Common Genetics Questions

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VTC | Virginia Tech Carilion School of Medicine and Research Institute

Carilion Clinic

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Learning Objectives

- Recognize common clinical situations for which genetic counseling and/or genetic testing may be indicated.
- Locate appropriate Internet genetics resources for professionals and patients.
- Give examples of recent advances in genetic testing.

Talk Overview

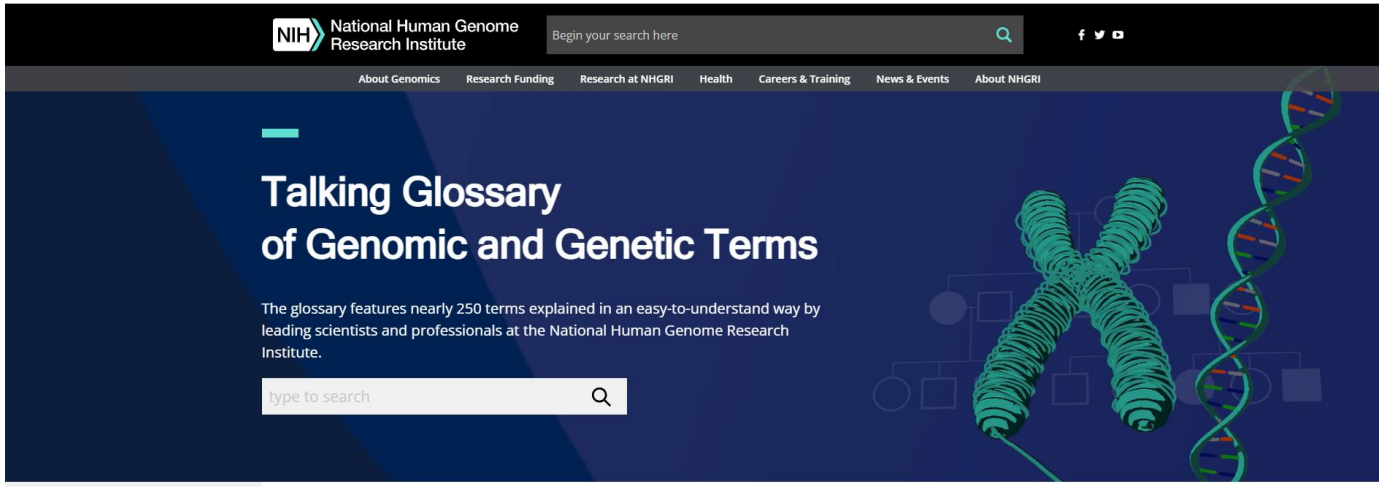
- Genetic testing in 2023: easier than ever
- Cardiology questions
- Neurology questions
- Direct-to-consumer genetic testing questions
- Pharmacogenetic questions
- New technology questions

Genetics Services at Carilion Clinic

- Cancer Genetics
- Maternal Fetal Medicine
- Clinical Genetics (my office) “Peds Genetics Electric Rd”

My Favorite Genetics Resources

MedlinePlus
Trusted Health Information for You



Genetic Testing in 2023: Easier than Ever

- Most patients will not pay more than $250 for common cardiology and neurology genetic tests
- Patients with Medicaid and Medicare typically pay $0
- Buccal swab testing available
- Results in a few weeks
- Insurance only covers genetic testing of the subscriber and enrolled dependents

Genetic Counseling Should Occur Before- and After- Genetic Testing

- The decision to proceed with genetic testing requires discussion regarding the clinical use of genetic information to be obtained for both the proband and family members
- As well as consideration of the implications of positive genotyping on:
  - psychological outcome,
  - finances,
  - employment,
  - disability,
  - and life insurance

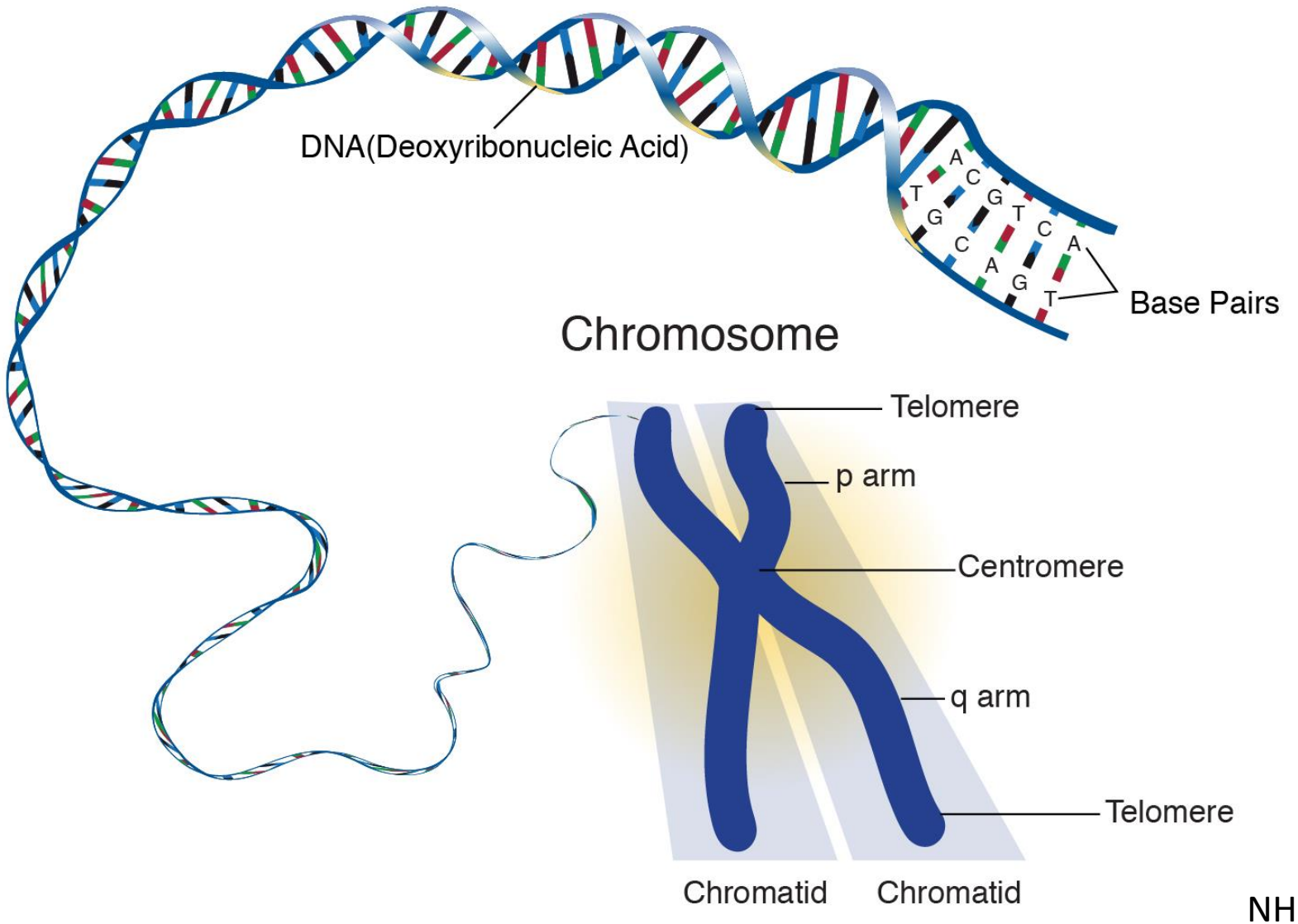
2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Genetic Counseling Should Occur Before- and After- Genetic Testing

- Challenges include:
- Balancing privacy of health care information for the proband with the “right to know” for family members
- Appropriate communication of information to all potentially affected family members, given family dynamics, geographic proximity, and access to health care
- A combined approach of genetic counseling with medical guidance may appropriately individualize the decision to proceed with genetic testing

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Chromosomes and Genes



NHGRI Talking Glossary

What is Targeted Testing?

Panel

Gene 1: ATGCATCGATGCATCGATGC

Gene 2: TATGCATGCATGCATGCATG

Gene 3: ATGCATCGCTGCATGCATGC

Gene 4: GCATGCATGCATGCATGCTT

Targeted Test

Gene 1: ATGCATCGATGCATCGATGC

Gene 2: TATGCATGCATGCATGCATG

Gene 3: ATGCATCGCTGCATGCATGC

Gene 4: GCATGCATGCATGCATGCTT

What if your patient requests targeted testing for her dad's mutation?

- Try to get a copy of her dad's actual test report. He may have to sign a ROI for his doctor or hospital to send it to you.
- Expect that some people will misinterpret their test results. The dad could have a VUS but he might not be medically sophisticated enough to understand this.

Insurance

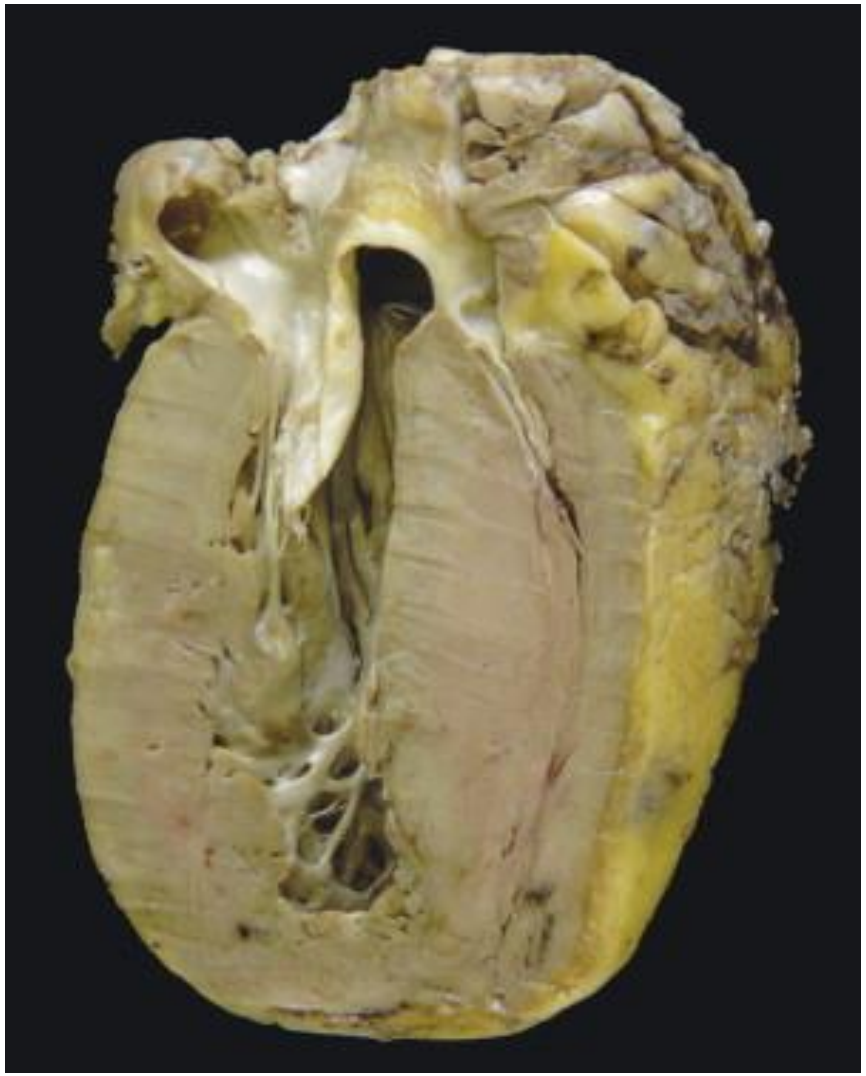
- Insurance typically covers genetic testing for the subscriber when the results are expected to change the medical management
- Provider mindset: “What is wrong with my patient?”
- Insurance mindset: “How will this test result affect your management plan?”
- Insurance does not cover genetic testing of relatives or DNA banking

Cardiology Questions

Cardiology Questions

- Hypertrophic cardiomyopathy
- Long QT syndrome
- Thoracic aortic dilatation

Hypertrophic Cardiomyopathy

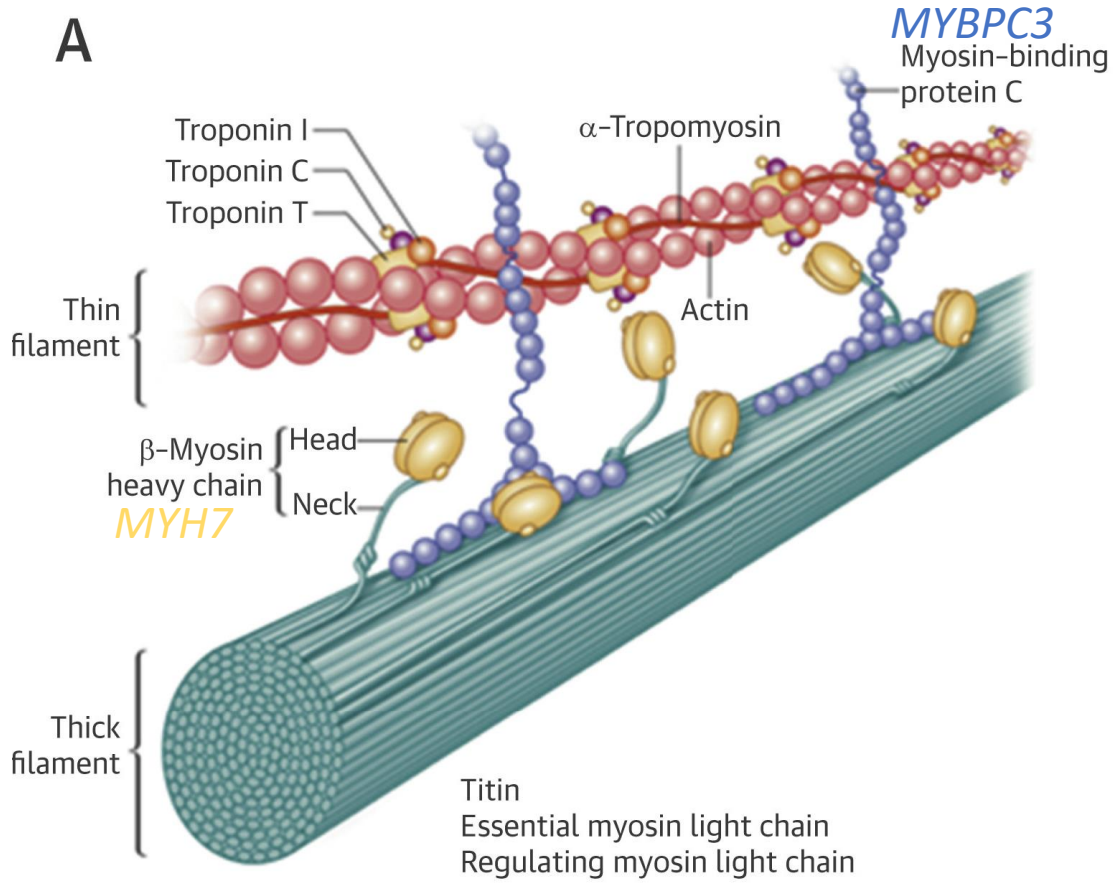


Photograph of hypertrophic cardiomyopathy with thickened L ventricle.
From “High-Yield Thoracic Pathology” 1st ed, 2012

Top 10 Take-Home Messages– 2020 AHA/ACC Hypertrophic Cardiomyopathy Guideline

3. “Counseling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference. As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years.”

Genetics of Hypertrophic Cardiomyopathy



- Population incidence of HCM is estimated at 1:500
- 9 definitive genes plus others
- A study of 2,912 nonsyndromic unrelated HCM probands identified mutations in 32% and inconclusive results in 15% of patients
- 80% of mutations were either found in *MYBPC3* or *MYH7*

Semsarian C, Ingles J, et al (2015)

Alfares AA, Kelly MA, et al (2015)

Screening with ECG and Echocardiography in Asymptomatic Family Members

Age of 1st degree relative	Screen initiation age	Repeat ECG, echo
Children and adolescents from genotype-positive families & families with early-onset disease	At the time HCM is diagnosed in another family member	Every 1-2 yr
All other children and adolescents	At any time after HCM is diagnosed in a family member but no later than puberty	Every 2-3 yr
Adults	At the time HCM is diagnosed in another family member	Every 3-5 yr

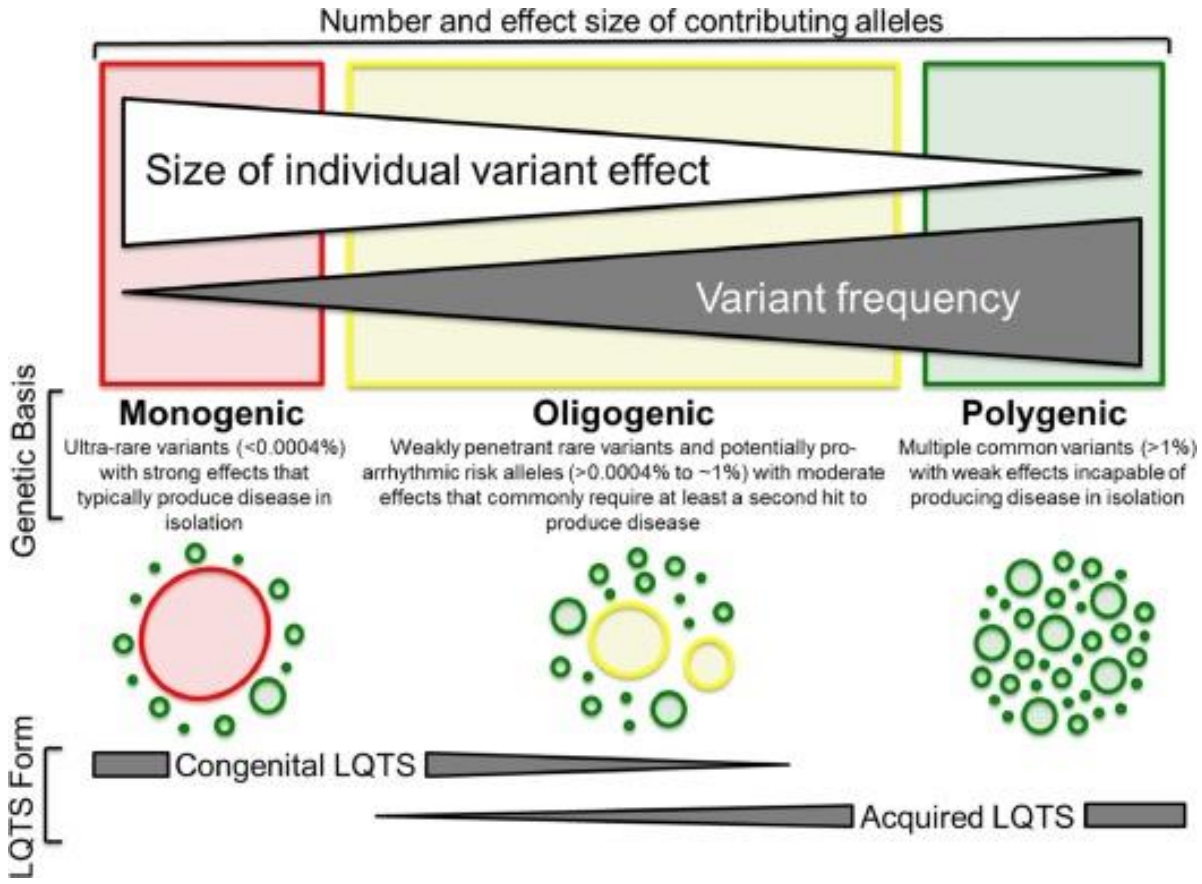
2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Other syndromic causes of LVH mimicking HCM

Typical Presentation Age	Possible Etiology
School age & adolescence	Friedrich ataxia, Danon disease, Mitochondrial disease
Adulthood	Fabry disease, Glycogen storage disease, Infiltrative disorders such as amyloidosis and hemochromatosis

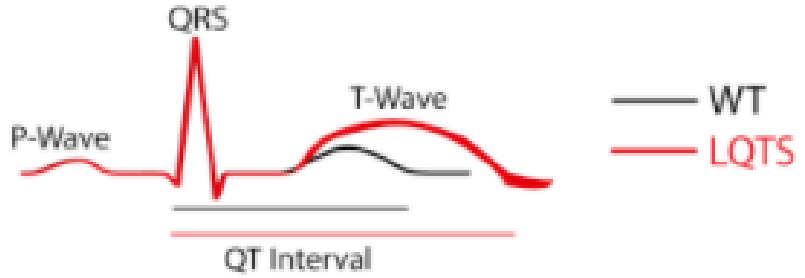
2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

LQTS and channelopathies



Giudicessi JR, Wilde AAM, et al. (2018)

ECG



Ponce-Balbuena D & Deschênes I (2021)

Genetic LQTS

Phenotype	Genes
Definitive non-syndromic LQTS	*KNCQ1* (LQT1): swimming *KCNH2* (LQT2): alarm clocks *SCN5A* (LQT3): sleep
Moderate LQTS-susceptibility genes	(lists 4)
Syndromic LQTS	*CACNA1C* (Timothy): syndactyly *KCNQ1* & *KCNE1* (Jervell Lange-Nielsen): deafness

Adapted from Giudicessi JR, Wilde AAM, et al. (2018)

Marfan syndrome and related disorders with aortic dilatation

Revised Ghent Nosology for Marfan syndrome (when no fam hx)

- Aortic root enlargement (Z-score ≥2.0 in adults) and one of the following:
  - Ectopia lentis
  - A pathogenic *FBN1* (fibrillin) mutation
  - A systemic score ≥7

Loeys et al, 2010

Physical Features of Marfan Syndrome

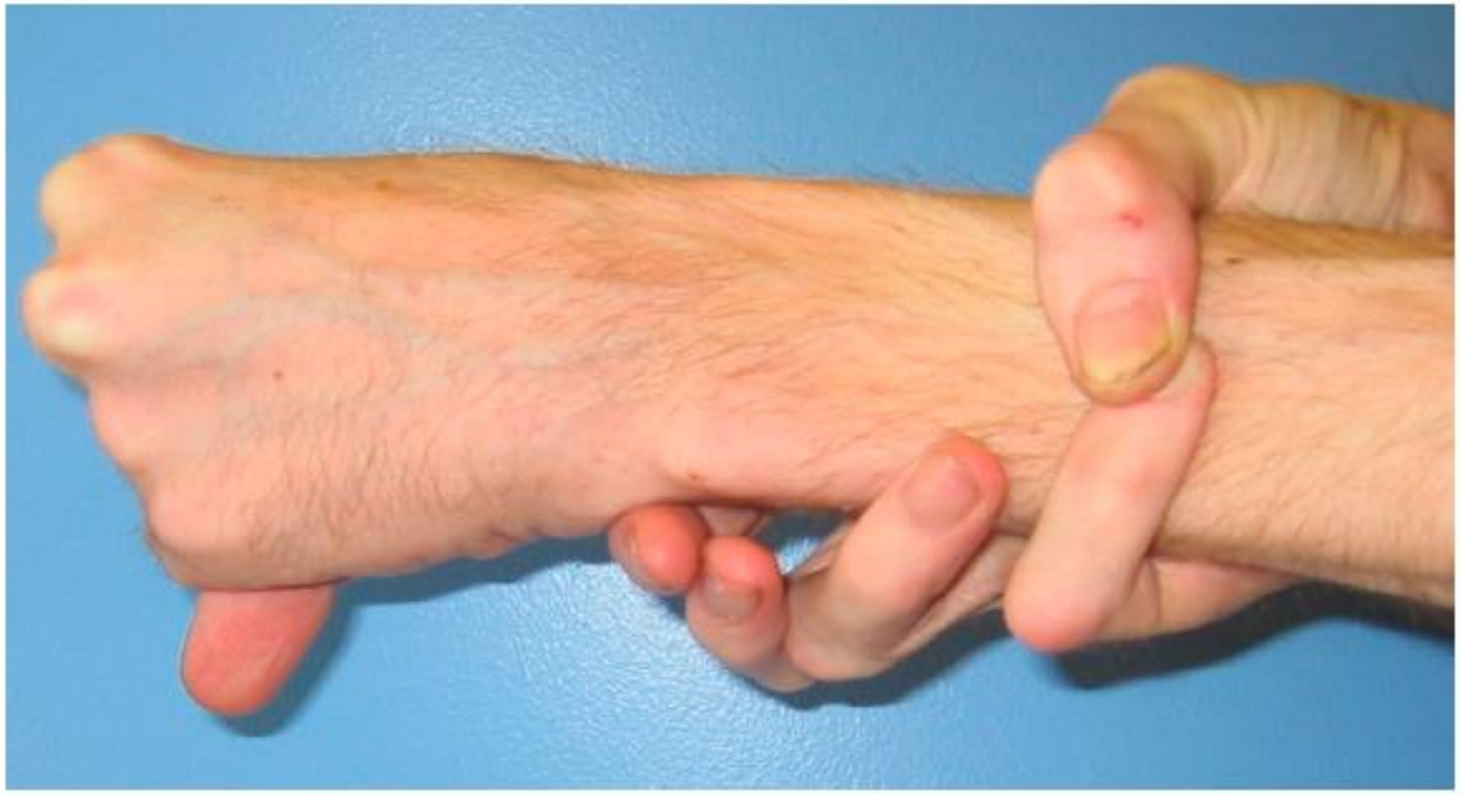


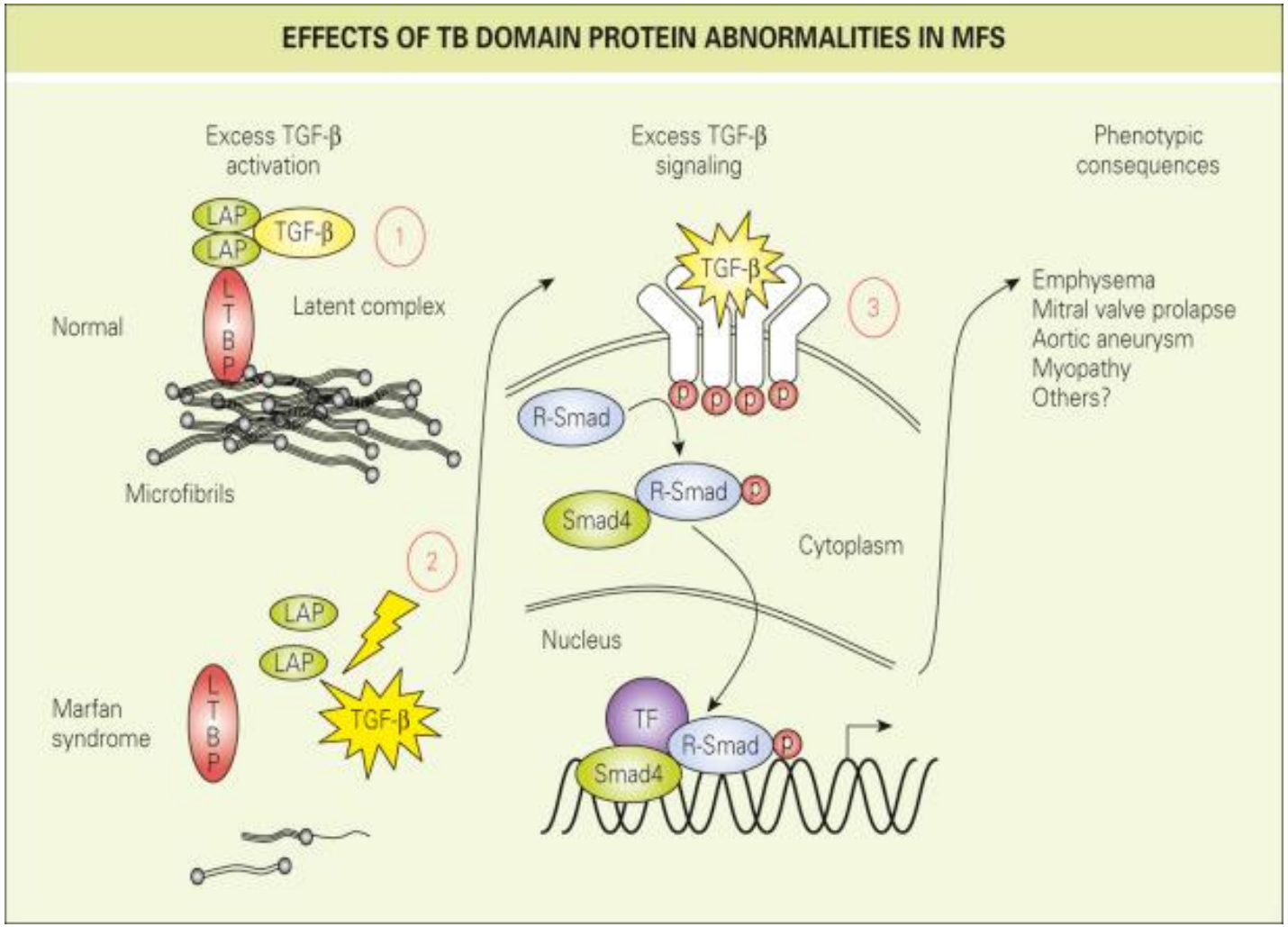
Fig. 1
Positive thumb and wrist signs.

Sponseller et al, 2010

Mechanism of Disease in Marfan Syndrome

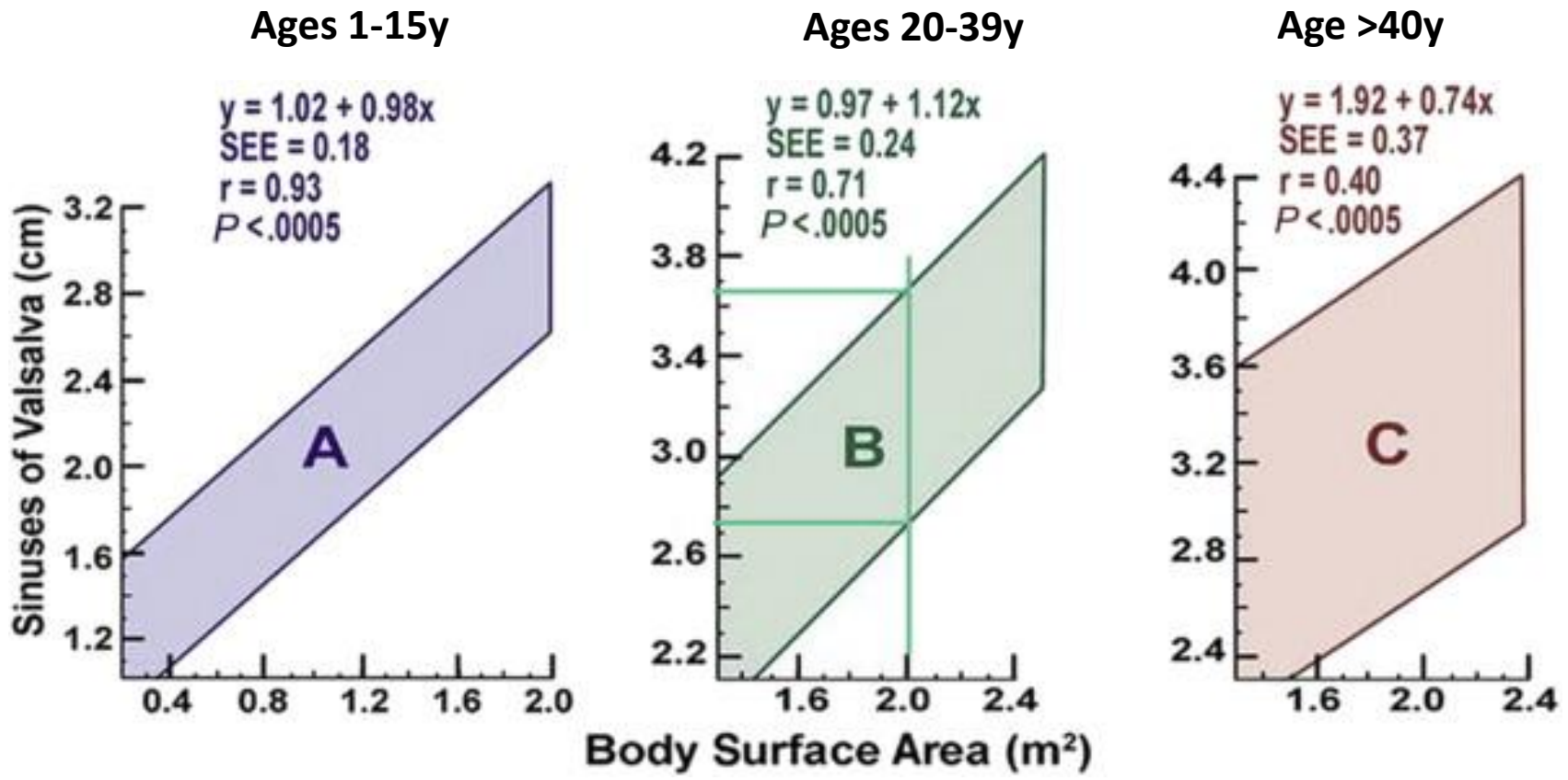
- Used to be thought of as an intrinsic abnormality of connective tissue but this did not explain other findings in MS such as over-growth of bones.
- It is now known the fibrillin plays an important role in regulating Transforming Growth Factor Beta (TGF-b)
- TGF-b causes apoptosis, cellular disarray, fragmentation of elastic lamellae, inflammation

Marfan syndrome mutations cause increased concentrations of TGF-b



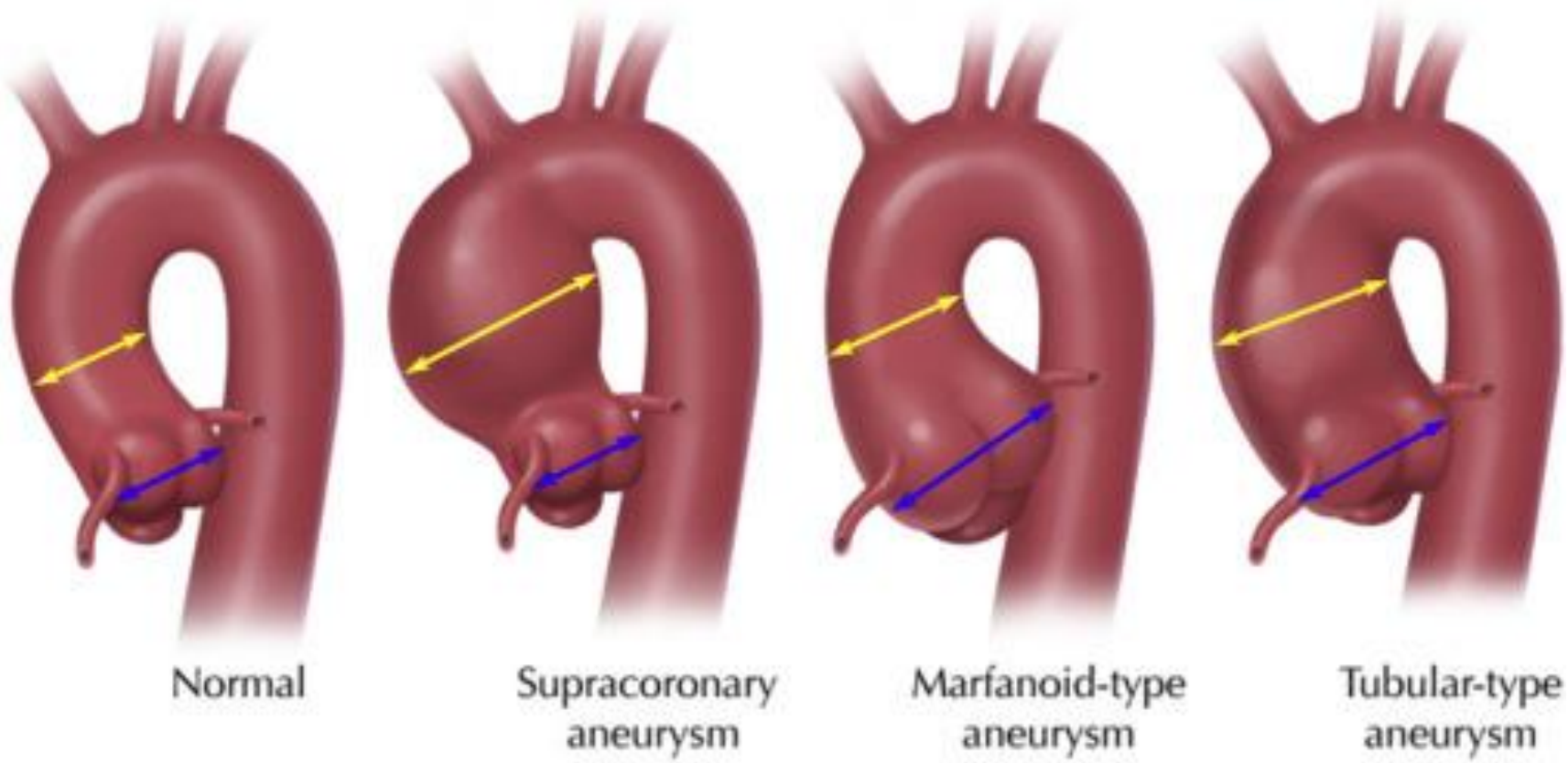
Ramirez & Dietz (2007)

Age and BSA-based Nomograms for Aortic Root Measurement



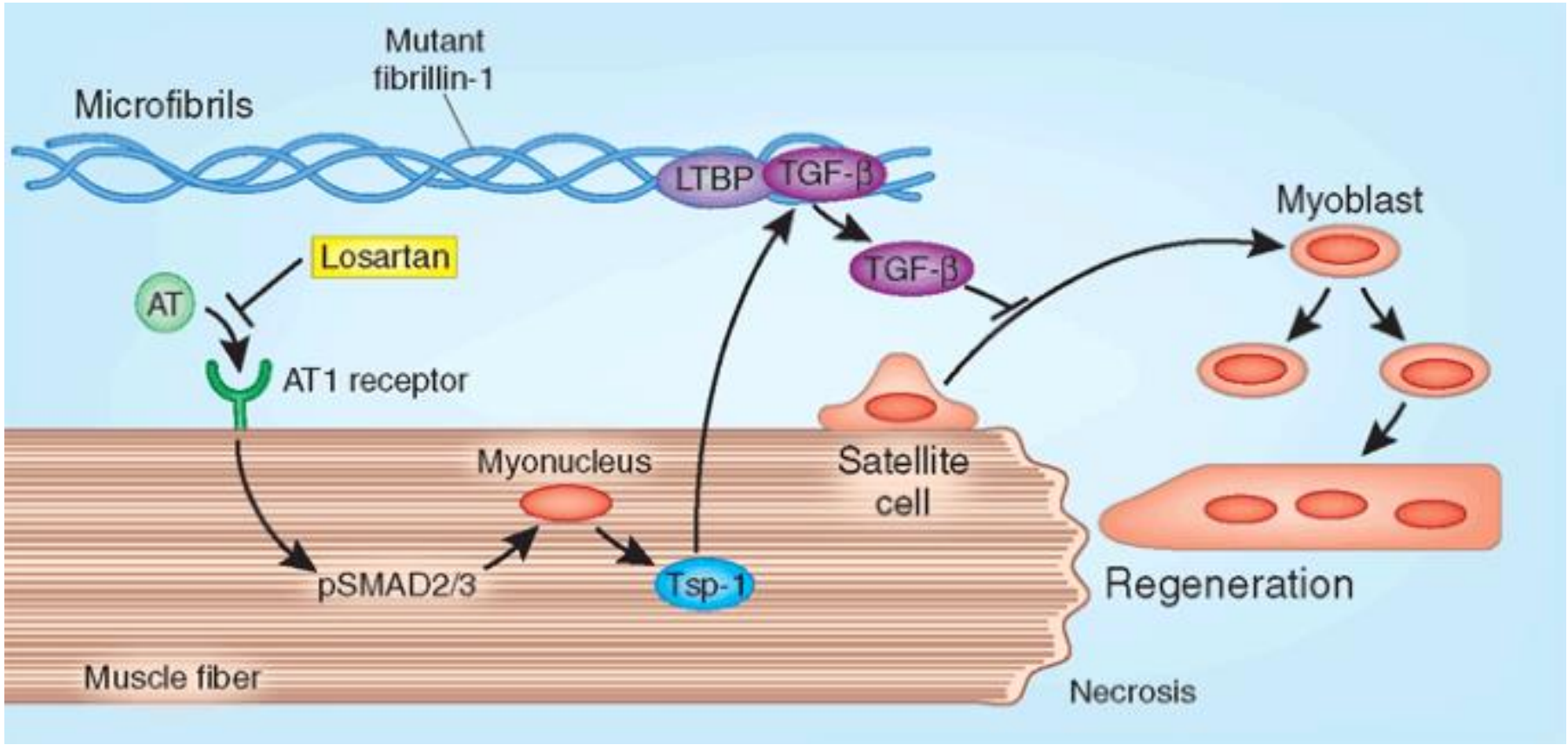
Goldstein SA et al, 2015

Patterns of Ascending Aortic Aneurysm



Elefteriades et al, 2020

Losartan (ARB) works in the biochemical pathway to prevent aortic dilatation

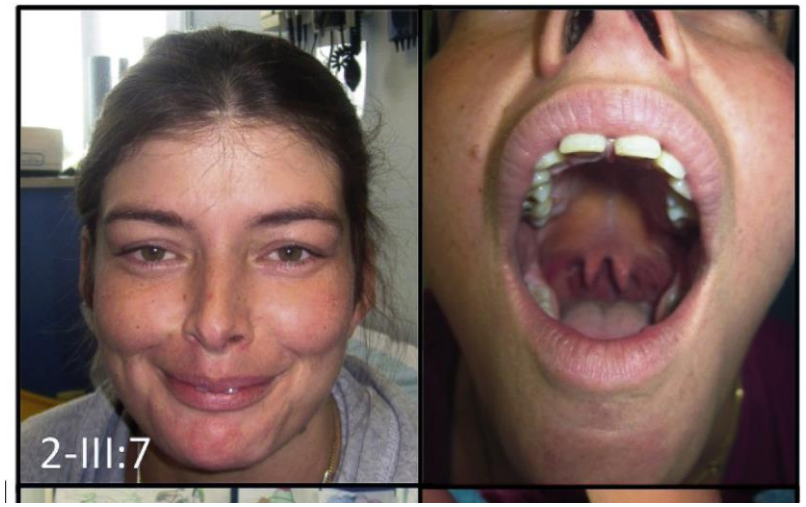


Chamberlain JS (2007)

Losartan (ARB) works in the biochemical pathway to prevent aortic dilatation

- Meta-analysis (Elbadawy A et al, 2019) of 7 randomized trials found that losartan was associated with a significantly smaller change in aortic root diameter in patients with Marfan syndrome
- Meta-analysis (Al-Abcha A et al, 2020) found that ARBs added to beta blockers also appear to slow aortic root dilatation compared to beta blocker therapy alone

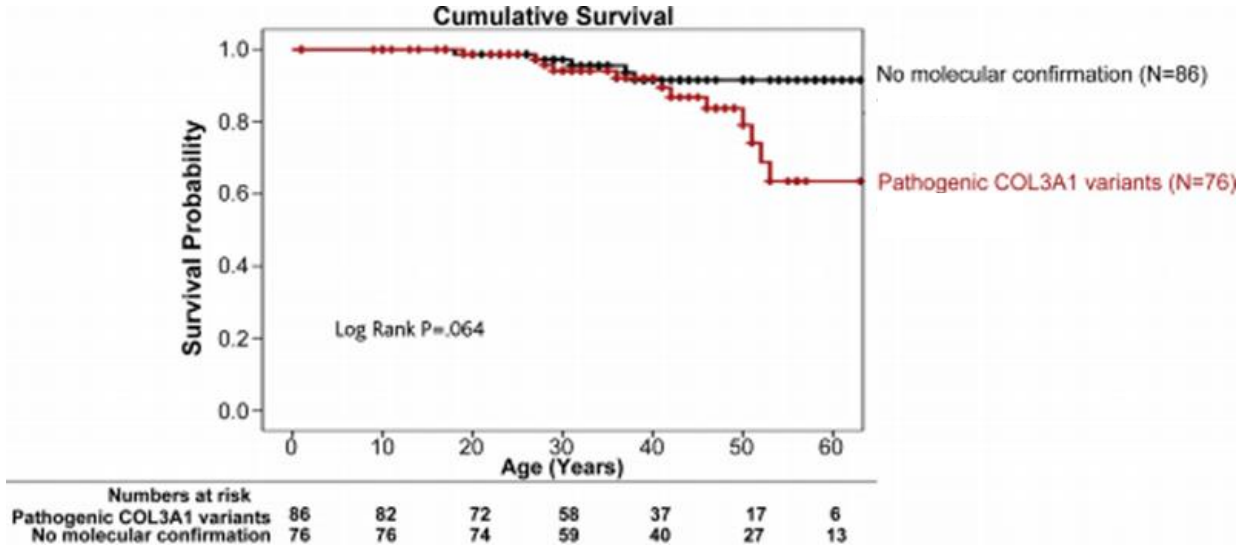
Loeys-Dietz syndrome



Patient with *TGFB3* mutation, widely spaced eyes, and bifid uvula.
Bertoli-Avella AM, Gillis E (2015)

- Similar to Marfan syndrome because of risk of thoracic aortic dilatation and dissection
- Six genes known
- Patients may also have cleft palate and/or clubfoot
- The thoracic aortic disease tends to be more aggressive, and repair at smaller diameter is recommended

Vascular Ehlers-Danlos syndrome



VEDS is a rare subtype of EDS.
The major diagnostic criteria for vEDS include:

- arterial rupture
- intestinal rupture
- uterine rupture during pregnancy

The typical primary care patient who requests an EDS evaluation is asking about hypermobile EDS, not vEDS.

Shalhub S, Byers PH, et al (2020)

Heritable Thoracic Aortic Disease (HTAD)

- At least 10%, and up to 20%, of nonsyndromic individuals with thoracic aortic aneurysm have a first degree family member with thoracic aortic aneurysm
- Approximately 20% of families with HTAD have a mutation in *ACTA2*. Another 10% of families with HTAD have mutations in other aneurysm genes.
- “Nonsyndromic” TAD should prompt screening of family members

Milewicz DM, Regalado E. (2017)

2022 ACC/AHA Thoracic Aneurysm Genetic Testing Recommendations

Patients with thoracic aortic disease and...

- Features of Marfan syndrome, Loeys-Dietz syndrome, or vascular EDS
- Patients <60 yrs of age
- Patients >60 yrs of age with positive family history

Surgical Repair of Aortic Aneurysm

Condition	Aortic diameter
Nonsyndromic patients	5.5 cm
Loeys-Dietz syndrome	4.5 cm
Marfan syndrome	5 cm
Woman with Marfan syndrome contemplating pregnancy	4.5 cm
HTAD High risk HTAD patients under selected circumstances	5 cm 4.5 cm

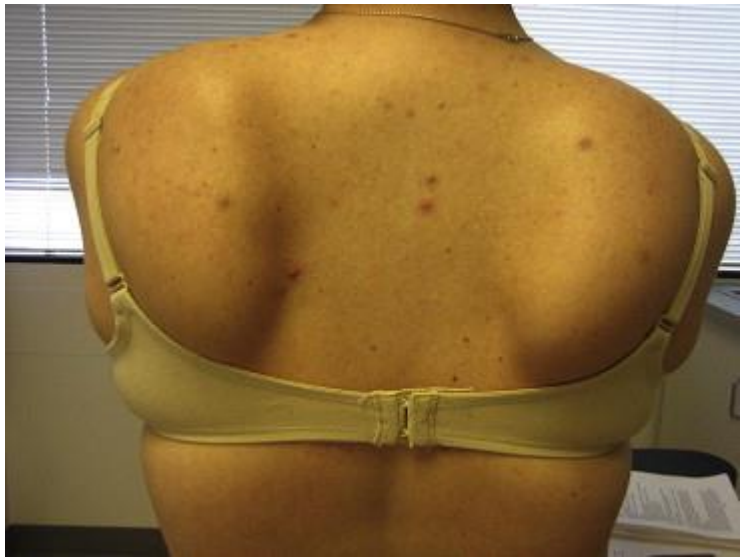
2022 Guidelines for the diagnosis and management of patients with thoracic aortic disease

Neurology Questions

Neurology Questions

- Limb-girdle muscular dystrophy
- Charcot-Marie-Tooth disease

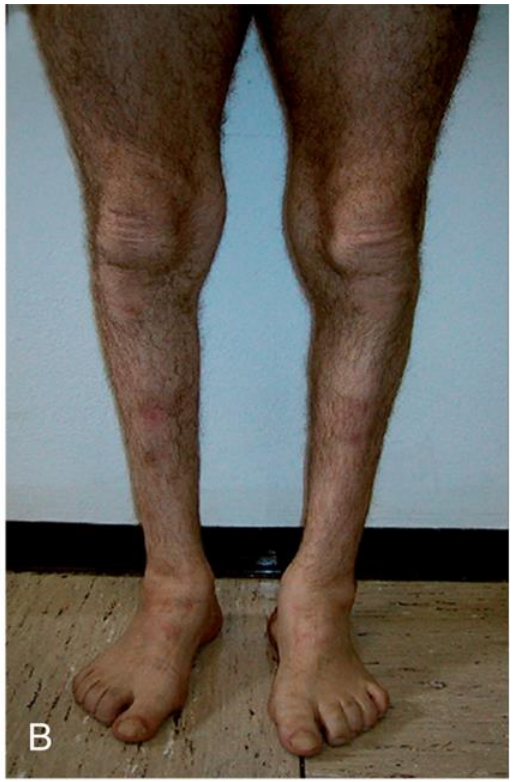
Limb-Girdle Muscular Dystrophy

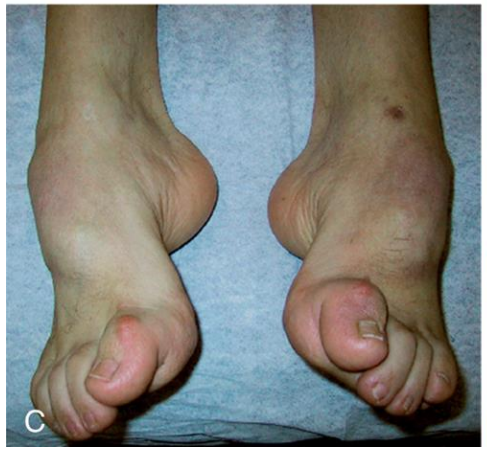


Weakness of scapular stabilizers in a patient with a CAPN3 mutation (LGMD2A) from Rosales XQ et al (2012).

- The identification of these dystrophies through genetic testing will not only inform long-term prognosis but will also assist in directing care more efficiently. For example, some dystrophies involve the cardiorespiratory system.
- Precise identification of the disorder also eliminates the need for repeated testing for an acquired, treatable disorder such as an inflammatory myopathy.
- The costs of continued investigation for other causes and the risks and expenses associated with empiric trials of immunosuppressants make a strong case for establishing a genetic diagnosis, which often provides patients a sense of closure. (Narayanswami et al, 2014)

Charcot-Marie-Tooth Disease





Ferri's Clinical Advisor

Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies... Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/ HNPP deletion, GJB1, and MFN2 mutation screening. (AAN Practice Parameter, 2009)

Direct-to-consumer testing questions

Direct-to-Consumer Genetic testing ACMG Practice Guideline (2016)

- The consumer should be fully informed regarding what the test can and cannot say about his or her health. Many direct-to-consumer genetic tests do not give a definitive answer regarding whether an individual will develop a given condition but instead only provide information about the risk or probability of developing a disease. This information needs to be... communicated to the consumer... in an understandable fashion that is linguistically and culturally appropriate.

Direct-to-Consumer Genetic testing ACMG Practice Guideline (2016)

- The clinical testing laboratory must be accredited by the CLIA (Clinical Laboratory Improvement Amendments) Program, the state, and/or other applicable accrediting agencies. The accreditation process ensures that laboratories adhere to strict standards and guidelines for clinical testing.

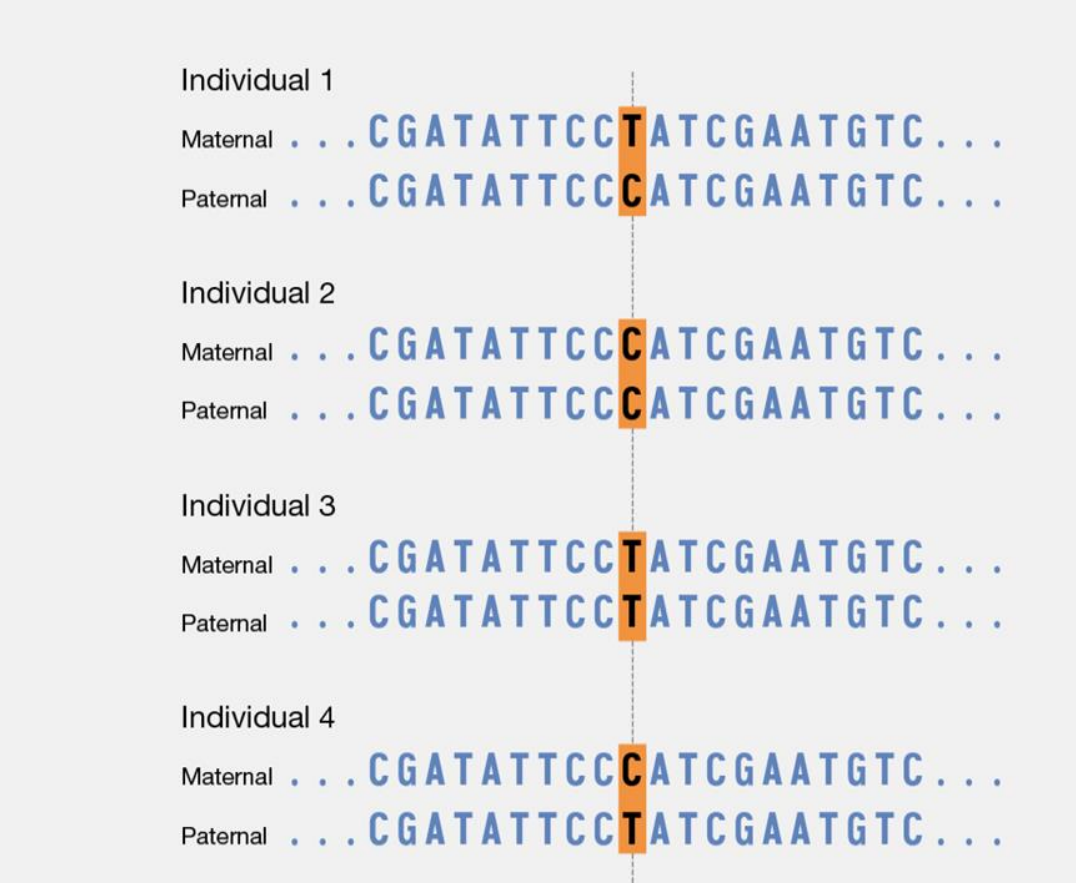
Direct-to-Consumer Genetic testing ACMG Practice Guideline (2016)

- Privacy concerns must be addressed. Prior to testing, the consumer should be informed as to who will have access to test results, what processes are in place to protect these results, what will happen to the DNA sample once testing is complete, and whether the test results may have any personal or family-related implications for life, long-term care, or disability insurance. Finally, whether data generated from testing will be sold to or shared with third parties should be clearly disclosed, as should ownership of the sample and generated data.

Direct-to-Consumer Genetic testing ACMG Practice Guideline (2016)

- A knowledgeable professional should be involved in the process of ordering a genetic test with medical implications. Laboratory results should be interpreted and delivered by a board-certified genetics professional.

Direct-to-Consumer Genetic Tests: Typically SNP typing



NHGRI Talking Glossary

- A single nucleotide polymorphism is a genomic variant at a single base position in the DNA.
- SNPs occur almost once in every 1,000 nucleotides on average = 4 to 5 million SNPs in a person's genome.
- Each variant present in at least 1 percent of the population.
- Most commonly, SNPs are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function.

Late-Onset Alzheimer's Disease

Alzheimer's disease is characterized by memory loss, cognitive decline, and personality changes. Late-onset Alzheimer's disease is the most common form of Alzheimer's disease, developing after age 65. Many factors, including genetics, can influence a person's chances of developing the condition. This test includes the most common genetic variant associated with late-onset Alzheimer's disease.

Name redacted you have **two copies** of the ε4 variant we tested.

People with this result have an increased risk of developing late-onset Alzheimer's disease. Lifestyle, environment, and other factors can also affect your risk.

Variant detected
in the APOE gene

How To Use This Test

This test does not diagnose Alzheimer's disease or any other health conditions.

Please talk to a healthcare professional if this condition runs in your family, you think you might have this condition, or you have any concerns about your results.

Intended Uses

- Tests for the **ε4** variant in the APOE gene associated with an increased risk of developing late-onset Alzheimer's disease.

Limitations

- Does **not** include all possible variants or genes associated with late-onset Alzheimer's disease.
- Does **not** include any variants or genes linked to early-onset Alzheimer's disease.
- Does **not** determine a person's full APOE genotype.

Important Ethnicities

- The ε4 variant included in this test is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of **European** descent.

You may have an increased risk of developing late-onset Alzheimer's disease based on your genetic result.

However, many people with this result do not develop late-onset Alzheimer's disease. Consider discussing your risk with a healthcare professional, especially if you have a family history or other risk factors for this condition.

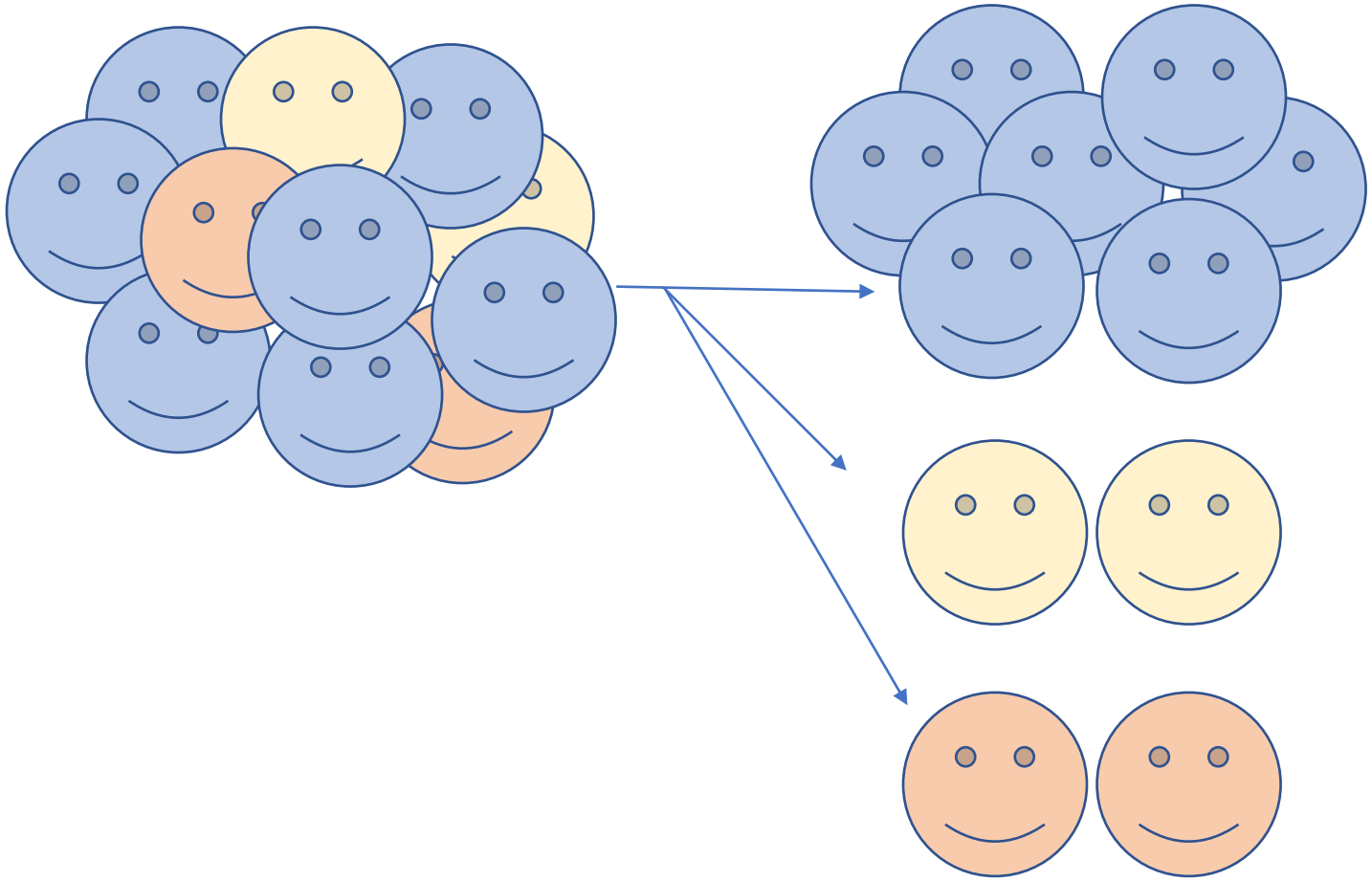
Direct-to-Consumer Genetic Testing

- "We found that providers felt generally unprepared and undertrained to respond to unsolicited genomic results. They articulated a high level of need and expectation for clinical decision support including access to consultants and materials for patients. Some physicians expressed resentment toward being expected to respond to tests that they had not ordered themselves, particularly if they doubted that [test result]s would be appropriately actionable or beneficial to care."
- About 30% of patients who purchased DTCGT shared results with at least one health care provider.

Pet, Holm et al (2019); Stewart, Wesselius et al (2018)

Pharmacogenetic testing questions

The Potential of Pharmacogenetics

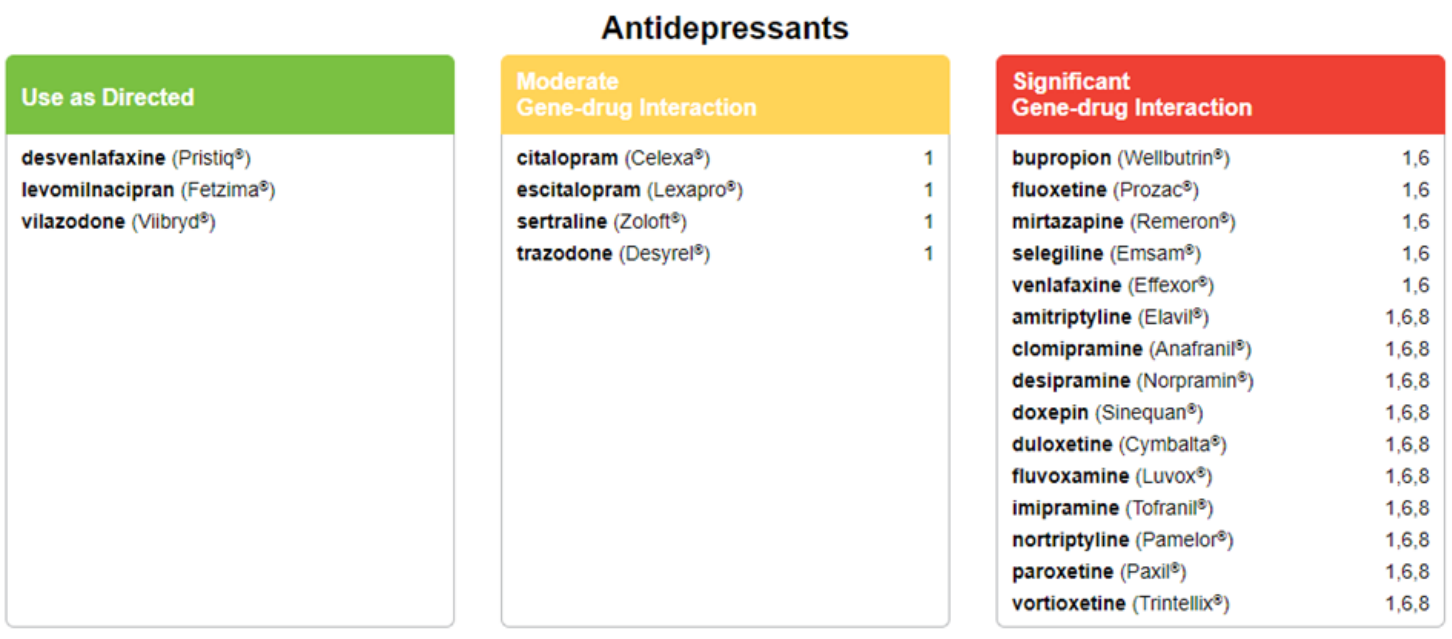


Treatment as usual.

Slow metabolizers. Need a lower starting dose.

Fast metabolizers. Need a higher starting dose.

Pharmacogenetic testing for antidepressants



Antidepressants

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®)	1	**bupropion** (Wellbutrin®)	1,6
levomilnacipran (Fetzima®)	**escitalopram** (Lexapro®)	1	**fluoxetine** (Prozac®)	1,6
vilazodone (Viibryd®)	**sertraline** (Zoloft®)	1	**mirtazapine** (Remeron®)	1,6
	trazodone (Desyrel®)	1	**selegiline** (Emsam®)	1,6
			venlafaxine (Effexor®)	1,6
			amitriptyline (Elavil®)	1,6,8
			clomipramine (Anafranil®)	1,6,8
			desipramine (Norpramin®)	1,6,8
			doxepin (Sinequan®)	1,6,8
			duloxetine (Cymbalta®)	1,6,8
			fluvoxamine (Luvox®)	1,6,8
			imipramine (Tofranil®)	1,6,8
			nortriptyline (Pamelor®)	1,6,8
			paroxetine (Paxil®)	1,6,8
			vortioxetine (Trintellix®)	1,6,8

HLA-B*1502 **Lower Risk**

Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

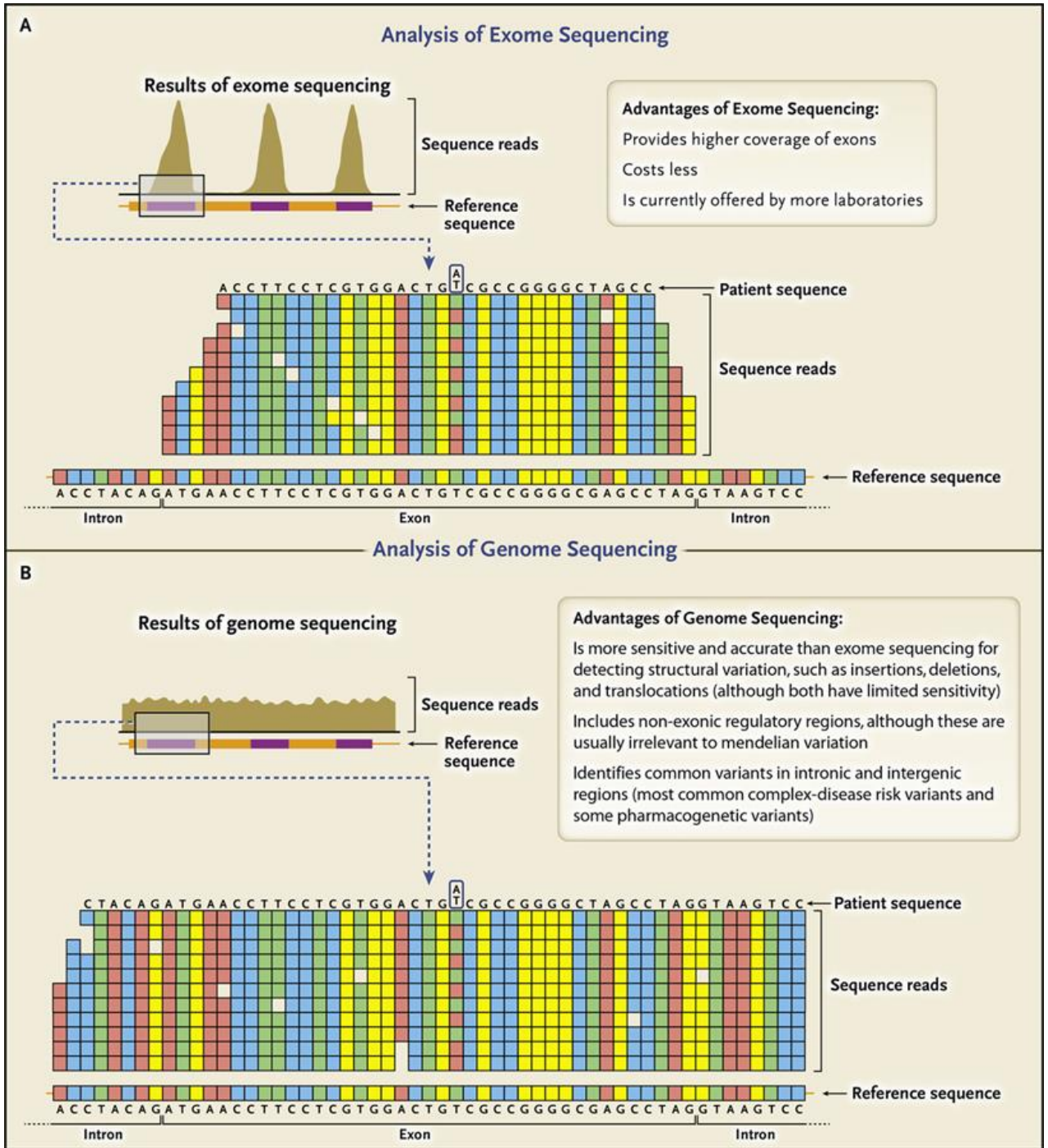
SLC6A4 **Normal Response**

L/L

This patient is homozygous for the long promoter polymorphism of the serotonin transporter gene. The long promoter allele is reported to express normal levels of the serotonin transporter. The patient is predicted to have a normal response to selective serotonin reuptake inhibitors.

The best available evidence suggests that PGx-guided care for moderate-to-severe adult depression is more likely to result in remission and response than treatment as usual. (Bunka M, Wong G et al, 2023)

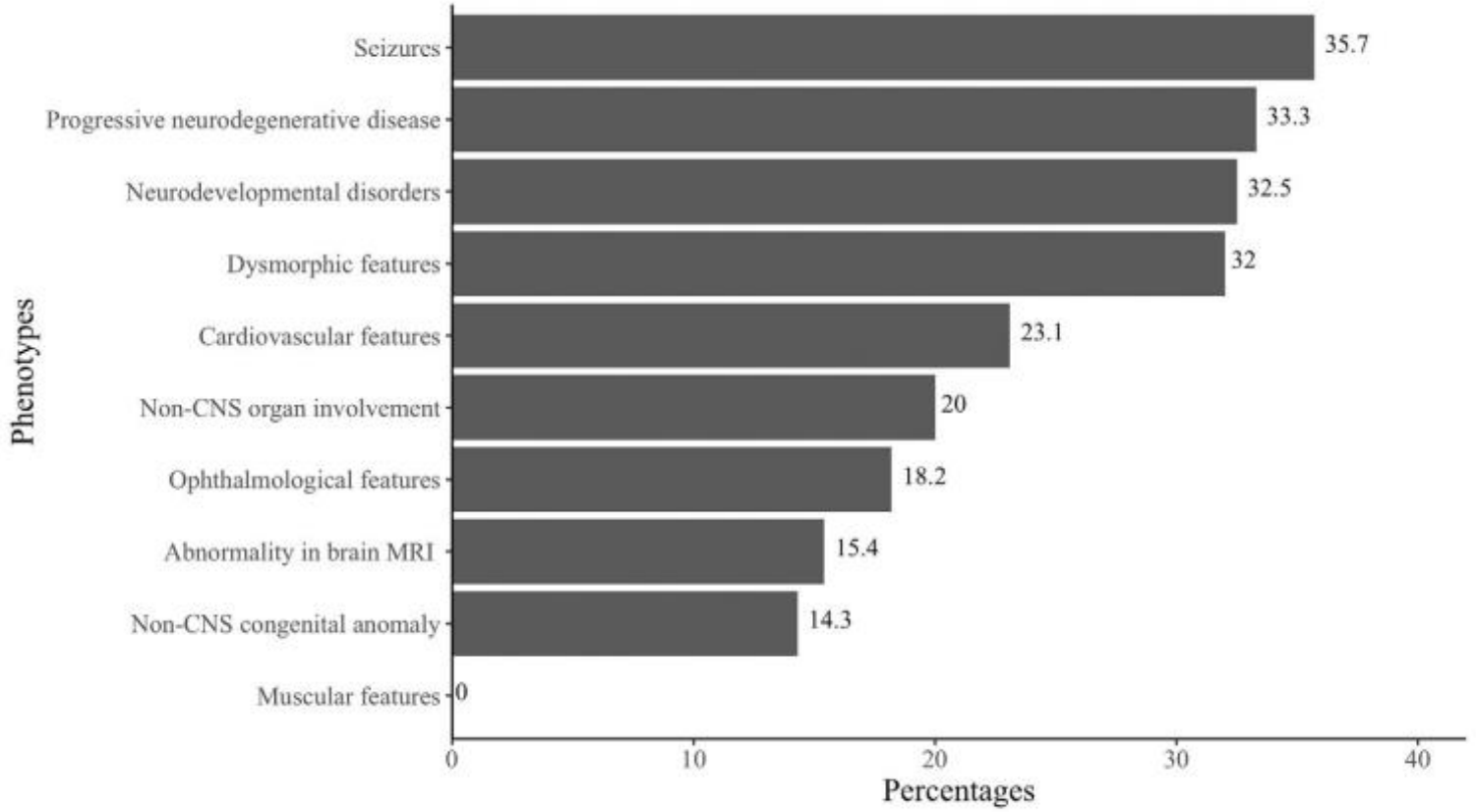
New Technology Questions: Exome



Biesecker & Green, 2014

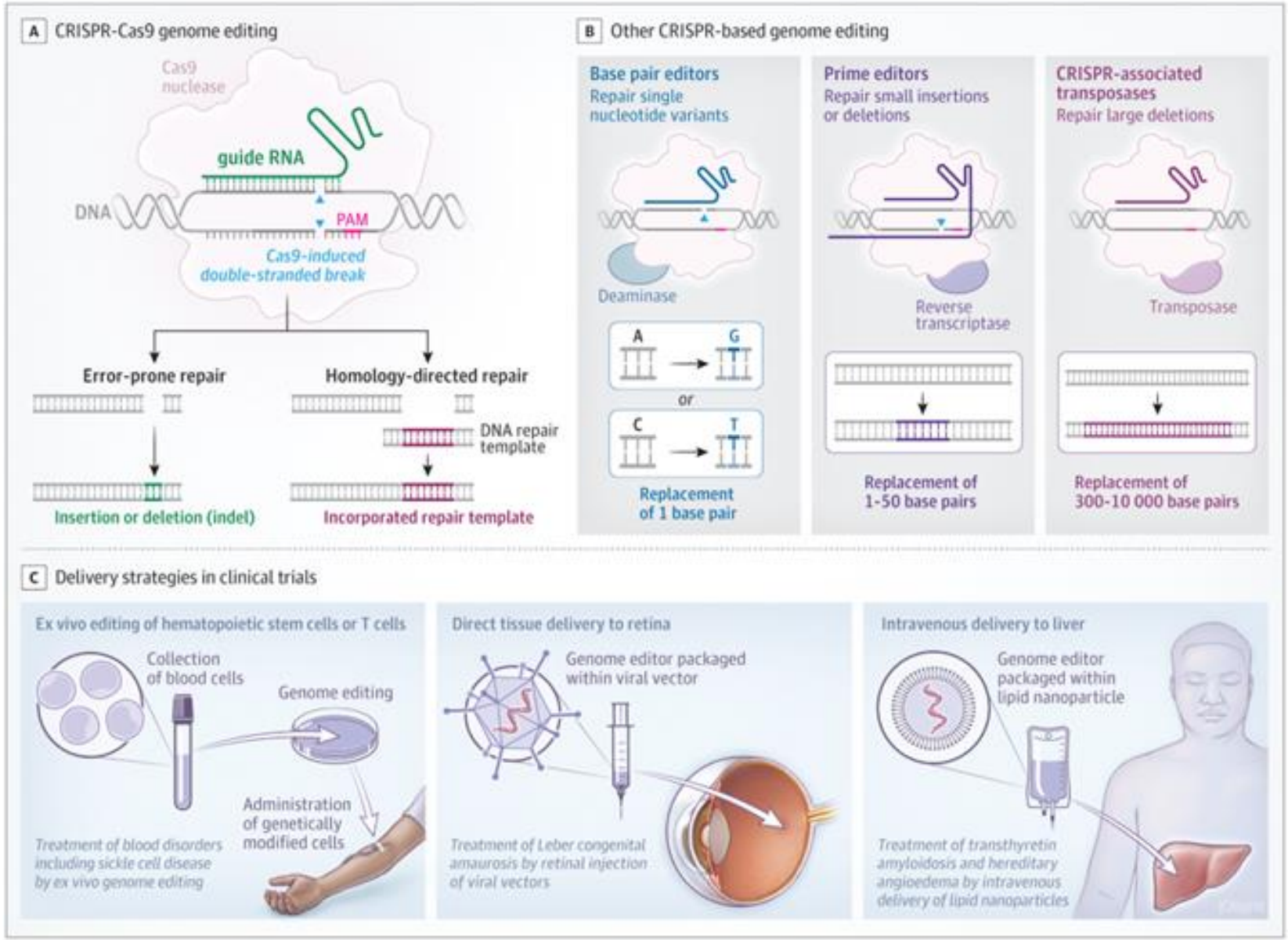
Diagnostic Yield of Exome was 19% in an Adult Genetics Clinic (77 patients)

FIGURE 2 Phenotypes and the diagnostic yield of ES in those phenotypes are depicted in this figure. ES, exome sequencing.



Mainali et al, 2022

New Technology Questions: CRISPR



Kan & Doudna, 2022

Talk Overview

- Genetic testing in 2023: easier than ever
- Cardiology questions
- Neurology questions
- Direct-to-consumer genetic testing questions
- Pharmacogenetic questions
- New technology questions

References

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