Washington State Health Care Authority

Cell-free DNA prenatal screening for chromosomal aneuploidies

Clinical Expert

Edith Yee Tak Cheng, MD

Vice Chair, Department of Obstetrics and Gynecology, University of Washington

Chief of Service, Obstetrics, University of Washington

Division Director, Maternal Fetal Medicine, University of Washington

Professor Division of Maternal Fetal Medicine, University of Washington

Associate Professor Division of Maternal Fetal Medicine, University of Washington

Applicant Name [redacted]

Address

1. Business Activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type

(b) If you or a member of your household ***did business under an assumed business name*** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type
N/A		

2. Honorarium

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed
N/A		

3. Sources of Income

(a) Identify ***income source(s) that contributed 10% or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type
UNIV. OF WASH.	E. Cheng	Salary
" " "	D. FIZPATRICK	Salary

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes ☑ No

If "yes", describe:

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☐ Yes ☑ No

If "yes", describe:

4. Business Shared With a Lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared
N/A		

Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000

List each source (***not amounts***) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source
N/A		

6. Business Investments of More Than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business Name	Business Address	Description of Business
N/A		

7. Service Fee of More Than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service
N/A	

****

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name EDITH Y. CHEANG

Check One: ☐ Committee Member ☐ Subgroup Member ☑ Contractor

Sig[redacted] Date 12/23/19

Edith Yee Tak Cheng, M.D.
Curriculum Vitae

PERSONAL DATA

Home Address [redacted]

Business Address Department of Obstetrics and Gynecology
University of Washington
Box 356460
Seattle, WA 98195-6460
206-616-4311
chengels@uw.edu

Place of Birth Hong Kong
Citizenship United States

EDUCATION

Undergraduate	B.A. Genetics, University of California, Berkeley, CA	1973 – 1977

POSTGRADUATE TRAINING

Graduate	M.S., Genetic Counseling Sarah Lawrence College, NY, NY	1977 - 1979
Medical	M.D. University of Washington, Seattle, WA	1983 - 1987
Residency	Obstetrics & Gynecology University of Washington, Seattle, WA	1987 - 1991
Fellowship	Medical Genetics University of Washington, Seattle, WA	1991 - 1993
Fellowship	Maternal Fetal Medicine University of Washington, Seattle, WA	1993 - 1995

FACULTY POSITIONS

Vice Chair, Department of Obstetrics and Gynecology	2019 – present
Chief of Service, Obstetrics	2013 – present
Division Director, Maternal Fetal Medicine	2014 – present

Professor 2010 – present
Division of Maternal Fetal Medicine
Associate Professor
Division of Maternal Fetal Medicine

Medical Director, Prenatal Diagnosis and Fetal Therapy Program 2001 – 2010

Department of Obstetrics and Gynecology, University of Washington

Director, Perinatal Genetics 2007 – present
Prenatal Diagnosis and Treatment Program
Seattle Children's Hospital

Medical Director, Outpatient Obstetrical Services 2009- present
Maternal and Infant Care Center
University of Washington Medical Center

Medical Director, Inpatient Obstetrical Services 2010 – present
University of Washington Medical Center

Assistant Director ???
Family Planning Program – Ryan Foundation
University of Washington Maternal and Infant Care Clinic

Adjunct Professor 2010 – Present
Division of Medical Genetics
Department of Internal Medicine, University of Washington.

Adjunct Associate Professor 2001 - 2010
Division of Medical Genetics
Department of Internal Medicine, University of Washington

Assistant Professor 1995 - 2001
Division of Perinatal Medicine
Co-Director, Prenatal Diagnosis and Fetal Therapy Program
Department of Obstetrics and Gynecology, University of Washington

Adjunct Assistant Professor 1995 - 2001
Division of Medical Genetics
Department of Internal Medicine, University of Washington

HOSPITAL POSITIONS

Genetic Counselor 1979 - 1983
Prenatal Diagnosis Unit, University of Washington
Biochemical Defects Unit, University of Washington
Division of Perinatal Medicine, Swedish Hospital Medical Center
Seattle, Washington

AWARDS AND HONORS

National Faculty Teaching Award, Dept. of Obstetrics and Gynecology	2009
University of Washington Service Excellence Award	2006
University of Washington Presidential Faculty Development Fellow	1999
National Faculty Teaching Award, Dept. of Obstetrics and Gynecology	1995
Award of Research Excellence in Genetics, Society of Perinatal Obstetricians	1995
Teaching Award, HUBIO 554, Medical Genetics, Univ. of Wash. School of Medicine	1994
March of Dimes Birth Defects Foundation Clinical Research Grant, "An Analysis of Nondisjunction in Human Oocytes"	1993-1995
Clinical Research Fellowship, Mead Johnson/American College of Ob/Gyn	1993
Washington State Ob-Gyn Research Award	1992
Best Research By Fellow In Training, Society of Perinatal Obstetricians	1992
Alpha Omega Alpha, University of Washington	1987
March of Dimes Medical Student Summer Research Grant	1984
March of Dimes Scholarship	1977-1978

BOARD CERTIFICATION

Diplomate American Board Obstetrics and Gynecology, Maternal Fetal Medicine	2000 - 2014
Diplomate American Board Obstetrics and Gynecology	1998 - 2014
Diplomate American Society of Human Genetics, Clinical Genetics	1993, 2011 - 2021
Diplomate American Society of Human Genetics, Genetic Counseling	1982, Continuous

CURRENT LICENSE TO PRACTICE

Washington MD00027989 1990 - present

PROFESSIONAL ORGANIZATIONS

American College of Medical Genetics, Fellow
American Society of Human Genetics, Fellow
Society for Maternal-Fetal Medicine, Fellow
American College of Obstetrics & Gynecology, Fellow
American Society of Genetic Counselor

TEACHING RESPONSIBILITIES

Course Instructor:

HUBIO 554 - Medical Genetics for second year medical students 1991 - Present
University of Washington School of Medicine

PATHOLOGY 530 - Human Cytogenetics 1996 – Present
Graduate level course on chromosome molecular structure,
identification of chromosomes, mapping, and pathology

Invited Faculty - “Prenatal Diagnosis and Screening, Genetic Counseling, and Preimplantation Genetic Diagnosis” — October 2005
Medical and Laboratory Applications of Genetics and Genomics
Zhejiang University and Affiliated Hospitals, Hangzhou, China

Research Preceptor:

1994 – 1996 — ISMS Project (Independent Research Project for Medical Students)
"Osteogenesis Imperfecta: Prenatal Genotype-Phenotype Correlation and Obstetrical Outcome"

Research Advisor:

1995 – 1996 — Undergraduate Honors independent lab research project: Genetics 499 "An Analysis of Interchromosomal Effects on Chromosome Pairing in Female Meiosis using Chromosome Painting"

1998 - 2000 — "Cryopreservation of Human Primordial Follicles: An analysis Using Fluorescent *In Situ* Hybridization"
David Lee, MD, Senior Fellow, Division of Fertility & Endocrine, Department Obstetrics and Gynecology.

2000 - 2002 — "Analysis of Meiotic Pairing in Subtelomeric Regions"
Thesis for Heather Christy Medford - MD, PhD Program
University of Washington School of Medicine.

2003 – 2004 — “Robertsonian Translocation Formation in Human Meiosis”
Resident research project for Santosh Pandipati, MD
Department of Obstetrics and Gynecology
University of Washington

2003 - 2004 — “The Effect of Maternal Cystic Fibrosis on Pregnancy”
Cara Debley, MD – Senior Fellow, Division of Gastroenterology
Department of Internal Medicine, University of Washington

2005 - 2007 — “Meiotic Recombination Patterns in Chromosomally Abnormal Fetal Oocytes”
Danielle Di Perna, MD – Fellow, Medical Genetics
Department of Internal Medicine, University of Washington

NATIONAL RESPONSIBILITIES

American Society of Human Genetics Annual Meeting — 2005
Prenatal Genetics Program Selection Subcommittee and Program Moderator

American Society of Human Genetics Annual Meeting — 2000
Prenatal Genetics Program Selection Subcommittee and Program Moderator

Judge for Society for Maternal-Fetal Medicine Oral Presentations — 2003
SMFM 23rd Annual Meeting, San Francisco, CA

Course Chairperson - Postgraduate Course in Genetics 2001
SMFM 21st Annual Meeting, Reno, Nevada.

LOCAL RESPONSIBILITIES

Royalty Research Fund Health Sciences and Medicine Selection Subcommittee 2001 – 2003
University of Washington

Symposium on Perinatal Genetics: New Directions in Perinatal Genetics September 2005
Program Coordinator and Course Chairman
University of Washington, Seattle, WA

Medical Genetics Fellowship/Residency, University of Washington 2005 – ongoing
steering committee on curriculum and program

ESCRO (University of Washington **E**mbryonic **S**tem **C**ell **R**esearch 2007 – present
Oversight Committee) and subcommittee on Determination of
Stem Cell Provenance

Prenatal Diagnosis: Outcomes and Transitions to Pediatric Care 2008
Seattle Children's Hospital, Program committee member, presented

University of Washington Physicians (UWP) 2007 – 2010
Trustee at Large

University of Washington Medical Center Ambulatory 2009 – present
Clinical Performance Council

University of Washington Medical Center Inpatient 2010 – present
Clinical Performance Council

RESEARCH FUNDING

Public Health Service, National Institutes of Health; A Program of Research in Population Cytogenetics; NICHD R01 HD21341; $500,000/year; PI: Terry Hassold, PhD, subcontract to Dr. Cheng $180,000/year; 09/01/05 – 09/30/10.

Public Health Service, National Institutes of Health; Chromosome Pairing and Nondisjunction in Human Meiosis; NICHD 1R29 HD33033-01A1; $70,000/year; Principal Investigator; 40% time; 03/01/96 - 02/28/03.

University of Washington, Royalty Research Fund; Nondisjunction in Human Oocytes; $15,000; Principal Investigator; 07/01/95 - 06/30/96.

Public Health Service, Maternal and Child Health: Innovative Approaches to Educating Clients and Providers for Effective Long-term Health Care of Metabolic Disorders; .5 FTE; 10/01/95 - 09/30/98; $915,000 (total).

March of Dimes Birth Defects Foundation: An Analysis of Nondisjunction in Human Oocytes. PI: E. Cheng; 04/01/1993 – 03/31/1997.

BIBLIOGRAPHY

Journals

1. Fisher NL, Luthy DA, Peterson A, Karp LE, Williamson R, **Cheng E**. Prenatal diagnosis of neural tube defects: Predictive value of AF-AFP in low risk population. Am J Med Genet 1981;9(3):201-9.

2. Luthy DA, Mack L, Hirsch J, **Cheng E**. Prenatal ultrasound diagnosis of thrombocytopenia with absent radii. Am J Obstet Gynecol 1981 Oct 1;141(3):350-1.

3. Jung JH, Luthy DA, Hirsch JH, **Cheng EY**. Serial ultrasound of a pregnancy at risk for infantile polycystic kidney disease (IPKD). Birth Defects Orig Artic Ser 1982;18(3 Pt A):173-179.

4. Murray JC, Karp LE, Williamson RA, **Cheng EY**, Luthy DA. Rh isoimmunization related to amniocentesis. Am J Med Genet 1983 Dec;16(4):527-34.

5. Ashwood ER, **Cheng E**, Luthy DA. Maternal serum alpha-fetoprotein and fetal trisomy-21 in women 35 years and older: Implications for alpha-fetoprotein screening programs. Am J Med Genet 1987 Mar;26(3):531-9.

6**.** **Cheng EY**, Luthy DA, Hickok DE, Hollenbach KA, Resta RG, Mahony BS, Luthardt FW. Transcervical chorionic villus sampling and midtrimester oligohydramnios. Am J Obstet Gynecol. 1991 Oct;165(4 Pt 1):1063-8.

7**.** **Cheng EY**, Luthy DA, Zebelman AM, Williams MA, Lieppman RE, Hickok DE. A prospective evaluation of a second-trimester screening test for fetal Down syndrome utilizing maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. Obstet Gynecol 1993 Jan;81(1):72-7.

8. Lieppman RE, Williams MA, **Cheng EY**, Resta R, Zingheim R, Hickok DE, Luthy DA. An association between elevated levels of human chorionic gonadotropin in the midtrimester and adverse pregnancy outcome. Am J Obstet Gynecol 1993 Jun;168(6 Pt 1):1852-6.

9. **Cheng EY** and Gartler SM. A fluorescent *in situ* hybridization analysis of X chromosome pairing in early human female meiosis. Hum Genet 1994 Oct;94(4):389-94.

10. Gill P, Uhrich S, Disteche C, **Cheng E**. Fetal t(5p;21q) misdiagnosed as monosomy 21: a plea for *in situ* hybridization studies. Am J Med Genet 1994 Oct 1;52(4):416-8.

11. Nyberg DA, Luthy DA, **Cheng, EY**, Sheley RC, Resta RG, Williams MA. Role of prenatal ultrasonography in women with positive screen for Down Syndrome on the basis of maternal serum markers. Am J Obstet Gynecol. 1995 Oct;173(4):1030-5.

12. **Cheng EY**, Chen YJ, Gartler SM. Chromosome painting analysis of early oogenesis in human trisomy 18. Cytogenet Cell Genet 1995;70(3-4):205-10.

13. **Cheng EY**, Luthy DA, Dunne DF, Luthardt FW, Disteche CM. Is the 15-*in situ* clone protocol necessary to detect amniotic fluid mosaicism? Am J Obstet Gynecol. 1995 Oct;173(4):1025-1030.

14. **Cheng EY**, Chen YJ, Bonnet G, Gartler SM. An analysis of meiotic pairing in trisomy 21 oocytes using fluorescent *in situ* hybridization. Cytogenet Cell Genet 1998;80(1-4):48-53.

15. Winter TC, Reichman JA, Luna JA, **Cheng EY,** Doll AM, Komarniski CA, Ngheim HV, Schmiedl UP, Shields LE, Uhrich SB. Frontal lobe shortening in second-trimester fetuses with trisomy 21: usefulness as a US marker. Radiology 1998 Apr;207(1):215-22.

16. Marcus S, **Cheng E**, Goff B. Extrauterine pregnancy resulting from early uterine rupture. Obstet Gynecol 1999 Nov;94(5 Pt 2):804-5.

17. **Cheng EY**, Chen YJ, Disteche CM, Gartler SM. Analysis of a paracentric inversion in human oocytes: nonhomologous pairing in pachytene. Hum Genet 1999 Sep;105(3):191-6.

18. Winter TC, Anderson AM, **Cheng EY,** Komarniski CA, Souter VL, Uhrich SB, Nyberg DA. Echogenic intracardiac focus in 2nd-trimester fetuses with trisomy 21: usefulness as a US marker. Radiology 2000 Aug;216(2):450-6.

19. Tait J, Gibson RL, Marshall SG, **Cheng E**, Sternen DL, Cutting GR. Cystic Fibrosis (March 2001, revision 2004) In: GeneClinics: Clinical Genetic Information Resource [database online]. Copyright, University of Washington, Seattle. Available at http://www.geneclinics.org.

20. Cubert R, **Cheng EY**, Mack S, Pepin MG, Byers PH. Osteogenesis imperfecta: mode of delivery and neonatal outcome. Obstet Gynecol 2001 Jan;97(1):66-9.

21. Bennett RL, Motulsky AG, Bittles A, Hudgins L, Uhrich S, Doyle DL, Silvey K, Scott CR, **Cheng E**, McGilvray B, Steiner RD, Olson D. Genetic counseling and screening of consanguineous couples and their offspring: recommendations of the National Society of Genetic Counselors. J Genet Couns 2002 Apr;11(2):97-119.

22. **Cheng EY,** Naluai-Cecchini T. FISHing for acrocentric associations between chromosomes 14 and 21 in human oogenesis. Am J Obstet Gynecol 2004 Jun;190(6):1781-5; discussion 1785–7.

23. Vallente RU, **Cheng EY,** Hassold TJ. The synaptonemal complex and meiotic recombination in humans: new approaches to old questions. Chromosoma 2006 Jun;115(3):241-9.

24. **Cheng EY,** Goss CH, McKone EF, Galic V, Debley CK, Tonelli MR, Aitken ML. Aggressive prenatal care results in successful fetal outcomes in CF women. J Cyst Fibros 2006 May;5(2):85-91.

25. Dighe M, Fligner C, **Cheng E,** Warren B, Dubinsky T. Fetal skeletal dysplasia: an approach to diagnosis with illustrative cases. Radiographics 2008 Jul-Aug;28(4):1061-77.

26. Moskowitz SM, Chmiel JF, Sternen DL, **Cheng E**, Gibson RL, Marshall SG, Cutting GR. Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders. Genet Med 2008 Dec;10(12): 851-68.

27. Dighe M, **Cheng E**, Dubinsky T. Ultrasound manifestations of unusual trisomies - excluding trisomy 13, 18, and 21: a literature review. Ultrasound Q 2009 Mar;25(1):15-24.

28. Houmard B, Small C, Yang L, Naluai-Cecchini T, **Cheng E**, Hassold T, Griswold M. Global gene expression in the human fetal testis and ovary. Biol Reprod 2009 Aug; 81(2):438-43.

30. **Cheng EY**, Hunt PA, Naluai-Cecchini TA, Fligner CL, Fugimoto VY, Pasternack TL, Schwartz JM, Steinauer JE, Woodruff TJ, Cherry SM, Hansen TA, Vallente RU, Broman KW, Hassold TJ. Meiotic recombination in human oocytes. PLoS Genet 2009 Sep;5(9):31000661.

31. Namavar Y, Barth PG, Kasher PR, van Ruissen F, Brockmann K, Bernert G, Writzl K, Ventura K, **Cheng EY**, et al. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. Brain 2011 Jan;134(Pt 1):143-56.

32. Dighe MK, Peterson SE, Dubinsky TJ, Perkins J, **Cheng E**. EXIT procedure: technique and indications with prenatal imaging parameters for assessment of airway patency. Radiographics 2011 Mar-Apr;31(2):511-26.

32. Adam MP, Fechner PY, Ramsdell LA, Badaru A, Grady RE, Pagon RA, McCauley E, **Cheng EY**, Parisi MA, Shnorhavorian M. Ambiguous genitalia: what prenatal genetic testing is practical? Am J Med Genet A 2012 Jun;158A(6);1337-43.

33. Tabor HK, Murray JC, Gammill HS, Kitzman JO, Snyder MW, Ventrua M, Lewis AP, Qui R, Simmons LE, Rubens CE, Santillan MK, Eichler EE, **Cheng EY**, Bamshad MJ, Shendure J. Non-invasive fetal genome sequencing: opportunities and challenges. Am J Med Genet A 2012 Oct;158A(10);2382-4.

34. Rowsey R, Kashevarova A, Murdoch B, Dickenson C, Woodruff T, **Cheng E**, Hunt P, Hassold T. Germline mosaicsim does not explain the maternal age effect on trisomy. Am J Med Genet A 2013 Oct;161A(10): 2495-503.

34. Mitchell T, **Cheng E**, Jolley J, Delaney S. Successful induction of labor of late-second-trimester conjoined twins: an alternative to hysterotomy. Obstet Gynecol 2014 Feb;123(2 Pt 2 Suppl 2):469-72.

35. Dy GW, Willihnganz-Lawson K, Shnorhavorian M, Delaney SS, Amies Oelschlager AM, Merguerian PA, Grady R, Miller JL, **Cheng EY**. Successful pregnancy in patients with exstrophy-epispadias complex: a University of Washington experience. J Pediatr Urol 2015 Aug;11(4):213.e1-6.

36. Neufeld-Kaiser W, **Cheng E**, Liu Y. Positive predictive value of non-invasive prenatal screening for fetal chromosome disorders using cell-free DNA in maternal serum: independent clinical experience of a tertiary referral center. BMC Med 2015 Jun 2;13:129.

Book Chapters

1. Cheng E and Katz V. Reproductive Genetics. Comprehensive Gynecology, 5th edition. Stenchever MA, Droegemueller W, Herbst AL, Mishell D. Mosby, 2006.

2. Cheng E and Katz V. Reproductive Genetics. Comprehensive Gynecology, 6th edition. Lentz GM, Lobo RA, Gershenson DM, Katz L. Elsevier Mosby, 2012.

3. Cheng E. Prenatal diagnosis: noninvasive screening. Advances in Obstetric Ultrasound. Vol 6 January 2011. Editors Theodore Dubinsky MD and Manjire Dighe MD.

4. Cheng E. Complex deliveries in obstetrics. Advances in Obstetric Ultrasound. Vol 6 January 2001. Editors: Theodore Dubinsky MD and Manjire Dighe MD.

PRESENTED PAPERS

1. Fisher NL, Luthy DA, Peterson A, Karp LE, Williamson R, **Cheng EY**: Amniotic fluid AFP in a low risk population: Analysis of 1200 cases. National Birth Defects Conference, New York, July 1980.

2. Fisher NL, Luthy DA, Peterson A, Karp LE, Williamson R, **Cheng EY**: Prenatal diagnosis of neural tube defects: Predictive value of AF-AFP in a low risk population. Robert Wood Johnson Clinical Scholars Meeting, Arizona, November 1980.

3. Jung J, Luthy DA, Hirsch J, **Cheng EY**: Serial ultrasonography in a pregnancy at risk for infantile polycystic kidney disease. National Birth Defects Meeting, San Diego, June 1981.

4. Luthy DA, **Cheng EY**: Experience with the prenatal diagnosis of TAR syndrome. Society of Perinatal Obstetricians, San Antonio, 1982.

5. Luthy DA, Ashwood ER, **Cheng EY**: Low maternal serum alpha-fetoprotein and trisomy 21. Society of Perinatal Obstetricians, San Antonio, 1986.

6. **Cheng EY**, Luthy DA, Hickok DE, Hollenbach KA, Resta RG, Mahony BS: Transcervical chorionic villus sampling and midtrimester oligohydramnios. Society of Perinatal Obstetricians, San Francisco, 1991.

7. **Cheng EY**, Luthy DA, Hickok DE, Lieppman RE, Resta RG, Williams MA, Zebelman A, Luthardt R: A prospective evaluation of triple marker maternal serum screening for trisomy 21. Society of Perinatal Obstetricians, Orlando, FL, 1992.

8. **Cheng EY**, Gartler SM: Reduced pairing of alpha satellite regions in human female meiosis. American Society of Human Genetics, San Francisco, 1992.

9. Esplin J, Greenspoon JS, **Cheng EY**, Perkins C, Westman JA, Grabowski GA: A gluecerase infusions in pregnant type l Gaucher patients. American Society of Hematology, December 3-7, 1993.

10. **Cheng EY** and Gartler SM: A fluorescent *in situ* hybridization analysis of X chromosome pairing in human female meiosis. National Down Syndrome Society-International Research Conference, Charleston, NC, 1994.

11. **Cheng EY**, Chen YJ, Gartler SM: A fluorescent *in situ* hybridization analysis of human oocytes in trisomy 18 and 21. American Society of Human Genetics, Montreal, Canada, October 1994.

12. **Cheng EY**, Chen YJ, Gartler SM: A cytological evaluation of the production line hypothesis in human oogenesis using chromosome painting. American Society of Human Genetics, Minneapolis, October 1995.

13. **Cheng EY**, Gartler SM, Storck K: Evidence for interchromosomal effects on pairing in female meiosis. American Society of Human Genetics, San Francisco, October 1996.

14. **Cheng EY**, Cubert R, Mack S, Pepin MG, Byers PH: Osteogenesis imperfecta: Mode of delivery and neonatal outcome. American Society of Human Genetics. San Francisco, CA, October 1999.

15. Lee D, **Cheng E,** Soules MR, Battaglia DE: Cryopreservation of human fetal ovarian tissue: Assessment of chromosomal damage using fluorescent in situ hybridization. Society for Gynecological Investigations, Chicago, IL. **Recipient of President's Award**. March 2000.

16. Bennett R, Motulsky A, Bittles A, Hudgins L, Uhrich S, Locher-Doyle D, Sylvie K, Scott CR, **Cheng E**, McGilvray B, Steiner R, Olson D: Genetic counseling and screening of consanguineous couples and their offspring: Recommendations of the National Society of Genetic Counselors. Presented at the American Society of Human Genetics. Philadelphia, PA. October 2000.

17. Pandipati S, Naluai-Cecchini T, **Cheng EY**: Acrocentric chromosomal associations on fetal oocytes. University of Washington, Dept. Ob/Gyn Senior Resident Research Presentation, April 2004.

18. **Cheng EY**, Galic V, Goss, CH, Debley CK, Aitken ML: The effect of maternal cystic fibrosis on pregnancy – 16 year experience at a single center. Society for Maternal Fetal Medicine, Reno, Nevada, February 2005 (abstract 317 in Am J OB/GYN 191(6):S94, December 2004).

19. Leppig K, Distech C, **Cheng E:** Intrachromosomal inverted insertions: a case report of a rare cytogenetic finding. 26th David W. Smith Workshop on Dysmorphology and Morphogenesis, Iowa City, Iowa, August 2005.

20. **Cheng EY,** Vallente R, de Perna D, Naluai-Cecchini T, Hassold T: Direct analysis of meiotic recombination in the human female. 55th Annual Meeting, American Society of Human Genetics, Salt Lake City, Utah, October 2005.

21. Robilio P, Galic V, Holing E, Aitken M, **Cheng E**: Glucose Profiles of Pregnant Cystic Fibrosis Patients with Diabetes. 27th Annual Meeting, Society of Maternal-Fetal Medicine, San Francisco, CA, February 2007.

22. **Cheng EY,** Vallente R, DiPerna D, Cherry S, Hansen T, Naluai-Cecchini T, Hassold T: Direct analysis of meiotic recombination in normal and trisomy 18 oocytes. 27th Annual Meeting, Society of Maternal-Fetal Medicine, San Francisco, CA, February 2007.

23. Hassold T, Naluai-Cecchini T, Cherry S, Hansen T, **Cheng E**: Cytogenetic studies of Meiotic recombination in human females. 41ST Annual Meeting, Society for the Study of Reproduction, Kailua-Kona, HI, May 2008.

24. Small C, Houmard B, **Cheng E**, Yang L, Griswold, M: Man or Mouse? A Comparison of global gene expression in the human and murine embryonic gonad. 41ST Annual Meeting, Society for the Study of Reproduction, Kailua-Kona, HI, May 2008.

25. Goiney C, Shurtleff D, Duguay S, Doherty D, **Cheng E**, Naluai-Cecchini T: Prenatal counseling for myelomeningocele: Prognoses, decisions, and outcomes. 52nd Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida, Providence, RI, June 2008. Abstract published in Cerebrospinal Fluid Research 2009, 6(Suppl 1);S11.

26. Hassold T, Naluai-Cecchini T, Cherry S, Hansen T, Broman K, **Cheng E**: Cytogenetic studies of meiotic recombination in human females. 58TH Annual Meeting, American Society of Human Genetics, Philadelphia, Pennsylvania, November 2008.

27. Kashevarova A, Hansen T, Hassold T, Naluai-Cecchini T, **Cheng E**: Synapsis and recombination in a 69,XXX fetus: implications for normal female meiosis. 58TH Annual Meeting, American Society of Human Genetics, Philadelphia, Pennsylvania, November 2008.

28. Bollag L, Kent C, Failor E, **Cheng E**, Landau R: Management of labor analgesia and CS anesthesia in a parturient with spinal muscular atrophy II and harrington rods. 41st Annual Meeting, Society of Obstetric Anesthesia and Perinatology, Washington D.C., April 2009.

29. Shah K, Cheng EY. The value of array comparative genomic hybridization in identifying genomic imbalances with congenital diaphragmatic hernia. 16th International Conference on Prenatal Diagnosis and Therapy, Miami, Florida, June 2012.

INVITED PRESENTATIONS

1. A study of human meiosis using FISH: New insights in human biology. Invited speaker at the American Association of the Advancement of Science. Seattle, WA. February 1997.

2. When amnio results are bad: Helping patients make tough decisions. Public Health Seminar - Reproductive Issues in Women. Seattle, WA. September 1997.

3. Cubert R, Mack S, Pepin MG, Byers PH. Osteogenesis imperfecta: Mode of delivery and neonatal outcome. Invited speaker at the 7th International Conference on Osteogenesis Imperfecta. Montreal, Canada. September 1999.

4. Update on prenatal diagnosis. Institute for Public Health Genetics Seminar Series. University of Washington. Seattle, WA. November 2000.

5. Primary prevention or eugenics? Learning to live with the Human Genome: Reasoned prudence or future shock. Washington State Department of Health. Tacoma, WA. January 2001.

6. Thrombophilia diseases in reproduction. Controversies and Clinical Issues in Maternal Fetal Medicine. Seattle, WA. April 2001.

7. Genetics in the 21st Century: Personalizing your genes. Controversies and Clinical Issues in Maternal Fetal Medicine. Seattle, WA. April 2001.

8. Prenatal Diagnosis. Ethics in the science classroom. Washington Association for Biomedical Research. Eatonville, WA. July 2001.

8. Reproductive issues in Marfans Syndrome. National Marfan Foundation Annual Conference. Seattle, WA. August 2001.

9. Cystic Fibrosis for the obstetrician/gynecologist: more than screening. Grand Rounds, University of Washington, Obstetrics and Gynecology, April 2, 2003.

10. Genetics and women's health. GIFT (Genetics in Faculty Teaching) Program speaker. School of Nursing, Oregon Health Sciences University, January 2004.

11. Viewing human oogenesis through FISH. Grand Rounds, Department of Obstetrics and Gynecology, Oregon Health Sciences University, January 2004.

12. Prenatal screening. OB Update 2004, Group Health Cooperative (CME course), Seattle, Washington, November 3, 2004.

13. Aneuploidy and Oocyte Genetics. American Association of Bioanalysts, 50th Anniversary Conference, Las Vegas, June, 2006.

14. Prenatal Risk Assessment – State of the Art. Department of Laboratory Medicine, University of Washington, Grand Rounds, October 3, 2007.

15. History of Prenatal Diagnosis, Technology Advances, and Current Practice. Prenatal Diagnosis: Outcomes and Transition to Pediatric Care, 1st annual symposium, sponsored by Seattle Children's Hospital, speaker and program committee.

16. New faces in women's health care: medical successes in critically ill young women. Women's Healthcare Update. University of Washington School of Medicine CME. March, 2008.

17. New faces in women's health care: challenges in pregnancies of women complex medical problems. Achieving Clinical Excellence in Perinatology. Evergreen Healthcare CME. Seattle, WA April 2009.

18. Application of Non-Invasive Prenatal Testing (NIPT): A Moving Target. Grand Rounds, Northwest Hospital and Medical Center, Seattle, WA. October 16, 2015.

OTHER

Sally Ride Women in Science Profile Stanford University, First Edition	2005
Seattle Best Doctors	2005, 2006, 2007, 2008 2009, 2010, 2011
Fertility Information for Females with Cystic Fibrosis: Adult Nutrition and Fertility Issues for People with Cystic Fibrosis, Cystic Fibrosis Foundation Webcast	February 2009

Order of scheduled presentations:

Cell-free DNA prenatal screening for chromosomal aneuploidies

	Name
1	Daniel S. Grosu, MD

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.	X	
3.	Status or position as an officer, board member, trustee, owner.	X	
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Genopraxis, LLC for #1, 2, 3, and 6 (travel arrangements)

LabCorp, Inc. for #1 and 6 (travel arrangements)

Coalition for Access to Prenatal Screening (CAPS) for #1, 3 and 6 (travel arrangements)

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources:

Representing the Coalition for Access to Prenatal Screening (CAPS), which is funded by industry sources (diagnostic companies offering cfDNA based non-invasive prenatal testing).

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 12/27/2019 Daniel S. Grosu, M.D.

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: dgrosu@genopraxis.com

Phone Number: 732.322.2813

Agency medical director comments

Cell-free DNA Prenatal Screening for Chromosomal Aneuploidies

Shana Johnson, MD
Clinical Quality - Care Transformation
Health Care Authority

January 17, 2020

Prenatal Screening: Key Questions

1. What is the evidence of efficacy of using cfDNA in **pregnant individuals not known to be at high risk** for chromosomal abnormalities?
2. What harms are associated with screening using cfDNA?
3. Do important outcomes vary by characteristics (i.e. age)?
4. What is the cost-effectiveness of using cfDNA in pregnant individuals not at high risk for aneuploidy?

2

Policy Question

Whether cfDNA should be covered for:

- General obstetric population (low risk for chromosomal abnormalities), or
- Limited to population at increased risk of aneuploidy (those with higher prevalence)

3

Current State Agency Policy: cfDNA

Agency	Status
PEBB/UMP	General obstetric population
Medicaid	High risk of aneuploidy

4

Washington State Health Care Authority

Other Insurer's Coverage Policies

Agency	Status
CMS (Centers for Medicare & Medicaid Services)	No national or local coverage decisions
Aetna	High risk aneuploidy
Regence, Cigna	General obstetric population

5

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Screening Testing

Prenatal genetic screening assesses whether a woman is at increased risk of carrying a fetus with aneuploidy

Diagnostic Testing

Determines if the condition is present in the fetus (i.e. amniocentesis).

6

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Screening Tests

- A test to a population which has no overt signs or symptoms of the disease in question, to **detect disease at a stage when treatment is more effective**.
- Used to identify people who require further investigation to determine the presence or absence of disease and is not primarily a diagnostic test.
- The potential benefits of an organized population screening program must outweigh any potential harms that may result in the use of a screening test in people who are otherwise well and there must be strong evidence that a screening program is effective.
- The cost of screening should be economically balanced in relation to possible expenditures on medical care; the implementation of a screening program is influenced by the distribution of limited resources across the whole population for maximum benefit.

Washington State Health Care Authority

A Good Screening Test

1. Test performance-Accurate
   - Sensitive—does not miss cases
   - Specific—does not lead to false positive results and unnecessary testing
2. Leads to improved health outcomes
3. Cost-effective

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Test Performance Metrics

- **Sensitivity (or detection rate):**
  Probability that a test result will be positive when the disease is present (true positive rate)[5]
- **Specificity (or true-negative rate):**
  Probability that a test result will be negative when the disease is not present (true negative **rate)**[5]
- **Positive predictive value (PPV)**:
  Probability that the disease is present when the test is positive[5]
- **Negative predictive value (NPV)**:
  Probability that the disease is not present when the test is negative[5]

- The **predictive value** is determined by the sensitivity and the specificity of the test and the **prevalence** of the condition.
- **Low prevalence conditions will lower the predictive value of the test.**

9

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Screening Tests

Minimize the problem by **concentrating screening efforts on people with a higher prevalence** of condition

The PPV of many screening tests is low due to low prevalence or low test specificity → **results in positive screening but no condition (false positives)**

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Example: Breast Cancer Screening

Breast cancer screening--finding cancer after an abnormal mammogram, varied according to the age of the women

- For women age 40 yrs, about 57 women without cancer experienced further workup for every woman who was found to have a malignancy with a **positive predictive value of 1.7%**
- For women age 80 yrs, the number dropped to about 10, with a **positive predictive value of 9.5%**

Carney PA, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med. 2003;138(3):168.

11

Evidence Summary: cfDNA v.s. Conventional Screening

1. Both tests have good NPV -- rule out disorder when not present (moderate quality evidence)
2. CfDNA has higher PPV (very low quality evidence) and less unnecessary procedures (moderate quality evidence)
3. PPV lower in low risk due to lower prevalence; PPV higher in those at high risk due to higher prevalence of the condition;
4. Cost-effectiveness study results varied from less costly to more costly and were sensitive to multiple inputs

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Cell-free DNA Screening

Table 8. Positive and Negative Predictive Values of cfDNA for T21, T18, and T13

Study ID	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Bianchi et al., 2014[11]	40.0% (27.5%-54.0%)	100%
del Mar Gil et al., 2014[12]	100%	99.5% (96.5%-99.9%)
Langlois et al., 2017[13]	75.0% (42.9%-92.3%)	100%
Nicolaides et al., 2012[14]Ashoor et al., 2013[10]	85.7% (65.7%-94.9%)	99.9% (99.6%-99.97%)
Palomaki et al., 2017[16,93]	75.0% (53.0%-88.8%)	100%
Pergament et al., 2014[17]	100%	100%
Quezada et al., 2015[18]	84.3% (72.8%-91.5%)	99.9% (99.6%-99.9%)

Abbreviation. cfDNA: cell-free DNA; CI: confidence interval; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21.

#1 Both tests have good NPV – rule out disorder when not present

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Standard Screening

Table 9. Positive and Negative Predictive Values of Standard Screening

Study ID	Condition	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Bianchi et al., 2014[11]	T21	4.2% (3.3%-5.2%)	100%
	T18	8.3% (4.8%-14.1%)	100%
	T13	14.3% (7.0%-27.0%)	100%
Langlois et al., 2017[13]	T21	7.4% (4.9%-10.9%)	99.91 % (99.46%-99.98%)
	T18	No cases of T18 occurred	100%
Norton et al., 2015[15]	T21	3.4% (2.9%-4.0%)	99.95 % (99.90%-99.97%)
	T18	14.0% (9.7%-19.9%)	99.99% (99.96%-100%)
	T13	3.5% (0.84%-13.0%)	99.99 % (99.96%-100%)
Quezada et al., 2015[18]	All trisomies (T21, T18 and T13)	28.3% (25.0%-31.9%)	100%

Abbreviations. CI: confidence interval; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21.

#1 Both tests have good NPV — rule out disorder when not present.

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Test Performance: T21, T18, T13

Six of 1,000 pregnancies would be expected to be affected

cfDNA screening

- Up to **6 of 1000** unaffected undergo unnecessary invasive testing (moderate quality evidence)
- **Median PPV for cfDNA was 79.7% (range 40%-100%)** (very-low-quality evidence from 6 studies)

Conventional screening

- Up to **44 in 1000** unaffected undergo unnecessary invasive testing (moderate quality evidence)
- **PPV 28% (95%CI, 25%-31.9%)** for conventional screening (moderate quality evidence from 1 study)

#2 CfDNA has a higher PPV; less unnecessary procedures

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Test Performance - Prevalence

Table 2. Test Performance for Trisomy 21 in the Primary Analysis Cohort, According to Maternal Age and Risk.*

Variable	Standard Screening	Cell-free DNA Testing		
	All Patients (N = 15,841)	All Patients (N = 15,841)	Maternal Age <35 Yr (N = 11,994)	Low Risk (N = 14,957)†
True positive — no.	30	38	19	8
True negative — no.	14,949	15,794	11,969	14,941
False positive — no.	854	9	6	8
False negative — no.	8	0	0	0
Sensitivity (95% CI) — %	78.9 (62.7–90.4)	100 (90.7–100)‡	100 (82.4–100)	100 (63.1–100)
Specificity (95% CI) — %	94.6 (94.2–94.9)	99.9 (99.9–100)§	99.9 (99.9–100)	99.9 (99.9–100)
Positive predictive value (95% CI) — %	3.4 (2.3–4.8)	80.9 (66.7–90.9)‖	76.0 (54.9–90.6)	50.0 (24.7–75.3)
Negative predictive value (95% CI) — %	99.9 (99.9–100)	100 (99.9–100)¶	100 (99.9–100)	100 (99.9–100)
Positive likelihood ratio	14.6	1755.9	1995.8	1868.6
Negative likelihood ratio	0.22	0	0	0

* P values are for the comparison between standard screening and cell-free DNA screening in the primary analysis cohort.

#3 PPV lower in the low risk group due to lower prevalence.

Norton ME. Cell-free DNA Analysis for Noninvasive Examination of Trisomy. The New England Journal of Medicine. 4-1-2015 at NEJM.org

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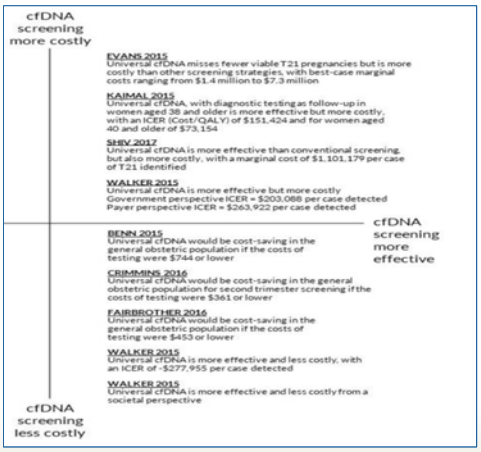
#4 Cost-effectiveness Studies: varies from less to more costly



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Cost-Effectiveness: Sensitivity Analyses

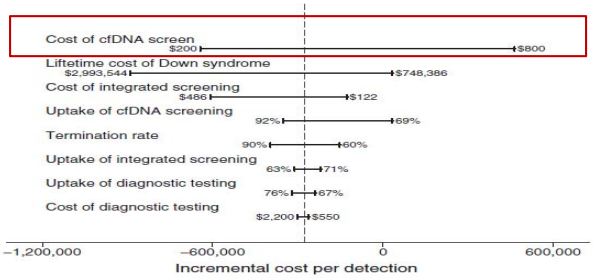

Figure 1 One-way sensitivity analyses on incremental cost-effectiveness ratio (ICER) for cell free DNA (cfDNA) versus integrated (baseline scenario). The figure shows the results of one-way sensitivity analyses on the ICER of the cfDNA versus the integrated screen. ICER is defined as (cost of cfDNA − cost of integrated)/(cases detected by cfDNA − cases detected by integrated). The dotted line represents the ICER using the baseline model parameters

Walker BS, Jackson BR, LaGrave D, Ashwood ER, Schmidt RL. A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome. Prenat Diagn. 2015;35(5):440-446.

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ICER dependent on the perspective

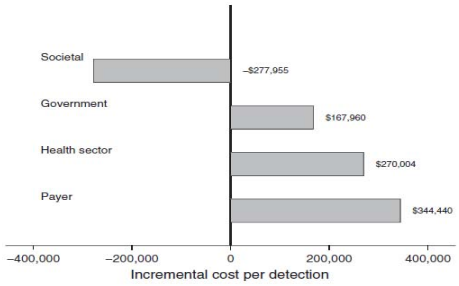

Figure 3 Incremental cost-effectiveness ratios by perspective. Cell free DNA screening is less costly than integrated screening from a societal perspective but is more costly than integrated screening when a narrower perspective is taken

Walker BS, Jackson BR, LaGrave D, Ashwood ER, Schmidt RL. A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome. Prenat Diagn. 2015;35(5):440-446.

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Costs

Medicaid FFS Rates

- **Conventional screening**
  - Triple screen ~$70
  - Quad screen ~$80
  - Ultrasound 1st NT ~$72
- **CfDNA tests**
  - 81420 ~$715

Amniocentesis

- **Diagnostic amniocentesis**
  - 59000 ($79-$122)

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Good Screening Test

- Accurate
- Leads to improved health outcomes
- Economic considerations; distribution of limited resources
- Balance screening efforts with condition prevalence (Lower prevalence, lower PPV)

Evidence Summary

- Both tests have good NPV to rule out disorder
- CfDNA has higher PPV & less unnecessary procedures
- Cost-effectiveness study results vary between more and less costly (per unit cfdna up to 10x cost)
- Cost analyses sensitive to inputs and perspective

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Health System Perspective

Both tests have good negative predictive value

For ruling out aneuploidy

Lower predictive value:

Lower prevalence in low risk population
→ Target higher prevalence population

Distribution of limited resources:

Cost of cfDNA up to 10x standard screening

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AMDG Recommendations

- Cell-free DNA prenatal screening **is not covered** for those not known to be at high risk for chromosomal abnormalities
- Cell-free DNA **is covered** following a positive test on standard screening

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Questions?

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Coalition for Access to Prenatal Screening

Washington Health Technology Clinical Committee: Access to Cell-Free DNA Non-Invasive Prenatal Screening

January 17, 2020

Coalition for Access to Prenatal Screening

Introduction: Daniel Grosu, MD, MBA

- First Chief Medical Officer for Illumina, Inc.
- First Chief Medical Officer for Sequenom, Inc.
- Founder of GENOPRAXIS, LLC
- Senior Medical Advisor for Integrated Genetics (LabCorp)
- Member of Coalition for Access to Prenatal Screening Clinical Advisory Board

Education

- Saint Louis University School of Medicine
- University of Oxford Saïd Business School

Key Takeaways

Coalition for Access to Prenatal Screening

- Cell-free DNA-based noninvasive prenatal screening is **increasingly utilized** across all pregnancy risk groups. Since 2011, it has offered improved detection of fetal chromosomal abnormalities.
- cfDNA-based NIPS is extensively studied in the general population (15+ studies with 88,000+ patients) and shows a **very high PPV compared to traditional screening**, with equal or better NPV, for all major aneuploidies.
- NIPS provides better detection of Trisomy 21, 18, and 13. Its lower false positive rate, compared to traditional screening, **leads to fewer invasive follow up procedures and procedure-related losses.**
- **All major professional societies endorse** or recognize cfDNA-based NIPS as a clinically valid screening option for all pregnancies.
- There is a **clear disparity in access to NIPS coverage for many women enrolled in Washington Medicaid.** There should be a single standard of high-quality care for **all** pregnant women.

Choosing the Right Screening Test

Coalition for Access to Prenatal Screening

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)

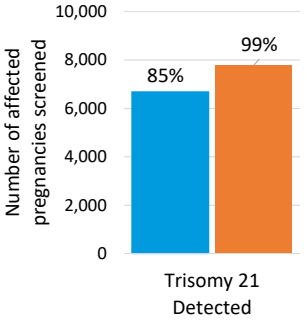
Goal: Provide patients a screening option with a high sensitivity/specificity; ensure all patients have equal access, i.e. one standard of care for all

Clinical Value of NIPS

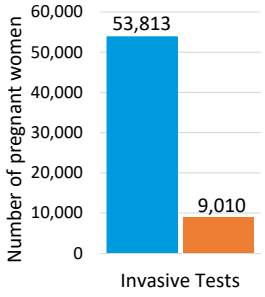
Coalition for Access to Prenatal Screening

Why is NIPS better than conventional screening in the general obstetric population?

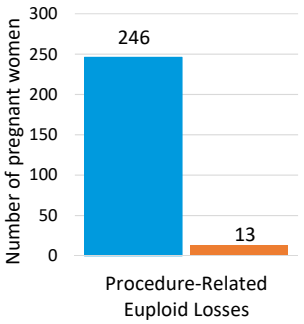
Better detection



Fewer false positives -> Fewer invasive procedures



Fewer procedure related losses



Conventional Screening **NIPS**

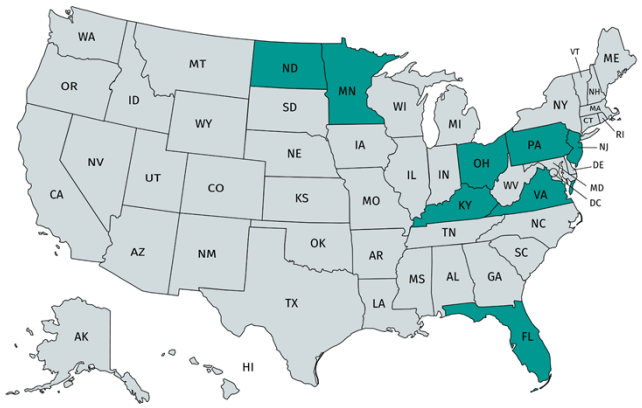
Source: Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. *PLoS One.* 2015;10(7):e0132313.

5

Medicaid Programs with NIPS Coverage Regardless of Risk

Coalition for Access to Prenatal Screening

- Florida
- Kentucky
- Minnesota
- New Jersey
- North Dakota
- Ohio
- Pennsylvania
- Virginia



WA Medicaid Policy

Coalition for Access to Prenatal Screening

Our request: Streamline criteria to read: *"The agency considers cell-free DNA-based prenatal screening for fetal aneuploidy (also known as NIPT or NIPS) to be medically necessary in women with singleton pregnancies, who have had genetic counseling."*

Physician-Related Services/Health Care Professional Services

EPA Code 87000-	Service Name	CPT/HCPCS/ Dx	Criteria
1342	Alloderm	**CPT code:** Q4116	All of the following must be met: • It is medically necessary • The client has a diagnosis of breast cancer • The servicing provider is either a general surgeon or a plastic surgeon
1344	Noninvasive prenatal diagnosis of fetal aneuploidy (NIPT)	**CPT code:** 81507 and 81420	The agency considers NIPT for serum marker screening for fetal aneuploidy to be medically necessary in women with high-risk singleton pregnancies, who have had genetic counseling, when one or more of the following are met: • Pregnant woman is age 35 years or older at the time of delivery • History of a prior pregnancy with a trisomy or aneuploidy • Family history of aneuploidy (first degree relatives or multiple generations affected) • Positive first or second trimester standard biomarker screening test for aneuploidy, including sequential, or integrated screen, or a positive quadruple screen • Parental balanced Robertsonian translocation with increased risk for fetal T13 or T21 • Findings indicating an increased risk of aneuploidy

WA Commercial Coverage

Coalition for Access to Prenatal Screening

Covers NIPS for all women in Washington

CAMBIA HEALTH SOLUTIONS

LifeWise

PREMERA BLUE CROSS

Regence
Idaho and select counties of Washington

8

Coalition for Access to Prenatal Screening

There is a clear disparity in access to prenatal screening for women enrolled on WA Medicaid

9

Cell-free DNA Prenatal Screening for Chromosomal Aneuploidies

Washington HTA Committee
January 17, 2020
Valerie J. King, MD, MPH, and Beth Shaw, BSc, MSc

Overview

- Background and policy context
- Methods and search results
- Summary findings and conclusions
- Questions
- Detailed results, as requested by the Committee

Image: Creative Commons license.
http://www.greenlivingpedia.org/images/9/93/Green_checklist.jpg

1

Background and Policy Context

Background

- Prenatal screening is a part of standard maternity care
- Prenatal genetic screening assesses whether a patient is at an increased risk of carrying a fetus affected by a genomic disorder
- Diagnostic testing determines, as definitively as possible, whether a specific genetic disorder or condition is present in the fetus

Image: Creative Commons license.
https://farm5.staticflickr.com/4132/5022568891_022c8fd55a_z.jpg

Source. Committee on Practice Bulletins-Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine. Practice Bulletin No. 163: screening for fetal aneuploidy. Obstet Gynecol. 2016;127(5):e123-137. doi: 10.1097/AOG.0000000000001406.

3

Background

- The results of maternal blood screens for fetal aneuploidy represent the level of risk that a disorder might be present
  - A positive screening test indicates the fetus is at higher risk than expected of having a disorder compared with the general population. It does not definitively diagnose a disorder
  - A negative screening test indicates the fetus is at lower risk than expected of having a disorder compared with the general population. It does not definitively rule out the possibility that the fetus has a disorder

Image: Creative Commons license. https://redoubtnews.com/wp-content/uploads/2016/07/yes-no-maybe.jpg

Source. Committee on Practice Bulletins-Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine. Practice Bulletin No. 163: screening for fetal aneuploidy. Obstet Gynecol. 2016;127(5):e123-137. doi: 10.1097/AOG.0000000000001406

4

Background

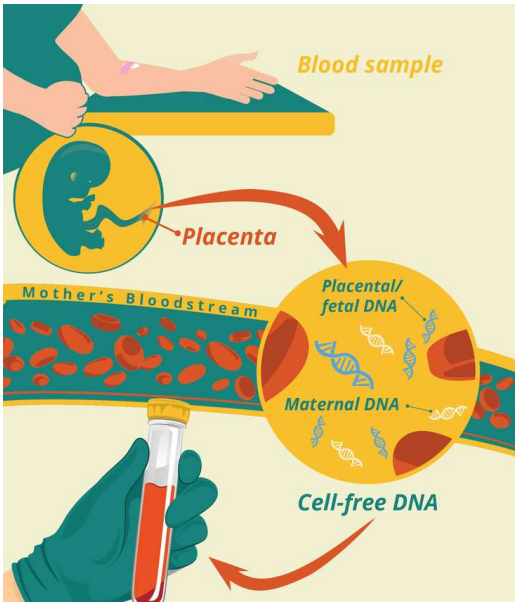
- Screening for aneuploidy involves identifying the risk of a fetus having an extra or missing copy of a chromosome
  - Down syndrome (T21, caused by an extra chromosome 21)
  - Edwards syndrome (T18, caused by an extra chromosome 18)
  - Patau syndrome (T13, caused by an extra chromosome 13)
  - Extra or missing copies of the X and Y chromosomes (sex chromosomes)
- Prevalence and impact vary by condition

Image: Creative Commons license. https://futurism.com/wp-content/uploads/2017/08/Conceptual-image-of-a-cell-karyotype-exhibiting-trisomy-three-copies-of-one-chromosome-1200x800.jpg

5

Background

- Cell-free DNA (cfDNA) screening is a type of noninvasive prenatal testing (NIPT) or screening (NIPS) used to determine the risk that a fetus has certain cytogenomic abnormalities
- cfDNA screening analyzes fragments of placental DNA present in maternal blood
- Noninvasive compared with traditional testing methods (amniocentesis or chorionic villus sampling)



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Sources. U.S. National Library of Medicine. Genetics home reference. What is noninvasive prenatal testing (NIPT) and what disorders can it screen for? 2019; https://ghr.nlm.nih.gov/primer/testing/nipt. Accessed June 17, 2019. Creative Commons license. Image from https://www.futurelearn.com/courses/making-babies/0/steps/14141.

Policy Context

- cfDNA screening covered by most commercial and public insurance plans for women known to be at higher than average risk for fetal aneuploidy
- Some insurance companies cover cfDNA screening for all pregnancies
- Clinical practice guideline recommendations vary
- Questions remain as to whether cfDNA screening should be used universally in the general obstetric population or for people with an increased risk of aneuploidy

Image credit: Fernando Zhiminaicela from Pixabay

7

Methods

Scope

Populations	Pregnant individuals with a singleton or multifetal pregnancy, **not known as being at high risk** for the target fetal conditions
Interventions	Screening for T21, T18, and T13 and for common SCAs using cfDNA
Comparators	• For trisomies: active screening approaches, including standard screening with serum biomarkers and ultrasound, screening with another cfDNA test, or question-based screening • For common SCAs: any active screening approach, screening with another cfDNA test, or no screening • Invasive diagnostic testing (e.g., amniocentesis)
Outcomes	• Primary outcomes: pregnancy outcomes; use of cfDNA results • Secondary outcomes: uptake of cfDNA screening; maternal/parental/family QoL • Safety: harms directly related to screening using cfDNA tests • Indirect outcomes: measures of cfDNA screening test performance • Economic: cost-effectiveness outcomes or cost-utility outcomes
Setting	Any outpatient or inpatient clinical setting in countries categorized as very high on the UN HDI

Abbreviations. cfDNA: cell-free DNA; HDI: Human Development Index; QoL: quality of life; SCA: sex chromosome aneuploidies; UN HDI: United Nations Human Development Index.

9

Key Questions

1. What is the efficacy and effectiveness of using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities?
2. What direct harms are associated with screening using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities?
3. Do important outcomes or harms vary by:
   a. Maternal characteristics (e.g., age)
   b. Singleton or multifetal pregnancy
   c. Timing of screening (e.g., gestational age)
4. What are the cost-effectiveness and other economic outcomes of screening using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities?

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Eligible Studies

- Key Questions 1–4
  - Randomized controlled trials
  - Systematic reviews of randomized controlled trials
  - Nonrandomized comparative studies
- Additional studies/data for Key Questions 2 and 3 (harms)
  - Nonrandomized studies without a comparator and with 10 or more participants
- Additional studies/data for Key Question 4
  - Cost-effectiveness studies and other formal comparative economic evaluations
  - Systematic reviews of cost-effectiveness studies and other formal comparative economic evaluations

11

Range of Evidence Sources

- Including
  - Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print
  - Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials)
  - NHS Economic Evaluation Database (EED) and the National Institute for Health Research (NIHR) Health Technology Assessment Program (HTA) database
  - Agency for Healthcare Research and Quality (AHRQ)
  - National Institute for Health and Care Excellence (NICE) – Evidence
  - Veterans Administration Evidence-based Synthesis Program
  - Guideline databases
  - Medicare Coverage Database
  - ClinicalTrials.gov, maintained by the National Library of Medicine at the National Institutes of Health

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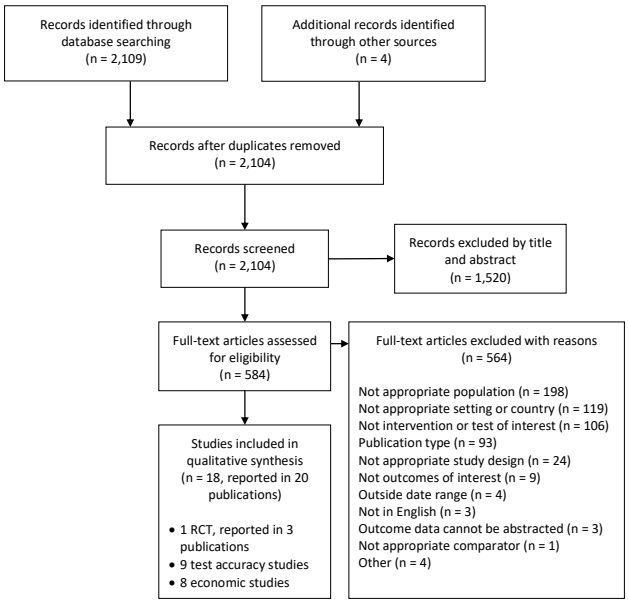
PRISMA Study Flow Diagram



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Overall Certainty of Evidence

- We assigned a summary judgment for the overall certainty of evidence for each key outcome

High	Very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect
Moderate	True effect is likely to be close to the estimate of the effect, but there is a possibility that it is different
Low	Little confidence in the estimate of the effect of the intervention on the outcome and the true effect may be substantially different from the estimate of the effect
Very Low	No confidence in the estimate of the effect of the intervention on the outcome and the true effect is likely to be substantially different from the estimate of effect

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GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

Common Diagnostic Test Accuracy Measures

Sensitivity (true positive [TP] rate)	• Probability that the screening test will be positive, given the fetus has aneuploidy (sometimes called the detection rate)
Specificity (true negative [TN] rate)	• Probability that the screening test will be negative, given the fetus does not have aneuploidy
False-Positive (FP) Rate	• Percentage of screening tests that are incorrectly positive within a population of screened pregnant women
False-Negative (FN) Rate	• Percentage of screening tests that are incorrectly negative within a population of screened pregnant women
Positive Predictive Value (PPV)	• Probability that the condition is present when the screening test is positive
Negative Predictive Value (NPV)	• Probability that the condition is not present when the screening test is negative

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Evidence Review

Summary of the Evidence and Conclusions

Key Findings

- Effectiveness and harms
- Test performance
- Cost-effectiveness

Effectiveness and Harms

Number of Participants (N) Studies (k)	Findings	Certainty of Evidence	Rationale
Outcome: FP Rate for T21			
N = 1,400 1 RCT[9]	cfDNA screening had a lower FP screening rate than conventional FTS (0% vs. 2.5%; *P* value not reported).	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Test Failures			
N = 30,238 1 RCT, 8 cohort studies, and 1 case-control[9-18]	cfDNA test failure rates ranged from 0.9% to 8.5%. The highest rates of failures occurred in studies with twin pregnancies only or with a mixed risk population.	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency, and imprecision (i.e., not assessable)[a]
Outcome: Invasive Testing			
N = 1,400 1 RCT[9]	Overall, 1.7% (12 of 688) of women in the FTS group and 0.3% (2 of 688) in the cfDNA plus ultrasound group opted for invasive testing.	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
N = 3,117 2 cohort studies[11,13]	cfDNA screening was associated with lower rates of invasive testing.	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness (author estimates, not observed effects), and imprecision (i.e., not assessable)

Abbreviations. cfDNA: cell-free DNA; CI: confidence interval; FP: false positive; FTS: first-trimester screening; RCT: randomized controlled trial; T21: trisomy 21. Note. [a]For test failure rates, we combined information from the RCT, cohort studies, and the case-control study. The certainty of evidence started as low.

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Test Performance: T21, T18, and T13

- 6 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss no cases (moderate-quality evidence from 6 studies[10,11,13,14,16-18]) and up to 6 of 1,000 unaffected pregnant women would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 6 studies[10,11,13,14,16-18])
- Conventional screening would be expected to miss up to 1 case in 1,000 (moderate-quality evidence from 1 study[18]), and 44 in 1,000 women with unaffected pregnancies (range, 37-52) would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 1 study[18])
- The median PPV for cfDNA was 79.7% (range, 40.0%-100%) (very-low-quality evidence from 6 studies[10,11,13,14,16-18]) compared with 28.3% (95% CI, 25.0%-31.9%) for conventional screening (moderate-quality evidence from 1 study[18])

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cfDNA Test Performance: T21, T18, and T13

Test Results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0.41% Seen in the Study with the Lowest Prevalence	Prevalence 0.57% Seen in the Study with the Median Prevalence	Prevalence 1.69% Seen in the Study with the Highest Prevalence			
True positives	4 to 4	5 to 6	15 to 17	10,856 participants, 6 studies[10,11,13,14,16-18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False negatives	0 to 0	0 to 1	0 to 2			
True negatives	990 to 996	988 to 994	977 to 983	10,856 participants, 6 studies[10,11,13,14,16-18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	0 to 6	0 to 6	0 to 6			

Conventional Screening Test Performance: T21, T18, and T13

Test Results	Number of Results per 1,000 Patients Tested (95% CI)		Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0.57% Median from the cfDNA Studies	Prevalence 1.73% Seen in the Study with Highest Prevalence			
True positives	6 (5 to 6)	17 (16 to 17)	2,836 participants, 1 study[18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False negatives	0 (0 to 1)	0 (0 to 1)			
True negatives	950 (942 to 957)	939 (931 to 946)	2,836 participants, 1 study[18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	44 (37 to 52)	44 (37 to 52)			

Screening Test Performance: T21, T18, and T13

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
cfDNA Screening				
PPV	10,856 participants, 6 studies[10,11,13,14,16-18]	79.7% (40.0% to 100%)	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
NPV	10,856 participants, 6 studies[10,11,13,14,16-18]	100% (99.9% to 100%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Conventional Screening				
PPV	2,836 participants, 1 study[18]	28.3% (25.0% to 31.9%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
NPV	2,836 participants, 1 study[18]	100% (NA)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

Abbreviations. CI: confidence interval; CoE: certainty of evidence; NPV: negative predictive value; PPV: positive predictive value.

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Test Performance: T21, T18, and T13 in Twin Pregnancies

- 52 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss 5 cases (from none to 23; low-quality evidence from 1 study[12]) and no unaffected pregnant women (from none to 19) would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 1 study)
- The PPV for cfDNA was 100% (moderate-quality evidence from 1 study[12])

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cfDNA Test Performance: T21, T18, and T13 in Twin Pregnancies

Test Results	Number of Results per 1,000 Patients Tested (95% CI) Prevalence 5.73% Seen in This Study	Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
True positives	52 (34 to 57)	192 participants, 1 study[12]	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
False negatives	5 (0 to 23)			
True negatives	943 (924 to 943)	192 participants, 1 study[12]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	0 (0 to 19)			

Outcome	Number of Participants and Studies	Effect (95% CI)	Test Accuracy CoE	Rationale
PPV	192 participants, 1 study[12]	100% (NA)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
NPV	192 participants, 1 study[12]	99.5% (96.5% to 99.9%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

Test Performance: Sex Chromosome Aneuploidies

- 4 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss no cases (from none to 3) (very-low-quality evidence from 1 study) and no unaffected pregnant women (from none to 8) would undergo ultimately unnecessary invasive testing (very-low-quality evidence from 1 study[17])
- The PPV for cfDNA was 100% (low-quality evidence from 1 study[17])

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cfDNA Test Performance: Sex Chromosome Aneuploidies

Test Results	Number of Results per 1,000 Patients Tested (95% CI) Prevalence 0.42% Seen in This Study	Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
True positives	4 (1 to 4)	474 participants, 1 study[17]	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness (i.e., 45,X only), and imprecision (i.e., wide CIs)
False negatives	0 (0 to 3)			
True negatives	996 (988 to 996)	474 participants, 1 study[17]	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness (i.e., 45,X only), and imprecision (i.e., wide CIs)
False positives	0 (0 to 8)			

Outcome	Number of Participants and Studies	Effect (95% CI)	Test Accuracy CoE	Rationale
PPV	474 participants, 1 study[17]	100% (NA)	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and indirectness (i.e., 45,X only)
NPV	474 participants, 1 study[17]	100% (NA)	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and indirectness (i.e., 45,X only)

Source. Pergament E, Cuckle H, Zimmermann B, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. Obstet Gynecol. 2014;124(2 Pt 1):210-218. doi: 10.1097/AOG.0000000000000363.

Cost-Effectiveness

Number of Participants (N) Studies (k)	Findings	Certainty of Evidence	Rationale
Outcome: Cost-Effectiveness			
N > 10,000,000 (women in theoretical cohorts) 7 economic studies[19,21-26]	cfDNA was more effective than conventional screening in the first trimester, but may be more costly.	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and inconsistency (i.e., differences in results between studies)
N = 590 (women from a single urban center) 1 economic study[20]	cfDNA was more effective than conventional screening in the second trimester, but may be more costly, depending on the cost of the cfDNA test.	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness and imprecision (i.e., not assessable)

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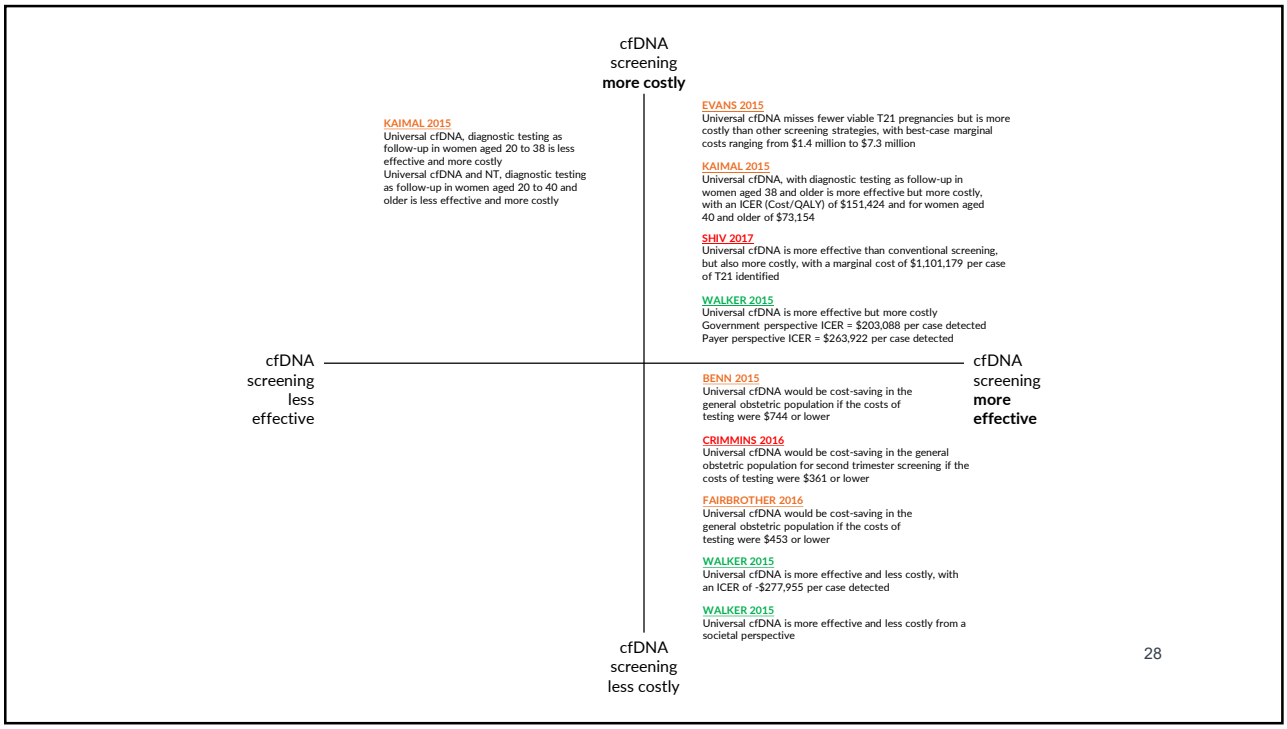

Clinical Practice Guidelines and Payer Coverage Policies

Clinical Practice Guidelines

- 2 of 13 good-methodological-quality guidelines differ in their recommendations on the use of cfDNA as a primary screening tool
  - HGSA and RANZOG guideline recommends its use
  - NHS guideline deferred universal use until the impact of the method's adoption has been explored
- 1 of 13 fair-methodological quality Canadian guideline recommends the use of primary cfDNA screening where available, but recognizes that it may not be funded by the healthcare system
- None of the 13 guidelines recommended the use of cfDNA screening for SCAs, although women could be made aware of the option

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Payer Policies

- Policies from private payers on the use of cfDNA as a universal screening tool for trisomies 21, 18, and 13 vary
  - Aetna restricts the test's use to women known to be at high risk
  - Cigna covers the use of cfDNA for all pregnant women
  - Both Aetna and Cigna consider the use of cfDNA to be experimental and investigational for multifetal pregnancies
  - Only limited details from Regence, with no publicly available policy for the common trisomies
  - All 3 private payers consider the use of cfDNA to be experimental and investigational for SCAs
- No relevant Medicare NCD or LCD policy

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Ongoing Studies

NCT Number Study Name Study Type	Participants	Treatment Groups	Outcomes	Study Completion Date
NCT03831256 PEGASUS-2 RCT	Pregnant women with singleton pregnancies opting for prenatal screening; target enrollment 10,000	First tier cfDNA screening (specific test not specified) Second tier cfDNA screening (test not specified) after a positive conventional FTS	• Gestational age at diagnosis • No-call tests • Length of time between a FP screening result and confirmation of diagnosis • Quality of life • Patient experience • Rate of invasive testing	December 2021

Abbreviations. cfDNA: cell-free DNA; FP: false positive; FTS: first-trimester screening; RCT: randomized controlled trial.

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Conclusions

- Universal screening with cfDNA is more accurate than conventional screening for T21, T18, and T13 in general obstetric populations
- Universal cfDNA testing is likely to be more expensive than conventional screening, but depends on the cfDNA test costs
- Policy makers will need to consider expanding cfDNA screening to all pregnant women and decide whether it represents value for money
- Economic modeling studies suggest that universal cfDNA screening can be cost-effective

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Questions?

Methods

Risk of Bias for Studies

- Two independent Center researchers evaluated studies for methodological risk of bias
- Each study assessed using Center instruments adapted from international standards and assessments
- A rating of high, moderate, or low risk of bias was assigned to each study based on adherence to recommended methods and potential for bias
- Risk-of-bias criteria are listed in Appendix B

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GRADE Domains

- Risk of bias
- Inconsistency
- Imprecision
- Indirectness
- Publication bias

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Contextual Question

Accuracy of cfDNA Screening in Women at High Risk

Contextual Question

What are the benefits and harms of screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA in pregnant individuals **known to be at high risk** for chromosomal abnormalities?

- Aim is to contextualize the performance of cfDNA screening in the general obstetric population
- Question addressed using high-quality systematic reviews

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Contextual Question

Condition	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
MPSS		
T21	99.7% (98.0% to 100%)	99.9% (99.8% to 100%)
T18	97.8% (92.5% to 99.4%)	99.9% (99.8% to 100%)
T13	95.8% (86.1% to 98.9%)	99.8% (99.8% to 99.9%)
45,X	91.7% (78.3% to 97.1%)	99.6% (98.9% to 99.8%)
TMPS		
T21	99.2% (96.8% to 99.8%)	100% (99.8% to 100%)
T18	98.2% (93.1% to 99.6%)	100% (99.8% to 100%)
T13	100% (83.9% to 100%)	100% (98.7% to 100%)
45,X	92.4% (84.1% to 96.5%)	99.8% (98.3% to 100%)

Abbreviations: CI: confidence interval; MPSS: massively parallel shotgun sequencing; T13: trisomy 13; T18: trisomy 18; T21: trisomy 12; TMPS: targeted massively parallel sequencing.

Source. Badeau M, Lindsay C, Blais J, et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. Cochrane Database Syst Rev. 2017;11(11):CD011767. doi: 10.1002/14651858.CD011767.pub2

Contextual Question

- In the Cochrane review, Badeau et al. concluded that

> *"non-invasive prenatal testing methods appear to be sensitive and highly specific for detection of fetal trisomies 21, 18, and 13 in high-risk populations"*

- However, the authors emphasized that invasive fetal karyotyping remains the required diagnostic approach to confirm the presence of a chromosomal abnormality prior to making irreversible decisions relative to the pregnancy outcome

Source. Badeau M, Lindsay C, Blais J, et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. Cochrane Database Syst Rev. 2017;11(11):CD011767. doi: 10.1002/14651858.CD011767.pub2

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Evidence Review

Key Questions 1 and 2

Effectiveness and Harms

- 10 studies that evaluated the benefits and harms of universal cfDNA screening in pregnant women
  - 1 RCT[9] had a moderate risk of bias due to concerns about blinding and allocation concealment
  - 7 test performance studies[11-17] had a moderate risk of bias due to concerns about patient selection, conflicts of interest, and test interpretation
  - 2 studies[10,18] had a high risk of bias due to substantial concerns about limited reporting on the methods used and conflicts of interest

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Effectiveness and Harms

Study ID Study Risk of Bias	Study Design Setting	Population	Conditions	Test (Manufacturer)	Outcomes
Ashoor et al., 2013[10] High	Prospective cohort and case-control U.K. and U.S.	Pregnant women with singleton pregnancies Confirmed cases of T13	T13	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures
Bianchi et al., 2014[11] Moderate	Prospective cohort U.S.	Pregnant women with singleton pregnancies	T21, T18	verifi (Illumina)	Test performance Test failures Pregnancy outcomes
del Mar Gil et al., 2014[12] Moderate	Retrospective cohort U.K.	Pregnant women with twin pregnancies	T21, T18, T13	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures
Kagan et al., 2018[9] Moderate	RCT Germany	Pregnant women with singleton pregnancies	T21, T18, T13	Harmony Prenatal (Roche-Ariosa)	Pregnancy outcomes Risk for trisomies Test failures FP rates Invasive testing
Langlois et al., 2017[13] Moderate	Prospective cohort Canada	Pregnant women with singleton pregnancies	T21, T18, T13	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures Pregnancy outcomes Invasive testing

Abbreviations. FP: false positive; RCT: randomized controlled trial; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21.
Note. Nicolaides et al., 2012 and Ashoor et al., 2013 reported on the same population, but for different trisomies.

Effectiveness and Harms

Study ID Study Risk of Bias	Study Design Setting	Population	Conditions	Test (Manufacturer)	Outcomes
Nicolaides et al., 2012[14] Moderate	Prospective cohort U.K.	Pregnant women with singleton pregnancies	T21, T18	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures Pregnancy outcomes
Norton et al., 2015[15] Moderate	Prospective cohort U.S., Belgium, Canada, Italy, Netherlands, and Sweden	Pregnant women with singleton pregnancies	T21, T18, T13	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures Pregnancy outcomes
Palomaki et al., 2017[16] Moderate	Prospective cohort U.S.	Pregnant women with singleton or twin pregnancies	T21, T18, T13, and 45,X	Panorama (Natera)	Test performance Test failures Pregnancy outcomes Invasive testing
Pergament et al., 2014[17] Moderate	Prospective cohort U.S., Czech Republic, Japan, Turkey, Ireland, Spain, and Poland	Pregnant women with singleton pregnancies	T21, T18, T13	Panorama (Natera)	Test performance Test failures
Quezada et al., 2015[18] High	Prospective cohort U.K.	Pregnant women with singleton pregnancies	T21, T18, T13	Harmony Prenatal (Roche-Ariosa)	Test performance Test failures Pregnancy outcomes

Abbreviations. T13: trisomy 13; T18: trisomy 18; T21: trisomy 21.
Note. Nicolaides et al., 2012 and Ashoor et al., 2013 reported on the same population, but for different trisomies.

Effectiveness and Harms

- In the Kagan RCT,[9] 1,400 pregnant women with a normal first-trimester ultrasound examination were randomized for risk assessment using cfDNA screening and ultrasound findings or conventional first trimester screening (FTS)
  - cfDNA plus ultrasound group had a significantly lower FP screening rate than the conventional FTS group
  - In the cfDNA group, there were no FP cases, vs. 2.5% in the FTS
  - In the cfDNA plus ultrasound group, median risk for T21 was 1 in 10,000 and no individual had a risk for T13, T18, or T21 greater than 1:100
  - In the conventional FTS group, the median risk for T21 was 1 in 3,787 and 17 cases had a risk greater than 1:100.
  - The risk of T21 in the cfDNA plus ultrasound group was significantly lower than in the conventional FTS group (risk above 1:100: 0% cfDNA; 95% CI, 0% to 0.5%; 2.5% FTS; 95% CI, 1.2% to 3.6%; P < .001)

Effectiveness and Harms

- Of the 9 test accuracy studies[10-18]
  - 7 included women with singleton pregnancies
  - 1 included twin pregnancies only
  - 1 included singleton and twin pregnancies
- Tests evaluated
  - 6 Harmony Prenatal (Roche-Ariosa)
  - 2 Panorama (Natera)
  - 1 verifi (Illumina)
- Conducted mainly in North America and Europe

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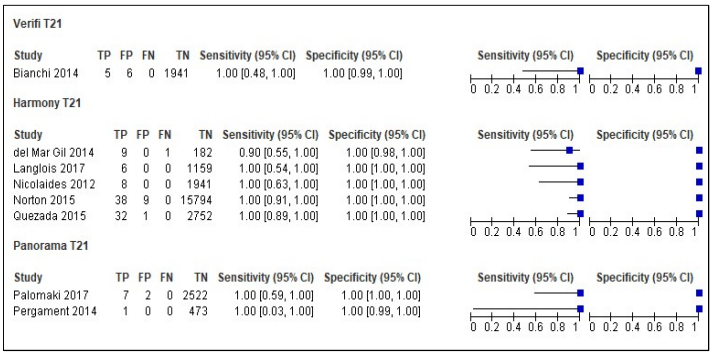
Effectiveness and Harms of cfDNA: T21

- In general obstetric populations, screening with cfDNA had a median sensitivity of 100% (range, 90.00%-100%) and a median specificity of 99.98% (range, 99.69%-100%)
- PPVs ranged from 45.45% to 100% (median, 98.48%) and NPVs from 99.45% to 100% (median, 100%)



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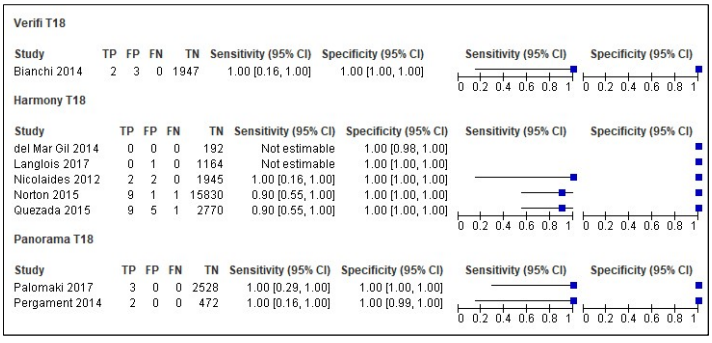
Effectiveness and Harms of cfDNA: T18

- In general obstetric populations, screening with cfDNA had a median sensitivity of 100% (range, 90.0%-100%) and a median specificity of 99.95% (range, 99.8%-100%)
- PPVs ranged from 40.0% to 100% (median, 77.1%) and NPVs from 99.96% to 100% (median, 100%)



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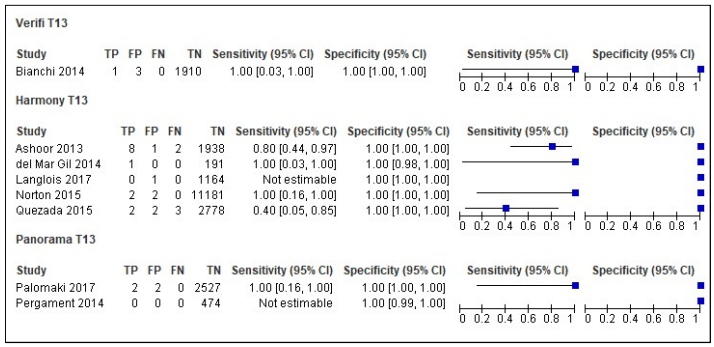
Effectiveness and Harms of cfDNA: T13

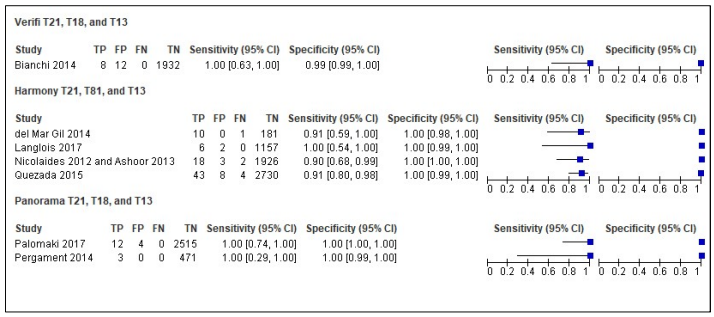
- In general obstetric populations, screening with cfDNA had a median sensitivity of 100% (range, 40.0%-100%) and a median specificity of 99.94% (range, 99.84%-100%)
- PPVs ranged from 25.0% to 100% (median, 50.0%) and NPVs from 99.9% to 100% (median, 100%)



54

Effectiveness and Harms of cfDNA: T21, T18, and T13

- In general obstetric populations, screening with cfDNA had a median sensitivity of 100% (range, 90.0%-100%) and a median specificity of 99.8% (range, 99.4%-100%) for the 3 trisomies
- PPVs ranged from 40.0% to 100% (median, 84.3%) and NPVs ranged from 99.5% to 100% (median, 100%)



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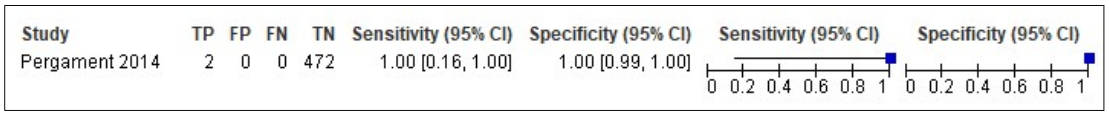
Effectiveness and Harms of cfDNA: SCAs

- In a general obstetric population, screening with cfDNA had a sensitivity of 100% and a specificity of 100% with a PPV and NPV of 100% each for the 45,X sex chromosome aneuploidy



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Effectiveness and Harms of Conventional Screening

- In general obstetric populations, conventional screening had:
  - For T21
    - Median sensitivity of 83.3% (range, 79.0%-100%)
    - Median specificity of 94.6% (range, 94.6%-96.4%)
    - PPVs ranged from 4.2% to 7.4% and NPVs ranged from 99.9% to 100%
  - For T18
    - Median sensitivity of 90.0% (range, 80.0%-100%)
    - Median specificity of 99.7% (range, 99.4 %-99.7%)
    - PPVs ranged from 8.3% to 14.0% and NPVs ranged from 99.99% to 100%
  - For T13
    - Median sensitivity of 75.0% (range, 50.0%-100%)
    - Median specificity of 99.5% (range, 99.3 %-99.8%)
    - PPVs ranged from 3.5% to 14.3% and NPVs ranged from 99.99% to 100%

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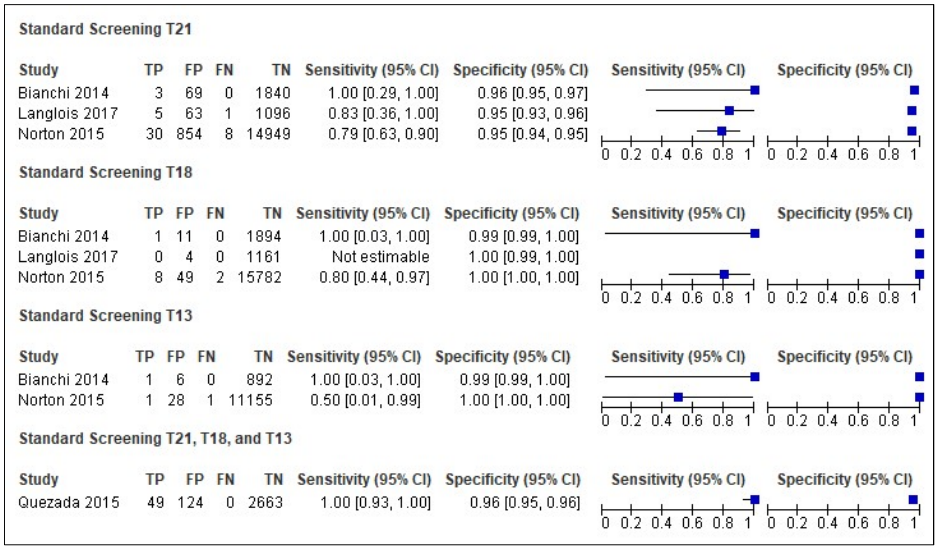
Effectiveness and Harms of Conventional Screening



Standard Screening T21

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bianchi 2014	3	69	0	1840	1.00 [0.29, 1.00]	0.96 [0.95, 0.97]
Langlois 2017	5	63	1	1096	0.83 [0.36, 1.00]	0.95 [0.93, 0.96]
Norton 2015	30	854	8	14949	0.79 [0.63, 0.90]	0.95 [0.94, 0.95]

Standard Screening T18

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bianchi 2014	1	11	0	1894	1.00 [0.03, 1.00]	0.99 [0.99, 1.00]
Langlois 2017	0	4	0	1161	Not estimable	1.00 [0.99, 1.00]
Norton 2015	8	49	2	15782	0.80 [0.44, 0.97]	1.00 [1.00, 1.00]

Standard Screening T13

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bianchi 2014	1	6	0	892	1.00 [0.03, 1.00]	0.99 [0.99, 1.00]
Norton 2015	1	28	1	11155	0.50 [0.01, 0.99]	1.00 [1.00, 1.00]

Standard Screening T21, T18, and T13

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Quezada 2015	49	124	0	2663	1.00 [0.93, 1.00]	0.96 [0.95, 0.96]

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Effectiveness and Harms: Test Failures

- In general, rates of cfDNA test failures were higher across all 10 studies[9-18] (range, 0.9%-8.5%; median, 2.8%) than for the failure rate for conventional screening (0.2%), reported in only 1 study[11]
- Reasons for cfDNA test failure were technical failures of the assay, low fetal fraction, and high variance in cfDNA count

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Effectiveness and Harms: Invasive Testing

- cfDNA screening reduced the rates of invasive testing
  - In the RCT by Kagan et al., 1.7% (12 of 688) of the women in the FTS group and 0.3% (2 of 688) of the women in the cfDNA plus ultrasound group opted for invasive testing[9]
  - Bianchi et al. estimated there would have been a relative reduction of 89% in the number of diagnostic invasive procedures required to confirm a positive screening result[11]
  - Langlois et al. estimated that if cfDNA had been conducted as the only primary screen, up to 62 amniocenteses would have been avoided[13]

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Test Performance: T21

- 3 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss no cases (moderate-quality evidence from 7 studies[11,13-18]) and up to 3 unaffected pregnant women would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 7 studies[11,13-18])
- Conventional screening would be expected to miss up to 1 case, assuming the same prevalence of T21 (very-low-quality evidence from 3 studies[11,13,15]), and from 36 to 54 unaffected pregnant women would undergo unnecessary invasive testing (moderate-quality evidence from 3 studies[11,13,15])
- The median PPV for cfDNA was 97.0% (range, 45.5%-100%) (very-low-quality evidence from 7 studies[11,13-18]) compared with 4.2% (range, 3.4%-7.4%) for conventional screening (moderate-quality evidence from 3 studies[11,13,15])

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cfDNA Test Performance: T21

Test Results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0.21% Seen in the Study with the Lowest Prevalence	Prevalence 0.28% Seen in the Study with the Median Prevalence	Prevalence 1.15% Seen in the Study with the Highest Prevalence			
True positives	2 to 2	3 to 3	11 to 12	26,697 participants, 7 studies[11,13-18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False negatives	0 to 0	0 to 0	-1 to 1			
True negatives	995 to 998	994 to 997	985 to 989	26,697 participants, 7 studies[11,13-18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	0 to 3	0 to 3	-1 to 4			

cfDNA Test Performance: T21

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
PPV	26,697 participants, 7 studies[11,13-18]	97.0% (45.5% to 100%)	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
NPV	26,697 participants, 7 studies[11,13-18]	100% (all 100%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

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Conventional Screening Test Performance: T21

Test Results	Number of Results per 1,000 Patients Tested (Range)				Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0.16% Seen in the Study with the Lowest Prevalence	Prevalence 0.24% Seen in the Study with the Median Prevalence	Prevalence 0.52% Seen in the Study with the Highest Prevalence	Prevalence 0.28% Median from the cfDNA Studies			
True positives	1 to 2	2 to 2	4 to 5	2 to 3	18,918 participants, 3 studies[11,13,15]	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
False negatives	0 to 1	0 to 0	0 to 1	0 to 1			
True negatives	944 to 962	943 to 962	941 to 959	943 to 961	18,918 participants, 3 studies[11,13,15]	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
False positives	36 to 54	36 to 55	36 to 54	36 to 54			

Conventional Screening Test Performance: T21

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
PPV	18,918 participants, 3 studies[11,13,15]	4.2% (3.4% to 7.4%)	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
NPV	18,918 participants, 3 studies[11,13,15]	99.95% (99.91% to 100%)	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias

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Test Performance: T18

- 1 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss no cases (moderate-quality evidence from 7 studies[11,13-18]) and up to 2 unaffected pregnant women would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 7 studies[11,13-18])
- Conventional screening would be expected to miss no cases (very-low-quality evidence from 3 studies[11,13,15]), and 3 to 6 unaffected pregnant women would undergo unnecessary invasive testing (moderate-quality evidence from 3 studies[11,13,15])
- The median PPV for cfDNA was 77.1% (range, 45.5%-100%) (very-low-quality evidence from 7 studies[11,13-18]) compared with 8.3% (range, 0%-14.0%) for conventional screening (moderate-quality evidence from 3 studies[11,13,15])

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cfDNA Test Performance: T18

Test Results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0% Seen in the Study with the Lowest Prevalence	Prevalence 0.1% Seen in the Study with the Median Prevalence	Prevalence 0.42% Seen in the Study with the Highest Prevalence			
True positives	0 to 0	1 to 1	4 to 4	26,697 participants, 7 studies[11,13-18]	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
False negatives	0 to 0	0 to 0	0 to 0			
True negatives	998 to 1,000	997 to 999	994 to 996	26,697 participants, 7 studies[11,13-18]	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
False positives	0 to 2	0 to 2	0 to 2			

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cfDNA Test Performance: T18

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
PPV	26,697 participants, 7 studies[11,13-18]	77.1% (40.0% to 100%)	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
NPV	26,697 participants, 7 studies[11,13-18]	100% (99.96% to 100%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

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Conventional Screening Test Performance: T18

Test Results	Number of Results per 1,000 Patients Tested (Range)				Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0% Seen in the Study with the Lowest Prevalence	Prevalence 0.05% Seen in the Study with the Median Prevalence	Prevalence 0.06% Seen in the Study with the Highest Prevalence	Prevalence 0.1% Median from the cfDNA Studies			
True positives	0 to 0	0 to 1	0 to 1	1 to 1	18,918 participants, 3 studies[11,13,15]	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
False negatives	0 to 0	-1 to 1	0 to 1	0 to 0			
True negatives	944 to 997	994 to 996	994 to 996	993 to 996	18,918 participants, 3 studies[11,13,15]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	3 to 6	4 to 6	3 to 5	3 to 6			

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Conventional Screening Test Performance: T18

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
PPV	18,918 participants, 3 studies[11,13,15]	8.3% (0% to 14.0%)	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
NPV	18,918 participants, 3 studies[11,13,15]	100% (99.99% to 100%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

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Test Performance: T13

- Up to 1 of 1,000 pregnancies would be expected to be affected
- cfDNA screening would be expected to miss up to 1 case (low-quality evidence from 7 studies[10,11,13,15-18]) and up to 2 unaffected pregnant women would undergo ultimately unnecessary invasive testing (moderate-quality evidence from 7 studies[10,11,13,15-18])
- Conventional screening would be expected to miss up to 1 case (very-low-quality evidence from 2 studies[11, 15]), and from 3 to 4 unaffected pregnant women would undergo unnecessary invasive testing (moderate-quality evidence from 2 studies[11, 15])
- The median PPV for cfDNA was 50.0% (range, 25.0%-88.9%) (very-low-quality evidence from 7 studies[10,11,13,15-18]) compared with 3.5% and 14.3% for conventional screening (low-quality evidence from 2 studies[11, 15])

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cfDNA Test Performance: T13

Test results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0% Seen in the Study with the Lowest Prevalence	Prevalence 0.05% Seen in the Study with the Median Prevalence	Prevalence 0.51% Seen in the Study with the Highest Prevalence			
True positives	0 to 0	0 to 1	2 to 5	22,003 participants, 7 studies[10,11,13,15-18]	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and inconsistency (i.e., differences in results across studies)
False negatives	0 to 0	-1 to 1	0 to 3			
True negatives	998 to 1,000	998 to 1,000	993 to 995	22,003 participants, 7 studies[10,11,13,15-18]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	0 to 2	-1 to 2	0 to 2			

cfDNA Test Performance: T13

Outcome	Number of Participants and Studies	Median (Range)	Test Accuracy CoE	Rationale
PPV	22,003 participants, 7 studies[10,11,13,15-18]	50.0% (25.0% to 88.9%)	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
NPV	22,003 participants, 7 studies[10,11,13,15-18]	100% (99.89% to 100%)	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

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Conventional Screening Test Performance: T13

Test Results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 0.02% Seen in the Study with the Lowest Prevalence	Prevalence 0.11% Seen in the Study with the Highest Prevalence	Prevalence 0.05% Median from the cfDNA Studies			
True positives	0 to 0	1 to 1	0 to 1	12,084 participants, 2 studies[11, 15]	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., different results across studies), and imprecision (i.e., wide CIs)
False negatives	0 to 0	0 to 0	-1 to 1			
True negatives	993 to 997	992 to 996	993 to 997	12,084 participants, 2 studies[11, 15]	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
False positives	3 to 7	3 to 7	3 to 4			

Conventional Screening Test Performance: T13

Outcome	Number of Participants and Studies	Effect	Test Accuracy CoE	Rationale
PPV	12,084 participants, 2 studies[11, 15]	3.5% and 14.3%	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
NPV	12,084 participants, 2 studies[11, 15]	99.99% and 100%	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias

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Evidence Review

Key Question 3

Variation by Sub-Group

- Maternal age
  - No studies compared outcomes or test performance by maternal age
- Maternal weight
  - Greater maternal weight appeared to be associated with higher rates of cfDNA test failures[13,15,16]
- Singleton or multifetal pregnancy
  - Only 2 studies included twin pregnancies, but direct comparisons of outcomes or test performance were not conducted for singleton vs. multifetal pregnancies[12,16]

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Variation by Sub-Group

- Gestational age
  - Lower gestational age may be associated with higher rates of test failures[17]
- Presence of aneuploidies
  - Prevalence of aneuploidies was lower in women with a successful cfDNA test compared with women with a failed cfDNA test[15]

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Evidence Review

Key Question 4

Cost Impact and Cost-Effectiveness

- 8 economic modeling studies, published in the last 5 years, that evaluated the costs and benefits of cfDNA screening in the U.S.
  - 2 modeling studies[25, 26] were rated low risk of bias with only minor methodological concerns
  - 4 modeling studies[19,21-23] were rated moderate risk of bias due to concerns about model assumptions and design (e.g., a lack of a complete model diagram, time horizons not being stated explicitly) and sensitivity analyses
  - 2 modeling studies[20,24] were rated high risk of bias due to substantial concerns about limited reporting on the models used, a lack of clarity on the time horizon used, and limited use of sensitivity analysis

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Cost Impact and Cost-Effectiveness

Study ID Study Risk of Bias	Population	Conditions	Economic Analytic Method
Benn et al., 2015[19] Moderate	Theoretical cohort of 3,952,841 live births, representing the U.S. general obstetric prenatal screening population in 2012	T21, T18, T13, and 45,X	Cost impact
Crimmins et al., 2017[20] High	Pregnant women choosing aneuploidy risk assessment, who presented for care between 15 and 21 weeks at a single urban center	T21	Cost impact
Evans et al., 2015[21] Moderate	Theoretical cohort of 1,000,000 pregnant women	T21	Cost impact
Fairbrother et al., 2016[22] Moderate	Theoretical cohort of 4,000,000 pregnant women, representative of the U.S. general obstetric prenatal screening population in 1 year	T21, T18, and T13	Cost impact
Kaimal et al., 2015[23] Moderate	Theoretical cohort of pregnant women desiring prenatal testing (screening or diagnostic or both)	T21, T18, T13, SCA (45,X; 47,XXX; 47,XXY; 47,XYY), microdeletion, duplication, other rare chromosomal abnormality, variant of uncertain significance	Cost effectiveness
Shiv et al., 2017[24] High	Theoretical cohort of 3,000 pregnant women	T21 and all detectable aneuploidies	Cost impact
Walker et al., 2015[25] Low	Theoretical cohort of 1,000,000 pregnant women at 10 weeks' gestation	T21	Cost effectiveness
Walker et al., 2015[26] Low	Theoretical cohort of 1,000,000 pregnant women representative of the U.S. general obstetric prenatal screening population	T21, T18, and T13	Cost effectiveness

Abbreviations. 45,X: Turner syndrome; 47,XXX: Triple X syndrome; 47,XXY: Klinefelter syndrome; 47,XYY: Jacob's syndrome; SCA; sex chromosome aneuploidy; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21.

Cost Impact and Cost-Effectiveness

- Universal cfDNA testing varied in its estimated effectiveness and value for money
- Results were sensitive to model variables, including the cost of testing, the perspective being taken, and maternal age

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Clinical Practice Guidelines

Clinical Practice Guidelines

- 13 eligible guidelines
  - 10 assessed as poor-methodological quality, due to a lack of reporting on how the evidence base was identified and appraised and how the recommendations were made
  - 1 assessed as fair- methodological quality, due to concerns about the recommendation development process
  - 2 assessed as good-methodological quality

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Clinical Practice Guidelines

Organization	Topic
Good Methodological Quality	
Human Genetics Society of Australia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists	Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions
NHS Fetal Anomaly Screening Programme	cfDNA testing for Down syndrome and other trisomies
Fair Methodological Quality	
Society of Obstetricians and Gynaecologists of Canada, Canadian College of Medical Geneticists	Prenatal screening for fetal aneuploidy, fetal anomalies, and adverse pregnancy outcomes

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Clinical Practice Guidelines

Organization	Topic
Poor Methodological Quality	
American College of Medical Genetics and Genomics (ACMG)	Noninvasive prenatal screening for fetal aneuploidy
American College of Obstetricians and Gynecologists, Society for Maternal–Fetal Medicine	Screening for fetal aneuploidy
Society for Maternal–Fetal Medicine	Role of ultrasound in women who undergo cfDNA screening
Austrian Society of Obstetrics and Gynecology, Austrian Society of Ultrasound in Medicine, Austrian Society of Pre- and Perinatal Medicine, Austrian Society of Human Genetics, German Society of Ultrasound in Medicine, Fetal Medicine Foundation Germany, Swiss Society of Ultrasound in Medicine	Cell-Free DNA testing for fetal chromosomal anomalies
Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis	Screening tests for detecting fetal chromosome abnormalities
European Society of Human Genetics, American Society of Human Genetics	Noninvasive prenatal testing for aneuploidy
International Society of Ultrasound in Obstetrics and Gynecology	cfDNA aneuploidy testing: impact on screening policies and prenatal ultrasound
Israeli Society of Medical Genetics NIPT Committee	Non-invasive prenatal testing of cfDNA in maternal plasma for detection of fetal aneuploidy
National Society of Genetic Counselors	Prenatal cfDNA screening
Polish Gynecological Society, Polish Human Genetics Society	cfDNA testing in prenatal diagnosis

HTCC Coverage and Reimbursement Determination

Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Test failures		
False positive		
False negative		
Invasive testing		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Sensitivity		
Specificity		
Positive Predictive Value		
Negative Predictive Value		

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Race		
Gender		
Ethnicity		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not covered _____ Covered unconditionally _____ Covered under certain conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines

[from page 71 of final evidence report]

We did not identify any Medicare National or Local Coverage Determinations related to prenatal screening with cfDNA. Of the 3 private payers that we reviewed, we found detailed policies on prenatal screening using cfDNA from Aetna and Cigna, but only limited detail from Regence.[39-41]

[From page 56 of final evidence report]

Clinical Practice Guidelines

A search for clinical practice guidelines related to prenatal screening using cfDNA identified 13 eligible guidelines.[1,27-38] We included any guideline that met basic eligibility criteria and discussed the use of cfDNA in prenatal screening for the general obstetric population. We assessed the majority of clinical practice guidelines as having poor methodological quality due to a lack of reporting on how the evidence base was identified and appraised and how the recommendations were made.[1,28-30,32,33,35-38] We assessed the clinical practice guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC) Genetics Committee and the Canadian College of Medical Geneticists (CCMG) as having fair methodological quality due to concerns about the recommendation development process.[27] We assessed the clinical practice guidelines from the Human Genetics Society of Australasia (HGSA) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) as having good methodological quality due to minor concerns about recommendation development and stakeholder involvement.[31] We also assessed the screening recommendations from the U.K. National Screening Committee as having good methodological quality with only minor concerns about clarity and applicability.[34]

Table 1. Clinical Practice Recommendations on cfDNA Prenatal Screening

Organization	Topic	Excerpted Recommendation(s)	Status
Good Methodological Quality			
Human Genetics Society of Australia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists[31]	Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions	• Acceptable first-line screening tests for fetal chromosome abnormalities in the first trimester include either: a) combined FTS with nuchal translucency and serum PAPP-A and β-hCG measurements, or b) cfDNA-based screening • The choice of first-line screening test will depend on local resources, patient demographics, and individual patient characteristics. • Pre-test counselling for cfDNA-based screening should include informed decision making regarding testing for fetal sex and sex chromosome aneuploidy. The potential for other unanticipated findings of relevance to maternal health (including maternal genomic imbalances), should be included in pre-test counselling. • Acceptable first-line screening tests for chromosome conditions in second trimester include: a) maternal serum screening (MA + AFP + βhCG +UE3 +/- Inhibin) and, b) cfDNA-based screening. • The choice of first-line screening test will depend on local resources, patient demographics, and individual patient characteristics. • The option of cfDNA-based screening as a second-tier test should be discussed with all women at increased probability of a chromosome condition after primary screening. The advantages and disadvantages of second tier cfDNA-based screening, compared with diagnostic testing, or no further assessment, should be discussed by a clinician with appropriate expertise. • Diagnostic testing with amniocentesis or chorionic villus sampling should be recommended prior to definitive management decisions (e.g. termination of pregnancy) in cases of “increased chance” screening results, including cfDNA-based screening. • In twin pregnancies, cfDNA-based screening may be offered with appropriate pre-test counselling regarding an increased test failure rate, and less available performance data compared with singletons.	Adopted in 2018, due for updating in 2021 or as required
NHS Fetal Anomaly Screening Programme[34]	cfDNA testing for Down syndrome and other trisomies	• Although cfDNA is thought to be very accurate, there is still a chance that it would incorrectly identify a pregnancy as high risk of Down syndrome. For this reason it should not replace the current diagnostic test used in FASP. Its improved accuracy compared to the combined test does mean that	Guidance issued in 2015 with updates published in 2019

Organization	Topic	Excerpted Recommendation(s)	Status
		fewer women will go on to have the invasive diagnostic test when their baby does not in fact have Down syndrome. • There is the potential for cfDNA to replace the current combined screening test in the future. However, as the technology stands, the number of tests which don't give a result would mean that more women would be offered invasive testing than now. • Also, cfDNA may be very accurate when identifying which babies are at a higher risk of Down syndrome, but there is not enough evidence to be sure of its accuracy when looking for Edwards' syndrome and Patau's syndrome. • The UK National Screening Committee will continue to keep emerging evidence under review.	
Fair Methodological Quality			
Society of Obstetricians and Gynaecologists of Canada, Canadian College of Medical Geneticists[27]	Prenatal screening for fetal aneuploidy, fetal anomalies, and adverse pregnancy outcomes	• All pregnant women in Canada, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for the most common fetal aneuploidies. • First-trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this fetal screening service and when there is ongoing quality assurance. For aneuploidy, it should be offered as a screen with maternal serum biochemical markers in singleton pregnancies. • Maternal age alone is a poor minimum standard for prenatal screening for aneuploidy, and it should not be used as a basis for recommending invasive fetal diagnostic testing when prenatal screening for aneuploidy is available. • Health care providers should be aware of the prenatal screening modalities available in their province or territory. A reliable prenatal system needs to be in place ensuring timely reporting of results. Prenatal screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high-quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding opportunities to adjust the program to new technology and protocols. • A discussion of the risks, benefits, and alternatives of the various prenatal diagnoses and screening options, including the option of no testing, should be undertaken with all patients prior to any prenatal screening. Following this counselling, patients should be offered (1) no aneuploidy screening, (2) standard prenatal screening based on locally-offered paradigms, (3) ultrasound-guided invasive testing when appropriate indications are present, or (4) maternal plasma cfDNA screening where available, with the understanding that it may not be provincially funded. • Regardless of aneuploidy screening choice, all women should be offered a fetal ultrasound (optimally between 11 and 14 weeks) to confirm viability, gestational age, number of fetuses, chorionicity in	Adopted in 2017 with a review date of 2022

Organization	Topic	Excerpted Recommendation(s)	Status

		multiples, early anatomic assessment, nuchal translucency evaluation where available. The nuchal translucency measurement for aneuploidy risk estimation (combined with maternal serum) should not be performed if cfDNA screening has been used. Every effort should be made to improve access to high-quality first trimester ultrasound for all Canadian women. In areas where nuchal translucency assessment is not available, a first trimester dating ultrasound improves the accuracy of maternal serum screening and the management of pregnancy.
		• A large nuchal translucency (>3.5 mm) should be considered a major marker for fetal chromosomal and structural anomalies and requires genetic counselling, an offer of invasive testing with chromosomal microarray analysis, and detailed second-trimester ultrasound follow-up.
		• Women who are considering undergoing maternal plasma cfDNA screening should be informed that:
		  ○ It is a highly effective screening test for the common fetal trisomies (21, 18, 13), performed after 10 weeks' gestation.
		  ○ There is a possibility of a failed test (no result available), FN or FP fetal result, and an unexpected fetal or maternal result.
		  ○ All positive cfDNA screening results should be confirmed with invasive fetal diagnostic testing prior to any irrevocable decision.
		  ○ Management decisions, including termination of pregnancy, require diagnostic testing and should not be based on maternal plasma cfDNA results alone because it is not a diagnostic test.
		  ○ If a fetal structural abnormality is identified in a woman regardless of previous screening test results, the woman should undergo genetic counselling and be offered invasive diagnostic testing with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive.
		  ○ Although cfDNA screening for aneuploidy in twin pregnancy is available, there is less validation data than for a singleton pregnancy and it should be undertaken with caution.
		  ○ Routine cfDNA screening for fetal microdeletions is not currently recommended.
		• If a fetal structural abnormality is identified, regardless of previous screening test results, genetic counselling and invasive fetal diagnostic testing should be offered with rapid aneuploidy detection, and chromosomal microarray analysis should be considered to confirm those malformations associated with a high frequency of abnormal results.
		• The sonographic "soft markers" of echogenic intracardiac focus and chorionic plexus cysts should not be used to adjust the a priori risk for fetal aneuploidy.
		• Universal screening for adverse pregnancy outcomes using maternal serum markers is currently not recommended outside of an investigational protocol with informed consent.	

Organization	Topic	Excerpted Recommendation(s)	Status
Poor Methodological Quality			
American College of Medical Genetics and Genomics (ACMG)[30]	Noninvasive prenatal screening for fetal aneuploidy	**ACMG recommends:** • Allowing patients to select diagnostic or screening approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences. • Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes). • Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS. • Offering diagnostic testing when a positive screening test result is reported after NIPS. • Providing accurate, balanced, up-to-date information, at an appropriate literacy level when a fetus is diagnosed with a chromosomal or genomic variation in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis. • Informing all pregnant women, as part of pretest counseling for NIPS, of the availability of the expanded use of screening for sex chromosome aneuploidies. • Providers should make efforts to deter patients from selecting sex chromosome aneuploidy screening for the sole purpose of biologic sex identification in the absence of a clinical indication for this information. • Informing patients about the causes and increased possibilities of false-positive results for sex chromosome aneuploidies as part of pretest counseling and screening for these conditions. Patients should also be informed of the potential for results of conditions that, once confirmed, may have a variable prognosis (e.g., Turner syndrome) before consenting to screening for sex chromosome aneuploidies. • Referring patients to a trained genetics professional when an increased risk of sex chromosome aneuploidy is reported after NIPS. **ACMG does not recommend:** • NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21.	Adopted in 2016 with no specific review date listed
American College of Obstetricians and Gynecologists, Society for	Screening for fetal aneuploidy	• Screening for aneuploidy should be an informed patient choice, with an underlying foundation of shared decision making that fits the patient's clinical circumstances, values, interests, and goals. • Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy, ideally at the first prenatal visit.	Adopted in 2016 with no specific review date listed

Organization	Topic	Excerpted Recommendation(s)	Status
Maternal–Fetal Medicine[1]		• All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age. • Some women who receive a positive test result from traditional screening may prefer to have cfDNA screening rather than undergo definitive testing. This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy. • Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed. • Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a FP test result. • Women who undergo FTS should be offered second-trimester assessment for open fetal defects (by ultrasonography, maternal serum alpha-fetoprotein screening, or both) and ultrasound screening for other fetal structural defects. • Because cfDNA is a screening test, it has the potential for FP and FN test results and should not be used as a substitute for diagnostic testing. • All women with a positive cfDNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken. • Women whose cfDNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy. • Women with a positive screening test result for fetal aneuploidy should be offered further detailed counseling and testing. • No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher-order multifetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies.	
Society for Maternal‑Fetal Medicine[38]	Role of ultrasound in women who undergo cfDNA screening	• In women who have already received a negative cfDNA screening result, ultrasound at 11 to 14 weeks of gestation solely for the purpose of nuchal translucency measurement (CPT code 76813) is not recommended. • Diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cfDNA screen. • In women with an isolated soft marker that has no other clinical implications (i.e., choroid plexus cyst or echogenic intracardiac focus) and a negative cfDNA screen, we recommend describing the finding as not clinically significant or as a normal variant.	Adopted in 2017 with no specific review date listed

Organization	Topic	Excerpted Recommendation(s)	Status
		• In women with an isolated soft marker without other clinical implications (i.e., choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant. • We recommend that all women in whom a structural abnormality is identified by ultrasound be offered diagnostic testing with chromosomal microarray.	
Austrian Society of Obstetrics and Gynecology, Austrian Society of Ultrasound in Medicine, Austrian Society of Pre- and Perinatal Medicine, Austrian Society of Human Genetics, German Society of Ultrasound in Medicine, Fetal Medicine Foundation Germany, Swiss Society of Ultrasound in Medicine[36]	Cell-Free DNA testing for fetal chromosomal anomalies	• cfDNA testing should be offered only after, or in conjunction with, a qualified ultrasound and following appropriate counseling about the nature, scope and significance of the test. • cfDNA tests are screening tests. A high-risk cfDNA testing result should always be confirmed by an invasive diagnostic test (Chorionic villous sampling, amniocentesis), before a clinical consequence is drawn from the findings. • cfDNA testing can be used as secondary screening test for trisomy 21 (Down syndrome) for the reduction of invasive procedures after a high or intermediate risk result from First-trimester combined test (1 in 1,000 or > 1:500). It should be noted that, even when cfDNA testing is used as a secondary screening, invasive diagnostic testing (Chorionic villous sampling, amniocentesis) is still the method of choice when the adjusted risk for T21 after the combined test is > 1:10 or the fetal nuchal translucency thickness is > 3.5 mm or a fetal malformation is present. • cfDNA tests can also be used as a primary screening method for fetal T21 in pregnant women of every age and risk group. • In general, it should be noted that the performance of cfDNA screening for T18 (Edwards syndrome) and T13 (Patau syndrome) is lower than that for T21. • Based on the available evidence the use of cfDNA tests to screen for aneuploidy of sex chromosomes and microdeletion syndromes can currently not be recommended without reservation.	Adopted in 2015 with no specific review date listed
Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis[28]	Screening tests for detecting fetal chromosome abnormalities	The following protocol options are currently considered appropriate: • cfDNA screening as a primary test offered to all pregnant women, completed weeks (e.g. 10 = 10 weeks 0 days to 10 weeks 6 days) • cfDNA secondary to a high-risk assessment based on serum and ultrasound screening protocols • cfDNA contingently offered to a broader group of women ascertained as having high or intermediate risks by conventional screening; contingent provision of cfDNA could also include a protocol in which women with very high risks are offered invasive prenatal diagnosis, while those with intermediate risk are offered cfDNA	Adopted in 2015 with no specific review date listed
European Society of Human Genetics,	Noninvasive prenatal testing for aneuploidy	1. NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis: FPs occur for a variety of reasons (including that the DNA sequenced is both maternal and	Adopted in 2014 with no specific review date listed

Organization	Topic	Excerpted Recommendation(s)	Status
American Society of Human Genetics[29]		fetal in origin, and that the fetal fraction derives from the placenta as well as the developing fetus). Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy. 2. The better test performance, including lower invasive testing rate of NIPT-based screening should not lead to lower standards for pretest information and counseling. This is especially important in the light of the aim of providing pregnant women with meaningful options for reproductive choice. There should be specific attention paid to the information needs of women from other linguistic and cultural backgrounds or who are less health literate. 3. If NIPT is offered for a specific set of conditions (e.g., trisomies 21, 18 and 13), it may not be reasonably possible to avoid additional findings, such as other chromosomal anomalies or large scale insertions or deletions. As part of pretest information, women and couples should be made aware of the possibility of such additional findings and the range of their implications. There should be a clear policy for dealing with such findings, as much as possible also taking account of pregnant women's wishes with regard to receiving or not receiving specific information. 4. Expanding NIPT-based prenatal screening to also report on SCAs and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended. 5. Emerging opportunities for combining prenatal screening for fetal abnormalities with screening aimed at prevention may undermine adequate counseling by sending mixed messages. The objective of any prenatal screening activity should be made explicit and, as far as possible, forms of prenatal screening with different aims should be presented separately. If not physically possible, this separation should at least be made conceptually when providing the relevant information. 6. In countries where prenatal screening for fetal abnormalities is offered as a public health programme, governments and public health authorities should adopt an active role to ensure the responsible introduction of NIPT as a second or first-tier screening test for Down syndrome and other common autosomal aneuploidies. This entails ensuring quality control also extending to the non-laboratory aspects of NIPT-based prenatal screening (information, counseling), education of professionals, systematic evaluation of all aspects of the screening programme, as well as promoting equity of access for all pregnant women within the confines of the available budget, and setting up a governance structure for responsible further innovation in prenatal screening. 7. Different scenarios for NIPT-based screening for common autosomal aneuploidies are possible, including NIPT as an alternative first-tier option. The inevitable trade-offs underlying those scenarios should not just be regarded as a matter of screening technology and health economics; the question is also how these trade-offs enable or impede meaningful reproductive choices and how they affect	

Organization	Topic	Excerpted Recommendation(s)	Status
		both the balance of benefits and burdens for pregnant women and their partners, and the screening goals and values acceptable to society. 8. In order to adequately evaluate prenatal screening practices, there is a need to further develop and validate measures of informed choice as well as interventions aimed at enabling informed choices. The transition to NIPT-based prenatal screening presents an opportunity to fill this gap in knowledge. 9. In the light of sequencing technologies becoming better and cheaper, there is an acute need for a proactive professional and societal debate about what the future scope of prenatal screening for fetal abnormalities should be. As argued […], there are strong ethical reasons for not expanding the scope of prenatal screening beyond serious congenital and childhood disorders. 10. The scenario in which prenatal screening would open up possibilities for fetal therapy in addition to autonomous reproductive choice raises fundamental questions about the relation between reproductive autonomy and parental responsibility that require an in depth proactive ethical analysis.	
International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[35]	cfDNA aneuploidy testing: impact on screening policies and prenatal ultrasound	All women should be offered a first-trimester ultrasound scan according to ISUOG guidelines, regardless of their intention to undergo cfDNA testing. • If the woman has had a negative cfDNA test result, nuchal translucency thickness should still be measured and reported as a raw value and centile. The management of increased nuchal translucency with a normal cfDNA test result is currently based on local guidelines. However, it is not necessary to compute first-trimester risk estimates for trisomies 21, 18 and 13 based on nuchal translucency measurements and maternal biochemistry in a woman known to have a normal cfDNA result. Accordingly, soft markers for T21 should not be assessed in women with a normal cfDNA test result due to their high FP rate and poor positive predictive value. • If the woman has not had a cfDNA test, pretest counseling is essential. Various options regarding screening or testing for T21 and, to a lesser extent, trisomies 18 and 13 should be explained clearly, including information on the expected test performance, potential adverse effects, and pros and cons of each option. Following a normal first-trimester scan, as defined by ISUOG guidelines, three options might be considered for women who wish to have further risk assessment: (1) Screening strategies based on individual risk calculated from maternal age and nuchal translucency measurement and/or maternal serum markers and/or other ultrasound markers in the first trimester (defined by the conventional crown–rump length range of 45–84 mm). Following such screening, women can be offered a choice, according to their calculated individual risk, of having no further testing, cfDNA testing or invasive testing. Cut-offs, defining two (low/high risk) or three (low/intermediate/high risk) groups, should be defined on a local/national basis and will be affected by public health priorities and available resources. Offering cfDNA testing should always be balanced with the potential and risk of conventional karyotyping, with or without microarray analysis, following invasive sampling. More importantly, the role of cfDNA	Adopted in 2017, updates produced on a regular basis but no specific review date listed

Organization	Topic	Excerpted Recommendation(s)	Status
		testing as an alternative to standard invasive testing in women considered to be at very high risk after combined screening (>1:10) but with no ultrasound anomaly should be evaluated in prospective studies. Expert opinion currently suggests that cfDNA testing should not replace routinely invasive testing in this group, based on the fact that, in this population, only 70% of the chromosomal abnormalities are trisomy 21, 18 or 13, and that chromosomal microarray analysis, if offered, is able to detect a large number of additional anomalies. (2) cfDNA testing as a first-line screening test. Most current guidelines endorse cfDNA testing only for high- or intermediate-risk populations, for which comprehensive data exist. Experience in low-risk populations is increasing, apparently confirming the high detection rates published for high-risk populations. However, testing in low-risk women may impact on the quality of both pretest counseling and subsequent ultrasound screening. In particular, cfDNA testing should not replace first-trimester ultrasound and should not be offered when an ultrasound anomaly or markedly increased nuchal translucency is detected. Using cfDNA in low-risk patients might be endorsed as a widely available option only when more data emerge and cfDNA costs decrease. (3) Invasive testing based on a woman's preference or background risk (maternal age, previous history, fetal ultrasound anomaly) with no further individual risk calculation. An invasive test might be discussed in light of the recently reported reduction in the risk of invasive procedures, as well as the increase in cytogenetic resolution provided by microarray techniques. However, the cost of this option is not usually covered by most national insurance policies and it should not be recommended beyond the context of clinical trials and until sufficient peer-reviewed data and validation studies have been published. • cfDNA test results should always be interpreted and explained individually in relation to the a-priori risk and the fetal fraction. • In the presence of a fetal structural anomaly, the indications for fetal karyotyping and/or microarray testing should not be modified by a previously normal cfDNA test result. • In the case of a failed cfDNA test, the patient should be informed about the increased risk of anomalies as well as alternative screening and testing strategies. • cfDNA testing is not diagnostic, and confirmatory invasive testing is required in the presence of an abnormal result. Whenever there is discordance between an abnormal cfDNA test result and a normal ultrasound examination, amniocentesis rather than chorionic villus sampling should be performed. • Accuracy of cfDNA testing in twin pregnancies should be investigated further. • Variations in cfDNA test performance by different providers should be investigated further. It is becoming technically feasible to test non-invasively, not only for trisomies but also for other genetic syndromes. Both healthcare providers and women should be clearly aware of the tests being	

Organization	Topic	Excerpted Recommendation(s)	Status
		performed and of their performance, as having multiple tests increases the overall FP rate and failure rate. The detection rate for microdeletions has yet to be established and most national guidelines currently do not support testing for microdeletions on cfDNA. Screening for microdeletions also raises complex issues regarding pretest and post-test counseling. • Prospective, publicly funded studies assessing the cost-effectiveness of various screening strategies should be performed as a matter of urgency.	
Israeli Society of Medical Genetics NIPT Committee[32]	Non-invasive prenatal testing of cfDNA in maternal plasma for detection of fetal aneuploidy	• NIPT should be considered for women at high risk for fetal chromosomal abnormalities, in singleton pregnancies, from 10 weeks of gestation. The following categories are considered high risk: ○ Maternal age of 35 years or above at the time of conception. ○ Sonographic 'soft markers' of chromosomal anomaly (such as intracardiac echogenic foci, mild pyelectasis, etc.). ○ Personal or familial history of a chromosomal anomaly detectable by NIPT. ○ Abnormal Down syndrome screening result (first or second trimester). ○ A parent carrier of a Robertsonian translocation involving chromosomes 13 or 21	Adopted in 2014 with no specific review date listed
National Society of Genetic Counselors[33]	Prenatal cfDNA screening	• The National Society of Genetic Counselors supports prenatal cfDNA screening, also known as NIPT or NIPS, as an option for pregnant patients. • Because cfDNA screening cannot definitively diagnose or rule out genetic conditions, qualified providers should communicate the benefits and limitations of cfDNA screening to patients prior to testing. • Many factors influence cfDNA screening performance, therefore it may not be the most appropriate option for every pregnancy. • Prior to undergoing cfDNA screening, patients should have the opportunity to meet with qualified prenatal care providers who can facilitate an individualized discussion of patients' values and needs, including the option to decline all screening or proceed directly to diagnostic testing. • Clinicians with expertise in prenatal screening, such as genetic counselors, should provide post-test genetic counseling to patients with increased-risk screening results. • Diagnostic testing should be offered to patients with increased-risk results to facilitate informed decision making.	Adopted in 2016 with no specific review date listed
Polish Gynecological Society, Polish	cfDNA testing in prenatal diagnosis	• NIPT should not replace FTS based on fetal ultrasound scan and biochemical testing of maternal blood. NIPT should be ordered by a physician who has experience in obstetrics, perinatology or clinical genetics.	Adopted in 2017 with no specific review date listed

Organization	Topic	Excerpted Recommendation(s)	Status
Human Genetics Society[37]		• NIPT should be performed between the 10th and 15th week of pregnancy. NIPT is not recommended for low risk pregnancies with a risk less than 1:1000 as indicated by integrated tests (ultrasound+ biochemical testing of maternal blood). • NIPT should be offered to pregnant women with a risk of fetal chromosomal aberration from 1:100 to 1:1000. If the risk is higher than 1: 100, invasive prenatal diagnosis should be offered. When fetal congenital anomalies are diagnosed based on ultrasound but the NIPT results are correct, the patient must be referred to a genetics specialist for further diagnostics and genetic counselling. • NIPT is not recommended for multiple pregnancies (triplets and higher). • Before NIPT ultrasound scan should be performed to assess the number of fetuses and the gestational age. • NIPT should not replace fetal ultrasound examination. Ultrasound scan has to be performed following the guidelines of the Ultrasound Section of the Polish Gynaecological Society. • When NIPT results could not be obtained (up to 5%) the NIPT test may be repeated or invasive diagnostics has to be offered. • NIPT and invasive diagnostics should not be performed at the same time. When NIPT shows high risk of chromosomal aberration amniocentesis is indicated as a method of invasive diagnostics. • When NIPT estimates high risk of fetal chromosomal aberration the patient has to be consulted by clinical geneticist or specialist in perinatology. • Pregnancy cannot be terminated based only on NIPT result. NIPT results should be signed by a specialist in medical laboratory diagnostics.	

Abbreviations. *ACMG: American College of Medical Genetics and Genomics; AFP: alpha-fetoprotein; cfDNA: cell-free DNA; cFTS: combined first-trimester screen; CPT: Current Procedural Terminology; FASP: Fetal Anomaly Screening Programme; FN: false negative; FP: false positive; FTS: first-trimester screen; hCG: human chorionic gonadotropin; ISUOG: International Society of Ultrasound in Obstetrics and Gynecology; MA: maternal age; NIPS: noninvasive prenatal screening; NIPT: noninvasive prenatal testing; PAPP-A: pregnancy-associated plasma protein A; SCA: sex chromosome aneuploidy; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21; UE3: estriol.*