Coalition for Access to Prenatal Screening

Medical Assistance Program Oversight Council (MAPOC)
Women and Children's Health Committee

Improving Access to Non-Invasive Prenatal Screening for Connecticut Medicaid Beneficiaries

Monday, August 10, 2020

Presenters:

Coalition for Access to Prenatal Screening

- Ashley Svenson, MS, CGC: Employee of Myriad Genetics Laboratories, Inc.
- Julie Pawelczyk: Coalition for Access to Prenatal Screening
- Amanda Vitale: Coalition for Access to Prenatal Screening

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Choosing the Right Screening Test

Impact of false negative results:

- Missed diagnosis (unprepared for birth of baby with special medical needs)
- Missed opportunity for specialized care
- Provider: medical-legal risk

Impact of false positives results:

- Anxiety
- Wait to see specialist (discussion of results, diagnostic testing)
- Unnecessary invasive procedures (risk, cost)
- Provider: office resources (time counseling/procedures, cost to healthcare system)

Goal: Provide patients a screening option with a high sensitivity/specificity; ensure all patients have equal access, i.e. one standard of care for all.

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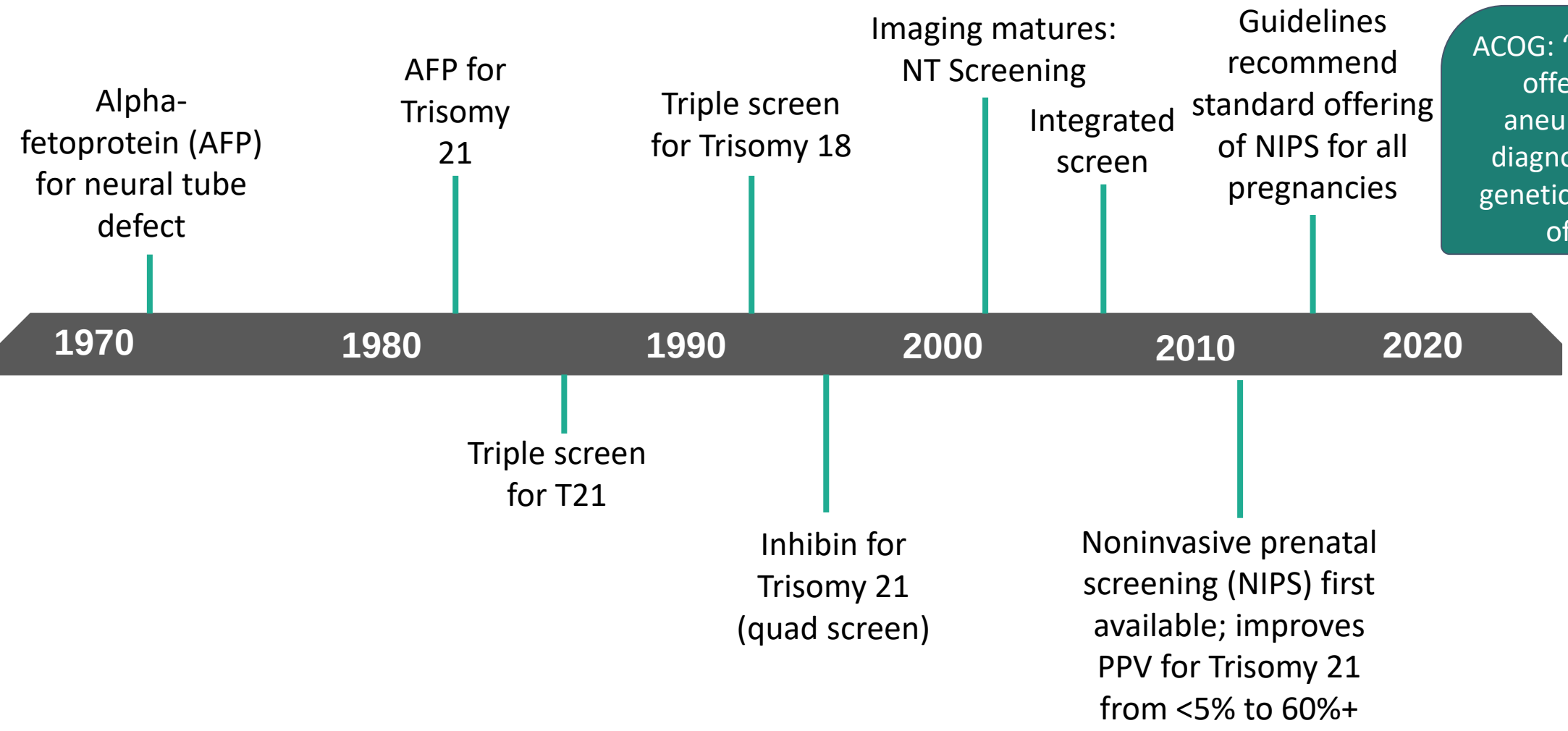
Screening Through the Years



ACOG: "All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders regardless of maternal age."

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NIPS vs. Quad Screen

NIPS	Quad Screen
Maternal and **placental cfDNA fragments are sequenced** and counted (WGS method) or ratios are compared (SNP method)	In combination with maternal factors (age, weight, race, diabetes), **four serum analytes (AFP, hCG, Inhibin A, and uE3) are measured** and compared to median values for gestational age
Risk assessed for T21, T13, T18, and sex chromosome abnormalities (optional)	Risks assessed for T21, T18, and ONTD's (may also indicate risk for adverse outcomes)
Can be done ≥ 10 weeks gestational age	Must be done 15-22 weeks, inaccurate dating leads to decreasing accuracy
>99% detection rate for T21 with 0.5% FPR	81% detection rate for T21 with 5% FPR

"Women who undergo cell free DNA screening should be offered assessment for open fetal defects by ultrasound, MS-AFP, or both" – ACOG Practice Bulletin 163

Clinical Experience in Average Risk Population

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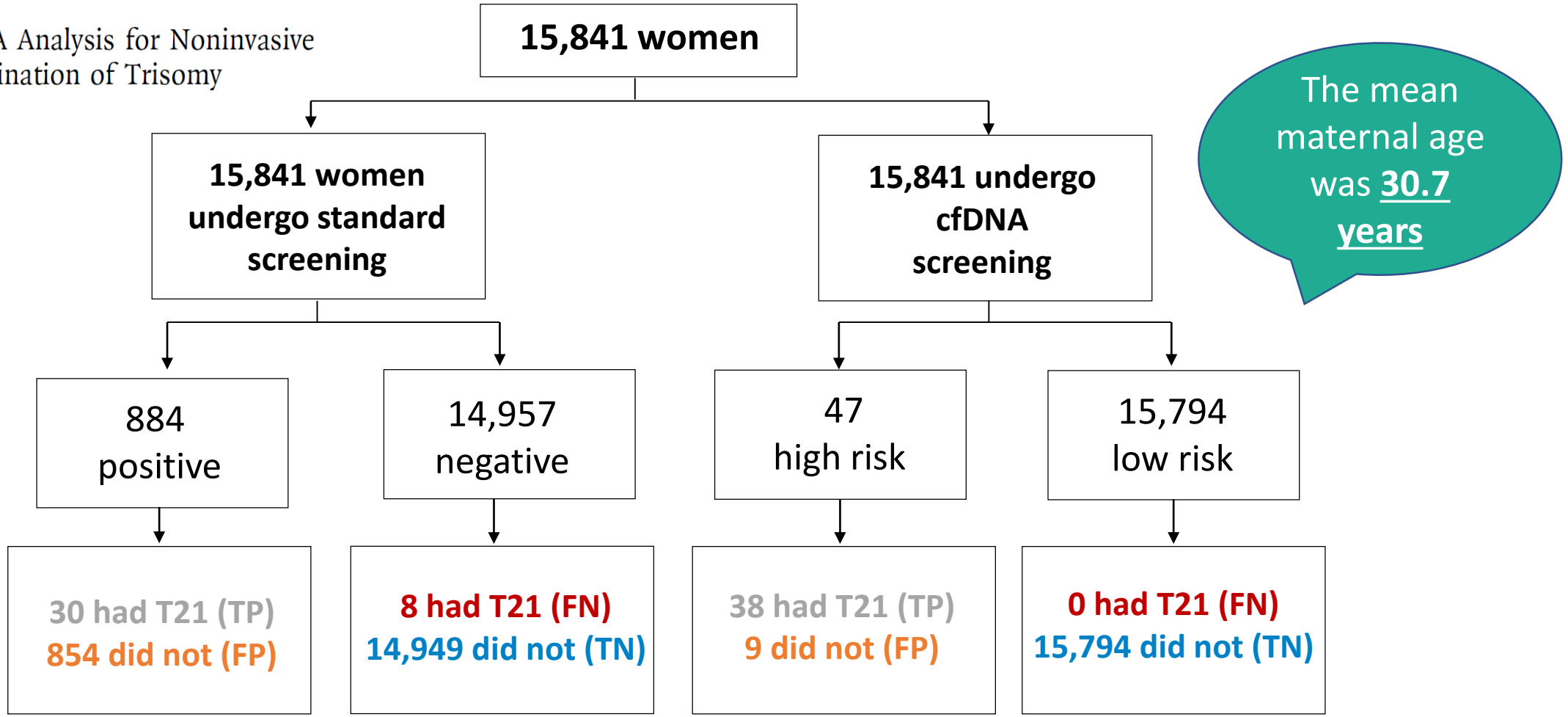
The NEW ENGLAND JOURNAL of MEDICINE

Cell-free DNA Analysis for Noninvasive Examination of Trisomy

NEXT Study (2015): Standard Screening vs. cfDNA Analysis by NGS for Trisomy 21



The mean maternal age was **30.7 years**

Norton, M. et al Cell free DNA analysis for noninvasive examination of Trisomy. The New England Journal of Medicine April 2015; 372: 1589-1597.

Clinical Experience in Average Risk Population

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NEXT Study (2015): Standard Screening vs. cfDNA by NGS for Trisomies 13 & 18

The NEW ENGLAND JOURNAL of MEDICINE

Cell-free DNA Analysis for Noninvasive Examination of Trisomy

	Test Metric	NIPS	Serum screening
Trisomy 21	PPV	80.9%	3.4%
	False Positive Rate	0.06%	5.6%
Trisomy 18	PPV	90.0%	14%
	False Positive Rate	0.01%	0.31%
Trisomy 13	PPV	50%	3.4%
	False Positive Rate	0.02%	0.25%

Norton, M. et al Cell free DNA analysis for noninvasive examination of Trisomy. The New England Journal of Medicine April 2015; 372: 1589-1597.

2018 New England Journal of Medicine Review

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- In low-risk population, sensitivities and specificities are similar to those in high-risk population.

- In three large-scale studies, performance of cfDNA sequencing was compared to multiple-marker screening in the general obstetrical population. All three studies found:

  - False positive rates associated with cfDNA screening less than 1/10th as high as with multiple-marker screening
  - Significantly higher positive predictive values

National Institutes of Health

Bianchi DW & Chiu RW. Sequencing of circulating cell-free DNA during pregnancy. N Engl J Med 2018;379: 464-473

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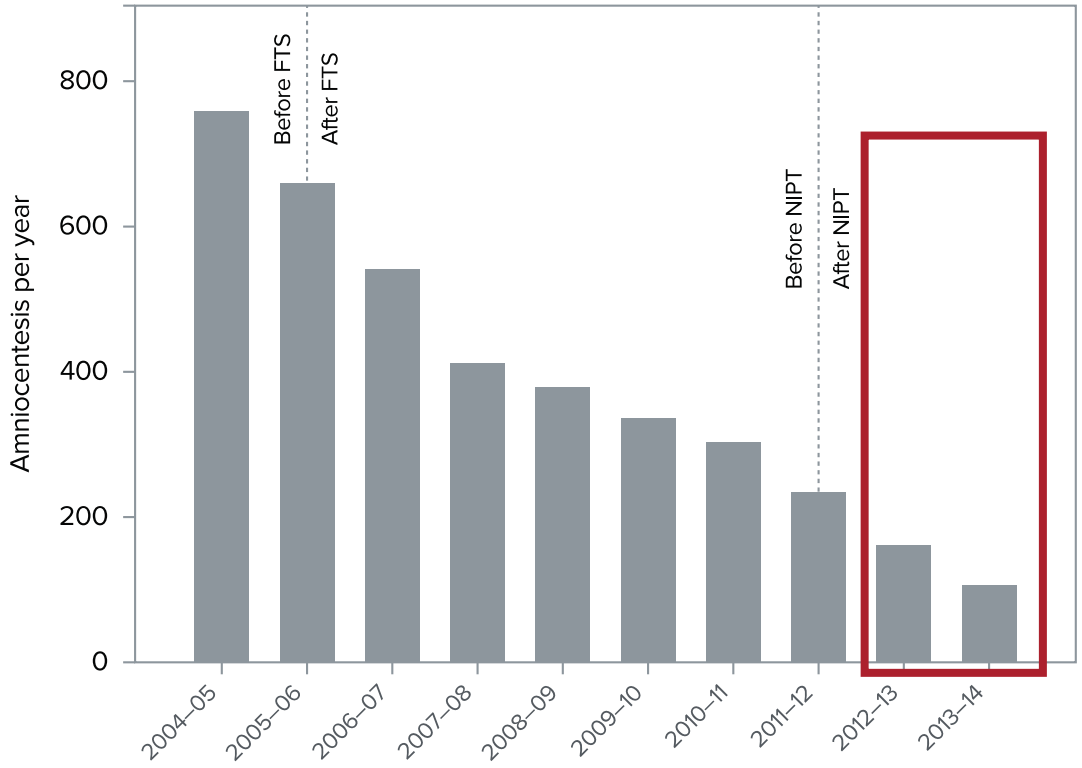
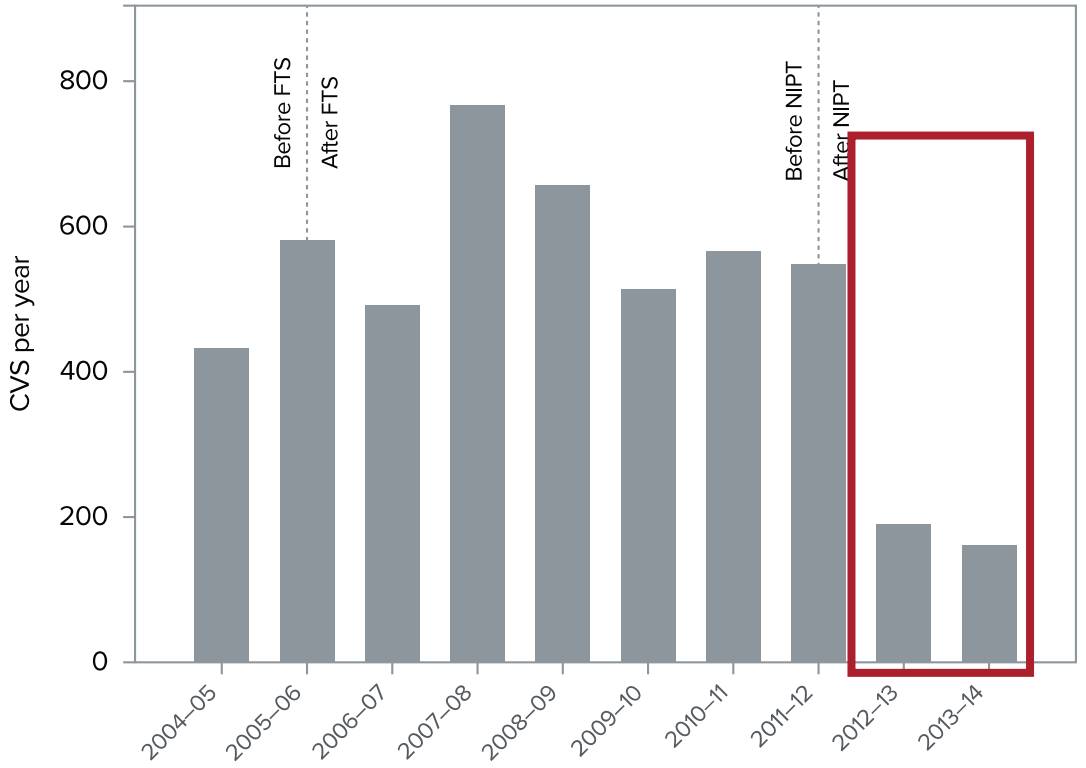
NIPS Reduces Invasive Procedures

Trends in invasive procedures: example from US center with >15,000 pregnancies over observation period[1]





Invasive testing rates have declined considerably (often by >50%) at many centers in the US and globally [2,3]

1. Larion S, Warsof SL, Romary L, et al. Association of combined first-trimester screen and noninvasive prenatal testing on diagnostic procedures. Obstet Gynecol 2014;123:1303–10.
2. Warsof SL et al. Overview of the impact of noninvasive prenatal testing on diagnostic procedures Prenatal Diagnosis 2015, 35, 1–8
3. Allyse M et al. Non-invasive prenatal testing: a review of international implementation and challenges. Int J Women's Hlth 2015:7 113–126

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Clinical Evidence in the General Population

17 Publications with > **88,000** Average Risk Patients

Author	Date	Journal	N
Nicolaides et al.	Nov-2012	American Journal of Obstetrics and Gynecology	2,049
Dan et al.	9-Nov-2012	Prenatal Diagnosis	1,387
Fairbrother et al.	15-Mar-2013	Prenatal Diagnosis	289
Gil et al.	6-June-2013	Ultrasound Obstetrics & Gynecology	1,111
Song et al.	17-Jun-2013	Prenatal Diagnosis	1,741
Shaw et al.	20-Nov-2013	Fetal Diagnosis and Therapy	101
Lau et al.	10-Feb-2014	Ultrasound Obstetrics & Gynecology	368
Bianchi et al.	27-Feb-2014	New England Journal of Medicine	1,914
Zhou et al.	4-Jul-2014	Prenatal Diagnosis	26
Pergament et al.	Aug-2014	Obstetrics & Gynecology	518

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Clinical Evidence in the General Population

Continued

Author	Date	Journal	N
Comas et al.	12-Aug-2014	Journal of Maternal-Fetal & Neonatal Medicine	278
Korostelev et al.	9-Sep-2014	Gynecological Endocrinology	190
Quezada et al.	20-Nov-2014	Ultrasound Obstetrics & Gynecology	2,851
Zhang et al.	8-Apr-2015	Ultrasound in Obstetrics & Gynecology	40,287
Norton et al.	23-Apr-2015	New England Journal of Medicine	15,841
Palomaki et al.	12-Jan-2017	Genetics in Medicine	2691
Caldwell et all.	1-Feb-2017	SMFM Annual Meeting 2017	16,585
		TOTAL	88,227

cfDNA performance in the general obstetric population has been documented in at least **17 studies** covering over **88,000 subjects**

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What does NIPS coverage look like across the country?

Map of State Medicaid Coverage of cfDNA-based Noninvasive Prenatal Screening

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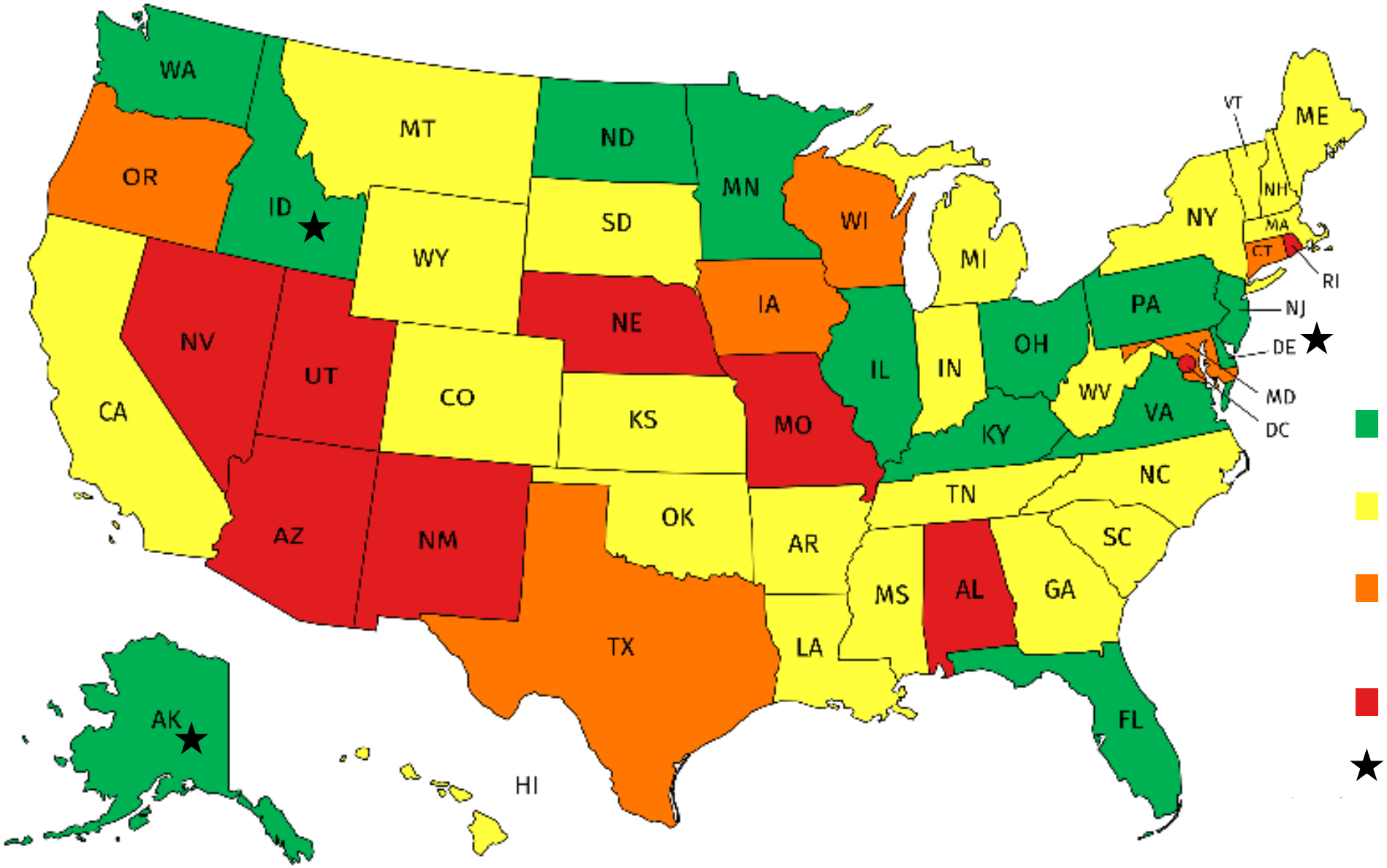

- Covers NIPS for Average Risk Women
- Covers NIPS for Only High Risk Women
- Reviewing High Risk Policy, Average Risk Under Consideration
- Denies NIPS Completely
- ★ Temporary Coverage due to COVID-19

Examples of Recent Clinical Reviews of NIPS by Medicaid

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Washington

Washington State Health Care Authority

Health Technology Clinical Committee
DRAFT Findings and Decision

Topic: Cell-free DNA prenatal screening for chromosomal aneuploidies
Meeting date: January 17, 2020
Final adoption: Pending

Meeting materials and transcript are available on the HTA website.

Number and coverage topic:

20200117A – Cell-free DNA prenatal screening for chromosomal aneuploidies (cfDNA)

HTCC coverage determination:

Cell-free DNA prenatal screening for chromosomal aneuploidies is a covered benefit.

HTCC reimbursement determination:

Limitations of coverage: N/A

Non-covered indicators: N/A

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Conducted year-long assessment of NIPS.
On January 17, 2020, WA Health Technology Clinical Committee ***voted 8-2-0 to cover NIPS for Medicaid enrollees***.

- 8 votes were “unconditional”, 2 votes for “with conditions” and zero votes for restricted coverage.

Health Technology Assessment (HTA) draft findings document states: ***“A majority of committee members found the evidence sufficient to determine that use of cfDNA prenatal screening for chromosomal aneuploidies is safer, more effective or more cost-effective than comparators.”***

Iowa

Department of HUMAN SERVICES

Meeting Minutes	
Division:	Iowa Medicaid Enterprise Quality Improvement Organization (QIO)
Meeting Title:	Clinical Advisory Committee (CAC)
Facilitator:	Bill Jagielo, D.O.
Location:	Lucas building, 321 E. 12th St., Des Moines, 5th Floor, Rm 517/518
Date:	October 18, 2019 — **Time:** 1:00 p.m. – 4:00 p.m.

Meeting Objectives

The purpose of the CAC is to increase the efficiency, quality and effectiveness of the Medicaid healthcare system. The CAC provides a process for physician and other health care provider contributions to promote quality care, member safety, cost effectiveness and positive physician and provider relations through discussion about Medicaid benefits and healthcare services.
The CAC is charged with recommending clinically appropriate healthcare utilization management and coverage decision to the Department of Human Services (DHS) for the Iowa Medicaid program.

Meeting Participants

Name	Organization
Bill Jagielo, D.O.	IME
Mark Randeman, D.O.	IME
Dr. Nick Galioto- Family Practice	
Dr. Dennis Zachary- Family Practice	
Dr. Kathy Lange- Family Practice	
Dr. Andrea Silvers- Family Practice	
Dr. Alex Hubbell- Family Practice	
Clarice Blanchard, PA-C - Family Practice/Emergency Medicine	
Dr. Daniel Wright- Pediatrician	
Dr. Angela Kloepfer	Amerigroup
Tami Sova	Biogen
Tami Lichtenberg	IME
Barb Cox	IME
Shelley Horak	IME
Cassie Reece	IME
Becky Carter	IME
Jennifer Ober	IME

October 2019: IA Medicaid Clinical Advisory Committee voted to ***“open testing to all pregnant women with singleton pregnancy, consistent with ACOG recommendation.”***

Blue Cross Blue Shield TEC Assessment

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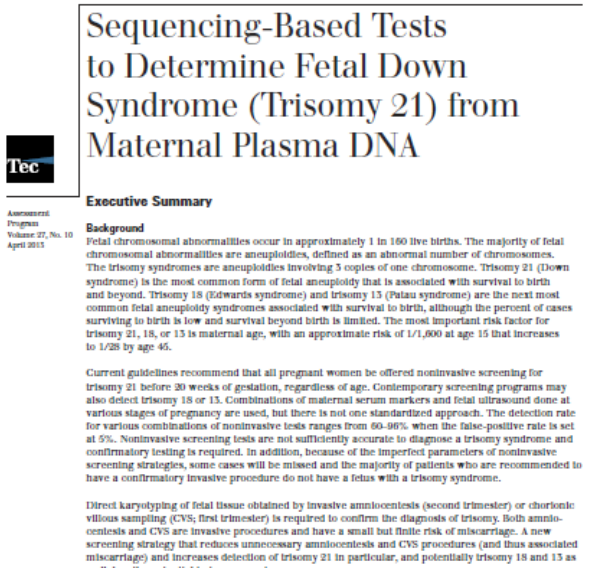
- TEC Assessment 2013: Trisomy 21

Blue Cross Blue Shield Technology Evaluation Center Assessment: Sequencing-Based Tests to Determine Fetal Down Syndrome (Trisomy 21) from Maternal Plasma DNA



Sequencing-Based Tests to Determine Fetal Down Syndrome (Trisomy 21) from Maternal Plasma DNA

Tec

Assessment Program Volume 27, No. 10 April 2013

Executive Summary

Background

Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. The majority of fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving 3 copies of one chromosome. Trisomy 21 (Down syndrome) is the most common form of fetal aneuploidy that is associated with survival to birth and beyond. Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are the next most common fetal aneuploidy syndromes associated with survival to birth, although the percent of cases surviving to birth is low and survival beyond birth is limited. The most important risk factor for trisomy 21, 18, or 13 is maternal age, with an approximate risk of 1/1,600 at age 15 that increases to 1/28 by age 45.

Current guidelines recommend that all pregnant women be offered noninvasive screening for trisomy 21 before 20 weeks of gestation, regardless of age. Contemporary screening programs may also detect trisomy 18 or 13. Combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy are used, but there is not one standardized approach. The detection rate for various combinations of noninvasive tests ranges from 60–96% when the false-positive rate is set at 5%. Noninvasive screening tests are not sufficiently accurate to diagnose a trisomy syndrome and confirmatory testing is required. In addition, because of the imperfect parameters of noninvasive screening strategies, some cases will be missed and the majority of patients who are recommended to have a confirmatory invasive procedure do not have a fetus with a trisomy syndrome.

Direct karyotyping of fetal tissue obtained by invasive amniocentesis (second trimester) or chorionic villous sampling (CVS; first trimester) is required to confirm the diagnosis of trisomy. Both amniocentesis and CVS are invasive procedures and have a small but finite risk of miscarriage. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures (and thus associated miscarriage) and increases detection of trisomy 21 in particular, and potentially trisomy 18 and 13 as

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 with confirmatory testing of positive results (as expected to be performed in a real-world clinical setting) in **both high-risk and average-risk women screened for trisomy 21 meets TEC criteria.**

In decision model, sequencing-based maternal plasma fetal trisomy 21 testing:

- Reduced invasive confirmatory procedures needed and consequent associated miscarriages
- Improved detected cases of trisomy 21, compared to standard screening procedures in either high- or average-risk pregnant women

Blue Cross Blue Shield Association. Technology Evaluation Center Assessment. Sequencing-based tests to determine fetal Down syndrome (trisomy 21) from maternal plasma DNA. April 2013.

Connecticut's Commercial Insurance Coverage of NIPS

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Covers NIPS for all pregnant women in Connecticut

- Anthem BlueCross BlueShield
- Cigna
- ConnectiCare
- Harvard Pilgrim Health Care
- aetna™ *

*Coverage due to COVID19

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

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 640 • September 2015 (This Committee Opinion Replaces Committee Opinion Number 545)

Use in the General Obstetric Population

Data on the performance of cell-free DNA testing in the general obstetric population have become available (1, 8, 11, 16, 17). The sensitivity and specificity in the general obstetric population are similar to the levels previously published for the aforementioned high-risk population. The positive predictive value, however, is lower in this population, given the lower prevalence of aneuploidy in the general obstetric population. That is, fewer women with a positive test result will actually have an affected fetus, and there will be more false-positive test results (Fig. 1).

As of July 2018, ACOG Committee Opinion 640 is **not** current

Committee Opinion No. 640 September 2015

Cell-free DNA Screening for Fetal Aneuploidy (Withdrawn) | ACOG

Cell-free DNA Screening for Fetal Aneuploidy Number 640 September 2015 ... Jump to Close ... Search page ... Search Page ... Resources Close ... Facebook ... This document has been withdrawn or is no longer available. ... Please contact the Resource Center at the American College of Obstetricians and ... Current clinical guidance from ACOG is available online at https://www.acog.org/ ...

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

Society for Maternal-Fetal Medicine

(Published Electronically Ahead of Print on March

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 163, MAY 2016 (Replaces Practice Bulletin Number 77, Janua

(See also Practice Bulletin Number 162, *Prenatal Diagnostic Testing for Genetic Di*

Screening for Fetal Aneuploidy

PB 163 is the current opinion: "All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age."

Restated in CO 693

Professional Society Positions

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International Society for Prenatal Diagnosis *April 2015*	"cfDNA screening as a primary test offered to all pregnant women [is currently considered an appropriate protocol option]." [1]
American College of Obstetricians and Gynecologists (ACOG), jointly with the Society for Maternal Fetal Medicine (SMFM) *May 2016*	"Aneuploidy screening or diagnostic testing should be discussed and offered to **all** women early in pregnancy, ideally at the first prenatal visit. All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age."[2]
American College of Medical Genetics and Genomics (ACMG) *July 2016*	Recommends "Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)"[3]
National Society of Genetic Counselors (NSGC) *October 2016*	"The National Society of Genetic Counselors supports prenatal cell-free DNA (cfDNA) screening, also known as NIPT or NIPS, as an option for pregnant patients."[4]

1. Benn, P., et al. Position Statement from the Chromosome Abnormality Screening Committee on Behalf of the Board of International Society for Prenatal Diagnosis. Prenatal Diagnosis. 2015 Aug [cited 2017 Mar 23]; 35(8). Available from: https://ispdhome.org/docs/ISPD/Society%20Statements/PositionStatement_Current_8Apr2015.pdf
2. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. The American College of Obstetricians and Gynecologists. The Society for Maternal-Fetal Medicine. 2016 May. [cited 2017 Mar 23]. Available from: https://s3.amazonaws.com/cdn.smfm.org/publications/224/download-491f0e6962960848d2097447ab57a024.pdf
3. Gregg, A.R., et al. "Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics" *American College of Medical Genetics*. 2016 Jul. [cited 2017 Mar 23] Available from: http://www.acmg.net/docs/NIPS_AOP.pdf
4. Position Statement: Prenatal Cell-Free DNA Screening, National Society of Genetic Counselors. 2018 April. Available from: https://www.nsgc.org/p/bl/et/blogaid=805

One Standard of Care for All Patients

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of pregnancies in the United States are to women considered high risk (>35, family history of affected pregnancy)

- NIPS is a *widely available* screening and regularly utilized.

of pregnancies in the United States are to women considered low or average risk

- NIPS access *can be sporadic*, often dependent on a patient's location or health insurance plan -- creating two different standards of care.

Goal: Ensure all patients receive the best quality care and establish a single standard of care.