The Evolving Paradigm of Prenatal Therapy for Cystic Fibrosis

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Conflicts of Interest

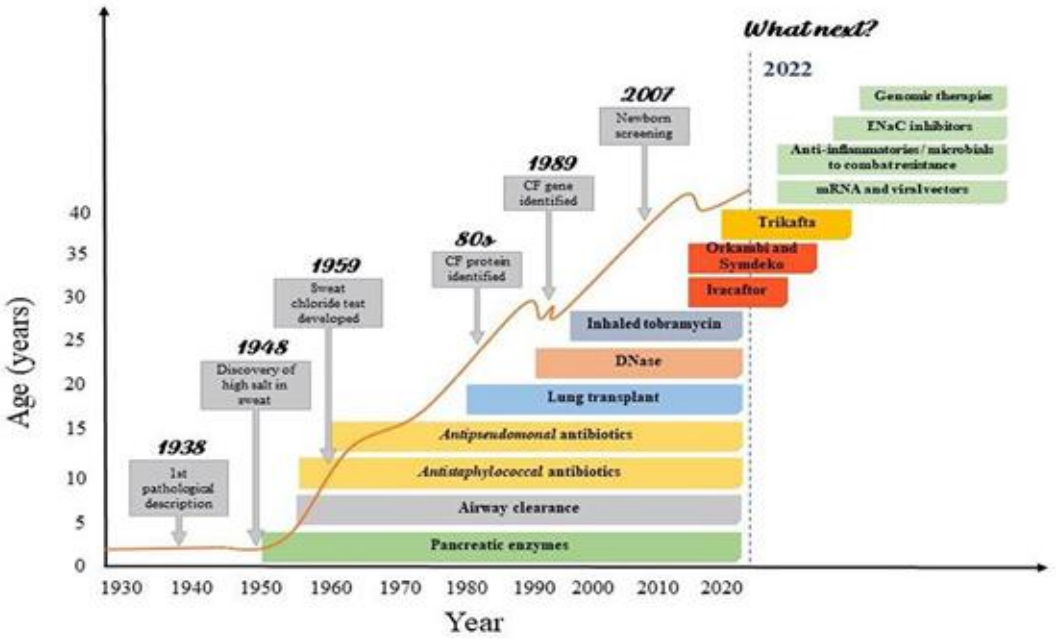
Medical advisor to BillionToOne

I am fortunate to work with cystic fibrosis experts

Objectives

- Review emerging evidence on prenatal therapy for CF
- Review case studies and outcomes
- Review ongoing research efforts and future studies

Why Now?



CF survival and fertility have improved dramatically

People with CF are becoming pregnant and staying on modulators

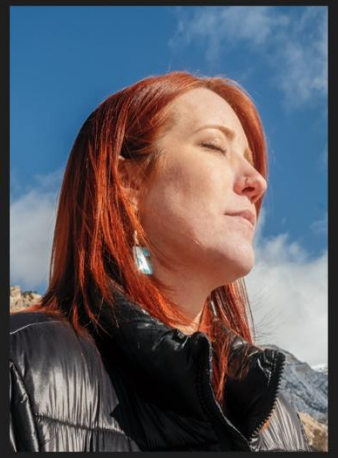
Prenatal therapy is already happening outside of trials

Garcia et al., Front Pediatr, 2022

THE CYSTIC-FIBROSIS BREAKTHROUGH THAT CHANGED EVERYTHING

The disease once guaranteed an early death—but a new treatment has given many patients a chance to live decades longer than expected. What do they do now?

By Sarah Zhang
Photographs by Fumi Nagasaka



Before she started taking Trikafta, in 2019, Jenny Livingston hoped more than anything to survive long enough to see her daughter graduate from high school.

HEALTH

The Mothers Who Aren't Waiting to Give Their Children Cystic-Fibrosis Drugs

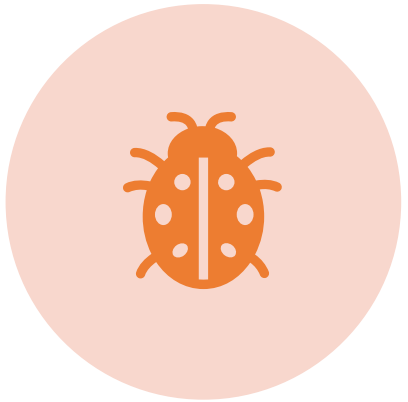
A new treatment can change a person's life, but is not officially approved for anyone under 2.

By Sarah Zhang

Fetal Therapy

INVASIVE

MINIMALLY INVASIVE



NON-INVASIVE

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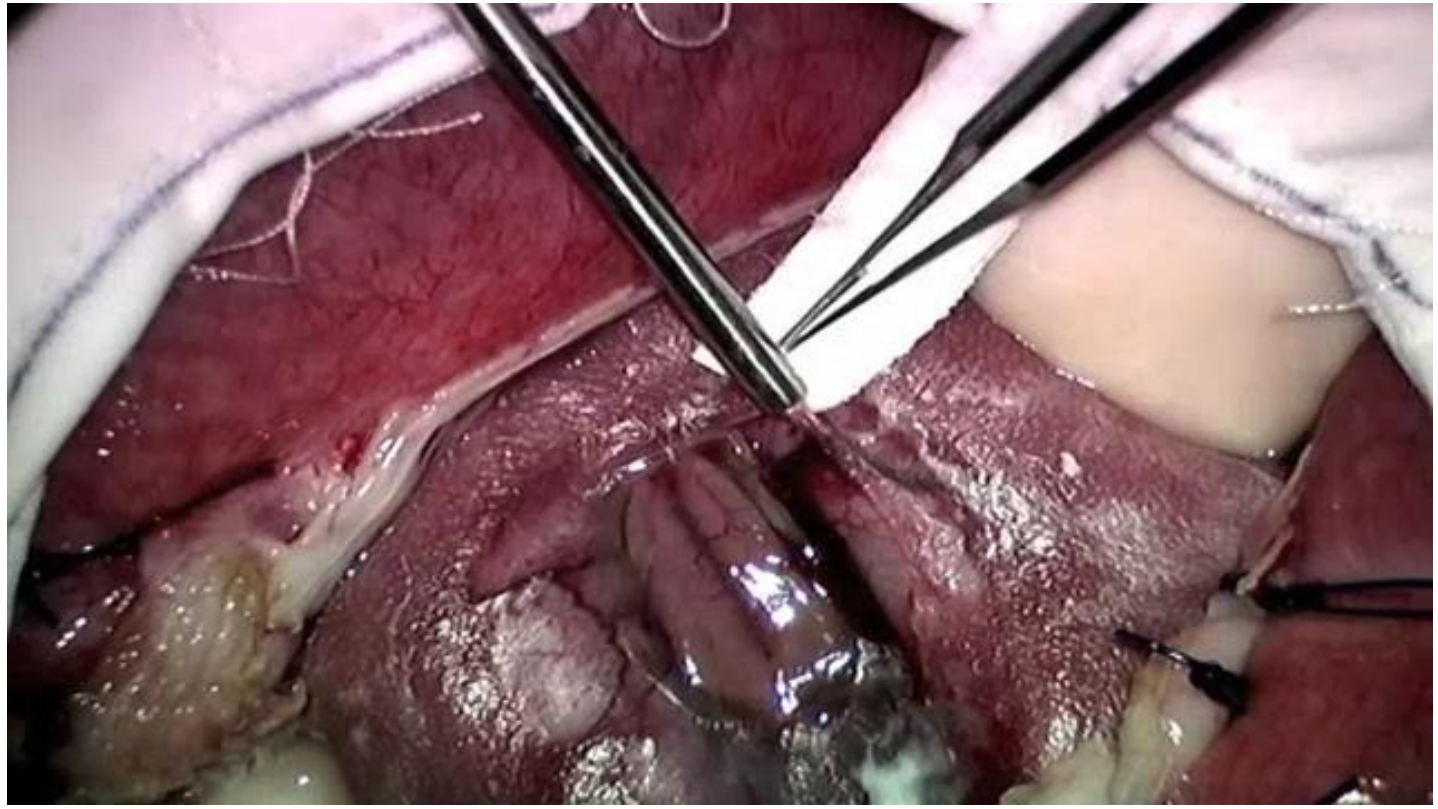
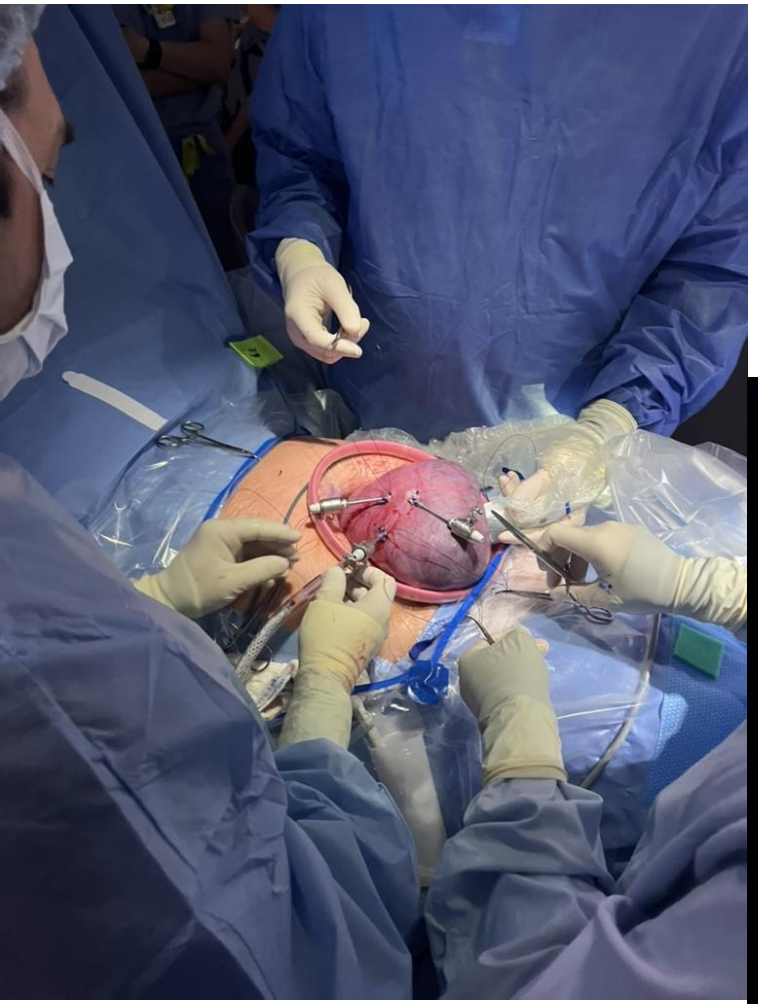
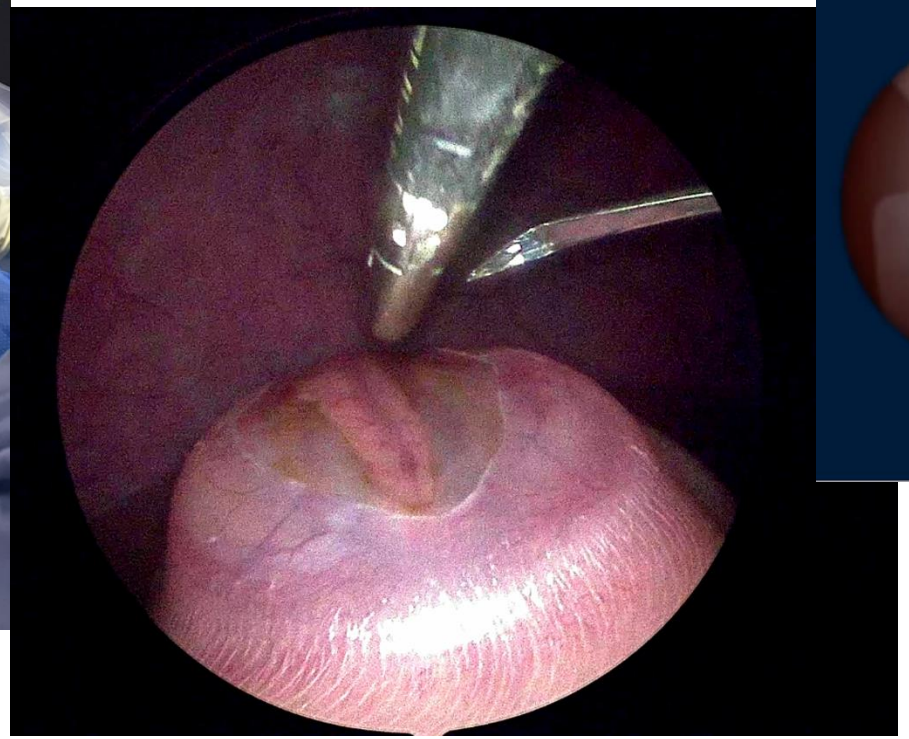
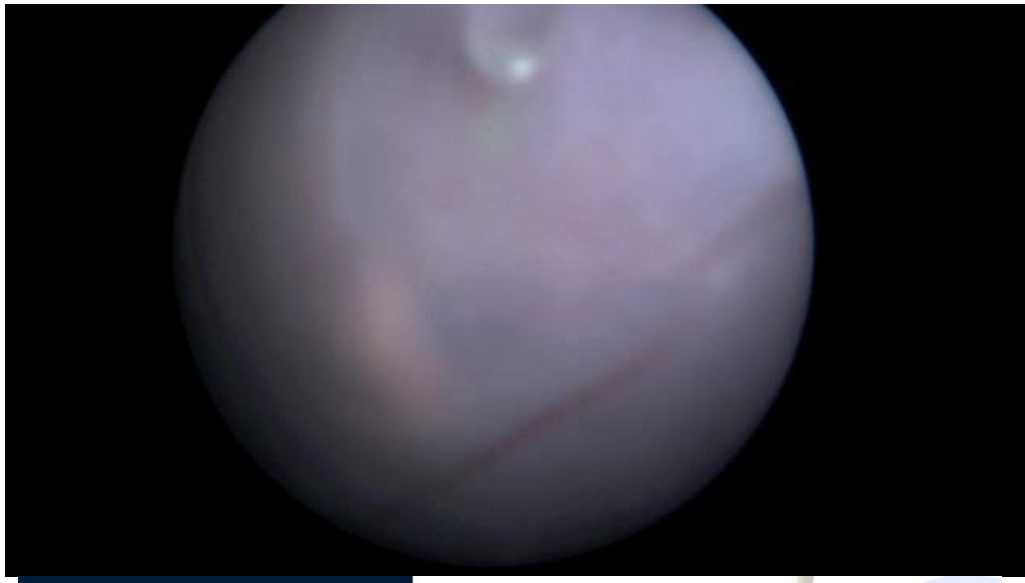
Invasive Fetal Therapy

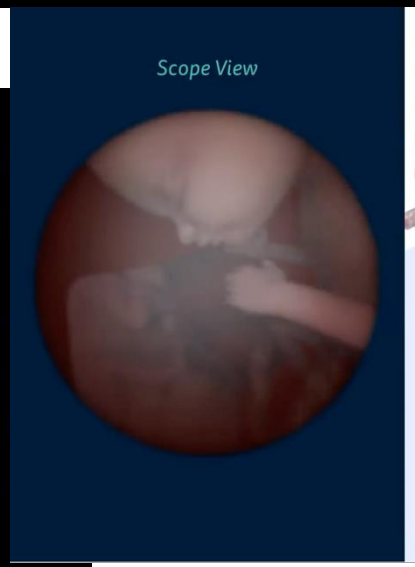


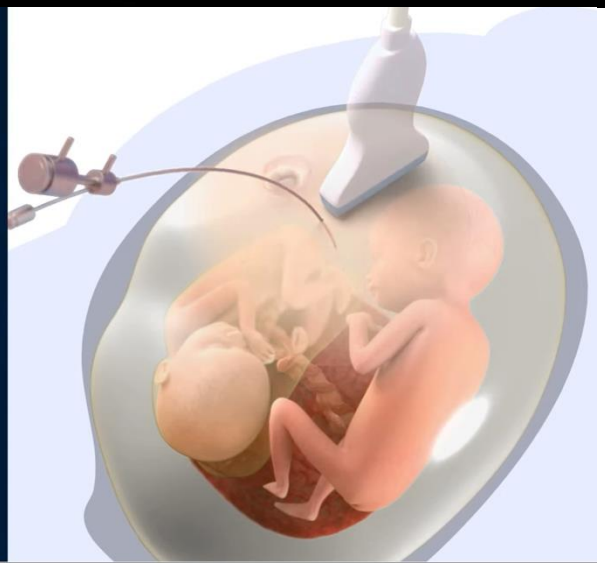
Minimally Invasive Fetal Therapy











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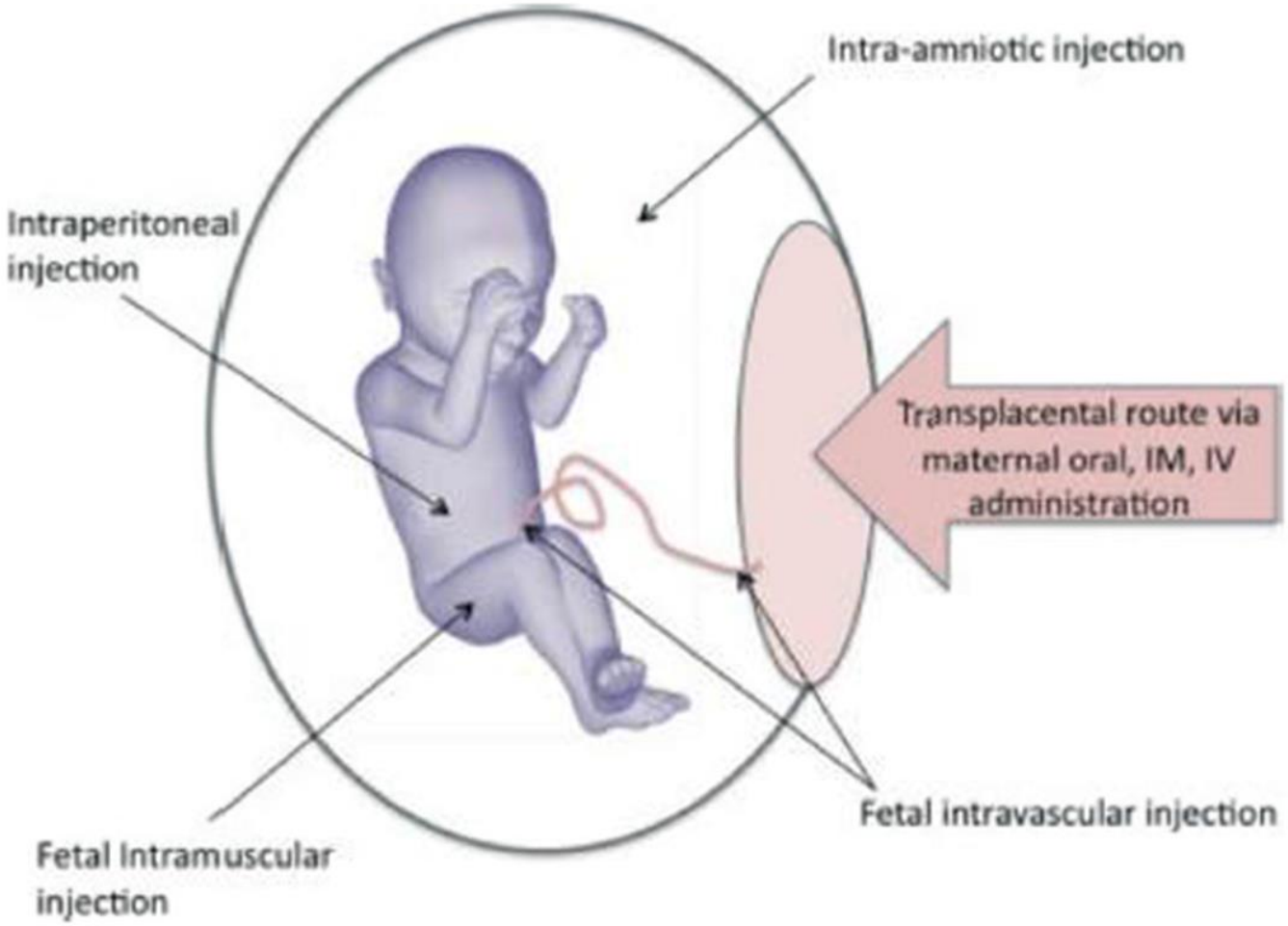
Non-invasive Fetal Therapy

- Does not require physical access to the fetal compartment



Transplacental Route- *Common Uses*

Corticosteroids
for fetal lung maturity

Rhogam prophylaxis
for maternal alloimmunization

Folic acid
open neural tube defects

Vaccination for passive fetal/neonatal immunity
TDAP
Influenza
Covid
RSV

Magnesium sulfate
for neuroprotection in premature delivery

Antibiotics
PPROM and GBS prophylaxis
Syphilis

Transplacental Route- Un*Common Uses*

Maternal thioamides and levothyroxine

Fetal goiter

Indomethacin

Circular shunt in Epstein's cardiac

IVIG +/- corticosteroids

NAIT

Early onset fetal anemia from alloimmunization

Fetal Congenital heart block

Corticosteroids

Large Congenital lung lesions

Bisphosphonates

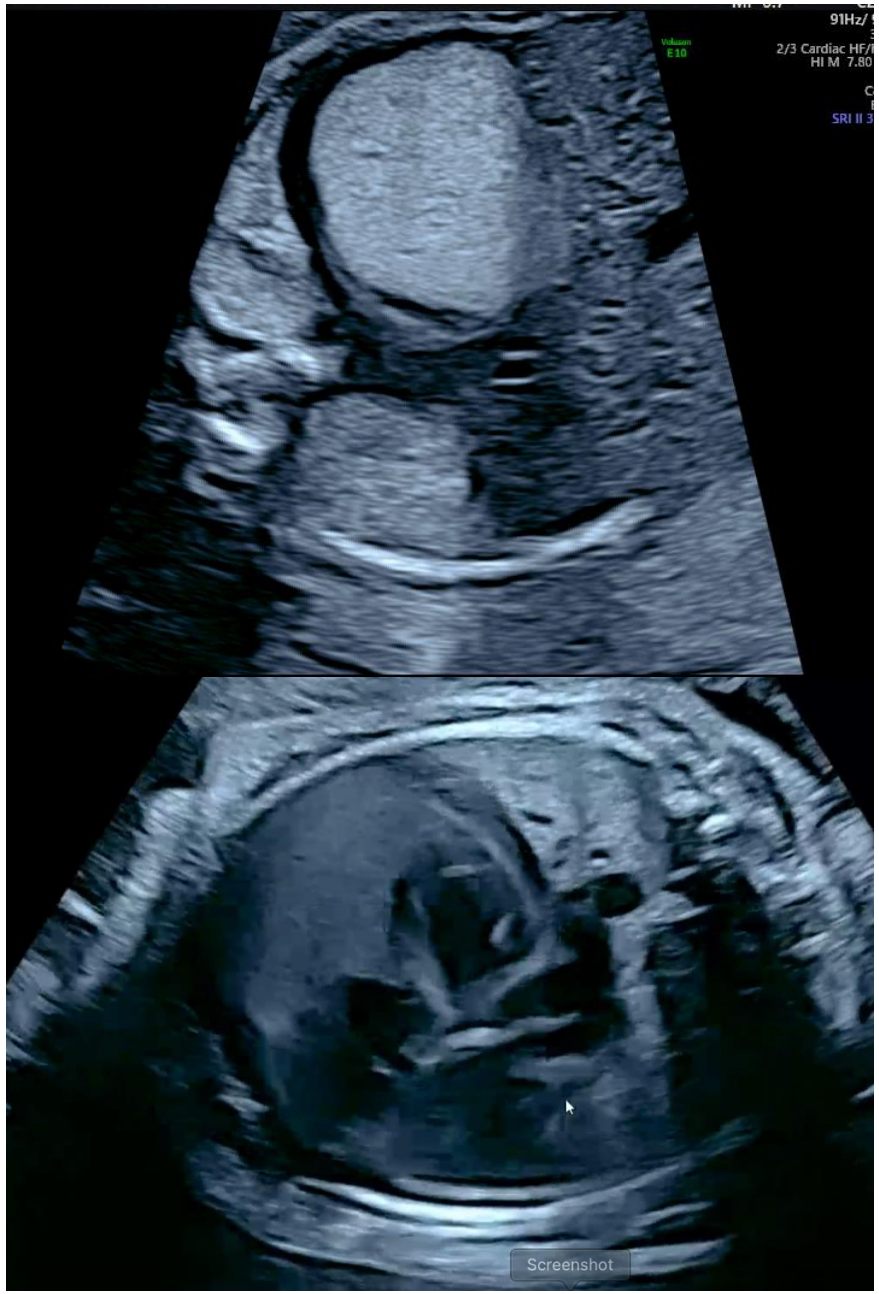
Generalized arterial calcification of infancy (GACI)

Antiarrhythmic agents for fetal tachyarrhythmias

Digoxin, flecainide, sotalol, amiodarone

Transplacental Route- *Uncommon Uses*

- *mTOR inhibitor*
  - Fetal rhabdomyoma



Brain. 2025 Apr 7:awaf123. doi: 10.1093/brain/awaf123. Online ahead of print.

In utero therapy for spinal muscular atrophy: closer to clinical translation

Eduardo F Tizzano [1] [2], Georg Lindner [1], Ellie Chilcott [3], Richard S Finkel [4], Rafael J Yáñez-Muñoz [5]

Affiliations + expand

PMID: 40193572 DOI: 10.1093/brain/awaf123

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Risdiplam for Prenatal Therapy of Spinal Muscular Atrophy

TO THE EDITOR: Risdiplam, a small-molecule drug that modulates splicing of the gene *SMN2*, increases the level of the protein SMN (survival motor neuron) in persons with spinal muscular atrophy (SMA) and ameliorates disease manifestations.[1,2] A fetus at risk for the severe form of SMA — type 1 SMA — owing to having a deceased older sibling with genetically confirmed type 1 SMA, was tested for SMA by means of 5 days' gestation and delivery at 38 weeks 6 days' gestation. The mother was monitored weekly for obstetric health and drug-related side effects, and the fetus was monitored for growth, activity, and anatomical development by means of ultrasonography. Risdiplam was subsequently administered orally to the infant 8 days after birth and has been continued daily to the present time (30 months of age in February 2025).

Cystic Fibrosis

- Autosomal recessive disease (~40,000 in U.S.; ~100,000 worldwide).
- 1 in 3,000 to 4,000 newborns in the U.S. – about **800 newborns** each year
- Mutations in CF transmembrane conductance regulator (CFTR) protein, an anion channel expressed at apical membrane of epithelial cells
- CFTR dysfunction
  - Chronic sinopulmonary infections
  - Progressive lung disease
  - Pancreatic insufficiency
  - Gastrointestinal dysfunction
  - Hepatic cirrhosis
  - Diabetes

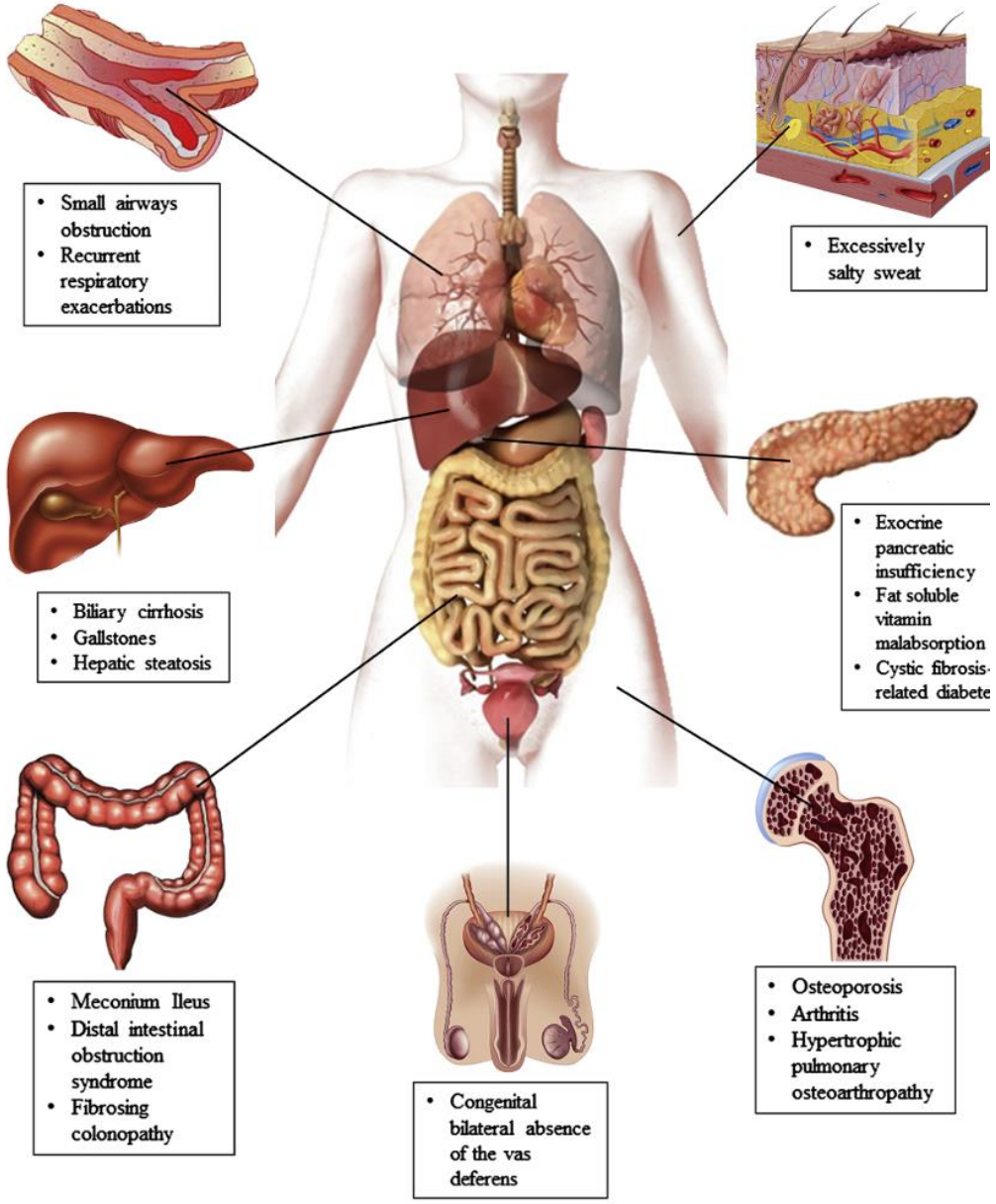


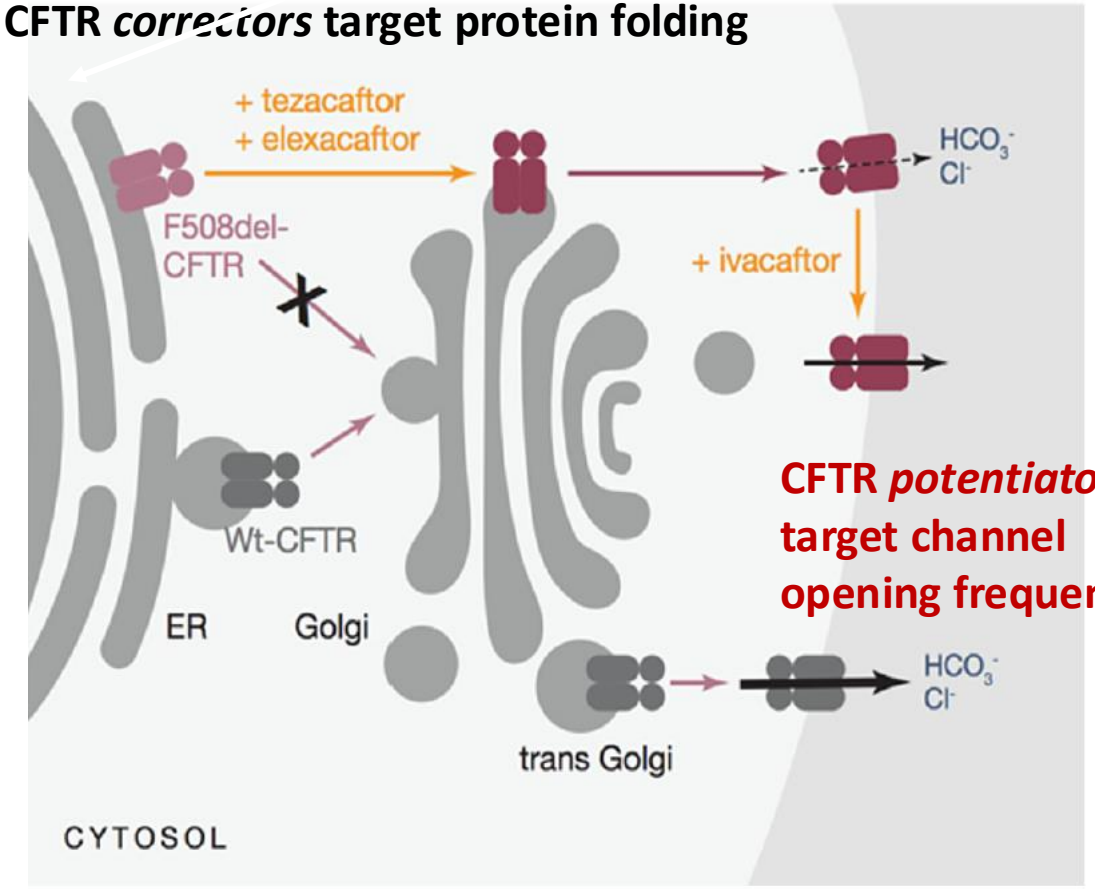
FIGURE 12.1 Common clinical manifestations of cystic fibrosis. While cystic fibrosis is primarily characterized by a progress ob pulmonary disease and exocrine pancreatic dysfunction, many organ systems can be affected. Variations in prevalence of extrapulmonary sy are not completely understood, but evidence suggests some disease manifestations are related to the severity of the underlying CFTR mutation as environmental and genetic modifiers [5].

ETI- Trikafta and now newer **VTD**- Alyftrek

- CFTR modulators are a key therapeutic for CF
- **Elexacaftor** , **tezacaftor, vanzacaftor** bind sites on CFTR protein, have an additive effect facilitating cellular processing and trafficking for select mutations (i.e., F508del) increasing amount of protein delivered to cell surface
- **Ivacaftor, deutivacaftor** potentiates gating of the CFTR protein at the cell surface.
- In 2019, two landmark phase 3 clinical- remarkable clinical benefits of (ETI) triple therapy in people with CF, 12 years of age and older, with at least one copy of the F508del mutation in the CF gene
- Approved down to 6 years in 2021, and 2 years in 2023
- VTD approved down to 6 years
- >90% of CF patients are eligible for ETI therapy
- **Costs ~$311,503/yr**

Middleton PG, New England journal of medicine 2019; 381: 1809-1819
Heijerman HGM, Lancet (London, England) 2019; 394: 1940-1948
Zemanick ET, Am J Resp Crit Care Med, 2021: 203: 15221532
Goralski JL, Am J Respir Crit Care Med. 2023 Mar 15. Epub ahead

CFTR *correctors* target protein folding



CFTR *potentiators* target channel opening frequency

FIGURE 1: Mechanism of action of Trikafta on a cellular level

Figure: Zaher A, 2021, Cureus 13(7):E16144

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CF in 2026: A Different Disease

- CFTR modulators have transformed CF from a once life-limiting disease into a chronic condition for most patients.
  - Life span heading above median of 65 years
- Quality of life, nutrition, lung function all improved on modulators
- Increased pregnancies in people with CF
- Fertility improved from overall health and direct reproductive tract effects

ETI and Pregnancy

- Maternal and Fetal Outcomes in the Era of Modulators (MAYFLOWERS; ClinicalTrials.gov identifier: NCT04828382)
  - Case series- maintains health of patients with CF without known adverse fetal outcomes

Maternal Outcomes on CFTRm in Pregnancy

- No increase in miscarriage rates vs general population
- Obstetric complications similar to baseline population
- Associated with preserved maternal pulmonary function, comparable to nonpregnant peers
- Stopping therapy can worsen maternal pulmonary status in pregnancy

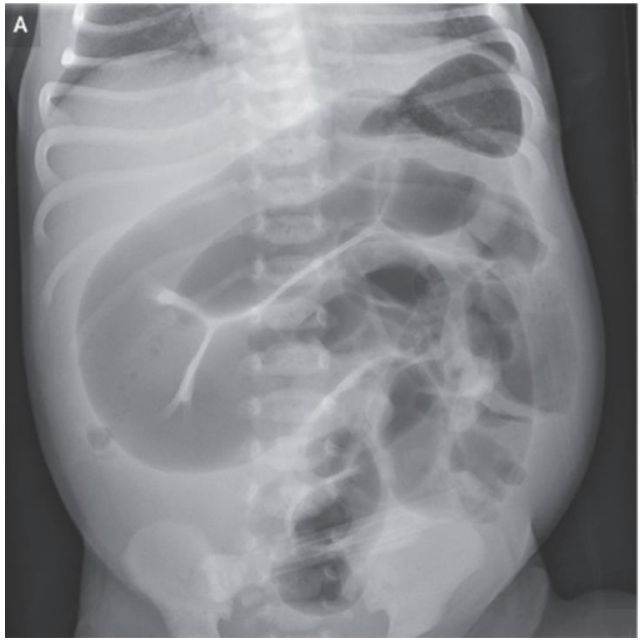
Fetal Safety

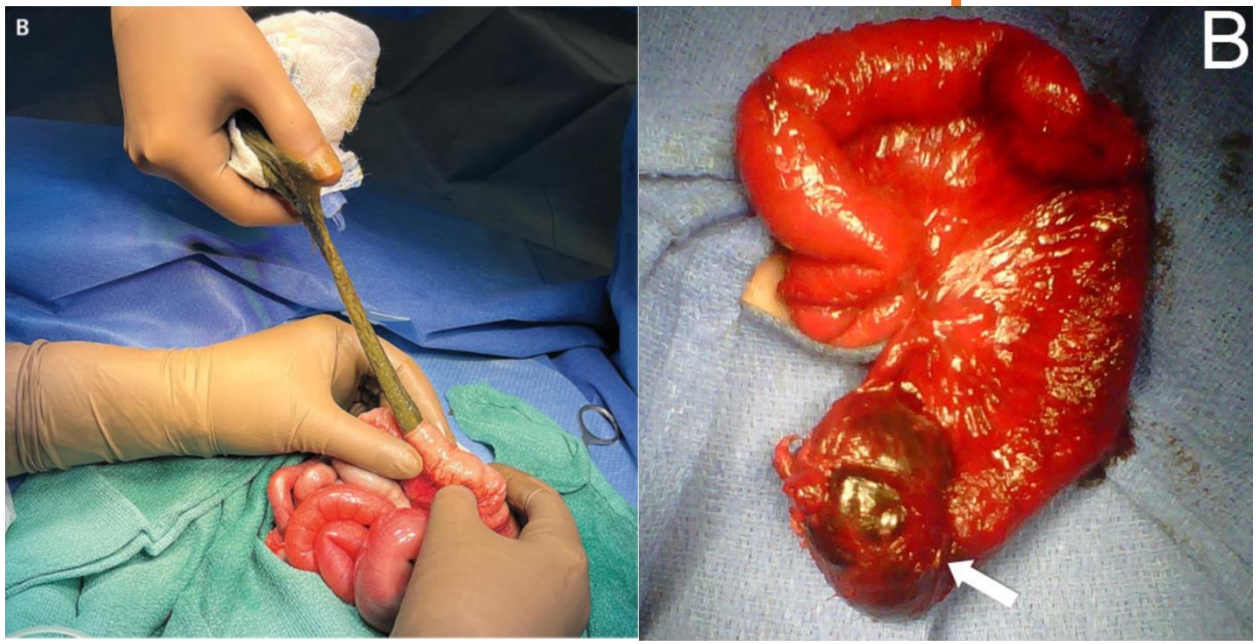
- No increase in major congenital anomalies in observational cohorts to date.
- Cataracts seen in juvenile rat model with ivacaftor; not reproduced in CF ferret
- Rare tiny, clinically insignificant opacities reported in one series in infants (3 of 23 infants)
- CFTR modulators show CNS penetration in fetal rat brain → human relevance unknown
- Potential hepatotoxicity → monitor both maternal and infant LFTs.

Placental & Breastmilk Transfer

- CFTRm crosses the placenta readily
- Fetal levels can equal or exceed maternal levels
- Breastmilk levels are low, relatively limited exposure for breastfed infants.

Meconium Ileus (MI)





- Affects up to 20% of newborns with CF
- Can lead to long-term morbidity and can impact mortality.
- Simple MI - viscid meconium obstructing the terminal ileum
- Complex MI (40%) - can result in volvulus, ischemic necrosis, atresia, and perforation resulting in meconium peritonitis, meconium pseudocyst
- Most studies report worse growth and lung function, require more nutritional interventions, and are hospitalized more frequently than those without MI

Diagnosis of MI

- Presence of echogenic bowel as bright as surrounding bone
- Echogenic mass in the terminal ileum
- Dilated bowel
- Evidence of meconium peritonitis with presence of peritoneal calcification, ascites, and pseudocysts

MI

- Approximately 80–90% of neonates with MI have CF
- CF found in 2.2% of cases with fetal echogenic bowel.
- The absence of visualization of the gallbladder is a transient finding in most cases (75%) but in 15% of cases is related to CF

D'Amico A, Buca D, Rizzo G, Khalil A, Silvi C, Makatsariya A, et al. Outcome of fetal echogenic bowel: a systematic review and meta-analysis. Prenat Diagn. 2021;41(4): 391–9. https://doi.org/10.1002/pd.5638

Available from: https://fetalmedicine.org/ education/fetal-abnormalities/ gastrointestinal-tract/not-visible-gallbladder

Gorter RR, Karimi A, Sleeboom C, Kneepkens CM, Heij HA. Clinical and genetic characteristics of meconium ileus in newborns with and without cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50(5): 569–72. https://doi.org/10.1097/MPG. 0b013e3181bb3427

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2020, VOL. 33, NO. 4, 633–638
https://doi.org/10.1080/14767058.2018.1498837

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Reference curves for the normal fetal small bowel and colon diameters; their usefulness in fetuses with suspected dilated bowel

Chiara C. Lap[a], Charlotte S. Voskuilen[a], Lourens R. Pistorius[a,b], Eduard J. H. Mulder[a], Gerard H. A. Visser[a] and Gwendolyn T. R. Manten[a,c]

[a]Department of Obstetrics, University Medical Center Utrecht, Division Woman and Baby, Utrecht, The Netherlands; [b]Department of Obstetrics and Gynaecology, University of Stellenbosch, Stellenbosch, South Africa; [c]Department of Obstetrics and Gynecology, Isala Women and Children's Hospital, Zwolle, The Netherlands

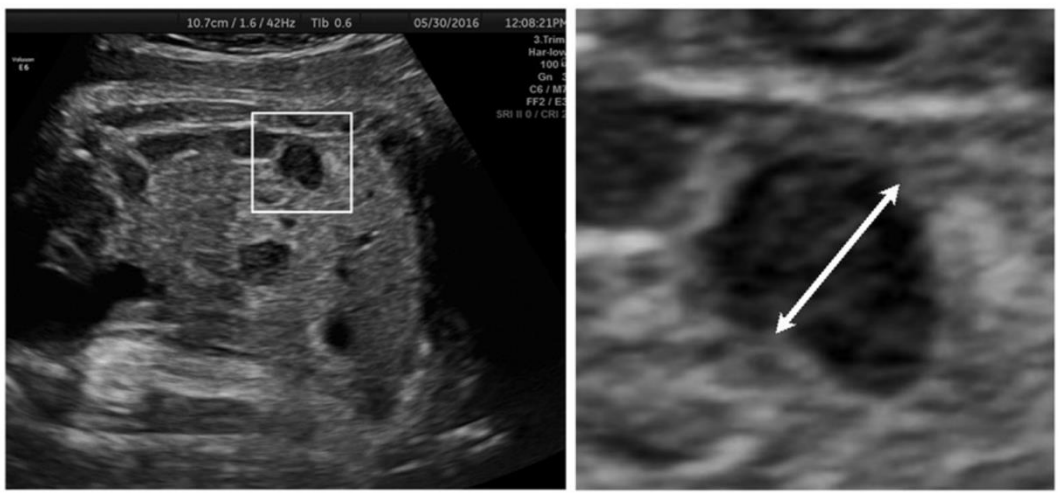
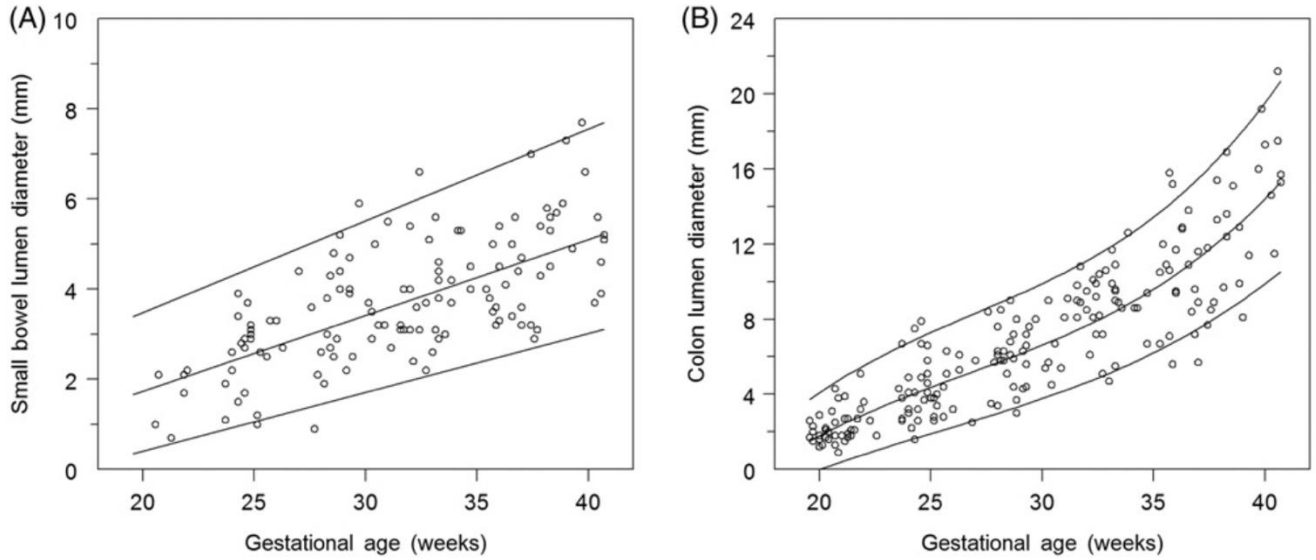


Figure 1. Identification of the largest loop of the colon (coronal plane) at 35 weeks of gestation. Measurement of the short axis of the bowel lumen (inner to inner bowel wall).

Mean and 95% intervals for bowel

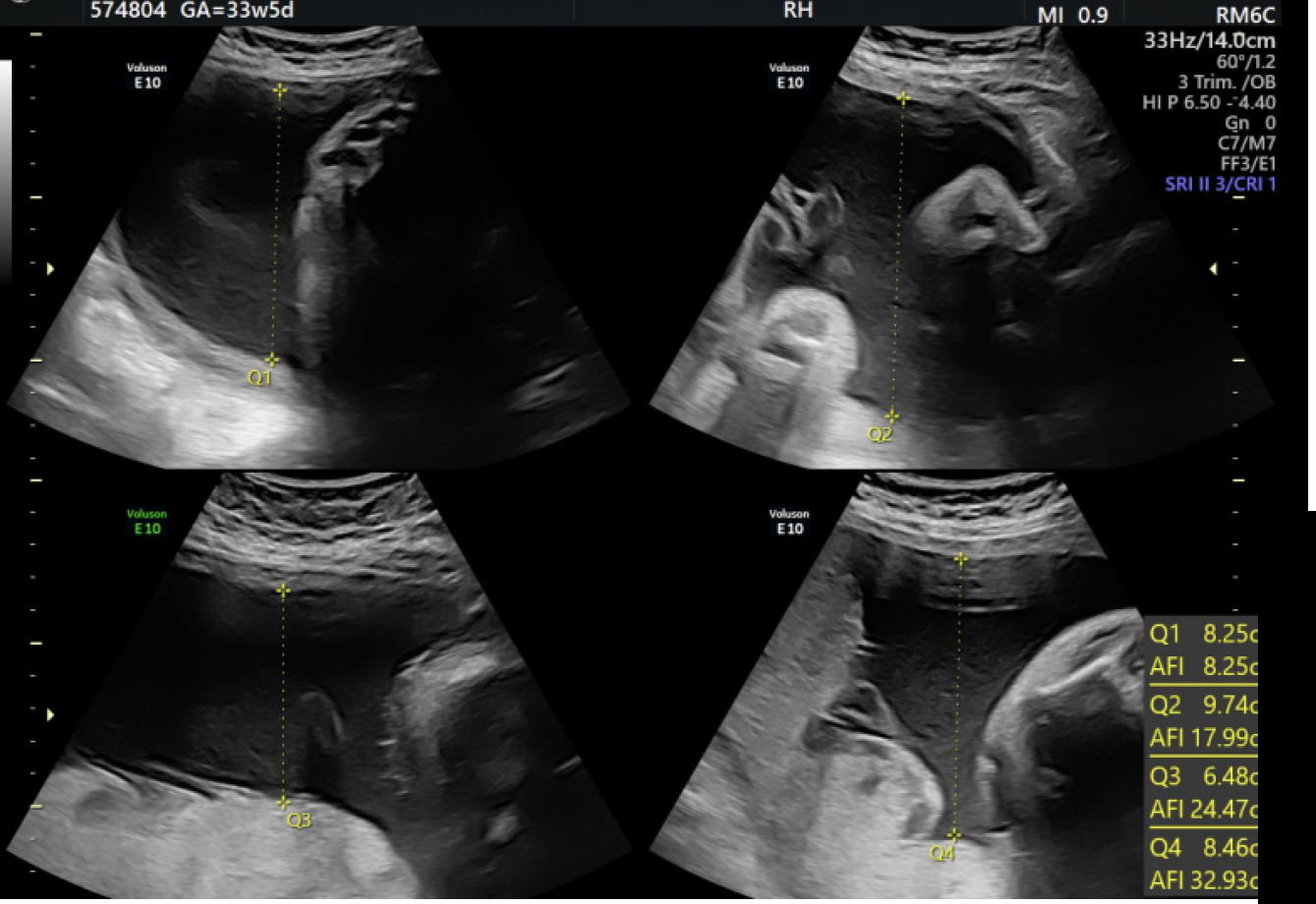
Table 1. Small bowel and colon diameters according to gestational age.

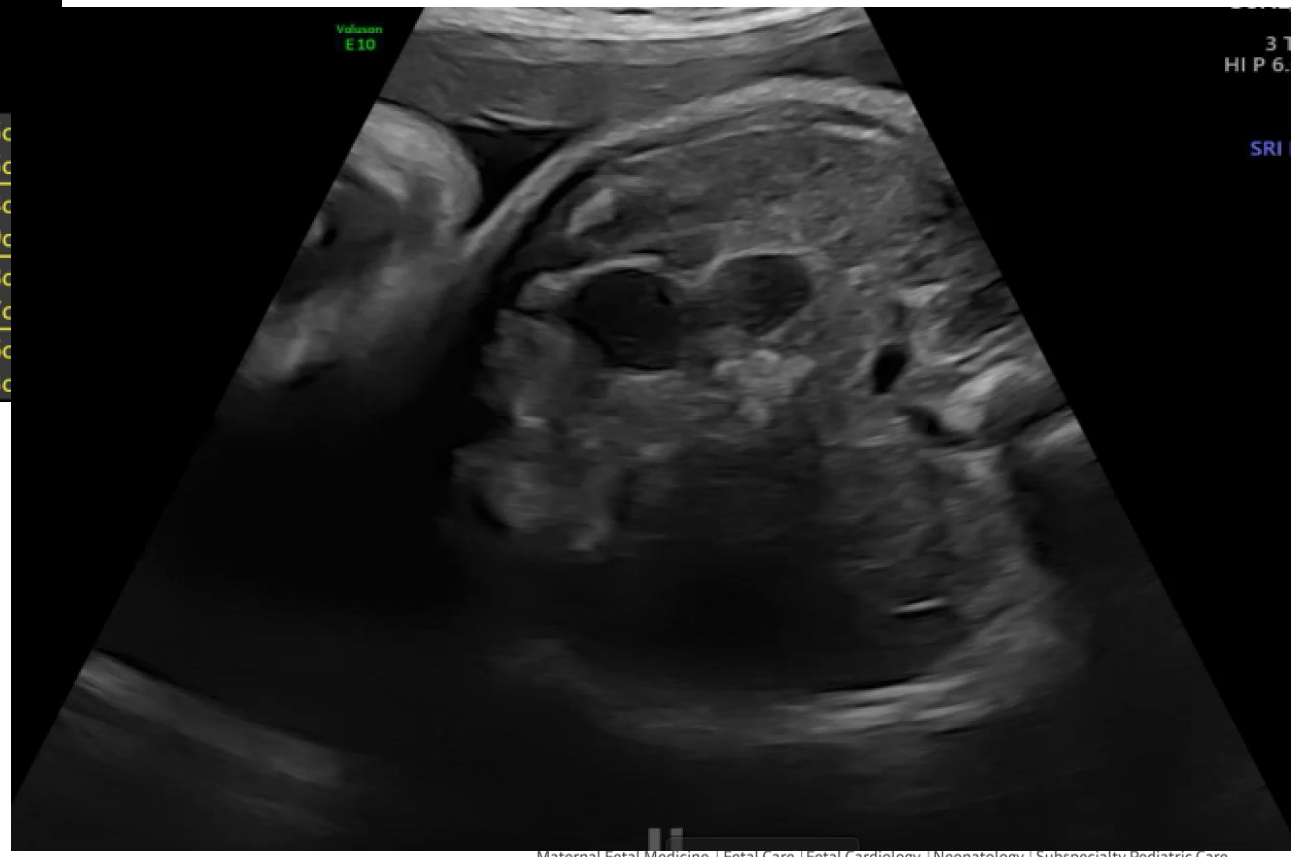
	Small bowel diameter (mm)		Colon diameter (mm)	
Weeks of gestation	Mean	95% prediction interval	Mean	95% prediction interval
20	1.7	0.4–3.5	1.8	0.0–4.0
22	2.1	0.7–3.9	2.9	0.8–5.5
24	2.4	0.9–4.3	3.9	1.5–6.7
26	2.7	1.2–4.7	4.8	2.2–7.8
28	3.1	1.4–5.1	5.7	3.0–8.8
30	3.4	1.7–5.5	6.6	3.7–9.8
32	3.8	2.0–5.9	7.7	4.6–11.0
34	4.1	2.2–6.3	8.9	5.6–12.5
36	4.4	2.5–6.7	10.4	6.8–14.3
38	4.8	2.8–7.1	12.3	8.2–16.5
40	5.1	3.0–7.6	14.5	9.8–19.4

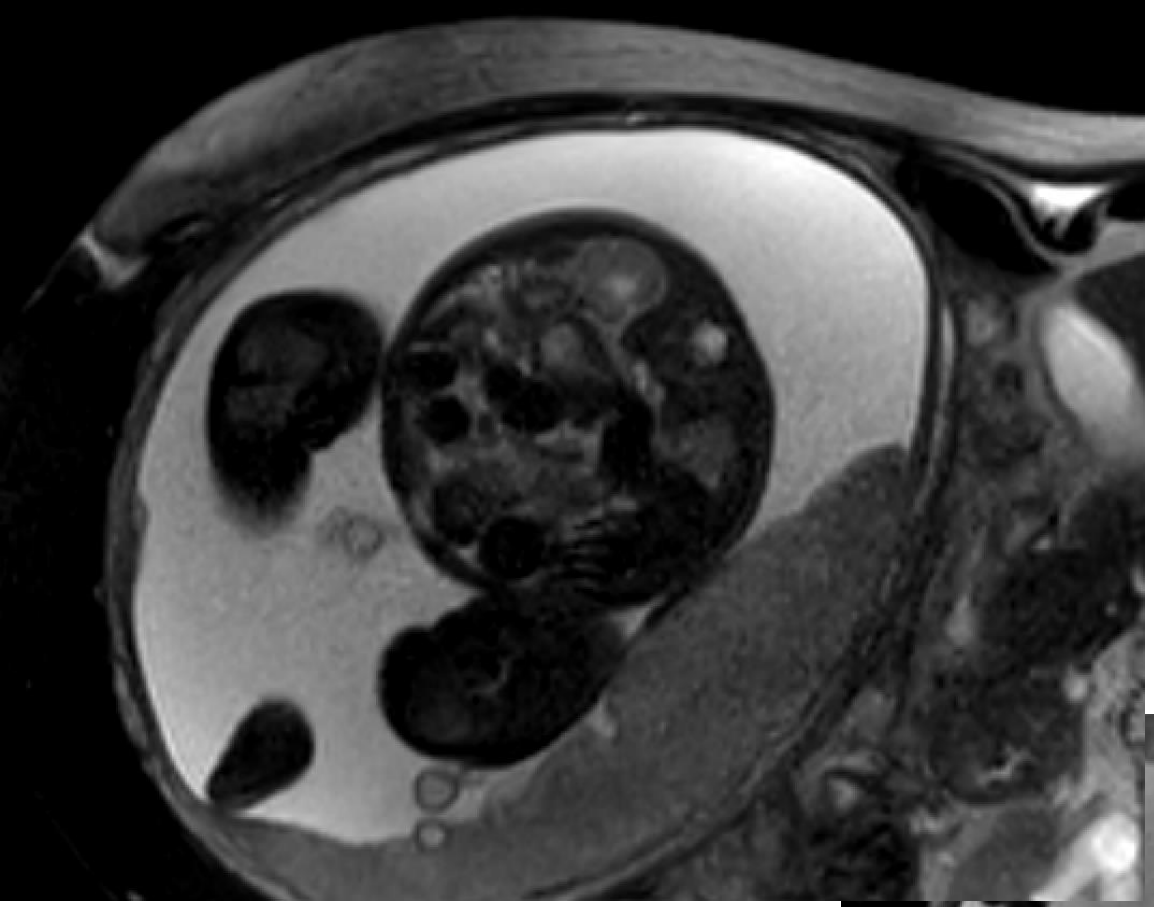


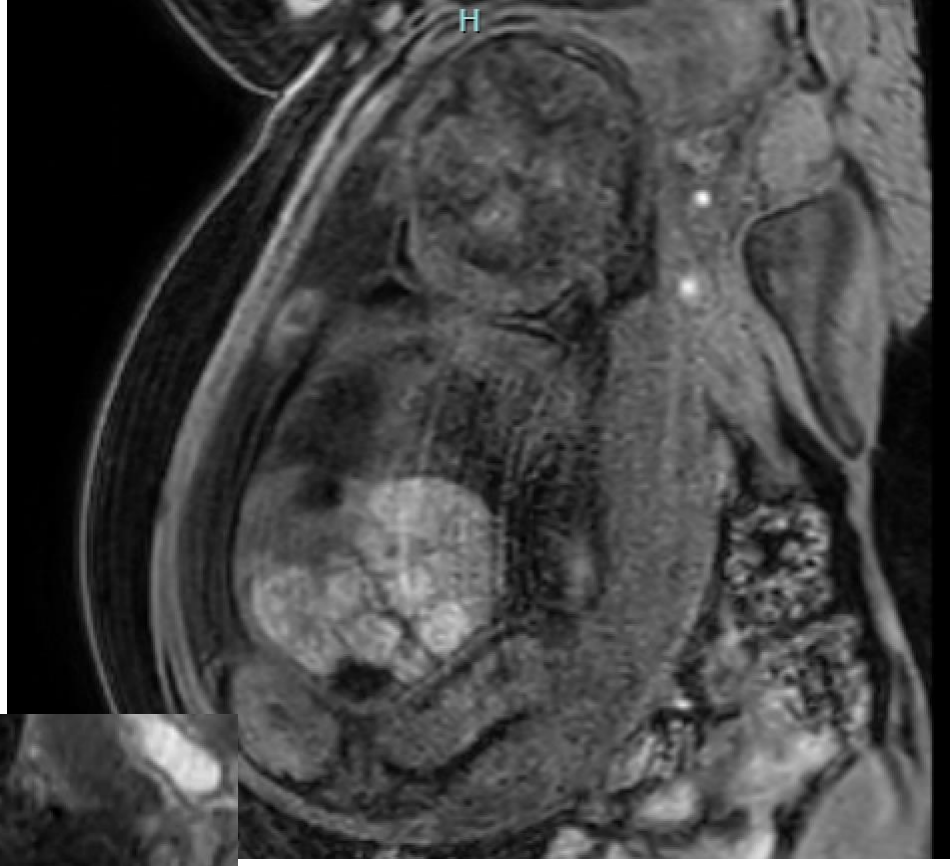
Example of What Are We Wanting To Prevent

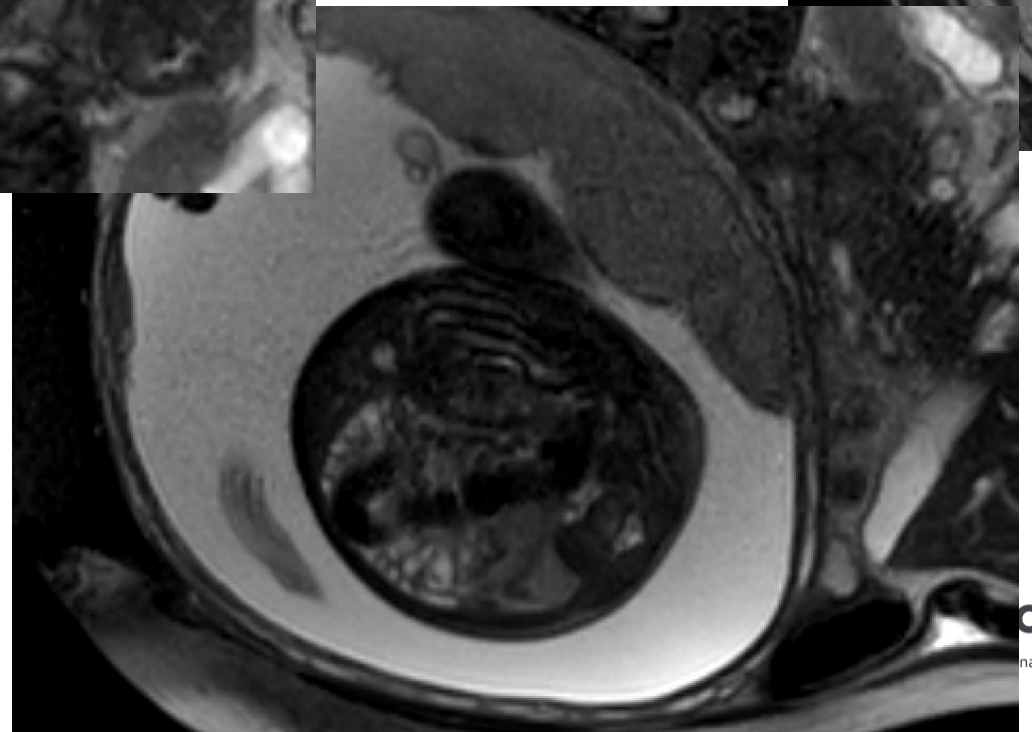
- Case
  - 32 yrs old G4 P2012 at 33w 5d. She was sent to us for ultrasound and consultation for polyhydramnios and dilated bowel.
    - Low risk NIPS
    - Maternal carrier for CF (f508)
    - No paternal carrier testing


574804 GA=33w5d
RH
MI 0.9
RM6C
33Hz/14.0cm
60°/1.2
3 Trim. /OB
HI P 6.50 -4.40
Gn 0
C7/M7
FF3/E1
SRI II 3/CRI 1
Voluson E10
Q1
Q2
Q3
Q4
Q1 8.25c
AFI 8.25c
Q2 9.74c
AFI 17.99c
Q3 6.48c
AFI 24.47c
Q4 8.46c
AFI 32.93c


Voluson E10







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Neonatal surgery

- Very dilated small bowel filled with meconium consistent with meconium ileus
- The bowel was so heavy that it had caused a mesenteric tear and an internal hernia with necrotic small bowel.
- .The loop of bowel that had herniated through the mesentery and was full of inspisated meconium was not viable and had to be resected. There was 150cm of small intestine as well as the ileocecal valve and the entire colon left. An ileostomy and mucus fistula were created.
- Ongoing neonatal care now >60 days in NICU

ETI and MI

- Ferret model of CF
  - G551D mutation, ivacaftor prevented intestinal pathology in utero, preserve exocrine pancreatic function, and male kits born with preserved vas deferens

Sun X, Yi Y, Yan Z, Rosen BH, Liang B, Winter MC, Evans TIA, Rotti PG, Yang Y, Gray JS, Park SY, Zhou W, Zhang Y, Moll SR, Woody L, Tran DM, Jiang L, Vonk AM, Beekman JM, Negulescu P, Van Goor F, Fiorino DF, Gibson-Corley KN, Engelhardt JF. **In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis**. Sci Transl Med. 2019 Mar 27;11(485):eaau7531. doi: 10.1126/scitranslmed.aau7531. PMID: 30918114; PMCID: PMC6489481

ETI and MI Case Report

- Homozygous F508del infant, born to mother with CF on ETI therapy
  - Ultrasound at 20 weeks echogenic bowel, repeat ultrasound at 32 weeks was normal
  - False-negative newborn screen for CF, normal pancreatic function, and lower-than expected sweat chloride levels

Fortner CN, Seguin JM, Kay DM. **Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy.** J Cyst Fibros 2021;20(5):835–6 official journ l of the Euro- pean Cystic Fibrosis Society

ETI and MI Case Report

- F508del carrier patient and F508del homozygous fetus
  - Dilated, hyperechoic bowel at 28 weeks gestation consistent with MI
  - Mother requested maternal ETI therapy and ETI initiated at 32 weeks gestation
  - 36 weeks gestation the bowel dilatation had resolved.
  - After delivery, no evidence of MI
  - ***ETI continued while breastfeeding***
    - Neonate had preserved exocrine pancreatic function at 2 weeks of age
    - Lower-than-expected sweat chloride levels at one month of age

Szentpetery S, Foil K, Hendrix S, Gray S, Mingora C, Head B, Johnson D, Flume PA. **A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus**. J Cyst Fibros. 2022 Jul;21(4):721-724. doi: 10.1016/j.jcf.2022.04.005. Epub 2022 Apr 11. PMID: 35422395.

ETI and MI Case Report

- Pregnant F508del carrier with fetus CF (F508del homozygous) and had prenatal ultrasound findings concerning for MI at 24 weeks gestation
- Maternal ETI therapy was initiated at 31 weeks gestation and no dilated bowel was observed at 39 weeks
- No signs of bowel obstruction after birth
- Maternal ETI was continued during breastfeeding

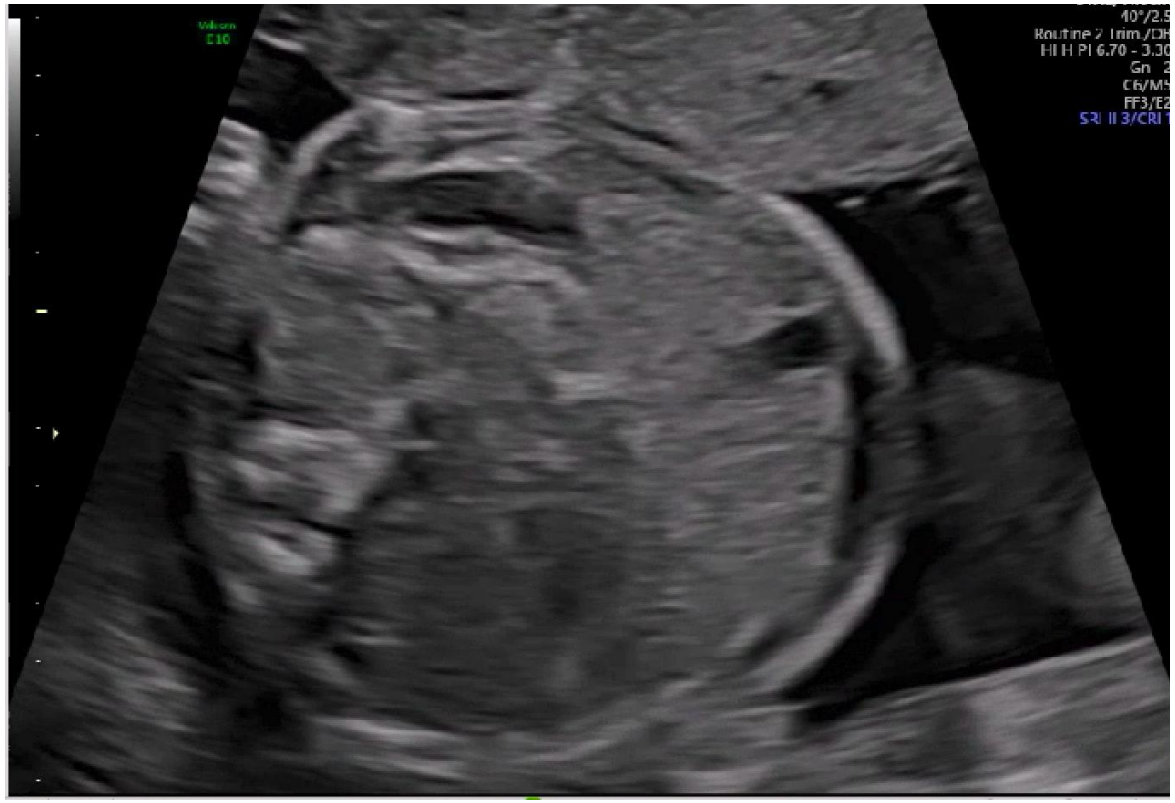
Gómez-Montes E, Salcedo Lobato E, Galindo A, García Alcázar D, Villalain C, Moral-Pumarega MT, Bustos Lozano G, Luna-Paredes C. **Prenatal cystic fibrosis transmembrane conductance regulator modulator therapy: A promising way to change the impact of cystic fibrosis**. Fetal Diagn Ther. 2023 Mar 30. doi: 10.1159/000530261. Epub ahead of print. PMID: 36996799.

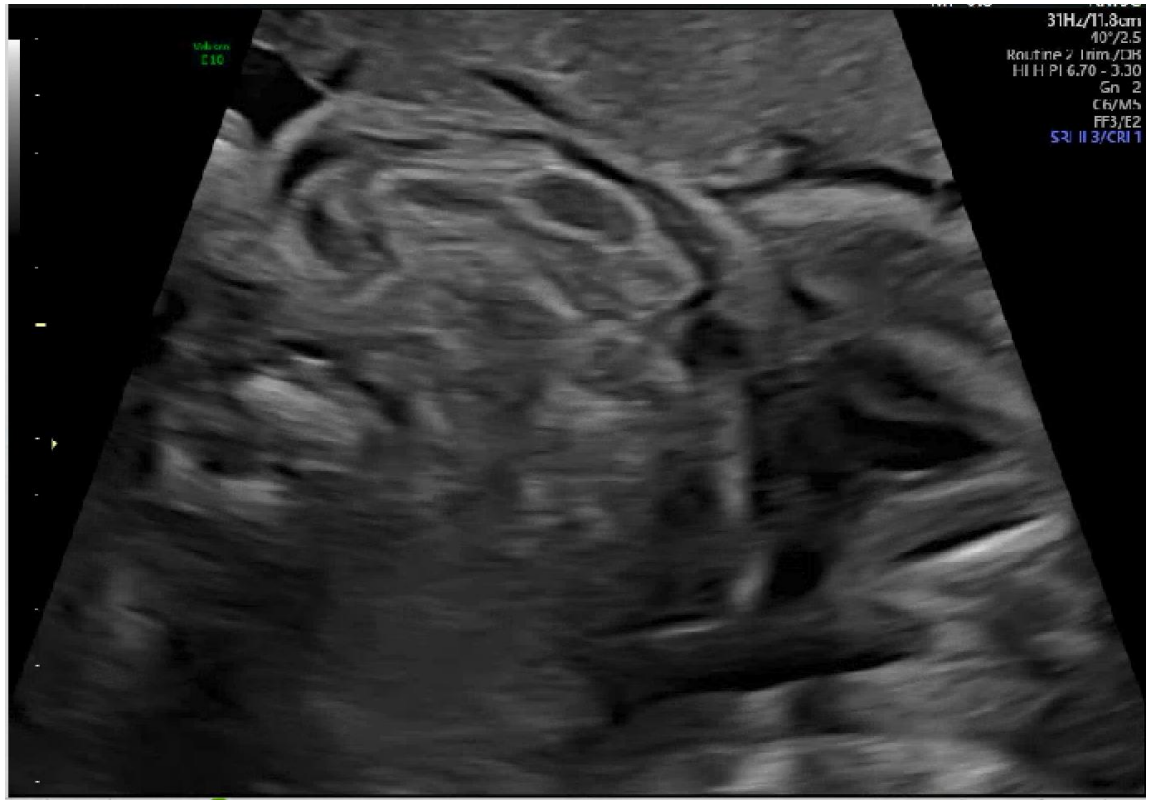
CFCC Cases of MI

Case 1

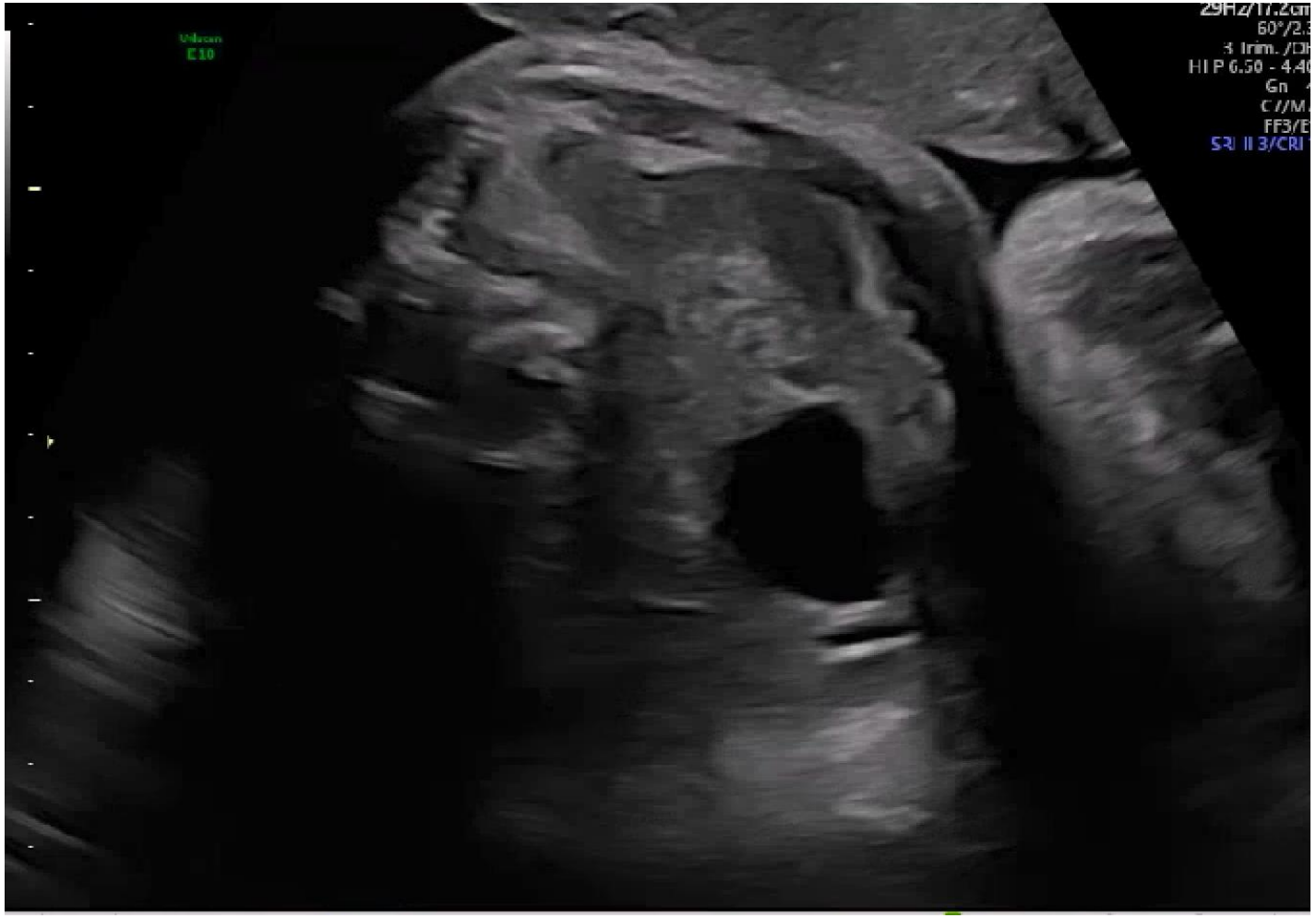
- 30 yo G1
- Both parents CF carriers for dF508
- Referred for diagnosis of fetal cystic fibrosis at 23w3d due to dilated echogenic bowel
- Started ETI at 31w3d
- Several weeks were spent trying to obtain medication
- Ultimately family opted to pay for ETI without insurance coverage
  - **$50K for 2 months of Therapy**

23 weeks





36 weeks- after a month of ETI



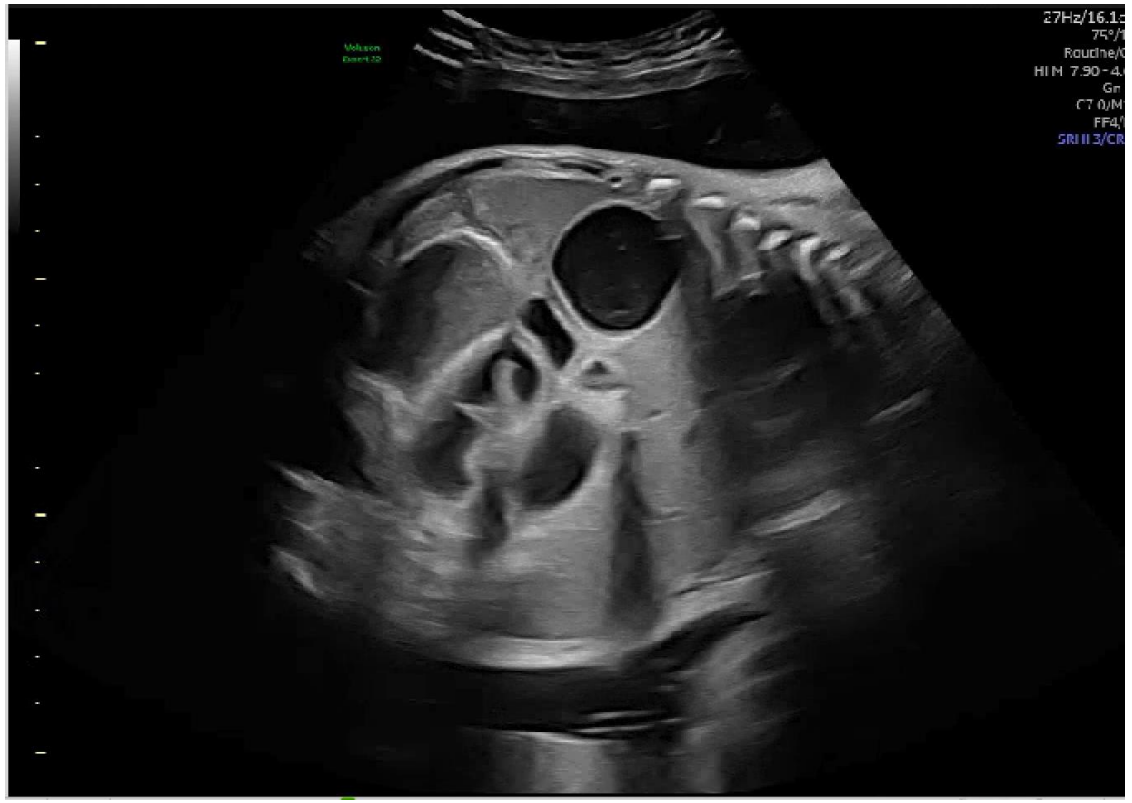
Neonatal Findings

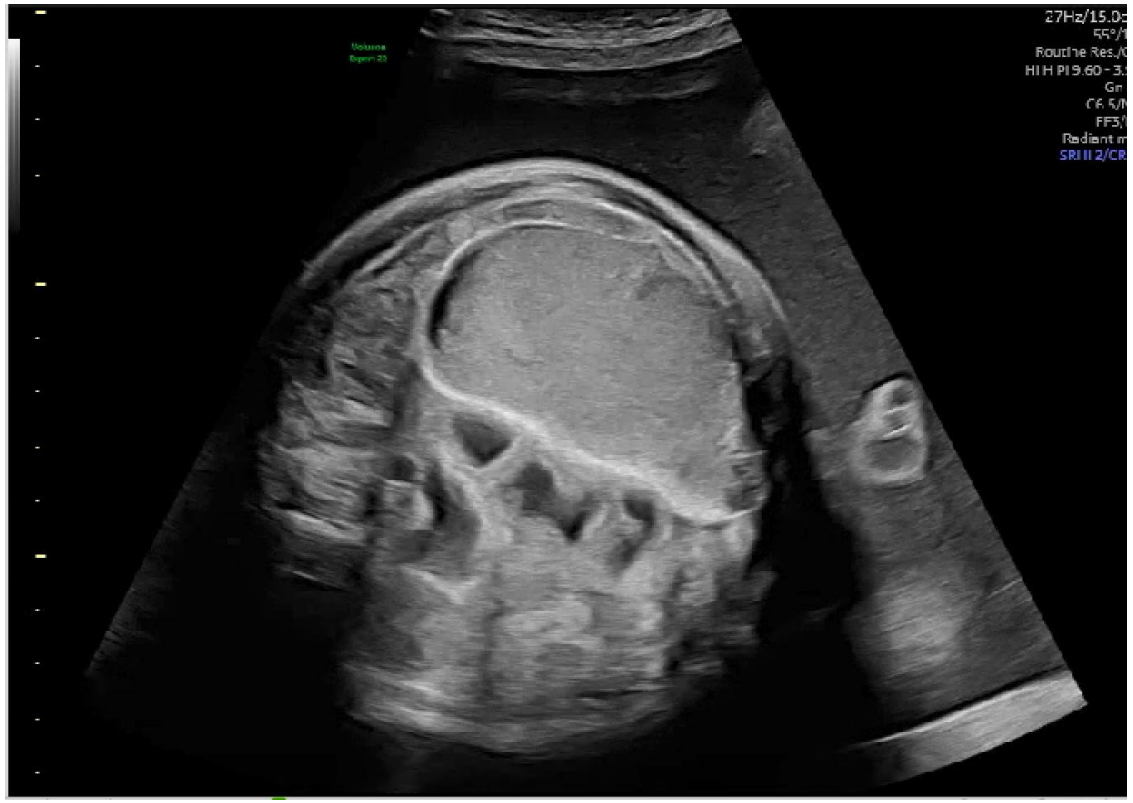
- Induction at 39 weeks, stopped ETI after delivery
- No evidence of MI after delivery
- **Discharge day of life 2**
- Immunoreactive Trypsinogen IRT was elevated on newborn screen
- Borderline pancreatic elastase test (100-200 mcg/g),
  Consistent with slight to moderate pancreatic insufficiency .
- Initial sweat chloride result: Cystic fibrosis unlikely
  - Ultimately turned positive
- Receiving standard therapy with enzyme replacement, nutritional support, regular monitoring, will start lumacaftor/ivacaftor (Orkambi) or tezacaftor/ivacaftor (Symdeko) at age 1 and ETI at age 2

Case 2

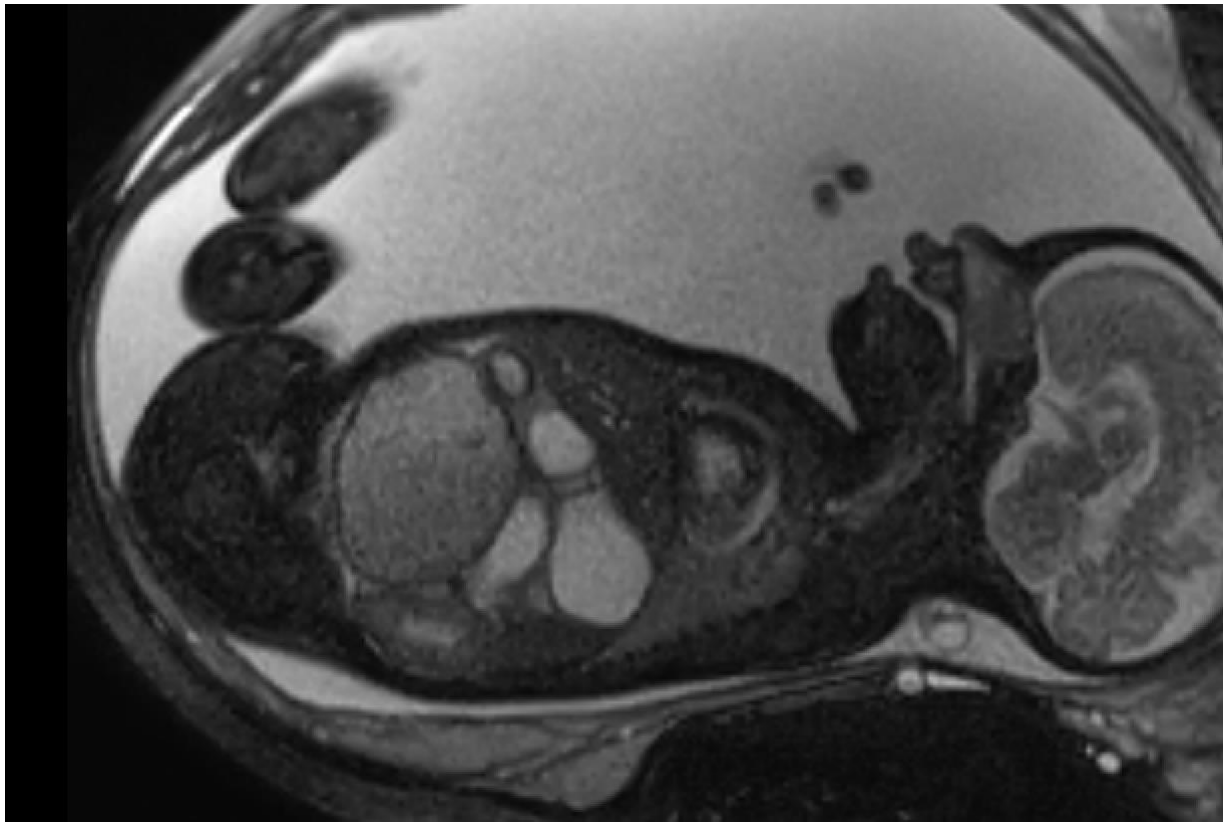
- 32 yo G3P2 referred at 33w6d
- Prior Son with CF and both parents known CF carriers
- Bowel dilated (1.2-1.6 cm) with echogenic walls
- 6.7 x 4.3 x 3.9 cm meconium pseudocyst.
- Polyhydramnios with AFI 40.7 cm.
- 2400 ml amnioreduction completed- genetics sent
- ETI approved and started at 35w5d

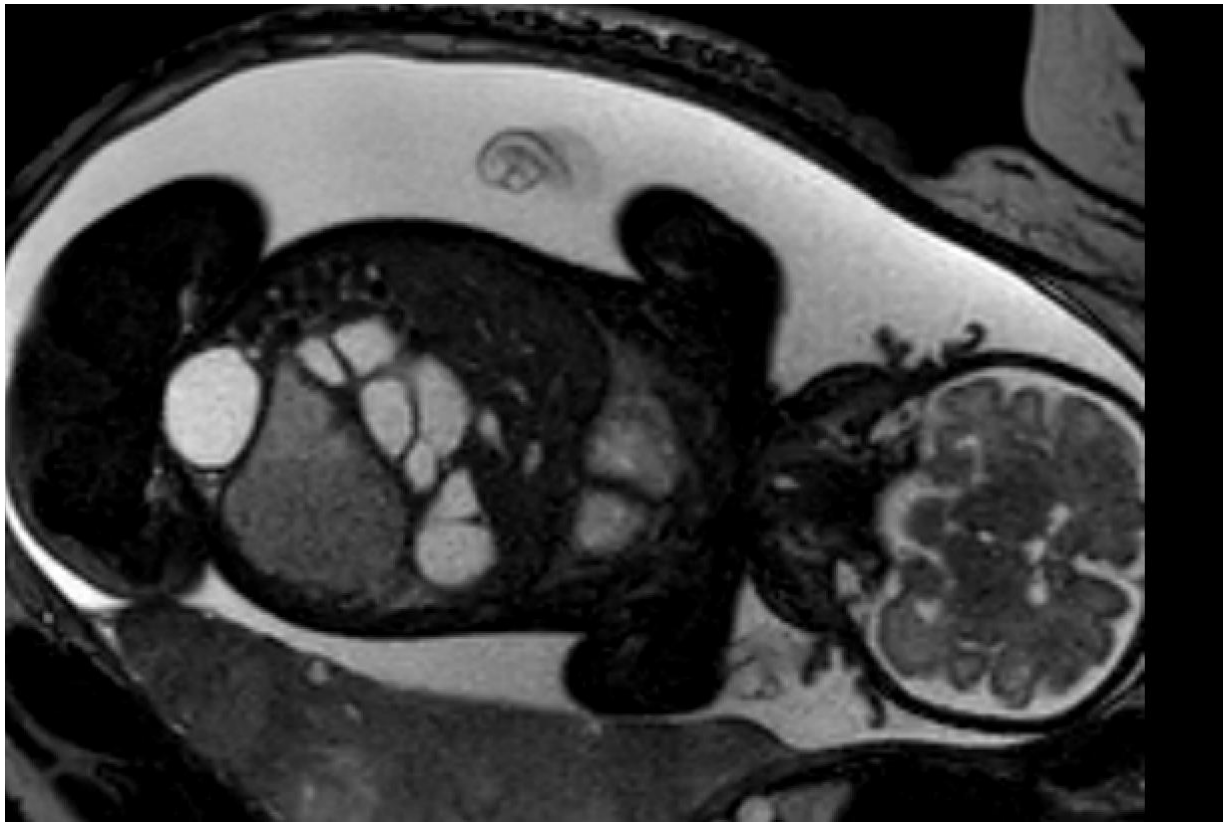
33 weeks 6 days



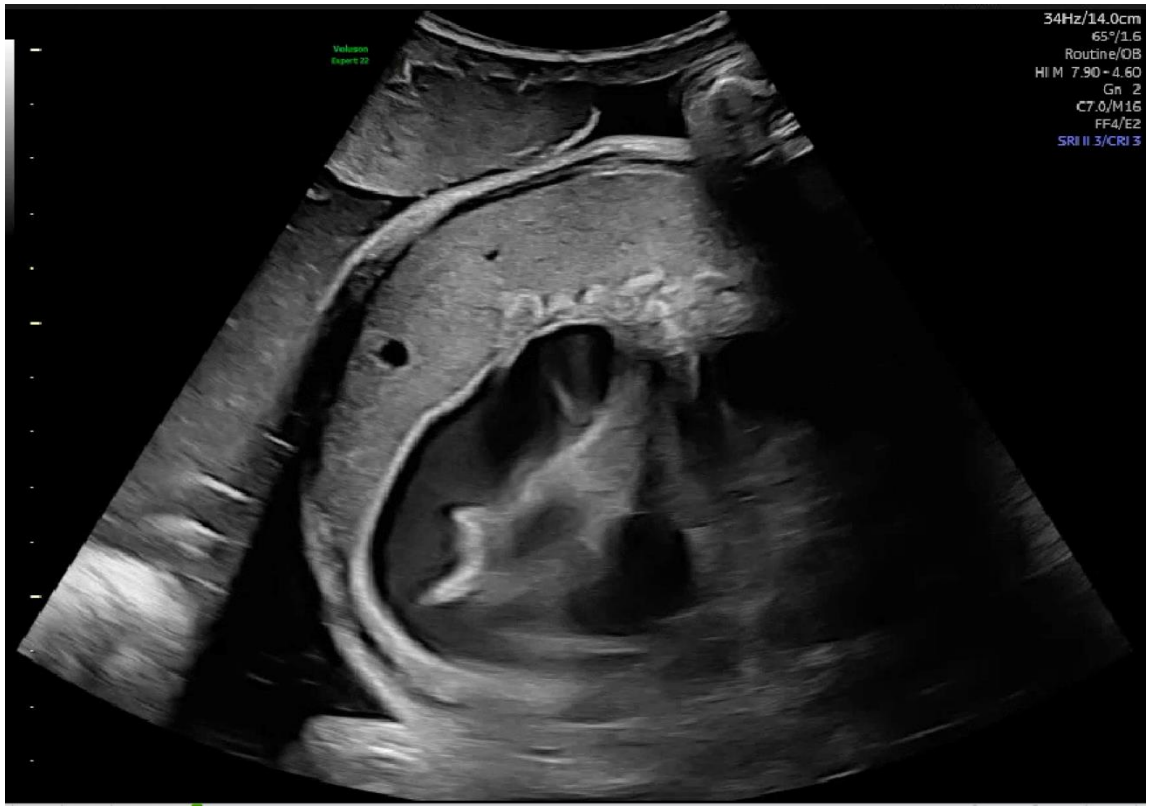


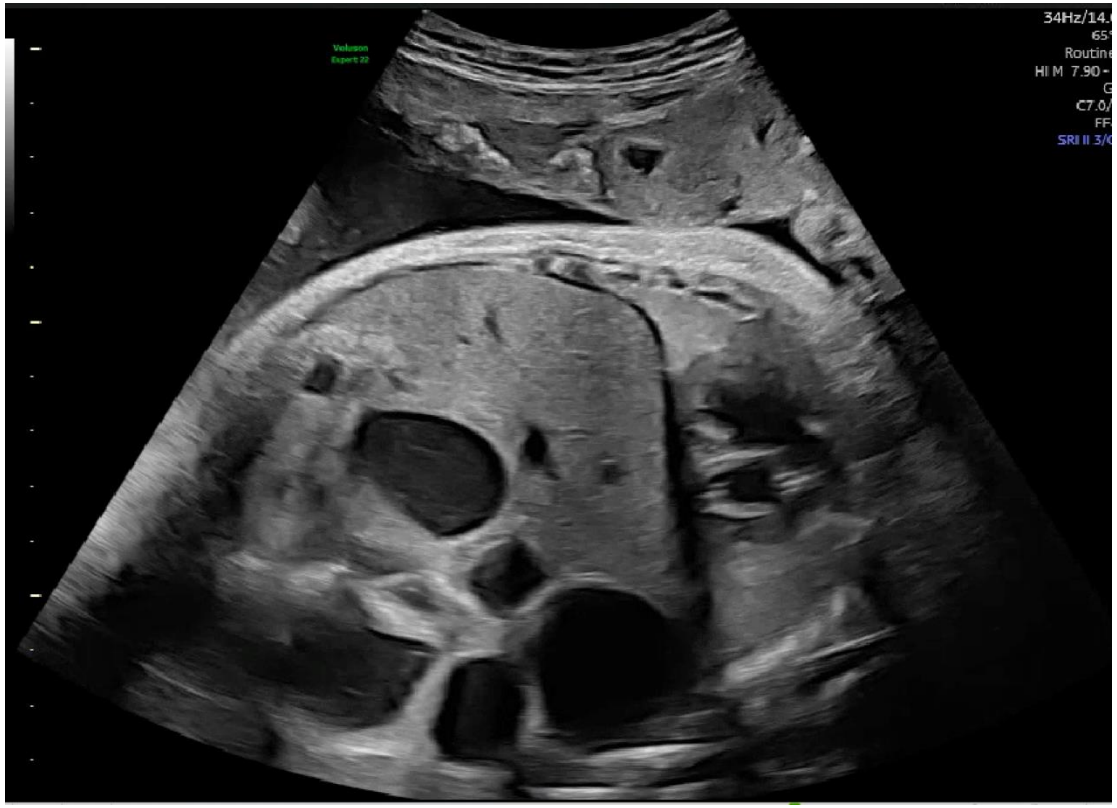
Fetal MRI





37 weeks and 6 days- 2 weeks on ETI





Neonatal Course

- Delivered at 38-39 weeks, stopped ETI after delivery
- MI with pseudocyst
  - Laparotomy with lysis of adhesions.
  - Distal bowel irrigation.
  - Bishop-Koop jejunostomy formation followed by takedown
- IRT newborn screen was negative
- Sweat chloride test was abnormal
- Pancreatic elastase-slight to moderate pancreatic insufficiency
- **LOS 58 days**

Published Cases

20 cases currently available in the literature

- 4 preventative (ETI started prophylactically)
- 15 treated for meconium ileus
- 1 who declined treatment for MI

Location of Cases

- 13 France Modul-CF
  - 4 preventative
  - 1 Decline
  - 1 interruption after treatment start
- 3 Colorado
- 1 Utrecht
- 1 South Carolina
- 1 Spain
- 1 Stanford

Cases

- Average Maternal Age
  - 31.7 mean
  - 26-39

- Diagnostic Testing
  - Amnio 15/20
  - CVS 4/20
  - NIPS 1 case (preventative use)

- Fetal Sex
  - Male 5/18
  - Female 13/18

Meconium Ileus findings

16 cases

- Echogenic bowel
  - 16/16
- Dilation of bowel
  - 11/16
- GB assessed in 7 cases
  - Not visualized in 2 cases
- Peritonitis
  - 2 cases
    - 1 interrupted

Modulator Use

- ETI 18/19 cases
- IVA 1/19
- 1 pt declined in Modul-CF
- Maternal Intolerance in one after 13 days of ETI
  - Rash/pruritus

MI Treatment

- GA at Diagnosis
  - Mean 23.8 weeks
  - Range 17-32 weeks

- GA at Treatment initiation
  - Mean 30.4 weeks
  - Range 19-36.3 weeks

- Resolution of Ultrasound in **11/16** cases of MI
  - 1 spontaneous resolution in patient that declined
  - **10 of 15 MI treated cases had resolution of ultrasound findings**

Non-resolution of MI

- 5 without resolution
  - Modul- CF
    - 1 termination of pregnancy for volvulus (Modul-CF)
    - 1 required surgery- 36-week initiation in setting of peritonitis
  - Colorado
    - 1 simple meconium ileus- 27-week initiation and 37.9 week delivery- no surgery required- gastrografin enema
    - 1 atresia with pseudocyst- 35.7 week ETI start- required jejunostomy and take down
  - Utrecht
    - 27 week initiation
      - Enterotomy required
      - Found low fetal levels at delivery
      - Attributed perhaps to high maternal BMI or poor placental transfer

Preventative Cases

- 4 Cases in MODUL-CF
  - Normal pregnancy in all 4
  - No maternal complications
  - 1 infant GGT elevated, 1 with Bilirubin
  - All female- so no vas deferens info
  - Sweat chloride first week- ND in 3 and positive in one
  - Fecal elastase borderline in one and insufficient in 3
  - IRT Positive in 3 and negative in 1

Newborn Testing

- Newborn screening was positive in 61%
- initial sweat chloride testing was negative in 27%
- Pancreatic function was sufficient or borderline in 67% and
-
- There were no cases of cataracts.
- The *vas deferens* was not confidently identified in 2 of 5 males in one series, owing to the challenges of imaging this anatomic structure in infants.
- In one case of maternal intolerance to ETI, a pregnant patient had to stop therapy after 13 days due to rash and pruritus with MI resolving despite early discontinuation.
- In six cases therapy was continued while breastfeeding and in the one case of poor placental transfer, low levels of drug were also found in breastmilk and the infant received off label direct administration of ETI

- IRT in 18 treated (minus interruption and decline)
  - 11/18 positive IRT
- Initial Sweat Chloride
  - 8/11 positive
  - 1/11 intermediate
  - 2/11 negative
- Fecal elastase
  - 11/18 borderline
  - 7/18 insufficient
  - 1/18 sufficient
- Cataracts
  - 0/18
- LFTs in infant
  - Module CF reports GGT x 2, GGT and Bb x1, and Bb x1
- Vas deferens
  - 5 males in Modul-CF
  - 2 evaluated and Vas not identified- cannot confidently say for sure

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Breastfeeding & Postnatal Continuation

- Mothers may continue ETI while breastfeeding
- Drug levels in milk are low
- Infants also receiving off-label ETI dosing after birth (<2 years old for ETI)

The Critical Challenge of Timing and Delays

- Mean time for MI diagnosis occurred early, at **23.8 weeks** of gestation.
- The time of treatment initiation was, on average, nearly **8 weeks later**, at **30.4 weeks** of gestation.
- Delays stem from diagnostic hurdles and insurance/financial barriers.
- Nonresolution of MI was more common when therapy began **late in gestation** (e.g., 36 weeks) or when existing complications like meconium peritonitis or meconium pseudocyst were already present, often requiring surgery.

Cost and Screening Barriers

- Annual cost of ETI (Trikafta®) > $300k
  - High out-of-pocket costs (e.g., $50k for two months)
- Early identification is crucial for effective treatment.
- Societal recommendations for routine prenatal screening
  - Uptake of expanded carrier screening is inadequate
  - Partner screening completion is less than half.
- Early identification through CVS or amniocentesis is critical,
  - Especially if preventative therapy becomes the accepted practice for fetal CF.

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Routine cell-free DNA prenatal screening identifies pregnancies at high risk for cystic fibrosis that may benefit from fetal therapy

J. Wynn [a,*], S. Rego [a], D. Chandler-Brown [a], R. Carter [a], A. Talati [b], M. Zaretsky [c], A. Trimble [d]

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Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Letter to the editor: False reassurance following single gene non-invasive prenatal testing for cystic fibrosis

ARTICLE INFO

Keywords:
Cystic fibrosis
Prenatal diagnosis
Non-invasive prenatal testing
Newborn screen
Cell-free DNA
Autosomal recessive

vasive prenatal testing.

	Sibling with CF	Meconium ileus	Gestational age testing completed	Maternal variant	Paternal variant	Fetal fraction cfDNA/ variant detected	Risk assessment	Newborn screen results
Case 1	Yes	No	10w1d	F508del	A559T	6.7 % A559T	Low (1 in 200)	Elevated IRT, F508del/A559T
Case 2	Yes	No	10w2d	F508del	F508del	4.4 %	Low (<1 in 5000)	Elevated IRT, F508del/F508del
Case 3	No	Yes	29w2d	F508del	G330X	11 %	Low (1 in 1500)	Elevated IRT, F508del/ G330X

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The EPIC *Registry*

Maternal *E*TI for *P*revention of *I*ntestinal *C*omplications in Fetal Cystic Fibrosis

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CF Foundation PRenatal MOdulator Treatment to PrEvent CF ComplicaTions **(PROTECT)**

PROTECT Study Design Working Group

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Knowledge Gaps Identified at the Workshop

- Whether brain accumulation of CFTR modulators (CFTRm) observed in rats treated *in utero* is relevant to the human fetus is unknown.
- The pharmacokinetics of CFTRm in pregnancy are currently under study/not yet known.
- The critical time point for initiating CFTRm during pregnancy to effectively prevent complications is unknown.
- In an infant exposed to CFTRm *in utero*, the minimal effective dose to prevent withdrawal syndrome post-birth is unknown.
- Safety of administration of ETI to children and infants ≤ 2 years of age is relatively unknown/under study.

The PROTECT Study

- Study design prospective 2-part observational study
  - Those who can obtain ETI treatment versus those who decline or cannot obtain
  - Preventative and MI

- Goal: investigate if CFTRm administration to a pregnant carrier female will prevent complications of CFTR dysfunction (MI, pancreatic insufficiency, bilateral absence of the *vas deferens*, delayed growth) and be safe for the fetus with CF and pregnant female.

- Safety and efficacy of treatment of the CF infant
  - Breast milk and/or 2)
  - Direct CFTRm dosing of the infant

Summary

- Emerging data suggests prenatal CFTRm therapy is promising for preventing or treating MI, preserving pancreatic function, and is safe and tolerable for the pregnant patient.
- Initiation of ETI prior to marked findings of MI is likely of great importance
- Overcoming barriers to obtaining and shortening time needed to obtain ETI is a necessity for equitable care
- Knowledge gaps will be addressed by ongoing registries and the **PROTECT prospective observational study**, which is being developed and anticipated to begin recruitment in 2027.

- Discussion and Questions