Practical Genetics 101

April 5, 2025
Delta Hotel, Utica NY

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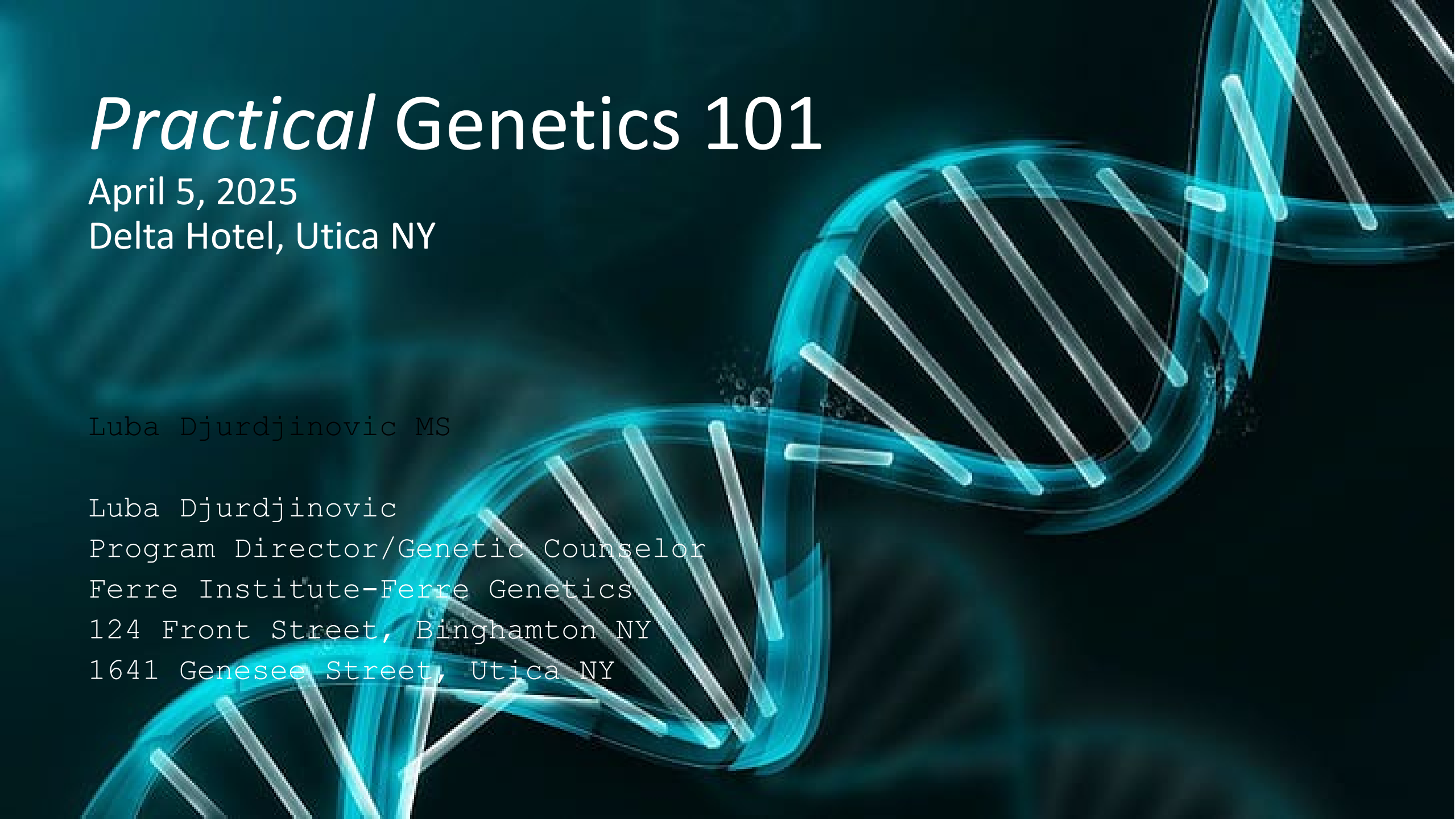


No financial disclosures

- Ferre Institute, Inc
- Established in Utica NY in 1974
-

Community-based genetic service

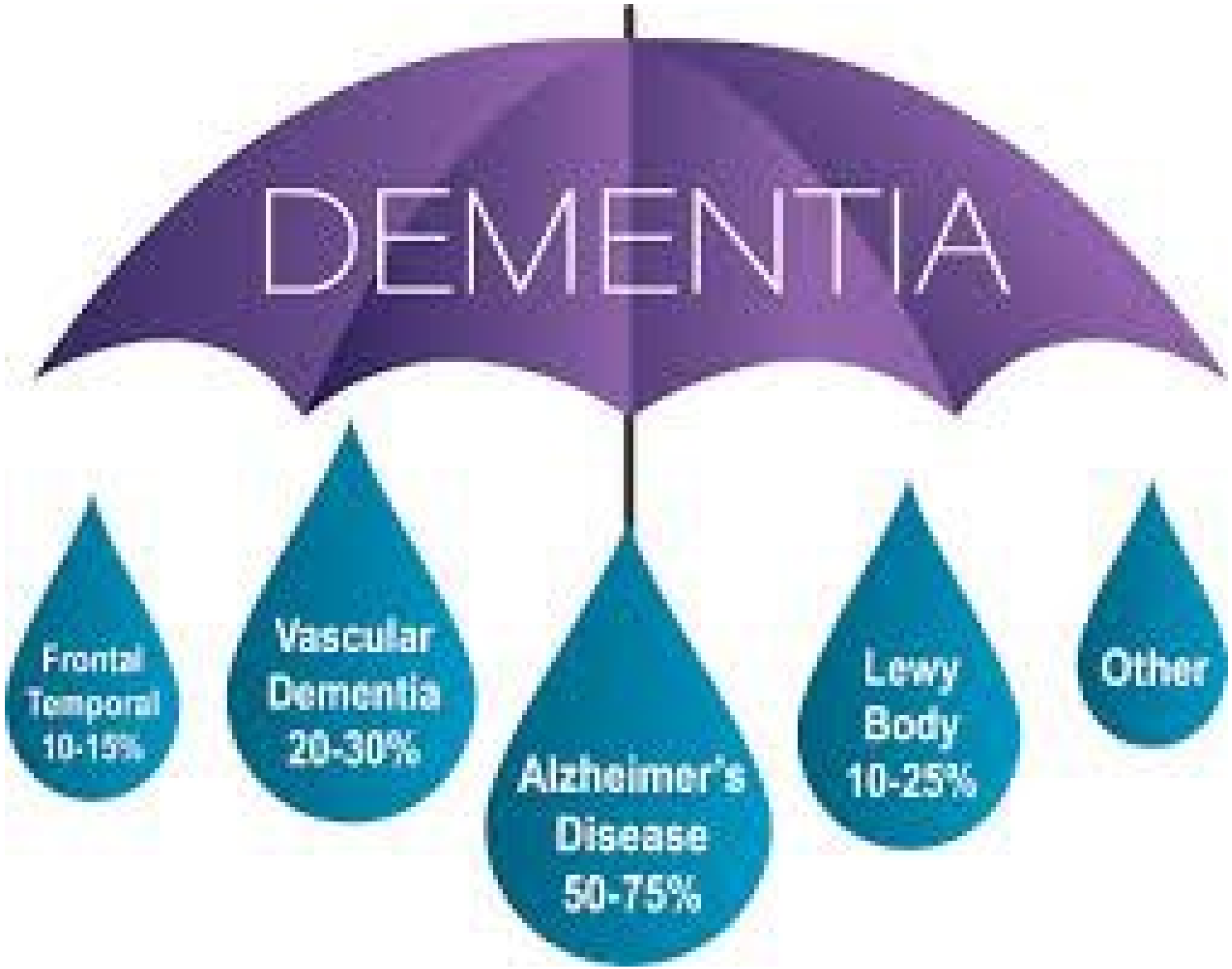
- We are committed to assuring access to genetic risk assessment for patients and their medical providers in the communities where they live and work
- We are committed to integrating genetic and genomic advances into daily medical practice

Genetic risk assessment and opportunities in primary care

- Consider genetic diagnoses in differential diagnosis
- Judge value of genetic information for health outcomes
- Offer balanced perspective on role of genetic tests


Marital Status
Married
Employment: (Type)
FAMILY HISTORY (Siblings, pare
High Blood Pressure
Anesthesia
No Diseases
Asthma
Arthritis
Cancer
Diabetes
Stroke

Family history



Case: Simon

- Simon’s is 52yrs and software developer. Recently noticed some forgetfulness
- Pursued 23&Me and learned he has the “the gene for Alzheimer”.
- Seeking treatment options

Featured In

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Special Feature	Easy To Use
Test type	["olester"]
Diagnostic Test Sample Type	Saliva

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Case

- Peggy is 58 yrs old and experiencing some difficulty with word retrieval
- Peggy's family history of dementia/Alzheimer Disease: Father was 60 years with initial symptoms and raised concern.
- Peggy's risk -20%-25% based on sporadic family history
- 95% of dementia/Alzheimer Disease after 60 years of age
- She would like testing- "I want to know".
- Is there a role for APOE testing?
- APOE variants maybe associated with late onset but not predictive

What do we know about APOE genotyping

- Three versions: e2, e3, or e4

e3: The most common allele, considered neutral in terms of AD risk.

e4: Carrying the e4 allele increases the risk of AD, and having two copies (e4/e4) increases the risk even more. Only 2% of US population have this combination.

e2: The e2 allele is associated with a lower risk of AD

APO e4 allele has about a 10%-20% chance of developing AD by age 75, whereas an *APO* e4 homozygote has about a 25%-35% risk.

Patients are seeking answers

- Genetic testing for the APOE gene will continue to be marketed.

Case

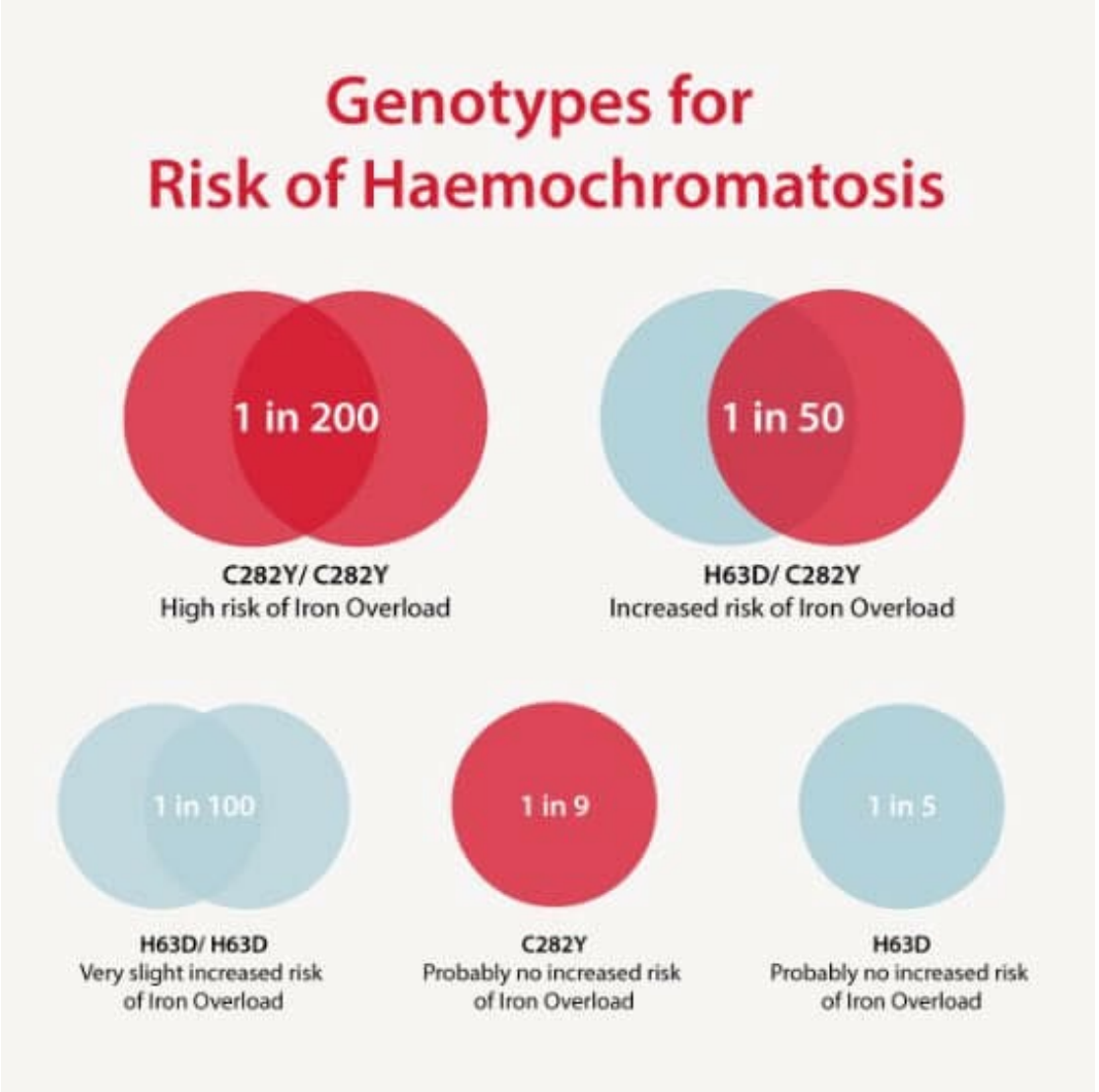
- Thomas is 41 years old, and his mother was diagnosed with hemochromatosis. She is requiring phlebotomy.
- Thomas is concerned.
- Hemochromatosis an AR disorder
- Results from increased intestinal iron absorption and increased recycling of iron derived from senescent red blood cells leading to elevated ferritin levels
- Thomas ferritin level is within normal range

HFE and prolonged ferritin levels

- cirrhosis of liver,
- changes in skin pigmentation,
- diabetes mellitus,
- a range of heart conditions
- men often experience impotence

- Ferritin is a non-specific test and can be elevated for reasons other than hemochromatosis.

- The HFE gene – two common variants
- "C282Y" or "H63D"
- It is estimated that 1 in 10 people of European background



Thomas

- Mother’s diagnosis and phlebotomy most likely linked to homozygous variants: **C282Y / C282Y**
- Thomas must inherit one **C282Y**
- Thomas’s genotype **C282Y/?**

- With a 1in 9 or 1 in 5 chance that Thomas may have inherited a second HFE variant….
- Testing was offered to Thomas
  - HFE gene "C282Y"
  - HFE gene "H63D"
  - Compound heterozygote
  - Risks…

Genotype/phenotype

C282Y / C282Y – Severe iron overload occurring in most if not all of the individuals.

C282Y / H63D – compound heterozygous Significant iron overload occurs in only 15% of these individuals.

H63D / H63D –Iron overload is unusual,

Case

- Ivan is 58 years old is frustrated with his unexpected difficultly in competing in long distance races. He is highly active with past marathons and more recently limiting himself to half-marathons.
- He runs 10 miles a day when possible- he is sales representative and is on the road a lot. He has experienced bilateral lower extremities-”falling asleep” after 2-3 hours driving.
- He is frustrated with the fatigue he is experiencing during training and after competing his daily run. Has had episodes of presyncope or syncope.
- Cardiology eval: moderated LVH/RVH, mild pulmonary hypertension associated with right atrial enlargement. Suspected cardiac amyloidosis
- Note: Father had an MI at 65 years of age-no other history.

Hereditary Transthyretin Amyloidosis (hATTR)

- Transthyretin (TTR) is a transport protein for retinol and thyroxine
  - The amyloidosis results from abnormal “clumping” of the TTR protein.
- Clinical findings. Slowly progressive sensorimotor and/or autonomic neuropathy that is frequently
- accompanied by one or more of the following:
- • Cardiac conduction blocks
- • Cardiomyopathy
- • Nephropathy
- • Vitreous opacities
- • Glaucoma

Genotype/phenotype

- Over 150 reported pathogenic variants
- Ivan's result: p.Thr80Ala- associated with familial cardiomyopathy
- p.Val50Met is also one of the most common pathogenic variants worldwide.

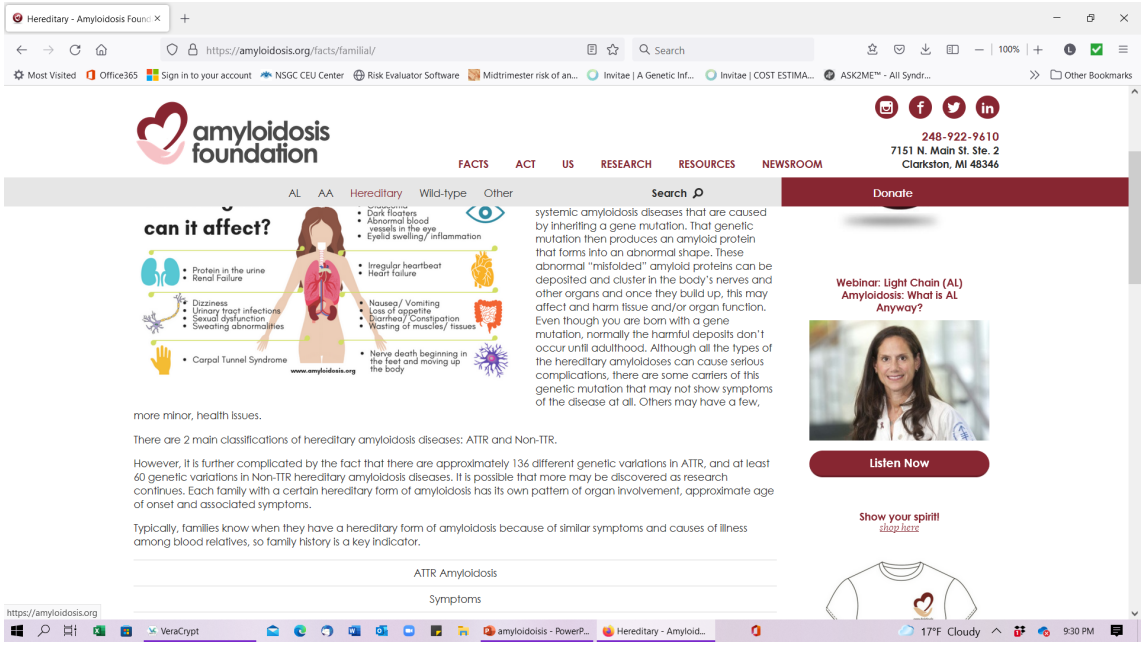
p.Val142Ile in the African American population is 3.0%-3.9%; late-onset cardiac amyloidosis. Note: cardiac amyloidosis x four times more common among Blacks than Whites

Genotype/phenotype

Common features	p.Val50Met	Other TTR variants
Sensory neuropathy	84%	60%
Motor neuropathy	52%	29%
Autonomic dysfunction	60%	45%
GI issues	47%	33%
Cardiac symptoms	39%	59%

Treatment

Penetrance is not 100% with some being symptom free till late age

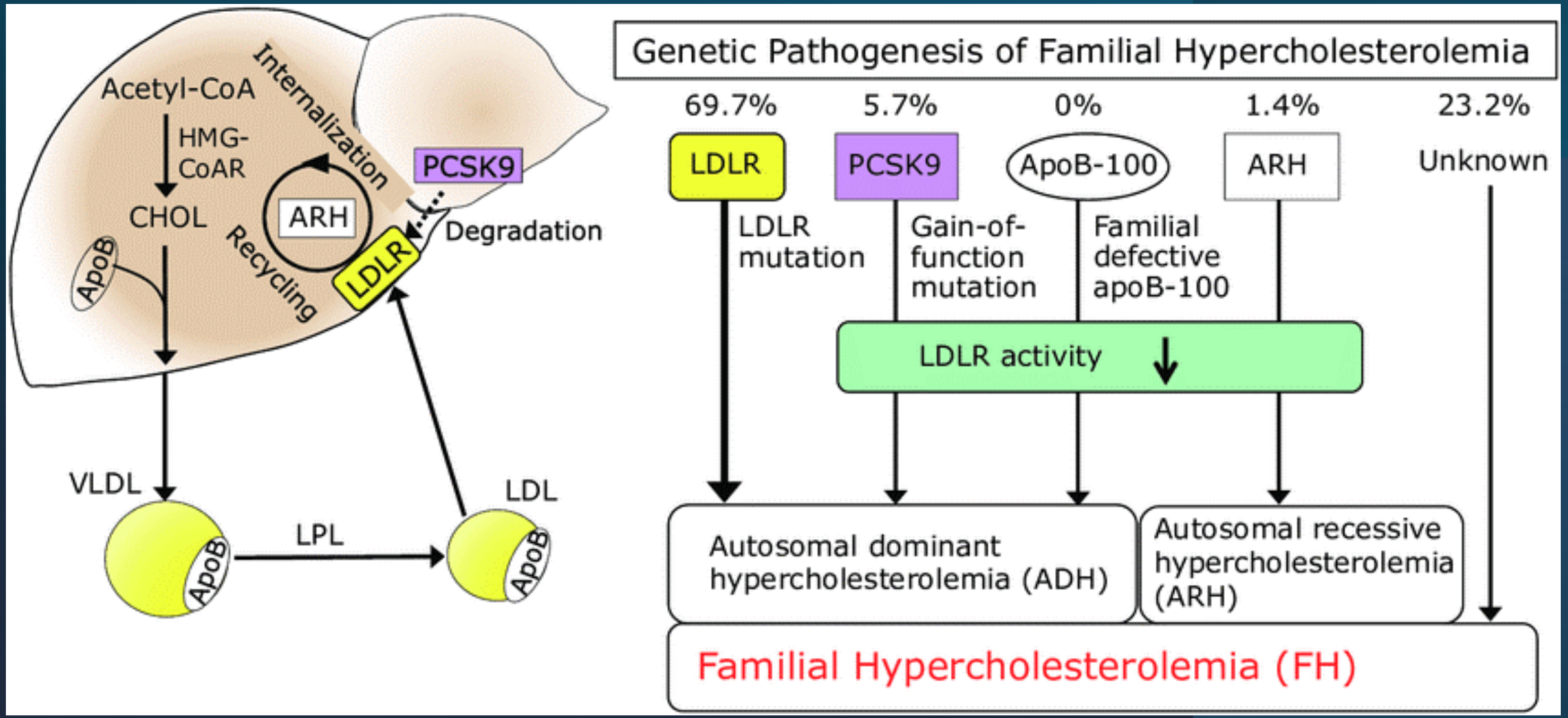


Case

- Tina is 52 years old and followed for her elevated LDL levels.
- After 16-month dietary modifications and exercise routine 4 times week , there was minor improvement.

- Tina was offered a statin to decrease her LDL levels. She declined based on her father’s and paternal aunt’s frustration with use of statins with small improvement and their reported side effects.

- She was referred to evaluate the family cholesterol/ LDL history and consider genetic testing.
- Genetic testing options: LDLR gene are the most common cause of FH


Acetyl-CoA
HMG-CoAR
CHOL
ApoB
VLDL
Internalization
ARH
Recycling
PCSK9
LDLR
Degradation
LPL
LDL
ApoB
ApoB
Genetic Pathogenesis of Familial Hypercholesterolemia
69.7%
5.7%
0%
1.4%
23.2%
LDLR
PCSK9
ApoB-100
ARH
Unknown
LDLR mutation
Gain-of-function mutation
Familial defective apoB-100
LDLR activity
Autosomal dominant hypercholesterolemia (ADH)
Autosomal recessive hypercholesterolemia (ARH)
Familial Hypercholesterolemia (FH)

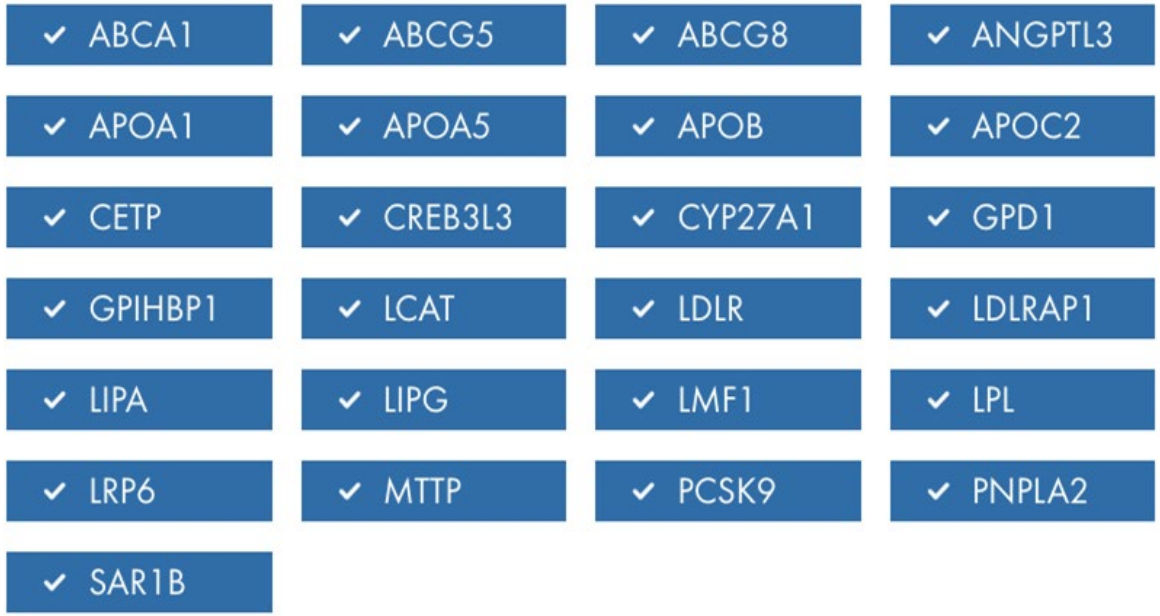
Result informed Tina treatment approach

- Test result
- APOB c.10580G>A (p.Arg3527Gln)/ heterozygous- pathogenic
  - Note: These mutations in this gene are family specific

- The APOB gene is associated with autosomal dominant familial hypercholesterolemia (FH)
- Statin will reduce LDL levels- some individuals still will have elevated APOB levels and a residual risk for a cardiovascular episode.
- Some may benefit from an apolipoprotein B synthesis inhibitor

25 genes linked to hypercholesterolemia and lipidemia

- Three most common genes linked to Familial Hypercholesterolemia: LDLR, PCSK, APOB
- Comprehensive lipidemia panels- may be helpful



Case

Mark is 28 years old

His sister is 32 years old has elevated cholesterol levels and just experienced a cardiac arrest.

Risk assessment and testing recommendation

- Sister should consider genetic testing
- Mark's sister declined genetic testing
- Mark has an elevated LDL and he is frustrated as he has recently become a vegan after his sister's event

Lipidemia panel

Pathogenic variant identified in ABCG8

Pathogenic variant in ABCG5

Testing result: ABCG8/ABCG5

- The ABCG8 gene is associated with AR -sitosterolemia leading to hypercholesterolemia due to increased absorption of plant sterols and associated with premature atherosclerosis, coronary artery disease, myocardial infarction.
- Plant-based foods with high sterol levels sesame oil, wheat germ oil, mayonnaise, pistachio nuts, olive oil, sage, oregano, thyme, paprika, cocoa butter oil, almond butter, avocado, macadamia nuts, broccoli, red onion, carrot, corn and other vegetables.
- Sitosterolemia is linked to variants in the ABCG5 or ABCG8 genes. Mark is a compound heterozygote for ABCG5/ABCG8 gene variants that links him to sitosterolemia.
- Management Dietary restriction of food high in sterols. Medication that inhibits the absorption of cholesterol and plant sterols in the intestine and sometimes addition of bile acid sequestrants

What to do with requests for Ehlers-Danlos Syndromes (EDS) testing

A group of rare inherited conditions that affect connective tissue/ overlapping autoimmune symptoms

Symptoms of Classic EDS

- Joint hypermobility
- Loose joints that dislocate easily
- Stretchy velvety skin
- Fragile skin that can split easily
- Wounds that are slow to heal
- Hernias and organ prolapse

➲ There are 13 different types of EDS that vary depending on genetics and symptoms

Genes that are linked to EDS

- COL1A1
- COL1A2
- COL1A3
- COL5A1
- COL5A2
- COL3A1
- ZNF469
- SLC39A13
- CHST14
- COL12A1
- C1R
- C1S
- ADAMTS2
- PLOD1
- TNXB

➲ There is currently no genetic test for hypermobile EDS. A diagnosis is only based on medical history and physical exam

Many tests –many choices

GeneticTesting Registry (GTR) was created in 2008

200 laboratories 37,124 current clinical tests

29 laboratories performed whole exome sequencing (WES)

17 laboratories performed whole genome sequencing (WGS)

Clinical application of genetic test results

Positive

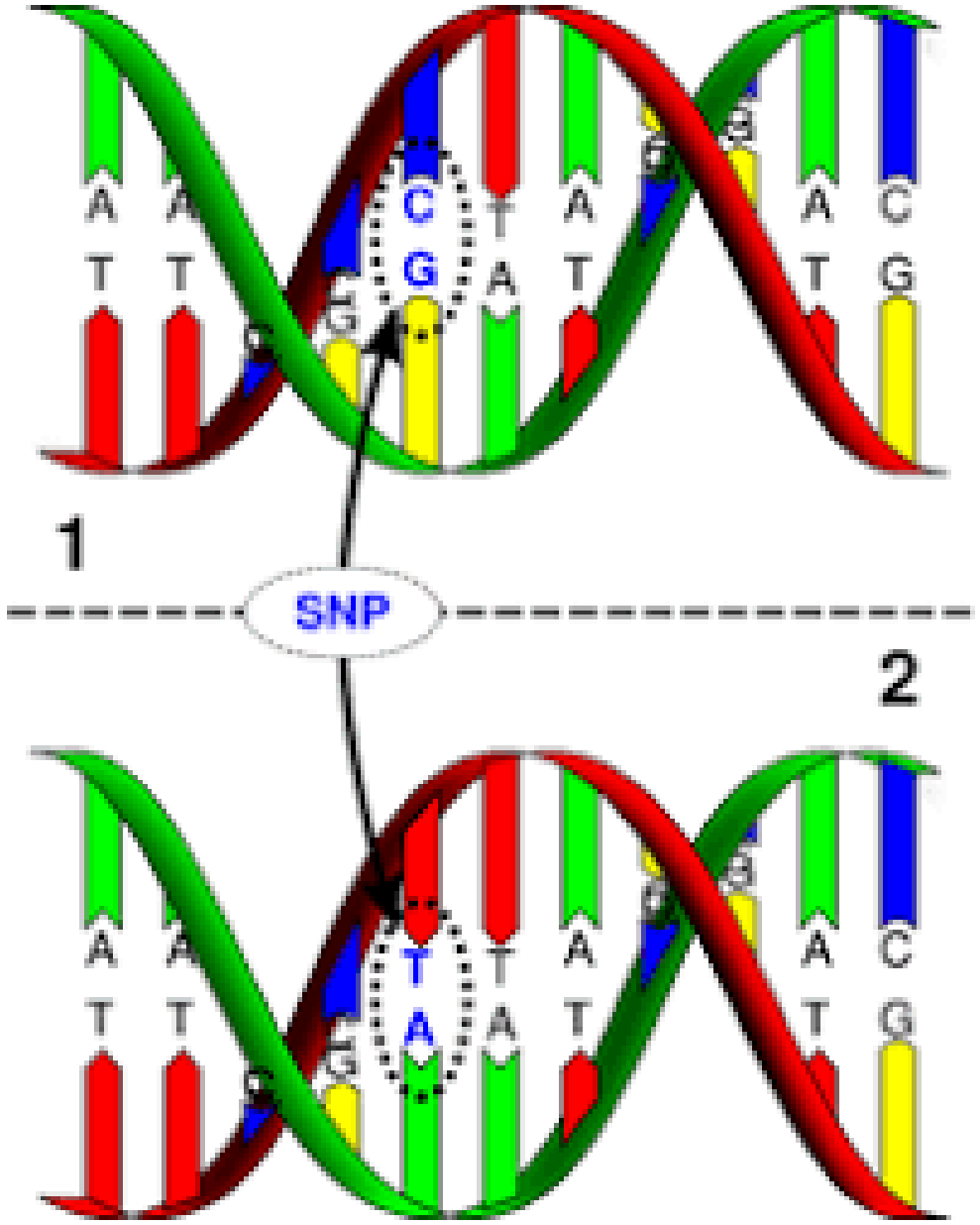
- Management guidelines
- Edibility for research
- Eligibility for clinical trials

Negative

- Negative test results does not eliminate a clinical diagnosis

Variants of Uncertain Significance (VUS)

- Temporary evaluation of identified variant


1
SNP
2

Understanding variants of uncertain significance in clinical practice

Cardiac gene testing

- Kaitlyn is 32 years old had a routine pre-surgical EKG reported a Long QT interval. 10 years prior during your pregnancy a similar finding and 5 years ago, she was hospitalized for an unexplained fainting episode with no EKG findings.
- Father has been hospitalized several times for unexplained fainting episodes.

Cancer gene testing

- Beth breast cancer at 49 years of age.
- Her mother had breast cancer diagnosis at 56 and maternal aunt was 69 years old.

VUS test results-

Kaitlyn Test result

- Test: CACNA1C CALM1 CALM2 CALM3 KCNE1 KCNH2 KCNJ2 KCNQ1 SCN5A TRDN
- KCNQ1 coding variation c.1861G>A
  - Gene linked to Loing QT
- SCN10A coding variation c. 40C>T.
  - Gene linked to Brugada

Beth test results

- APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM FH, FLCN, HOXB13, MET, MLH1, MSH2, MSH6, MBD4, MSH3, MUTYH, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, TSC1, TSC2 and VHL
- CHEK2 gene Gain (exon 2-8)

Role of family testing

To identify who in the family maybe at risk

To help learn more about a variant of uncertain significance and is associated with affected family members in the family.

Selecting a testing lab

- Some test are best ordered from a reference lab: Quest Diagnositics, LabCorp, ARUP, Mayo
- Chromosome testing, thrombophilia testing (i.e. Factor V Leiden), hemochromatosis common variants
- Specialty laboratories for Cancer predisposition syndromes, cardiovascular predisposition, neuromuscular disorders and rare disorders
- NYS approved (if not, must submit NYS non-permit lab request to Wadsworth)
- Variant re-classification protocols
- Patient assistance options
- Family testing option for positive findings

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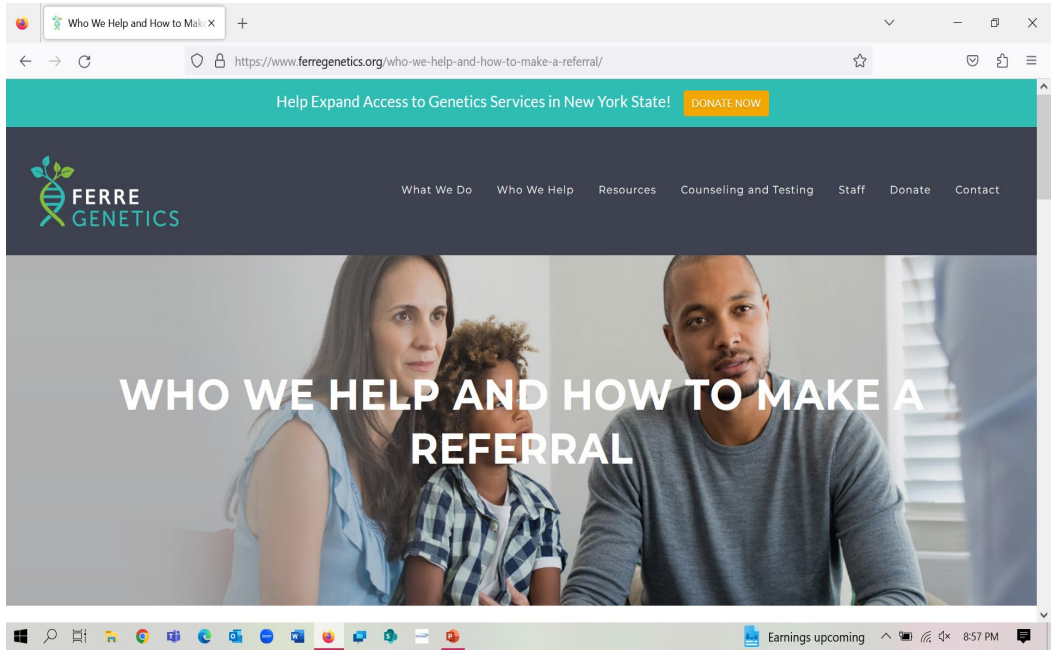

Our catchment area and offices


Thank you!
Questions?