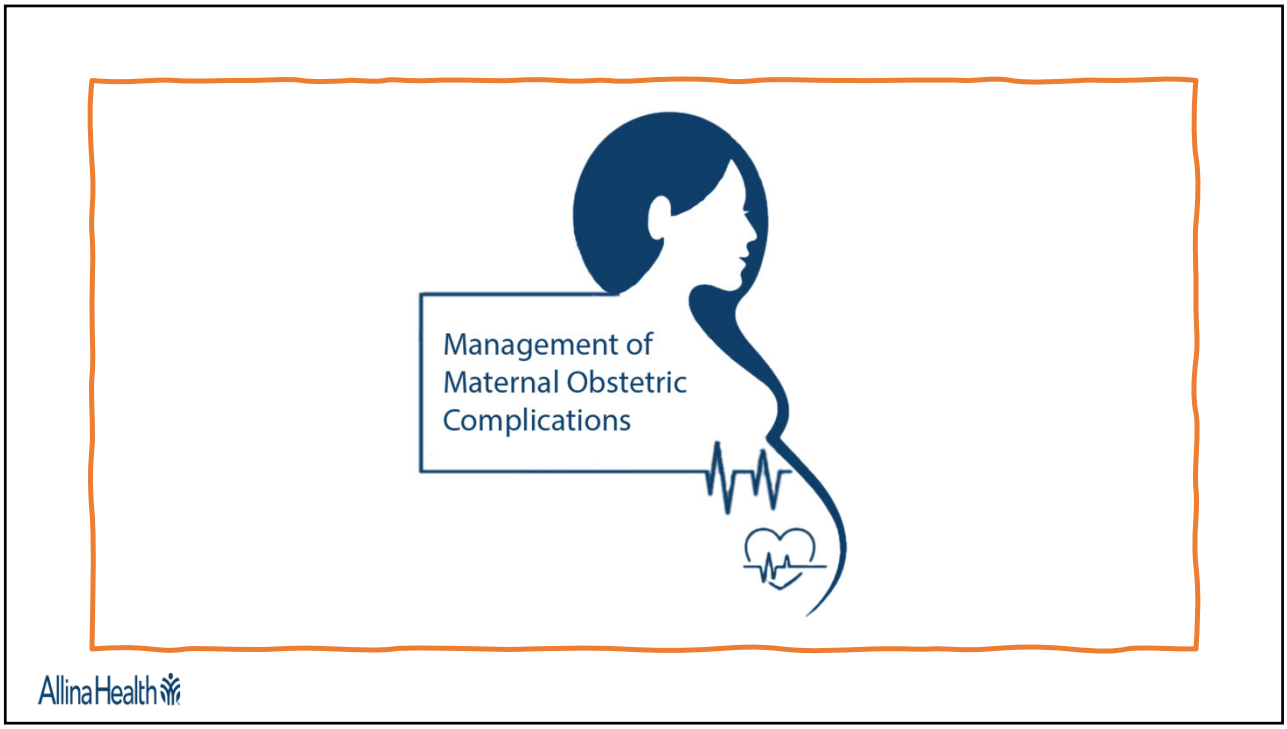


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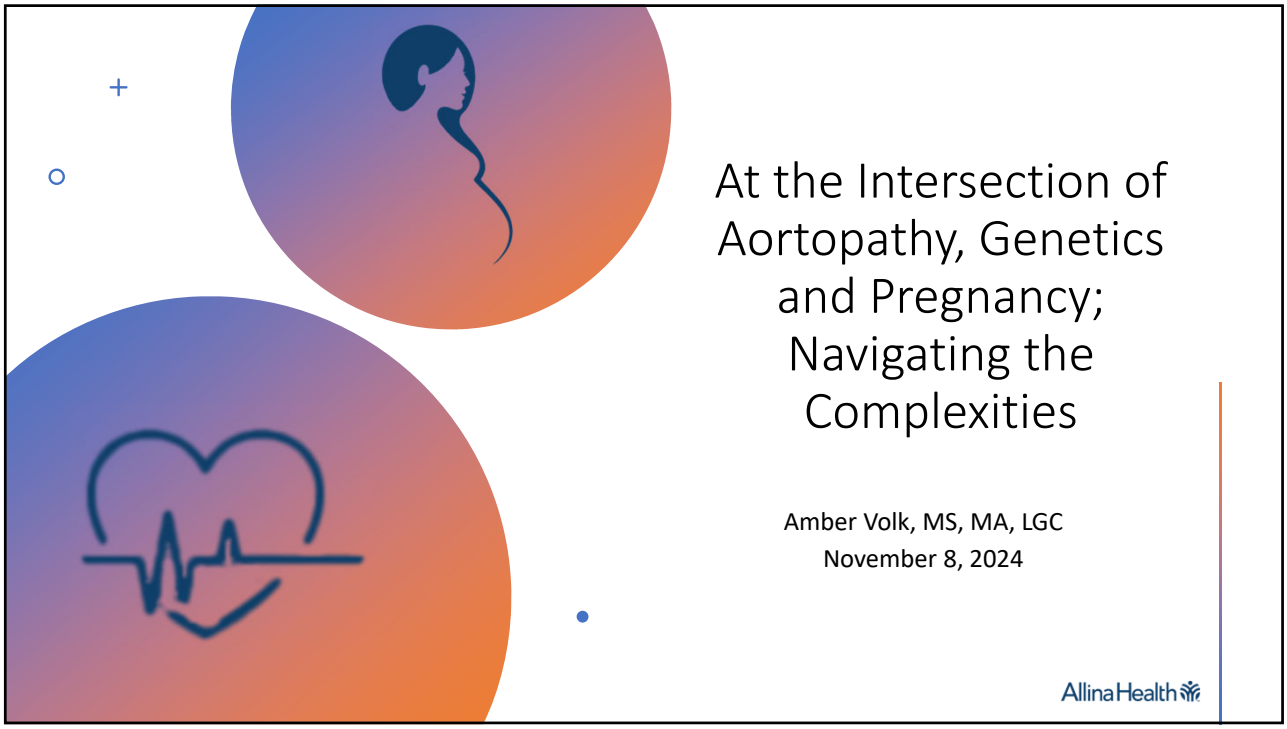


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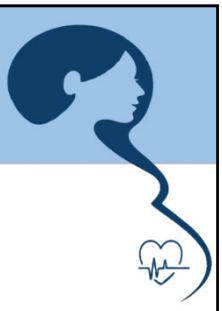
# Disclosures



- Genetic counselor with Minnesota Perinatal Physicians

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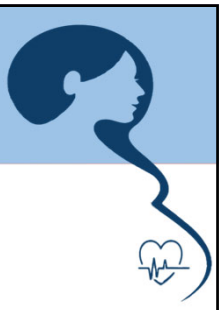
# Objectives



- Define aortopathy
- Examine data regarding aortopathy and pregnancy
- Analyze how genetics assists

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# Aortopathy

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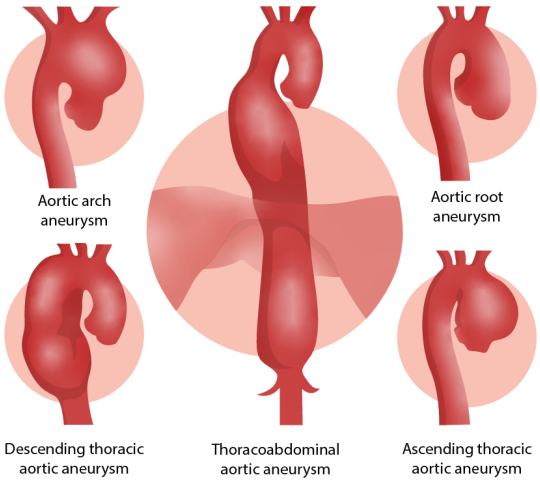
# Aortopathy Defined

## Aortic Aneurysm

- Localized increase of aortic diameter
- Abdominal aortic aneurysm (AAA)
  - Atherosclerotic disease, genetic?
- Thoracic aortic aneurysm (TAA)
  - Up to 25% will have mutation found (Heritable thoracic aortic disease HTAD)
  - Aortic root/ascending – 60% (highest genetic risk)
  - Descending – 40%
  - Arch – 10%
  - Thoracoabdominal – 10%

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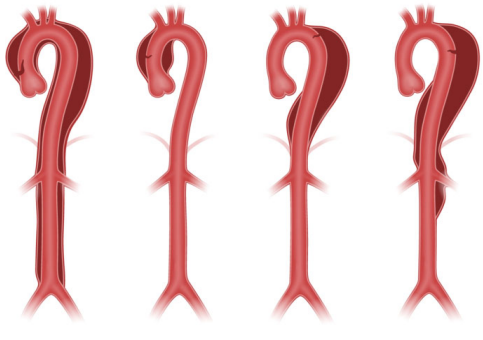
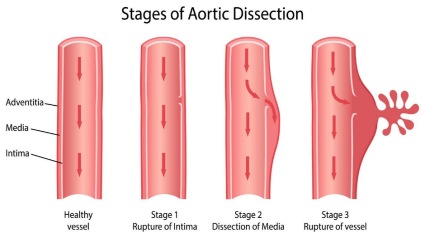
# Aortopathy Defined




## Aortic dissection

- Tear in intima, leading to dissection of media and without treatment, rupture of vessel
- Prompt diagnosis crucial as mortality increases 1-2% per hour without therapy

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# Aortopathy and Pregnancy

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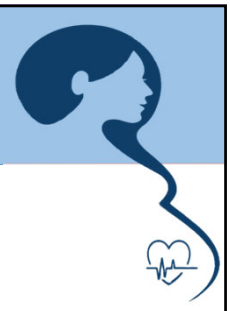
# Aortopathy in Pregnancy



- Most common cause of death in pregnancy?
  - Aortic dissection
- Occurs in 0.0004% of pregnancies
  - ~25% risk for death if during pregnancy
- Most events occur in 3rd trimester or first 12 weeks postpartum

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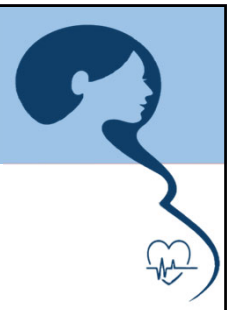
# Registry of Pregnancy & Cardiac Disease



- Prospective Registry
- 6,000+ individuals
- 189 thoracic aortic disease
  - 50% had an underlying condition
    - Marfan, BAV, Turner (Monosomy X), vEDS
- Most events occur in 3rd trimester or within 12 weeks postpartum

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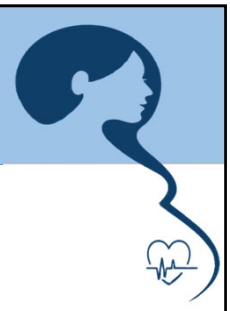
# International Registry of Acute Aortic Dissection



- 1998-2018; multicenter
- 105 individuals with aortic dissections
- 25% occurred during pregnancy or within 12 weeks postpartum (27)
  - 74% had underlying TAA disease or a family history (20)
  - Additional data on 15 individuals –
    - 53% had known predisposing aortopathy prior to dissection (8)
    - 47% discovered specific aortopathy only after dissection occurred (7)
- 47% did not have aortopathy recognized themselves until the dissection
  - Netherlands study – mortality was 3 per 100,000 – 45% due to aortic dissection

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# Importance of Genetics to Understand and Manage Risk

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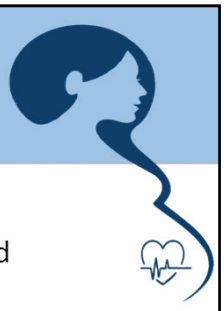
## GenTAC information



- National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions
- 184 individuals with Marfan Syndrome
- 10% experienced a pregnancy-related aortic complication
  - 8 dissections; 2 significant aortic growth
    - 63% dissections postpartum period
  - 38% didn't know they had Marfan until after the dissection (3)

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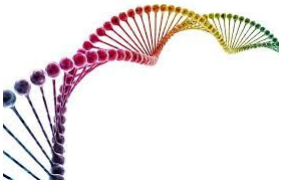
## 2023 Kim et. al. paper

- 575 enrolled individuals (2016-2020) from Genetic Aortopathy Registry in Seoul, Korea
  - Patients with dissection, aortic root aneurysm and their first-degree relatives (FDRs)
- Genetic finding:
  - 27.1% with dissection
  - 39.4% with aneurysm
  - If family history – increased to 72.4%!
    - 20% of FDRs that were screened were identified to have an aortic aneurysm!



- Common genes:
  - *FBN1, TGFBR1, TGFBR2, SMAD3, COL3A1, COL5A2, ACTA2*
- Both syndromic and nonsyndromic genetic aortopathy conditions identified

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## Syndromic vs Nonsyndromic

- 40+ genes currently known
- Syndromic –
  - HTADs that have associated extracardiac features which may be noted on physical exam or diagnostic workup
  - May have pregnancy risk beyond aortopathy
    - vEDS with 2% risk for uterine rupture
- Nonsyndromic –
  - Familial HTADs without evidence of connective tissue disorder or other congenital conditions
  - Higher risk to learn secondary to an event
    - ACTA2 example: accounts for 15% of nonsyndromic TAD; accounts for 20% of pregnancy dissection risk
- Features may be subtle or nonexistent beyond family history
- Either changes general risk and management, as well as pregnancy management

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## Syndromic HTAD

| Condition | Gene | Clinical Features |
|---|---|---|
| **Syndromic HTAD*** | | |
| Marfan syndrome | *FBN1* | Aortic root aneurysm, aortic dissection, TAA, MVP, long bone overgrowth, arachnodactyly, dolichostenomelia, scoliosis, pectus deformities, ectopia lentis, myopia, tall stature, pneumothorax, dural ectasia |
| Loeys-Dietz syndrome | *TGFBR1, TGFBR2, SMAD3,† TGFB2, TGFB3* | TAA, branch vessel aneurysms, aortic dissection, arterial tortuosity, MVP, craniosynostosis, hypertelorism, bluish sclera, bifid/broad uvula, translucent skin, visible veins, club feet, dural ectasia, and premature osteoarthritis and peripheral neuropathy† |
| Vascular Ehlers-Danlos syndrome | *COL3A1* | TAA, AAA, arterial rupture, aortic dissection, MVP, bowel and uterine rupture, pneumothorax, translucent skin, atrophic scars, small joint hypermobility, easy bruising, carotid-cavernous fistula |
| Arterial tortuosity syndrome | *SLC2A10* | Tortuous large and medium sized arteries, aortic dilation, craniofacial, skin and skeletal features |
| Shprintzen-Goldberg syndrome | *SKI* | Craniosynostosis, skeletal features, aortic dilation |
| Ehlers-Danlos syndrome with periventricular nodular heterotopia | *FLNA* | X-linked, periventricular nodular heterotopia, TAA, BAV, MV disease, PDA, VSD, seizures, joint hypermobility |
| Meester-Loeys syndrome | *BGN* | X-linked, TAA, aortic dissection, MV disease |
| *LOX*-related TAA | *LOX* | TAA, BAV, aortic dissection, Marfanoid habitus in some |
| Smooth muscle dysfunction syndrome | *ACTA2* | TAA, moyamoya-like cerebrovascular disease, pulmonary hypertension, pulmonary disease, hypoperistalsis, hypotonic bladder, congenital mydriasis[11] |

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## Nonsyndromic HTAD

| Nonsyndromic HTAD (Familial TAA) | | |
|---|---|---|
| FTAA | *ACTA2* | TAA, aortic dissection, premature CAD and moyamoya-like cerebrovascular disease, livedo reticularis, iris flocculi |
| FTAA | *MYH11* | TAA, aortic dissection, PDA |
| FTAA | *MYLK* | Aortic dissection at relatively small aortic size |
| FTAA | *PRKG1* | Aortic dissection at young ages at small aortic sizes |
| FTAA | *MAT2A* | TAA, aortic dissection, BAV |
| FTAA | *MFAP5* | TAA, aortic dissection, skeletal features may be present |
| FTAA | *FOXE3* | TAA, aortic dissection |
| FTAA | *THSD4* | TAA, aortic dissection |

| Condition | Gene | Clinical Features |
|---|---|---|
| **Bicuspid Aortic Valve–Associated Ascending Aortic Aneurysm** | | |
| Familial BAV/AS and TAA | *NOTCH1* | Aortic valve stenosis, TAA |
| BAV with TAA | *TGFBR2, MAT2A, GATA5, SMAD6, LOX, ROBO4, TBX20* | Syndromic and nonsyndromic HTAD and FTAA with an increased frequency of BAV |
| Turner syndrome | *XO, Xp* | BAV, CoA, TAA, aortic dissection, short stature, lymphedema, webbed neck, premature ovarian failure |

Nonsyndromic HTAAD – reduced penetrance, age-dependent penetrance, variable expressivity

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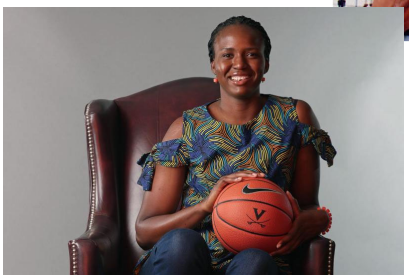
## Marfan Syndrome

- *FBN1*
- Ghent criteria
  - ~78% meet Ghent
- From suspicion to diagnosis - average 641 days
- Median diagnostic age – 19
- Up to 10% experience pregnancy related aortic complication
  - Study noting ~35% were unaware they had Marfan syndrome before aortic complication during pregnancy



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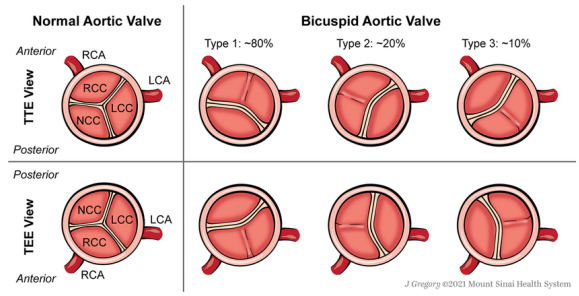
# Bicuspid Aortic Valve




- ~2% general population
  - If FDR has BAV, risk is 10 times higher
- 50% will need some form of surgery/medical management
  - 25% will need aortic surgery
  - 8-fold risk for an emergency aortic dissection over the general population
- Risk increases for dissection when aortic dilation >40mm
  - 35-80% will have dilation of ascending aorta
- Up to 10% underlying single gene mutation identified
  - *NOTCH1, TGFBR2, FBN1, SMAD6*
- Monosomy X (Turner's syndrome)
  - Those with BAV typically have aortic complications in their 20s/30s versus older for HTAD

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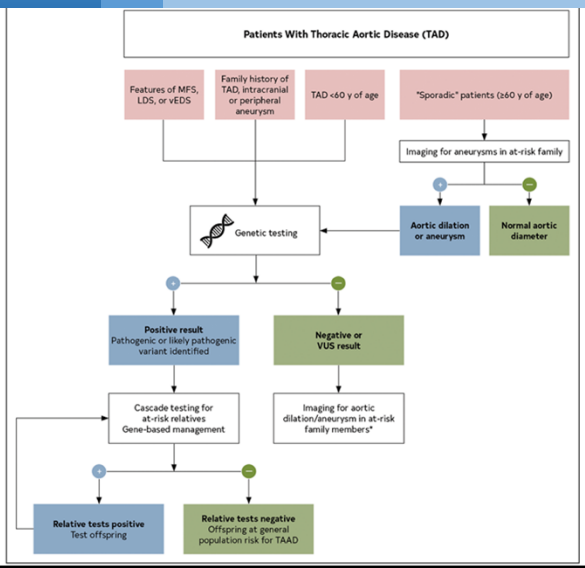
# Further investigation – When?

- Personal history aortic root aneurysm
- Personal history dissection <50 years of age
- Personal history multiple aneurysm(s) and/or dissection
- Family history of any of above

- No gene found? May still have underlying condition; FDRs still need screening
  - Also important that if there isn't a genetic test ruling a FDR out, they are still at risk. A single normal aortic size does not equal no disease.
  - Nonsyndromic HTAAD is familial 20-25% of the time

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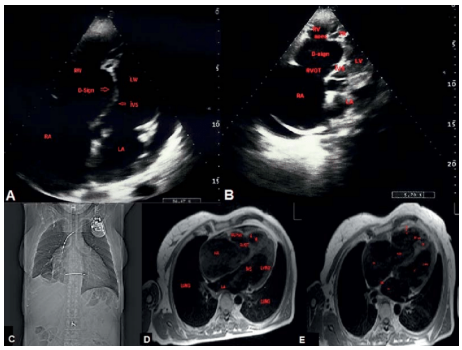
## The So What? Surveillance/Management

- Surveillance may require more than just TTE, but CT and MRI
  - During pregnancy, may need more often
  - Marfan and Loeys Dietz both known to have pregnancy accelerated aortic root growth
- Early screening
- Exercise restrictions
- Abstinence from smoking
- Medical therapy
- Surgical therapy



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## Recommendations for Prophylactic Surgery

| Genetic condition | Aortic root size (cm)/aortic size index (cm/m$^2$) to consider prophylactic surgery |
|---|---|
| Marfan syndrome | >4.5 cm |
| | 4.0–4.5 cm if there are other risk factors present (family history of aortic dissection, rapid aortic growth >3 mm/year) |
| Loeys-Dietz syndrome | ≥4.0 cm if *TGFBR1*, *TGFBR2*, *SMAD3* variants |
| | ≥4.5 cm if *TGFB2*, *TGFB3* variants |
| Bicuspid aortic valve | ≥5.0 cm |
| Turner syndrome | ≥2.5 cm/m$^2$ |
| Non-syndromic heritable thoracic aortic aneurysm disease | ≥4.5 cm |

Adapted from ACC/AHA guidelines (20). ACC/AHA, American College of Cardiology/American Heart Association.

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## Recommendations for Pregnancy

| Preconception | Antepartum | Delivery | Postpartum |
|---|---|---|---|
| • Discussion of CV risk<br>• Medication review<br>• Imaging of aorta, vascular, and spine for risk assessment<br>• Discussion of heritability risk to offspring | • Assembly of multi-disciplinary team (cardiac, obstetric, genetics, anesthesia) for pregnancy care and delivery planning<br>• Confirm CV surgery available at planned delivery hospital<br>• Administration of beta-blocker if tolerated<br>• Aortic imaging surveillance in pregnancy | • Multi-disciplinary care plan for mode and timing of delivery based on genetic condition, pathogenic mutation, and aortic imaging<br>• Anesthesia consultation and plan of care to minimize fluctuations in blood pressure and heart rate during delivery | • Patient and care team education about risks of aortic events postpartum<br>• Imaging of aorta vasculature 3–6 months after delivery<br>• Ensure long-term follow-up plan in place for CV care |

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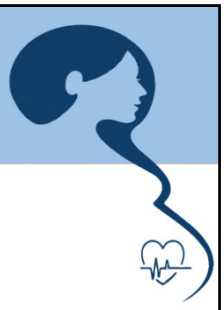
## More Specifically…..



- Receive multidisciplinary evaluation and counseling in preconception setting
  - Discuss both maternal (6-10%) and fetal (10-20%) risk before pregnancy
- Genetic testing offered and recommended before pregnancy
  - Risks/repair are different by gene
- Pre-pregnancy imaging
  - Provides risk information - 1% vs 10%
- Beta blocker therapy
  - Metoprolol preferred in pregnancy through 6-12 weeks postpartum
- Delivery in hospital with emergency cardiothoracic surgery
  - Adequate analgesia/anesthesia recommended
- Prophylactic surgery as indicated
  - In setting of significant dilation, before conception/avoid pregnancy

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## Barriers/Options for Genetic Testing

| Barriers | Options |
|---|---|
| Insufficient awareness | Preparation/Management |
| Additional cost | Preimplantation Genetic Testing – Mutation |
| Concern for stigma | Prenatal diagnosis |
| Guilt | Surrogacy |
| Access | Donor gametes |
| Lack of simple, straightforward testing | Adoption |

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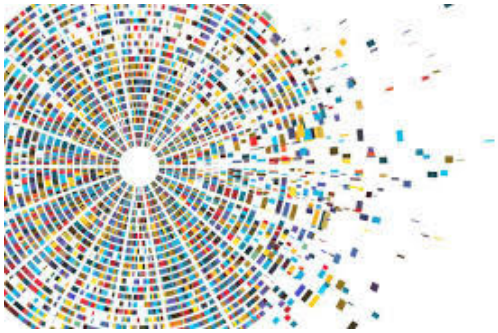
## Pearls for Practice

- Personal and family history questions are important
- Additional information can save lives
- Genetics plays an important role
- Refer/reach out to specialists



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# Questions? Concerns?

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651.241.6210 (direct)

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