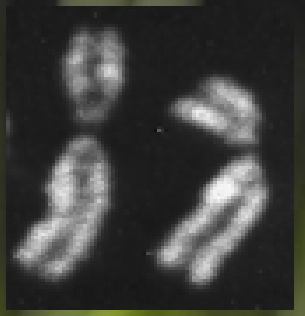

vantaggi e svantaggi dei "non invasive prenatal tests" nella ricerca delle aneuploidie

leda dalprà

CAM
20 settembre 2013

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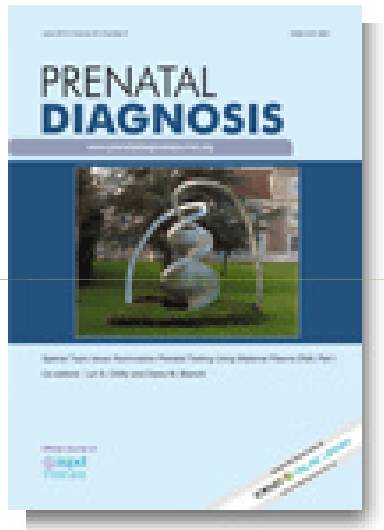

Special Issue: Noninvasive Prenatal Testing Using Maternal Plasma DNA: Part I

June 2013

Volume 33, Issue 6
Pages 511–618

Issue edited by: Lyn S. Chitty, Diana W. Bianchi

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Editorial

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Noninvasive prenatal testing: the paradigm is shifting rapidly (pages 511–513)

Lyn S. Chitty and Diana W. Bianchi

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4136

Abstract | Full Article (HTML) | PDF(69K) | References | Request Permissions

Reviews

Jump to…

Fetal aneuploidy detection by maternal plasma DNA sequencing: a technology assessment (pages 514–520)

Judith M. E. Walsh and James D. Goldberg

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4109

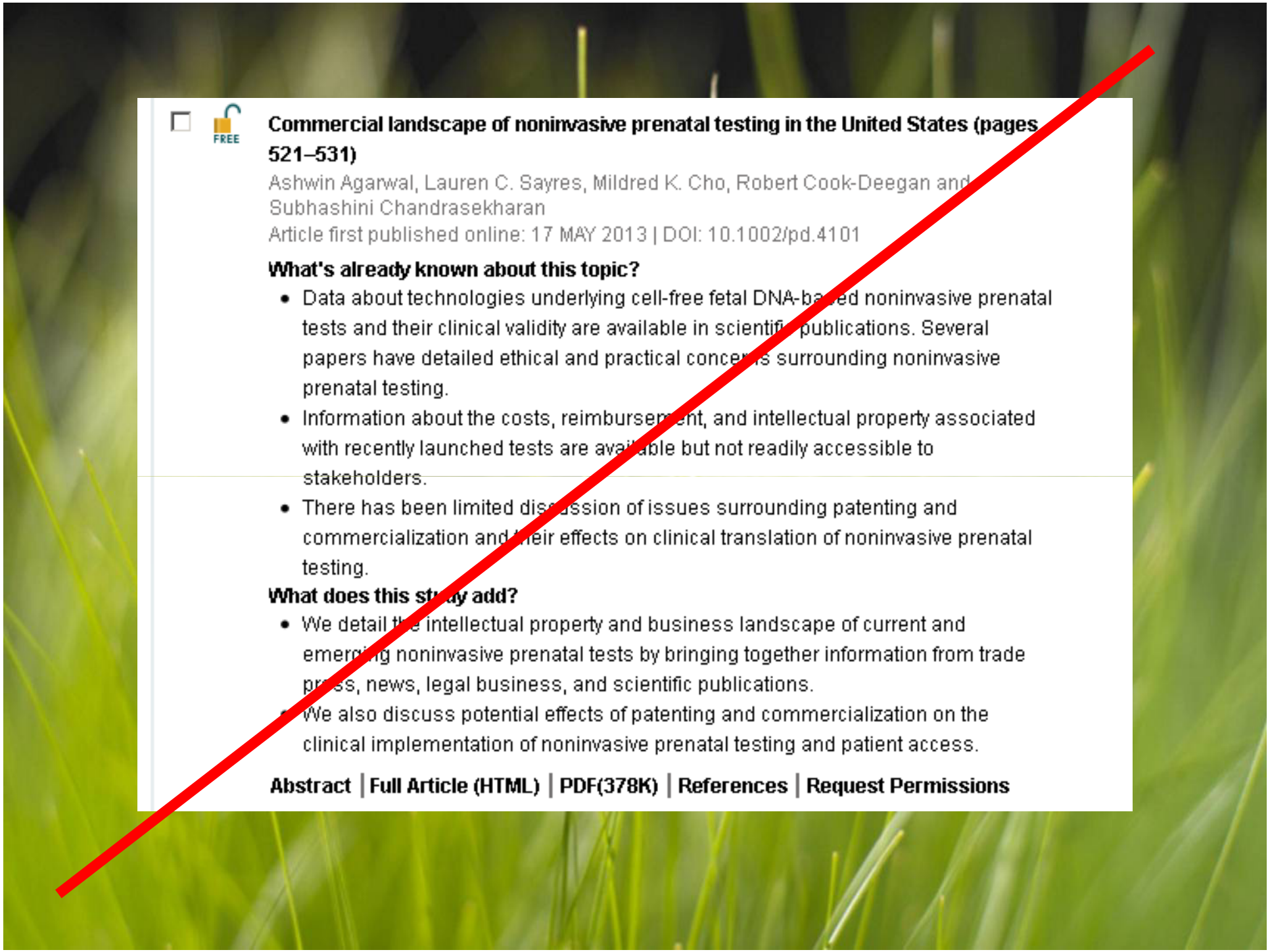
What's already known about this topic?

- Noninvasive prenatal testing by analysis of cell-free DNA has the potential to accurately diagnose common fetal aneuploidies, although how best to use this test in the context of other available prenatal tests has not yet been determined.

What does this study add?

- This study critically assesses the published literature on the use of maternal plasma DNA sequencing for fetal aneuploidy detection and compares it with the established alternatives. Finally, it provides guidelines for evidence-based use of maternal plasma DNA sequencing for the detection of fetal aneuploidy

Abstract | Full Article (HTML) | PDF(93K) | References | Request Permissions



Commercial landscape of noninvasive prenatal testing in the United States (pages 521–531)

Ashwin Agarwal, Lauren C. Sayres, Mildred K. Cho, Robert Cook-Deegan and Subhashini Chandrasekharan

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4101

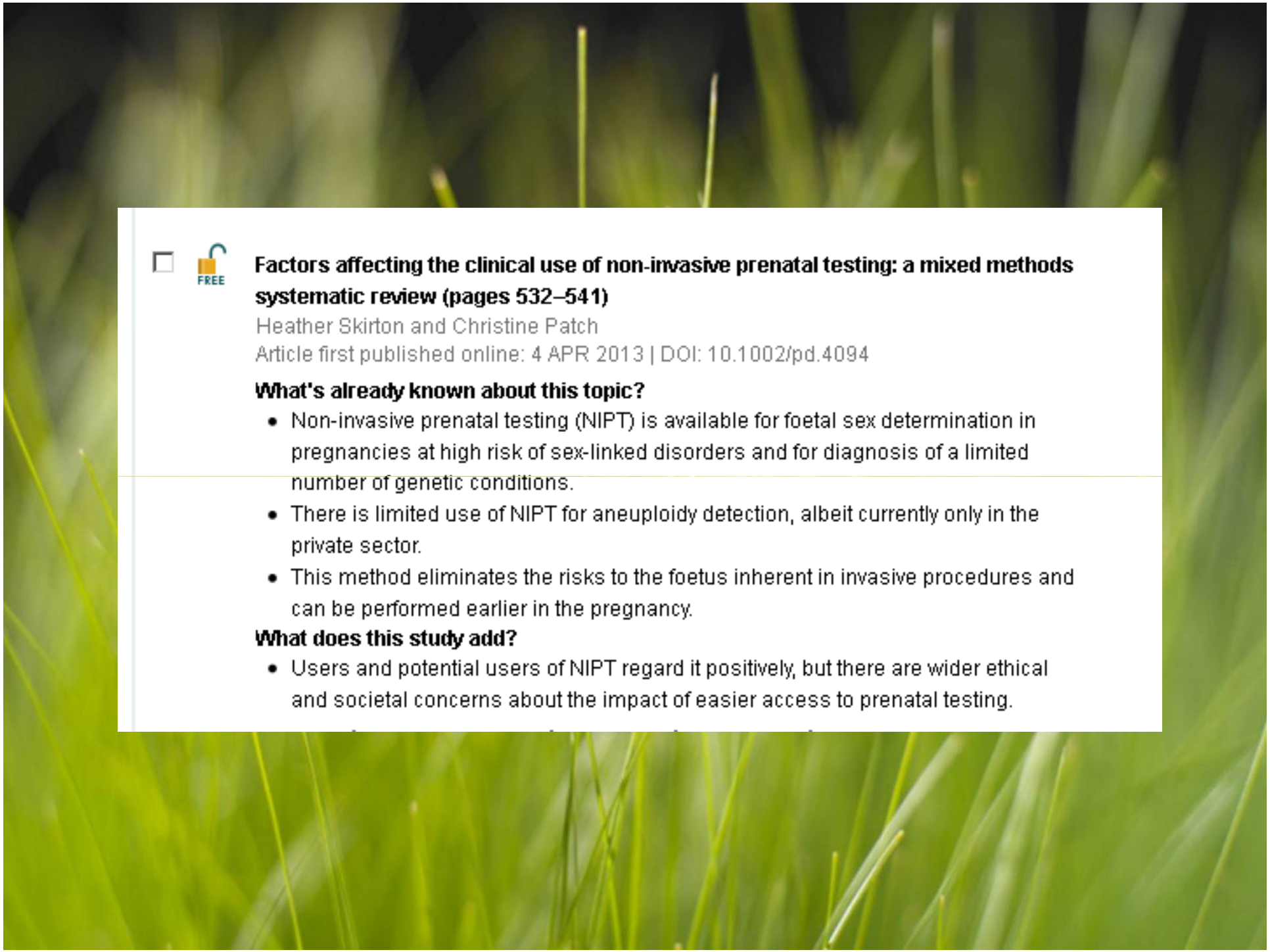
What's already known about this topic?

- Data about technologies underlying cell-free fetal DNA-based noninvasive prenatal tests and their clinical validity are available in scientific publications. Several papers have detailed ethical and practical concerns surrounding noninvasive prenatal testing.
- Information about the costs, reimbursement, and intellectual property associated with recently launched tests are available but not readily accessible to stakeholders.
- There has been limited discussion of issues surrounding patenting and commercialization and their effects on clinical translation of noninvasive prenatal testing.

What does this study add?

- We detail the intellectual property and business landscape of current and emerging noninvasive prenatal tests by bringing together information from trade press, news, legal business, and scientific publications.
- We also discuss potential effects of patenting and commercialization on the clinical implementation of noninvasive prenatal testing and patient access.

Abstract | Full Article (HTML) | PDF(378K) | References | Request Permissions



Factors affecting the clinical use of non-invasive prenatal testing: a mixed methods systematic review (pages 532–541)

Heather Skirton and Christine Patch

Article first published online: 4 APR 2013 | DOI: 10.1002/pd.4094

What's already known about this topic?

- Non-invasive prenatal testing (NIPT) is available for foetal sex determination in pregnancies at high risk of sex-linked disorders and for diagnosis of a limited number of genetic conditions.
- There is limited use of NIPT for aneuploidy detection, albeit currently only in the private sector.
- This method eliminates the risks to the foetus inherent in invasive procedures and can be performed earlier in the pregnancy.

What does this study add?

- Users and potential users of NIPT regard it positively, but there are wider ethical and societal concerns about the impact of easier access to prenatal testing.

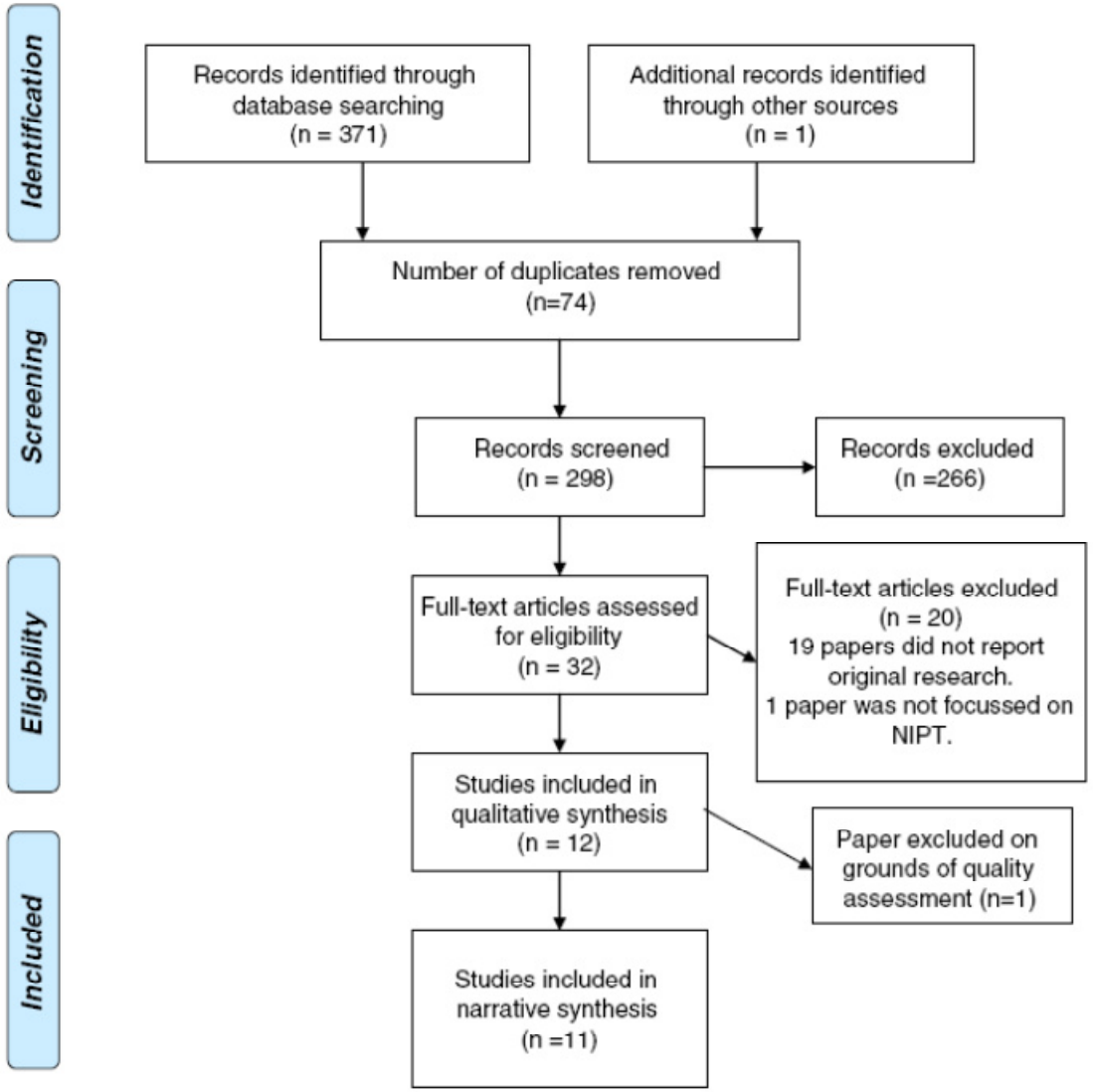


Figure 1 Search flow diagram based on PRISMA[15]

15. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bri Med J 2009;339:b2700.

Table 1 Summary of papers included in the review

Authors, title and country	Aims	Method	Sample	Analysis	Findings/results	Quality issues
Hill *et al.* 'Incremental cost of non-invasive prenatal diagnosis versus invasive prenatal diagnosis of fetal sex in England', UK	'To evaluate the incremental cost of NIPD compared with IPD for fetal sex determination in the English NHS' (p. 268)	Cost analysis Care pathways derived from empiric data. Costs established from NHS data. Perspective NHS costs	Comparison of NIPD and IPD in two conditions: congenital adrenal hyperplasia and Duchenne muscular dystrophy	Mean costs of pregnancy Univariate and probabilistic sensitivity analysis to determine limits of uncertainty Monte Carlo simulation model	No significant difference in cost between IPD and NIPD. Costs of fetal sexing with NIPD were offset by the smaller proportion of women who required CVS.	88%; Limitations: care pathways derived from a study that was primarily concerned with diagnostic accuracy. Costs were calculated to end of pregnancy and did not consider lifetime costs of a diagnosis.
Hill *et al.* 'Determination of foetal sex in pregnancies at risk of haemophilia: a qualitative study exploring the clinical practices and attitudes of health professionals in the United Kingdom', UK	'To determine the current practices of health professionals in offering prenatal care for women who are carriers of haemophilia and explore the introduction and use of NIPD for foetal sex determination' (p. 576)	Qualitative cross-sectional study based on grounded theory	32 health professionals who were involved in management of women who were carriers of haemophilia during pregnancy. Of these, 12 worked in haemophilia centres, six in genetics units and six in foetal medicine units.	Grounded theory method	Offering NIPD for foetal sexing was felt to enhance prenatal care of carrier women. Use of NIPD was not felt to increase workload for staff. Although respondents reported that most women were relaxed about use of NIPD, the main questions asked by carriers focussed on the accuracy and timing of the test. Respondents felt it was important the test was not seen as routine.	90%; No evidence given of researcher reflexivity, otherwise an excellent paper
Kelly and Farrimond 'Non-invasive prenatal genetic testing: a study of public attitudes', UK	'To identify the range of viewpoints on NIPD amongst a sample of the UK public with a diversity of experiences and demographic characteristics' (p. 75)	Qmethodology. Qualitative data were collected via postal self-completion questionnaires.	Purposive sample of 71 UK individuals aged between 18 and 60 years (73% RR). Sample recruited via media sources.	Thematic analysis of participants' first responses to brief factual information about NIPD.	Although 63% of first responses were positive, many of those respondents had concerns. Ambivalence about testing focussed on increased safety and utility by individual parents, contrasting with more ethical concerns about increase ease leading to more casual use, changes in attitudes to disabled children and increased termination rates.	80%; Good theoretical underpinning for study but lacked sufficient information on sampling procedure and data analysis.
Kooij *et al.* 'The attitude of women toward current and future possibilities of diagnostic testing in maternal blood using fetal DNA', The Netherlands	To determine 'women's attitudes toward current and future testing possibilities' (p. 165) concerning NIPD.	Cross-sectional survey. Questions were derived from a questionnaire used in a previous study. Participants used Likert scales to indicate level of agreement with statements on use of NIPD.	Women recruited from two groups: (1) pregnant women and (2) female Master's level students. A power calculation indicated 100 women needed in each group, recruitment continued until sample obtained.	Descriptive statistics calculated. Chi-square distribution to determine differences in responses between the two groups.	Pregnant women were more likely than students to state that NIPD for Down syndrome should be offered to all pregnant women. The majority in both groups supported use of NIPD for prenatal diagnosis of gender-specific condition, but not for family balancing.	75%; Study questionnaire is well described. Rationalisation for using only female Master's students rather than broadening recruitment to other young women not given. Does not state if the students had children.

Given the societal concerns about possible impact of the use of NIPT and the need for more evidence on the clinical use of this type of prenatal testing, we suggest the following:

1. Consideration needs to be made with respect to the needs of specific patient groups before the introduction of NIPT into clinical practice. For example, although it may be appropriate to offer NIPT in high-risk pregnancies, introduction for population screening may not be warranted without further research, public consultation and discussion at policy level to address concerns about the ethical and social implications.
2. Specific provision needs to be made to ensure parents have the time and information needed to make an informed choice about the use of NIPT. This may require building in time for reflection between information giving and seeking informed consent, as well as ensuring health professionals are appropriately trained.
3. Further empirical research is needed in a range of cultural settings to ensure that clinical practice is appropriate for the population served.

Benefits and limitations of whole genome versus targeted approaches for noninvasive prenatal testing for fetal aneuploidies (pages 563–568)

Elles M. J. Boon and Brigitte H. W. Faas

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4111

What's already known about this topic?

- Since the discovery of cell-free fetal DNA in maternal plasma, large progress has been made in the development of noninvasive prenatal tests.
- The first applications in noninvasive prenatal diagnosis were single polymerase chain reaction-based.
- Since 2008, a new era in the development of noninvasive aneuploidy testing was opened by the first successful application of massively parallel sequencing for this purpose.

What does this study add?

- For fetal aneuploidy testing, whole genome massively parallel sequencing is still rather expensive and to reduce costs, targeted sequencing approaches are being developed.
- This review highlights benefits and limitations of both whole genome and targeted approaches for noninvasive prenatal testing for fetal aneuploidy detection for now and the near future as a shift in the most cost effective approach is anticipated in the near future.

Table 1 Overview of large-scale validation studies for NIPT for Down syndrome

	No. of samples	T21 samples	NGS platform	Whole genome (WG)/Targeted (T) approach	Number of mapped reads per sample	Sensitivity (%)	Specificity (%)
Ehrich 2011[12]	449 (4-plex)	39	Illumina GAIIx	WG	3–5 million	100	99.7
Chiu 2011[11]	2-plex $n=314$ 8-plex $n=753$	86	Illumina GAIIx	WG	2.3 million (2-plex) 0.3 million (8-plex)	100 (2-plex) 79.1 (8-plex)	97.9 (2-plex) 98.9 (8-plex)
Palomaki 2011[14]	4664 (4-plex)	212	Illumina High Seq 2000	WG	n.s.	98.6	99.8
Sparks 2012[26]	298	39	Illumina High Seq 2000	T	204000/410000/ 620000	100	100
Sparks 2012[24]	163	35	Illumina High Seq 2000	T	1 million		
Ashoor 2012[27]	397	50	n.s.	T	n.s.	100	100
Norton 2012[28]	3228	81	n.s.	T	n.s.	100	99.7
Bianchi 2012[31]	2882 (6-plex)	89	Illumina High Seq 2000	WG	n.s.	100	100

NIPT, noninvasive prenatal testing; NGS, next-generation sequencing; n.s., not specified.

A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing (pages 584–590)

Shengpei Chen, Tze Kin Lau, Chunlei Zhang, Chenming Xu, Zhengfeng Xu, Ping Hu, Jian Xu, Hefeng Huang, Ling Pan, Fuman Jiang, Fang Chen, Xiaoyu Pan, Weiwei Xie, Ping Liu, Xuchao Li, Lei Zhang, Songgang Li, Yingrui Li, Xun Xu, Wei Wang, Jun Wang, Hui Jiang and Xiuqing Zhang

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4110

What's already known about this topic?

- Sequencing-based noninvasive prenatal detection of fetal aneuploidy has been proven to be highly accurate. However, it is still a challenge to detect fetal deletion/duplication syndrome because of the interference from maternal DNA in maternal plasma.

What does this study add?

- Here, we developed a practical bioinformatic methodology to detect fetal chromosomal deletions/duplications of >10 Mb using low coverage whole genome sequencing of maternal plasma.

Secondary findings from non-invasive prenatal testing for common fetal aneuploidies by whole genome sequencing as a clinical service (pages 602–608)

Tze Kin Lau, Fu Man Jiang, Robert J. Stevenson, Tsz Kin Lo, Lin Wai Chan, Mei Ki Chan, Pui Shan Salome Lo, Wei Wang, Hong-Yun Zhang, Fang Chen and Kwong Wai Choy

Article first published online: 2 APR 2013 | DOI: 10.1002/pd.4076

What's already known about this topic?

- Non-invasive prenatal testing (NIPT) by maternal plasma DNA sequencing is highly sensitive and specific in detecting fetal aneuploidies.

What does this study add?

- We report five cases of secondary findings of abnormal chromosome copy number when performing NIPT by maternal plasma sequencing for fetal aneuploidies.

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Research Letters

Jump to...

Discordant noninvasive prenatal testing results in a patient subsequently diagnosed with metastatic disease (pages 609–611)

C. Michael Osborne, Emily Hardisty, Patricia Devers, Kathleen Kaiser-Rogers, Melissa A. Hayden, William Goodnight and Neeta L. Vora

Article first published online: 4 APR 2013 | DOI: 10.1002/pd.4100

What's already known about this topic?

- Noninvasive prenatal testing for detection of trisomies 21, 18, and 13 is clinically available and is reported to have a false positive rate of 1% or less
- This technology utilizes massively parallel shotgun sequencing of cell-free DNA, of maternal and placental origin, present in maternal plasma

What does this study add?

- Unexplained abnormal noninvasive prenatal testing results should prompt consideration of a maternal source of the abnormal cell-free DNA, such as malignancy

Noninvasive prenatal testing creates an opportunity for antenatal treatment of Down syndrome (pages 614–618)

Faycal Guedj and Diana W. Bianchi

Article first published online: 17 MAY 2013 | DOI: 10.1002/pd.4134

What's already known about this topic?

- DS is the most common autosomal aneuploidy associated with intellectual disability.
- Worldwide, most screening programs focus on prenatal detection of DS.
- Research to improve neurocognition in people with DS is almost exclusively focused on adults.
- Pregnant women carrying affected fetuses with DS can choose to continue or terminate their pregnancies, but there is no fetal treatment available.

What does this study add?

- We present data to show that many pregnant women continue their pregnancies when their fetus is affected with DS.
- We review the published literature on brain pathology in human fetuses with DS and embryonic mice affected with a model form of the disease.
- We summarize the limited available information on prenatal treatment approaches for DS and make the case that there is an important window of opportunity to positively impact neurogenesis and brain morphogenesis by providing treatment during fetal life.

Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis†

Peter Benn[1]*, Antoni Borell[2], Rossa Chiu[3], Howard Cuckle[4], Lorraine Dugoff[5], Brigitte Faas[6], Susan Gross[7], Joann Johnson[8], Ron Maymon[9], Mary Norton[10], Anthony Odibo[11], Peter Schielen[12], Kevin Spencer[13], Tianhua Huang[14], Dave Wright[15] and Yuval Yaron[16]

Prenatal Diagnosis 2013, 33, 622–629

Table 2 Large clinical trials of cfDNA screening for fetal trisomies 21, 18 and 13

		Trisomy 21				Trisomy 18				Trisomy 13			
Study	Method	DR (%)	FPR (%)	NR[a] (%)	Unclass[b] (%)	DR (%)	FPR (%)	NR[a] (%)	Unclass[b] (%)	DR (%)	FPR (%)	NR[a] (%)	Unclass[b] (%)
1. Chiu *et al.*[7]	Shotgun	86/86 (100)	3/146 (2.1)	11/764 (1.4)									
2. Ehrich *et al.*[8]	Shotgun	39/39 (100)	1/410 (0.2)	18/467 (3.9)									
3. Palomaki *et al.*[9,10]	Shotgun	209/212 (98.6)	3/1471 (0.2)	13/1686 (0.8)		59/59 (100)	5/1688 (0.3)	17/1988 (0.9)		11/12 (91.7)	16/1688 (0.9)	17/1988 (0.9)	
4. Bianchi *et al.*[11]	Shotgun	89/89 (100)	0/404 (0)	16/532 (3.0)	7/503 (1.4)	35/36 (97.2)	0/461 (0)	16/532 (3.0)	5/502 (1.0)	11/14 (78.6)	0/488 (0)	16/532 (3.0)	2/502 (0.4)
5. Sparks *et al.*[12]	Targeted	36/36 (100)	1/123 (0.8)	8/338 (2.4)[c]		8/8 (100)	1/123 (0.8)	8/338 (2.4)[c]					
6. Ashoor *et al.*[13]	Targeted	50/50 (100)	0/297 (0)	3/400 (0.8)		49/50 (98.0)	0/297 (0)	3/400 (0.8)					
7. Norton *et al.*[14]	Targeted	81/81 (100)	3/2888 (0.1)	148/3228 (4.6)		37/38 (97.4)	3/2888 (0.1)	148/3228 (4.6)					
Total		590/593 (99.5)	11/5739 (0.2)	217/7415 (2.9)	7/503 (1.4)	188/191 (98.4)	9/5457 (0.2)	192/6486 (3.0)	5/502 (1.0)	22/26 (84.6)	16/2,176 (0.7)	33/2520 (1.3)	2/502 (0.4)

DR, detection rate; FPR, false-positive rate.

[a]NR, no result due to low fetal DNA fraction or other causes of test failure. Excludes samples that were considered to be inadequate or ineligible prior to testing. Additional cases needed more than one sample to achieve a result.

[b]Unclass, intermediate results that the laboratory interpreted as 'unclassified'. On the basis of proportion of affected pregnancies in the unclassified groups [trisomy 21 14% (1/7); trisomy 18 40% (2/5); trisomy 13 100% (2/2)], these women should be considered to be at high risk. Including them as positive changes the total discriminatory power: trisomy 21 DR 100% (90/90), FPR 1.5% (6/410); trisomy 18 DR 97.3 (37/38), FPR 0.6% (3/464); trisomy 13 DR 81.3% (13/16), FPR 0% (0/488).

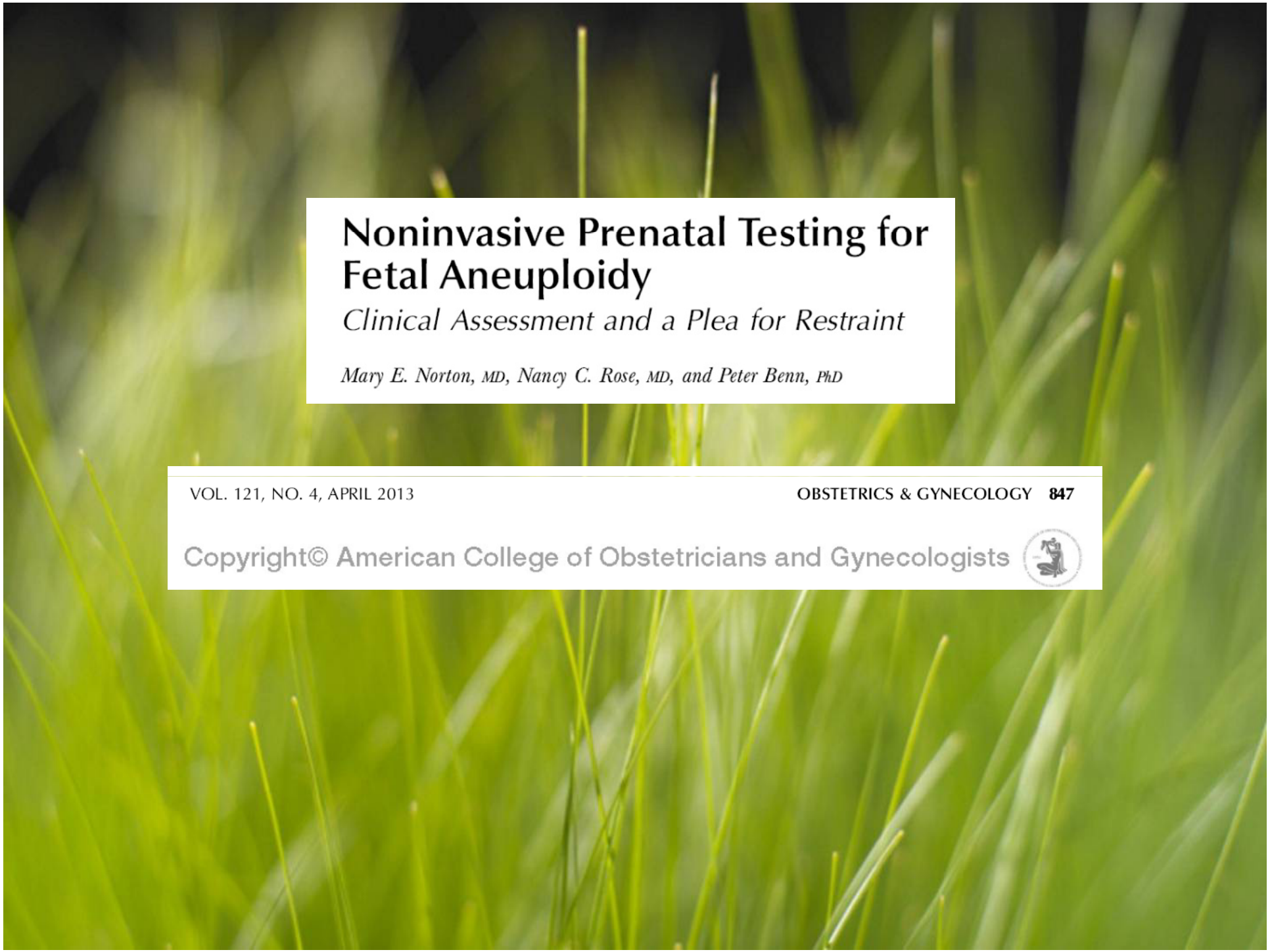
[c]No result rate based on training and validation samples combined.

GENERAL CONSIDERATIONS FOR ALL ANEUPLOIDY SCREENING

When there is a known history of a previous pregnancy with trisomy 21, 13, or 18 or if a translocation involving these chromosomes is known to be segregating in the family, risks should be adjusted to allow for this additional information. Genetic counseling and prenatal diagnosis may be indicated. For those women who are at increased risk of a child with a prenatally diagnosable disorder with Mendelian pattern of inheritance, microdeletion syndrome, and some other conditions, amniocentesis or CVS would still be indicated.

There may also be limitations in the availability of reproductive genetic services, including but not limited to proficient sonographers, certified genetic counselors and physicians, or requisite computer programs used to calculate risks. Early pregnancy referral patterns and economic considerations are also likely to result in geographic differences in the protocols used. The choice of protocol also must to take into consideration the need to screen for open neural tube defects either through second trimester AFP or second trimester ultrasound.

No single combination of markers or screening cut-offs will therefore be appropriate for all situations.



Noninvasive Prenatal Testing for Fetal Aneuploidy

Clinical Assessment and a Plea for Restraint

Mary E. Norton, MD, Nancy C. Rose, MD, and Peter Benn, PhD

VOL. 121, NO. 4, APRIL 2013 OBSTETRICS & GYNECOLOGY 847

The recent introduction of clinical tests to detect fetal aneuploidy by analysis of cell-free DNA in maternal plasma represents a tremendous advance in prenatal diagnosis and the culmination of many years of effort by researchers in the field. The development of noninvasive prenatal testing for clinical application by commercial industry has allowed much faster introduction into clinical care, yet also presents some challenges regarding education of patients and health care providers struggling to keep up with developments in this rapidly evolving area. It is important that health care providers recognize that the test is not diagnostic; rather, it represents a highly sensitive and specific screening test that should be expected to result in some false-positive and false-negative diagnoses. Although currently being integrated in some settings as a primary screening test for women at high risk of fetal aneuploidy, from a population perspective, a better option for noninvasive prenatal testing may be as a second-tier test for those patients who screen positive by conventional aneuploidy screening. How noninvasive prenatal testing will ultimately fit with the current prenatal testing algorithms remains to be determined. True cost–utility analyses will be needed to determine the actual clinical efficacy of this approach in the general prenatal population.


grazie per l’attenzione