

Heart disease of Genetic Diseases



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Goals:

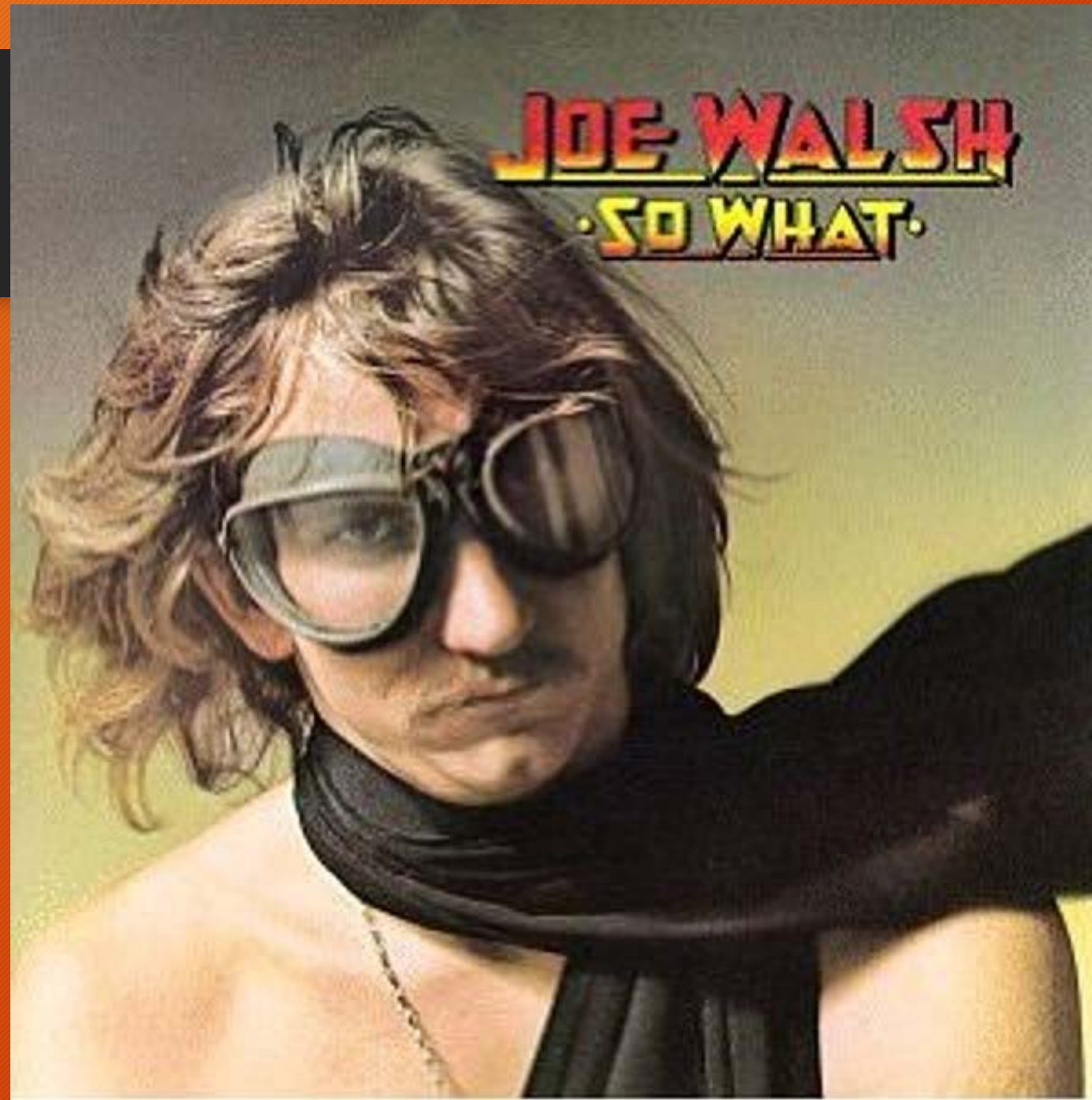
- Review common genetic disease
 - Phenotype
 - Genetic Lesion
- Discuss the associated cardiac lesion
 - Frequency
 - Severity
 - Repair/Palliation

This stuff is everywhere

- 19-36% of spontaneous abortion have chromosomal AND cardiac defects
- Congenital heart defects are the most congenital malformation
 - Depending on who you read it may be as high as 1:100
- Of those born with genetic syndrome 13-18% will have some form of congenital heart disease.

The genetics of congenital heart disease...





Now onto the meat of the presentation





Trisomy 21

- First completely described by a British physician John Down in 1866. Genetic cause was found in 1959.
- Complete trisomy secondary to maternal non disjunction in 94% of patients, mosaicism in about 6%.

Heart disease breakdown

- ~50% are born with congenital heart disease of which ~40% are complete AV canal defects, ~60% when primum atrial septal defects, inlet VSDs and transitional AV canals are included.
- ~75% of patients with complete AV canal have Down syndrome.
- Other associated CHDs include: ASD, VSD, PDA, TOF, coarctation of aorta.

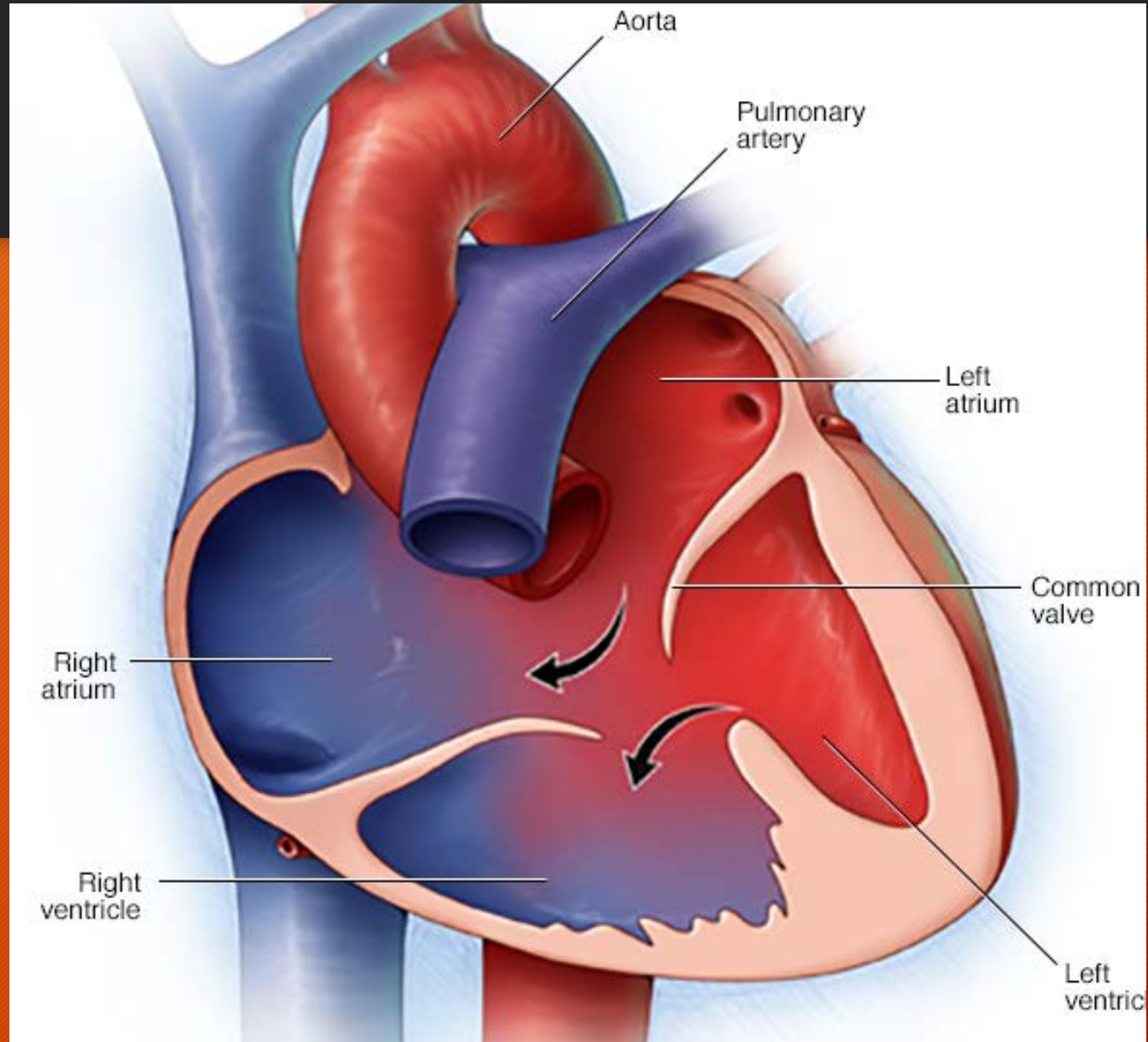


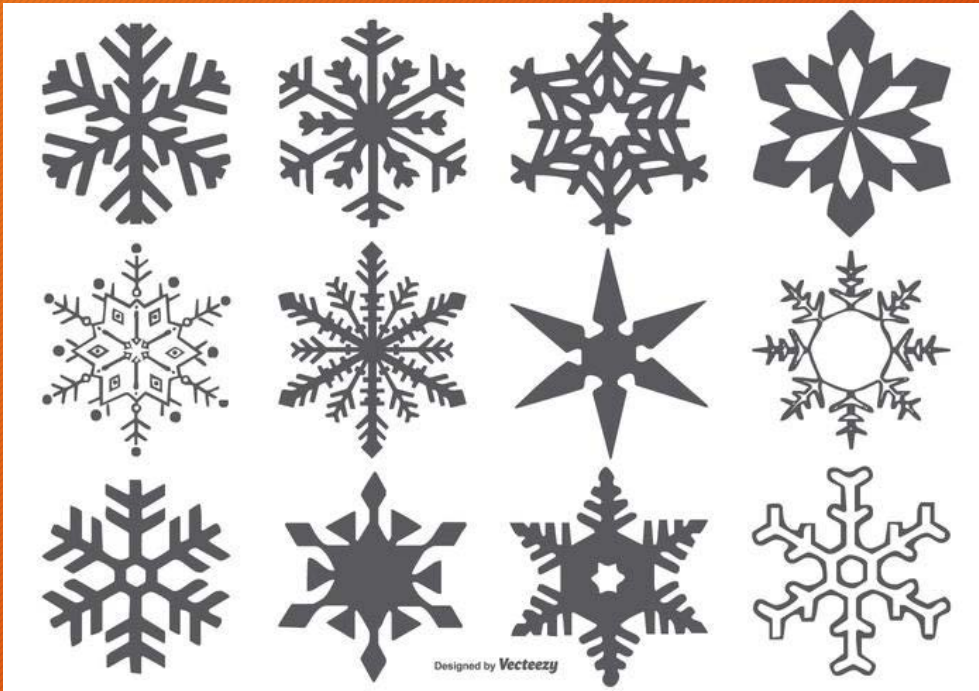
Image from the Mayo Clinic

So how bad is it?



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Well, it's a spectrum



- AV Canals are probably the most varied presentation
 - Some can be safely ignored
 - Some can be tolerated well for the first several months
 - Some are quickly fatal because they may be shunt dependent

Trisomy 21

- Median age at death has increased from 25 to 49 years from 1983 to 1997.
- Similar post operative results as compared to genetically normal patients.
 - 4350 Down syndrome pts/45779 total pts
 - Mortality rates not different
 - Younger at the time of surgery for TOF and AVSD repair
 - Longer duration of stay post ASD/VSD/TOF repair
 - Higher incidence of heart block requiring pacemaker placement post VSD closure

Fudge et al. Congenital heart surgery outcomes in Down Syndrome: Analysis of a national clinical database. Pediatrics, 2010.
Marino et al. Outcome in Down syndrome fetuses with cardiac anomalies. J of Med Gen, 2004.
Reller et al. Is Down syndrome a risk factor for poor outcome after repair of congenital heart disease. J of Peds. 2002



Trisomy 18

- Described in 1960
- Prevalence 1:3000-1:8000 at birth. 3:1 F:M, ~90% died in their first year in life.
- ~90% are complete trisomy, 10% mosaic, <1% translocation
- ~95% have a cardiac lesion. Most common cardiac lesions are: perimembranous VSD, TOF, DORV, polyvalvar dysplasia, AVSD.
- Other comorbidities: Severe developmental delay, growth restriction, central apnea, renal dysplasia, severe reflux.



Trisomy 13

- Incidence 1:2000-1:5000 live births. M=F, 75% complete trisomy, 20% translocation, 5% mosaicism
- ~40% die in first 1 month of life, ~85-90% die within the first year of life.
- ~50-80% have cardiac defects. TOF, DORV, VSD, ASD, PDA, AVSD, polyvalvar disease.
- Other comorbidities: developmental delay, FTT, holoprosencephaly, polydactyly, seizures, deafness, microcephaly, omphalocele, renal dysplasia

Their heart are a little rough



- Not only is there a high incidence of complex heart disease in these patients
 - Very high incidence of pulmonary hypertension
 - Frequently are trach/vent dependent
 - Post operative course is *challenging*

My Data is old

- Several groups have been quite aggressive in managing 13/18
 - Japan reports that cardiothoracic surgery has been effective in increasing the lifespan of these patients
 - Several TS13/18 centers of excellence have sprouted up across the country
- Ethically the debate continues





Turner Syndrome

- Incidence is ~1:2000 live births. ~50% true monosomy, ~33% structurally abnormal X chromosome (milder phenotype), ~13% mosaic turner's 45X/46XY.
- ~30% have CHD. BAV (~25%) may progress to aortic stenosis (~10%), PAPVC (~13%), aortic coarctation (~7-10%), MVP (~5%), HLHS (rare), LSVC, arch anomalies.
- CHD significantly associated with neck webbing.

Mazzanti et al. Congenital heart disease in patients with Turner's syndrome. J of Pediatrics, 1998.
Sybert et al. Turner's syndrome. NEJM 2004.

Turner's Syndrome

- Long term follow up for recoarctation, hypertension, aortic stenosis and regurgitation, and CAD.
- ~33% aortic dilation, ~1.4% aortic dissection. MRI preferred for evaluation in adults, every 5-10 years.
- Spontaneous puberty ~10%, pregnancies 2-5%.
 - Risk for major pregnancy complication ~10%
 - Risk for maternal death ~3.5%

Ho et al. Major vascular anomalies in Turner syndrome: prevalence and MR angiographic features. Circulation, 2004.

Hadnott et al. Exp Rev Obstet Gynecol, 2011.

Trisomy 22

- Complete trisomy 22 is very rare and most fetuses die in utero or shortly after birth.
- Mosaic trisomy 22 is associated with cardiac abnormalities (ASD, VSD, TOF), developmental delay, FTT.
- Emmanuel syndrome: unbalanced translocation 11/22
- Cat eye syndrome/Schmid-Fraccaro syndrome: partial trisomy or tetrasomy. Developmental delay, coloboma of iris (~50% cases), anal atresia, cardiac anomalies (TAPVR/PAPVR), renal anomalies, short stature, scoliosis.



22q11.2 Deletion Syndrome

- Occurs in about 1 in 6000 live births. 6-10% are familial.
- CHD occurs in ~75-80% pts, conotruncal abnormalities (TOF ~15%, IAA type B ~50%, truncus arteriosus ~ 35%), VSD ~ 10%, VSD + aortic arch abnormalities ~45%.
- Hypocalcemia, absent thymus, immunodeficiency, palate anomalies, feeding and speech issues, renal and skeletal abnormalities, cognitive deficiencies and behavioral issues.



Williams-Beuren Syndrome

- 1 per 20,000 live births, AD.
- 7q11.23 deletion in ~90%. ELN gene affected.
- ~55-80 % have CHD, supralvalvar aortic stenosis (45-75%), supralvalvar pulmonary stenosis (30-75%) / pulmonary arterial stenosis, diffuse arteriopathy, VSD/ASD (10%), MVP.
- Hypertension ~ 50%, hypercalcemia ~ 15%, feeding disorders and growth retardation, skeletal and renal abnormalities (renal artery stenosis), cognitive defects, social personality.



Jacobsen Syndrome

- 11q23 deletion.
- ~55% with CHD, VSD 1/3rd, left sided abnormalities/LVOTO 1/3rd.
- Thrombocytopenia/abnormal platelets, short stature, genitourinary problems, pyloric stenosis, and eye issues, varying intellectual disabilities.

Smith-Magenis Syndrome

- 17p11.2 deletion
- CHD in ~10%, assorted CHDs
- Brachycephaly, moderate intellectual disability, aggressive/self injurious behavior, sleep disturbances, eye/ear abnormalities





Alagille Syndrome

- Deletion of ch 20p12. AD mutation of *JAG 1* (~94% patients) / *NOTCH 2* genes.
- Presence of bile duct paucity on liver biopsy with 3 out of the 5 following features:
 - CHD ~90%
 - PPS (~60%), PS, TOF, ASD, VSD, coarctation
 - Arteriopathy
 - Cholestasis
 - Skeletal abnormalities
 - Ocular abnormalities, embryotoxon
 - Typical facial features



Holt-Oram Syndrome

- Cardiomegalic syndrome
- AD, chromosome 12q24, *TBX 5* gene
- All have upper extremity skeletal abnormalities involving preaxial radial ray.
- CHD ~75%, ASD ~60%, VSD ~30%, AVSD, conotruncal anomalies, left sided lesions.
- AV block (1st-3rd degree) can also be seen.



Rasopathies

- Ras/mitogen- activated protein kinase (MAPK) pathway defects or Noonan Syndrome Spectrum.
- Role in cell proliferation, differentiation, survival and cell death.
- Noonan syndrome, cardiofasciocutaneous syndrome, Costello syndrome, LEOPARD syndrome.
- Distinctive facial appearance, cardiovascular abnormalities, musculocutaneous abnormalities, intellectual disability.
- CHD, HCM, arrhythmias.

Noonan Syndrome

- Incidence 1:1000-2500 live births. First described in 1962. M:F 1:1.
- Genes: *PTPN11* (most common, ~50%), *RAF1*, *SOS1*, *KRAS*, *NRAS*, *BRAF* and *SHOC2*.
- Cardiovascular abnormality ~80% (60% CHD, 20% HCM). PS (25-35%), ASD, VSD, TOF, pulmonary artery stenosis, coarctation, AVSD, polyvalvulopathy
- Other comorbidities: intellectual disability, abnormal lymphatic tissues, bleeding diathesis, cryptorchidism.

Other Rasopathies

- LEOPARD syndrome
 - PTPN11 gene mutation
 - Multiple Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary valve stenosis, HCM, Abnormal genitalia, growth Retardation, SN Deafness
- Costello syndrome
 - Ulnar hand deviation, hyperpigmentation, loose skin, deep palmer and planter creases, Chiari 1 malformation, developmental delay, rhabdomyosarcoma ~10%
 - HCM more common in Costello and LEOPARD syndrome
 - Multifocal atrial tachycardia
- Cardiofasciocutaneous syndrome
 - coarser facial features, dry skin, eczema, hyperkeratosis, severe intellectual disability

CHARGE Syndrome

- 1:10,000-15,000. Mutation of *CHD7* gene on chromosome 8q12.1, ~65% patients.
- Coloboma, Heart defects, choanal Atresia, growth Retardation/brain anomalies, Genitourinary problems, external Ear anomalies.
- CHD ~90%, conotruncal and arch anomalies.
- New associations: cranial nerve palsy (7th), oral clefts and swallowing difficulties, developmental/behavioral disorders (autism).



Kabuki syndrome

- *MLL2* gene mutation, encodes methyl transferase.
- Characteristic facial appearance.
- CHD ~45-55%, ASD, VSD, left sided lesions (HLHS, Shone's).
- Renal and digital abnormalities, immunological and feeding problems (cleft lip and palate), intellectual disability.



Cornelia de Lange syndrome



Rubinstein-Taybi syndrome



Other Autosomal Dominant Syndromes

- Cornelia de Lange syndrome
 - *NIPBL*, *SMC1A* gene
 - CHD ~25%, VSD, ASD, PS, HCM
 - Upper limb deficiencies, GI anomalies
- Rubinstein-Taybi syndrome
 - *CREBBP*, *EP300* genes
 - CHD ~ 40%, PDA, ASD, VSD, coarctation, HLHS
 - Broad thumbs and great toes
- Char Syndrome
 - *TFAP2B* gene
 - CHD ~20-70%, PDA, muscular VSD
 - Anomalies of 5th finger, supernumerary nipple



Ellis-van Creveld Syndrome



Smitz-Lemli-Opitz Syndrome

Autosomal Recessive Syndrome

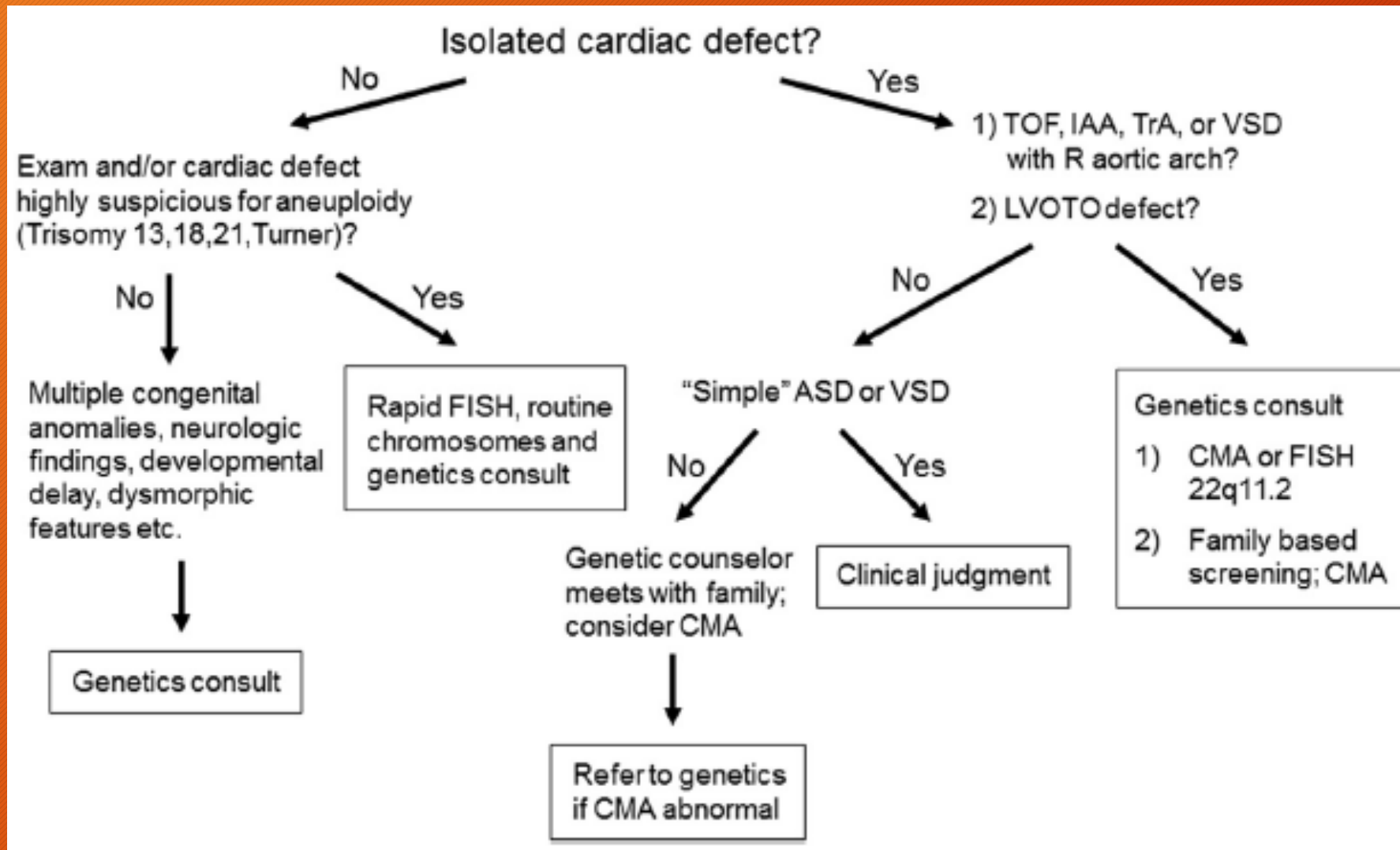
- Ellis-van Crevald Syndrome
 - *EVC* gene on ch 4, AR
 - CHD ~ 70%, common atrium and ASD most common (~40%), MV/TV abnormalities, AVSD.
 - Short limbs, polydactyly, hypoplastic nails, dental anomalies
- Smitz-Lemli-Opitz Syndrome
 - *DHCR7* gene
 - CHD ~ 45%, ASD, VSD, AVSD, TAPVR
 - Syndactyly, cleft palate, lung anomalies, genital anomalies, neuropsychiatric and neurodevelopmental issues (autism)

Pulmonary Outflow Obstruction

- Pulmonary valve stenosis
 - Noonan's syndrome
 - Alagille syndrome
 - Costello syndrome
 - LEOPARD syndrome
- PA branch stenosis
 - Alagille syndrome
 - William-Beuren syndrome
 - Noonan Syndrome
- Pulmonary atresia
 - Ring 9 chromosome abnormality

Aortic Outflow Obstruction

- BAV
 - Turners, trisomy 13, 18
- Aortic valve stenosis
 - Jacobsen's syndrome
 - Trisomies (13, 18)
- Supravalvar aortic stenosis
 - Williams-Beuren syndrome
- Coarctation of the aorta
 - Turner's syndrome



Thank you!

