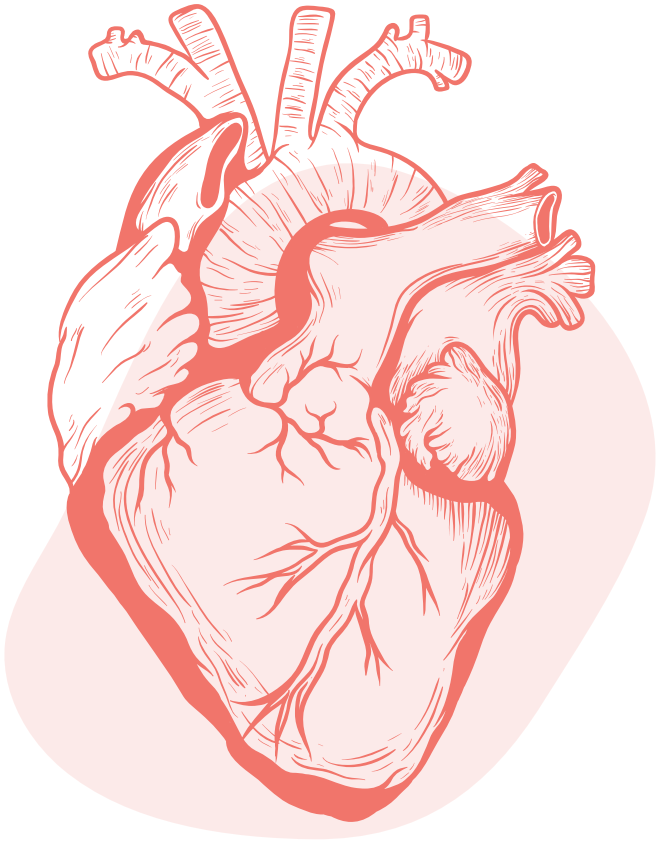


Inherited Cardiac Conditions

For the Non-Cardiac GC

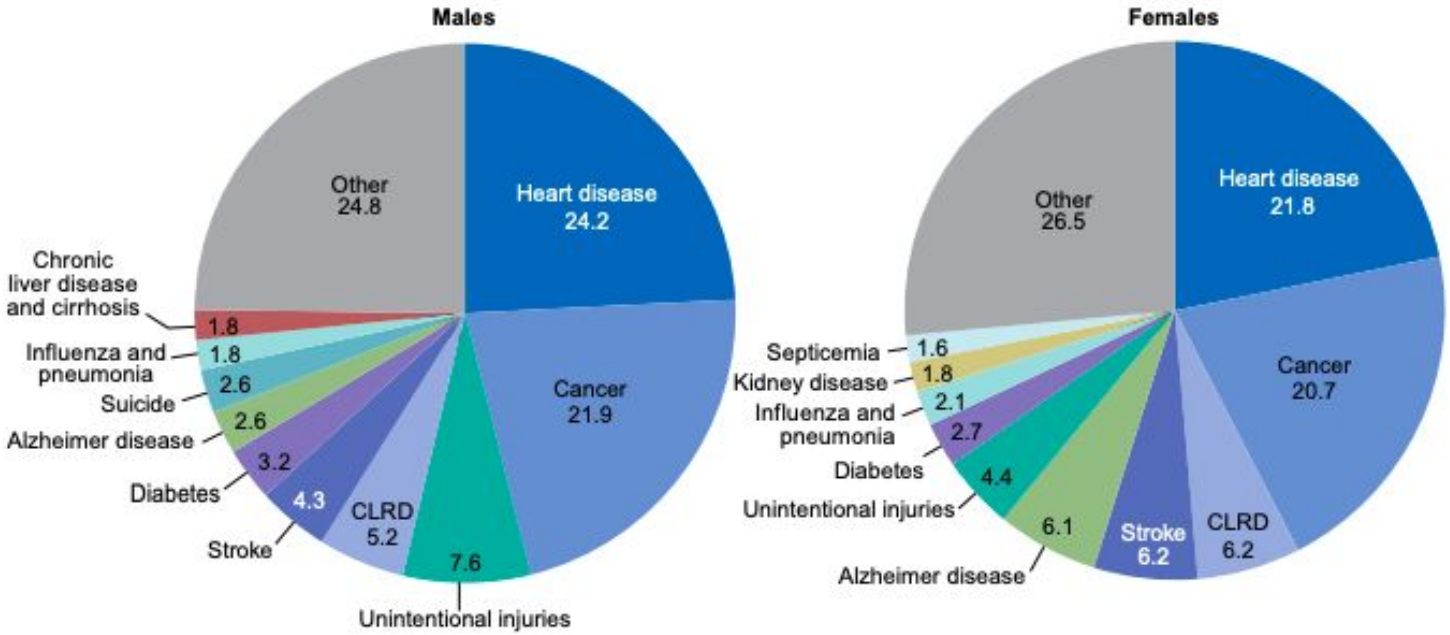
Lindsay Meyers, MS, CGC
Laila Andoni, MS, CGC

Conflict of Interest Disclosures

- No conflicts of interest to disclose

Learning Objectives

- Recognize hereditary conditions in cardiovascular genetics and when to refer to a specialist
- Identify contacts and resources for more information on cardiac disorders



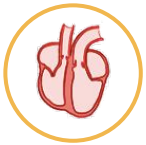
NOTES: CLRD is Chronic lower respiratory diseases. Values show percentage of total deaths. Totals may not add to 100 due to rounding.
SOURCE: NCHS, National Vital Statistics System, Mortality.

gure 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2017

AT LEAST 1 in 250 INDIVIDUALS HAVE A HEREDITARY CARDIAC CONDITION

Cardiovascular Disease with Genetic Component

Inherited Arrhythmias



Cardiomyopathies

Coronary Disease
and Dyslipidemia

Congenital Heart Defects

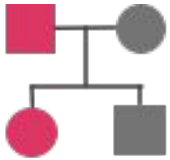
Muscular Dystrophies with
Cardiac Involvement

Aortopathies

Common Themes in Cardiovascular Genetics

Reduced Penetrance

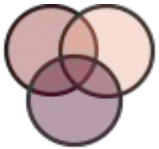
Variable Expressivity



Autosomal Dominant

Digenic Causes

Locus Heterogeneity

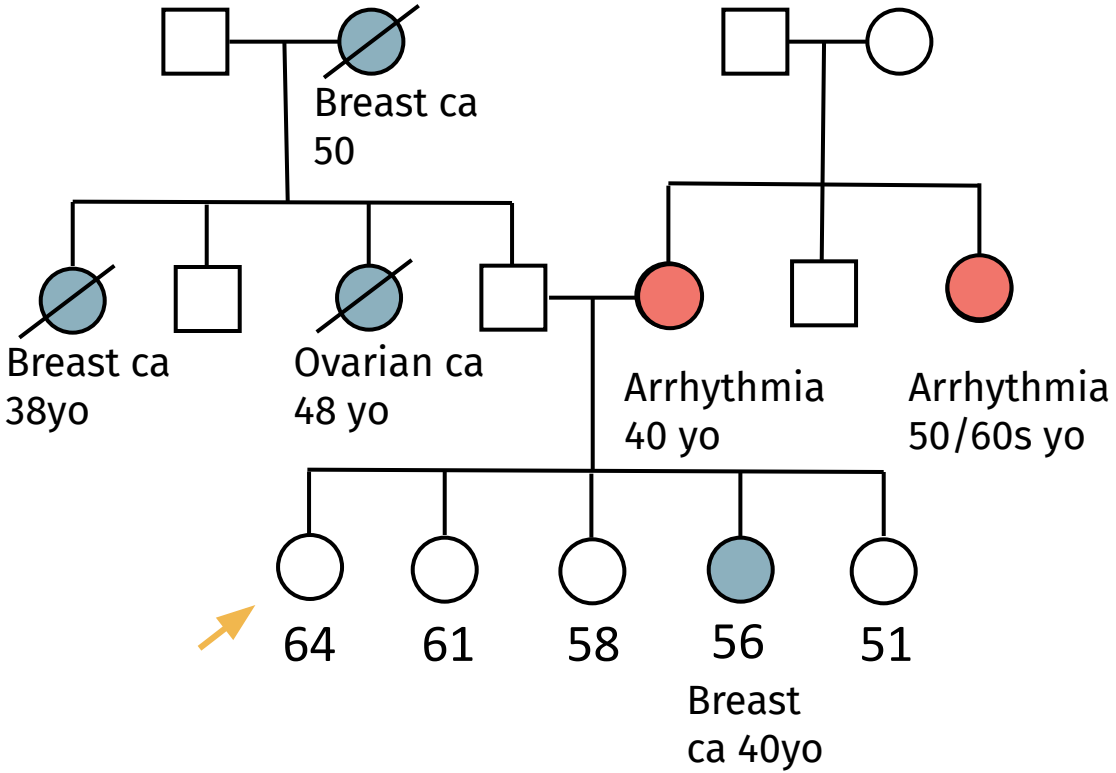


Genetic Overlap

Limited Detection Rate

Prevention

Let's look at a possible referral



Arrhythmias

Problem with heart's electrical system

Symptoms

Palpitations
Lightheadedness
Syncope
Sudden Cardiac Arrest

None
Chest Pain
Fatigue

Etiology

Varies
Most not monogenetic

Treatment

Medications
Ablation
Devices
Cardioversion

Clinical Evaluations

Resting ECG
Holter/event monitor
Stress test
EP study
Med challenge
Loop recorder

Types of Arrhythmias

Bradyarrhythmias

- <60 bpm
- Syncope

Conduction disease

- Heart block
- Sinus node dysfunction
- Bundle branch block

Ventricular Arrhythmias

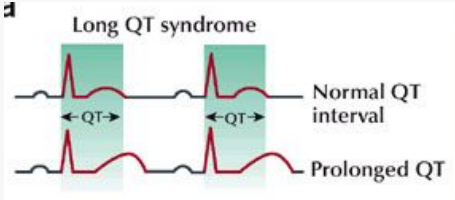
- Ventricular tachycardia
- Ventricular fibrillation
  - SCA risk
- Premature Ventricular beats (PVCs)

Supraventricular Arrhythmias

- Premature atrial contraction (PACs)
- Atrial Fibrillation (most common serious)
  - Environmental factors (risk increases with age)
- Paroxysmal Supraventricular Tachycardia (PSVT)
- Wolff Parkinson White (WPW)
  - Extra pathway to ventricles
  - Can lead to Vtac

Common Inherited Arrhythmias (IA)

LQTS

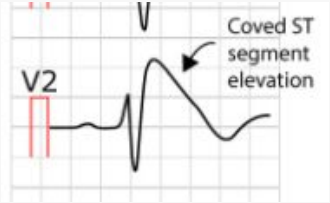


Most common IA

~1:2000 - 1:3000

- ➔ QTc* >440 ms in males
  >460 ms in females
- ➔ Syncope and SCA
- ➔ Torsade de pointe
- ➔ 75-80% DR

BrS

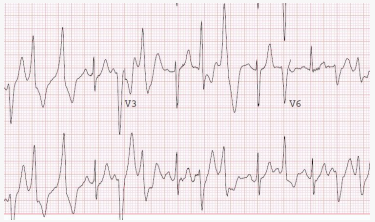


Penetrance Low

17-40%

- ➔ Type 1 Pattern on ECG
- ➔ *SCN5A*
  - ◆ *20-30% have diagnostic ECG*
- ➔ *Triggers: fever, alcohol, meds*
- ➔ *DR: ~25%*

CPVT



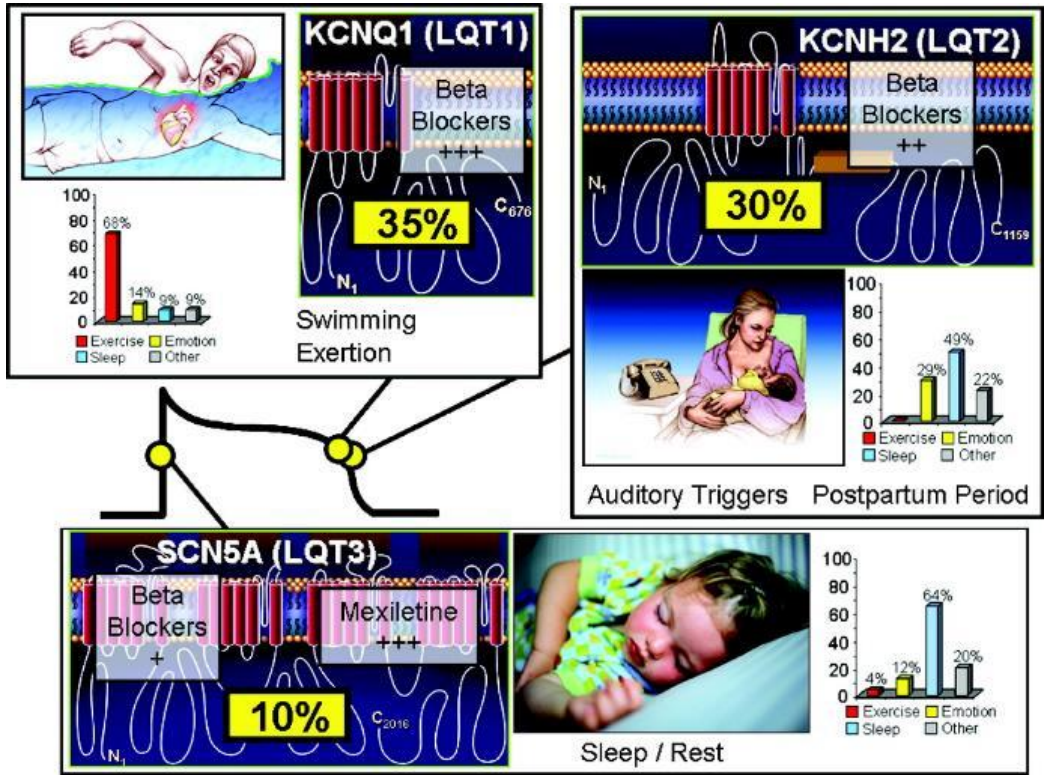
Highest Penetrance

~80% syncope, ~30% SCA

- ➔ RYR2: AD, CASQ2: AR
- ➔ DR ~65%
- ➔ De novo ~40%
- ➔ Triggers: emotion, exertion

Rasband, M. N. "Ion channels and excitable cells." *Nature Education* 3.9 (2010): 41.
https://ecgwaves.com/topic/brugada-syndrome-ecg-treatment-type-1-2-3/;

LQTS Genotype-Phenotype Correlations



Tester D J , Ackerman M J Circulation 2011;123:1021-1037

American Heart Association
Learn and Live

Arrhythmias - what else would you want to know

- How were they diagnosed?
  - Fainted? SCA? Palpitations?
- Workup (if known): resting ECG, holter monitor, event monitor, echo, MRI?
- Previous history?
  - Heart attack, thyroid issues, hypertension, smoker/heavy drinker? Any medications?
- Is there a trigger? Eg stress, caffeine, exercise, emotions
- Symptomatic? Fatigue, faint, SOB, chest pain? Cardioversion?
- What was the follow-up?
  - None (no meds, no needed f/u), watch and see, medications, ablation, device (pacer/ICD)?
- Other concerning fmhx?
  - SCA/SCD/SIDS, syncope, seizures, accidents, stillborns, devices, cardiac surgeries, transplants

A Word on Sudden Cardiac Death

Background

- <30/35 yo VERY concerning
- >30/35 yo most common cause is MI/ICM (70-75%)
  - Beware the unconfirmed MI
- SIDS: ~15% have underlying cardiac genetic cause

What you want to know

- Autopsy?
- What were they doing? Were they ill, on medications?
- Previous hx concerning for CAD risk factors? (eg smoking, HTN, overwt, high lipids, etc)
- Previous cardiac symptoms/procedures (eg syncope, pals, chest pain, HF sx, surgeries - including valve replacements)

Another Word....

Devices

- ➔ Most concerning: <50 yrs
- ➔ Not really concerning: >50
  - ◆ Pacer - usually Afib or bradycardia
  - ◆ Pacer for block or conduction disease - most often are acquired if no other concerning personal or fm hx
  - ◆ ICD <50 yo VERY concerning
  - ◆ ICD common in those with prior MI and ICM

Syncope

- ➔ If prodrome and a teenager - suggestive of vasovagal syncope
  - ◆ Blow drying hair, showering...
  - ◆ Just “drop” during emotion or exertion - concerning (did they injure themselves?)
  - ◆ Can be cardiac and non cardiac
    - POTS - not cardiac - autonomic nervous system

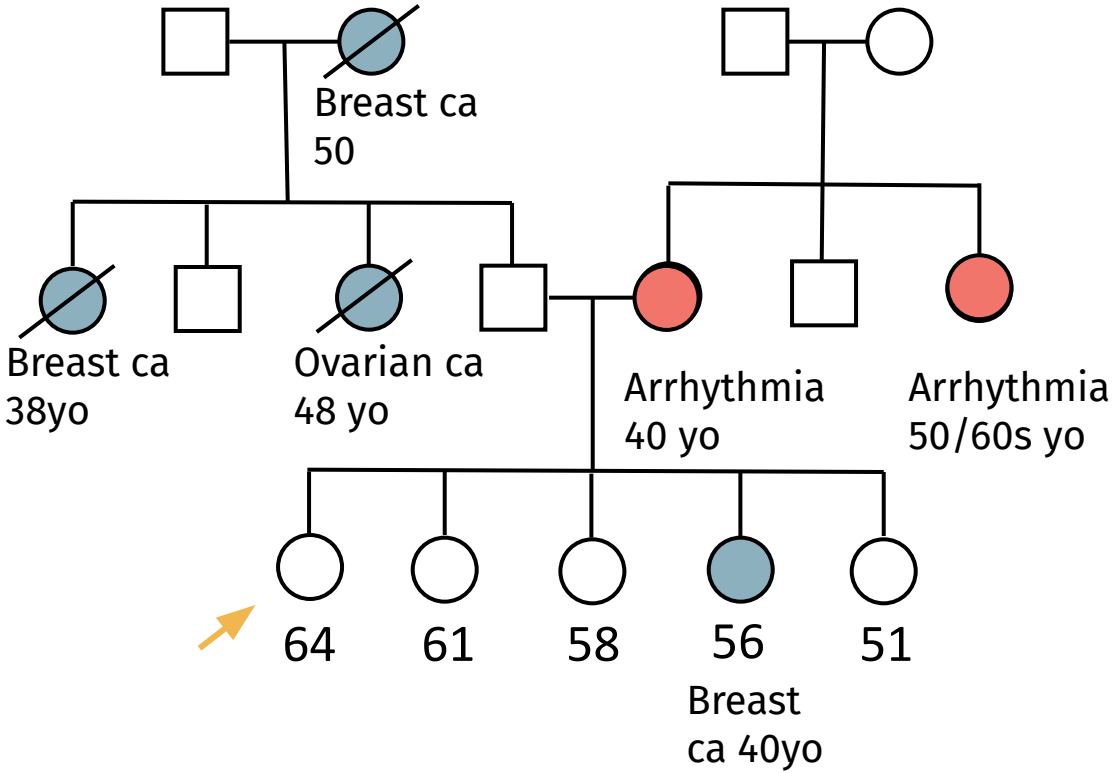
Take Home

- Arrhythmias are common
- Many causes and types differing in severity and etiology
  - 80 year old with Afib –probably no cause for concern
  - Multiple fm members with Afib presenting in 20s/30s - different story
- Be concerned when:
  - Multiple affecteds
  - Sudden cardiac death
  - Syncope
  - Devices (<50 yo)
  - Ventricular arrhythmias
  - Arrhythmia plus (eg CHD, other birth defects)

Why Care

- Prevention of sudden death
  - Treatment
  - Lifestyle modifications
    - Limit triggers
    - Avoid Medications
- Identify at risk family members

Back to our case

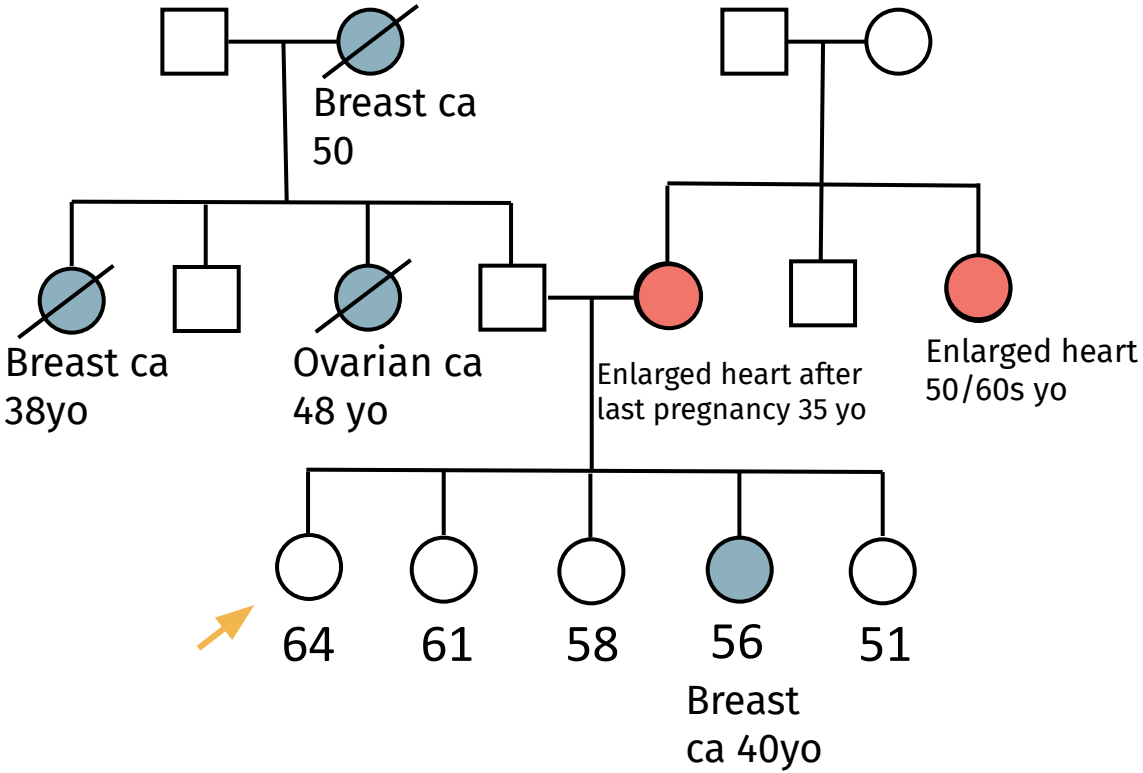


- Mom had ablation, aunt no treatment - not concerning
- Mom has a pacer, aunt has pacer - concerning
- Mom fainted and takes meds, not sure about aunt - concerning, want more info

Arrhythmia Resources

- AHA/HRS/ACC 2017 SCD prevention
  - Class I for familial mutation testing and genetic counseling
  - Class I: genetic testing recommended for LQTS
  - Class II: genetic testing is reasonable for:
    - CPVT, BrS, SQTS, HCM, ARVC, postmortem SCD
- HRS 2020 Consensus on SUD/SCD
  - Genetic counseling is strongly recommended
  - For SCD where the phenotype is suspected to be heritable, genetic testing is recommended
  - FDR of those with SCD should have either , phenotype-guided clinical screening or periodic comprehensive screening if no cause in proband
- HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes
  - Wilde, Arthur A., M. Horie, and Y. Cho. "HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes." *Europace* 15.1389 (2013): 406.
- Inherited cardiac arrhythmias
  - Schwartz, Peter J., et al. "Inherited cardiac arrhythmias." *Nature Reviews Disease Primers* 6.1 (2020): 1-22.

Same case, different history...



Cardiomyopathies

Problem with heart's muscle

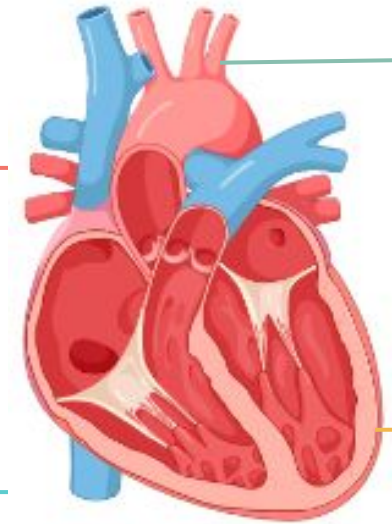
Etiology

Primary

Secondary

Clinical Evaluations

Resting ECG
Holter/event monitor
Stress test
Echocardiogram
Cardiac MRI



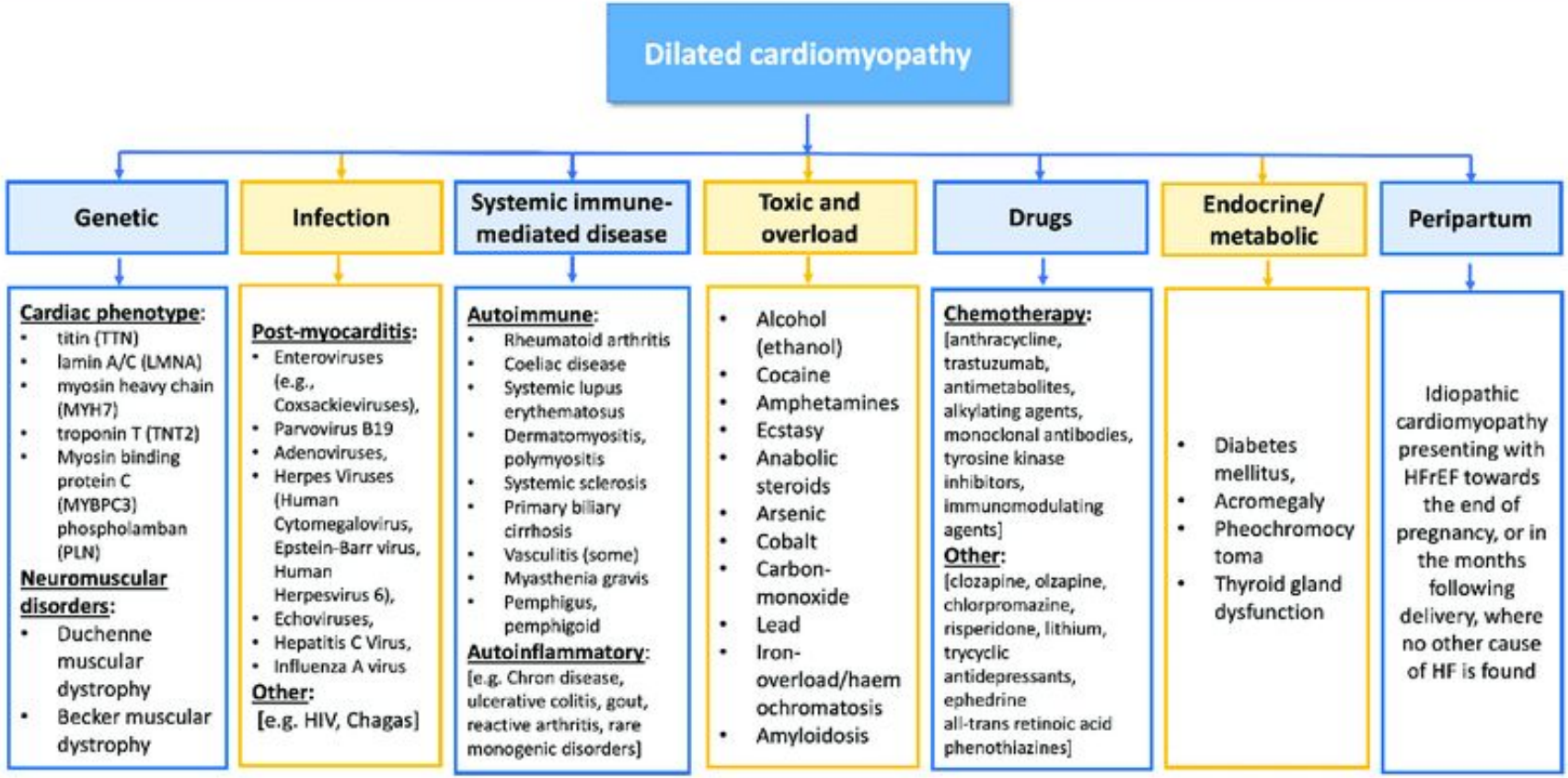
Symptoms

Palpitations
Lightheadedness
Syncope
Sudden Cardiac Arrest

None
Heart failure symptoms

Treatment

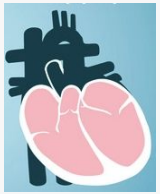
Medications
Devices
Septal ablation/myomectomy
Transplant



European Journal of Heart Failure (2019)

Common Inherited Cardiomyopathies

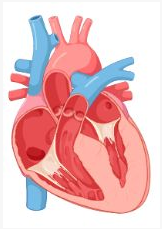
DCM



Left ventricular dilation

➔ Most common type of CM
➔ 20-30% have fmhx/~35% inherited disorder
➔ Heart failure symptoms
➔ 20-40% DR
➔ Heart transplant

HCM



Left ventricular hypertrophy

➔ Most common genetic form of CM (1/200-1/500)
➔ Sarcomere genes
➔ 40-60% detection rate

ARVC

Right ventricular fibrofatty replacement*

➔ Can have arrhythmias prior to structural changes
➔ Cardiac MRI
➔ Desmosome genes
➔ Low penetrance/Digenic

Reichart, D., et al. "Dilated cardiomyopathy: from epidemiologic to genetic phenotypes: a translational review of current literature." *Journal of internal medicine* 286.4 (2019): 362-372.

Cardiomyopathies - what else would you want to know

- ➔ Type of Cardiomyopathy?
  - ◆ “Enlarged heart”
- ➔ Environmental history/risk factors? (eg coronary artery disease)
- ➔ How were they diagnosed?
  - ◆ Age
  - ◆ Symptoms: Fainted? SCA? Palpitations? Heart Failure?
- ➔ What was the follow-up?
  - ◆ Transplant, medications, ICD, nothing
- ➔ Any other systems affected?
  - ◆ Specifically muscle disease (DCM), RASopathy signs (HCM), history of long term hypertension (hypertensive hypertrophy) or neuropathies (amyloidosis)

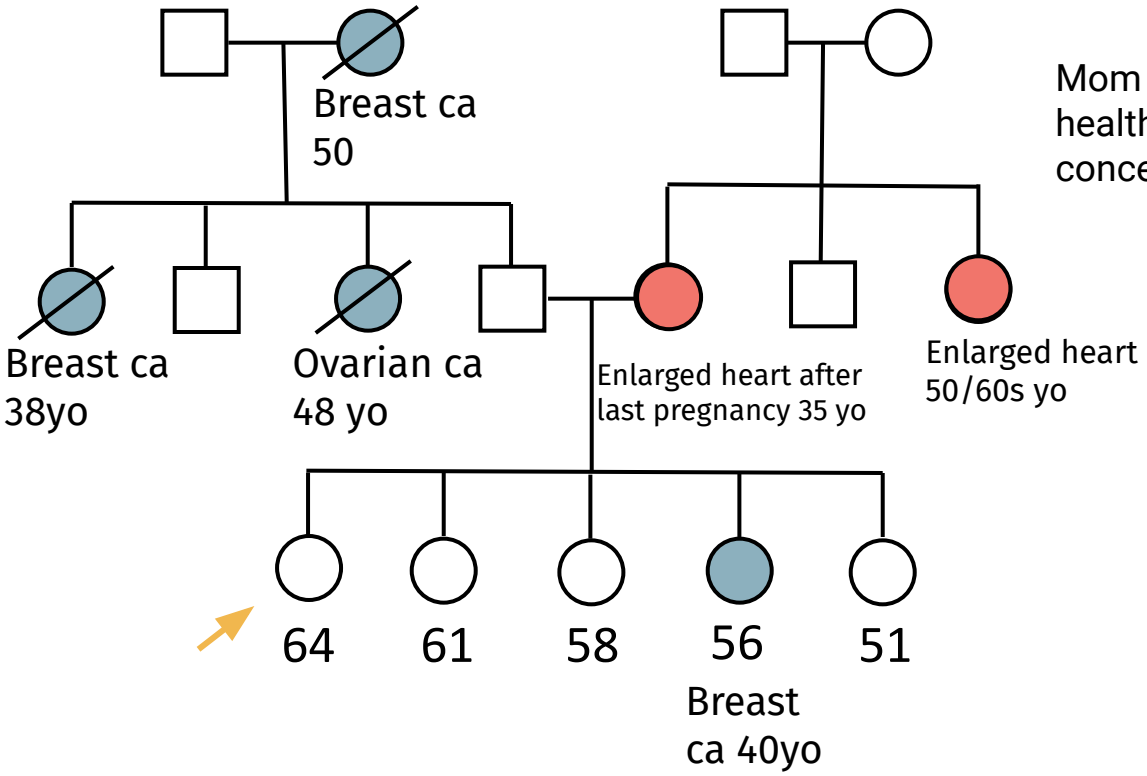
Take Home

- ➔ DCM is common and most often not monogenic
  - ◆ Look for nonischemic or idiopathic cardiomyopathy
  - ◆ 80 year old with CAD and heart failure –probably no cause for concern
  - ◆ Multiple fm members with enlarged heart and transplants - different story
- ➔ While other types of CM can have secondary causes, typically genetic testing is indicated
- ➔ Be concerned when:
  - ◆ Multiple affecteds (including peripartum)
  - ◆ Sudden cardiac death/Vtach
  - ◆ Syncope
  - ◆ Devices (<50 yo)

Why Care

- ➔ Prevention of sudden death
  - ◆ Treatment/Management
  - ◆ Lifestyle modifications
- ➔ Identify at risk family members

Back to the case...



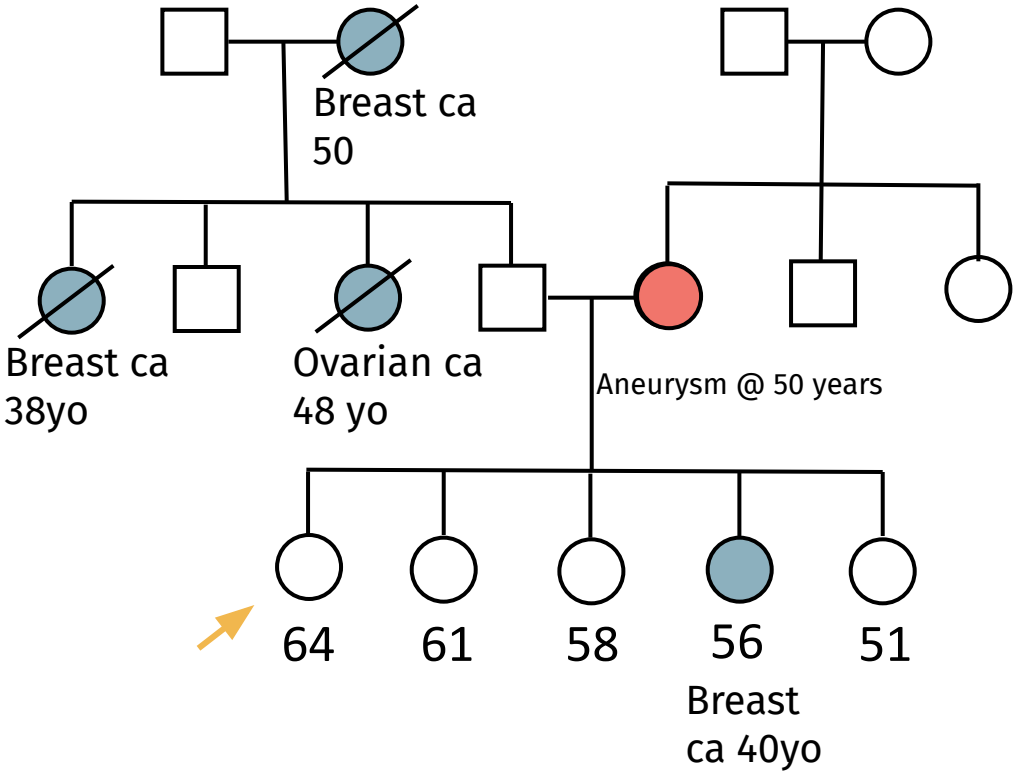
Mom's dilation resolved after pregnancy, aunt history of elevated chol, obese - not concering

Mom still takes medications, aunt is healthy that she knows of - more concerning, want more details

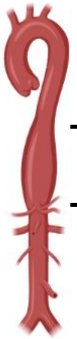
Cardiomyopathy Resources

- HFSA 2018
  - Genetic testing is recommended for patients with cardiomyopathy (level A for all CM, except RCM which is B)
  - Do not rec for LVNC if no fmhx and normal function
- 2019 HRS consensus statement on arrhythmogenic cardiomyopathy
  - Genetic testing is recommended for those with those with ACM, and cascade testing when PV
  - FDRs be screened 1-3 yrs
- AHA 2020 HCM guidelines
  - Genetic testing recommended for those with HCM or suspected HCM phenocopies with pre and post test GC
  - FDRs screened periodically based on age
- ACMG 2018 genetic eval CM
  - Genetic testing is recommended for cm

Same case, different history...



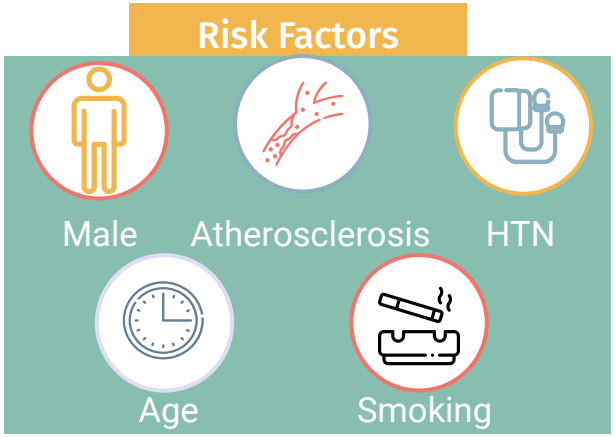
Aortopathies

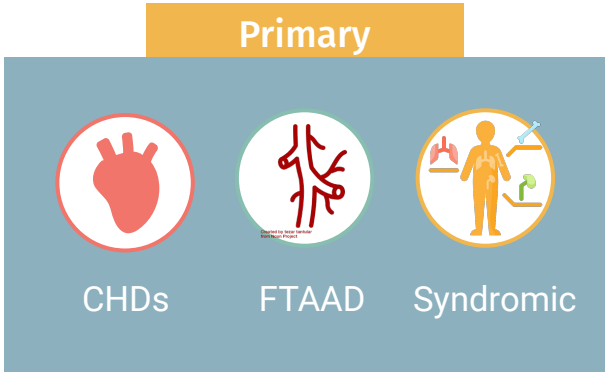


Aneurysm = bulge

Thoracic ~ 40%

Abdominal ~ 60%





Syndromic Aortopathies - Marfan Syndrome

A

Cardiovascular

Aortic Aneurysm and Dissection
Mitral Valve prolapse

B

Cutaneous

Hernia
Striae

C

Musculoskeletal

Disproportionate Pectus
Scoliosis
Craniofacial

Ocular

Ectopia lentils
myopia

D

Pulmonary

Pneumothorax

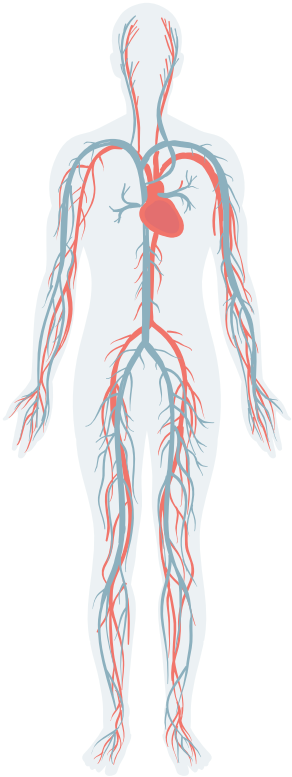
E

Other

Dural ectasia

F

Nonsyndromic Aortopathies - ACTA2



Aortic Aneurysm/Dissection

01

Vessel Occlusion

02

Coronary disease
Moyamoya like

Other

03

Iris flocculi
Livedo reticularis

Genetic aortopathy personal and family history red flags

- **Thoracic aortic dissection at any age (more concerning <50/60yo)**
- Mitral Valve Prolapse
- **Thoracic aortic dilation/aneurysm <50yo**
- Cerebral aneurysms < 50yo
- Stroke <50 yo
- **Sudden cardiac death <50yo**

- Pectus **carinatum**/excavatum
- Scoliosis
- Joint hypermobility/contractures
- Pes planus +/- hindfoot deformity
- Arachnodactyly
- **Disproportionate arm/leg length**

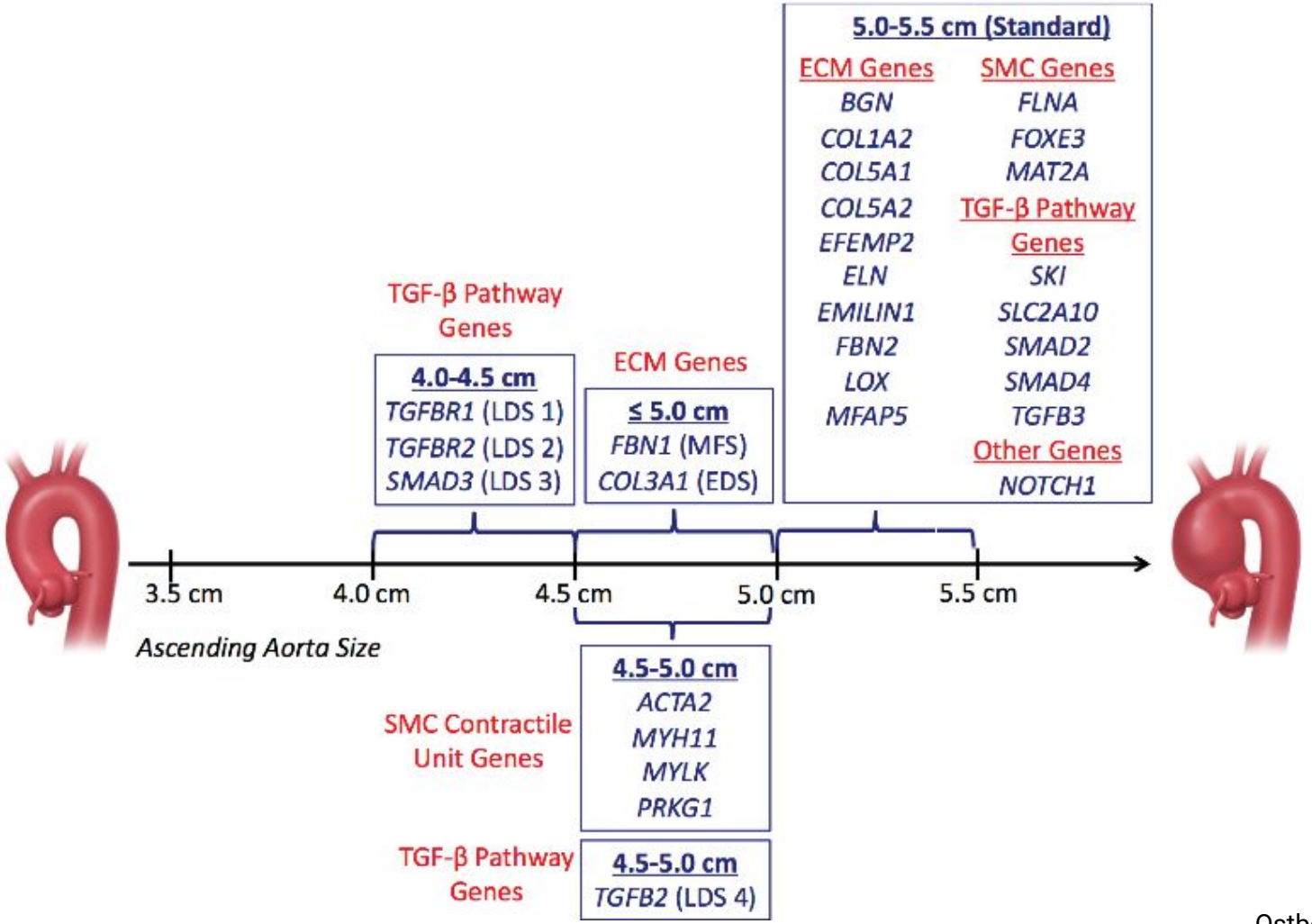
- Severe myopia
- **Ectopia lentis**
- Retinal detachments
- Easy bruising
- Abnormal scarring
- Thin/translucent skin
- Birth defects: Clubfoot, craniosynostosis
- Pneumothorax
- High arched palate/dental crowding
- GI dysmotility
- Hernias

Take Home

- ➔ Location matters
- ➔ Aneurysm in older individual most common - probably no cause for concern
  - ◆ AAA in 80 year old male
- ➔ Aneurysm or dissection in multiple family members or at young age is suggestive of genetic etiology
  - ◆ May also see other early onset common conditions in conjunction
  - ◆ Some CHDs are also associated with genetic etiologies
- ➔ Multisystemic involvement suggestive of genetic etiology

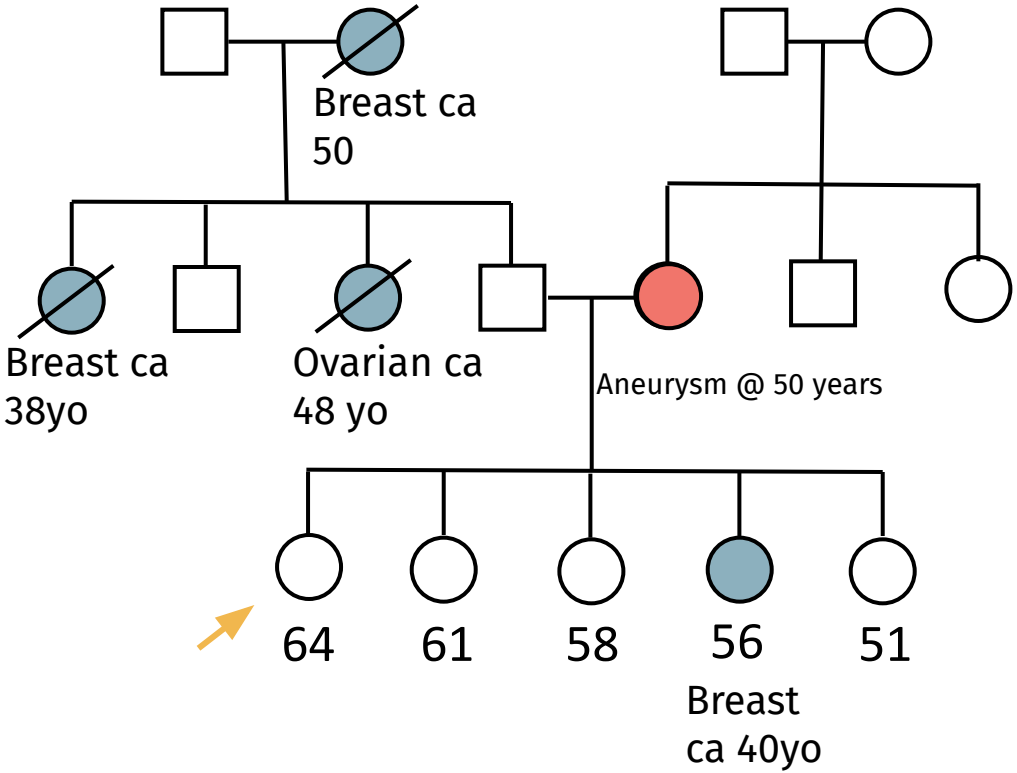
Why Care

- ➔ Prevention of sudden death
  - ◆ Treatment/Management
    - Prophylactic surgery saves lives
      - 3.2 % mortality and morbidity vs 20.1%
    - Typically repaired when:
      - 5.0-5.5cm
      - Underlying genetics can impact
    - Screening/Imaging
      - *TGFBR1/2* positive = increased risk for arterial aneurysms and tortuosity not detected by echo
      - *TGFBR1/2* positive = increased risk for arterial aneurysms and tortuosity not detected by echo
- ➔ Lifestyle modifications
- ➔ Identify at risk family members



Ostberg NP, et al 2020

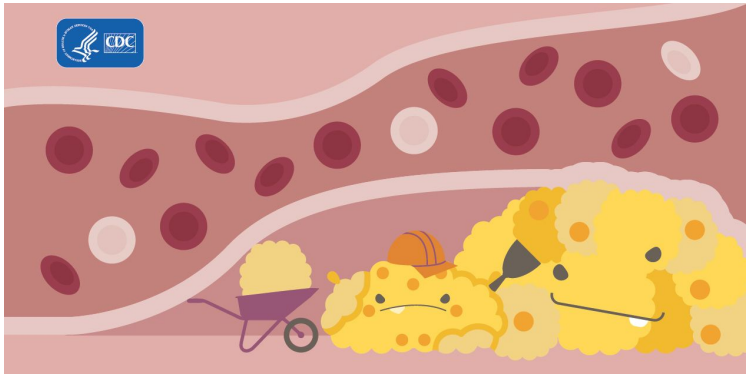
Same case, different history...

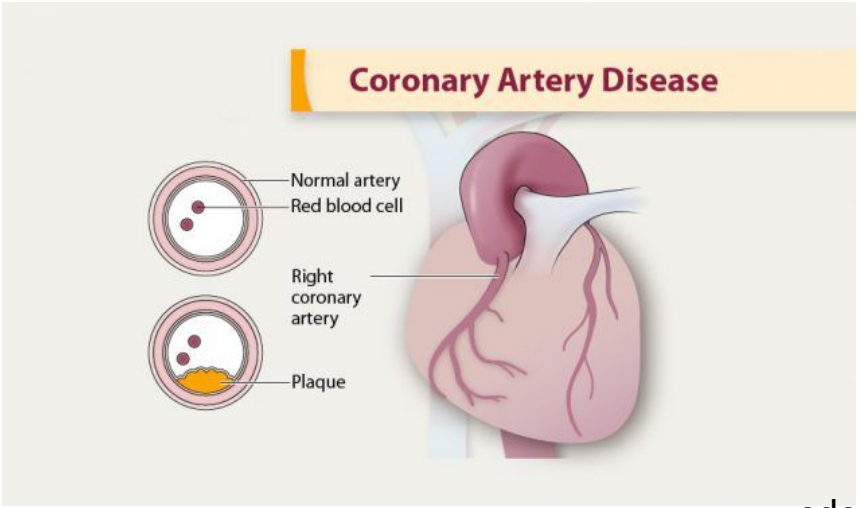


Bicuspid aortic valve and dilation - not concerning for TAAD

Dyslipidemia

- “Everyone in my family dies of heart attacks”
- Red flags: Consider
  - Age of CAD
    - <55 Men, <65 Women
  - Lifestyle- diet, exercise, smoking
  - LDL levels available
  - Stents, angioplasty, bypass surgery
  - Lipoprotein (a)
- AAP guidelines recommend universal lipid screening at ages 9-11 and 17-21 years
- Genetic conditions
  - Familial hypercholesterolemia- most common
  - Hypertriglyceridemia
  - Sitosterolemia





cdc.gov

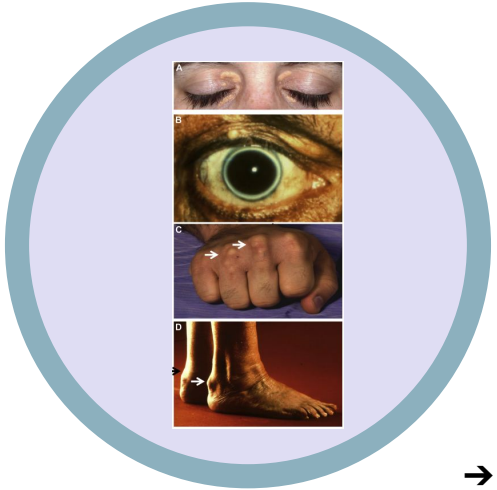
Familial Hypercholesterolemia

Cardiovascular

- Coronary artery disease
- MI & angina
- 50% risk coronary artery event by age 50 for untreated male
- 30% risk by age 60 for untreated female

Cutaneous

- Xanthomas-Eyes and tendons



Eyes

- Corneal arcus

Lipid Levels

- untreated adults LDL-C>190 mg/dL
  - total cholesterol levels >310 mg/dL;
- untreated children LDL-C levels >160 mg/dL
  - total cholesterol levels >230 mg/dL

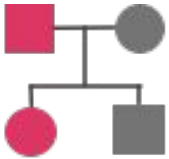
Sturm A, et al (2018); Genest, Jacques, et al. (2014): 1471-1481.

Familial hypercholesterolemia

1 in 200-250 people

Genes: *LDLR* (main), *APOB, PCSK9*

Heterozygous vs homozygous FH **



Autosomal dominant **

Panel detection rate about 80%

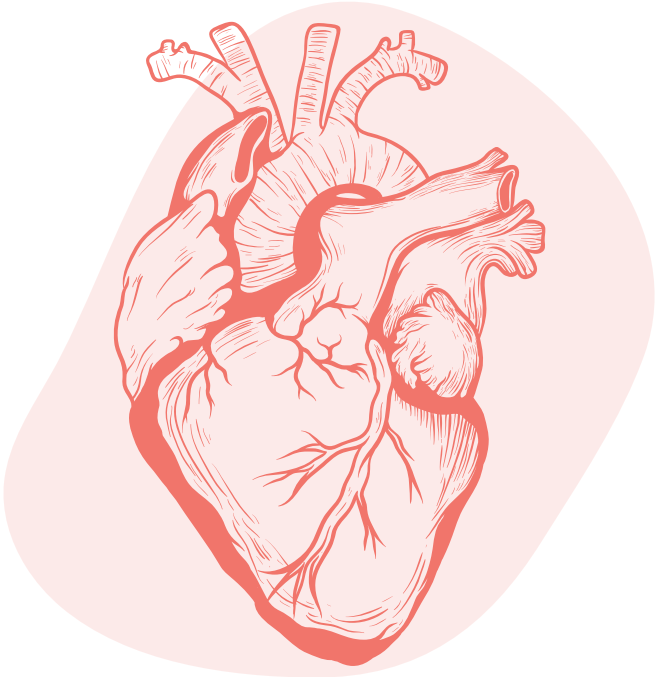
Familial Hypercholesterolemia - Resources

- ACC 2018 FH guidelines
  - Genetic testing should be offered to those with high suspicion of familial hypercholesterolemia
  - Cascade familial mutation should be offered to all FDRs

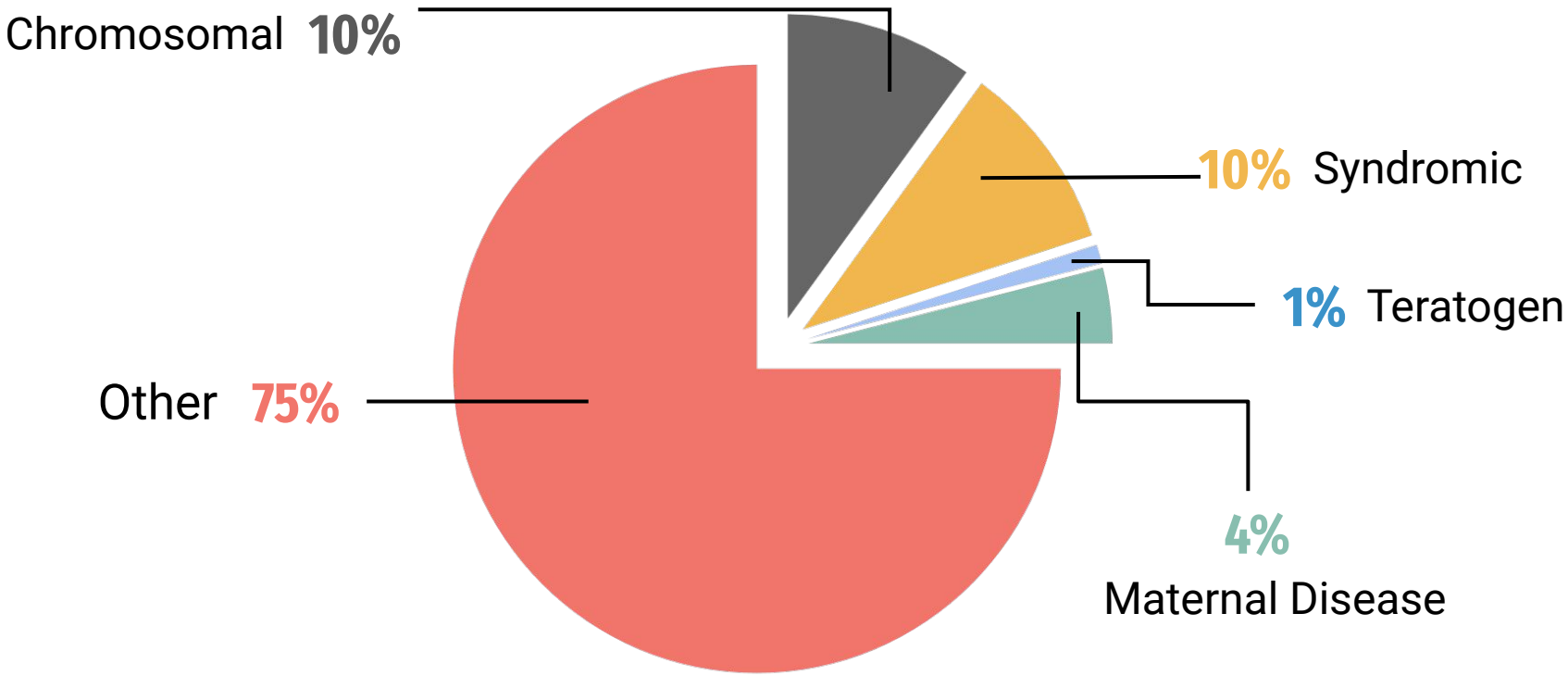
- **Genetic Testing Consensus Statement ACC**
  https://thefhfoundation.org/genetic-testing-consensus-statement
- **Medical Management**
  https://thefhfoundation.org/fh-diagnosis-management-and-family-screening

Congenital Heart Defects

- Structural defect
- Incidence 4-8/1,000 (~1%)
  - One of the most common birth defects
  - Increased if included bicuspid aortic valve (BAV)
- 70-80% isolated
  - Isolated still may have genetic component
    - Single genes identified, still multifactorial
  - 20-30% extra cardiac features



Causes of Congenital Heart Defects



CHDs: What to Consider

- **Exact diagnosis**
- **Isolated vs. extra-cardiac findings**
  - **May not be able to tell in infants/young children**
  - **Extra cardiac = syndromic evaluation**
    - And sometimes with apparently isolated
- **Family history**
- **Recurrence risk- Cowan & Ware 2015**
  - Left ventricular outflow tract obstruction (LVOTO)**
  - https://pubmed.ncbi.nlm.nih.gov/26042910/
- Any previous testing
  - Prenatal or postnatal
    - NIPT
- Maternal exposures
  - Diabetes
  - Maternal PKU
  - Maternal rubella/febrile conditions
  - Drug exposures

Conotruncal Defects - 22q11.2 Deletion Syndrome

- Example indications
  - A new 1 day old male is admitted to the CICU with truncus arteriosus and low calcium levels
  - A 2 year old female is seen in General Cardiology and has Tetralogy of Fallot

- Practical Guidelines for Managing 22q11.2 Deletion

  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3197829/

- Managing Adults

  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4526275/

22q11.2 deletion syndrome

Cardiovascular

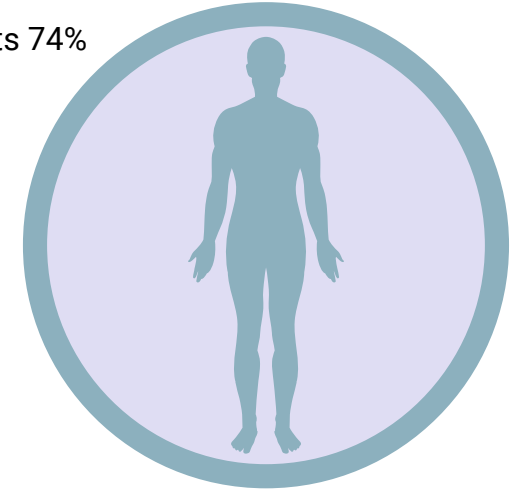
- Congenital heart defects 74%

Development

- Developmental delay
- Learning difficulties
- Increased risk psychiatric illness

Palate

- Palatal abnormalities 69%
- Velopharyngeal insufficiency



Other

- Distinctive facial features
- Hearing loss
- Cervical spine anomalies
- Ptosis & ocular anomalies

Endocrine/Immune

- Absent thymus
- Low calcium 50%
- Immune deficiency

Coarctation of the Aorta - Turner Syndrome/Monosomy X

- Example indications
  - 1 month old female with coarctation of the aorta
  - 14 year old female with short stature and delayed puberty

- **Turner Syndrome Medical Management**
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5761955/
- **American Heart Association- Cardiac management**
  - https://www.ahajournals.org/doi/full/10.1161/HCG.0000000000000048

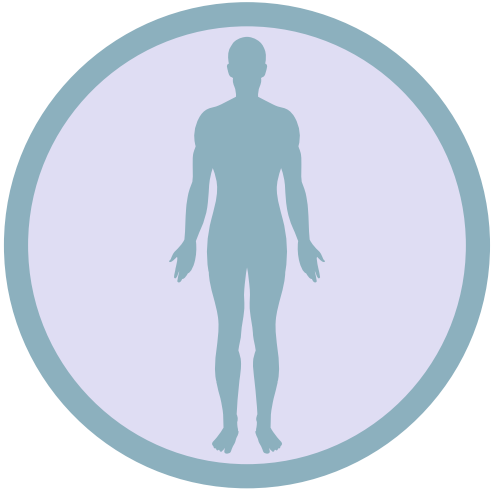
Turner Syndrome/Monosomy X

Cardiovascular

- ➔ Congenital heart defect, up to 50%

Endocrine

- ➔ Premature ovarian failure
- ➔ Infertility



Other/Physical features

- ➔ Short stature
- ➔ Lymphedema
- ➔ Webbed neck
- ➔ Low hairline
- ➔ Widely spaced nipples

Supravalvular aortic stenosis- Williams Syndrome

- Example indication
  - 3 year old male with supravalvular aortic stenosis and developmental delay
- **AAP Guidelines**
  - https://pediatrics.aappublications.org/content/107/5/1192

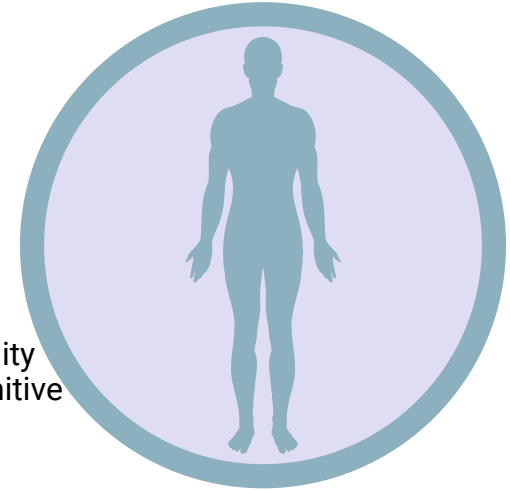
Williams Syndrome

Cardiovascular

- Supravalvular aortic stenosis
- Elastin arteriopathy

Musculoskeletal

- Hypotonia
- Hyperextensible joints



Development

- Developmental delay/intellectual disability
- Unique personality/cognitive profile

Endocrine

- High calcium

Pulmonary stenosis- Noonan Syndrome

- Example indication
  - 6 month old female with pulmonary stenosis, distinctive facial features
  - Adult male with pulmonary stenosis, short stature and history of developmental delay

- **RASopathies Network**
  - https://rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf

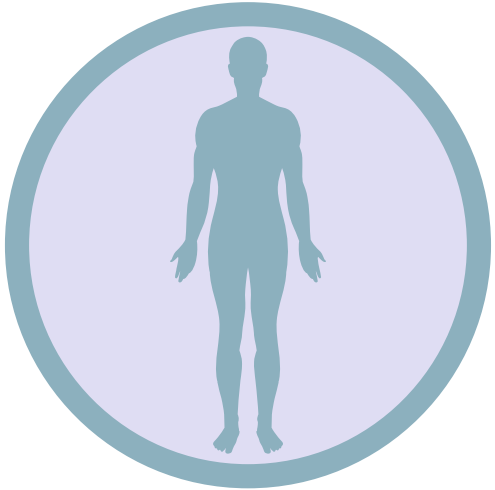
Noonan Syndrome

Cardiovascular

- Pulmonary stenosis
- Hypertrophic cardiomyopathy
- Atrial septal defects

Development

- Variable degree of developmental delay



Other

- Short stature
- Broad, webbed neck
- Pectus abnormality
- Wide set nipples
- Cryptorchidism in males
- Coagulation abnormalities

THANKS!

Do you have any questions?

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laila.andoni.gc@gmail.com

Locate a Local Cardiovascular Genetic Counselor

- Cardiovascular Genetic Counselor Map
  - https://www.google.com/maps/d/u/0/viewer?msa=0&mid=1xJ-mj1q6I-VyBhphsoAmQelVpSY&ll=11.243062693489742%2C-142.97607399999993&z=3
  - Can link to from CV SIG homepage https://www.nsgc.org/Members/Special-Interest-Groups-SIGs/Cardiovascular-Genetics-SIG
- NSGC Find a Genetic Counselor Tool https://findageneticcounselor.nsgc.org/
- Many telehealth genetic counseling companies have cardio services

Resource Examples

- CHDs & Related Syndromes
  - The Children's Heart Foundation https://www.childrensheartfoundation.org/about-chds/resources.html
  - Little Hearts https://www.littlehearts.org/
  - 22q11.2 Foundation https://www.22q.org/
  - Williams Syndrome Association https://williams-syndrome.org/
  - Noonan Syndrome Foundation https://www.teamnoonan.org/
  - Turner Syndrome Foundation https://turnersyndromefoundation.org/
- Inherited Arrhythmias
  - SADs https://www.sads.org/
- Cardiomyopathies
  - DCM Foundation https://dcmfoundation.org/additional-support/
  - HCM Association https://www.4hcm.org/
  - Children's Cardiomyopathy Foundation https://www.childrenscardiomyopathy.org

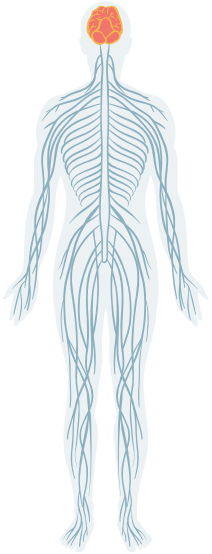
Resource Examples

- ➔ Aortopathies
  - Marfan Foundation https://www.marfan.org/
  - Loeys Dietz Syndrome Foundation https://www.loeysdietz.org/
  - Mended Hearts; Aortic Aneurysm Support Group https://connect.mendedhearts.org
  - John Ritter Foundation https://www.johnritterfoundation.org/

- ➔ Familial Hypercholesterolemia/Dyslipidemias
  - The FH Foundation https://thefhfoundation.org/
  - Lp(a) Support Group https://familylipoproteina.org

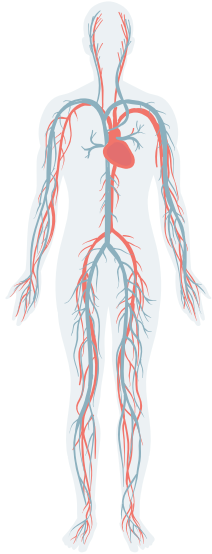
- ➔ Find Guidelines
  - American Heart Association https://www.heart.org/
  - Heart Failure Society of America https://hfsa.org/
  - American College of Cardiology https://www.acc.org
  - Heart Rhythm Society https://www.hrsonline.org/
  - National Lipid Association https://www.lipid.org/

Anatomy Infographics



Nervous

Earth is the third planet from the Sun

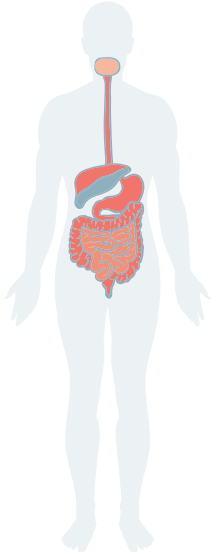


Circulatory

Neptune is the farthest planet from the Sun

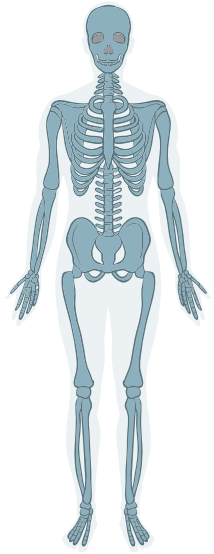
Respiratory

It’s composed of hydrogen and helium



Digestive

Despite being red, Mars is a cold place



Skeletal

Mercury is the closest object to the Sun

Anatomy Infographics

Kidneys

Earth is the third planet from the Sun

Lungs

Neptune is the farthest planet from the Sun

Heart

It’s composed of hydrogen and helium

Tooth

Despite being red, Mars is a cold place

Brain

Mercury is the closest object to the Sun

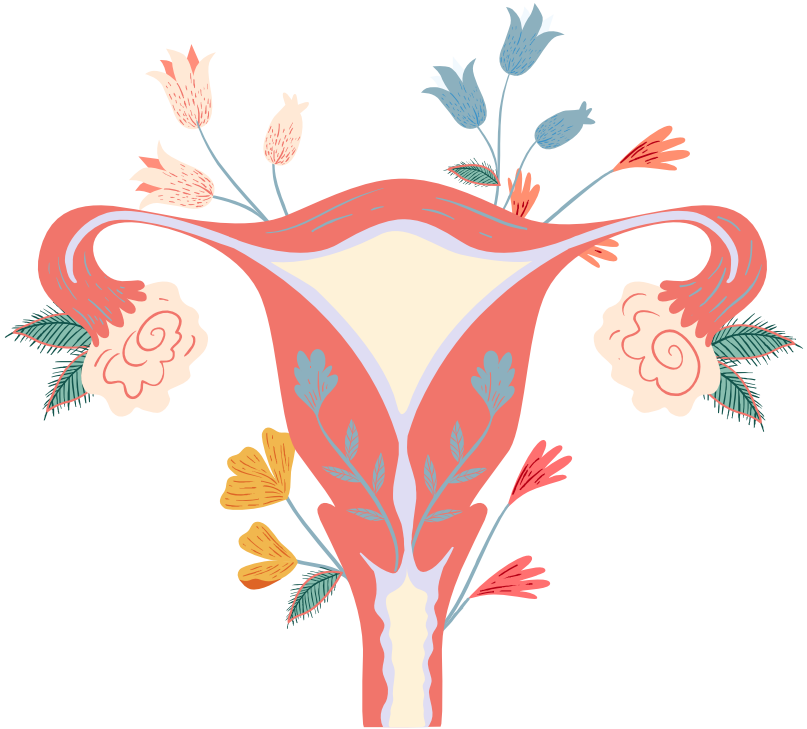
Anatomy Infographics

Ovary

Saturn is composed mostly of hydrogen and helium

Internal os

It’s a gas giant and the biggest object in the Solar System



Fallopian tube

Despite being red, Mars is actually a very cold place

Uterus

It’s the closest planet to the Sun and the smallest one

Anatomy Infographics

45%

Heart

It's a gas giant and the biggest object in the Solar System

65%

Lungs

Despite being red, Mars is incredibly a very cold place

75%

Brain

It is the ringed planet. It is composed of hydrogen and helium

85%

Stomach

It's the closest planet to the Sun and the smallest one

Anatomy Infographics

72 - 76

Despite being red, Mars is a cold place full of iron oxide dust

20 years

72 - 78

Saturn is the ringed planet. It is composed of hydrogen and helium

30 years

74 - 78

Jupiter is a gas giant and the biggest planet in the Solar System

40 years

76 - 82

Mercury is the closest planet to the Sun and the smallest one

50 years

Anatomy Infographics

01

Brain

Neptune is the farthest planet from the Sun

02

Heart

Saturn is a gas giant and has several rings

03

Bones

Despite being red, Mars is a cold place

04

Lungs

Mercury is the closest object to the Sun

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