Giant Leaps in Prenatal Genetic Testing and Prenatal Treatments

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- **Financial Disclosures:**
  - Director of Medical Partnerships at BillionToOne
  - Shareholder of BillionToOne

“Discovery consists of seeing what everybody has seen and thinking what nobody has thought.”

-Albert Szent-Györgyi

An association between low maternal serum α-fetoprotein and fetal chromosomal abnormalities

Irwin R. Merkatz, M.D., Harold M. Nitowsky, M.D., James N. Macri, Ph.D., and Walter E. Johnson, Ph.D.

Bronx and Stony Brook, New York, and Cleveland, Ohio

An index case of "undetectable" maternal serum α-fetoprotein at 16 weeks in the first pregnancy of a 28-year-old woman was associated with birth of an infant with trisomy 18. This fortuitous finding stimulated a retrospective study of prenatally diagnosed chromosomal abnormalities. From among a series of 3,862 genetic amniocenteses, 32 cases of fetal autosomal trisomy were diagnosed for which corresponding maternal serum and amniotic fluid α-fetoprotein data could be retrieved. From a second laboratory, nine additional cases were added. The maternal serum α-fetoprotein levels expressed as multiples of the median were significantly lower in distribution for these 41 women than those from a group of normal matched control subjects ($p < 0.001$). Since maternal age is shown to be a less than adequate predictor of autosomal trisomic birth, we proposed that a low level of maternal serum α-fetoprotein obtained through routine screening may prove to be valuable in improving the prenatal detection of these serious anomalies.
(AM. J. OBSTET. GYNECOL. 148:886, 1984.)

ANEUPLOIDIES

Trisomy 21
Trisomy 18
Trisomy 13
Monosomy X
XXX/XXY/XYY

FETAL SEX

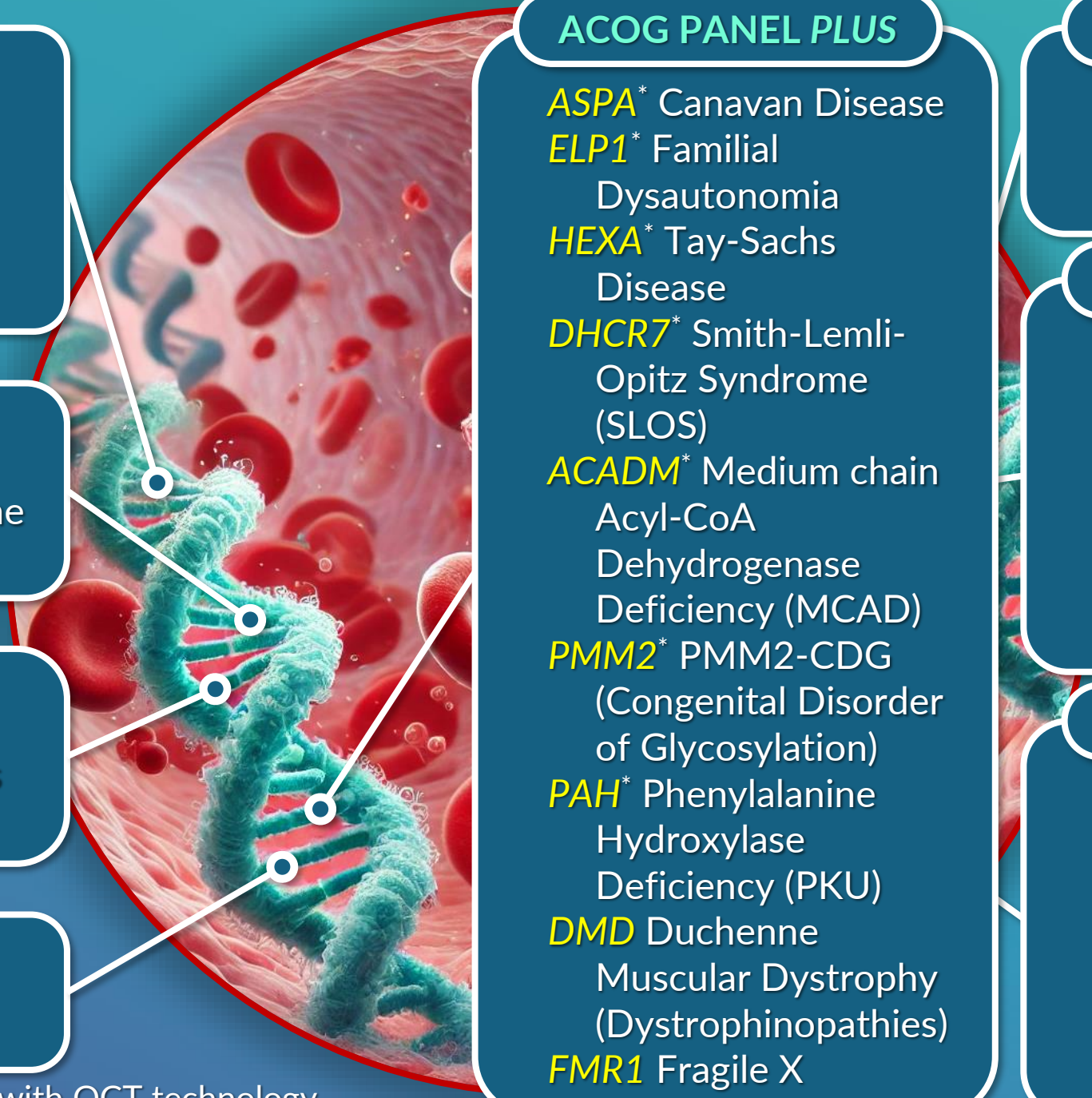
Y Chromosome
Paternal X Chromosome
SRY Gene

MICRODELETIONS

22q11.2 DS
Nested Microdeletions
Maternal vs. Fetal

ZYGOSITY

Monozygotic
Dizygotic



ACOG PANEL *PLUS*

*ASPA** Canavan Disease
*ELP1** Familial Dysautonomia
*HEXA** Tay-Sachs Disease
*DHCR7** Smith-Lemli-Opitz Syndrome (SLOS)
*ACADM** Medium chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
*PMM2** PMM2-CDG (Congenital Disorder of Glycosylation)
*PAH** Phenylalanine Hydroxylase Deficiency (PKU)
DMD Duchenne Muscular Dystrophy (Dystrophinopathies)
FMR1 Fragile X

FETAL *RHD*

*RHD**
RHDψ
RHD-CE-D

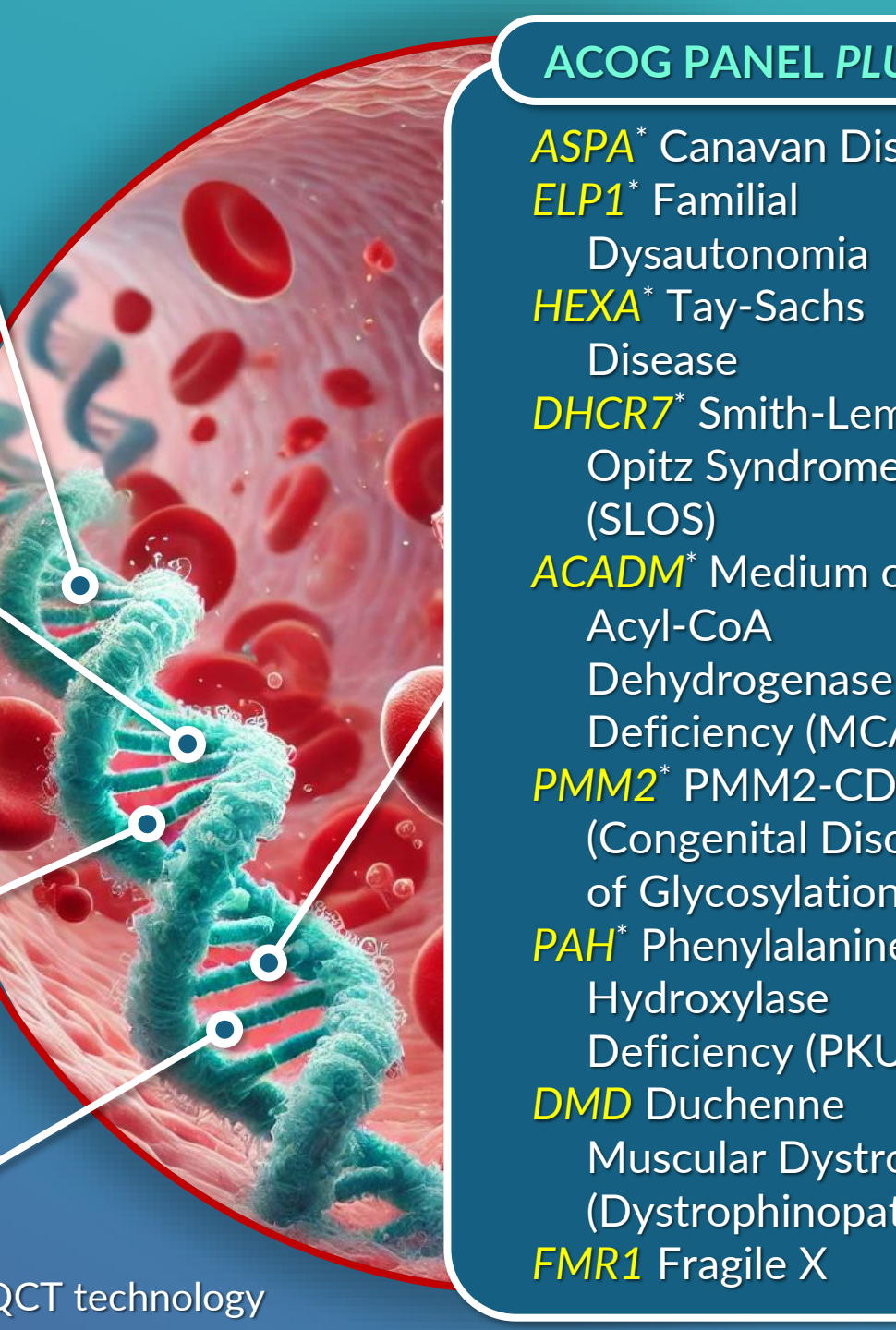
HDFN ANTIGENS

K "Kell" Antigen *KEL**
Fya "Duffy" Antigen *ACKR1*(*FY*)*
D Antigen *RHD**
C "Big C" Antigen *RHCE**
c "little c" Antigen *RHCE**
E Antigen *RHCE**

ACOG PANEL

*CFTR** Cystic Fibrosis
*SMN1** Spinal Muscular Atrophy
*HBA1/HBA2** Hemoglobin H/Barts
*HBB** sickle cell anemia, Hgb C/E, ***β***-thal

*Quantification made possible with QCT technology



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ACOG PANEL

*CFTR** Cystic Fibrosis
*SMN1** Spinal Muscular Atrophy
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*HBB** sickle cell anemia, Hgb C/E, ***β***-thal

HDFN ANTIGENS

k "little k" Antigen *KEL**
Fyb "Duffy" Antigen *ACKR1**
e "little e" Antigen *RHCE**
Jka & Jkb Kidd Antigens *SLC14A1**
M & N Antigens *GYPA**
S & s Antigens *GYPB**
U Antigen *GYPB**

FNAIT ANTIGENS

Human Platelet Antigens
HPA-1 *ITGB3**
HPA-2 *GP1BA**
HPA-3 *ITGA2B**
HPA-4 *ITGB3**
HPA-5 *ITGA2**
HPA-9 *ITGB3**
HPA-15 *CD109**
HLA-*DRB3*01:01*

QCT technology

PAST

PRESENT

FUTURE

PAST

PRESENT

FUTURE

Carrier screen detection rate

>99%[1]

in a general population setting

Fetal risk sensitivity across all 14 genes

>95%[2]

in a general population setting

1. Excludes Alpha Thalassemia which has a detection rate of >95% and Spinal Muscular Atrophy which has a detection rate of >91%
2. For autosomal recessive conditions, the clinical sensitivity refers to the estimated clinical detection rate of high-risk fetuses by cfDNA fetal risk assessment. For X-linked conditions, for which cfDNA testing is only clarified via fetal sex, the clinical sensitivity refers to carrier screening detection and does not account for *de novo* mutations

References:
Wynn, J., et al. (2023). Performance of single-gene noninvasive prenatal testing for autosomal recessive conditions in a general population setting. Prenatal Diagnosis, 43(10), 1344–1354.https://doi.org/10.1002/pd.6427
Plus Panel Validation, April 2025. Data on File.
FARA (Fragile X) Assay Validation, August 2024. Data on File.

POSITIVE CARRIER

CONDITIONS SCREENED	MATERNAL CARRIER STATUS	FETAL RISK BY sgNIPT
Alpha-Thalassemia ***(HBA1, HBA2)***	**POSITIVE** Silent Carrier; aa/a-	*See Results Below*
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies ***(HBB)***	**POSITIVE** Sickle cell: c.20A>T (p.Glu7Val)	*See Results Below*
Cystic Fibrosis ***(CFTR)***	**POSITIVE** c.1865G>A (p.Gly622Asp)	*See Results Below*
Spinal Muscular Atrophy ***(SMN1)***	**Negative** 3 *SMN1* copies, SNP present	

sgNIPT RESULT DETAILS

CONDITIONS SCREENED	FETAL RISK	Risk *Before* sgNIPT	Risk *After* sgNIPT	Fetal Fraction
Alpha-Thalassemia	**LOW**	**1 in 372** (Asian paternal ethnicity) **1 in 2,280** (General population)		**3.1%**
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies	**LOW**	**1 in 32 - 1 in 656**		**3.1%**
Cystic Fibrosis	**LOW**	**1 in 100 - 1 in 472**		**3.1%**

*Unless otherwise noted, fetal risk before and after sgNIPT assumes paternal carrier status is unknown. See disease carrier frequencies based on ethnicity on the last page of the report.

SUMMARY OF RESULTS

POSITIVE Carrier

11.1% fetal fraction

Recommended Follow-Up

Genetic counseling is recommended to review the implications of this result. The patient may contact BillionToOne at **(650) 460-2551** to schedule an appointment for a complimentary telephone genetic consultation to review these results.

Carrier Screen + cfDNA Fetal Risk Assessment

CARRIER SCREEN		cfDNA FETAL RISK ASSESSMENT *(pregnant carriers only)*
Conditions Screened	**Patient Carrier Status**	**Risk *Before* cfDNA**
ACOG Guideline Panel		
Cystic Fibrosis *CFTR*	**POSITIVE** c.1521_1523del (p.Phe508del)	**1 in 100 - 1 in 472**
Spinal Muscular Atrophy *SMN1*	**POSITIVE** 1 *SMN1* copy	**1 in 188 - 1 in 288**
***Plus* Panel**		
Phenylalanine Hydroxylase Deficiency *PAH*	**POSITIVE** c.1066-11G>A	**1 in 68 - 1 in 580**

When applicable, fetal risk before and after cfDNA analysis assumes paternal carrier status is unknown (unless otherwise noted).
Condition carrier frequencies can be found at www.unityscreen.com/carrier-frequencies.

SUMMARY OF RESULTS

POSITIVE Carrier

5.2% fetal fraction

Recommended Follow-Up

Prenatal diagnosis via chorionic villus sampling or amniocentesis is **recommended** for sickle beta-thalassemia.

Genetic counseling is recommended to review the implications of this result. The patient may contact BillionToOne at **(650) 460-2551** to schedule an appointment for a complimentary telephone genetic consultation to review these results.

Carrier Screen + cfDNA Fetal Risk Assessment

CARRIER SCREEN		cfDNA FETAL RISK ASSESSMENT *(pregnant carriers only)*	
Conditions Screened	**Patient Carrier Status**	**Risk *Before* cfDNA**	
ACOG Guideline Panel			
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies *HBB*	**POSITIVE** Sickle cell: c.20A>T (p.Glu7Val)	**1 in 32 - 1 in 656**	

When applicable, fetal risk before and after cfDNA analysis assumes paternal carrier status is unknown (unless otherwise noted).
Condition carrier frequencies can be found at www.unityscreen.com/carrier-frequencies.

SUMMARY OF RESULTS

POSITIVE Carrier

HIGH RISK Fetus

5.2% fetal fraction

Recommended Follow-Up

Prenatal diagnosis via chorionic villus sampling or amniocentesis is **recommended** for sickle beta-thalassemia.

Genetic counseling is recommended to review the implications of this result. The patient may contact BillionToOne at **(650) 460-2551** to schedule an appointment for a complimentary telephone genetic consultation to review these results.

Carrier Screen + c

CARRIER SCREEN

Conditions Screened	Patient Carrier Status
ACOG Guideline Panel	
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies *HBB*	**POSITIVE** Sickle cell: c.20A>T (p.Glu7Val)

When applicable, fetal risk before and after cfDNA analysis assumes paternal car
Condition carrier frequencies can be found at www.unityscreen.com/carrier-frequ

9 in 10

Gene Therapy for Sickle Cell Disease

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

For Immediate Release:

December 08, 2023

Today, the U.S. Food and Drug Administration approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older. Additionally, one of these therapies, Casgevy, is the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy.

Sickle cell disease is a group of inherited blood disorders affecting approximately 100,000 people in the U.S. It is most common in African Americans and, while less prevalent, also affects Hispanic Americans. The primary problem in sickle cell disease is a mutation in hemoglobin, a protein found in red blood cells that delivers oxygen to the body's tissues. This mutation causes red blood cells to develop a crescent or "sickle" shape. These sickled red blood cells restrict the flow in blood vessels and limit oxygen delivery to the body's tissues, leading to severe pain and organ damage called vaso-occlusive events (VOEs) or vaso-occlusive crises (VOCs). The recurrence of these events or crises can lead to life-threatening disabilities and/or early death.

SUMMARY OF RESULTS

POSITIVE Carrier

3.3% fetal fraction

Recommended Follow-Up

Prenatal diagnosis via chorionic villus sampling or amniocentesis is **recommended** for Smith-Lemli-Opitz syndrome.

Genetic counseling is recommended to review the implications of this result. The patient may contact BillionToOne at **(650) 460-2551** to schedule an appointment for a complimentary telephone genetic consultation to review these results.

Carrier Screen + cfDNA Fetal Risk Assessment

CARRIER SCREEN		cfDNA FETAL RISK ASSESSMENT *(pregnant carriers only)*	
Conditions Screened	**Patient Carrier Status**	**Risk *Before* cfDNA**	
***Plus* Panel**			
Smith-Lemli-Opitz Syndrome *DHCR7*	**POSITIVE** c.964-1G>C	**1 in 172 - 1 in 732**	

When applicable, fetal risk before and after cfDNA analysis assumes paternal carrier status is unknown (unless otherwise noted).
Condition carrier frequencies can be found at www.unityscreen.com/carrier-frequencies.

SUMMARY OF RESULTS

POSITIVE Carrier

HIGH RISK Fetus

3.3% fetal fraction

Recommended Follow-Up

Prenatal diagnosis via chorionic villus sampling or amniocentesis is **recommended** for Smith-Lemli-Opitz syndrome.

Genetic counseling is recommended to review the implications of this result. The patient may contact BillionToOne at **(650) 460-2551** to schedule an appointment for a complimentary telephone genetic consultation to review these results.

Carrier Screen + cfDNA Fetal Risk Assessment

CARRIER SCREEN

Conditions Screened	Patient Carrier Status
***Plus* Panel**	
Smith-Lemli-Opitz Syndrome *DHCR7*	**POSITIVE** c.964-1G>C

When applicable, fetal risk before and after cfDNA analysis assumes paternal car
Condition carrier frequencies can be found at www.unityscreen.com/carrier-freque

7 in 10

Fetal Diagnosis and Therapy

Fetal Diagn Ther 1999;14:133–137

Received: March 24, 1998
Accepted: December 9, 1998

Antenatal Therapy of Smith-Lemli-Opitz Syndrome

Mira B. Irons[a,b] Jose Nores[b] Theresa L. Stewart[b] Sabrina D. Craigo[b]
Diana W. Bianchi[a,b] Mary E. D'Alton[b] G. Stephen Tint[c] Gerald Salen[c]
Linda A. Bradley[d]

[a]Departments of Pediatrics and [b]Obstetrics and Gynecology, New England Medical Center, Tufts University School of Medicine, Boston, Mass.; [c]Department of Veterans Affairs Medical Center, East Orange, N.J. and Department of Medicine, UNDNJ – New Jersey Medical School, Newark, N.J., and [d]Foundation for Blood Research, Scarborough, Me., USA

Carrier Screen with **Reflex sgNIPT**

POSITIVE CARRIER

CONDITIONS SCREENED	MATERNAL CARRIER STATUS	FETAL RISK BY sgNIPT
Alpha-Thalassemia *(HBA1, HBA2)*	**Negative**	
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies *(HBB)*	**Negative**	
Cystic Fibrosis *(CFTR)*	**POSITIVE** c.1521_1523del (p.Phe508del)	
Spinal Muscular Atrophy *(SMN1)*	**Negative** 3 *SMN1* copies, SNP not present	
Fragile X Syndrome *(FMR1)*	**Negative** 30 / 29 CGG repeats	

sgNIPT RESULT DETAILS

CONDITIONS SCREENED	FETAL RISK	Risk *Before* sgNIPT		Fetal Fraction
Cystic Fibrosis	HIGH	1 in 100 - 1 in 472		1.7%

*Unless otherwise noted, fetal risk before and after sgNIPT assumes paternal carrier status is unknown. See disease carrier frequencies based on ethnicity on the last page of the report.

Carrier Screen with **Reflex sgNIPT**

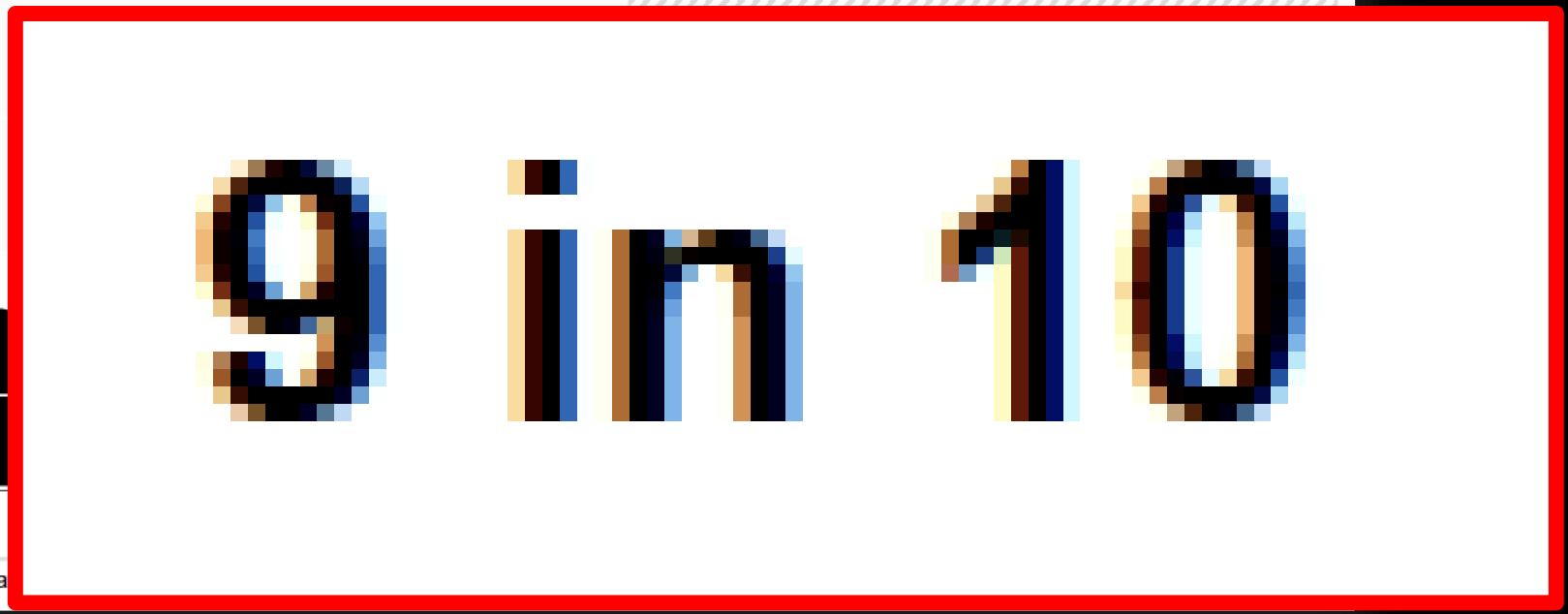
POSITIVE CARRIER **HIGH RISK** FETUS

CONDITIONS SCREENED	MATERNAL CARRIER STATUS	FETAL RISK BY sgNIPT
Alpha-Thalassemia *(HBA1, HBA2)*	**Negative**	
Sickle Cell Disease / Beta-Thalassemia / Hemoglobinopathies *(HBB)*	**Negative**	
Cystic Fibrosis *(CFTR)*	**POSITIVE** c.1521_1523del (p.Phe508del)	**HIGH RISK** *See Results Below*
Spinal Muscular Atrophy *(SMN1)*		
Fragile X Syndrome *(FMR1)*		

sgNIPT RESULT DETAILS

CONDITIONS SCREENED	FETAL RISK
Cystic Fibrosis	HIGH

*Unless otherwise noted, fetal risk before and after sgNIPT assumes pa



Fetal Diagnosis and Therapy

Fetal Therapy

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DOI: 10.1159/000530261

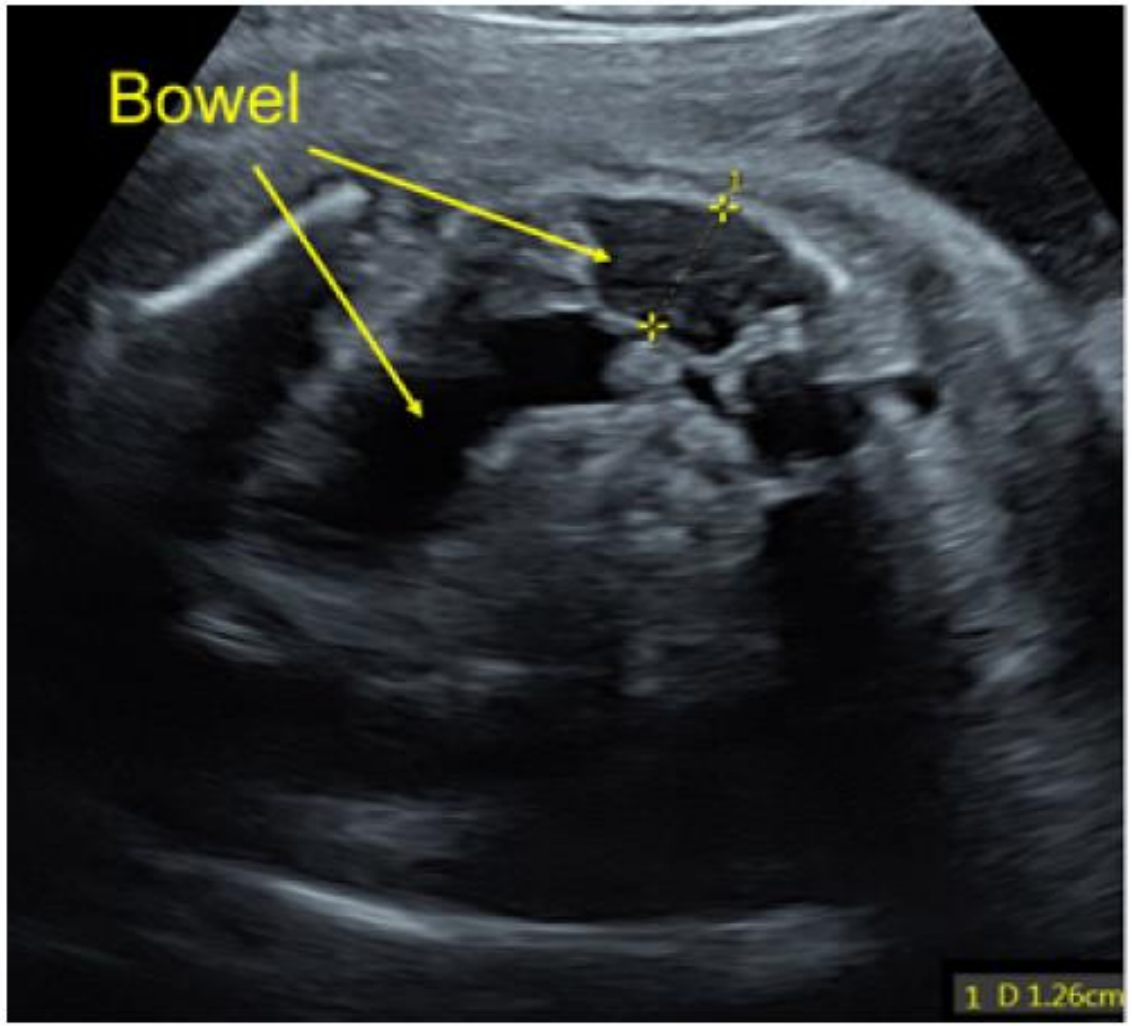
Received: January 20, 2023
Accepted: March 16, 2023
Published online: March 30, 2023

Prenatal Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy: A Promising Way to Change the Impact of Cystic Fibrosis

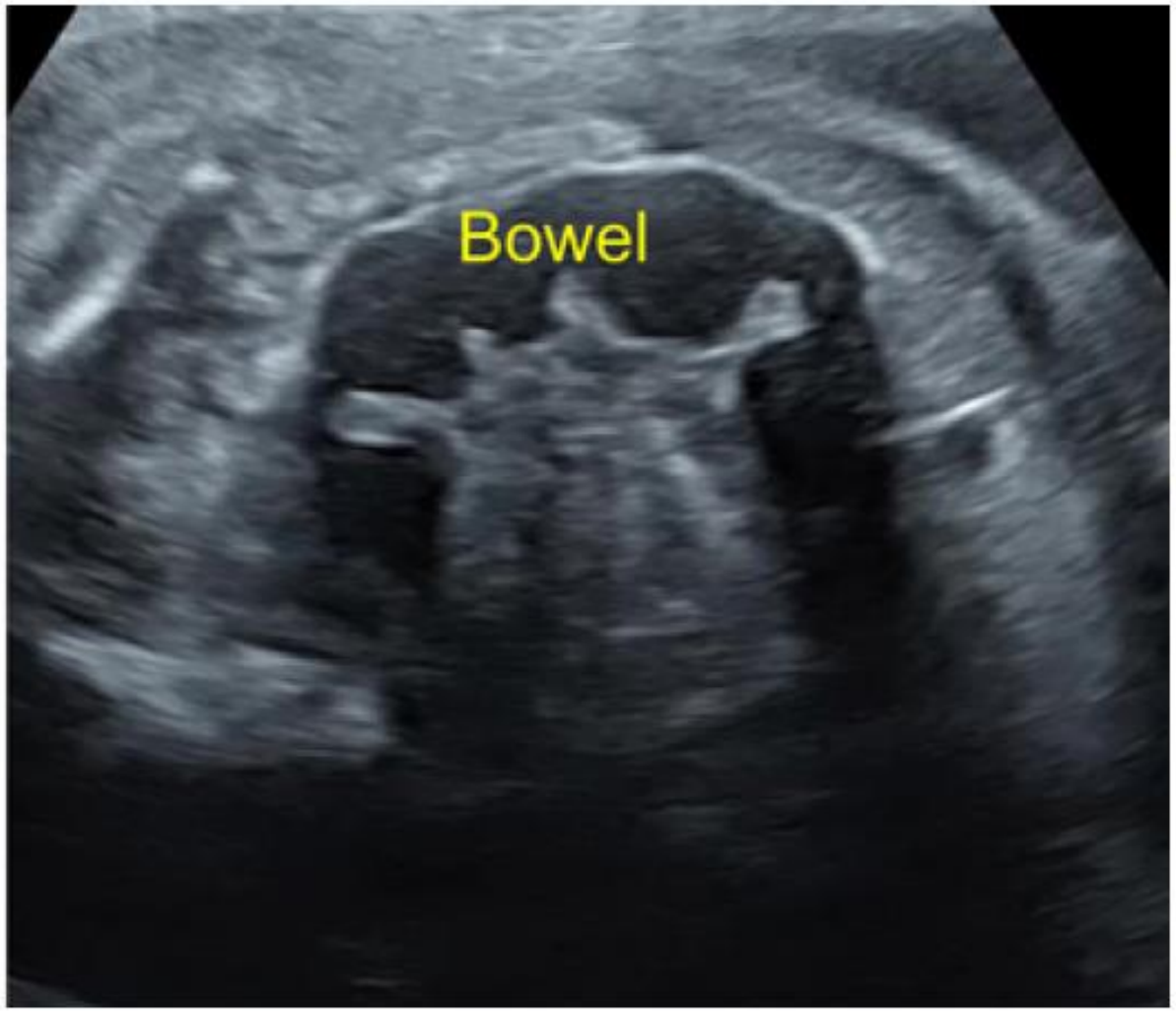
Enery Gómez Montes[a] Enrique Salcedo Lobato[b] Alberto Galindo Izquierdo[a]
Diana García Alcázar[c] Cecilia Villalaín González[a]
María Teresa Moral-Pumarega[d] Gerardo Bustos Lozano[d] Carmen Luna-Paredes[e]

[a]Fetal Medicine Unit, Department of Obstetrics and Gynecology, Research Institute Hospital 12 de Octubre (imas12), Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin (RICORS Network), University Hospital 12 de Octubre, Complutense University, Madrid, Spain; [b]Paediatric Gastroenterology, Hepatology and Nutrition Unit, Cystic Fibrosis Multidisciplinary Unit, University Hospital 12 de Octubre, Madrid, Spain; [c]Perinatal Medicine Unit, Department of Obstetrics and Gynecology, University Hospital 12 de Octubre, Madrid, Spain; [d]Neonatology Department, University Hospital 12 de Octubre, Madrid, Spain; [e]Paediatric Pneumology and Allergy Unit, Cystic Fibrosis Multidisciplinary Unit Coordinator, University Hospital 12 de Octubre, Madrid, Spain

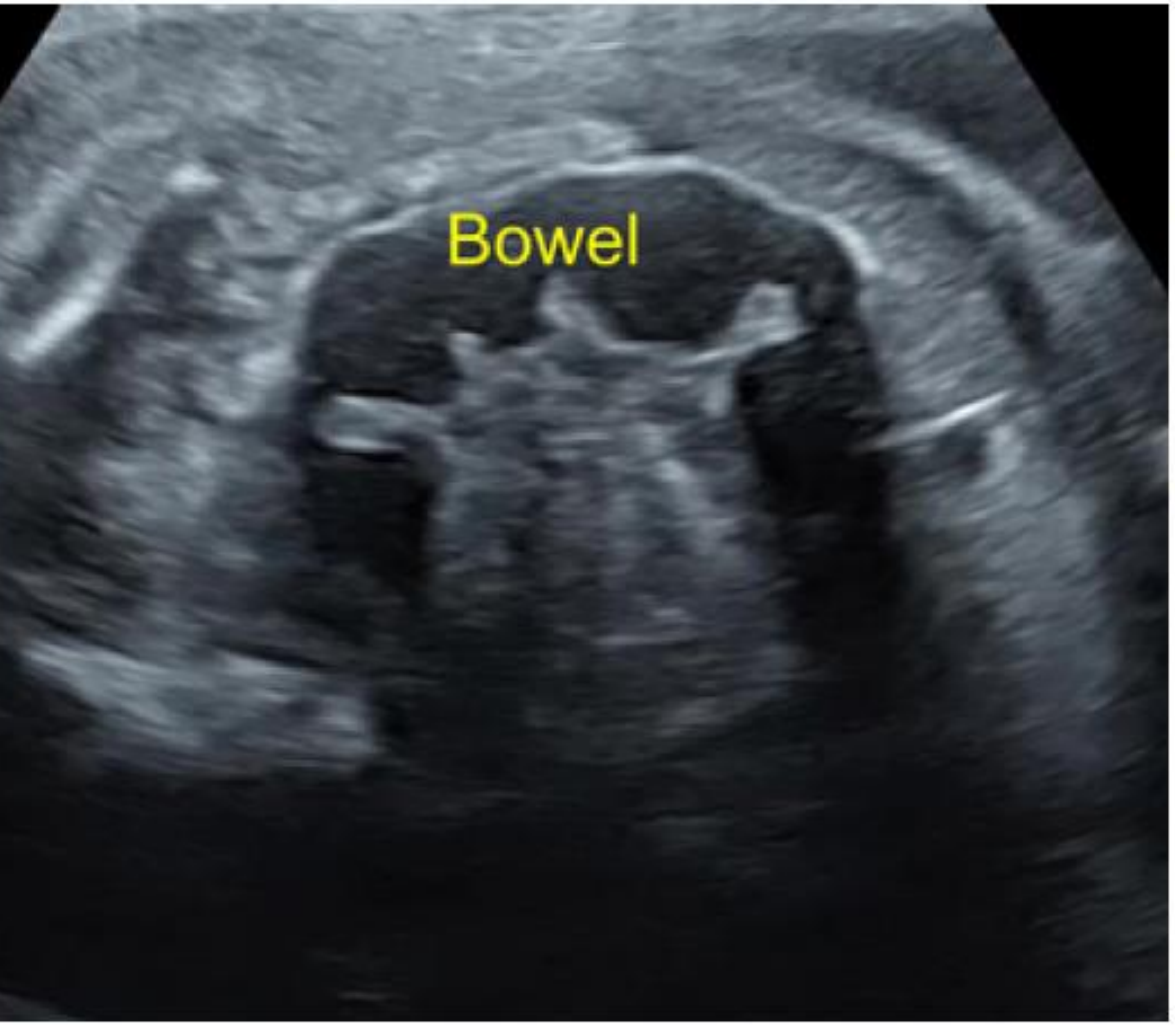
27 weeks



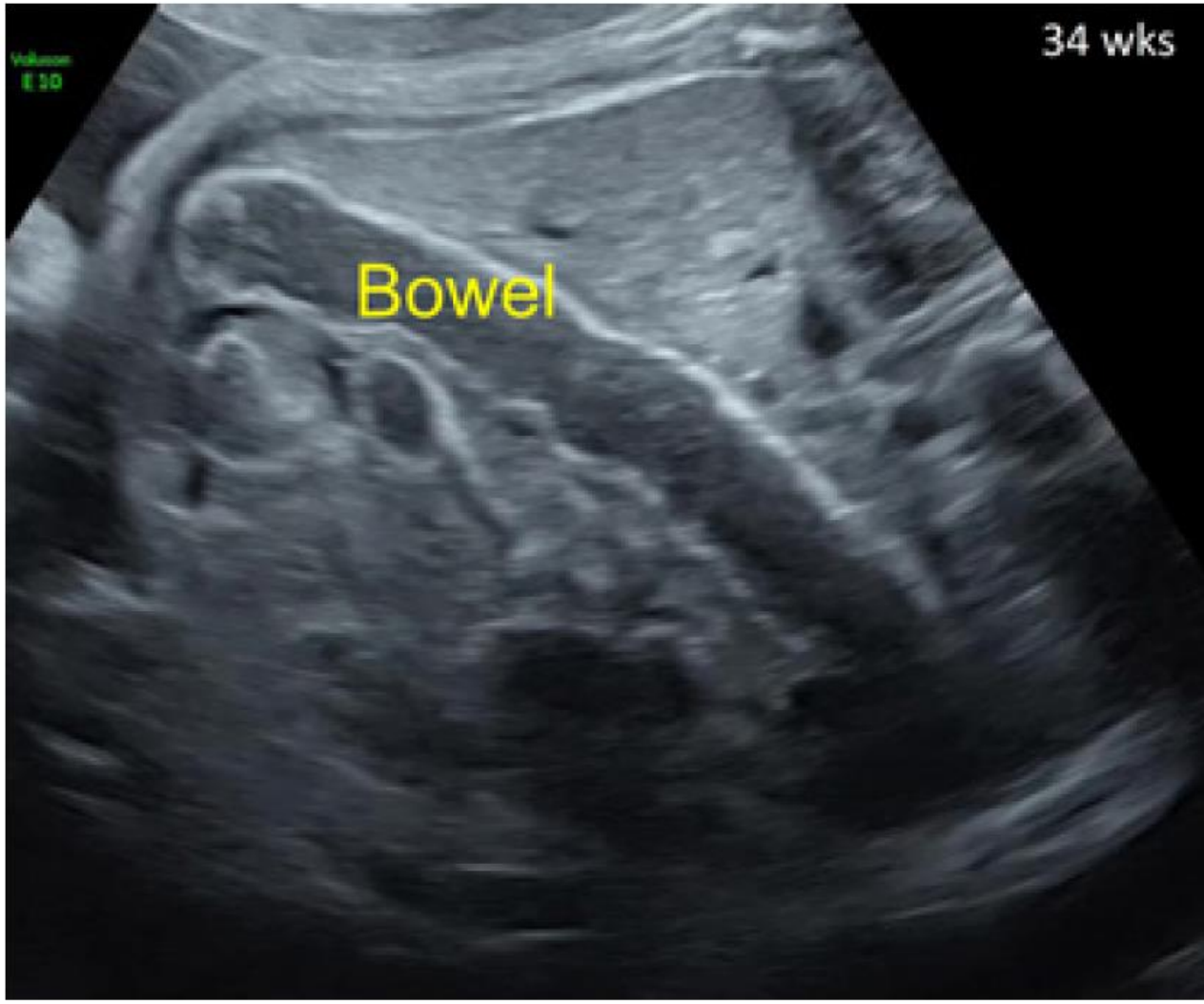
27 weeks



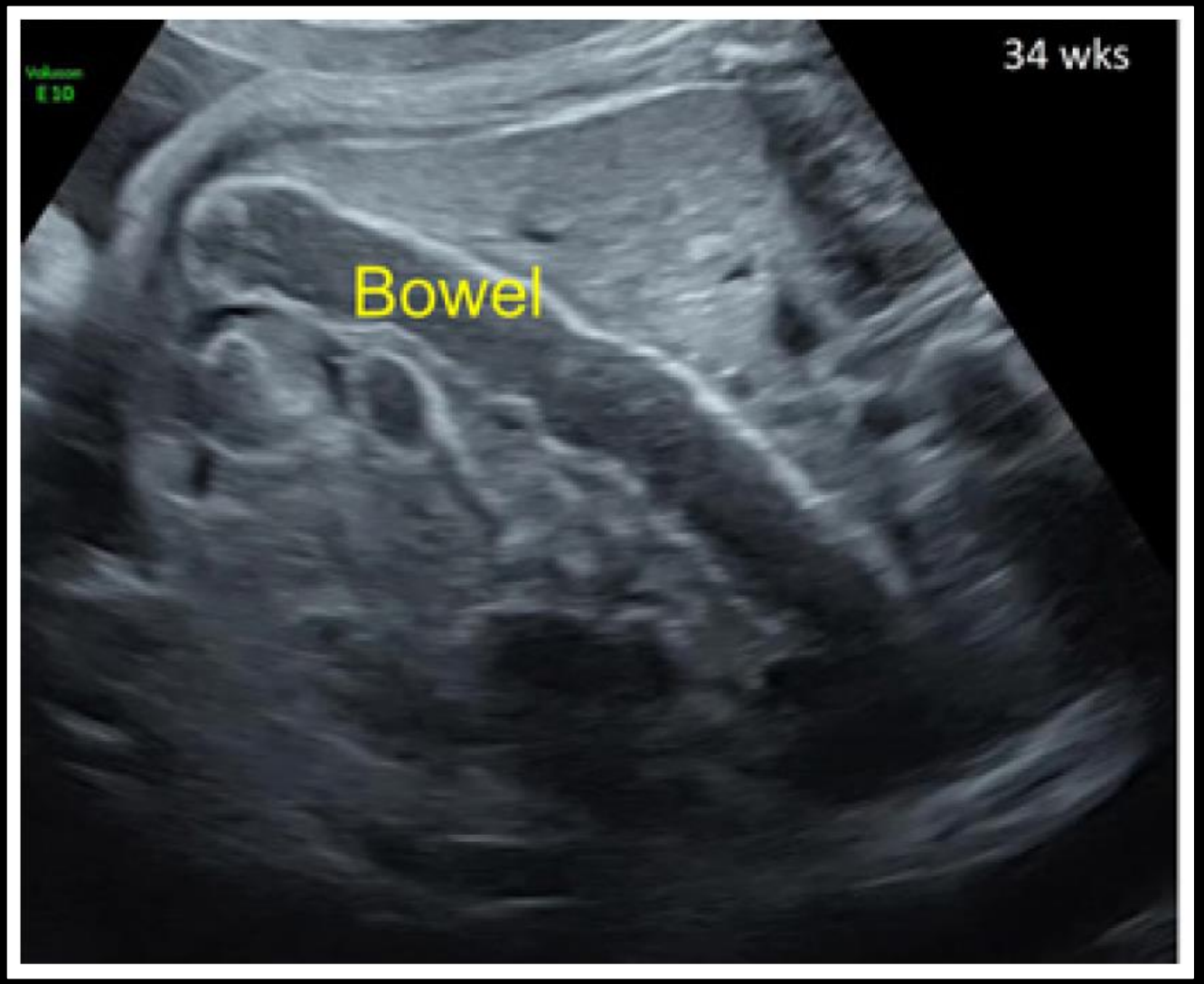
27 weeks



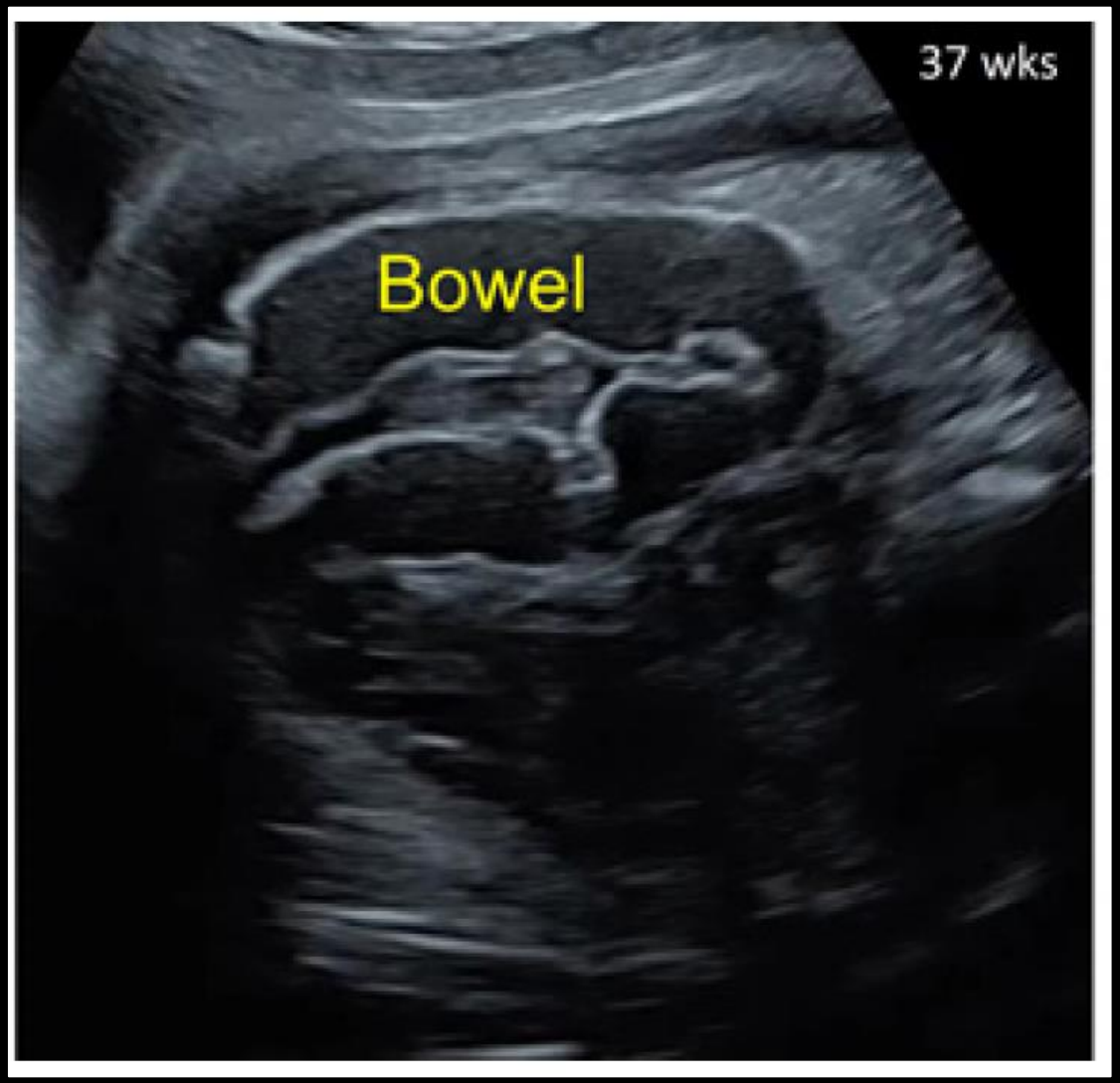
34 weeks



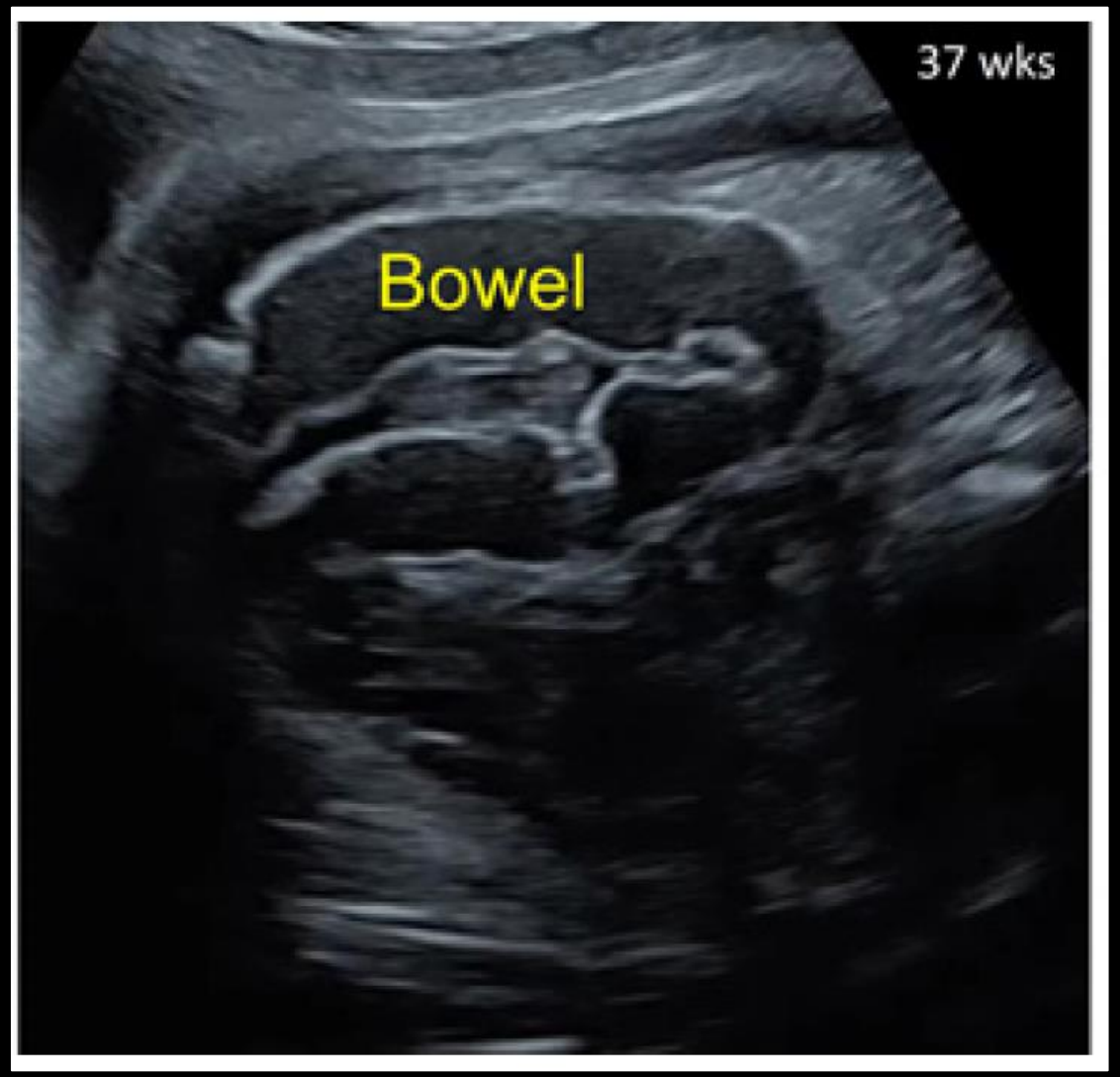
34 weeks



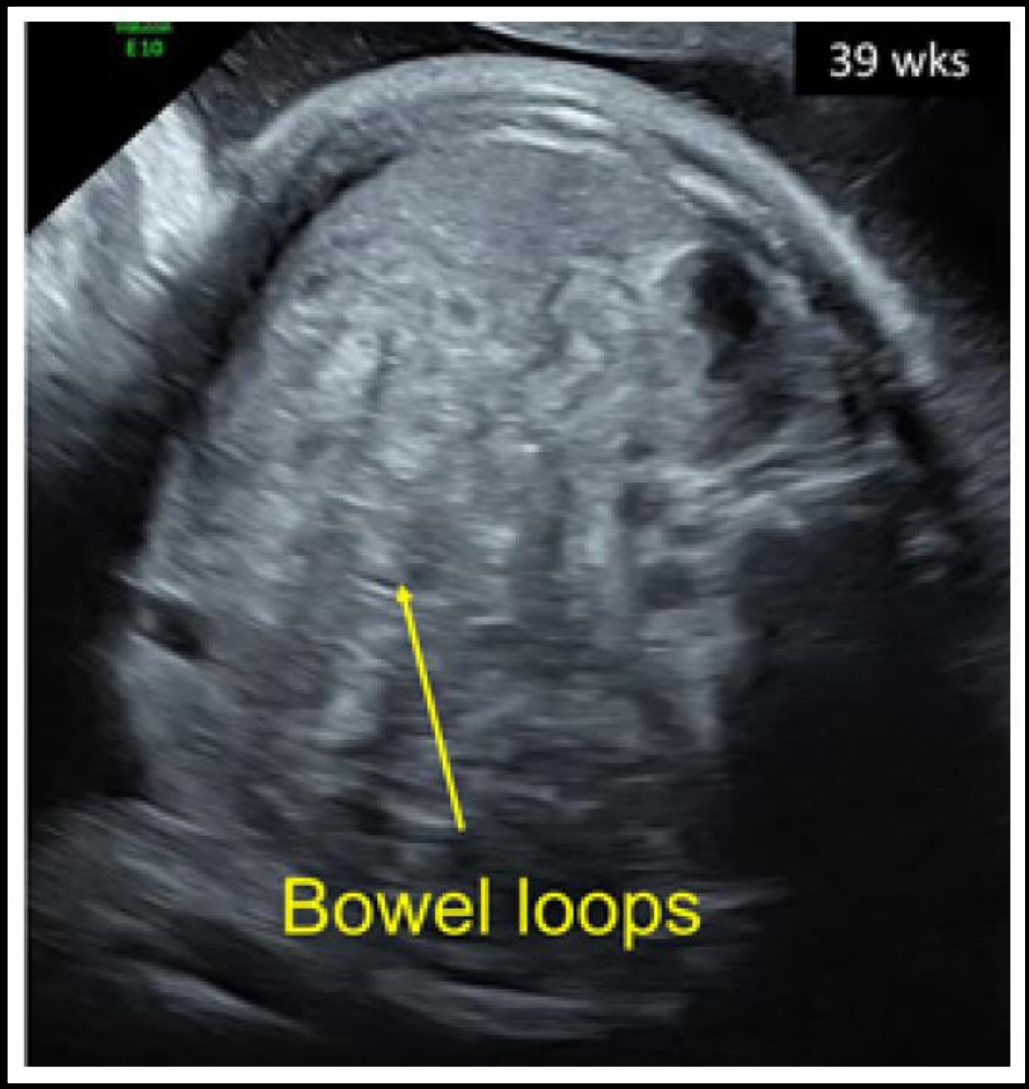
37 weeks



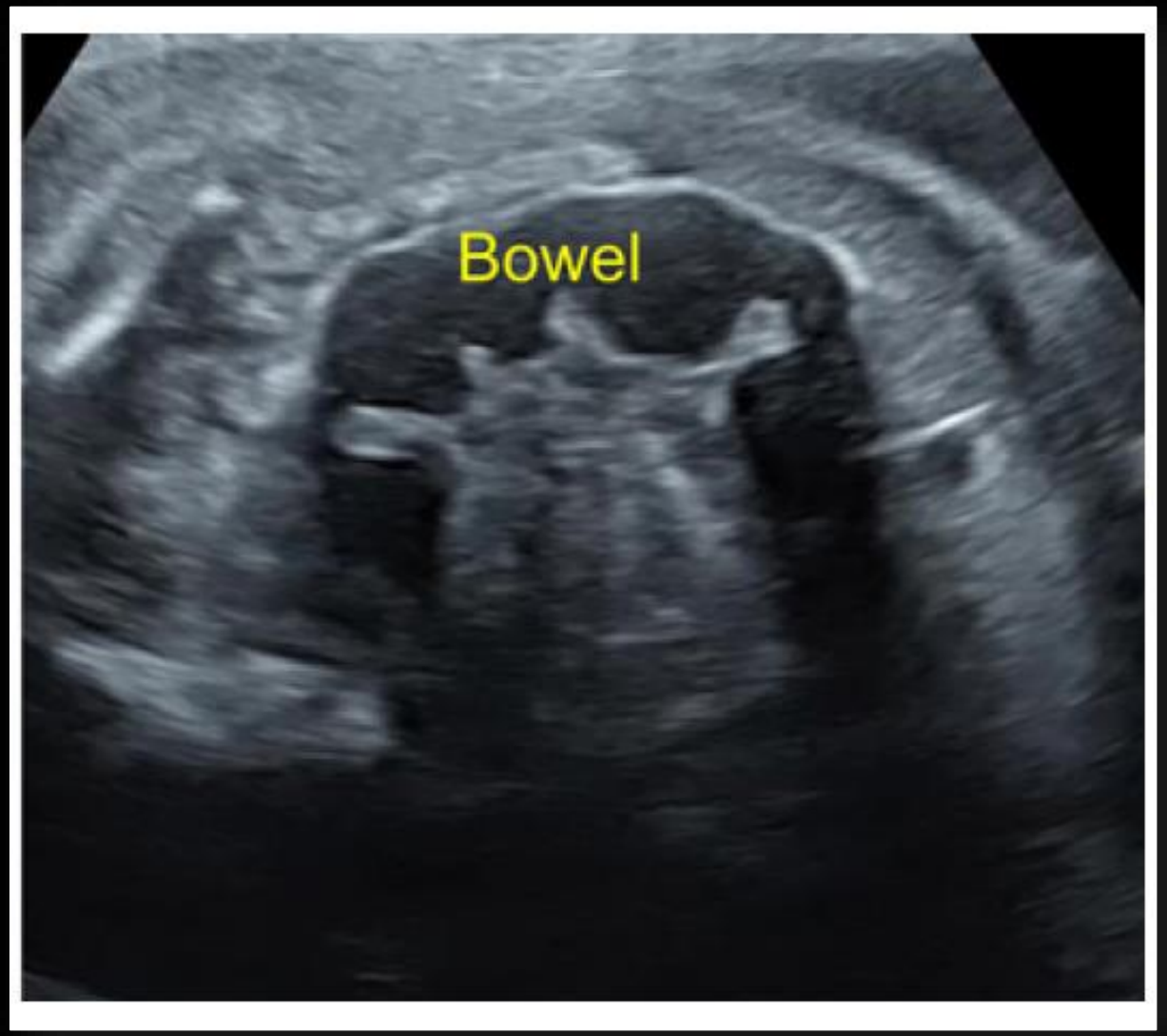
37 weeks



39 weeks



27 weeks



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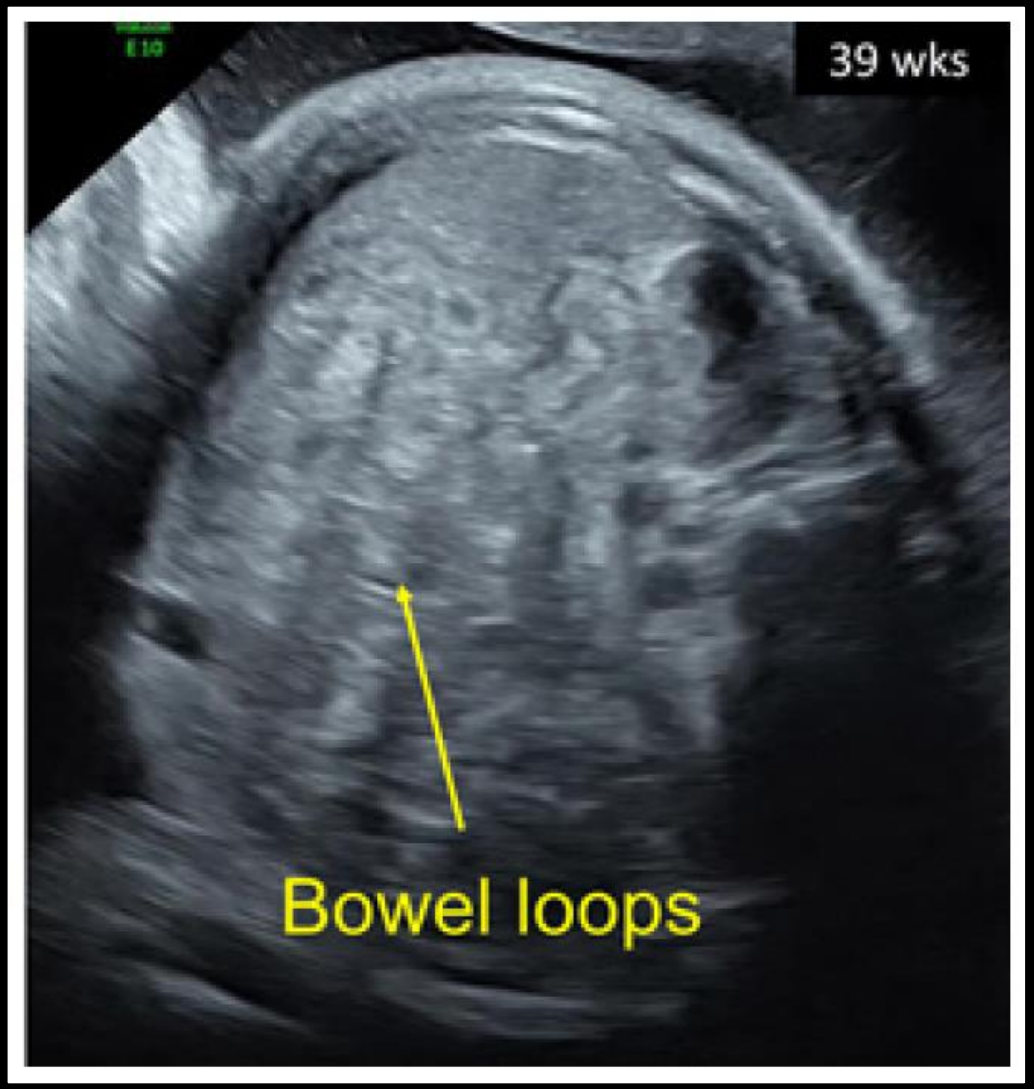

Journal of Cystic Fibrosis 21 (2022) 721–724

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Case Report

A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus

Sylvia Szentpetery*, Kimberly Foil, Sara Hendrix, Sue Gray, Christina Mingora, Barbara Head, Donna Johnson, Patrick A. Flume

Medical University of South Carolina, Charleston, SC 29424, USA

Journal of Cystic Fibrosis 21 (2022) 721–724

OBSERVATION: CASE REPORT

Treatment of Fetal Cystic Fibrosis With Cystic Fibrosis Transmembrane Conductance Regulator Modulation Therapy

Background: Cystic fibrosis (CF) is a life-shortening, autosomal recessive disease affecting approximately 150 000 people worldwide (1). The clinical manifestations of CF result from abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and 80% to 90% of cases in populations of Northern European ancestry are due to a biallelic pathogenic variant (F508del) in the *CFTR* gene (2). Professional societies recommend screening for CF either in the preconception period or in early pregnancy (3).

Journal of Cystic Fibrosis 21 (2022) 721–724
Journal of Cystic Fibrosis 20 (2021) 402–406

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Maternal and fetal outcomes following elexacaftor-tezacaftor-ivacaftor use during pregnancy and lactation

Jennifer L. Taylor-Cousar*, Raksha Jain

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Journal of Cystic Fibrosis 20 (2021) 835–836

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Case report

Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Christopher N. Fortner[a,*], Julie M. Seguin[a], Denise M. Kay[b]

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Journal of Cystic Fibrosis 23 (2024) 1027–1030

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Case Report

Clinical outcomes of two infants with cystic fibrosis, including presence of the vas deferens, born to a woman with cystic fibrosis taking CFTR modulators during both pregnancies

Aleksandra Kowalik [a,*], Emma Roberts [a], Anna Hedborg Harris [a], Marie Sund [b], Sara Wird [b], Ola Kvist [b,c], Lena Hjelte [a]

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Journal of Cystic Fibrosis 24 (2025) 1090–1093

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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Elevated serum lipase in infants with cystic fibrosis exposed to prenatal and postnatal elexacaftor/tezacaftor/ivacaftor

Haley Haskett [a,*], Christopher Fortner [b], Laura Shanley [a], Clement L Ren [a]

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[b] Division of Pulmonary and Sleep Medicine, SUNY Upstate Medical Center, Syracuse, NY, USA

ARTICLE INFO

Keywords:
Pancreatitis
CFTR modulators
Fetal therapy
Pancreatic cell injury

ABSTRACT

Cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction leads to progressive exocr
pancreatic insufficiency, resulting in difficulty in the secretion of digestive enzymes and subsequent mal
sorption of nutrients. Case reports have described preserved pancreatic function with prenatal elexacaft
tezacaftor/ivacaftor (ETI) exposure. However, little is known about pancreatic function and injury as
exposure decreases postnatally. Here, we discuss four infants with cystic fibrosis (CF) who were prenata
exposed to ETI, with pancreatic function ranging from preserved to mild insufficiency. All four develop

Journal of Cystic Fibrosis 24 (2025) 457–465

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Original Article

First real-world study of fetal therapy with CFTR modulators in cystic fibrosis: Report from the MODUL-CF study

Anne-Sophie Bonnel [a,b,1], Tiphaine Bihouée [c,1], Mélanie Ribault [d,2], Marine Driessen [e,2], David Grèvent [f], Frantz Foissac [g,h,i], Ngoc Hoa Truong [g,h,i], Myriam Benhamida [c], Baptiste Arnouat [j], Roxana Borghese [k], Frédérique Chedevergne [a], Laure Couderc-Kohen [l], Jennifer da Silva [m], Dominique Grenet [n], Véronique Houdouin [o], Anais Le [a], Sarah Marchal [p], Eric Deneuville [d], Delphine Pouradier [b], Véronique Rousseau [q], Jean-Marc Treluyer [g,h,i], Arnaud Francart [r], Julie Steffann [k,s], Philippe Reix [t,u], Sihem Benaboud [g,h,i], Marie France Mamzer [s,v], Yves Ville [d,s], Clémence Martin [m,s,w], Pierre-Régis Burgel [m,s,w],

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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[b] Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
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ARTICLE INFO

Keywords:
Reproductive carrier screening
Cell-free DNA testing
In utero diagnosis
CFTR modulator therpay

ABSTRACT

Recent improvements in cell-free DNA technology have enabled non-invasive prenatal testing (NIPT) to screen for fetal single-gene autosomal recessive conditions from maternal blood as early as the first trimester. This technique can determine the fetal risk for cystic fibrosis (CF) with a single blood sample from a pregnant person without the need for a partner sample, which is required for traditional carrier screening.

A retrospective review of 100,106 consecutive general-risk pregnant patients who underwent CF carrier screening was completed. All positive CF carriers underwent cell-free DNA testing, which reported a risk of the fetus being affected with CF. Pregnancies with at least a 1 in 4 risk were classified as high risk. Results of confirmatory testing were solicited from all high-risk cases, and a random sample of 50 % of low-risk cases were used to compute test performance analytics.

The study cohort included 2,587 CF carriers and 20 cases with high-risk cell-free DNA results where the CF-affected status of the fetus/neonate was known, of which 13 were affected. All cases ($n = 8$) with a 9 in 10 cell-free DNA estimated risk were affected. The assay correctly identified all known affected fetuses as high risk (sensitivity of 100 %). Of the 13 affected, 12 cases had at least one *CFTR* variant eligible for CFTR modulator therapy. Additionally, 75 % of all cell-free DNA fetal risk results were returned before 18.5 weeks gestation, providing ample time for diagnostic testing and initiation of *in utero* treatment if indicated.

Carrier screening with reflex to cell-free DNA analysis provides a personalized fetal risk assessment and efficient turnaround times at an early gestational age, without the need for a partner sample for a general risk population. This screening method can precisely guide prenatal diagnostic testing to identify CF-affected fetuses that may benefit from *in utero* therapy.

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100,106 Patients
3,621 Carriers
296 CFTR variants
221 Pathogenic variants

40 Fetuses flagged for CF

- 30 Compound heterozygous
- 10 Homozygous

- 95% with CFTR variants that respond to ETI (Trikafta)

- 100% Sensitivity

- 8/8 with 9/10 risk were affected with CF

PAST

PRESENT

FUTURE

PAST

PRESENT

FUTURE

BREAKTHROUGH TIMELINE

BREAKTHROUGH TIMELINE

1955

1960

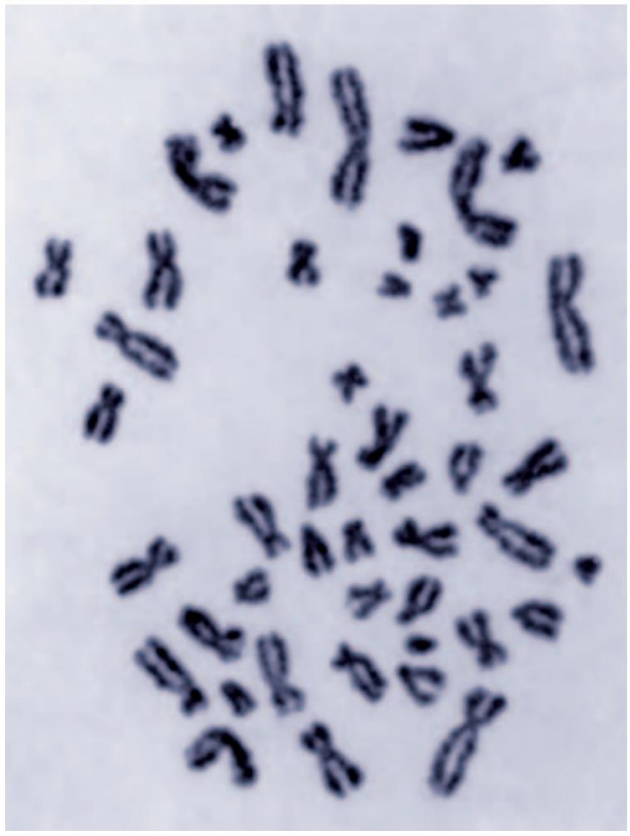

Figure 5 | **A human metaphase plate, from the original Tjio and Levan paper, showing 46 chromosomes.** Reproduced with permission from REF. 14 © (1956) Blackwell Publishing.

HUMAN CHROMOSOMES

~~48~~ → 46

BREAKTHROUGH T

1955

1960

MULTIPLE CONGENITAL ANOMALY CAUSED BY AN EXTRA AUTOSOME

KLAUS PATAU
Ph.D. Berlin

DAVID W. SMITH
M.D. Baltimore

EEVA THERMAN
Ph.D. Helsinki

STANLEY L. INHORN
M.D. New York

HANS P. WAGNER
M.D. Berne

From the Departments of Pathology and Pediatrics, Medical School, University of Wisconsin, Madison, Wisconsin

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January, 195

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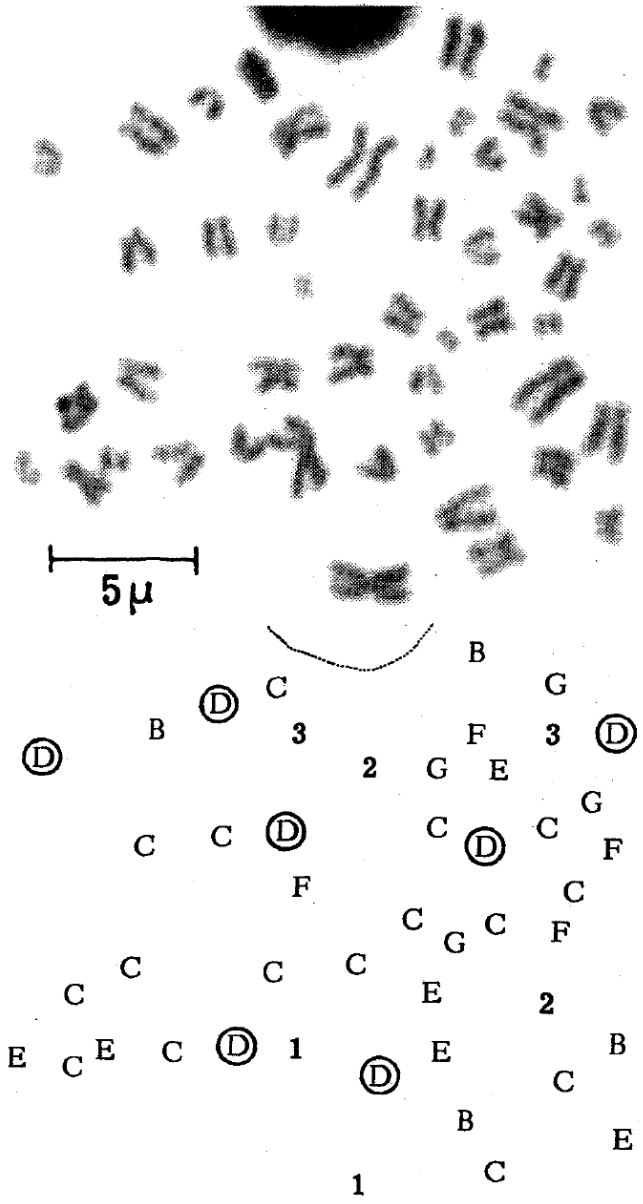


Fig. 3—A cell with 47 chromosomes, including 7 of the D group, from the bone-marrow of the left tibia. The letters designate chromosome groups as in fig. 2.

BREAKTHROUGH TIMELINE

1960

1966

The Lancet · Saturday 19 February 19

CHROMOSOME ANALYSIS OF HUMAN AMNIOTIC-FLUID CELLS

MARK W. STEELE
M.D. New York
RESEARCH ASSOCIATE IN CYTOGENETICS,
SOUTHBURY TRAINING SCHOOL, SOUTHBURY, CONNECTICUT
W. ROY BREG, Jr.
M.D. Yale
ASSISTANT CLINICAL PROFESSOR OF PEDIATRICS,
YALE UNIVERSITY SCHOOL OF MEDICINE

WHEN Fuchs and Riis (Fuchs and Riis 1956, Fuchs

Cell Culture

The other half of the cell susp
was placed either in a standard ' P
standard pyrex 199 ml. milk dilut
containing a layer of irradiated
culture. Growth medium at pH
cultures were gassed with 5% CO
bated at 37°C (see accompanying
The following growth media w

1. Medium 199 plus the aminoac
components of an equal quantity of E
fœtal-calf serum, 12% human serum, and 50 units per ml. of penicillin-
streptomycin.

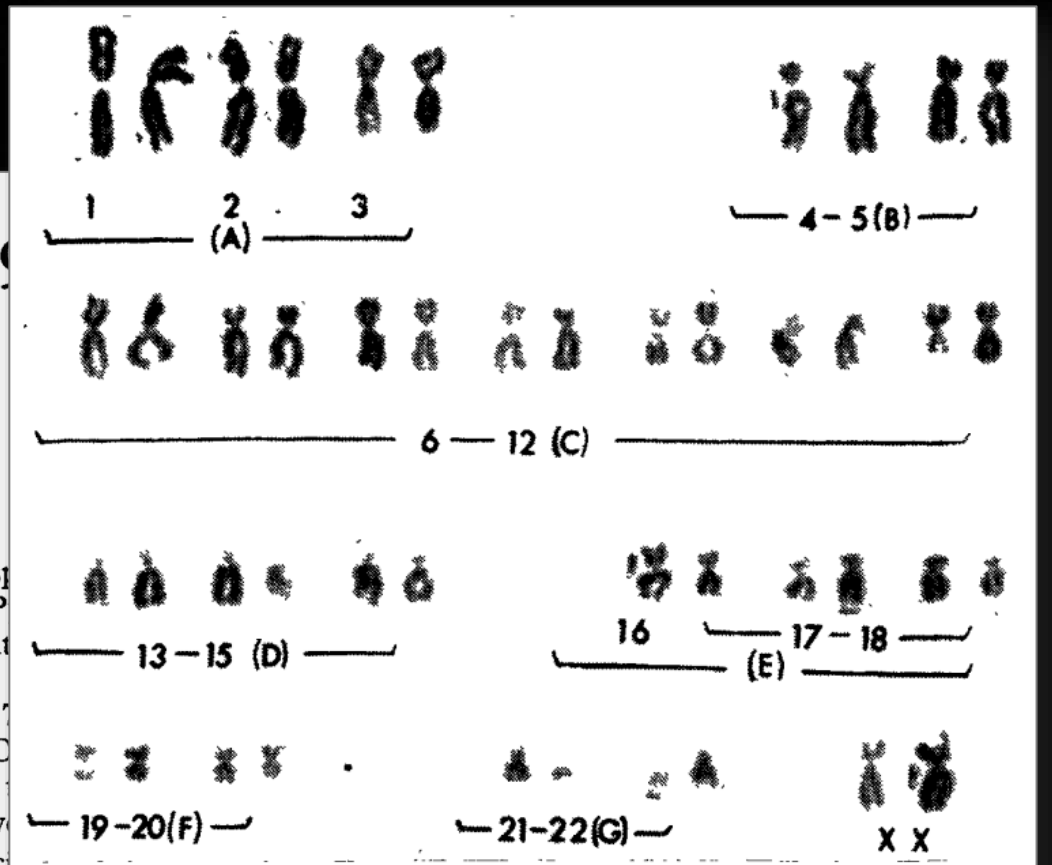


Fig. 3—Female karyotype from cultured amniotic-fluid cell.

BREAKTHROUGH TIMELINE

1984

1992

An association between low maternal serum α-fetoprotein and fetal chromosomal abnormalities

Irwin R. Merkatz, M.D., Harold M. Nitowsky, M.D., James N. Macri, Ph.D., and Walter E. Johnson, Ph.D.

Bronx and Stony Brook, New York, and Cleveland, Ohio

An index case of "undetectable" maternal serum α-fetoprotein at 16 weeks in the first pregnancy of a 28-year-old woman was associated with birth of an infant with trisomy 18. This fortuitous finding stimulated a retrospective study of prenatally diagnosed chromosomal abnormalities. From among a series of 3,862 genetic amniocenteses, 32 cases of fetal autosomal trisomy were diagnosed for which corresponding maternal serum and amniotic fluid α-fetoprotein data could be retrieved. From a second laboratory, nine additional cases were added. The maternal serum α-fetoprotein levels expressed as multiples of the median were significantly lower in distribution for these 41 women than those from a group of normal matched control subjects ($p < 0.001$). Since maternal age is shown to be a less than adequate predictor of autosomal trisomic birth, we proposed that a low level of maternal serum α-fetoprotein obtained through routine screening may prove to be valuable in improving the prenatal detection of these serious anomalies.

(AM. J. OBSTET. GYNECOL. 148:886, 1984.)

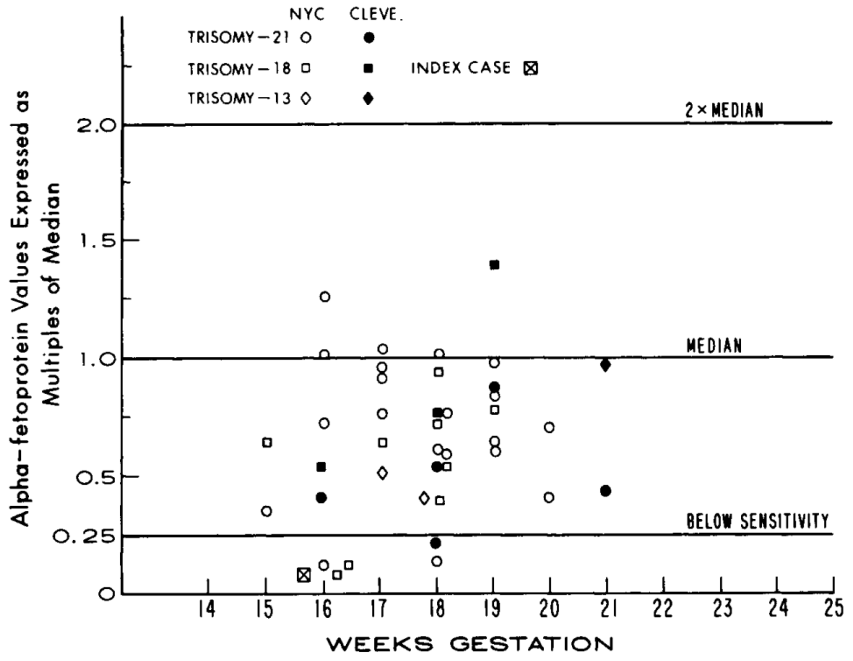


Fig. 4. Serum α-fetoprotein values (MOM) from mothers of trisomic fetuses plotted against weeks of gestation. The type and location by city (*NYC* = New York City; *Cleve.* = Cleveland) for each instance of aneuploidy is designated by key.

BREAKTHROUGH TIMELINE

1984

1992

1997

Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy

K H Nicolaides, G Azar, D Byrne, C Mansur, K Marks

Abstract

***Objective*—To examine the significance of fetal nuchal translucency at 10-14 weeks' gestation in the prediction of abnormal fetal karyotype.**

***Design*—Prospective screening study.**

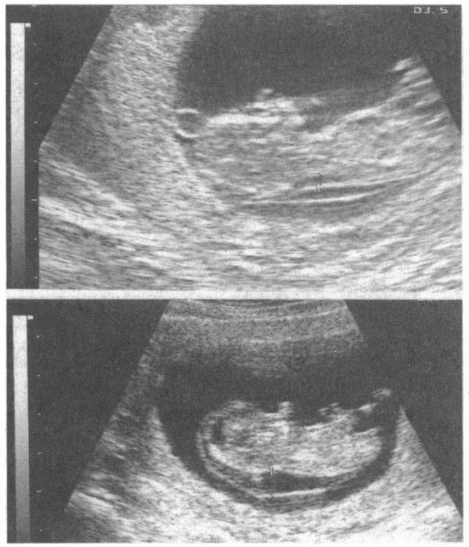
***Setting*—The Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London.**

***Subjects*—827 fetuses undergoing first trimester karyotyping by aminocentesis or chorionic villus sampling.**

***Main outcome measure*—Incidence of chromosomal defects.**

***Results*—The incidence of chromosomal defects was 3% (28 of 827 cases). In the 51 (6%) fetuses with nuchal translucency 3–8 mm thick the incidence of chromosomal defects was 35% (18 cases). In contrast, only 10 of the remaining 776 (1%) fetuses were chromosomally abnormal.**

***Conclusion*—Fetal nuchal translucency ⩾3 mm is a useful first trimester marker for fetal chromosomal abnormalities.**



Ultrasonic appearances of subcutaneous nuchal translucency. Both skin and amnion appear as thin membranes (top). In some cases translucency extends over wide area of fetus but is most prominent behind neck (bottom)

Introduction

In the second and third trimesters of pregnancy there is a high association between fetal nuchal cystic hygromas or nuchal oedema and chromosomal

TABLE III—*Incidence of chromosomal abnormalities in relation to maternal age (years) and presence or absence of nuchal translucency ⩾3 mm thick. Figures are numbers (percentages) of fetuses*

Maternal age (years)	Total	Nuchal translucency	
		Absent	Present
22-23	0/3	0/2	0/1
24-25	0/5	0/5	0/0
26-27	0/5	0/5	0/0
28-29	0/8	0/8	0/0
30-31	0/19	0/19	0/0
32-33	0/27	0/27	0/0
34-35	2/87 (2)	0/81	2/6 (33)
36-37	3/222 (1)	1/213 (0)	2/9 (22)
38-39	7/242 (3)	2/228 (1)	5/14 (36)
40-41	6/119 (5)	3/111 (3)	3/8 (38)
42-43	7/73 (10)	3/64 (5)	4/9 (44)
44-45	2/14 (14)	0/10	2/4 (50)
46-47	1/3 (33)	1/3 (33)	0/0
Total	28/827 (3)	10/776 (1)	18/51 (35)

BREAKTHROUGH TIMELINE

1992

1997

THE LANCET

Early report

Presence of fetal DNA in maternal plasma and serum

Y M Dennis Lo, Noemi Corbetta, Paul F Chamberlain, Vik Rai, Ian L Sargent, Christopher W G Redman, James S Wainscoat

Summary

Background The potential use of plasma and serum for molecular diagnosis has generated interest. Tumour DNA has been found in the plasma and serum of cancer patients, and molecular analysis has been done on this material. We investigated the equivalent condition in pregnancy—that is, whether fetal DNA is present in maternal plasma and serum.

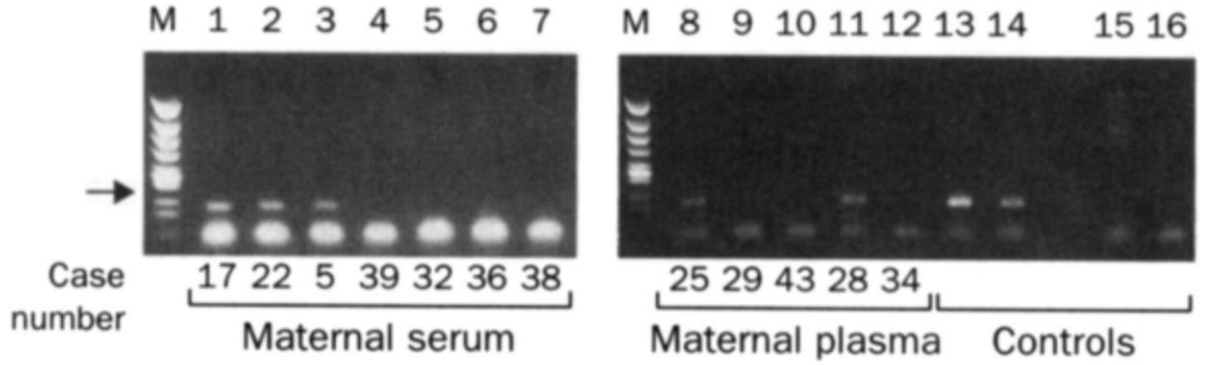
Methods We used a rapid-boiling method to extract DNA from plasma and serum. DNA from plasma, serum, and nucleated blood cells from 43 pregnant women underwent a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses.

Findings Fetus-derived Y sequences were detected in 24 (80%) of the 30 maternal plasma samples, and in 21 (70%) of the 30 maternal serum samples, from women bearing male fetuses. These results were obtained with only 10 μL

Introduction

The passage of nucleated cells between mother and fetus is well recognised.[1,2] One important clinical application is the use of fetal cells in maternal blood for non-invasive prenatal diagnosis.[3] This approach avoids the risks associated with conventional invasive techniques, such as amniocentesis and chorionic-villus sampling. Substantial advances have been made in the enrichment and isolation of fetal cells for analysis.[3,4] However, most techniques are time-consuming or require expensive equipment.

There has been much interest in the use of DNA derived from plasma or serum for molecular diagnosis.[5] In particular, there have been reports that tumour DNA can be detected by molecular techniques in the plasma or serum of cancer patients.[6-8] Such reports prompted us to investigate whether fetal DNA can be detected in maternal plasma and serum.



Amplification of fetal Y-chromosomal sequences from maternal plasma and serum

Lanes 13 and 14=Y-PCR on male genomic DNA (positive controls); lane 13 DNA equivalent to ten male cells; lane 14 DNA equivalent of one male cell. Land 15, 1 μg female genomic DNA (negative control). Lane 16, water (negative control). Arrow marks position of 198 bp Y-PCR product. M=molecular weight marker (ϕX174 DNA digested with *Hinc*II).

BREAKTHROUGH TIMELINE

2011 2014 2017 20 20

The New York Times

A Less Risky Down Syndrome Test Is Developed

Share full article

By Andrew Pollack

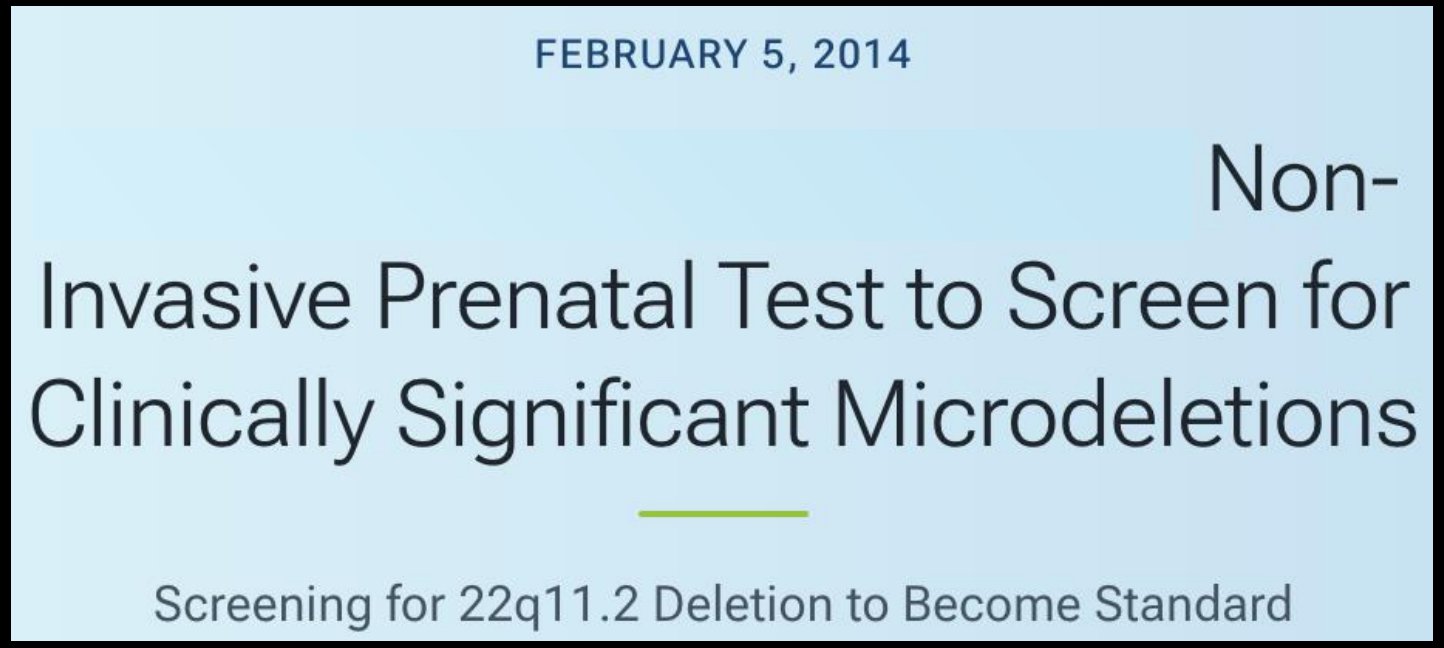
Oct. 17, 2011

New tests are coming to market that can detect Down syndrome in a fetus using a sample of the mother's blood, potentially reducing the need for riskier invasive tests while also stirring ethical concerns.

NIPT Resolution: 10's of millions (10^7) of base pairs

BREAKTHROUGH TIMELINE

2011 | **2014** | 2017 | 20 | 2020 | 2022



NIPT Resolution: Millions (10^6) of base pairs

BREAKTHROUGH TIMELINE

2011 2014 2017 20 2020 2022 20 20 20

Noninvasive Prenatal Testing Moves Beyond Chromosomal Abnormalities to Single-Gene Disorders

Jul 14, 2017 | Monica Heger

Premium *Save for later*

SAN FRANCISCO (GenomeWeb) – Early this year, launched a noninvasive prenatal 30-gene test that focuses on identifying *de novo* mutations that indicate autosomal dominant or X-linked disorders.

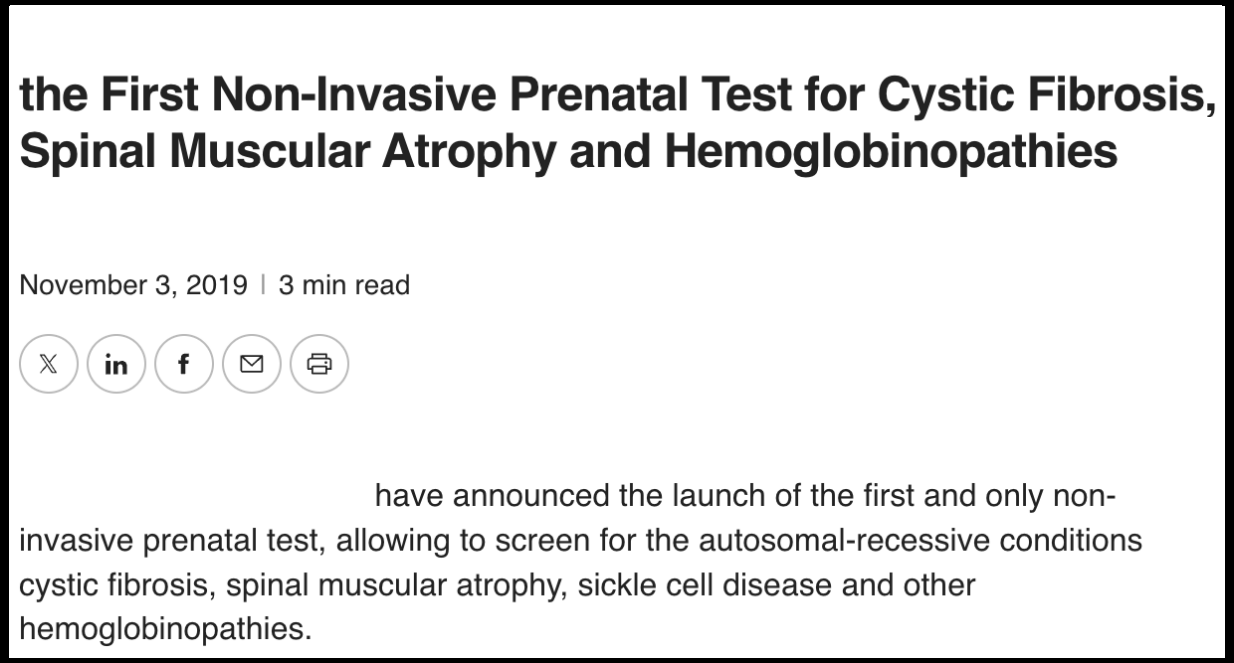
It is the first time individual genes have been analyzed in a noninvasive prenatal test in the US and it pushes the field closer to analyzing entire fetal genomes for disease risk.

Courtesy of Michelle Tribe/Wikimedia Commons

NIPT Resolution: thousands (10^3-10^5) of base pairs

BREAKTHROUGH TIMELINE

2011 2014 2017 2019 20 2022 20 20 2026



the First Non-Invasive Prenatal Test for Cystic Fibrosis, Spinal Muscular Atrophy and Hemoglobinopathies

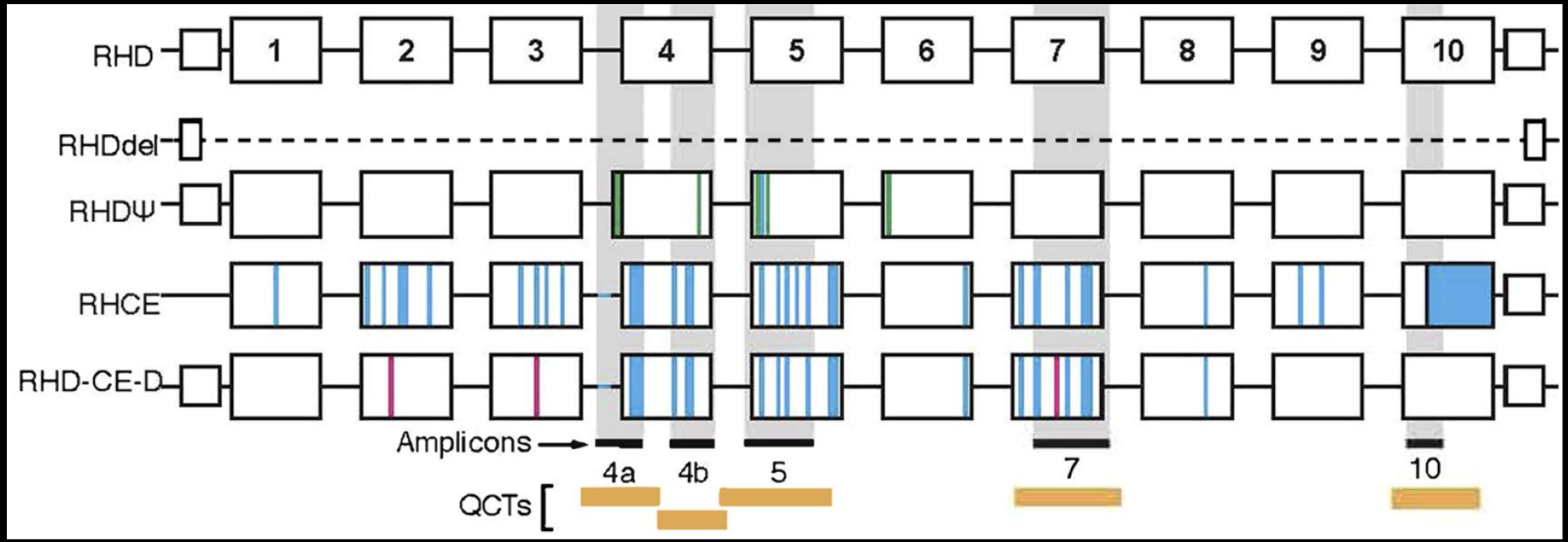
November 3, 2019 | 3 min read

have announced the launch of the first and only non-invasive prenatal test, allowing to screen for the autosomal-recessive conditions cystic fibrosis, spinal muscular atrophy, sickle cell disease and other hemoglobinopathies.

NIPT Resolution: single base pair (10^0)

BREAKTHROUGH TIMELINE

11 2014 2017 20 2020 2022 20 20 2026

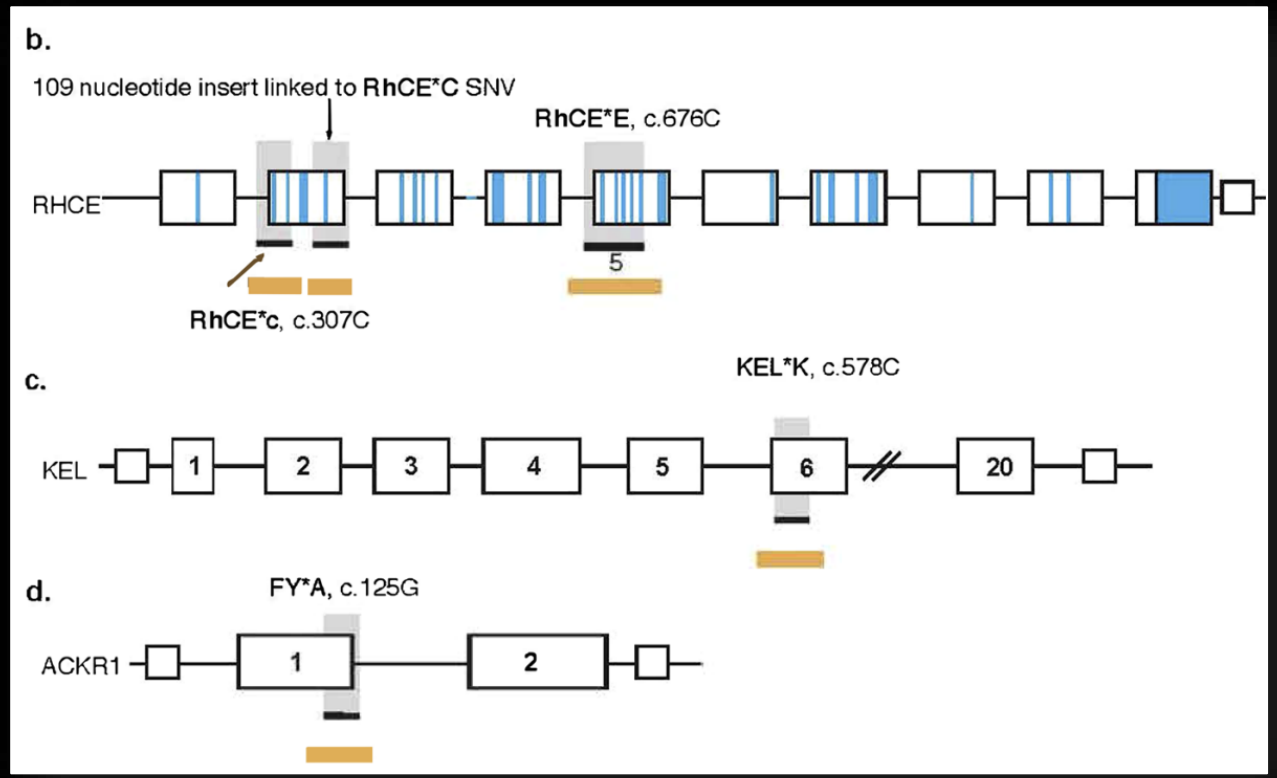


BREAKTHROUGH TIMELINE

2014 2017 20 2020 2022 20 20 2026

Fetal Antigen NIPT

- K (Kell)
- Fya (Duffy)
- D (RhD)
- C (Big C)
- c (little c)
- E



BREAKTHROUGH TIMELINE

2017 20 2020 2022 2024 2026

CLINICAL PRACTICE UPDATE

ACOG
The American College of Obstetricians and Gynecologists

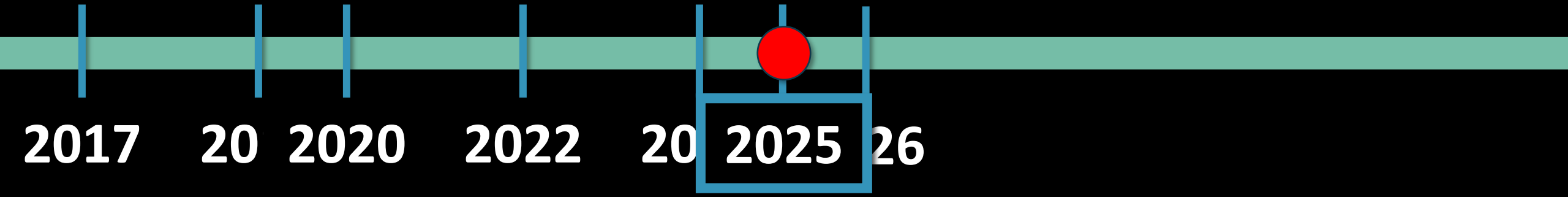
AUGUST 2024

Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy

This Clinical Practice Update was developed by the American College of Obstetricians and Gynecologists with the assistance of Russell Scott Miller, MD, Laura Mercer, MD, Brian Lincoln Shaffer, MD, Andrea Denise Shields, MD, MS, and Manisha Gandhi, MD.

This Clinical Practice Update clarifies guidance on paternal genotyping and provides new recommendations on the role of noninvasive fetal red blood cell antigen genotyping using cell-free DNA (cfDNA). This document updates Practice Bulletin No. 192, *Management of Alloimmunization in Pregnancy* (Obstet Gynecol 2018;131:e82–90).

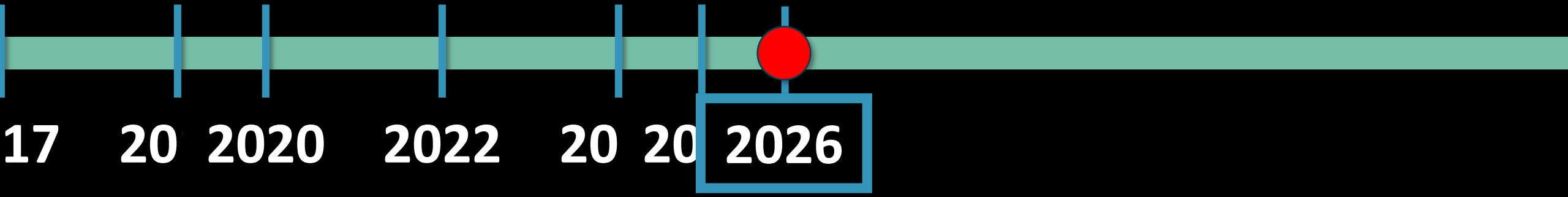
BREAKTHROUGH TIMELINE



Non-invasive Prenatal Tests (NIPT)

- ***HEXA*** - Tay Sachs disease
- ***ASPA*** - Canavan disease
- ***ELP1*** - Familial dysautonomia
- ***DHCR7*** - Smith-Lemi-Opitz syndrome
- ***ACADM*** - Medium-chain Acyl-CoA dehydrogenase deficiency
- ***PMM2*** - Congenital disorder of glycosylation
- ***PAH*** - Phenylalanine hydroxylase deficiency (phenylketonuria)

BREAKTHROUGH TIMELINE



HDFN Antigens (16)	
D (RhD)	Fyb
C (Big C)	Jka (Kidd)
c (little c)	Jkb
E	M
e	N
K (Kell)	S (Big S)
k	S (little s)
Fya (Duffy)	U

FNAIT Antigens (14)	
HPA-1a	HPA-1b
(reflex to maternal HLA-DRB3*01:01)	
HPA-2a	HPA-2b
HPA-3a	HPA-3b
HPA-4a	HPA-4b
HPA-5a	HPA-5b
HPA-9a	HPA-9b
HPA-15a	HPA-15b

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 181, AUGUST 2017

(Replaces Practice Bulletin Number 4, May 1999)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Robert M. Silver, MD.

Prevention of Rh D Alloimmunization

Advances in the prevention and treatment of Rh D alloimmunization have been one of the great success stories of modern obstetrics. There is wide variation in prevalence rates of Rh D-negative individuals between regions, for example from 5% in India to 15% in North America (1). However, high birth rates in low prevalence areas means Rh hemolytic disease of the newborn is still an important cause of morbidity and mortality in countries without prophylaxis programs (1). In such countries, 14% of affected fetuses are stillborn and one half of live born infants suffer neonatal death or brain injury (1). The routine use of Rh D immune globulin is responsible for the reduced rate of red cell alloimmunization in more economically developed countries. First introduced in the 1970s, the postpartum administration of Rh D immune globulin reduced the rate of alloimmunization in at-risk pregnancies from approximately 13–16% to approximately 0.5–1.8% (2, 3). The risk was further reduced to 0.14–0.2% with the addition of routine antepartum administration (2, 3). Despite considerable proof of efficacy, there are still a large number of cases of Rh D alloimmunization because of failure to follow established protocols. In addition, there are new data to help guide management, especially with regard to weak D phenotype women. The purpose of this document is to provide evidence-based guidance for the management of patients at risk of Rh D alloimmunization.

immune globulin prophylaxis suggested that it was only cost effective in primigravid women (27, 47), more recent data indicate that prophylactic administration to all women at risk is cost beneficial (48).

Noninvasive determination of fetal Rh status is now possible through the analysis of cell-free DNA in maternal plasma. Up to 40% of Rh D-negative pregnant women will carry an Rh D-negative fetus. In this clinical situation, antenatal anti-D immune globulin administration is unnecessary. Concerns have been raised about the unwarranted exposure of these pregnant women to a plasma-based product (49). Some parts of the world now are using circulating cell-free DNA testing to ascertain the fetal Rh D status and to establish candidates for antenatal anti-D

Rho(D) Immune Globulin Shortages

Practice Advisory | March 2024

By reading this page you agree to ACOG's Terms and Conditions. Read terms

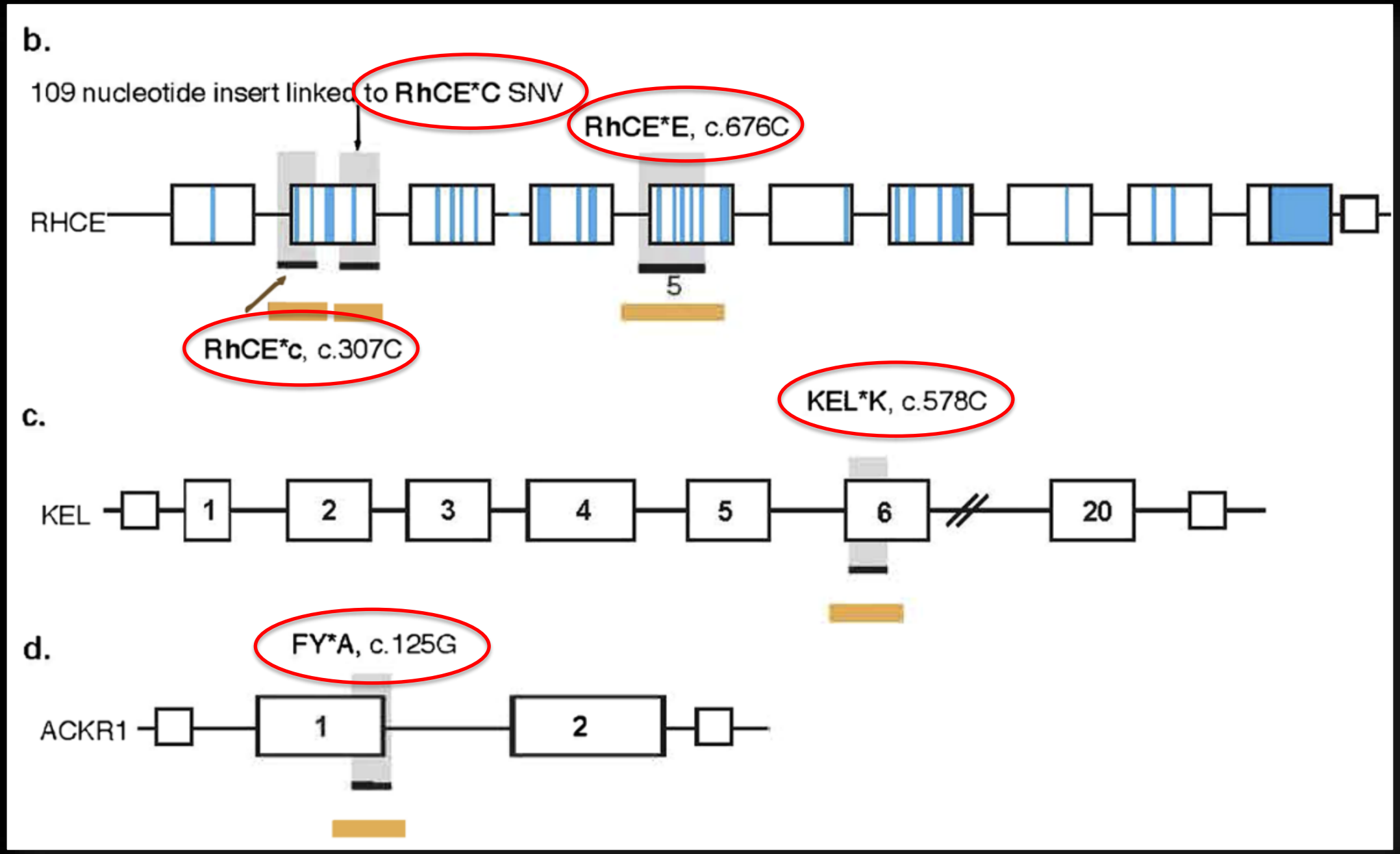
Last updated July 9, 2024

This Practice Advisory is provided to specifically address settings in human Rho(D) immune globulin (RhIg) shortages are present. This P Advisory was developed by the American College of Obstetricians ar Gynecologists with the assistance of Manisha Gandhi, MD, and Andrea Shields, MD, MS.

Rho(D) Immune Globulin Shortages

Practice Advisory | March 2024

- Although current ACOG guidance does not recommend routine use of noninvasive prenatal testing (NIPT) to determine fetal Rh(D) status based on cost-effectiveness analyses [5], the use of NIPT to prioritize use of RhIg and conserve RhIg supply is a reasonable consideration in the practice setting that is experiencing RhIg shortages. Noninvasive fetal red blood cell antigen genotyping utilizing cell-free DNA (cfDNA) isolated from maternal plasma has demonstrated high sensitivity and specificity for detection of fetal Rh(D) antigen status [6] [7] [8] [9] [10]. If cfDNA testing results confirm an Rh(D)-negative fetus, RhIg would not need to be routinely administered in the antepartum period (for bleeding, abortion, pregnancy loss, or at 28 weeks of gestation). Available cfDNA testing options for Rh(D) may vary depending on location and practice setting (eg, companies offering the test; whether the test is offered as a stand-alone or combined with aneuploidy testing; timing of results; insurance coverage) and should be confirmed before implementation.



Alford B, Landry BP, Hou S, Bower X, Bueno AM, Chen D, Husic B, Cantonwine DE, McElrath TF, Carozza JA, Wynn J, Hoskovec J, Gray KJ. Validation of a non-invasive prenatal test for fetal RhD, C, c, E, K and Fy[a] antigens. Sci Rep. 2023 Aug 7;13(1):12786. doi: 10.1038/s41598-023-39283-3. PMID: 37550335; PMCID: PMC10406947.

ACOG
The American College of Obstetricians and Gynecologists

CLINICAL PRACTICE UPDATE

AUGUST 2024

Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy

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This Clinical Practice Update clarifies guidance on paternal genotyping and provides new recommenda
of noninvasive fetal red blood cell antigen genotyping using cell-free DNA (cfDNA). This document u
Bulletin No. 192, *Management of Alloimmunization in Pregnancy* (Obstet Gynecol 2018;131:e82–90).

Determination of Paternal and Fetal Genotyping in Pregnant Patients with non–Rh-D alloimmunization

Cell-free DNA has been evaluated for noninvasive assessment of other fetal red blood cell antigens (7, 8). Recently, test performance was described for a commercially available product evaluating cfDNA to predict fetal Rh-D, C, c, E, K, and Fy^a status, demonstrating high accuracy for these red blood cell antigen determinations (8). Further research may help to clarify whether cfDNA can be recommended for the assessment of non–Rh-D fetal red blood cell antigen status among alloimmunized pregnant people, similar to the guidance provided here for noninvasive Rh-D antigen determination. Amniocentesis remains the primary modality for determining fetal blood type, using PCR on uncultured amniocytes when paternal genotype is thought to be heterozygous or is unknown. **Cell-free DNA for the assessment of selected non–Rh-D red blood cell antigens may be considered for pregnant patients declining amniocentesis, after weighing cost, access, and the encouraging-yet-limited data supporting its use.**

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Validation of a non-invasive prenatal test for fetal RhD, C, c, E, K and Fy^a antigens

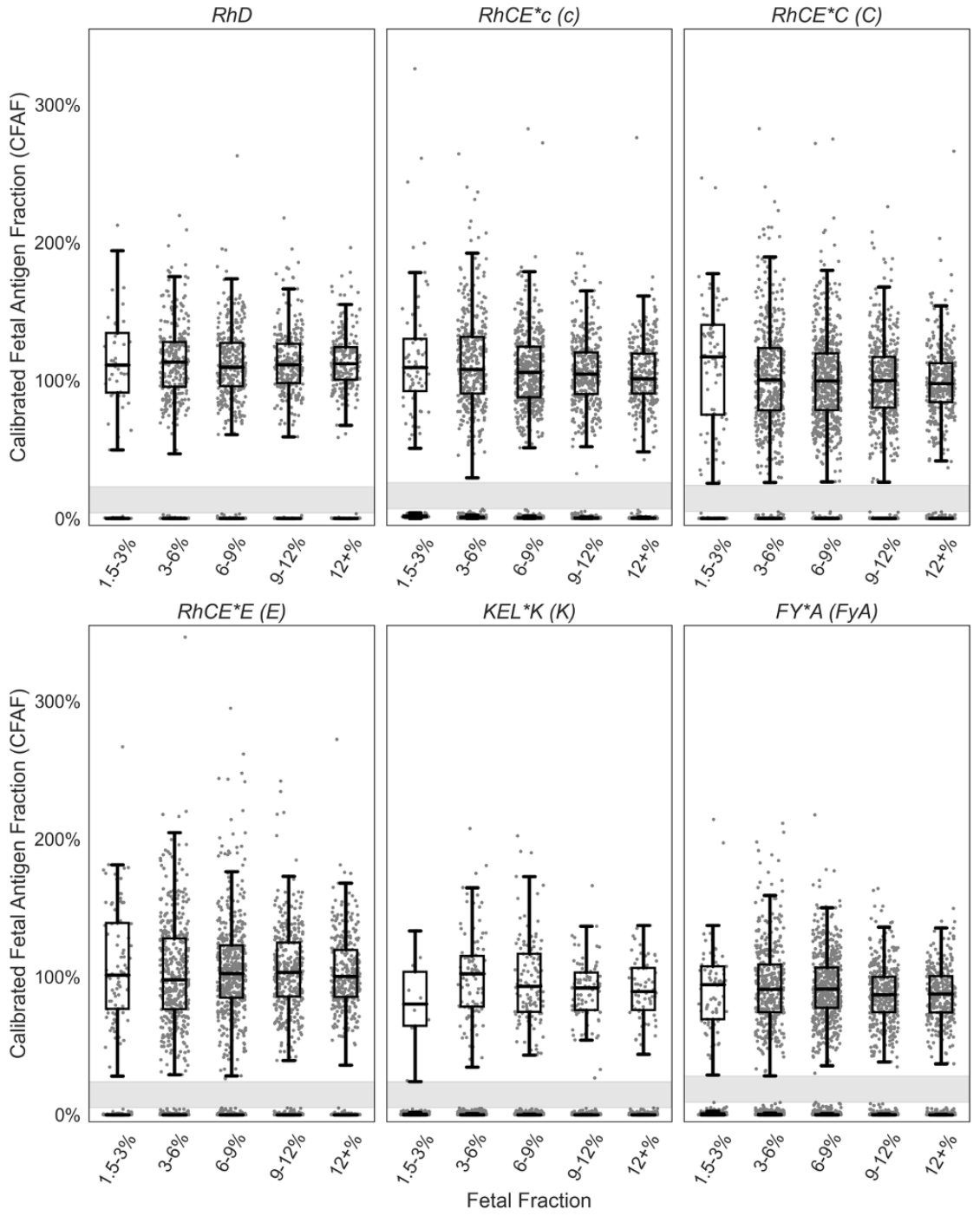
Brian Alford[1,3]✉, Brian P. Landry[1,3], Sarah Hou[1], Xavier Bower[1], Anna M. Bueno[1], Drake Chen[1], Brooke Husic[1], David E. Cantonwine[2], Thomas F. McElrath[2], Jacqueline A. Carozza[1], Julia Wynn[1], Jennifer Hoskovec[1] & Kathryn J. Gray[2]

Antigen	Total[a] (N)	NIPT fetal antigen detected (N)	NIPT fetal antigen not detected (N)	Sensitivity	95% CI	Specificity	95% CI
RhD	456	264	191	100%	(99–100%)	100%	(98–100%)
RhCE*C (C)	144	96	43	100%	(96–100%)	100%	(92–100%)
RHCE*c (c)	96	48	46	100%	(93–100%)	100%	(92–100%)
RHCE*E (E)	93	48	38	100%	(92–100%)	100%	(94–100%)
KEL*K (K)	192	96	95	100%	(96–100%)	100%	(96–100%)
FY*A (FyA)	96	48	48	100%	(93–100%)	100%	(93–100%)
Total fetal antigen	1077	600	461	100%	(99–100%)	100%	(99–100%)

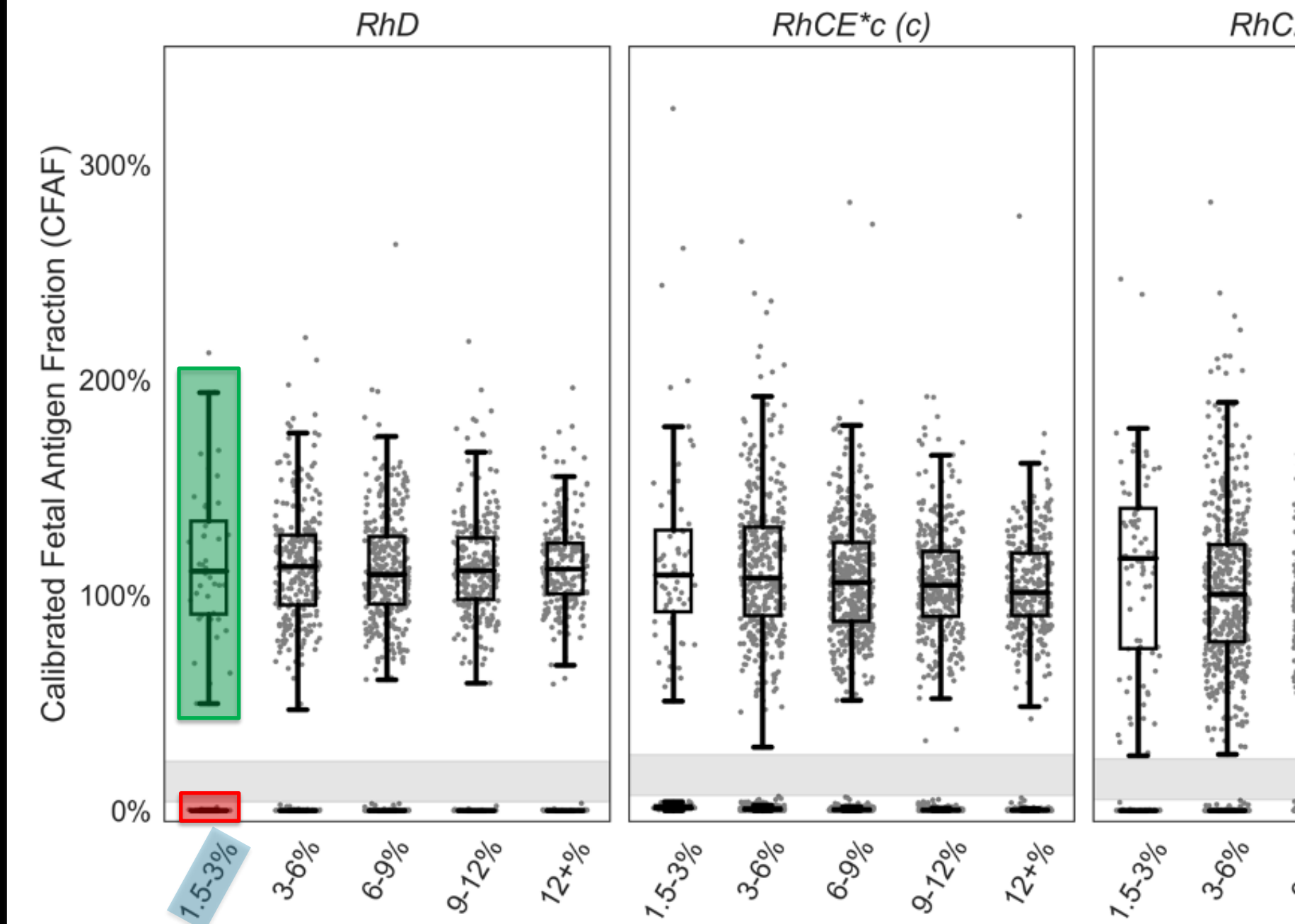
Table 1. Sensitivity, specificity of the NIPT assays on pre-clinical samples made from genomic DNA sheared and mixed to mimic cfDNA. [a]There were 16 samples where no results were issued due to low molecular count; absolute expected molecular (AEM) count below the antigen specific threshold (n=11) or calibrated fetal antigen fraction (CFAF) in the intermediate zone (n=5). Clopper–Pearson 95% confidence intervals (95% CI). Data are plotted in Fig. 2 and the pre-clinical samples are described in Table S3.

- 100% accurate on validation samples (*n* = 1061)
- 100% accurate on bio-banked samples (*n* = 23)
- 100% accurate on clinical samples (*n* = 93)

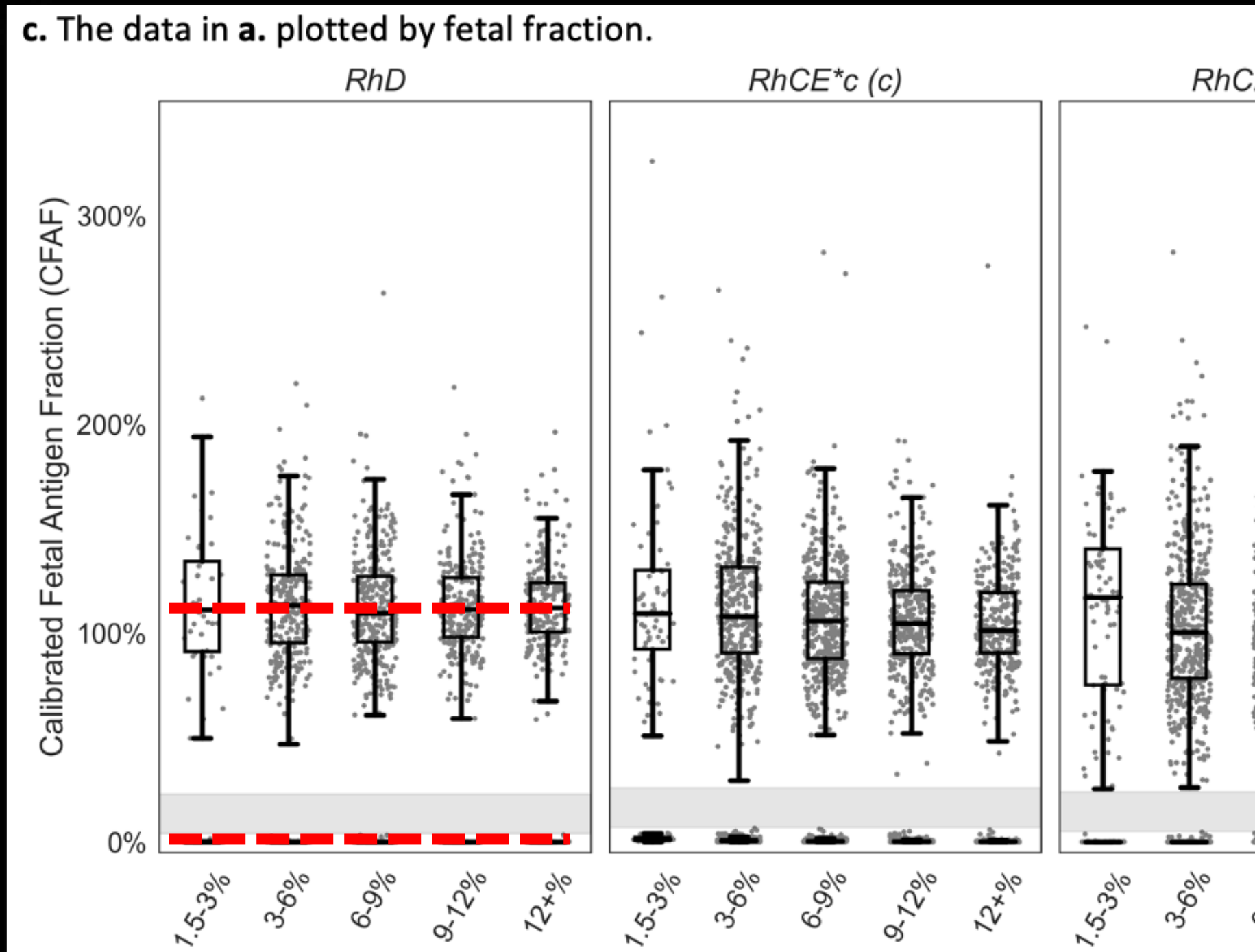
c. The data in **a.** plotted by fetal fraction.



c. The data in **a.** plotted by fetal fraction.



c. The data in **a.** plotted by fetal fraction.



OPEN

Original Research

Cell-Free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies

Shannon Rego, MS, Olaide Ashimi Balogun, MD, Kirsten Emanuel, MS, FNP, Rachael Overcash, MD, Juan M. Gonzalez, MD, PhD, Gregory A. Denomme, PhD, Jennifer Hoskovec, MS, Haley King, MS, Ashley Wilson, MS, Julia Wynn, MS, MS, and Kenneth J. Moise Jr, MD

OBJECTIVE: To evaluate the accuracy of next-generation sequencing–based quantitative cell-free DNA analysis for fetal antigen genotyping in individuals with alloimmunized pregnancies undergoing clinical testing in practices across the United States as early as 10 weeks of gestation, with the objective of identifying individuals with pregnancies at risk for hemolytic disease of the fetus and newborn and guiding management.

METHODS: This prospective cohort study included patients with alloimmunized pregnancies undergoing clinical fetal antigen cell-free DNA analysis between 10 0/7 and 37 0/7 weeks of gestation at 120 clinical sites. Both the pregnant person with the alloimmunized pregnancy and the neonates resulting from the pregnancies were included. The laboratory issued the cell-free DNA results prospectively as a part of clinical care. After delivery, neonatal buccal swabs collected between 0 and 270 days of life were sent to an outside independent laboratory for antigen genotyping. The outside laboratory was blinded to the fetal cell-free DNA results, and the results were compared. Concordance was reported for the fetal antigen cell-free DNA analysis for antigens to which the pregnant person was alloimmunized and for all antigens for which the pregnant person was genotype negative.

Table 4. Concordance Between Fetal Antigen Cell-Free DNA Results for All Antigens for Which the Pregnant Person Was Genotype Negative

	Neonatal Antigen Positive	Neonatal Antigen Negative	Total	% (95% CI)
cfDNA fetal antigen detected	145	0	145	
cfDNA fetal antigen not detected	0	320	320	
Total	145	320	465	
Sensitivity				100 (97.5–100)
Specificity				100 (98.9–100)

cfDNA, cell-free DNA.
Data are n unless otherwise specified.

NONINVASIVE DIAGNOSIS BY DOPPLER ULTRASONOGRAPHY OF FETAL ANEMIA DUE TO MATERNAL RED-CELL ALLOIMMUNIZATION

GIANCARLO MARI, M.D., FOR THE COLLABORATIVE GROUP FOR DOPPLER ASSESSMENT OF THE BLOOD VELOCITY IN ANEMIC FETUSES

ABSTRACT

Background Invasive techniques such as amniocentesis and cordocentesis are used for diagnosis and treatment in fetuses at risk for anemia due to maternal red-cell alloimmunization. The purpose of our study was to determine the value of noninvasive measurements of the velocity of blood flow in the fetal middle cerebral artery for the diagnosis of fetal anemia.

Methods We measured the hemoglobin concentration in blood obtained by cordocentesis and also the peak velocity of systolic blood flow in the middle cerebral artery in 111 fetuses at risk for anemia due to maternal red-cell alloimmunization. Peak systolic velocity was measured by Doppler velocimetry. To

only mild anemia. Currently, invasive techniques such as amniocentesis and cordocentesis[3-5] are used to identify fetuses with severe anemia.

We previously reported that the peak velocity of systolic blood flow in the middle cerebral artery, as measured by Doppler ultrasonography, was increased in fetuses with anemia.[6] We selected the middle cerebral artery for these measurements because cerebral arteries respond quickly to hypoxemia, owing to the strong dependence of brain tissue on oxygen. Moreover, the middle cerebral artery is easily visualized with an angle of close to 0 degrees between the ultrasound beam and the direction of blood flow, and this measurement has low intraobserver and in-

Red-cell alloimmunization was further investigated if the maternal serum titer of specific red-cell antibodies was 1:16 or more. The types and distribution of antibodies found in our study population are shown in Table 2.

Among the 111 fetuses at risk for anemia, 41 (37 percent) had normal hemoglobin concentrations, 35 (32 percent) had mild anemia, 4 (4 percent) had moderate anemia, and 19 (17 percent) had severe anemia without hydrops. Twelve fetuses (11 percent) had severe anemia with hydrops (Fig. 1). The mean (±SD) hemoglobin concentration among the fetuses with hydrops was 0.30±0.06 times the median, corresponding to a value of 3.8 g per deciliter.

"Critical Titer" cutoff of 1:16 has a PPV of 31.5% for moderate to severe anemia.

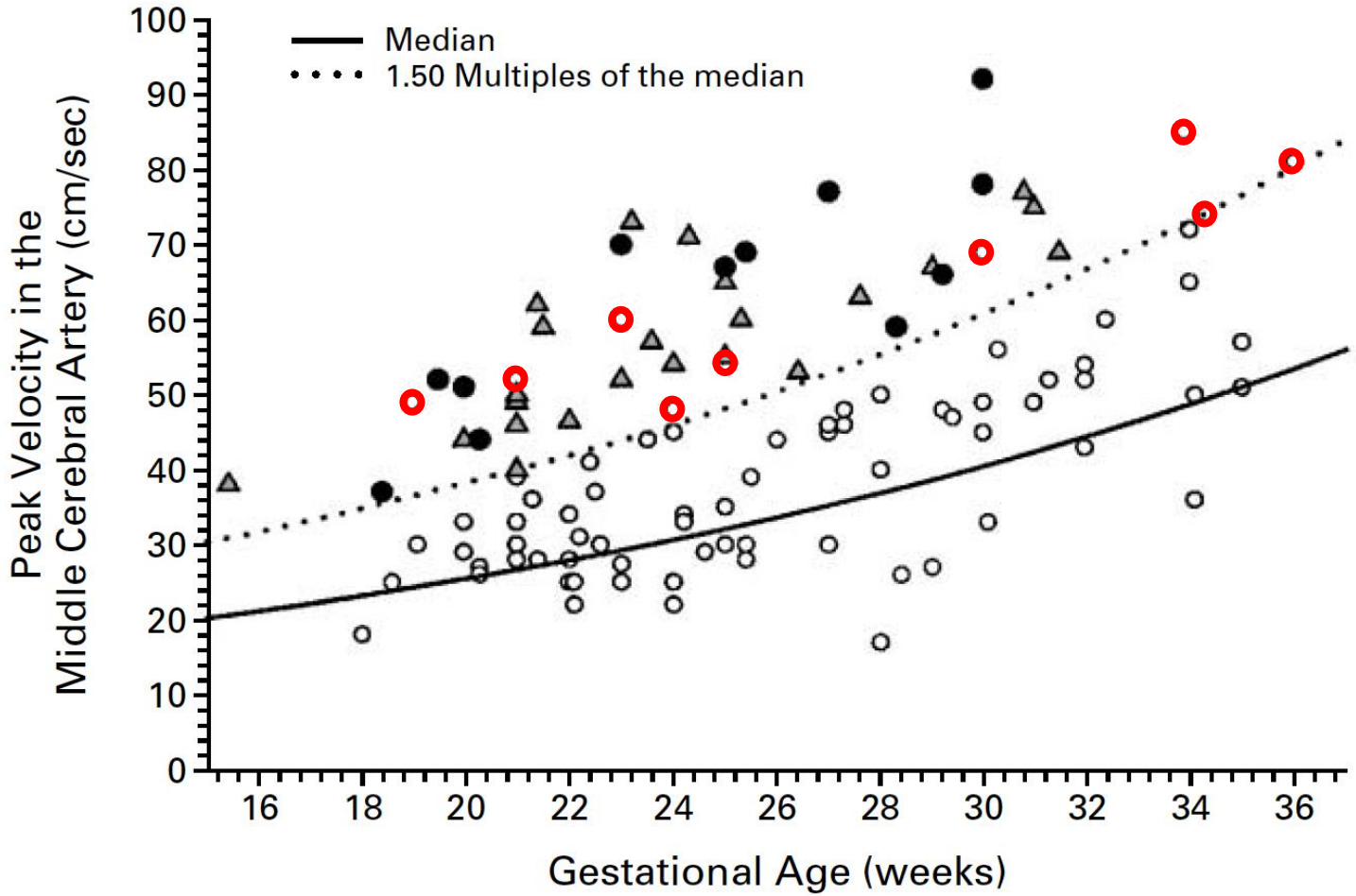


Figure 3. Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery in 111 Fetuses at Risk for Anemia Due to Maternal Red-Cell Alloimmunization.

Open circles indicate fetuses with either no anemia or mild anemia (≥0.65 multiples of the median hemoglobin concentration). Triangles indicate fetuses with moderate or severe anemia (<0.65 multiples of the median hemoglobin concentration). The solid circles indicate the fetuses with hydrops. The solid curve indicates the median peak systolic velocity in the middle cerebral artery, and the dotted curve indicates 1.5 multiples of the median.

The sensitivity of the peak systolic velocity for the prediction of moderate anemia (a hemoglobin concentration of less than 0.65 times the median) and severe anemia (a hemoglobin concentration of less than 0.55 times the median) in the fetuses without hydrops was 100 percent (95 percent confidence interval, 86 to 100), with a false positive rate of 12 percent. The positive and negative predictive values were 65 percent and 100 percent, respectively.

The relation between the multiples of the median of the peak systolic velocity and the multiples of the median of the hemoglobin concentration was strong even in fetuses of mothers with Kell sensitization ($R^2 = 0.55$, $P < 0.001$).

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

INTERIM UPDATE

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 192, MARCH 2018

(Replaces Practice Bulletin Number 75, August 2006)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics with the assistance of Calla Holmgren, MD, and T. Flint Porter, MD.

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect a limited, focused change to align with Practice Bulletin No. 181, *Prevention of Rh D Alloimmunization.*

Management of Alloimmunization During Pregnancy

When any fetal blood group factor inherited from the father is not possessed by the mother, antepartum or intrapartum fetal–maternal bleeding may stimulate an immune reaction in the mother. Maternal immune reactions also can occur from blood product transfusion. The formation of maternal antibodies, or "alloimmunization," may lead to various degrees of transplacental passage of these antibodies into the fetal circulation. Depending on the degree of antigenicity and the amount and type of antibodies involved, this transplacental passage may lead to hemolytic disease in

unknown. Amniocentesis is the primary modality used to determine fetal blood type using polymerase chain reaction (PCR) on uncultured amniocytes in 2 mL of amniotic fluid. The sensitivity and specificity of PCR typing are reported as 98.7% and 100%, respectively, with positive and negative predictive values of 100% and 96.9% (20). Chorionic villus biopsy also has been employed for this purpose, but its use should be discouraged because disruption of the villi may result in unnecessary fetomaternal hemorrhage and worsening alloimmunization (21). If the fetus is found to be

Review

Fetal RhD typing by polymerase chain reaction in pregnancies complicated by rhesus alloimmunization

Ignatia B. Van den Veyver, MD, and Kenneth J. Moise, Jr, MD

Objective: **To review the specificity and sensitivity of diagnostic techniques using the polymerase chain reaction (PCR) on amniotic fluid (AF) samples for the determination of fetal RhD status.**

Data Sources: **A MEDLINE computerized search was conducted for January 1991 through March 1996 using the key**

Table 3. RhD Typing Using Amniotic Fluid: Rate of Errors

Authors	No. of cases without amplification	RhD− results		RhD− results	
		N	Errors	*N*	Errors
Bennett et al[20]	0	10	0	5	0
Fisk et al[21]	0	2	0	3	0
Lighten et al[22]	1	96	0	38	2
Sagot et al[23]	0	16	0	5	0
Rossiter et al[24]	0	2	0	1	0
Van den Veyver et al[25]	2	100	0	7	1
Spence et al[26]	0	31	0	19	0
Harding et al*	0	46	0	29	0
Nelson et al†	0	66	0	21	2
Total	3 (0.60%)	369	0	128	5 (3.91%)

* Harding JA, Luthy DA, Skogerboe KJ. Fetal RhD typing with polymerase chain reaction of amniotic fluid [abstract]. Am J Obstet Gynecol 1995;172:397.

† Nelson L, Jackson GM, Ward K. Prospective assessment of the accuracy of fetal RhD status determination from uncultured amniocytes [abstract]. Am J Obstet Gynecol 1996;174:338.

ACOG
The American College of Obstetricians and Gynecologists

CLINICAL PRACTICE UPDATE

AUGUST 2024

Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy

This Clinical Practice Update was developed by the American College of Obstetricians and Gynecologists with the assistance of Russell Scott Miller, MD, Laura Mercer, MD, Brian Lincoln Shaffer, MD, Andrea Denise Shields, MD, MS, and Manisha Gandhi, MD.

This Clinical Practice Update clarifies guidance on paternal genotyping and provides new recommenda
of noninvasive fetal red blood cell antigen genotyping using cell-free DNA (cfDNA). This document u
Bulletin No. 192, *Management of Alloimmunization in Pregnancy* (Obstet Gynecol 2018;131:e82–90).

Clinical Trial Assay in Johnson & Johnson Phase 3 Clinical Trial of Nipocalimab in Hemolytic Disease of the Fetus and Newborn

In April 2023 U.S. Food and Drug Administration (FDA) approved an Investigational Device Exemption (IDE), to enable the UNITY Fetal Antigen CTA to be used in this trial, an important milestone to support the start of the Phase 3 AZALEA study of nipocalimab in HDFN in the U.S.

12 Dec, 2023, 09:00 ET

Breakthrough Therapy Designation for nipocalimab based on results from the Phase 2 UNITY clinical trial for HDFN

Phase 3 clinical trial enrollment underway, representing the only therapy reported to be under clinical development for this serious, life-threatening and rare condition

February 9, 2024

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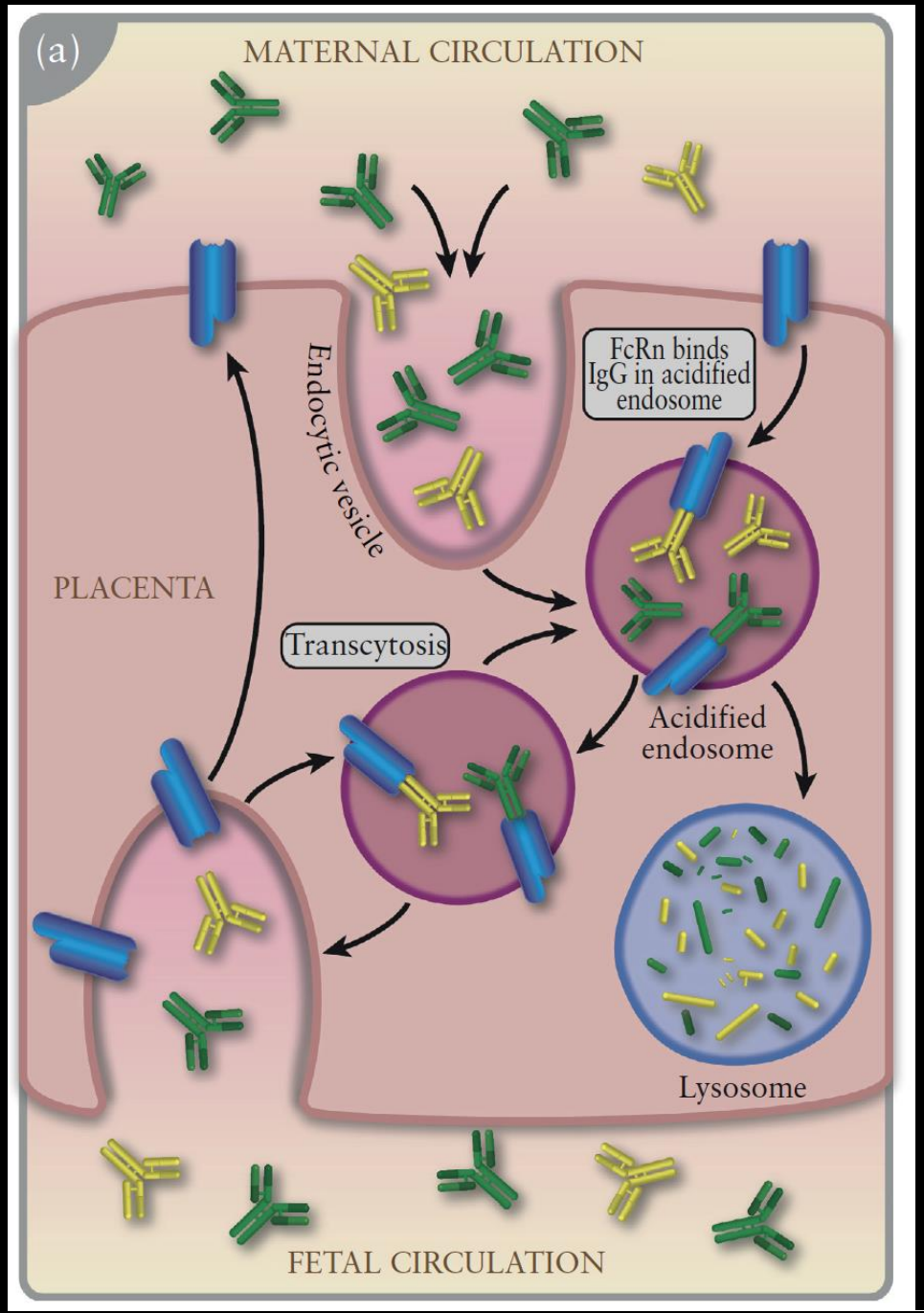
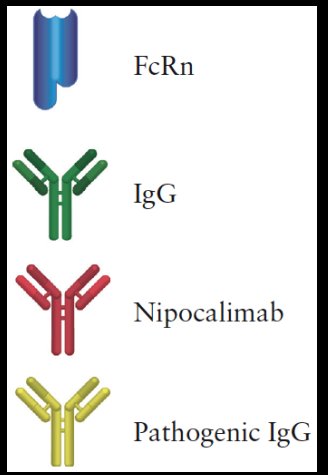




Moise KJ Jr, Oepkes D, Lopriore E, Bredius RGM. Targeting neonatal Fc receptor: potential clinical applications in pregnancy. Ultrasound Obstet Gynecol. 2022 Aug;60(2):167-175. doi: 10.1002/uog.24891. PMID: 35229965.

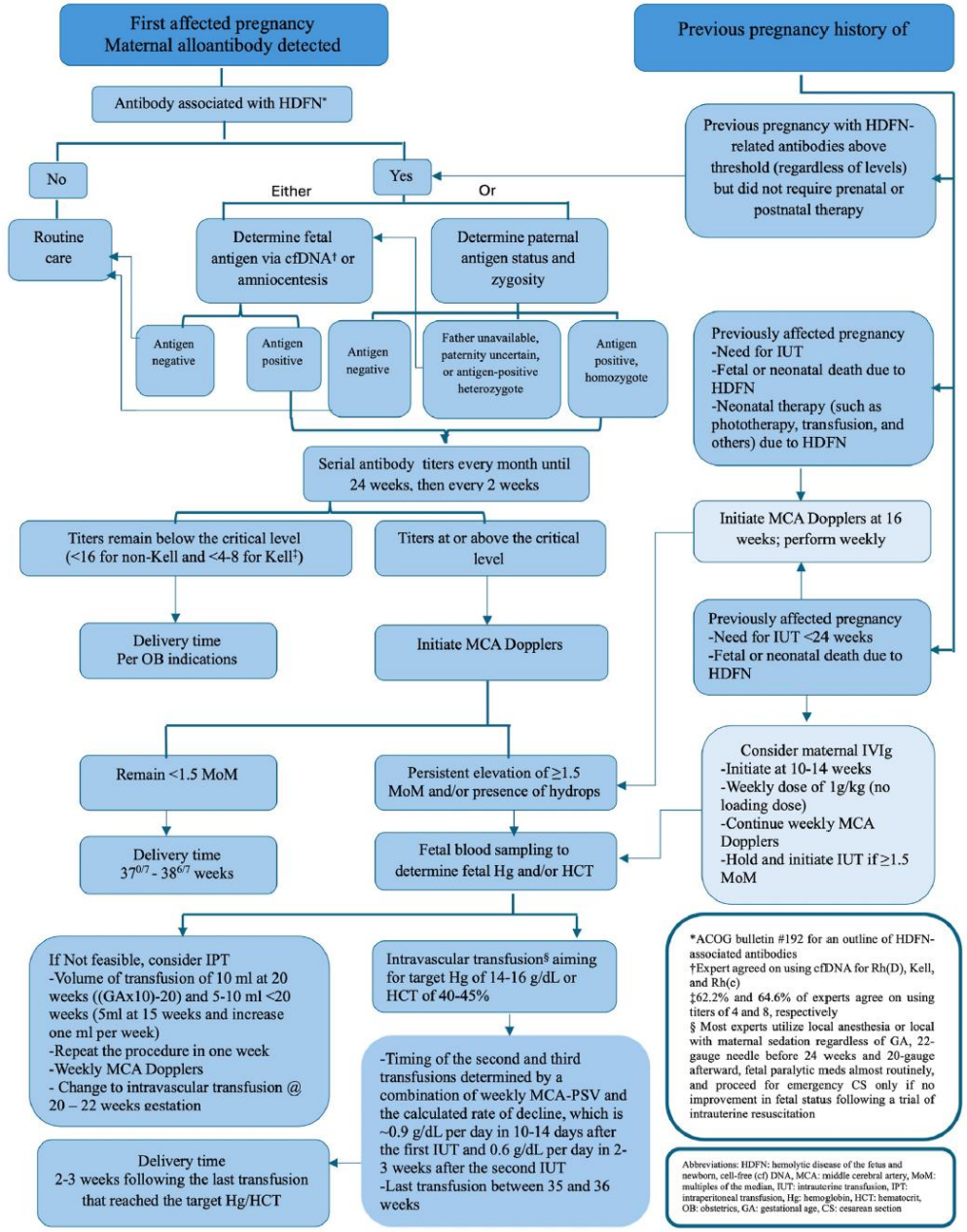
Monitoring and management of hemolytic disease of the fetus and newborn based on an international expert Delphi consensus

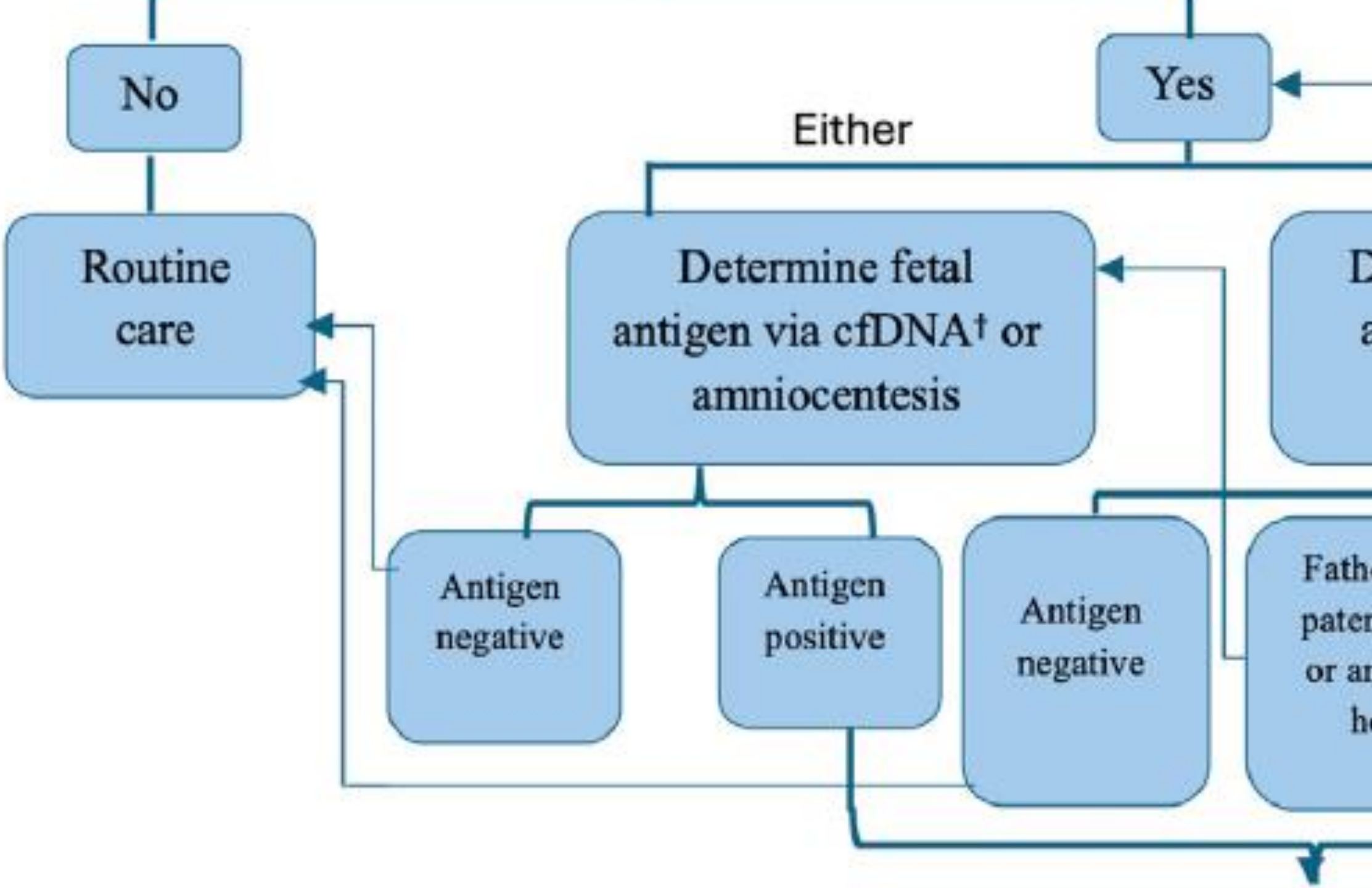
Hiba J. Mustafa, MD; Enaja V. Sambatur, MD; Alireza A. Shamshirsaz, MD; Sonia Johnson, MD; Kenneth J. Moise Jr, MD; Ahmet A. Baschat, MD; E. J. T. (Joanne) Verweij, MD; Ali Javinani, MD; Mark D. Kilby, MD, DSc; Enrico Lopriore, MD; Rebecca Rose, MD; Roland Devlieger, MD; Saul Snowise, MD; Ulrich J. Sachs, MD; Asma Khalil, MD, MSc; On behalf of the HDFN Delphi Working Group[†]

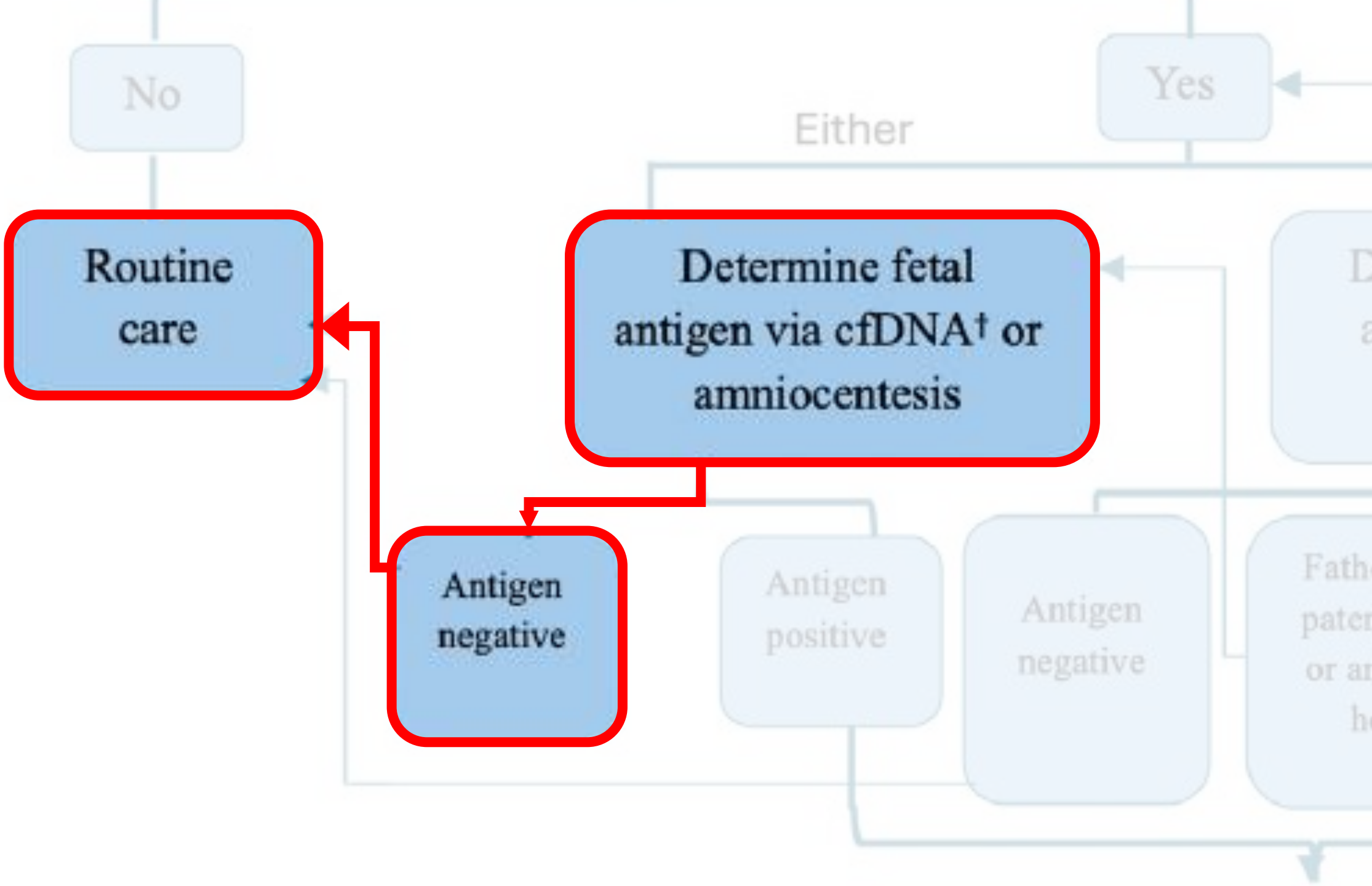
The study aimed to develop structured, expert-based clinical guidance on the prenatal and postnatal management of hemolytic disease of the fetus and newborn. A Delphi procedure was conducted among an international panel of experts in fetal medicine, neonatology, and hematology. Experts were selected based on their expertise, relevant publications, and affiliations. The domains were (i) prenatal workup, (ii) prenatal monitoring and management, (iii) intrauterine transfusion (IUT), (iv) delivery, and (v) postnatal management. The predefined cut-off for consensus was ≥70% agreement. One hundred-seven experts representing 25 countries across 6 continents completed the first round, and 100 (93.5%) completed the subsequent rounds. 75.3% agreed on using cfDNA to determine fetal antigen status, particularly for RhD, Kell, and Rhc antigens. The critical titer, requiring fetal monitoring via ultrasound, is considered when the threshold of ≥16 is for non-Kell antigens. 70.0% agreed on the use of maternal IVIg in pregnancies with prior IUT <24 weeks or fetal/neonatal death due to HDFN. The minimum GA for IUT is 16 to 18 weeks, and the maximum is $35^{0/7}$ to $35^{6/7}$ weeks. Postnatal management consensus was reached for the following: anemia labs should be investigated in the affected neonates before hospital discharge (92.0% agreement), and if they received IUT, the labs should be repeated within 1 week of discharge (84.0% agreement). 96.0% agreed that exchange transfusions should be centralized in hospitals with sufficient exposure and experience, and 92.0% agreed that the hemoglobin cut-off level to consider transfusion following hospital discharge is 7 g/dL, and the newborns need to be monitored until 2 to 3 months of age (96.0% agreement).

Key words: anemia, consensus, cordocentesis, Delphi, erythroblastosis, fetal, hemolytic disease, IUT, IVIg, pregnancy, PUBS

FIGURE
Consensus-based algorithm for management of HDFN




No
Yes
Either
Routine care
Determine fetal antigen via cfDNA† or amniocentesis
Antigen negative
Antigen positive
Antigen negative


No
Yes
Either
Routine care
Determine fetal antigen via cfDNA† or amniocentesis
Antigen negative
Antigen positive
Antigen negative

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Special Communication | Obstetrics and Gynecology

A Clinical Practice Guideline for the Management of Pregnancy Alloimmunized to Red Blood Cell Antigens

Kenneth J. Moise Jr, MD; Kara B. Markham, MD; Philip C. Spinella, MD; Molly R. Sherwood, BS; Karen A. Robinson, PhD; Lisa M. Wilson, ScM; Jay Malone, MD, PhD; Jimmy Espinoza, MD, MSc; Donna Dizon-Townson, MD; Laura Mercer, MD; Russell Miller, MD; Leonardo Pereira, MD, MCR; Anthony Sciscione, MD; Alireza A. Shamshirsaz, MD; Kathryn Shanahan, RN, MSn, CPNP; Saul Snowise, MD; Thomas Trevett, MD; Juan M. González Vélez, MD, PhD; Bethany Weathersby, MeEd

Abstract

IMPORTANCE Red blood cell alloimmunization is typically associated with the transplacental transfer of incompatible fetal red blood cells into maternal circulation. Subsequent pregnancies can be affected by fetal anemia, hydrops fetalis, and perinatal death. Most cases of Rhesus D (RhD) alloimmunization due to pregnancy can be prevented by the proper administration of Rhesus immune globulin. However, an emerging practice of using low-titer, O, RhD-positive whole blood (LTOWB) in cases of life-threatening hemorrhage has the potential to increase the exposure of the female population to a new source of incompatible red blood cells.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Special Communication | Obstetrics and Gynecology

A Clinical Practice Guideline for the Management of Pregnancy Alloimmunized to Red Blood Cell Antigens

Kenneth J. Moise Jr, MD; Kara B. Markham, MD; Philip C. Spinella, MD; Molly R. Sherwood, BS; Karen A. Robinson, PhD; Lisa M. Wilson, ScM; Jay Malone, MD, PhD; Jimmy Espinoza, MD, MSc; Donna Dizon-Townson, MD; Laura Mercer, MD; Russell Miller, MD; Leonardo Pereira, MD, MCR; Anthony Sciscione, MD; Alireza A. Shamshirsaz, MD; Kathryn Shanahan, RN, MSn, CPNP; Saul Snowise, MD; Thomas Trevett, MD; Juan M. González Vélez, MD, PhD; Bethany Weathersby, MeEd

Abstract

+ Supplemental content

of evidence [COE], moderate; pooled specificity, 98%; 95% CI, 97%-99%; COE, moderate) (**Figures 2** and **3**). Since some cffDNA studies compared its accuracy to genotyping by amniocentesis or chorion villus biopsy instead of fetal or neonatal serology, the accuracy of testing may have been overestimated. These results are consistent with Mackie et al,[8] which reported a pooled sensitivity of 99.3% (95% CI, 98.2%-99.7%) and pooled specificity of 98.4% (95% CI, 96.4%-99.3%).[8] Since the conduct of the current systematic review, an additional study by Rego and colleagues[10] compared 465 cffDNA samples including 143 for Kell, 124 for RhE, 60 for RhC, 50 for Fy^a, 47 for Rhc, and 41 for RhD, with 100% concordance with neonatal genotyping results.

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Innovative Medicine

Johnson & Johnson's nipocalimab granted U.S. FDA Fast Track designation to reduce the risk of fetal neonatal alloimmune thrombocytopenia (FNAIT) in alloimmunized pregnant adults

FNAIT is a rare disease that occurs when a pregnant person's immune system attacks fetal platelets, resulting in the risk of internal bleeding, which can be life threatening to the fetus or newborn

The Phase 3 FREESIA program is underway and nipocalimab is the only investigational therapy currently reported to be in clinical development for the treatment of FNAIT

March 26, 2024

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The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 690 • March 2017

(Reaffirmed 2020)

Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Stephanie Romero, MD; Britton Rink, MD; Joseph R. Biggio Jr, MD; and Devereux N. Saller Jr, MD.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

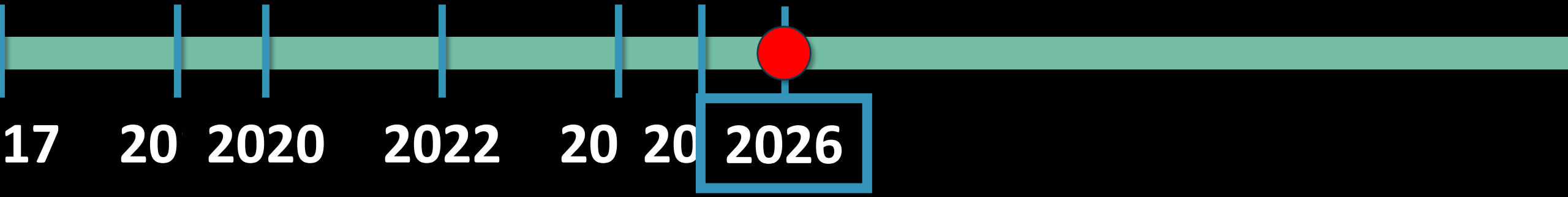
Carrier Screening in the Age of Genomic Medicine

ABSTRACT: Carrier screening, whether targeted or expanded, allows individuals to consider their range of reproductive options. Ultimately, the goal of genetic screening is to provide individuals with meaningful information that they can use to guide pregnancy planning based on their personal values. Ethnic-specific, panethnic, and

Recommendations

- Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening.
- If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives.
- All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity.
- Couples with consanguinity should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening.
- Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should

BREAKTHROUGH TIMELINE



HDFN Antigens (16)	
D (RhD)	Fyb
C (Big C)	Jka (Kidd)
c (little c)	Jkb
E	M
e	N
K (Kell)	S (Big S)
k	S (little s)
Fya (Duffy)	U

FNAIT Antigens (14)	
HPA-1a	HPA-1b
(reflex to maternal HLA-DRB3*01:01)	
HPA-2a	HPA-2b
HPA-3a	HPA-3b
HPA-4a	HPA-4b
HPA-5a	HPA-5b
HPA-9a	HPA-9b
HPA-15a	HPA-15b

BREAKTHROUGH TIMELINE

1905

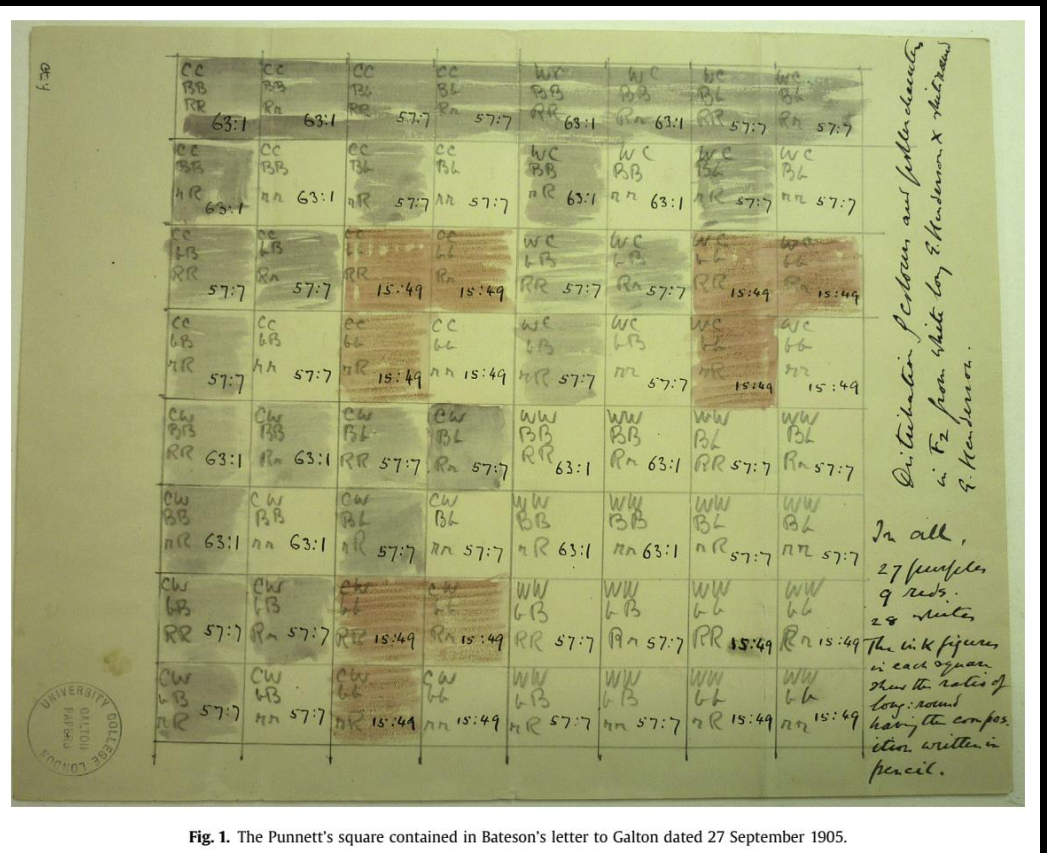


Fig. 1. The Punnett's square contained in Bateson's letter to Galton dated 27 September 1905.

Genetics in Medicine (2023) 25, 100858

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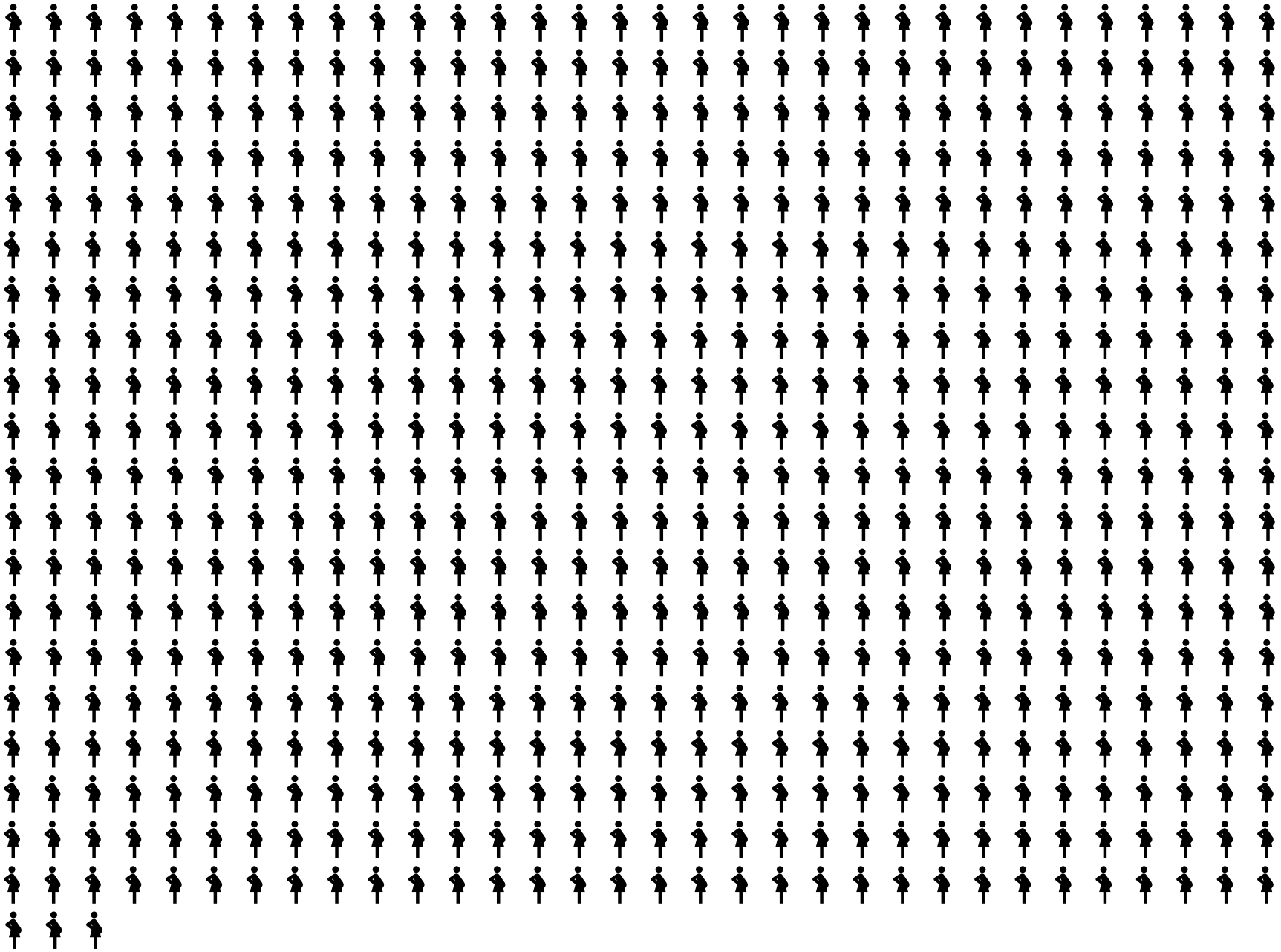
ARTICLE

Barriers to completion of expanded carrier screening in an inner city population

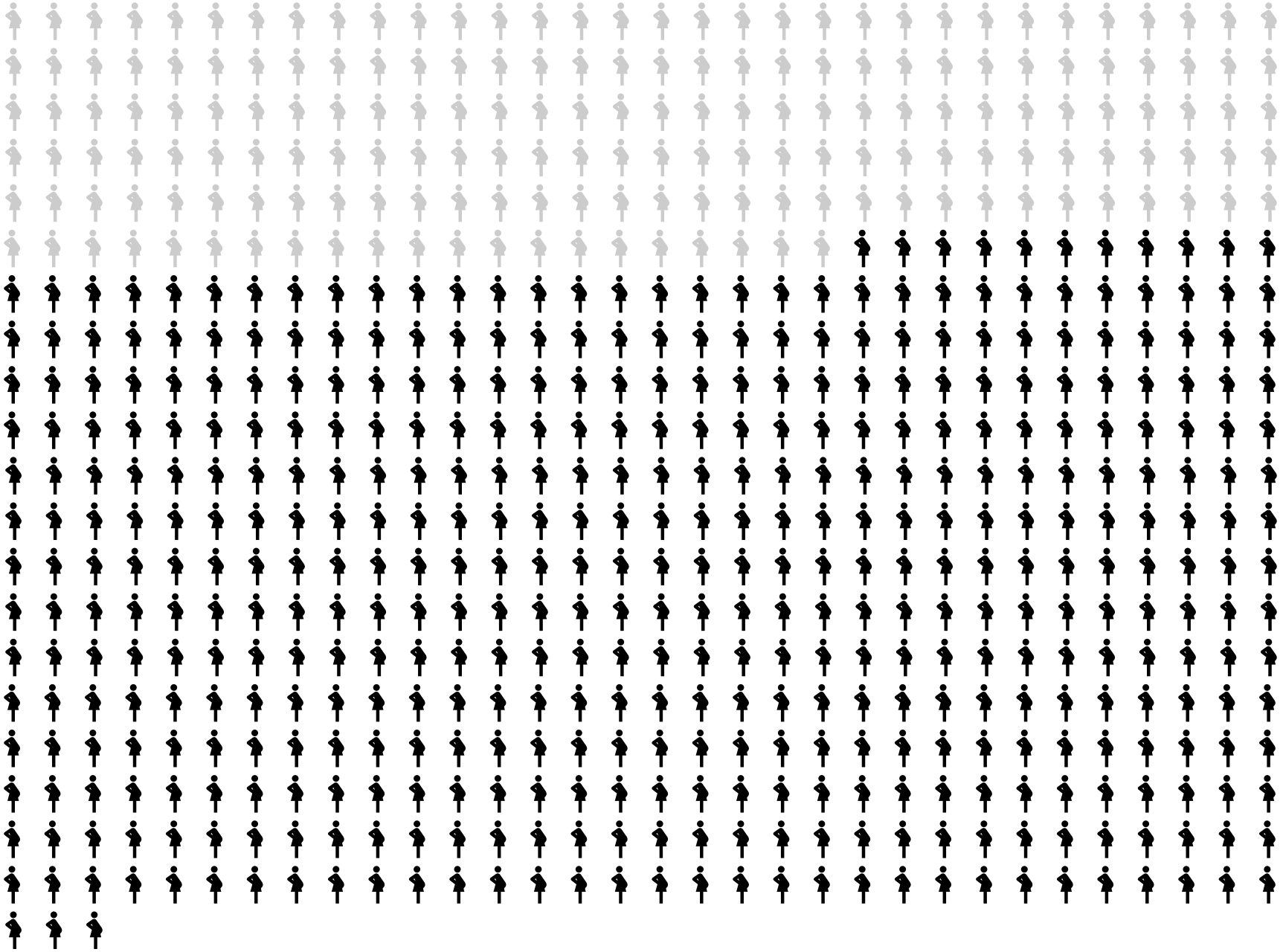
Tirtza S. Strauss[1,*], Emily Schneider[1], Emily Boniferro[1], Erika Brockhoff[1], Anna Johnson[1], Guillaume Stoffels[1], Kristina Feldman[1], Olivia Grubman[1], David Cole[1], Farrah Hussain[1], Graham Ashmead[1], Zainab Al-ibraheemi[1], Lois Brustman[1]

[1]*Division of Maternal Fetal Medicine, Mount Sinai West, Icahn School of Medicine at Mount Sinai, New York City, NY*

643 ECS



643 ECS ⇨ 462 (+)ECS



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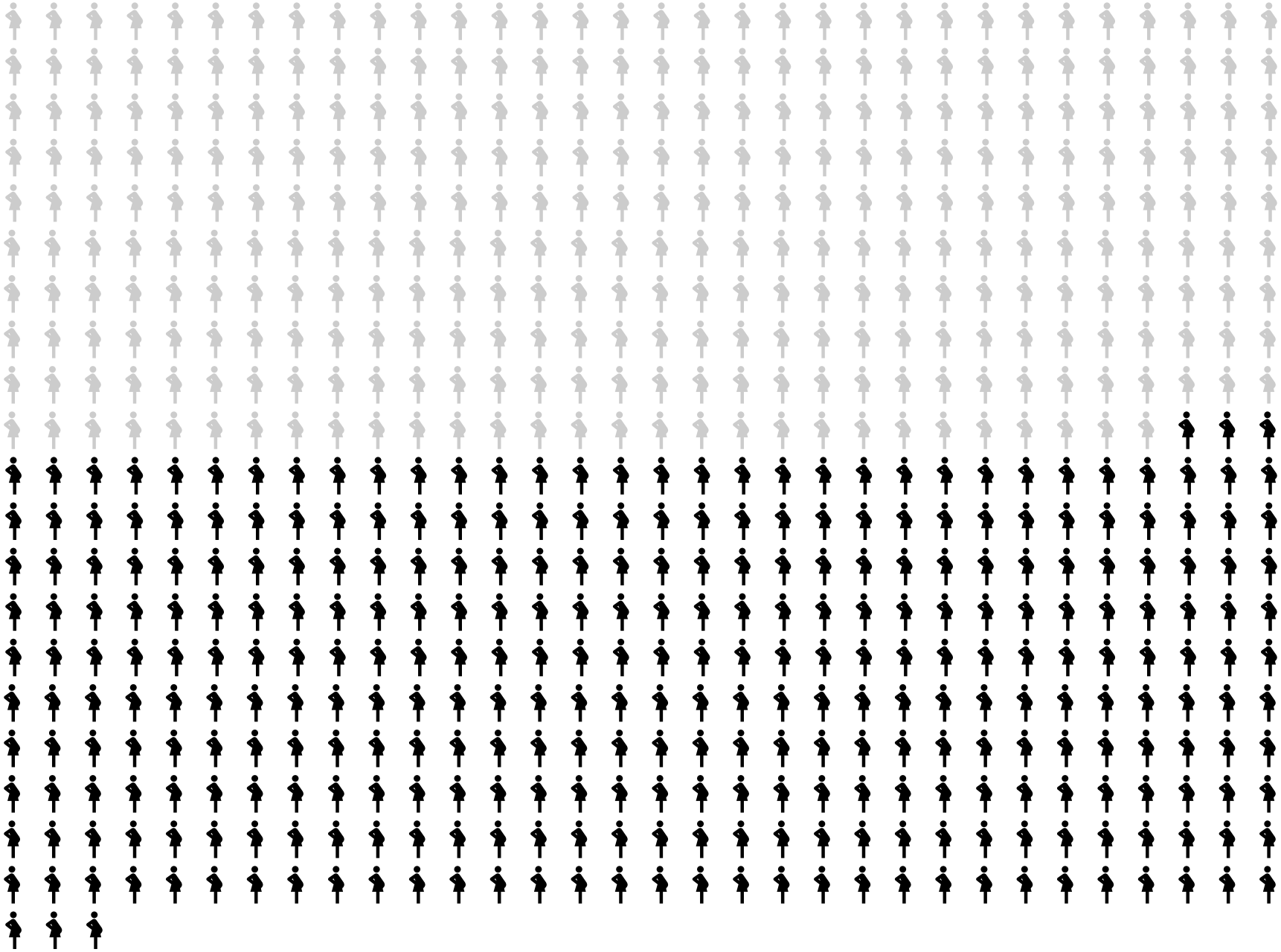

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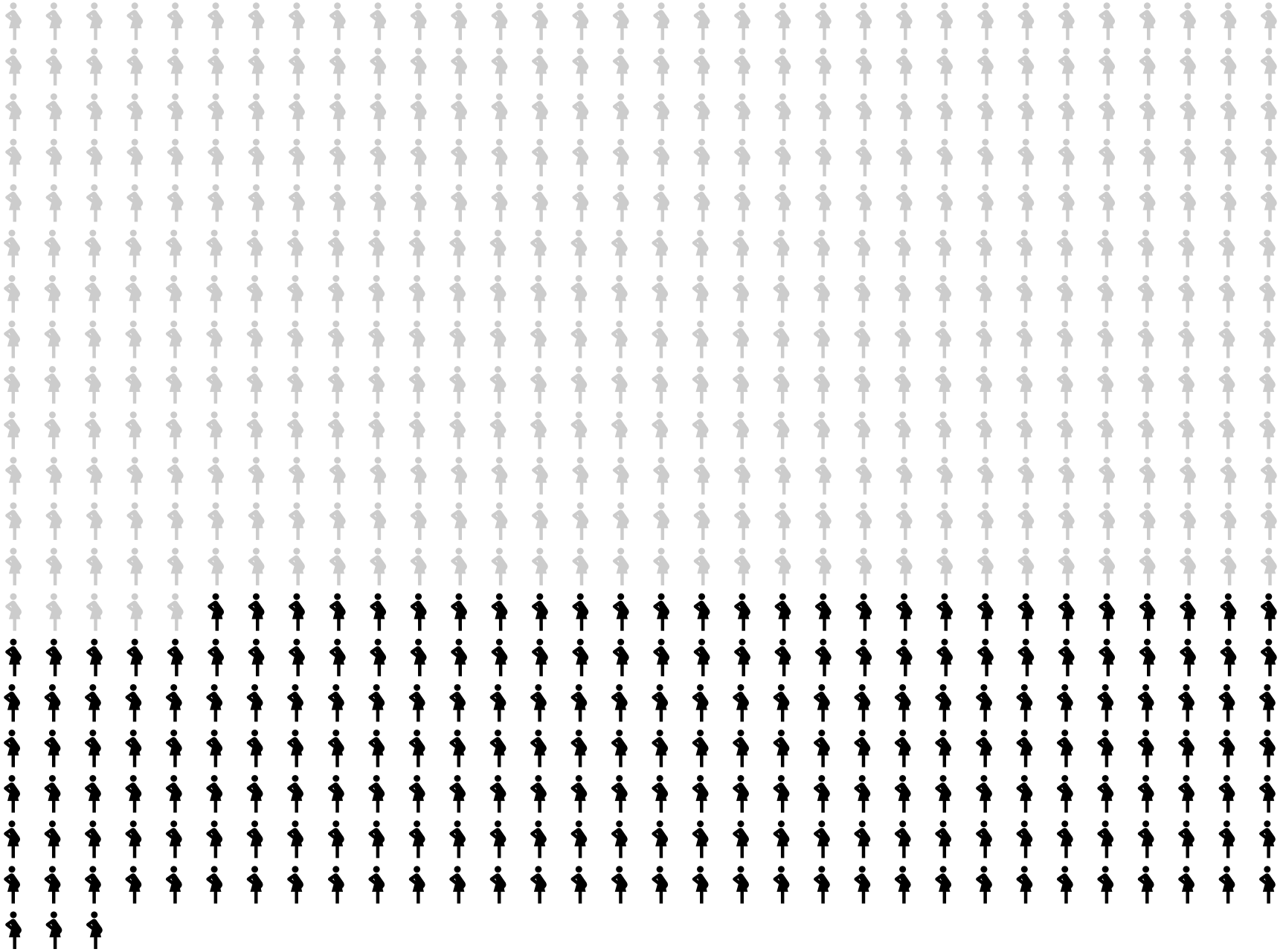

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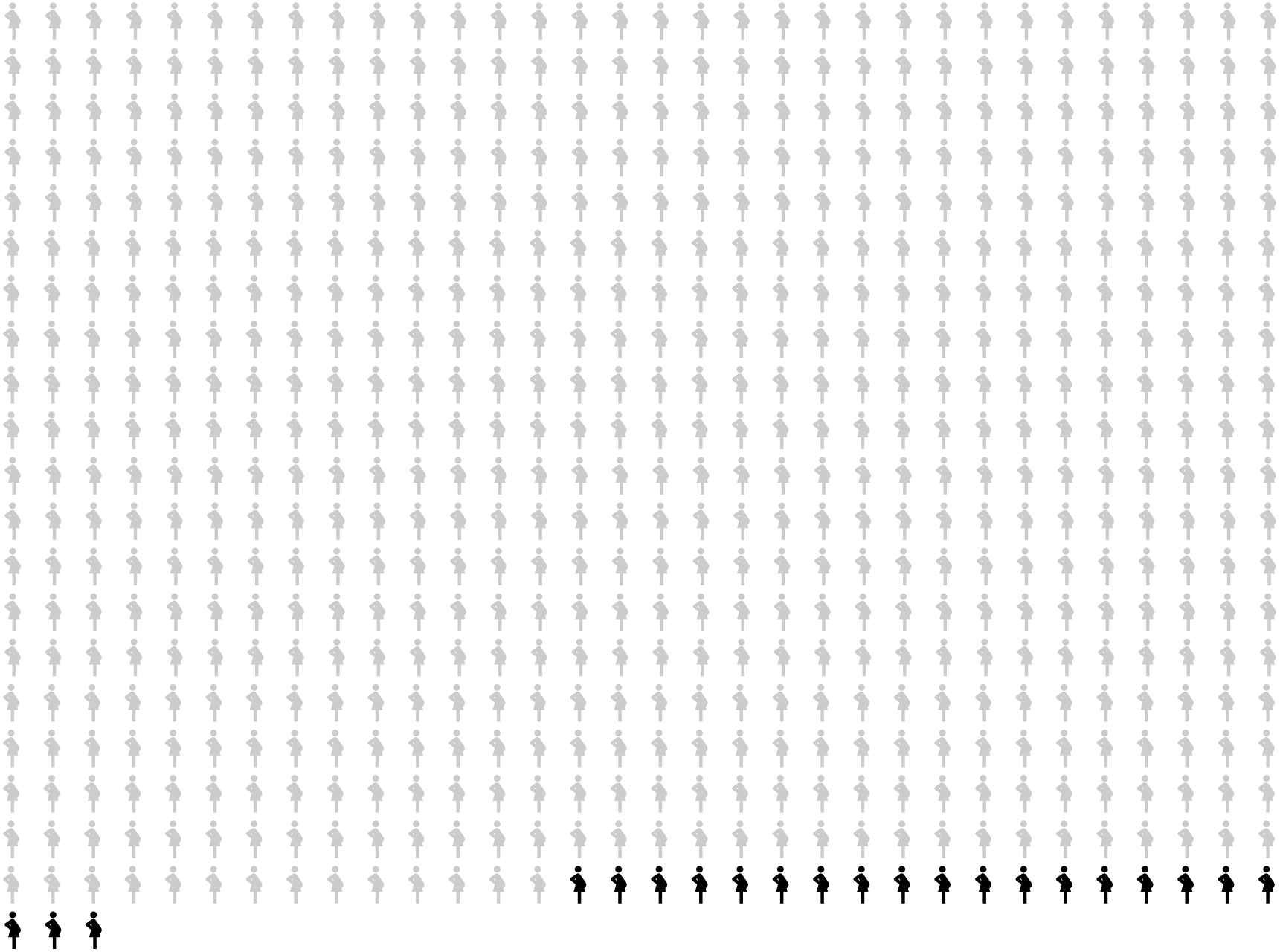
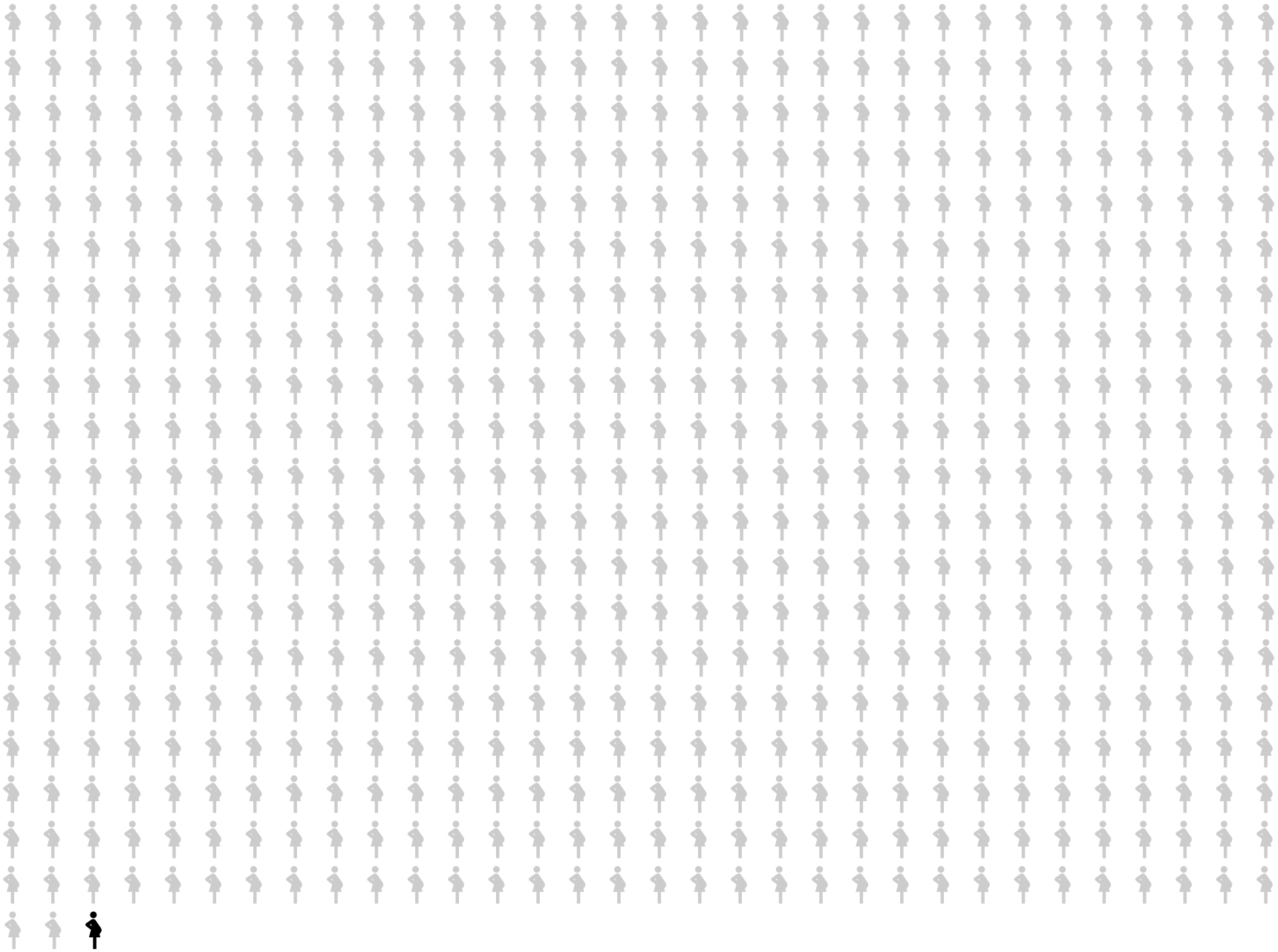


643 ECS ⇨ 462 (+)ECS ⇨ 326 GC ⇨ 222 FOB ⇨ 21 HRC ⇨ 1 amnio



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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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[b] Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
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ARTICLE INFO

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Reproductive carrier screening

ABSTRACT

Recent improvements in cell-free DNA technology have enabled non-invasive prenatal testing (NIPT) to screen for fetal single-gene autosomal recessive conditions from maternal blood as early as the first trimester. This

Traditional ECS

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ARTICLE

Barriers to completion of expanded carrier screening in an inner city population

Tirtza S. Strauss[1,*], Emily Schneider[1], Emily Boniferro[1], Erika Brockhoff[1], Anna Johnson[1], Guillaume Stoffels[1], Kristina Feldman[1], Olivia Grubman[1], David Cole[1], Farrah Hussain[1], Graham Ashmead[1], Zainab Al-ibraheemi[1], Lois Brustman[1]

[1]*Division of Maternal Fetal Medicine, Mount Sinai West, Icahn School of Medicine at Mount Sinai, New York City, NY*

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Keywords:
Carrier screening
Expanded carrier screening
Partner testing
Prenatal genetic screening
Reproductive genetics

ABSTRACT

Purpose: The American College of Medical Genetics and Genomics emphasizes a "consistent and equitable approach for offering carrier screening." At our academic center, publicly insured prenatal patients underwent universal expanded carrier screening (ECS) to promote equitable care. The aim of the study was to evaluate rates, time, and barriers to complete ECS. This was defined as post-test counseling and partner testing after a patient was found heterozygous for a pathogenic variant.

Methods: In this descriptive retrospective cohort study from 2018 to 2021, patients were offered ECS, consisting of 283 recessive and X-linked genes. Heterozygotes were contacted by genetic counselors (≤5 attempts) for education and partner testing. Rates of counseling, partner testing, diagnostic procedures, follow-up times, and barriers to completion were assessed.

Results: During this time, 643 women underwent ECS. Of these 643 women, 462 were heterozygotes and 326 of 462 had undergone counseling. Two hundred twenty-two of 462 partners obtained testing, with a median of 32 days from patient to partner result. Approximately 21 couples were heterozygous for the same pathogenic variant. One patient pursued diagnostic testing.

Conclusion: ECS offers useful information; however, this study highlights significant barriers to completion. There was suboptimal patient follow-up and low partner screening, perhaps from

cfDNA

Genetics in Medicine (2023) 25, 100334

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ARTICLE

Maternal carrier screening with single-gene NIPS provides accurate fetal risk assessments for recessive conditions

Jennifer Hoskovec[1,*], Emily E. Hardisty[2], Asha N. Talati[2], Jacqueline A. Carozza[1], Julia Wynn[1], Shan Riku[1], John R. ten Bosch[1], Neeta L. Vora[2]

[1]*BillionToOne, Inc, Menlo Park, CA;* [2]*Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC*

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Personalized fetal disease risk
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Single-gene NIPS
Single-gene recessive disorders

ABSTRACT

Purpose: The purpose of this study was to evaluate the clinical performance of carrier screening for cystic fibrosis, hemoglobinopathies, and spinal muscular atrophy with reflex single-gene noninvasive prenatal screening (sgNIPS), which does not require paternal carrier screening.

Methods: An unselected sample of 9151 pregnant individuals from the general US pregnant population was screened for carrier status, of which 1669 (18.2%) were identified as heterozygous for one or more pathogenic variants and reflexed to sgNIPS. sgNIPS results were compared with newborn outcomes obtained from parent survey responses or provider reports for a cohort of 201 pregnancies.

Results: Overall, 98.7% of pregnant individuals received an informative result (no-call rate = 1.3%), either a negative carrier report or, if identified as heterozygous for a pathogenic variant, a reflex sgNIPS report. In the outcomes cohort, the negative predictive value of sgNIPS was 99.4% (95% CI = 96.0%-99.9%) and average positive predictive value (PPV) of sgNIPS was 48.3% (95% CI = 36.1%-60.1%). Importantly, personalized PPVs accurately reflected the percentage of affected pregnancies in each PPV range, and all pregnancies with a sgNIPS fetal risk of >9 in 10 (90% PPV) were affected.

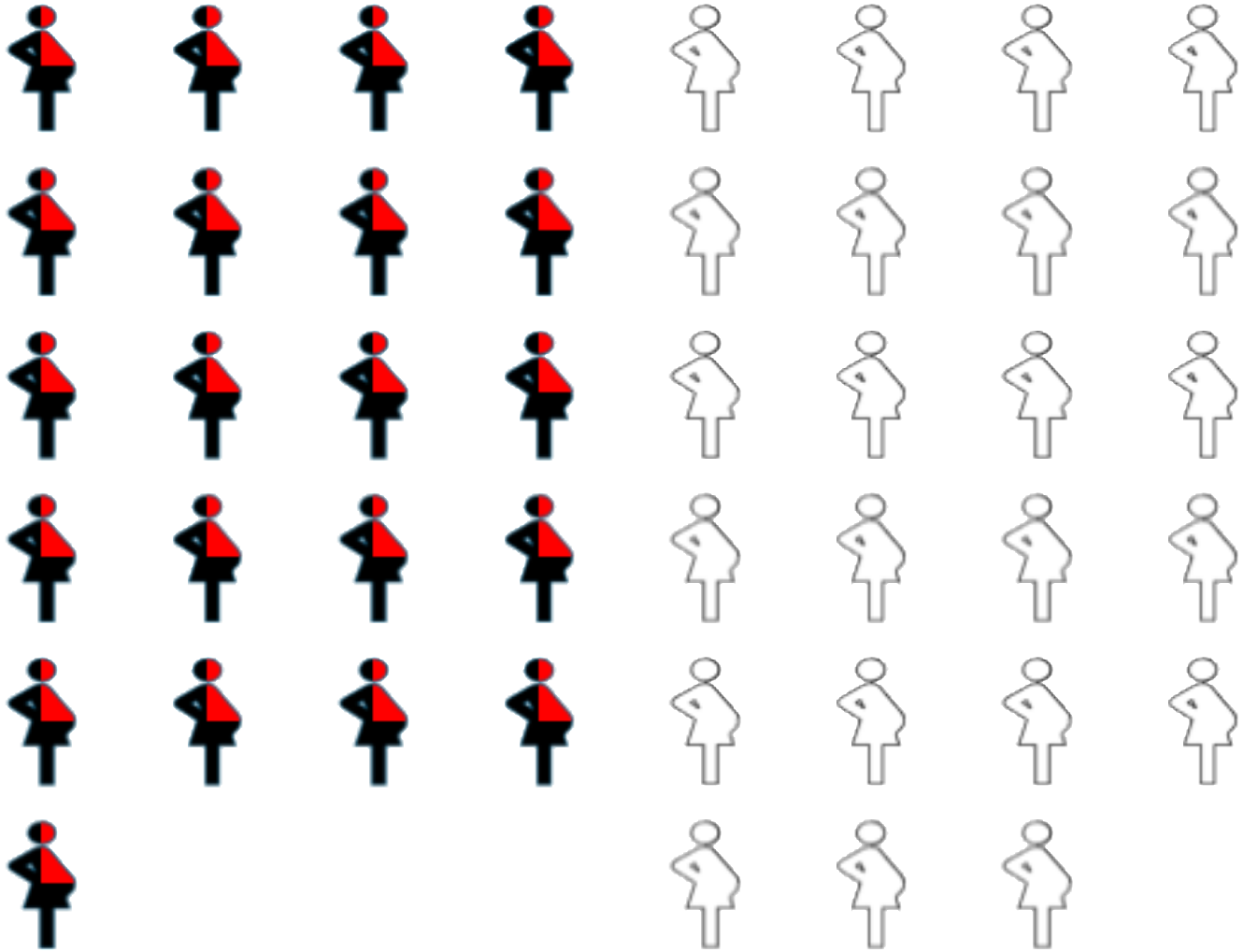
Conclusion: Although traditional carrier screening is most effective when used to assess reproductive

Traditional ECS

Strauss et al. (2023)

Traditional ECS

Strauss et al. (2023)



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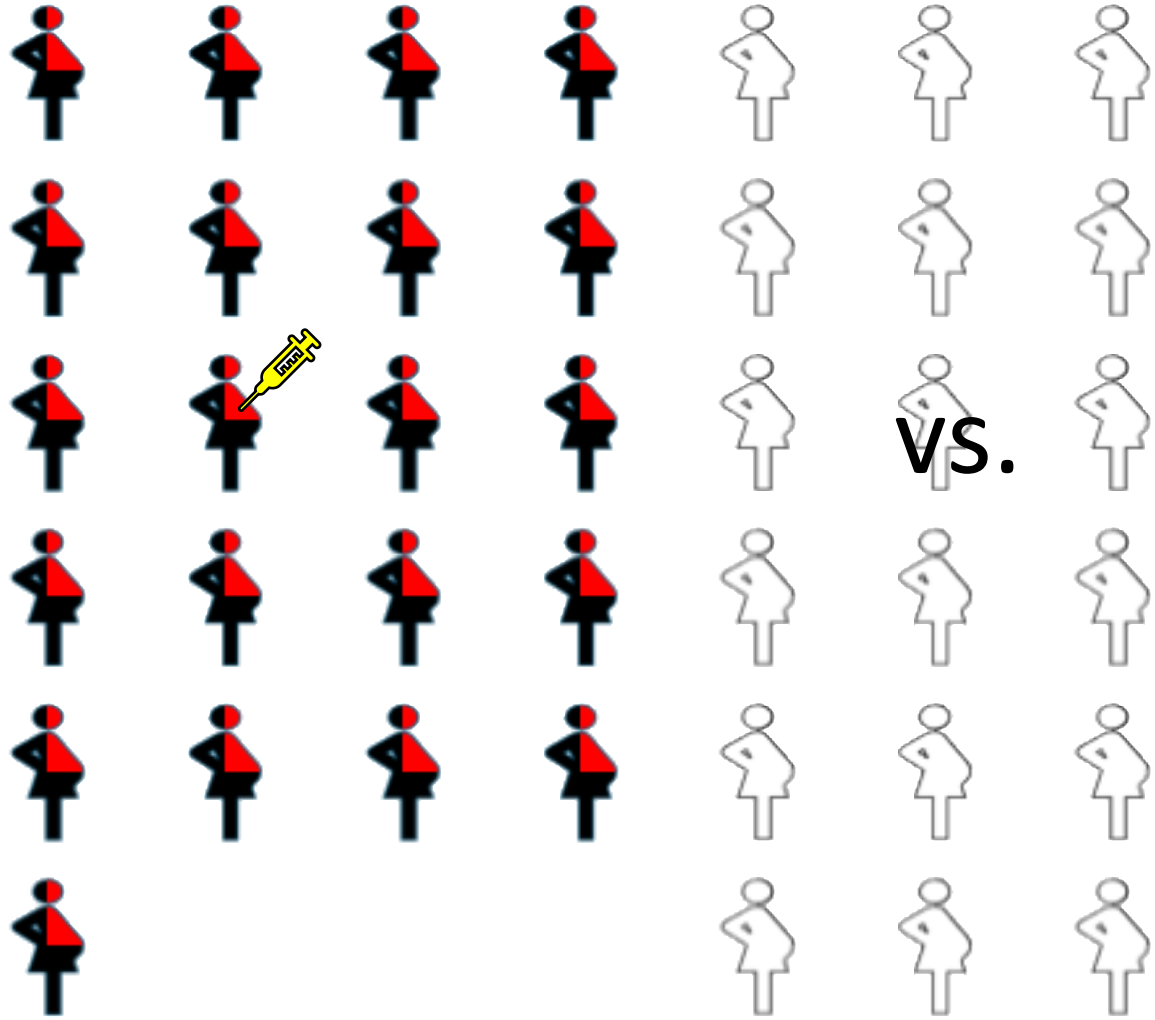
Strauss et al. (2023)



vs.

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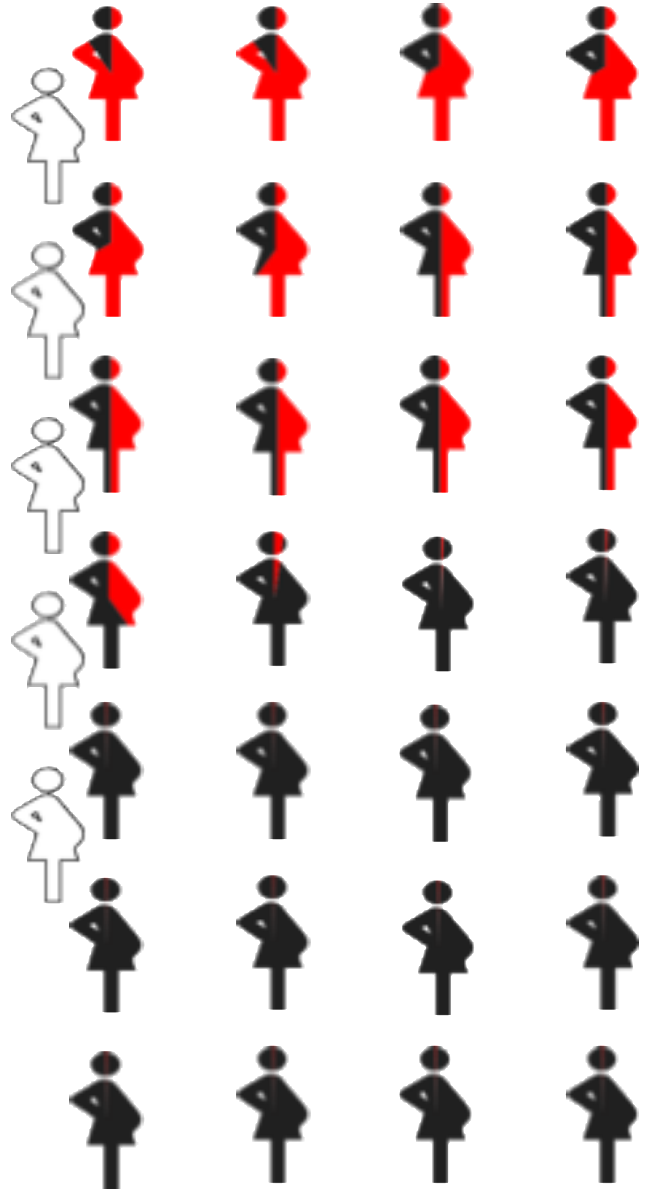
Hoskovec et al. (2023)



Traditional ECS

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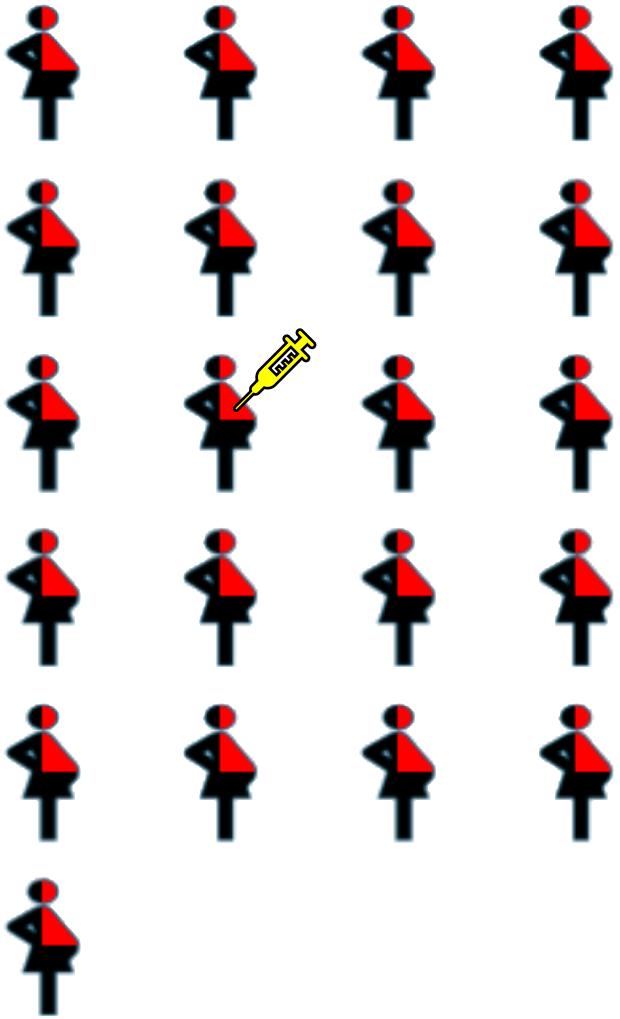

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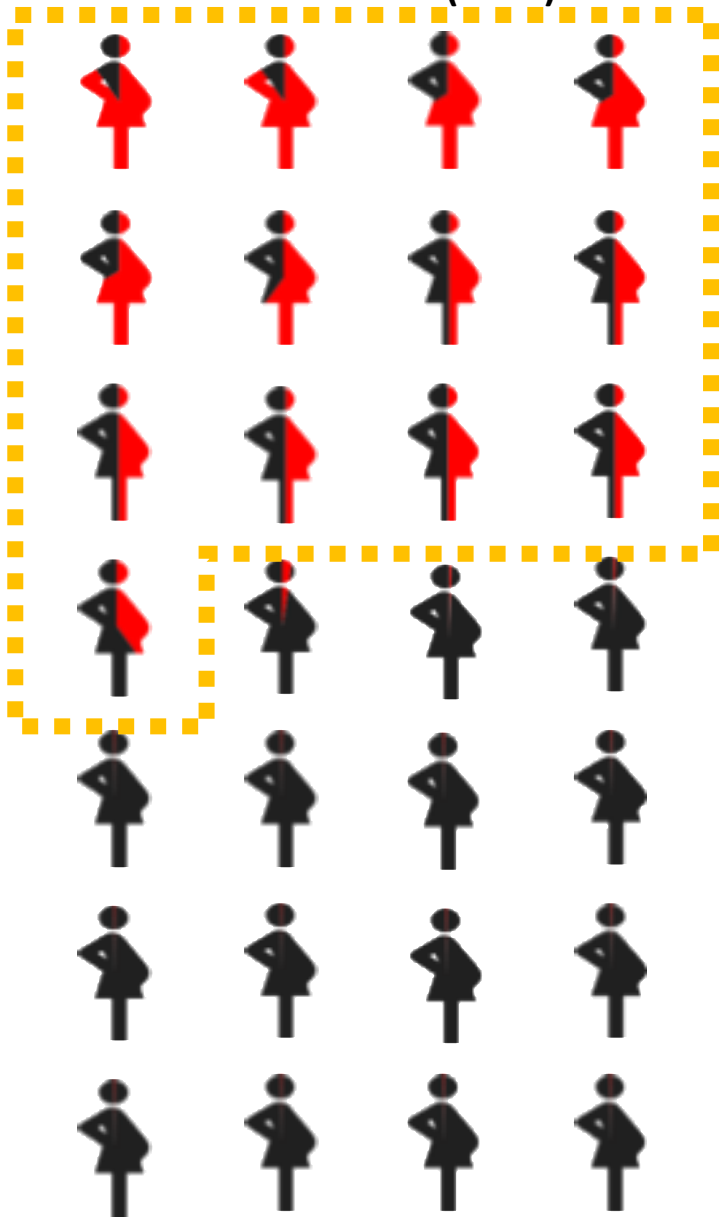

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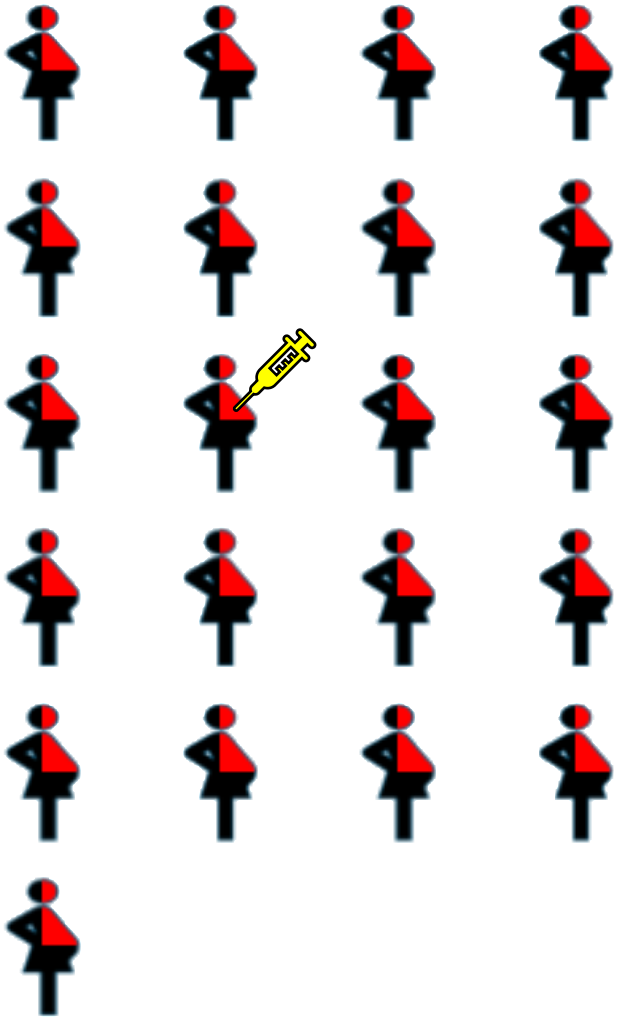
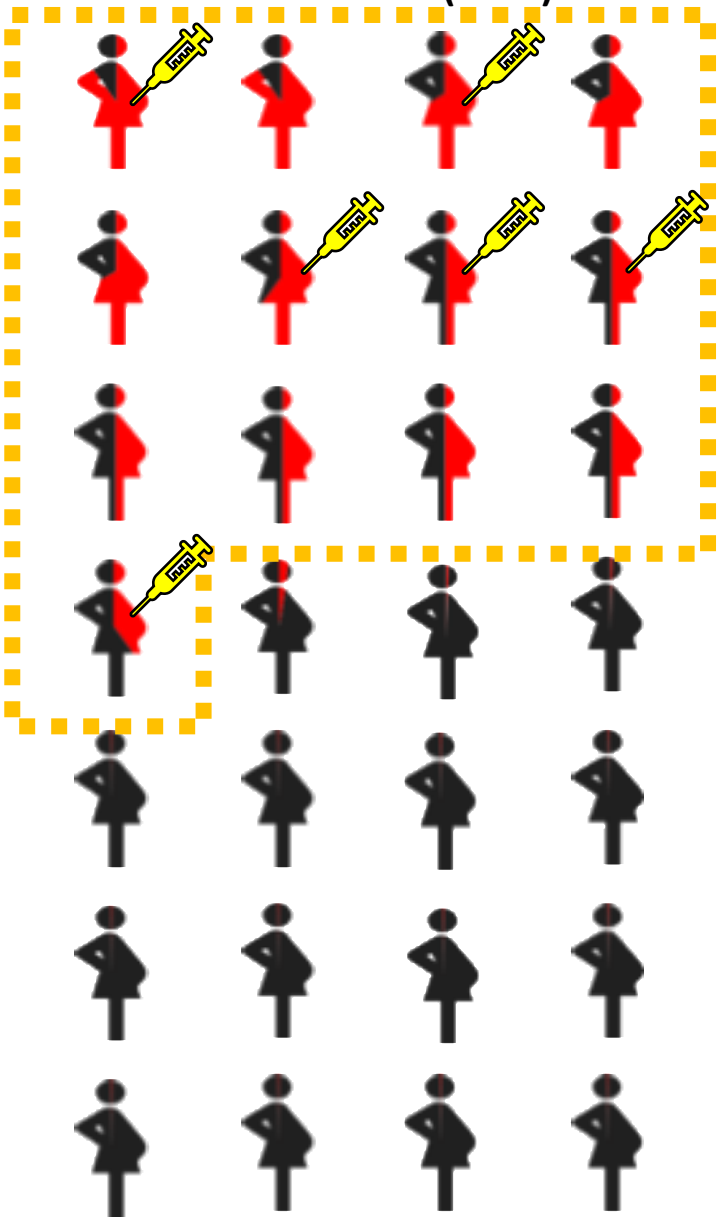
Strauss et al. (2023)



vs.

cfDNA

Hoskovec et al. (2023)



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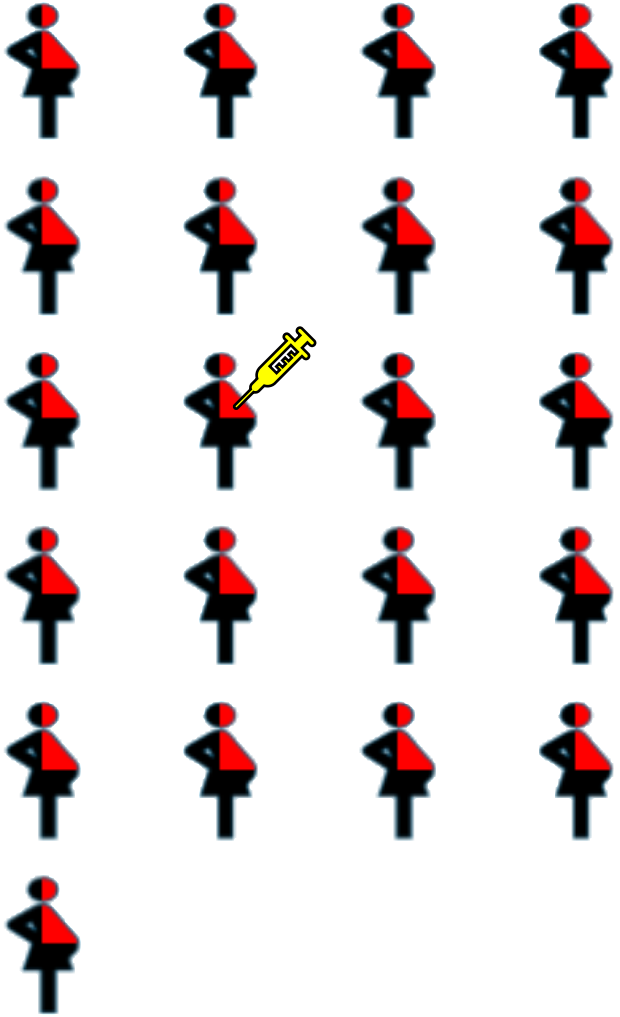

vs.

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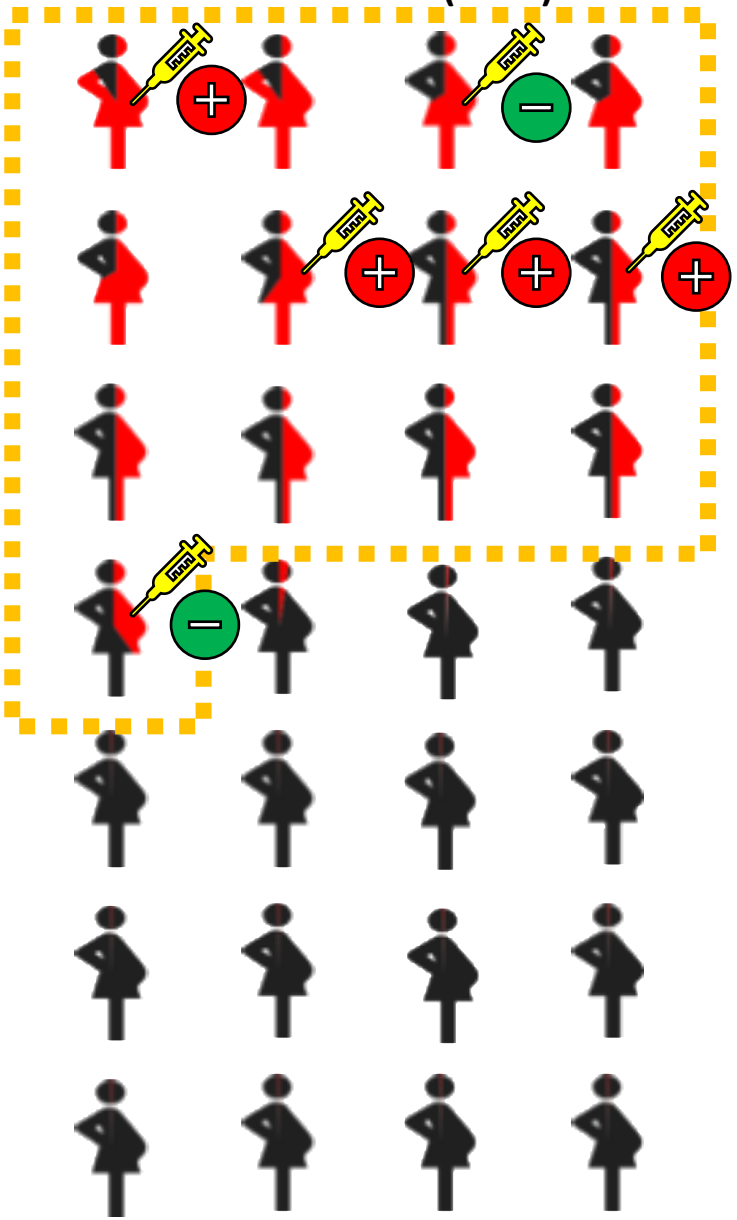
Hoskovec et al. (2023)



PAST

PRESENT

FUTURE

PAST

PRESENT

FUTURE

FUTURE PRENATAL TREATMENTS

- Prenatal Treatment of Cystic Fibrosis

Fetal Diagnosis and Therapy

Fetal Therapy

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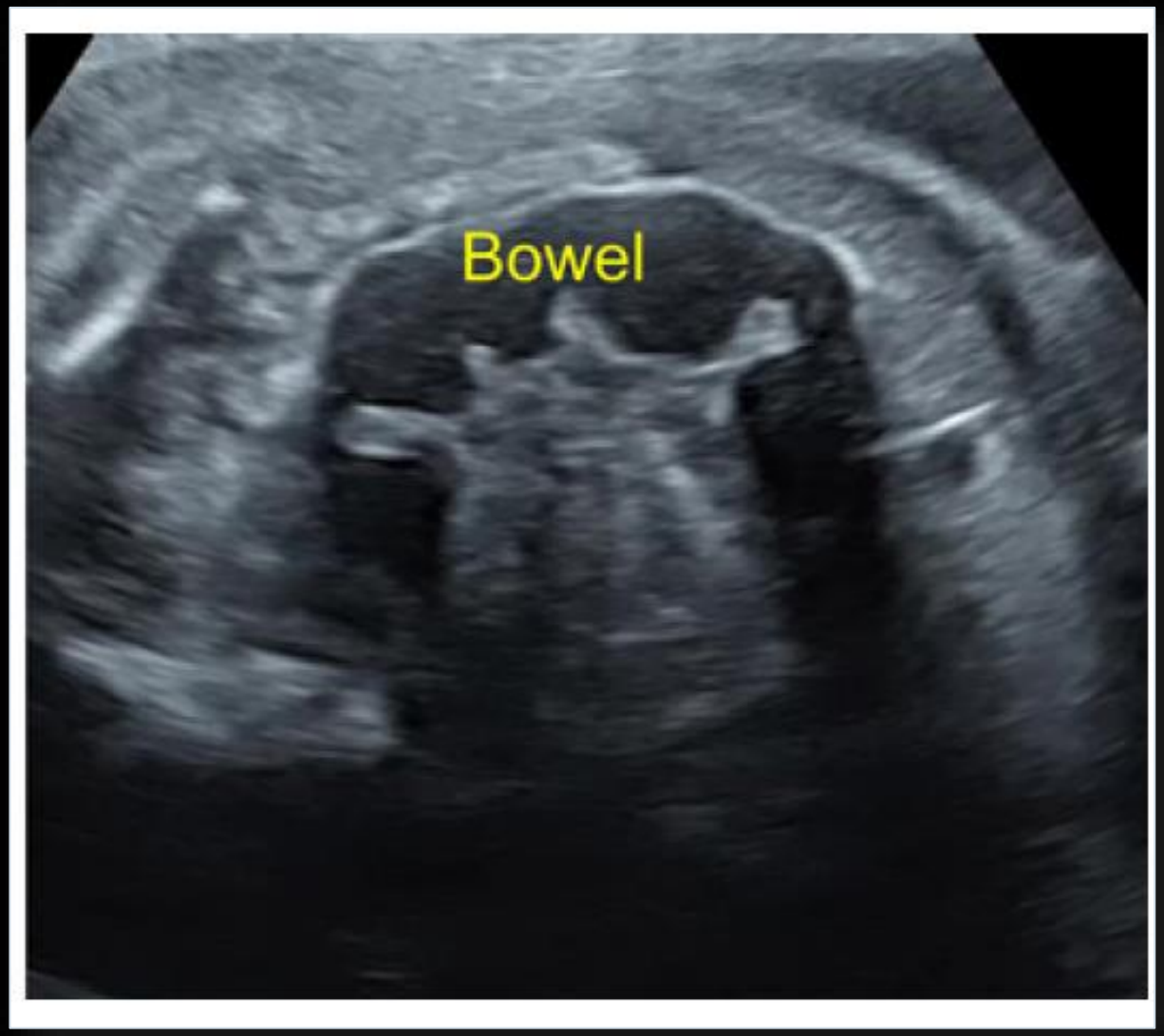
Prenatal Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy: A Promising Way to Change the Impact of Cystic Fibrosis

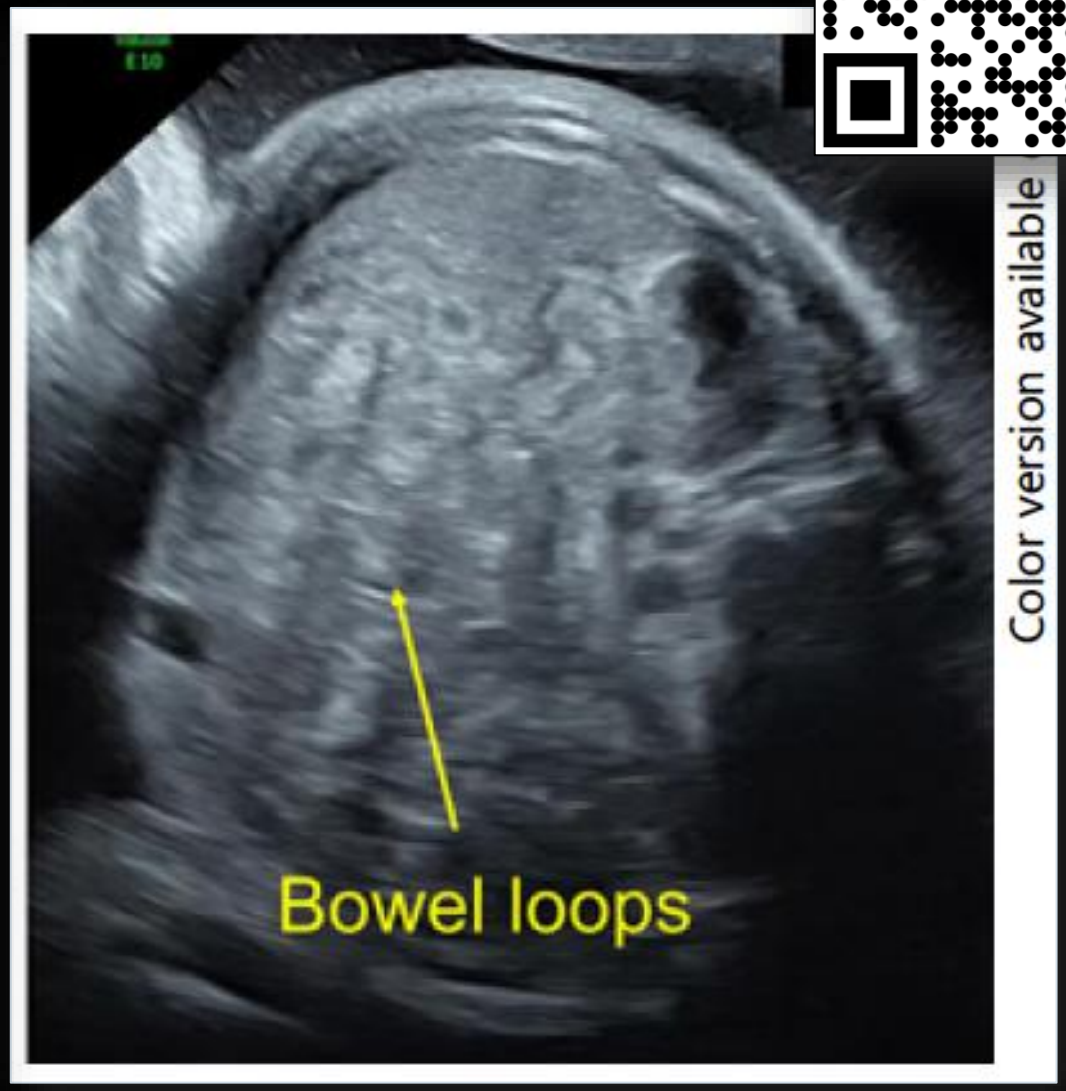
Enery Gómez Montes[a] Enrique Salcedo Lobato[b] Alberto Galindo Izquierdo[a]
Diana García Alcázar[c] Cecilia Villalaín González[a]
María Teresa Moral-Pumarega[d] Gerardo Bustos Lozano[d] Carmen Luna-Paredes[e]

[a]Fetal Medicine Unit, Department of Obstetrics and Gynecology, Research Institute Hospital 12 de Octubre (imas12), Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin (RICORS Network), University Hospital 12 de Octubre, Complutense University, Madrid, Spain; [b]Paediatric Gastroenterology, Hepatology and Nutrition Unit, Cystic Fibrosis Multidisciplinary Unit, University Hospital 12 de Octubre, Madrid, Spain; [c]Perinatal Medicine Unit, Department of Obstetrics and Gynecology, University Hospital 12 de Octubre, Madrid, Spain; [d]Neonatology Department, University Hospital 12 de Octubre, Madrid, Spain; [e]Paediatric Pneumology and Allergy Unit, Cystic Fibrosis Multidisciplinary Unit Coordinator, University Hospital 12 de Octubre, Madrid, Spain

27 weeks

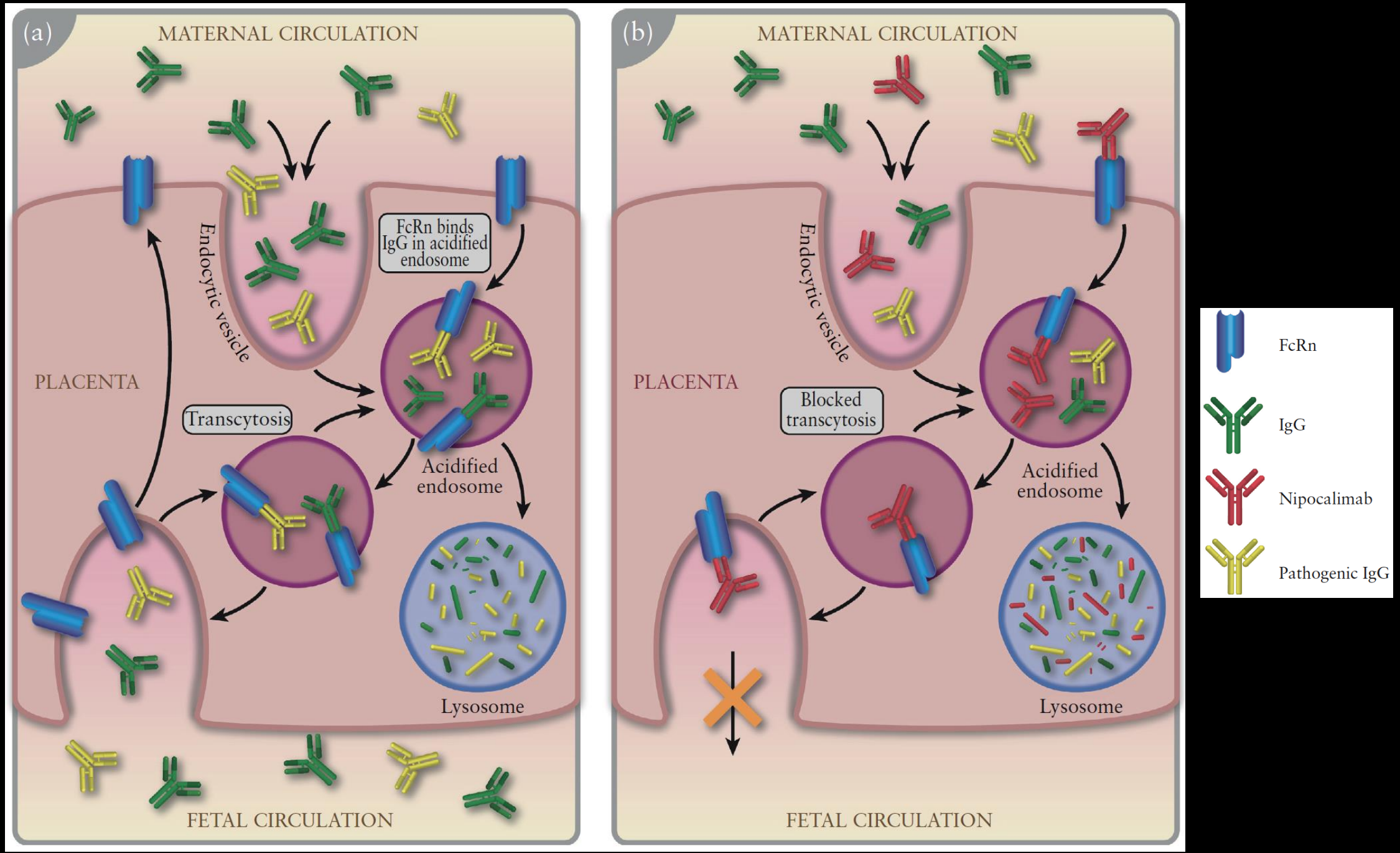


39 weeks



FUTURE PRENATAL TREATMENTS

- Prenatal Treatment of Cystic Fibrosis
- Nipocalimab - Phase 3 Clinical Trials to block IgG antibodies crossing from mom to baby



Moise KJ Jr, Oepkes D, Lopriore E, Bredius RGM. Targeting neonatal Fc receptor: potential clinical applications in pregnancy. Ultrasound Obstet Gynecol. 2022 Aug;60(2):167-175. doi: 10.1002/uog.24891. PMID: 35229965.

Innovative Medicine

Johnson & Johnson's nipocalimab granted U.S. FDA Breakthrough Therapy Designation for the treatment of individuals at high risk for severe hemolytic disease of the fetus and newborn (HDFN)

Innovative Medicine

Johnson & Johnson's nipocalimab granted U.S. FDA Fast Track designation to reduce the risk of fetal neonatal alloimmune thrombocytopenia (FNAIT) in alloimmunized pregnant adults

FUTURE PRENATAL TREATMENTS

- Prenatal Treatment of Cystic Fibrosis
- Nipocalimab - Phase 3 Clinical Trials to block IgG antibodies crossing from mom to baby
- In Utero Treatment for SMA

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 amniocentesis. Testing showed no copies of *SMN1* centrations, the drug concentration at delivery was 33% in amniotic fluid and 69% in cord blood. Serial measurements of SMN in blood samples and of light chain and phosphorylated heavy chain forms of neurofilament in plasma samples obtained from the mother and infant are summarized in Table 1.

The infant appeared normal at birth but was identified postnatally to have a heart murmur due to a ventricular septal defect, which resolved. The

FUTURE PRENATAL TREATMENTS

- Prenatal Treatment of Cystic Fibrosis
- Nipocalimab - Phase 3 Clinical Trials to block IgG antibodies crossing from mom to baby
- In Utero Treatment for SMA
- Gene therapy for sickle cell disease

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

For Immediate Release:

December 08, 2023

Today, the U.S. Food and Drug Administration approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older. Additionally, one of these therapies, Casgevy, is the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy.

Sickle cell disease is a group of inherited blood disorders affecting approximately 100,000 people in the U.S. It is most common in African Americans and, while less prevalent, also affects Hispanic Americans. The primary problem in sickle cell disease is a mutation in hemoglobin, a protein found in red blood cells that delivers oxygen to the body's tissues. This mutation causes red blood cells to develop a crescent or "sickle" shape. These sickled red blood cells restrict the flow in blood vessels and limit oxygen delivery to the body's tissues, leading to severe pain and organ damage called vaso-occlusive events (VOEs) or vaso-occlusive crises (VOCs). The recurrence of these events or crises can lead to life-threatening disabilities and/or early death.

FUTURE PRENATAL TREATMENTS

- Prenatal Treatment of Cystic Fibrosis
- Nipocalimab - Phase 3 Clinical Trials to block IgG antibodies crossing from mom to baby
- In Utero Treatment for SMA
- Gene therapy for sickle cell disease

THE END
Questions?

- Jay Chang, MD
- 512-825-3778