilia <i>(sub-type not determined yet)</i></p>	<p>Hemophilia <i>(sub-type not determined yet)</i></p>	<p>Hemophilia <i>(sub-type not determined yet)</i></p>



Understanding the Genetic Test Results


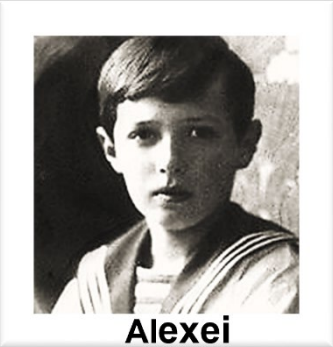
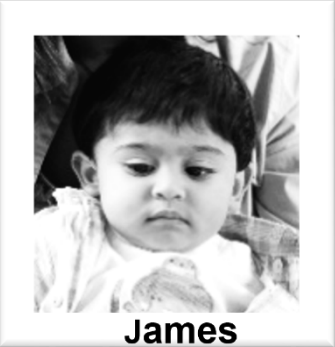

Open your **Genetic Test Report**



Genetic Variation(s)




**Laboratory
Assertion(s)**

Open your Genetic Test Report

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Genetic Variation(s)	NG_011403.1: g.4980_5005del	F9 c.278-3A>G	F8 p.Arg15Ter	F9 p.Asp110Gly
Laboratory Assertion(s)	variant of uncertain significance (VUS)	pathogenic	pathogenic	pathogenic

Learning about the identified variant


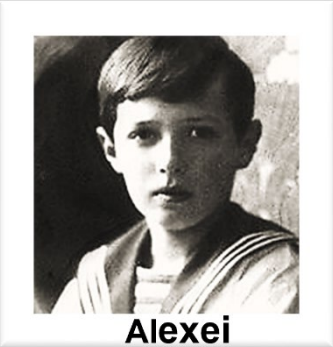
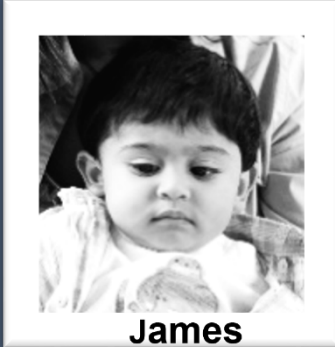

Search ClinVar with the Genetic Test Reported Variant

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Genetic Variation(s)	NG_011403.1: g.4980_5005del	F9 c.278-3A>G	F8 p.Arg15Ter	F9 p.Asp110Gly
Variant Information:				
<ul style="list-style-type: none"> • Asserted interpretation in ClinVar • HGVS names from ClinVar 				
<ul style="list-style-type: none"> • Is population data available in dbSNP? 				

Marco's genetic variant isn't showing up in ClinVar. Why?


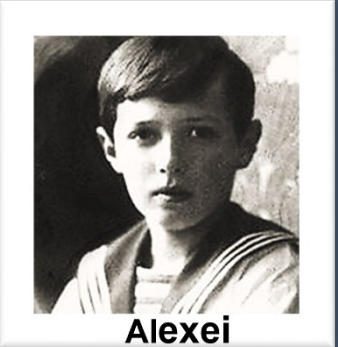
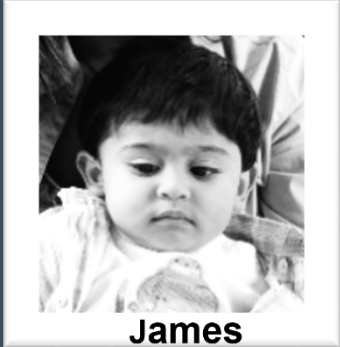

- A. Because I typed it in wrong.
- B. Because ClinVar's search isn't working.
- C. Because no one has ever found that variant before.
- D. Because no one in a clinical or research lab has submitted information about that particular variant.

Search **ClinVar** with the Genetic Test Reported Variant


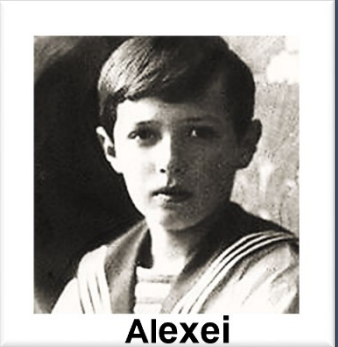
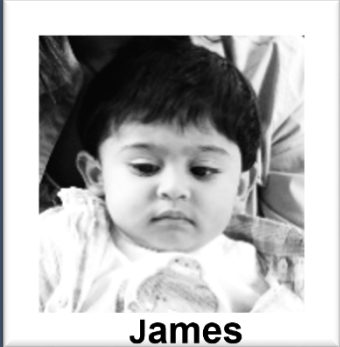

	 Marco	 Alexei	 James	 Bo
Genetic Variation(s)	NG_011403.1: g.4980_5005del	F9 c.278-3A>G	F8 p.Arg15Ter	F9 p.Asp110Gly
Variant Information:	not in ClinVar! <i>(assumed VUS)</i>	pathogenic	pathogenic	pathogenic
	<ul style="list-style-type: none"> Asserted interpretation in ClinVar HGVS names from ClinVar 	NG_011403.1(F8): g.4980_5005del Note: no protein HGVS	NG_007994.1(F9): g.15338A>G Note: no protein HGVS	NG_011403.2(F8): g.5214C>T NP_000123.1(F8): p.Arg15Ter
<ul style="list-style-type: none"> Is population data available in dbSNP? 	Not in Clinvar. Searching directly in dbSNP did not find anything.	rs398122990 Yes! And it is really, really rare.	rs387906432 Yes! And it is really, really rare.	rs137852234 Yes! And it is pretty darn rate.

Learning about the implicated gene


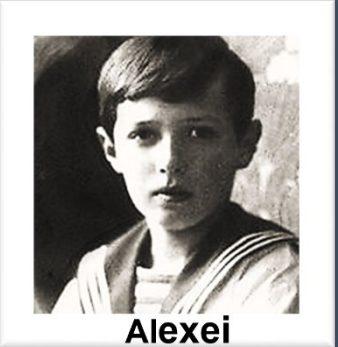
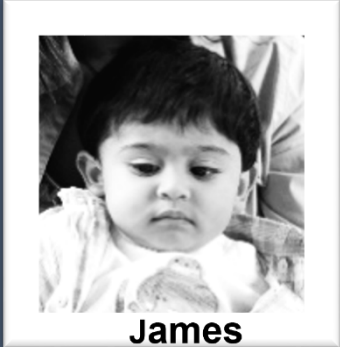

Search **Gene** with the Test Reported Gene Symbol

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Gene Symbol	F8	F9	F8	F9
Gene Information in NCBI Gene: <ul style="list-style-type: none"> • Gene Name • Gene Summary 				
	<ul style="list-style-type: none"> • Tissue Expression information 			
	<ul style="list-style-type: none"> • Gene Ontology information 			


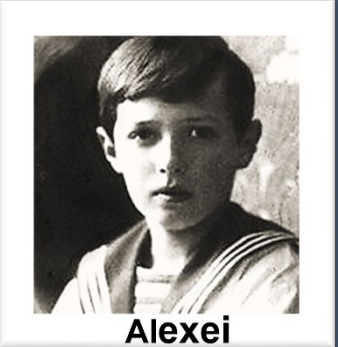
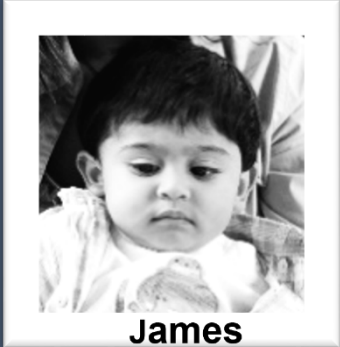

Search **Gene** with the Test Reported Gene Symbol

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Gene Symbol	F8	F9	F8	F9
Gene Information in NCBI Gene: <ul style="list-style-type: none"> • Gene Name • Gene Summary • Tissue Expression information • Gene Ontology information 	Coagulation factor VIII ...participates in the intrinsic pathway of blood coagulation; factor VIII is a cofactor for factor IXa which, in the presence of Ca ²⁺ and phospholipids, converts factor X to the activated form Xa.Defects in this gene results in hemophilia A, a common recessive X-linked coagulation disorder. [provided by RefSeq, Jul 2008]	Coagulation factor IX	Coagulation factor VIII ...participates in the intrinsic pathway of blood coagulation; factor VIII is a cofactor for factor IXa which, in the presence of Ca ²⁺ and phospholipids, converts factor X to the activated form Xa.Defects in this gene results in hemophilia A, a common recessive X-linked coagulation disorder. [provided by RefSeq, Jul 2008]	Coagulation factor IX
	Broad expression, especially in Liver, Spleen and others		Broad expression, especially in Liver, Spleen and others	
	Extracellular Blood coagulation Protein binding		Extracellular Blood coagulation Protein binding	

Search **Gene** with the Test Reported Gene Symbol

	 Marco	 Alexei	 James	 Bo
Gene Symbol	F8	F9	F8	F9
Gene Information in NCBI Gene:	Coagulation factor VIII	Coagulation factor IX	Coagulation factor VIII	Coagulation factor IX
Gene Name		...vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen....converted to an active form by factor XIa, ...activates factor X ... through interactions with Ca ²⁺ ions, membrane phospholipids, and factor VIII. Alterations of this gene...cause factor IX deficiency, which is a recessive X-linked disorder....[provided by RefSeq, Sep 2015]		...vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen....converted to an active form by factor XIa, ...activates factor X ... through interactions with Ca ²⁺ ions, membrane phospholipids, and factor VIII. Alterations of this gene...cause factor IX deficiency, which is a recessive X-linked disorder....[provided by RefSeq, Sep 2015]
Gene Summary				
Tissue Expression information		Pretty much just expressed in the liver		Pretty much just expressed in the liver
Gene Ontology information		Extracellular Blood coagulation Ca ²⁺ -binding & endopeptidase		Extracellular Blood coagulation Ca ²⁺ -binding & endopeptidase

Search **Gene** with the Test Reported Gene Symbol

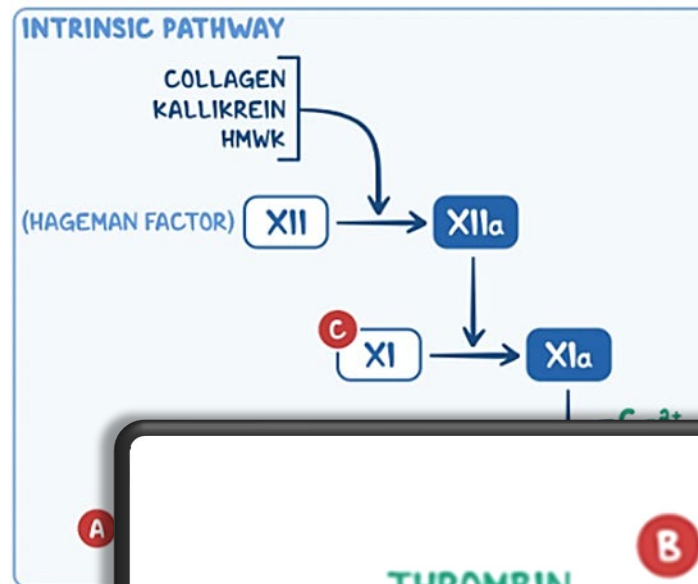
	 Marco	 Alexei	 James	 Bo
Gene Symbol	F8	F9	F8	F9
Gene Information in NCBI Gene: <ul style="list-style-type: none"> • Gene Name • Gene Summary • Tissue Expression information • Gene Ontology information 	Coagulation factor VIII ...participates in the intrinsic pathway of blood coagulation; factor VIII is a cofactor for factor IXa which, in the presence of Ca ⁺² and phospholipids, converts factor X to the activated form Xa.Defects in this gene results in hemophilia A, a common recessive X-linked coagulation disorder. [provided by RefSeq, Jul 2008]	Coagulation factor IX ...vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen....converted to an active form by factor XIa, ...activates factor X ... through interactions with Ca ⁺² ions, membrane phospholipids, and factor VIII. Alterations of this gene...cause factor IX deficiency, which is a recessive X-linked disorder....[provided by RefSeq, Sep 2015]	Coagulation factor VIII ...participates in the intrinsic pathway of blood coagulation; factor VIII is a cofactor for factor IXa which, in the presence of Ca ⁺² and phospholipids, converts factor X to the activated form Xa.Defects in this gene results in hemophilia A, a common recessive X-linked coagulation disorder. [provided by RefSeq, Jul 2008]	Coagulation factor IX ...vitamin K-dependent coagulation factor IX that circulates in the blood as an inactive zymogen....converted to an active form by factor XIa, ...activates factor X ... through interactions with Ca ⁺² ions, membrane phospholipids, and factor VIII. Alterations of this gene...cause factor IX deficiency, which is a recessive X-linked disorder....[provided by RefSeq, Sep 2015]
	Broad expression, especially in Liver, Spleen and others	Pretty much just expressed in the liver	Broad expression, especially in Liver, Spleen and others	Pretty much just expressed in the liver
	Extracellular Blood coagulation Protein binding	Extracellular Blood coagulation Ca ⁺² -binding & endopeptidase	Extracellular Blood coagulation Protein binding	Extracellular Blood coagulation Ca ⁺² -binding & endopeptidase

About the clotting cascade

Factor 8 (F8 a.k.a. FVIII)
& Factor 9 (F9 a.k.a. FIX)
are critical regulatory factors
for blood coagulation/clotting.

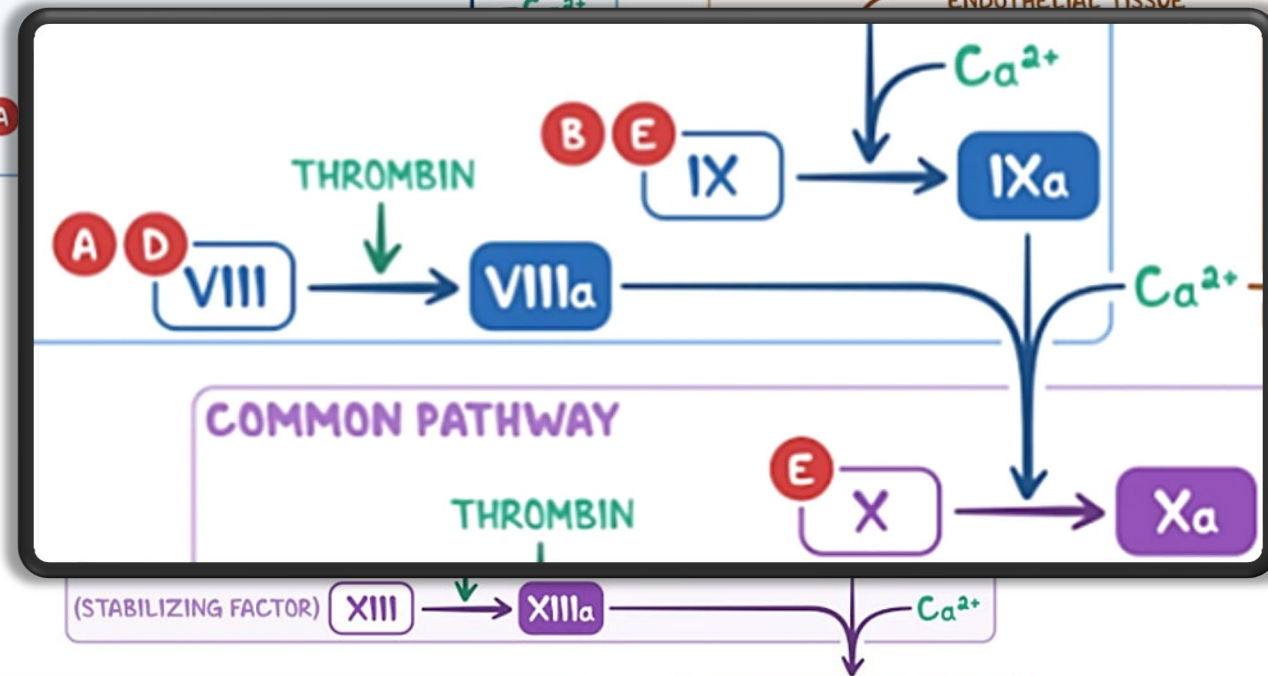
They also both happen to be
encoded on the
X-chromosome.

Males only have 1 copy of the
gene and therefore are
dramatically impacted
if there is a pathogenic variant
impacting even just one of
these two genes.



BACKGROUND

- * SERIES of STEPS in RESPONSE to BLEEDING CAUSED by TISSUE INJURY
- ~ EACH STEP ACTIVATES the NEXT & ULTIMATELY PRODUCES a BLOOD CLOT
- * aka SECONDARY HEMOSTASIS



COAGULATION DISORDERS

- * CAN EITHER CAUSE EXCESSIVE or INADEQUATE CLOTTING
- * DEFICIENCY in ≥1 CLOTTING FACTOR

A HEMOPHILIA A D von WILLEBRAND DISEASE
B HEMOPHILIA B E VITAMIN K DEFICIENCY
C HEMOPHILIA C

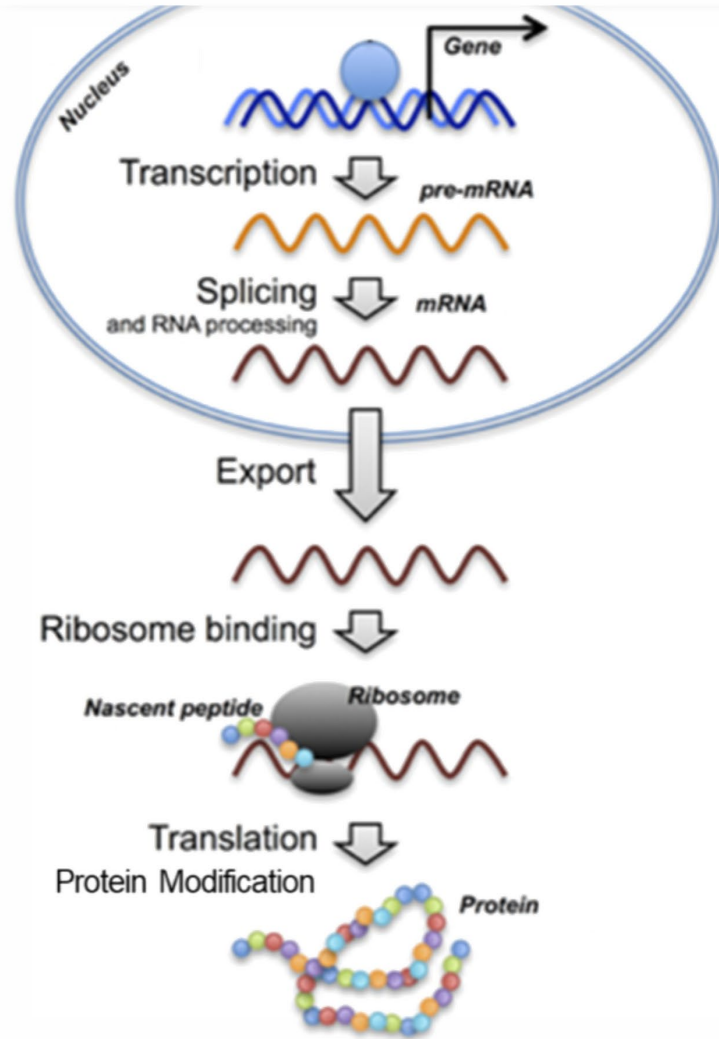


Mapping the variant

Map the Variant with **Genome/Sequence Browser Tools**

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Genetic Variation(s)	NG_011403.1(F8):g.4980_5005del	NG_007994.1(F9):g.15338A>G NP_000124.1(F9):p.Gly94Ter	NG_011403.2(F8):g.5214C>T NP_000123.1(F8):p.Arg15Ter	NG_007994.1(F9):g.15392A>G NP_000124.1(F9):p.Asp110Gly
Ultimate Impacted Biomolecule based on:				
<ul style="list-style-type: none"> • GDV to view the chromosome and gene region • RefSeqGene Graphics view of gene region and transcript(s) • RefSeq Protein Graphics view of protein and domains • CDD or iCn3D to view a structure 				

An overview of the central dogma & locating a genetic variation



An overview of the central dogma & locating a genetic variation

Is the variant in the:



Genome, assembly level → GRCh38

Chromosome/DNA → NC_ (RefSeq)



HGVS Variant Example: NC_000002.12:g.72888457A>G
might impact chromatin structure or function

Gene/DNA, gene *region* level → NG_* (RefSeqGene)



HGVS Variant Example: NG_008234.1(SCR):g.6075A>G
might impact expression for or splicing of a gene transcript

Transcript/RNA → NM_ , NR_ (“RefSeq RNA” | RefSeq Select)



HGVS Variant Example: NM_003124.5(SCR):c.448A>G
might impact transcript processing and/or translation

Protein, mRNA-encoded sequence → NP_* (“RefSeq Protein”)







HGVS Variant Example: NP_003115.1(SCR):p.Arg150Gly
might impact protein folding, processing or function

Structure

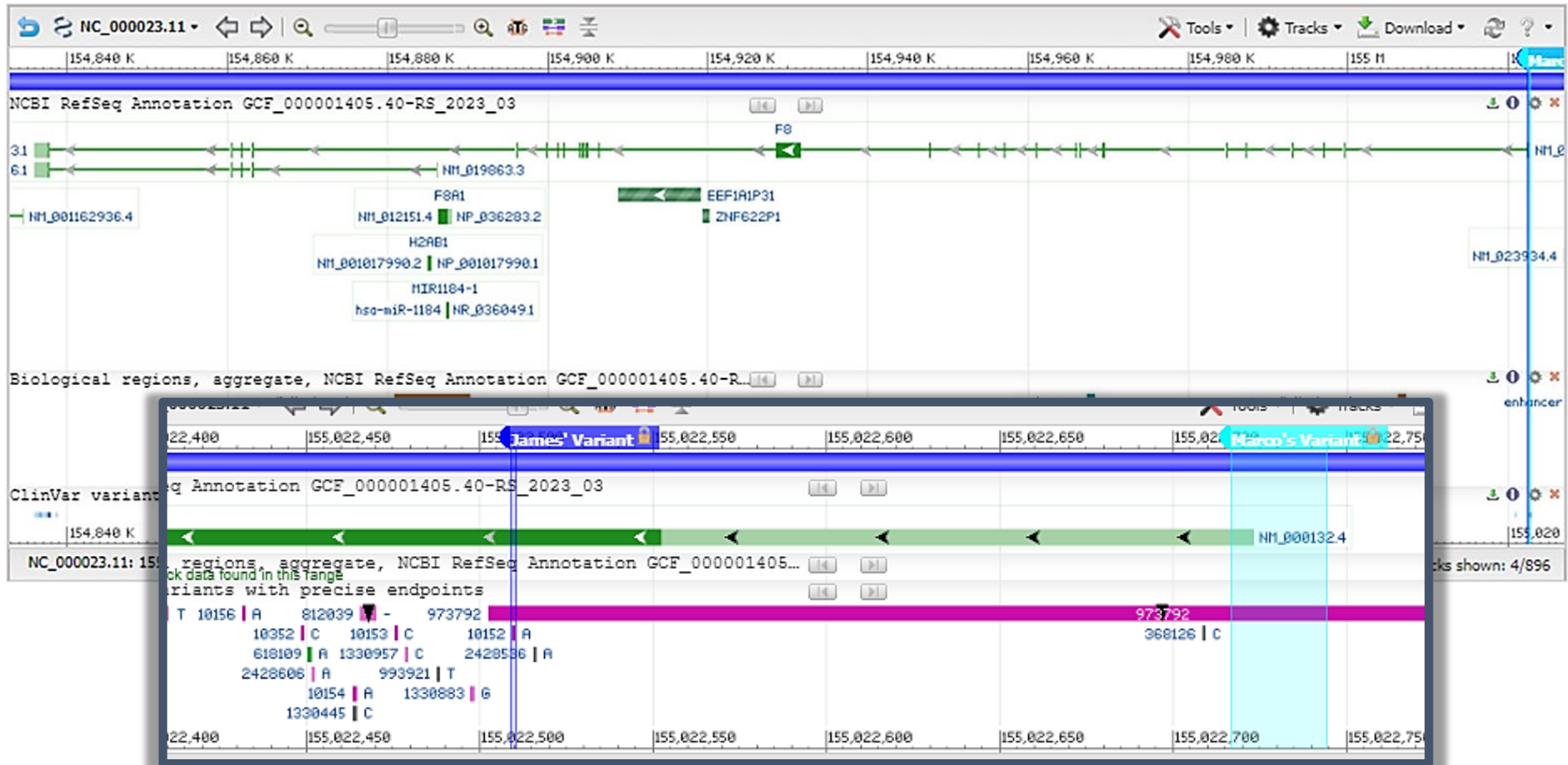
Map the Variant with **Genome/Sequence Browser Tools**

	 <p>Marco</p>	 <p>Alexei</p>	 <p>James</p>	 <p>Bo</p>
Genetic Variation(s)	NG_011403.1(F8):g.4980_5005del	NG_007994.1(F9):g.15338A>G NP_000124.1(F9):p.Gly94Ter	NG_011403.2(F8):g.5214C>T NP_000123.1(F8):p.Arg15Ter	NG_007994.1(F9):g.15392A>G NP_000124.1(F9):p.Asp110Gly
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Map the Variant with **Genome/Sequence Browser Tools**

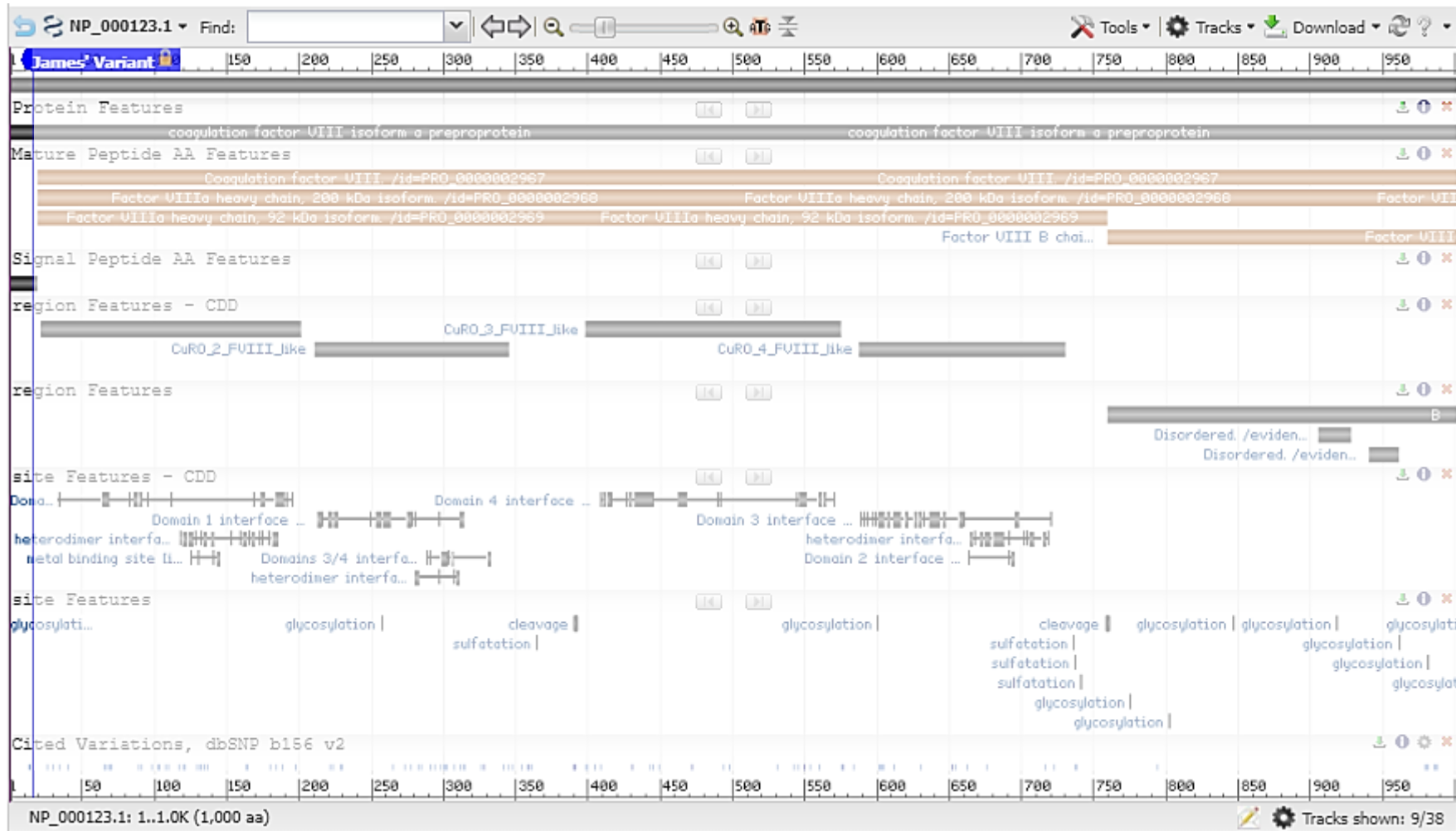
				
Genetic Variation(s)	NG_011403.1(F8):g.4980_5005del	NG_007994.1(F9):g.15338A>G NP_000124.1(F9):p.Gly94Ter	NG_011403.2(F8):g.5214C>T NP_000123.1(F8):p.Arg15Ter	NG_007994.1(F9):g.15392A>G NP_000124.1(F9):p.Asp110Gly
Ultimate Impacted Biomolecule based on: <ul style="list-style-type: none"> • GDV to view the chromosome and gene region • RefSeqGene Graphics view of gene region and transcript(s) • RefSeq Protein Graphics view of protein and domains • CDD or iCn3D to view a structure 	Deleted region upstream from through the beginning of the transcription start.		Located in the coding region within exon 1.	
	Transcripts are not expressed, therefore the variant does not impact biomolecules beyond the gene region in the chromosome.		Located within the first coding exon.	
			The coding sequence quickly terminates after only 14 residues – producing a non-functional peptide destined for degradation.	
			Most of the protein is never made so it cannot serve as a complex anchor for clotting factor aggregation.	

Marco's variant is a deletion of the region including the transcript start codon – so no transcript is produced.




James' variant is in the coding region of the transcript – thus directly impacts the protein sequence.

James' variant in the coding region of the transcript is a termination codon.

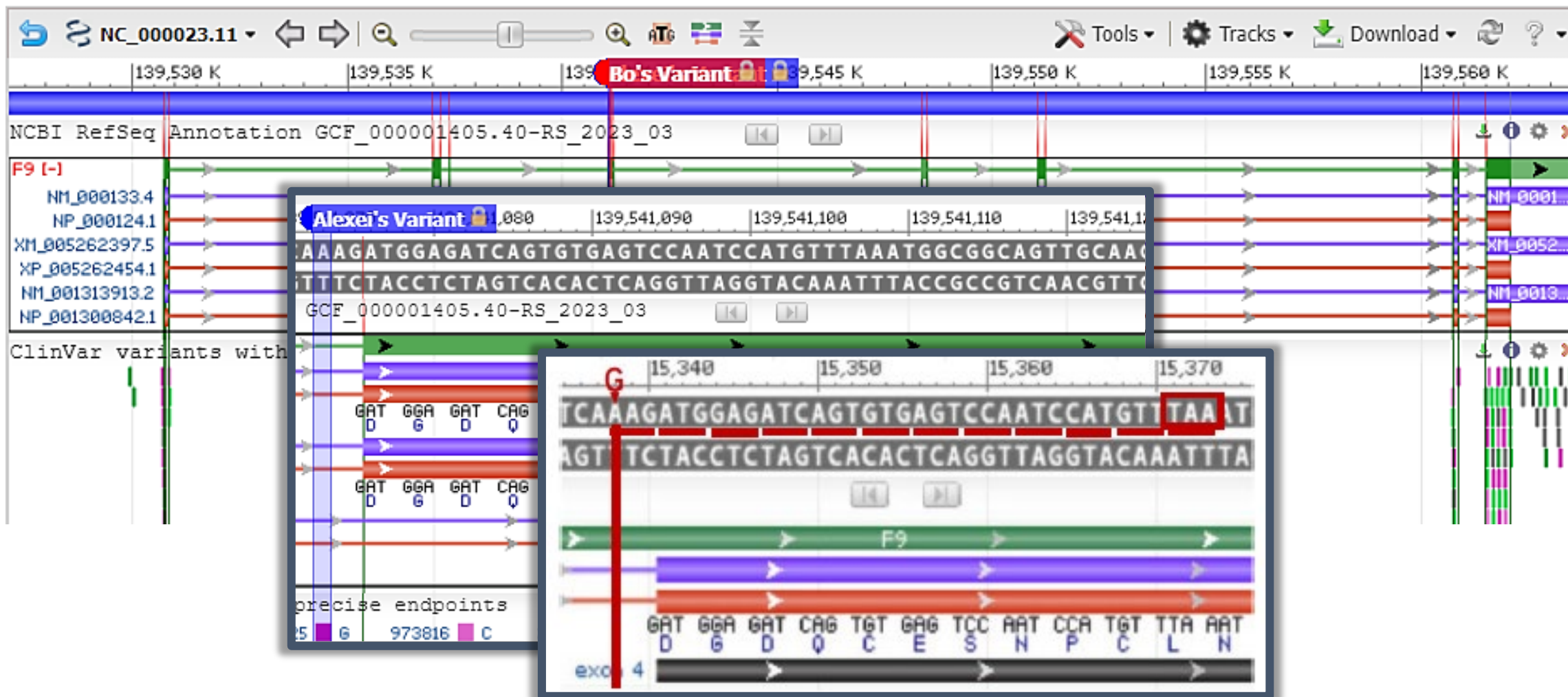


Thus, the full-length peptide is never made – actually most of it is gone!....so there is no functional protein made.

Map the Variant with **Genome/Sequence Browser Tools**

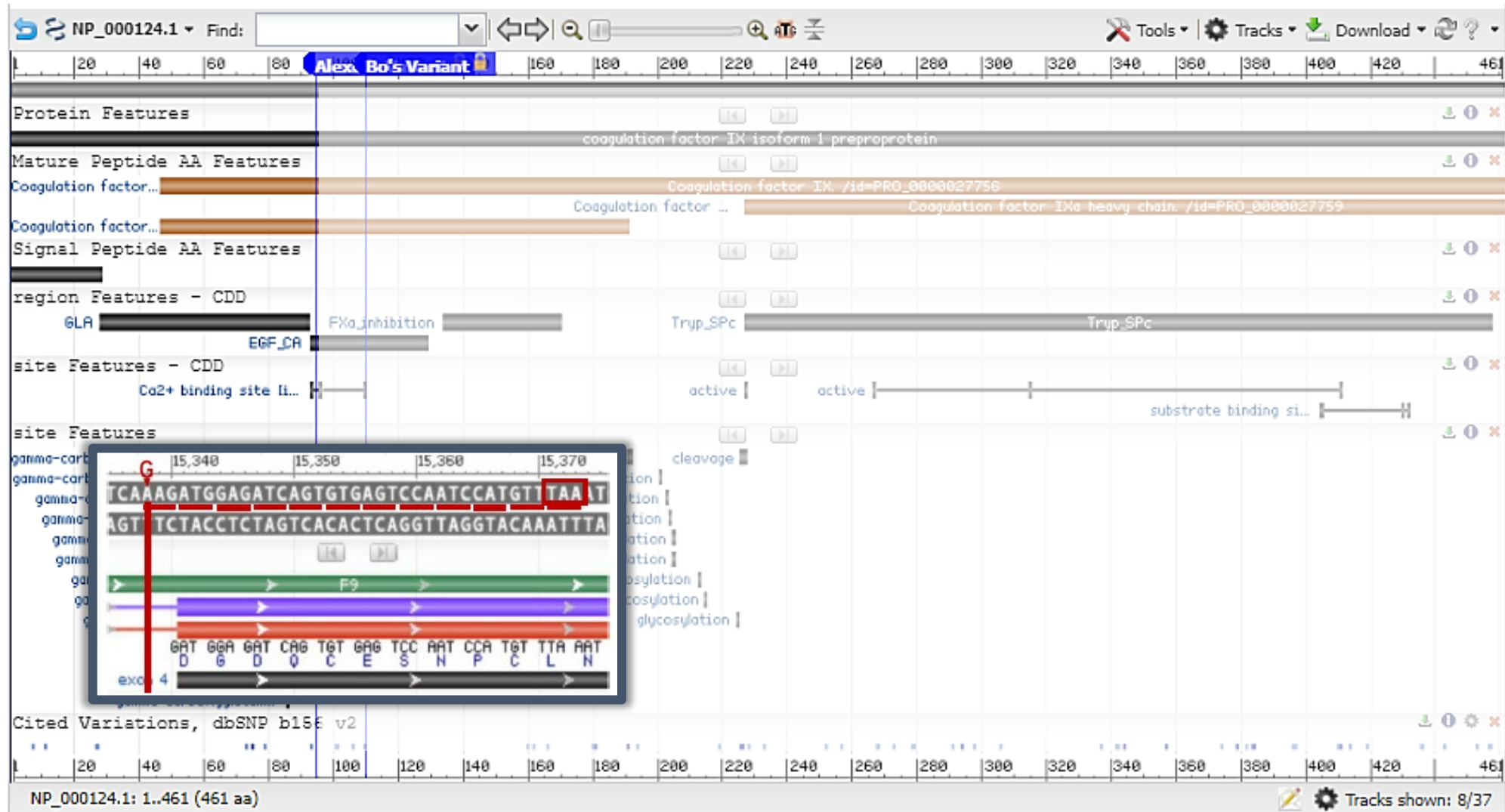
	 Marco	 Alexei	 James	 Bo
Genetic Variation(s)	NG_011403.1(F8):g.4980_5005del	NG_007994.1(F9):g.15338A>G NP_000124.1(F9):p.Gly94Ter	NG_011403.2(F8):g.5214C>T NP_000123.1(F8):p.Arg15Ter	NG_007994.1(F9):g.15392A>G NP_000124.1(F9):p.Asp110Gly
Ultimate Impacted Biomolecule based on: <ul style="list-style-type: none"> • GDV to view the chromosome and gene region • RefSeqGene Graphics view of gene region and transcript(s) • RefSeq Protein Graphics view of protein and domains • CDD or iCn3D to view a structure 		Located near a splice site in the gene just before exon 4.		Located in the coding region within exon 4.
		Exon 4's acceptor site is shifted back due to the variation – causing a frameshift of the coding sequence.		Located within the coding region within exon 4.
		The coding sequence frameshift encodes an 11-residue peptide and then a stop codon - prematurely terminating the protein.		The protein is made, but with a change in amino acid 110 from an acidic Aspartate to a neutral Glycine.
		A large portion of the protein is never made – especially the endopeptidase domain which is critical for activating FX – and propagating the clotting cascade.		The variant is one of 3 residues annotated as critical for binding to Ca ²⁺ . The change from acidic Aspartate residue to neutral Glycine impacts its binding to the Ca ²⁺ & protein folding, thus processing & activation.

Alexei's variant is near the end of a coding exon.



Because the variant creates an exon signal mimic, it shifts the exon splice site up two residues causing a frameshift in the protein coding sequence.





Alexei's splicing-shift and coding frameshift variant causes a short non-sense peptide with a termination codon.



Thus, only the beginning of the peptide is made....so no functional protein is created.

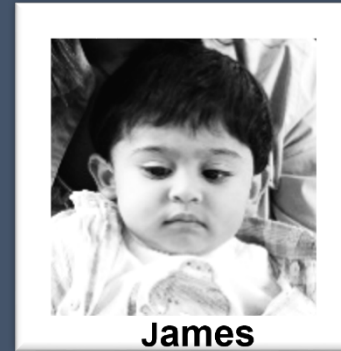
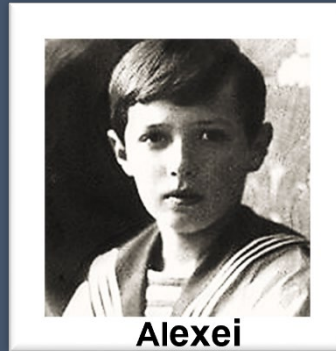
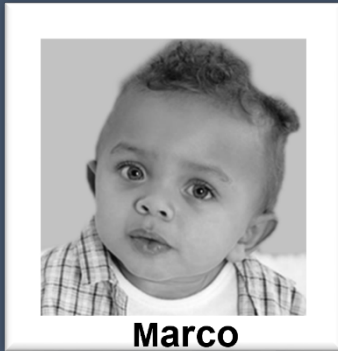
This is similar to what is seen for James' F8 protein.

Map the Variant with **Genome/Sequence Browser Tools**

	 Marco	 Alexei	 James	 Bo
Genetic Variation(s)	NG_011403.1(F8):g.4980_5005del	NG_007994.1(F9):g.15338A>G NP_000124.1(F9):p.Gly94Ter	NG_011403.2(F8):g.5214C>T NP_000123.1(F8):p.Arg15Ter	NG_007994.1(F9):g.15392A>G NP_000124.1(F9):p.Asp110Gly
Ultimate Impacted Biomolecule based on:	Deleted region upstream from through the beginning of the transcription start.	Located near a splice site in the gene just before exon 4.	Located in the coding region within exon 1.	Located in the coding region within exon 4.
	Transcripts are not expressed, therefore the variant does not impact biomolecules beyond the gene region in the chromosome.	Exon 4's acceptor site is shifted back due to the variation – causing a frameshift of the coding sequence.	Located within the first coding exon.	Located within the coding region within exon 4.
		The coding sequence frameshift encodes an 11-residue peptide and then a stop codon - prematurely terminating the protein.	The coding sequence quickly terminates after only 14 residues – producing a non-functional peptide destined for degradation.	The protein is made, but with a change in amino acid 110 from an acidic Aspartate to a neutral Glycine.
		A large portion of the protein is never made – especially the endopeptidase domain which is critical for activating FX – and propagating the clotting cascade.	Most of the protein is never made so it cannot serve as a complex anchor for clotting factor aggregation.	The variant is one of 3 residues annotated as critical for binding to Ca ²⁺ . The change from acidic Aspartate residue to neutral Glycine impacts its binding to the Ca ²⁺ & protein folding, thus processing & activation.

Putting it all together
tell the story....

Put it all together...




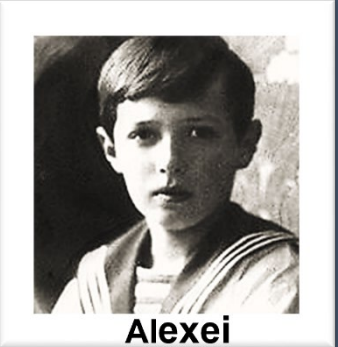
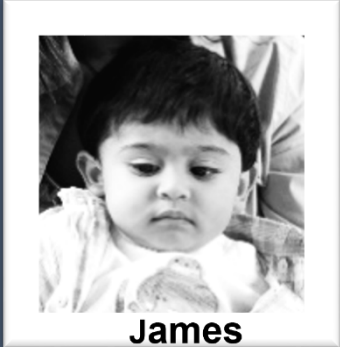

Diagnosis

Genetic Variation(s)

Proposed Molecular Mechanism of Variant Impact

How does this relate back to the phenotype (symptoms/ clinical features & diagnosis)?

Put it all together...

	 Marco	 Alexei	 James	 Bo
Diagnosis	Hemophilia A	Hemophilia B	Hemophilia A	Hemophilia B
Genetic Variation(s)	NG_011403.1(F8): g.4980_5005del	NG_007994.1(F9): g.15338A>Gr	NP_000123.1(F8): p.Arg15Ter	NP_000124.1(F9): p.Asp110Gly
Proposed Molecular Mechanism of Variant Impact	The deletion in the region just upstream and after the transcriptional start site - likely removes promoter elements and does not allow for gene expression.	This is a change in a splice site base – shifting the splicing back two positions, causing a coding frameshift and ending in premature termination.	This changes an amino acid coding codon to a premature termination codon.	This changes an acidic residue which is needed for binding a critical calcium ion which is required for F9 function.
How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	With a non-expressible F8, the clotting cascade will not be able to progress to create clots. This correlates with a severe phenotype.	With an F9 protein prematurely terminated, the catalytic domain for activating the next clotting factor is not made and the clotting cascade cannot progress to create clots. This correlates with a severe phenotype.	With an F8 protein prematurely terminated, the binding domains for activating the next clotting factor is not made and the clotting cascade cannot progress to create clots. This correlates with a severe phenotype.	With the loss of one of 3 coordinating residues for a critical calcium ion, the F9 protein is not fully functional and may not effectively activate the next clotting factor. This correlates with a less severe phenotype.

Leslie's Case

- your workflow practice -

A guided case to practice on your own!

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Session Information


- Introduction
- Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups
- Group Cases: Marco, Alexei, James & Bo
- Lightning Round: Speedy variant/phenotype research!
- Conclusion

^ | A Guided Case for Self-assessment: Leslie

- Welcome to Your Patient!
- Researching the Referral
- Finding a Genetic Test and Understanding the Results
- Learning about the Genetic Variant
- Learning about the Impacted Gene
- Mapping the Genetic Variant through the Central Dogma
- Understanding the Potential Impact of the Genetic Variant
- Take-away Message

Guided Practice Case: Leslie

Welcome to Your Patient!




Leslie, a 40-year-old mother of two, was referred for genetic testing by her gastroenterologist...

Key Symptoms: Changes in bathroom habits, bleeding and abdominal pain

She has a medical history of colonic polyps. Her family history reveals that her maternal grandmother, mother and uncle had several forms of cancers including colon, breast, and endometrium. Her gastroenterologist suspects Lynch Syndrome.

QUESTION: What do you think is wrong with Leslie?



Researching the Referral

In this scenario, Leslie was referred to the genetics clinic because their preliminary diagnoses suggested that she might have a potentially serious genetic condition. If a known pathogenic genetic variant is found, it can validate the diagnosis and provide additional patient-specific information that might help customize her case management plan.

To learn more about a case, please **click on the Referral icon above** to open the form. Read it over and fill in below what you can glean from the description and proposed preliminary diagnosis.

Notes	
Phenotype	
Preliminary Diagnosis	

Independent Cases

- *your workflow practice* -

In your career you are going to get a patient history and/or referral information and potentially a genetic test result.

You won't get guided research steps.

So, here are three practice cases that you can try out!

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Introduction

Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups

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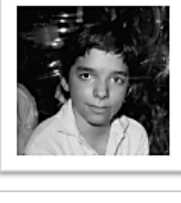


Lightning Round: Speedy variant/phenotype research!

Conclusion

A Guided Case for Self-assessment: Leslie

Independent Practice Cases for Self-assessment: Jeff, Jonathan, David

Independent Practice Cases for Self-assessment

Patient's Name	Patient Photo	Referral & Genetic Test Result Forms	Answers
Jeff			
Jonathan			
David			

But what if I'm in the clinic and *don't have time*
to spend getting critical information?

Lightning Round

- *your workflow practice* -

A quick way to find up-to-date genetic variant/disorder information.

The screenshot shows the NIH National Library of Medicine website. The top navigation bar includes the NIH logo, the text "National Library of Medicine", and a search box labeled "Search NLM". Below the navigation bar are four main menu categories: "PRODUCTS AND SERVICES", "RESOURCES FOR YOU", "EXPLORE NLM", and "GRANTS AND RESEARCH".

On the left side, there is a sidebar menu with the following items:

- Home
- Session Information
- Introduction
- Clinical Genetics/Genomics Toolkit: Research tips for patient work-ups
- Group Cases: Marco, Alexei, James & Bo
- Lightning Round: Speedy variant/phenotype research!** (highlighted with a red box)
- Conclusion
- A Guided Case for Self-assessment: Leslie
- Independent Practice Cases for Self-assessment: Jeff, Jonathan, David

The main content area features a large heading: "Lightning Round: Your turn to practice rapid-research for the clinic!". Below this heading is a paragraph: "The goal of this exercise is to practice quickly finding helpful data about a variant identified in a patient's genetic test result and to reinforce how to find additional information relevant for developing a case management plan for this particular patient."

A "Workflow" diagram is centered on the page. It shows a central "ClinVar" box with the URL "https://www.ncbi.nlm.nih.gov/clinvar" and the text "Learn about the patient's genetic variation(s)". Four arrows labeled "Link to" point from ClinVar to four other boxes: "MedGen" (with text "Link from a ClinVar record Identify resources for an associated disorder, condition or trait"), "PubMed" (with text "Link from a ClinVar record Find peer-reviewed publications about a phenotype or variant"), "dbSNP" (with text "Link from a ClinVar record Learn more about a genetic variant"), and "dbSNP" (with text "Link from a ClinVar record Learn more about a genetic variant").

At the bottom of the page, there are two blue buttons with white text: "HFE p.Cys282Tyr" and "HFE p.C282Y". Below each button is a small icon of a computer monitor and the text "Need a hint?".

Important Concepts

- *to know* -

- Why should I care about molecular science while preparing to be a physician?

knowledge is more power to act & act more effectively!

- How could understanding a patient's specific molecular pathology help you as a doctor?

***aiding in precision diagnosis,
implementation of proactive/preventative measures
including optimizing therapeutic selection,
communicating with the patient & patient's family***

- What in the patient's case record could start you thinking about *ordering* a genetic test?

***known genetic disorder with or without family history
(don't trust commercial tests for your diagnosis!)***

- Which databases are good places to start to find helpful disease/condition, gene information, and to validate a lab's call about a pathogenic genetic variation?

NCBI MedGen , NCBI Gene & NCBI ClinVar

Conclusion

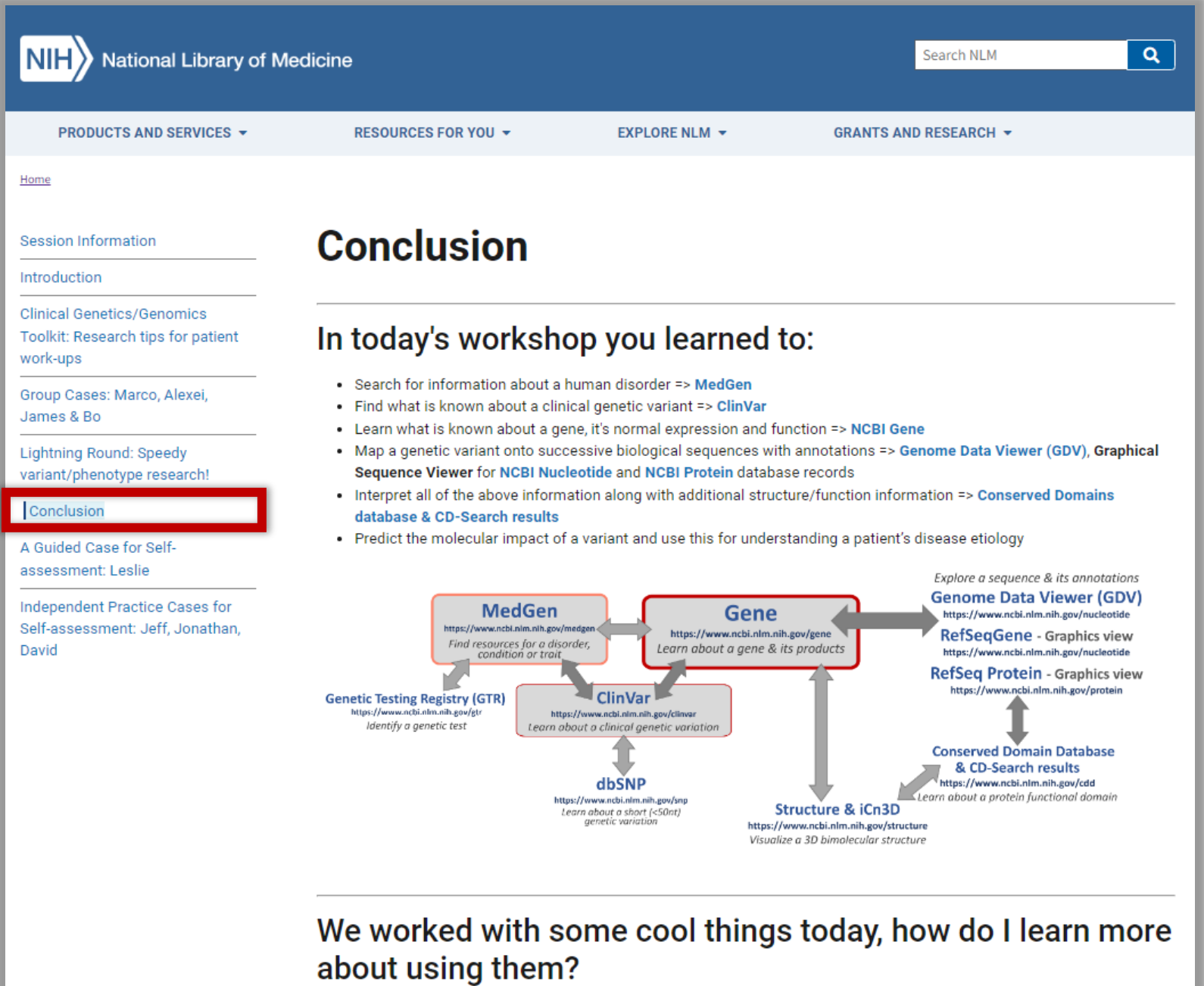
Thanks for participating today!

In today's session, you learned to use some NCBI resources to understand the impact of a genetic variation on a person's biology!

Here are some ways to learn more about the cool tools you used today!

NCBI has a lot of resources to help the clinical and scientific research community...

...and ways to keep up with news and developments!



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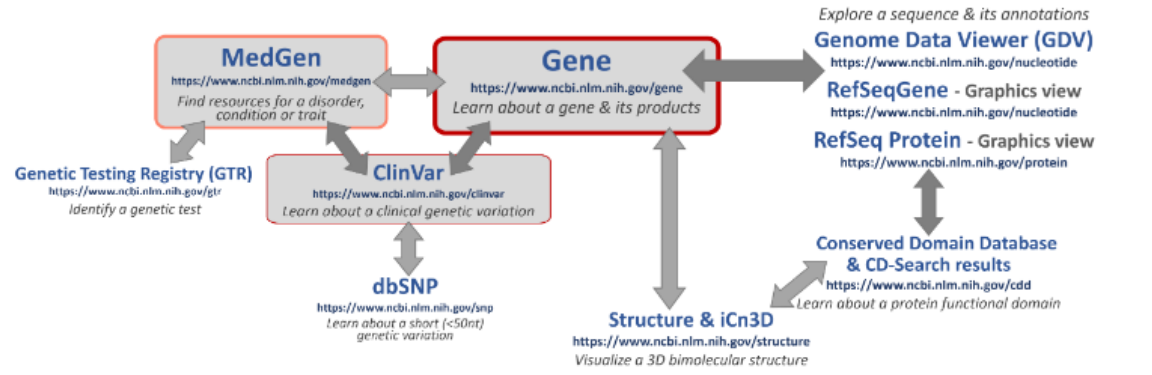
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Conclusion

In today's workshop you learned to:

- Search for information about a human disorder => **MedGen**
- Find what is known about a clinical genetic variant => **ClinVar**
- Learn what is known about a gene, it's normal expression and function => **NCBI Gene**
- Map a genetic variant onto successive biological sequences with annotations => **Genome Data Viewer (GDV)**, **Graphical Sequence Viewer** for **NCBI Nucleotide** and **NCBI Protein** database records
- Interpret all of the above information along with additional structure/function information => **Conserved Domains database & CD-Search results**
- Predict the molecular impact of a variant and use this for understanding a patient's disease etiology



MedGen
<https://www.ncbi.nlm.nih.gov/medgen>
Find resources for a disorder, condition or trait

Gene
<https://www.ncbi.nlm.nih.gov/gene>
Learn about a gene & its products

Genome Data Viewer (GDV)
<https://www.ncbi.nlm.nih.gov/nucleotide>
Explore a sequence & its annotations

RefSeqGene - Graphics view
<https://www.ncbi.nlm.nih.gov/nucleotide>

RefSeq Protein - Graphics view
<https://www.ncbi.nlm.nih.gov/protein>

Conserved Domain Database & CD-Search results
<https://www.ncbi.nlm.nih.gov/cdd>
Learn about a protein functional domain

Structure & iCn3D
<https://www.ncbi.nlm.nih.gov/structure>
Visualize a 3D biomolecular structure

Genetic Testing Registry (GTR)
<https://www.ncbi.nlm.nih.gov/gtr>
Identify a genetic test

ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar>
Learn about a clinical genetic variation

dbSNP
<https://www.ncbi.nlm.nih.gov/snp>
Learn about a short (<50nt) genetic variation

We worked with some cool things today, how do I learn more about using them?