Meet Me at the Crossroads:
The intersection of genetics and fetal intervention

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Objectives

- Examine traditional involvement of genetics within the fetal intervention space
- Illustrate the need for involvement of genetic counselors and advanced prenatal testing when assessing patient candidacy for fetal intervention

A brief history…

- The Fetal Treatment Center for UCSF – established in the early 1980s by Dr. Michael Harrison
  - First successful open surgery for LUTO – 1981
  - Open surgical resection of fetal congenital adenomatoid malformation – 1984
  - First open repair of CDH – 1989
- Many major centers then followed in numerous states
- UK and Europe later followed and Eurofetus was formed

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A brief history…

- North American Fetal Treatment Network est. in October 2004 by four perinatologists
- MFMs began leading many fetal centers in the country with their pediatric surgery colleagues
- ACOG Committee Opinion #501 (2011)
  - Commentary by ACOG and AAP regarding best practices for fetal care centers, such as having oversight, role of research, proper informed consent, multidisciplinary teams, accumulation of outcomes data

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Fetal therapy breakthroughs

- Fetal intervention for hemolytic disease of the fetus and newborn (HDFN) developed after decades of trial and error
- Twin-to-twin transfusion (TTTS) trial in Europe showed laser therapy ideal over then gold standard, amnioreduction
- Management of Myelomeningocele (MOMS) trial in the US
  - Vanderbilt, UCSF, CHOP with GWU monitoring data
- And many others…

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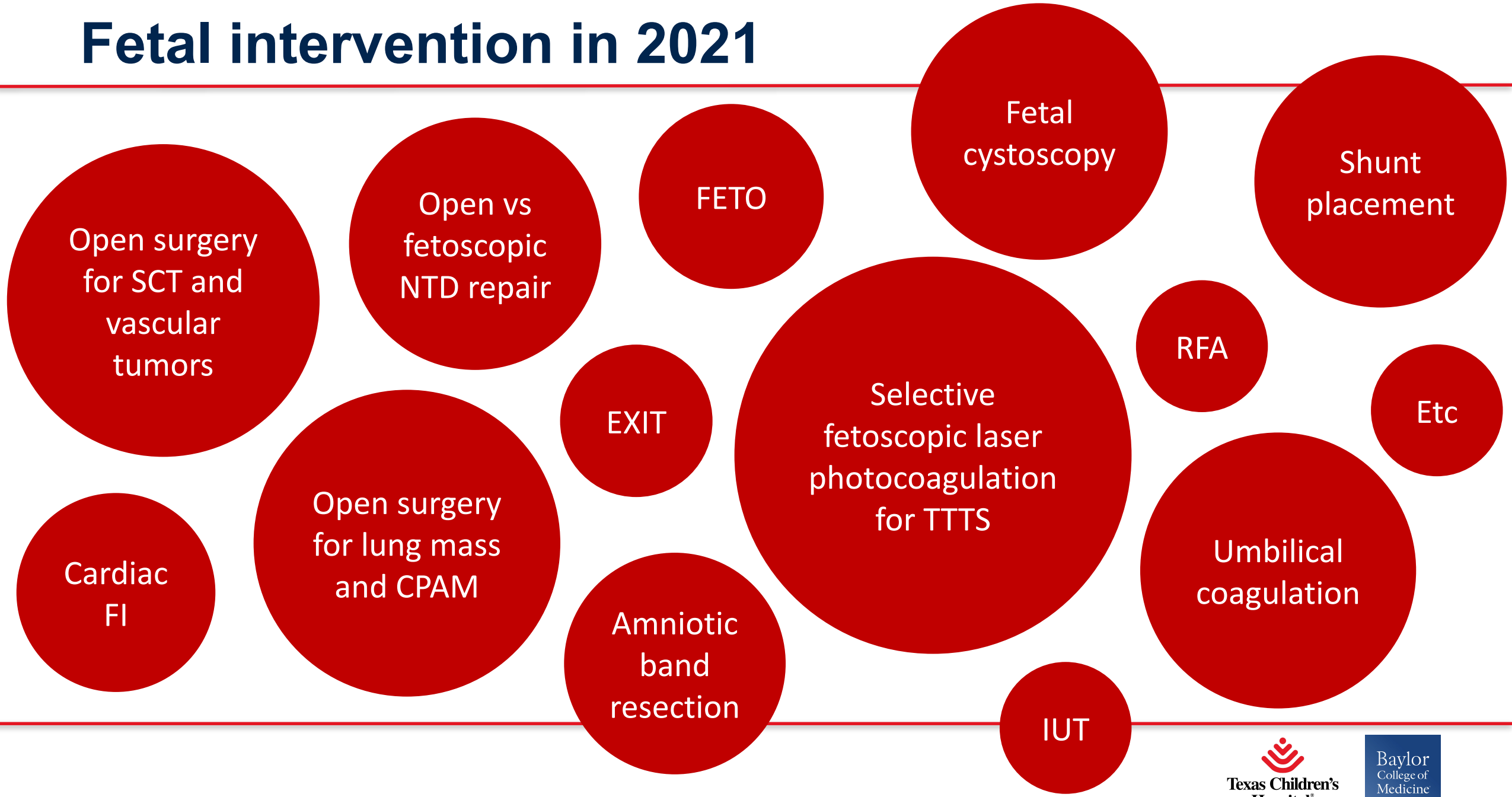
Fetal intervention in 2021



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Eligibility for fetal intervention

- Common inclusion criteria
  - Anomaly in which FI would improve outcome
  - No significant maternal health/obstetrical history
  - Availability within specific window
  - Singleton pregnancy
  - Support system
- Common exclusions include presence of other anomalies, significant maternal history, and multiples

Eligibility for fetal intervention

- Genetic testing criteria varies across protocols and centers
- Clinical trials and minimal testing requirements
  - MOMS: Karyotype
    - FISH adequate if pushing deadline for surgery
  - TOTAL and other FETO trials: Karyotype or CMA
  - RAFT: Karyotype or CMA
- Other forms of FI have limited or no requirements (ex: FISH for LUTO)

Examples of inclusion/exclusion criteria

- TOTAL trial: Anatomically and chromosomally normal fetus
- Fetoscopic NTD: Normal karyotype and/or normal chromosomal microarray (CMA)
  - FISH acceptable if the patient is at 24 weeks or more
- FETO (TCH): Fetal aneuploidy, known structural genomic variants, other major fetal anomalies, or known syndromic mutation
- RAFT: No significant pathogenic or likely significant pathogenic findings on Karyotype or Microarray

A day in the life of a fetal center GC

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Lower urinary tract obstruction

- G1P0 at 17w0d referred for megacystis
- No prenatal screening yet
- Family history of CAKUT
  - 1st brother's son – Prune Belly syndrome, currently in NICU
  - 2nd brother's son – IUFD, suspected renal disease but limited information

Lower urinary tract obstruction

- Multiple anomalies:
  - Dilated posterior urethra and bilateral mild hydronephrosis
  - Suspected CNS anomaly - cerebellum appeared abnormal with an increased cisterna magna
  - Complex CHD - ventricular septal defect, small pulmonary artery, and possible abnormal position of the aorta
- Amniocentesis possible
  - FISH and karyotype – trisomy 13
- Bladder shunt not offered

Neural tube defect

- G1P0 at 20w3d referred for suspected spina bifida
- NIPT low risk for common trisomies/SCAs, MSAFP 7.2 MoM
- Family history of recurrent pregnancy loss
  - Mother with history of SABx4 (all first trimester)
  - Only child
- US/MRI: myeloschisis (beginning at L3 and extending through the sacrum), Chiari II malformation, and mild supratentorial ventriculomegaly
- Patient elected amniocentesis as desired fetoscopic NTD repair

Neural tube defect

- Karyotype results:
  - 46,XY,t(12;14)(q22;q32.1)
- Many internal discussions – are they ineligible now?
  - Protocol stated normal karyotype or CMA
  - Decided CMA would need to be performed to determine candidacy
- CMA normal
  - Agreed to offer FI based on this result and that the translocation was likely familial given the history of RPL
- Patient confirmed to be balanced translocation carrier

Congenital diaphragmatic hernia – case 1

- G1P0 at 28w3d referred for FETO evaluation
- NIPT low risk for common trisomies
- Amniocentesis results pending at time of referral
- No pertinent family history
- US/MRI:
  - Severe IUGR (1st %ile)
  - Left CDH (O/E TFLV 20-23%), 38% liver herniated into chest
  - Relatively large and bilaterally symmetric germinal matrix pseudocysts

Congenital diaphragmatic hernia – case 1

- Results returned after first day of evaluations, but 1 hour before GC
- Abnormal CMA:
  - 3.16 Mb interstitial deletion of 15q25.2q25.3
- 15q25 deletion syndrome (OMIM 614294)
  - CDH, intellectual disability, neurodevelopmental/psychiatric conditions, poor growth, short stature, Diamond-Blackfan anemia, and cryptorchidism
- No longer FETO candidate
- Family elected palliative care

Congenital diaphragmatic hernia – case 2

- G6P3023 at 22w5d referred for FETO eval
- NIPT low risk for the common trisomies, monosomy X, triploidy/vanishing twin, and 22q11.2 deletion syndrome
- Niece with Down syndrome, cleft lip/palate, and CHD
- US/MRI:
  - Large left-sided CDH containing liver, stomach, spleen, and bowel
  - O/E TFLV of 60.8%, 26% of the liver herniated into the chest

Congenital diaphragmatic hernia – case 2

- Small copy number gain of 483 Kb at 1p32.3
  - Maternally inherited
  - No known disease association with this region
  - Likely a benign familial copy number variant
- Discussion amongst the team (many, many discussions)
  - Protocol stated known microdel/dup syndromes are exclusions
  - Since CNV expected to benign, still considered candidate for FETO after input from genetics team

Cardiac fetal intervention

- Aortic valvuloplasty and atrial septostomy
  - Offered by certain centers in the US with variable genetic testing requirements
- Initially diagnostic testing not required prior to CFI at our institution
  - Testing recommended (particularly FISH) but did not need karyotype or CMA results in advance due to timing of procedure and need to move quickly
- … but sometimes things need to change

Cardiac fetal intervention – case 1

- Critical aortic stenosis with evolving features of hypoplastic left heart syndrome
  - Fetal aortic balloon valvuloplasty
- Amniocentesis performed same day as CFI
- Post-op: pericardial effusions (drained), numerous moments of bradycardia, ascites/scalp edema, and signs of fetal anemia
  - IUFD on POD1
- Amniocentesis results:
  - Mosaic tetraploidy (92,XXYY/46,XY)
  - Detailed review of available cells showed ~60% of cells tetraploid

Cardiac fetal intervention – case 2

- Critical aortic stenosis, abnormal mitral valve, intact atrial septum, dilated left ventricle with severe dysfunction, endocardial fibroelastosis, IUGR
- Amniocentesis a few days before CFI procedure - FISH required due to critical AS/IUGR in a female fetus
- Normal FISH and aortic valvuloplasty scheduled
- Final amniocentesis results
  - CMA: contiguous regions of AOH on 8, data suspicious for low level T8M
  - Karyotype normal (46,XX) – T8M confirmed on postnatal blood sample
- Numerous other cases of chromosome abnormalities prompted team discussion and change – now require karyotype/CMA before CFI

Persistent fetal anemia

- G1P0 at 26w5d referred due to concerns for fetal anemia
  - Elevated MCA-PSV 1.8 MoM suggestive of fetal anemia
  - Cardiomegaly, placentomegaly, rim of pericardial effusion
- Underwent cordocentesis/IUT 7x due to unexplained fetal anemia
- Postnatal testing identified biallelic SPTA1 variants:
  - Hereditary spherocytosis
- Presented in next pregnancy with fetal anemia
  - Diagnosis helped prepare team for what to expect (i.e., frequent IUTs and need for frequent transfusions after birth)

Nonimmune fetal hydrops

- G2P1001 at 21w5d referred for bilateral pleural effusions
- Amniocentesis performed and all studies normal:
  - FISH, CMA, AFAFP, viral PCR
  - Rapid trio WES ordered
- While waiting for results, patient had 2nd opinion and fetus had developed hydrops (PEs, ascites, skin edema)
- De novo likely pathogenic variant identified in FLT4
  - Lymphatic malformation 1 (OMIM 153100)
- Provided explanation for NIHF and persistent fluid collection despite continued interventions

Take home messages

- Genetics has played an important role in the history of fetal intervention, and is definitely not going away!
- As both fetal therapy and prenatal diagnostic testing continue to advance, GCs are needed in this space more than ever:
  - Educate the patients and team on complex genetic testing results and the implications
  - Engage in team discussions regarding the ethics of offering vs denying FI in the setting of abnormal results
- Reality is messier than what was expected – keep an open mind

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Thank you!