GENOME-WIDE NIPT
國外及台灣經驗

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Annual Review of Genomics and Human Genetics

The Emergence and Global Spread of Noninvasive Prenatal Testing

2021

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Themes covered:

The structure of the healthcare system
How NIPT is offered
Counseling needs and resources
Cultural and legal context regarding disability and pregnancy termination.

Emerging issues:

Cost as a barrier to equitable access, the complexity of decision-making about public funding
A shortage of appropriate resources that promote informed choice.
Sociocultural values that underlie the use of NIPT vary greatly among countries. The issues described will become even more challenging as NIPT evolves from a second-tier to a first-tier screening test with expanded use.

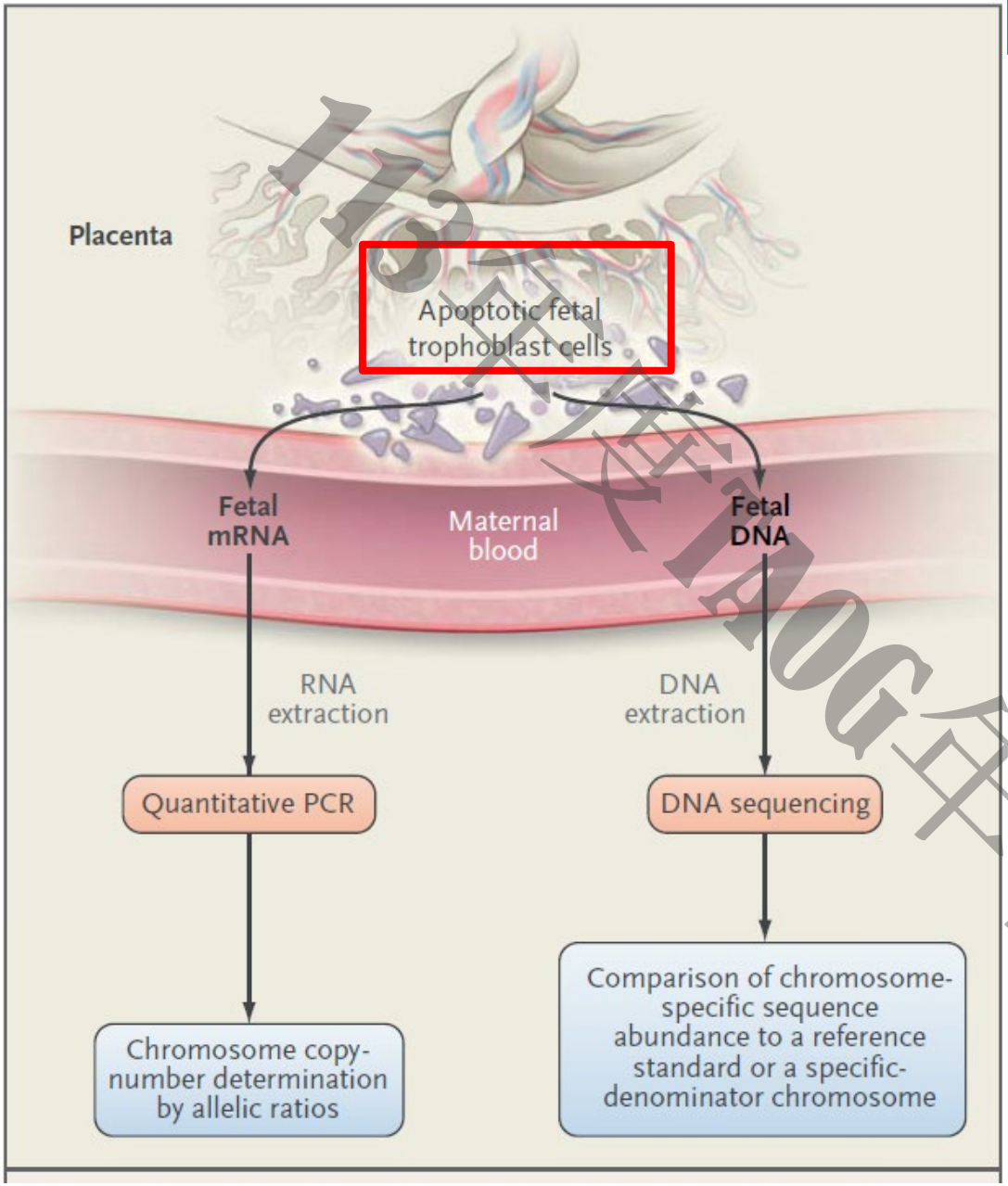
Agenda

- Comparison of different technologies
- Genome-wide NIPT
- Analytical vs. clinical validity
- The real world data
- Experience of a single diagnostic center in Taiwan
- The ACMG Committee Statement
- Take-home message

非侵襲性胎兒遺傳篩檢（Non-invasive fetal testing，NIPT）

原理

- 孕婦血清內的胎兒DNA含量大約是媽媽DNA的5%～20%。
- 使用分析DNA技術分析孕婦血清內的胎兒DNA，再透過統計學運算，估計胎兒有染色體異常的機率。



Noninvasive Prenatal Diagnosis with the Use of Plasma Cell-free Fetal RNA or DNA in Maternal Blood Derived from Dying Trophoblast Cells of the Placenta.

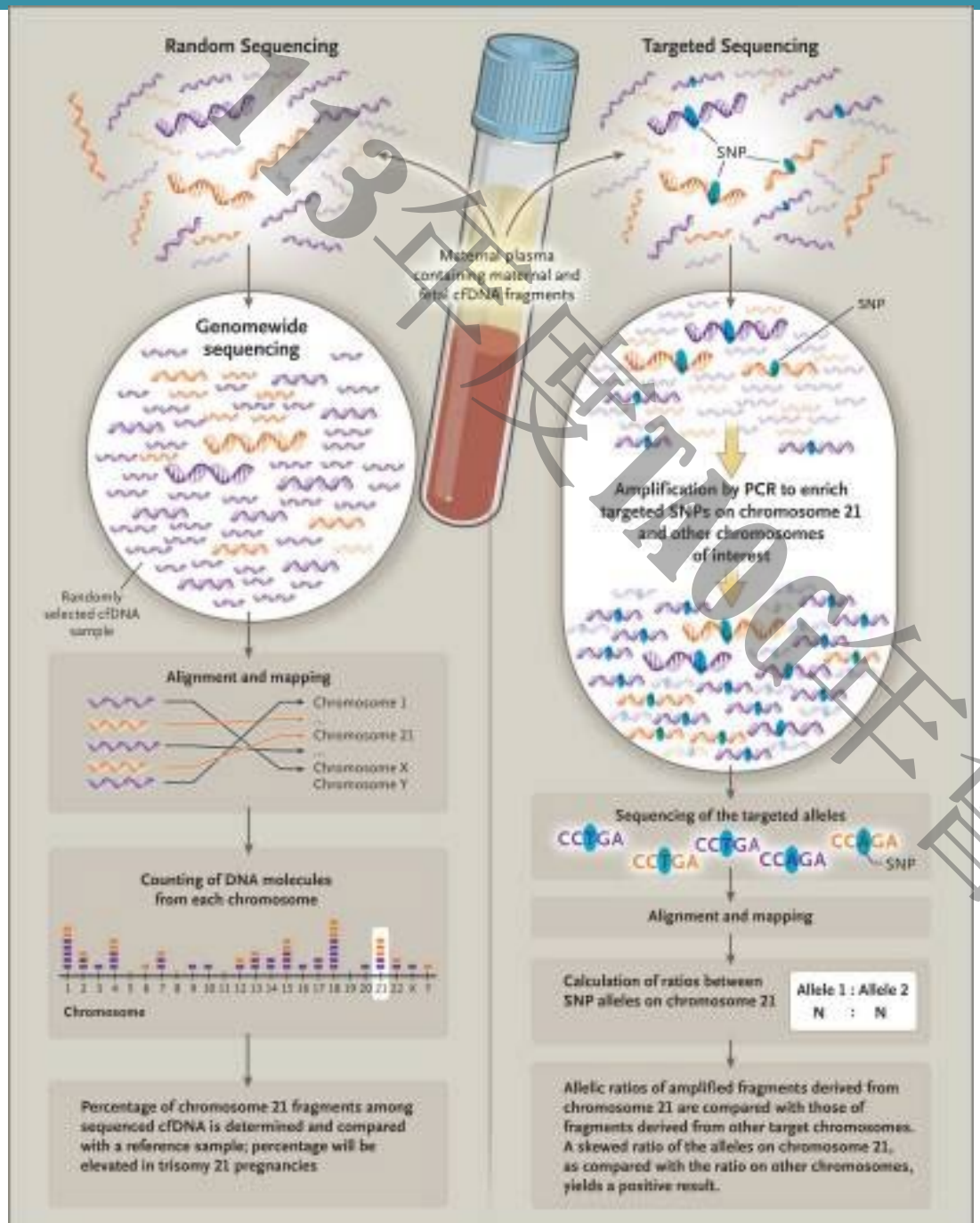
Joann Bodurtha and Jerome F. Strauss. ***Genomics and Perinatal Care.***
NEJM 2012;366:64-73

Potential applications of NIPT

- Aneuploidies
- Segmental aneuploidies (copy number variants, CNVs)
- Monogenic variants

Technologies

- Random sequencing (counting – based):
  MPS evaluates the quantitative change in the proportion of each chromosome-derived component in cffDNA in maternal plasma, that is it counts cffDNA fragments in maternal plasma using NGS, and thereby detects fetal chromosome abnormalities.
  (Ultra-low coverage whole genome sequencing < 1X)
- Targeted sequencing (SNP - based):
  This technique determines the difference between parent and child DNA, and the relative dosage of genetic variation to infer copy number. cfDNA is amplified by PCR using specific SNP targets.

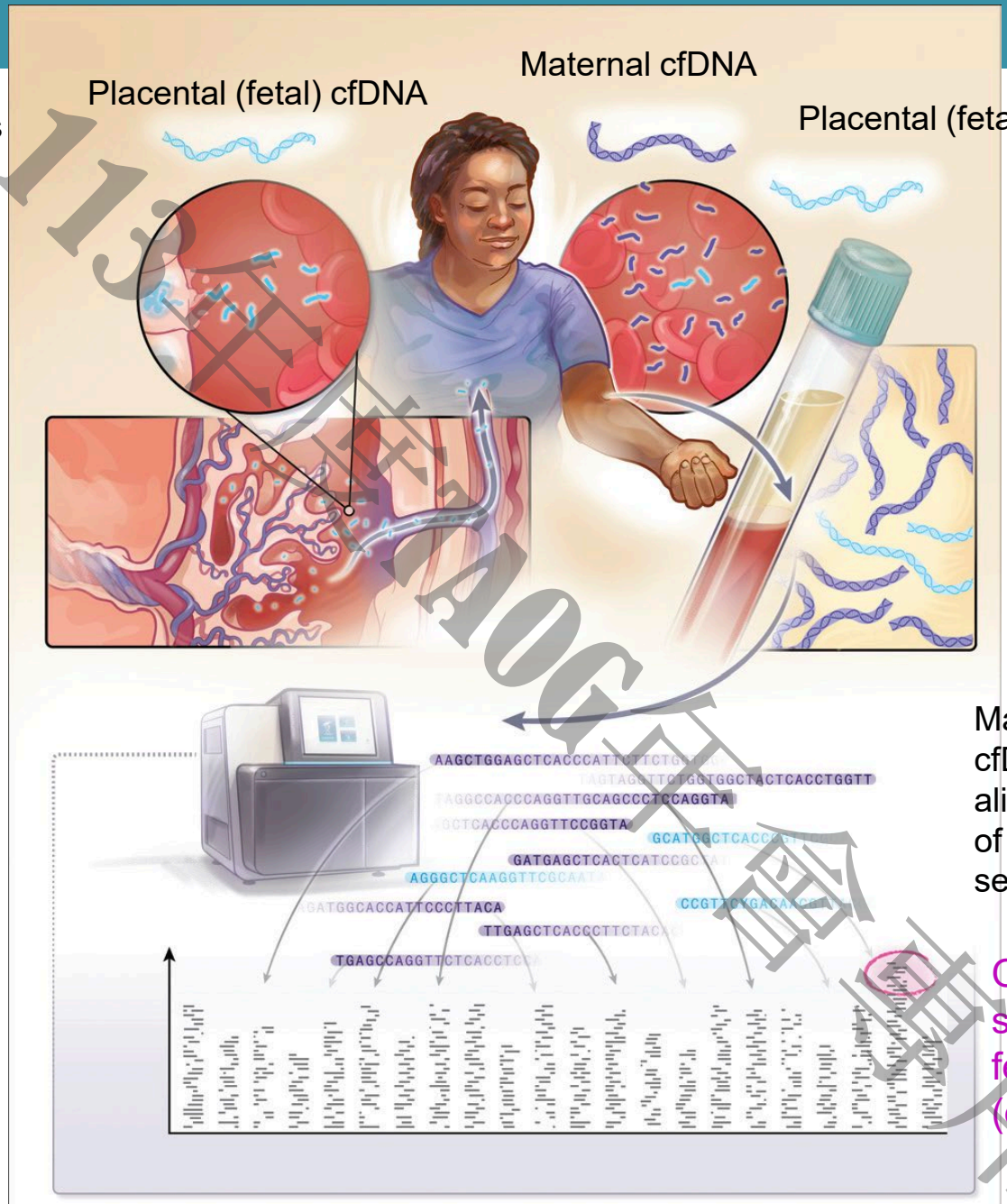


The Two Main Methods of Maternal Plasma DNA Sequencing for Prenatal Screening of Fetal Chromosomal Aneuploidies

Sequencing of Circulating Cell-free DNA during Pregnancy, NEJM 2018

Routine turnover of cells releases cfDNA (fragments of genomic DNA) into circulation

Placental (fetal) cfDNA passes from the placenta into maternal blood



Maternal and placental cfDNA is sequenced, aligned to a reference set of chromosome sequences, and quantified

Overrepresentation suggests fetal aneuploidy (e.g.,trisomy21)

Mary E. Norton. Circulating Cell-free DNA and Screening for Trisomies. NEJM 2022

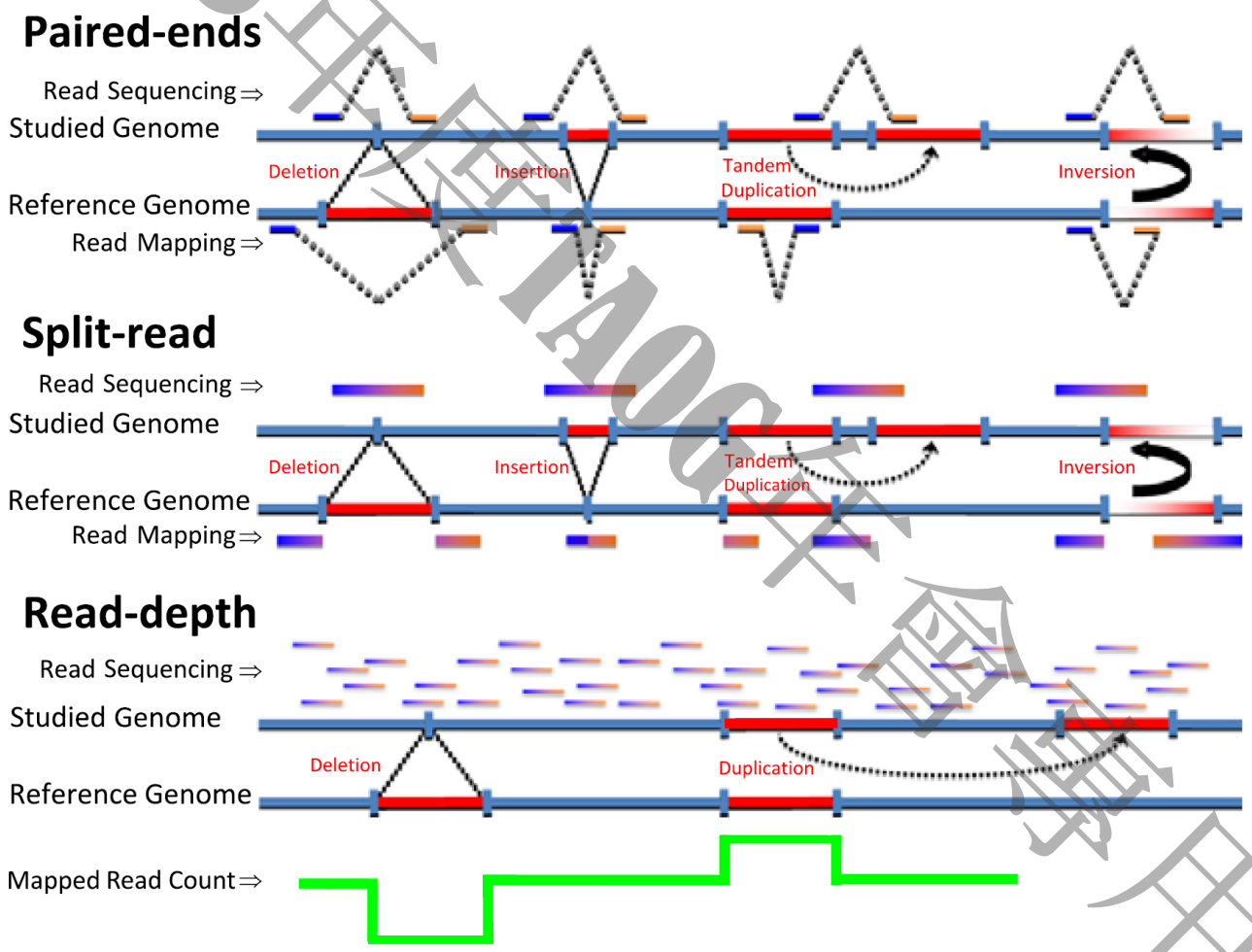
Sequencing depth

- Sequencing depth, also known as read depth or depth of coverage, refers to the number of times a specific base (nucleotide) in the DNA is read during the sequencing process.
- In other words, it's the average number of times a given position in the genome is sequenced.

Sequencing depth of different technologies

- Counting-based: 0.05 – 1 X depth
- SNP-based: 5 -25 X depth

The three approaches to analyzing 2nd-gedneration, high-output DNA sequencing reads to detect structural genomic variation. Paired-end DNA sequencing output can be analyzed for paired-end mapping (PEM) and then reanalyzed using split read analysis (SRA) and read-depth analysis (RDA).



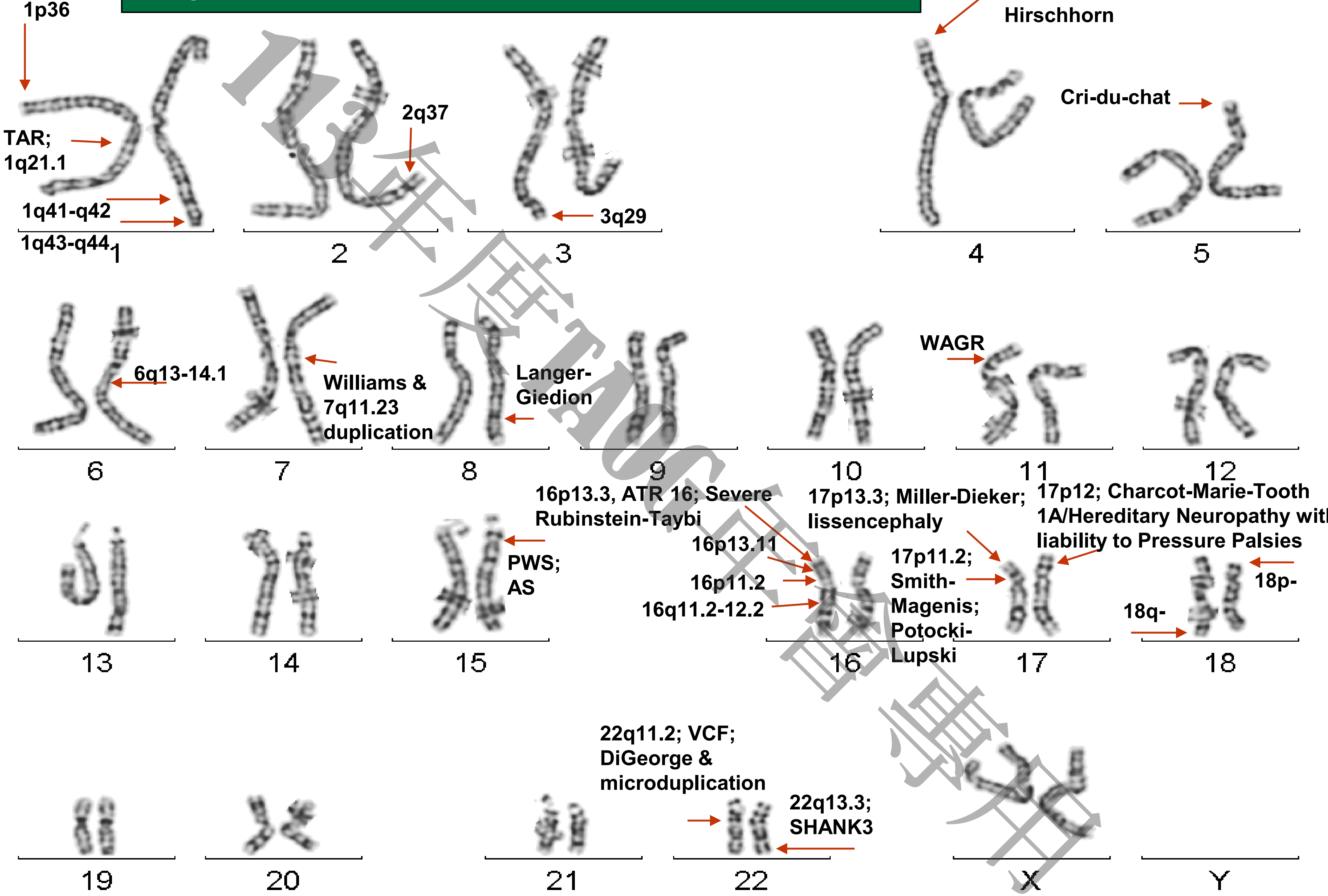
Ying Zhang et al. Child Development and Structural Variation in the Human Genome. Child Development 2013;84:34–48.

Table 2. Conditions for Which Cell-free DNA Testing Is Clinically Available.*

Common autosomal aneuploidies
Trisomy 21
Trisomy 18
Trisomy 13
Sex chromosome aneuploidies
45,X
47,XXX
47,XXY
47,XYY
Rare autosomal aneuploidies
Whole-chromosome aneuploidy of any autosome (trisomy 7, 15, 16, and 22 are the most commonly detected)
Microdeletion and microduplication syndromes
1p36 deletion
Wolf–Hirschhorn syndrome (terminal 4p deletion)
Cri du chat syndrome (terminal 5p deletion)
Langer–Giedion syndrome (8q24 deletion)
Jacobsen's syndrome (terminal 11q deletion)
Prader–Willi and Angelman syndromes (15q11.2-q13 deletion)
DiGeorge syndrome (22q11.2 deletion)
Copy-number variants larger than 7 Mb
Triploidy

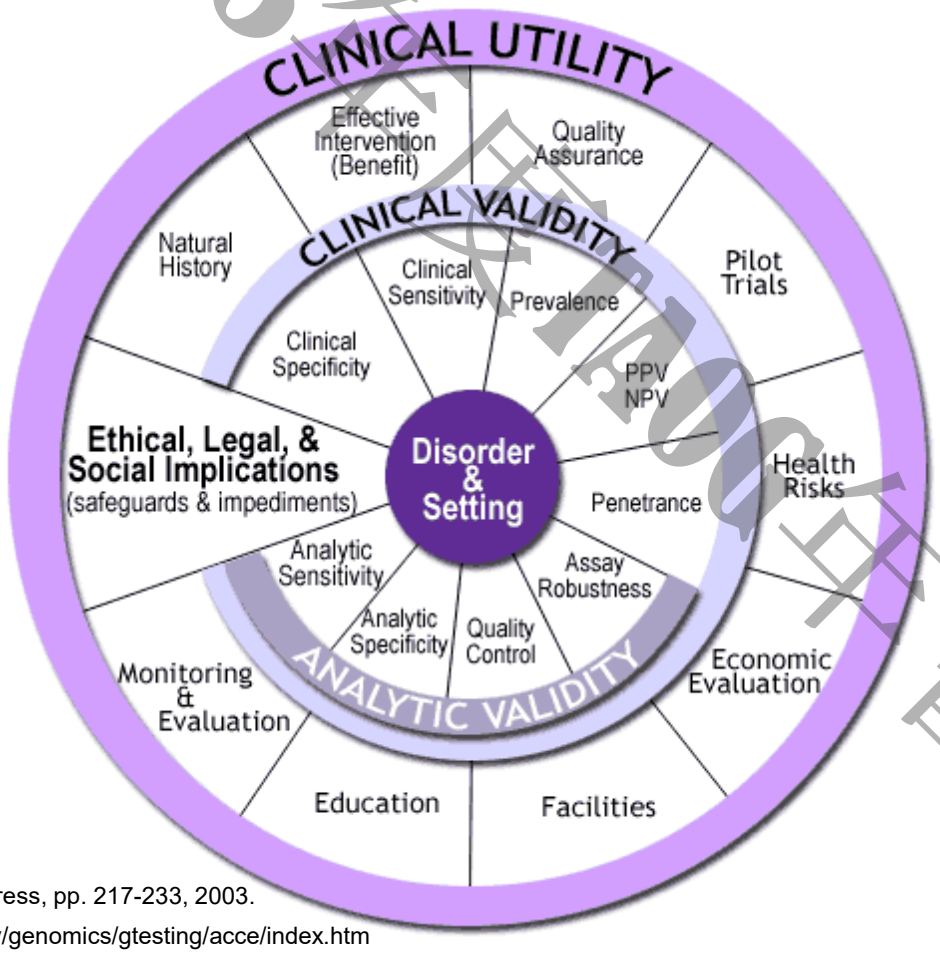
Sequencing of Circulating Cell-free DNA during Pregnancy, NEJM 2018

Major microdeletion/microduplication sites



Courtesy of Dr Jia-Chi (Jack) Wang

ACCE Model for Evaluation of Genetic Tests



Testing performance affects the patient's risk

Oxford University Press, pp. 217-233, 2003.

https://www.cdc.gov/genomics/gtesting/acce/index.htm

ACCE model (by CDC)

- Analytic validity (分析效度)：確效
- Clinical validity (臨床效度)：
  sensitivity, specificity, positive predictive value, negative predictive value,
- Clinical utility (臨床效用)：
  health risk, actionability, economic benefits, long-term monitoring, etc.
- Ethical, legal and social issues (相關的倫理、法律和社會影響)。

Clinical validity (e.g. cancer genetic testing)

- The clinical validity of a genetic test is the likelihood that cancer will develop in someone with a positive test result.
- A term that refers to the predictive value of a test for a given clinical outcome (e.g., the likelihood that cancer will develop in someone with a positive test).

https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/clinical-validity

Clinical Validity of Non-Invasive Prenatal Screening (NIPS)

Table 1 Performance of NIPS in a general-risk population for trisomy 21, trisomy 18, and trisomy 13 calculated in random-effects meta-analyses

Test Statistic	No. of Studies	Result (%) (95% CI)	I^2 (%)
Trisomy 21			
Sensitivity	17	98.80 (97.81-99.34)	0.0
Specificity	14	99.96 (99.92-99.98)	75.9
PPV	28	91.78 (88.43-94.23)	68.3
NPV	14	100 (99.99-100)	0.0
FPR	14	0.04 (0.02-0.08)	75.9
Accuracy	14	99.94 (99.91-99.96)	80.2
DOR[a]	14	110,000 (44,000-260,000); $P < .0001$	55.7
Trisomy 18			
Sensitivity	6	98.83 (95.45-99.71)	0.0
Specificity	7	99.93 (99.83-99.97)	94.9
PPV	17	65.77 (45.29-81.68)	88.5
NPV	7	100 (100-100)	0.0
FPR	7	0.07 (0.03-0.17)	75.9
Accuracy	6	99.91 (99.73-99.97)	95.7
DOR[a]	6	29,000 (4800-180,000); $P < .0001$	94.9
Trisomy 13			
Sensitivity	7	100 (0-100)	0.0
Specificity	8	99.96 (99.92-99.98)	81.5
PPV	18	37.23 (26.08-49.93)	71.9
NPV	8	100 (100-100)	0.0
FPR	8	0.04 (0.02-0.08)	81.5
Accuracy	8	99.95 (99.90-99.97)	82.2
DOR[a]	7	29,000 (8900-94,000); $P < .0001$	0

Results do not include studies without adequate data to include in meta-analyses.

DOR, diagnostic odds ratio; *FPR*, false positive rate; *NIPS*, noninvasive prenatal screening; *NPV*, negative predictive value; *PPV*, positive predictive value.

[a]Data presented as odds ratio.

Genetics in Medicine (2023) 25, 100336

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ACMG PRACTICE GUIDELINE

Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

檢測施行方式3/5

檢測預期效能及確效計畫：

✓應提供檢測確效報告

Accuracy	(TP + TN) / (FP + TP + FN + TN)
True positive rate (TPR)	TP / (TP + FN)
Sensitivity	see TPR
Recall	see TPR
Hit rate	see TPR
Probability of detection	see TPR
True negative rate (TNR)	TN / (TN + FP)
Specificity	see TNR
Selectivity	see TNR
Positive predictive value (PPV)	TP / (TP + FP)
Precision	see PPV
Negative predictive value (NPV)	TN / (TN + FN)
False negative rate (FNR)	FN / (FN + TP)
Miss rate	see FNR
False positive rate (FPR)	FP / (FP + TN)
Fall out	see FPR
False discovery rate (FDR)	FP / (FP + TP)
False omission rate (FOR)	FN / (FN + TN)

https://www.johndcook.com/blog/2018/09/06/accuracy-precision-and-recall/

Genome-wide NIPT

- Genome-wide NIPT (GW-NIPT) allows for the detection of chromosomal aberrations other than trisomies 13, 18, 21 (rare autosomal trisomies, RAT) and segmental aneuploidies (copy number variants).
- GW-NIPT can also detect maternal genetic aberrations including undiagnosed cancer.
- NIPT based on targeted seqeuencing: Not included

How to launch a NIPT

- *In silico* simulation:
  Preparation of artificial NIPT data sets followed by computation
- *In vitro* validation:
  Preparation of control DNA sample mixes, followed by standard experimental procedures and bioinformatic analysis
- Clinical validation with reanalysis of abnormal cases (retrospective studies)
- Prospective studies (The real world data)

The Trident Study

- In 2014, the Dutch NIPT Consortium, a national partnership of professionals and other stakeholders involved in public prenatal care, was granted a governmental license to introduce NIPT in the Dutch prenatal screening program. This implementation study was called the Trial by Dutch Laboratories for Evaluation of Non-invasive Prenatal Testing (TRIDENT).
- The aim of the TRIDENT study is to determine whether and how NIPT should be offered within the national prenatal screening program in the Netherlands **(an unbiased database)**

Trident 1

- The first phase (TRIDENT-1) offered NIPT as a second-tier screening test to **women with an elevated risk** for trisomy 21, 18, or 13 based on the first trimester combined test (FCT) or medical history (e.g., a previous child with a trisomy).
- TRIDENT-1 resulted in high NIPT uptake and a vast reduction of invasive tests, supporting the offer of NIPT to women with an increased risk for fetal trisomy.

Trident 2

- Phase 2 (TRIDENT-2) of the NIPT implementation study was
- initiated in 2017. NIPT as a first-tier screening test for trisomies 21, 18, and 13 and as an alternative to the FCT (first trimester combined test) became available to **the general obstetric population.**
- A unique aspect of the TRIDENT-2 study is that women opting for NIPT can choose a test aimed at the analysis of the common trisomies only or a genome-wide test that also reports other autosomal chromosomal aberrations.

- GW-NIPT was shown to be a reliable and highly accurate screening test for the detection of common trisomies 21, 18, and 13 in the general obstetric population.
- In addition, the study showed the ability of GW-NIPT to detect other and less common chromosomal aberrations, together with the origin of these additional findings.
- In some cases, false-positive results have been attributed to a chromosomal abnormality that is confined to the placenta, while the fetus has a normal chromosome complement. This known as confined placental mosaicism (CPM).

Official journal of the American College of Medical Genetics and Genomics ORIGINAL RESEARCH ARTICLE Genetics inMedicine

2019

Open

Origin and clinical relevance of chromosomal aberrations other than the common trisomies detected by genome-wide NIPS: results of the TRIDENT study

Diane Van Opstal, PhD[1], Merel C. van Maarle, MD, PhD[2], Klaske Lichtenbelt, MD, PhD[3], Marjan M. Weiss, PhD[4], Heleen Schuring-Blom, PhD[3], Shama L. Bhola, MSc[4], Mariette J.V. Hoffer, PhD[5], Karin Huijsdens-van Amsterdam, PhD[2], Merryn V. Macville, PhD[6], Angelique J.A. Kooper, PhD[7], Brigitte H.W. Faas, PhD[7], Lutgarde Govaerts, MD, PhD[1], Gita M. Tan-Sindhunata, MD[4], Nicolette den Hollander, MD, PhD[5], Ilse Feenstra, MD, PhD[7], Robert-Jan H. Galjaard, MD, PhD[1], Dick Oepkes, MD, PhD[8], Stijn Ghesquiere, PhD[6], Rutger W.W. Brouwer, PhD[9], Lean Beulen, MD, PhD[10], Sander Bollen, MSc[5], Martin G. Elferink, PhD[3], Roy Straver, MSc[4], Lidewij Henneman, PhD[4], Godelieve C. Page-Christiaens, MD, PhD[11] and Erik A. Sistermans, PhD[4]; for the Dutch NIPT Consortium

American Journal of Human Genetics 2019

TRIDENT-2: National Implementation of Genome-Wide Non-Invasive Prenatal Testing as a First-Tier Screening Test in the Netherlands

Karuna R.M. van der Meij,[1,18] Erik A. Sistermans,[1,18,*] Merryn V.E. Macville,[2] Servi J.C. Stevens,[2] Caroline J. Bax,[3] Mireille N. Bekker,[4] Caterina M. Bilardo,[5] Elles M.J. Boon,[1] Marjan Boter,[6] Karin E.M. Diderich,[6] Christine E.M. de Die-Smulders,[2] Leonie K. Duin,[7] Brigitte H.W. Faas,[8] Ilse Feenstra,[8] Monique C. Haak,[9] Mariëtte J.V. Hoffer,[10] Nicolette S. den Hollander,[10] Iris H.I.M. Hollink,[6] Fernanda S. Jehee,[6] Maarten F.C.M. Knapen,[11] Angelique J.A. Kooper,[12] Irene M. van Langen,[13] Klaske D. Lichtenbelt,[14] Ingeborg H. Linskens,[5] Merel C. van Maarle,[12] Dick Oepkes,[9] Mijntje J. Pieters,[15] G. Heleen Schuring-Blom,[14] Esther Sikkel,[16] Birgit Sikkema-Raddatz,[12] Dominique F.C.M. Smeets,[8] Malgorzata I. Srebniak,[6] Ron F. Suijkerbuijk,[12] Gita M. Tan-Sindhunata,[1] A. Jeanine E.M. van der Ven,[17] Shama L. van Zelderen-Bhola,[1] Lidewij Henneman,[1] Robert-Jan H. Galjaard,[6] Diane Van Opstal,[6] Marjan M. Weiss,[1] and The Dutch NIPT Consortium

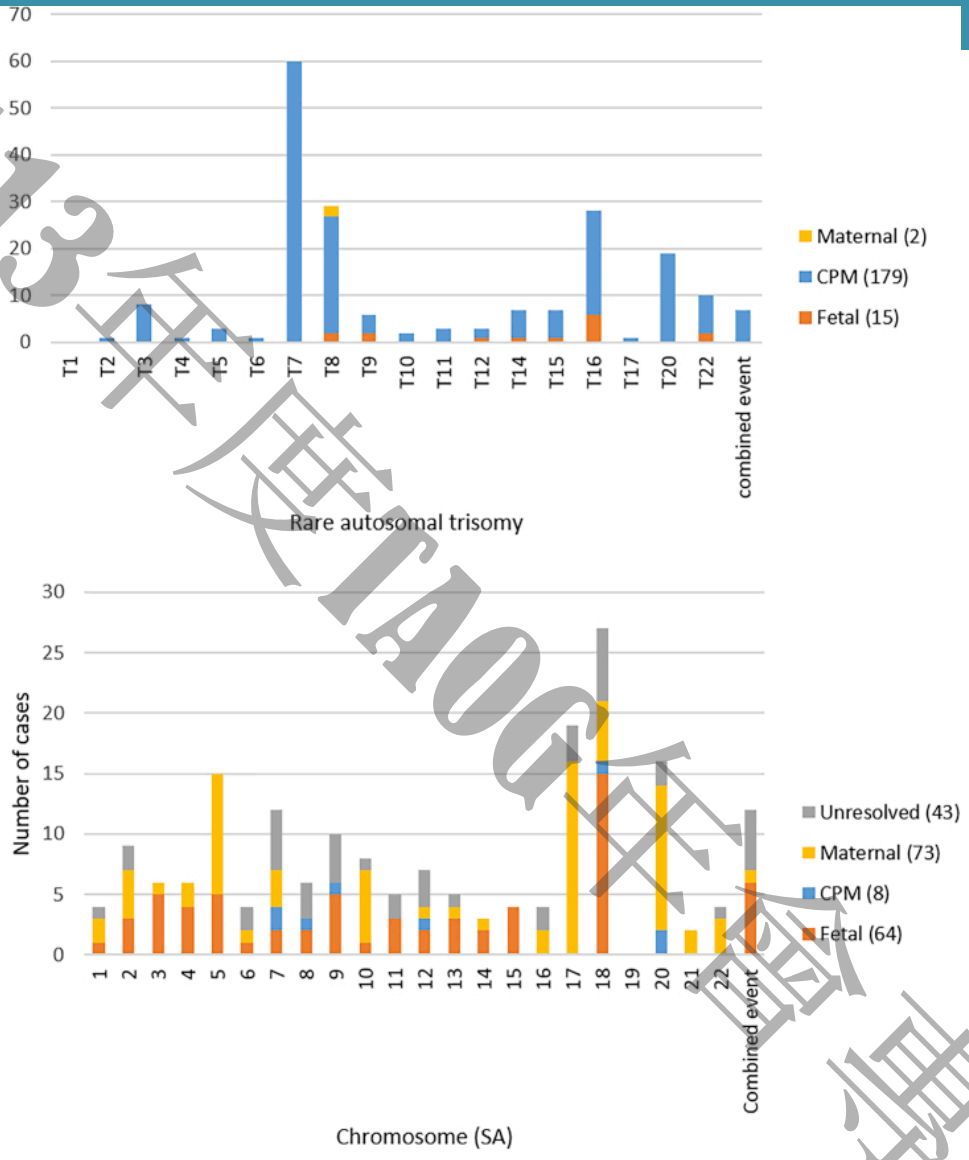
American Journal of Human Genetics 2022

ARTICLE

Clinical impact of additional findings detected by genome-wide non-invasive prenatal testing: Follow-up results of the TRIDENT-2 study

Lisanne van Prooyen Schuurman,[1,2] Erik A. Sistermans,[3] Diane Van Opstal,[1] Lidewij Henneman,[3] Mireille N. Bekker,[4] Caroline J. Bax,[5] Mijntje J. Pieters,[6] Katelijne Bouman,[7] Sonja de Munnik,[8] Nicolette S. den Hollander,[9] Karin E.M. Diderich,[1] Brigitte H.W. Faas,[8] Ilse Feenstra,[8] Attie T.J.I. Go,[10] Mariëtte J.V. Hoffer,[9] Marieke Joosten,[1] Fenne L. Komdeur,[3] Klaske D. Lichtenbelt,[11] Maria P. Lombardi,[3] Marike G. Polak,[12] Fernanda S. Jehee,[11] Heleen Schuring-Blom,[11] Servi J.C. Stevens,[13] Malgorzata I. Srebniak,[1] Ron F. Suijkerbuijk,[7] Gita M. Tan-Sindhunata,[3] Karuna R.M. van der Meij,[3] Merel C. van Maarle,[3] Vivian Vernimmen,[13] Shama L. van Zelderen-Bhola,[3] Nicolien T. van Ravesteyn,[2] Maarten F.C.M. Knapen,[10] Merryn V.E. Macville,[13] Robert-Jan H. Galjaard,[1,*] and The Dutch NIPT consortium[14]

Between April 2017 and April 2019, additional findings were detected in 402/110,739 pregnancies (0.36%). For 358 cases, the origin was proven to be either fetal (n = 79; 22.1%), (assumed) confined placental mosaicism (CPM) (n = 189; 52.8%), or maternal (n = 90; 25.1%). For the remaining 44 (10.9%), the origin of the aberration could not be determined.



Origin of additional findings per chromosome Rare autosomal trisomies (upper panel) and structural chromosome aberrations (lower panel). CPM, confined placental mosaicism; SA, structural aberration; T, trisomy.

Summary (1)

- Most fetal chromosomal aberrations were pathogenic and associated with severe clinical phenotypes (61/79; 77.2%).
- For CPM cases, occurrence of pre-eclampsia (8.5% [16/189] vs 0.5% [754/159,924]; RR 18.5), and birth weight <2.3 rd percentile (13.6% [24/177] vs 2.5% [3,892/155,491]; RR 5.5) were significantly increased compared to the general obstetric population.
- Of the 90 maternal findings, 12 (13.3%) were malignancies and 32 (35.6%) (mosaic) pathogenic copy number variants, mostly associated with mild or no clinical phenotypes.

CPM for individual chromosomes

- CPM trisomy 7 showed a significant increased risk for a birth weight
- CPM trisomy 16 showed a significant increased risk for pre-eclampsia
- CPM trisomy 20 was significantly associated with preeclampsia

Summary (2)

- For rare autosomal trisomy detected by NIPT, most cases were due to confined placental mosaicism.
- For segmental aneuploidies or structural variants, most cases were due to maternal CNVs (mosaic or non-mosaic).

A meta-analysis for RAT

- The positive predictive value of cell-free DNA in diagnosing RAT is approximately 11% according to a meta-analysis published in 2023.

(Melissa L. Acreman et al, The predictive value of prenatal cell-free DNA testing for rare autosomal trisomies: a systematic review and meta-analysis. American Journal of Obstetircs & Gynecology 2023).

Experience of a single diagnostic center

- Ultra-low pass whole genome sequencing
  NIFTY (6M = 0.2X sequencing depth)
  NIPTY Pro (25M = 0.8X sequencing depth)

- Z score:
  > 3 for common and segmental aneuploidies
  > 6 for rare autosomal trisomy (RAT)

Before launching the service, the protocols had passed the *in vitro* validation.

Reimbursement for fees of invasive testing
Insurance covered for false-negative cases

Table 3. 2014-2024/01/24 NIFTY 陽性案例統計

項目	NIFTY 高風險	真陽性	偽陽性	未確診	PPV (確診案例)
唐氏症(T21)	223	157	14	52	92%
愛德華氏症(T18)	94	41	27	26	60%
巴陶氏症(T13)	65	17	30	18	36%
透納氏症(X0)	94	18	57	19	24%
X 染色體三體症 (XXX)	41	17	15	9	53%
柯林菲特氏症 (XXY)	71	31	20	20	61%
XYY 症候群(XYY)	40	16	18	6	47%
缺失/重複異常 (CNV)	127	21	75	31	22%
其他三倍體 T9	3	1	2	0	33%
其他三倍體 T16	10	0	7	3	0%
其他三倍體 T22	9	1	6	2	14%
其他染色體異常	70	1	44	25	2%
總案件數	847	321	315	211	

※真陽性：確診結果為該項目之陽性

※真陰性個案必須進行個案確診與追蹤，若以尚未回報任何狀況為「真陰」，目前陰性預測值 NPV 為>99%

*口頭告知胎兒引產、流產、胎兒異常、胎兒死亡之個案歸類於未確診項目中

**其它染色體異常部分案例經口頭告知胎兒流產、異常個案，但皆無確診報告，故為 0

Genetics in Medicine (2023) 25, 100336

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ACMG PRACTICE GUIDELINE

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Recommendation:
AT THIS TIME, THERE IS INSUFFICIENT EVIDENCE TO RECOMMEND ROUTINE SCREENING FOR CNVs OTHER THAN 22q11.2 DELETIONS (NO RECOMMENDATION, OWING TO LACK OF CLINICALLY RELEVANT EVIDENCE AND VALIDATION)

AT THIS TIME, THERE IS INSUFFICIENT EVIDENCE TO RECOMMEND OR NOT RECOMMEND NIPS FOR THE IDENTIFICATION OF RATs (NO RECOMMENDATION, OWING TO LACK OF CLINICALLY RELEVANT EVIDENCE).

OBSTETRICS

Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome

AJOG 2022

Check for updates

Pe'er Dar, MD; Bo Jacobsson, MD, PhD; Rebecca Clifton, PhD; Melissa Egbert, MS; Fergal Malone, MD; Ronald J. Wapner, MD; Ashley S. Roman, MD; Asma Khalil, MD; Revital Faro, MD; Rajeevi Madankumar, MD; Lance Edwards, MD; Noel Strong, MD; Sina Haeri, MD; Robert Silver, MD; Nidhi Vohra, MD; Jon Hyett, MD; Zachary Demko, PhD; Kimberly Martin, MD; Matthew Rabinowitz, PhD; Karen Flood, MD; Ylva Carlsson, MD, PhD; Georgios Doulaveris, MD; Sean Daly, MD; Maria Hallingström, PhD; Cora MacPherson, PhD; Charlly Kao, PhD; Hakon Hakonarson, MD, PhD; Mary E. Norton, MD

Non GW-NIPT

Methods:

STUDY DESIGN: Patients who underwent single-nucleotide Polymorphism based prenatal cell-free DNA screening for 22q11.2 deletion syndrome were prospectively enrolled at 21 centers in 6 countries. Prenatal or newborn DNA samples were requested in all cases for genetic confirmation using chromosomal microarrays.

Results:

Of the 20,887 women enrolled, a genetic outcome was available for 18,289 (87.6%). A total of 12 22q11.2 deletion syndrome cases were confirmed in the cohort, yielding a prevalence of 1 in 1524. Overall, 9 of 12 cases of 22q11.2 were detected, yielding a sensitivity of 75.0%; specificity of 99.84%; positive predictive value of 23.7%, and negative predictive value of 99.98%.

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ACMG committee statement on CNV

- Most reports include information only about positivity rates, and therefore PPVs have been calculated from those cohorts. The cohorts in these studies are heterogeneous and many contain fetuses with ultrasound anomalies, suggesting that estimates are likely to be impacted by ascertainment bias.
- The SER (systemic evidence review) reported PPVs ranging from 0% to 80.56%.

Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2023

Continued

- An accurate determination of birth prevalence, sensitivity, and negative predictive value (NPV) was extremely difficult and not performed. Clinical validation of NIPT for rare disorders is challenging. Small CNV-driven syndromes or low-grade mosaicism often escape detection even at birth, making an accurate determination of birth prevalence, PPV and negative predictive value (NPV) difficult.
- Additional studies that include follow-up genomic testing of newborns are needed to correctly define the sensitivity, PPV and NPV.

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ACMG committee statement on RAT

- RATs identified during the prenatal period are generally present in a mosaic state. Nearly all RATs that occur in no-mosaic states result in an early miscarriage.
- Mosaicism identified at the time of chorionic villi sampling (CVS) occurs in 1% to 2% of pregnancies. Of these, the large majority represent confined placental mosaicism (CPM). Follow-up amniocentesis is generally recommended to clarify the status of the fetus with respect to the mosaicism detected on CVS.
- The incidence of mosaic RATs identified at the time of CVS is 0.6%. In this series of 52,673 CVS cases, only 8 of 316 (2.53%) mosaic RATs identified at CVS were confirmed through amniocentesis. The rare cases of mosaicism confirmed by amniocentesis, however, are associated with a wide range of phenotypic consequences.

Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2023

Continued

- CPM may be associated with growth restriction in the fetus, along with other adverse perinatal events, but there are currently no methods to predict which specific cases will result in adverse outcome. Identification of CPM for a RAT before potential manifestations, such as intrauterine growth restriction is also of questionable clinical utility.
- Surveillance interventions for pregnancies with CPM are likely to create anxiety and stress for the patient. Although NIPS may demonstrate analytical validity for RATs, there is low clinical utility.

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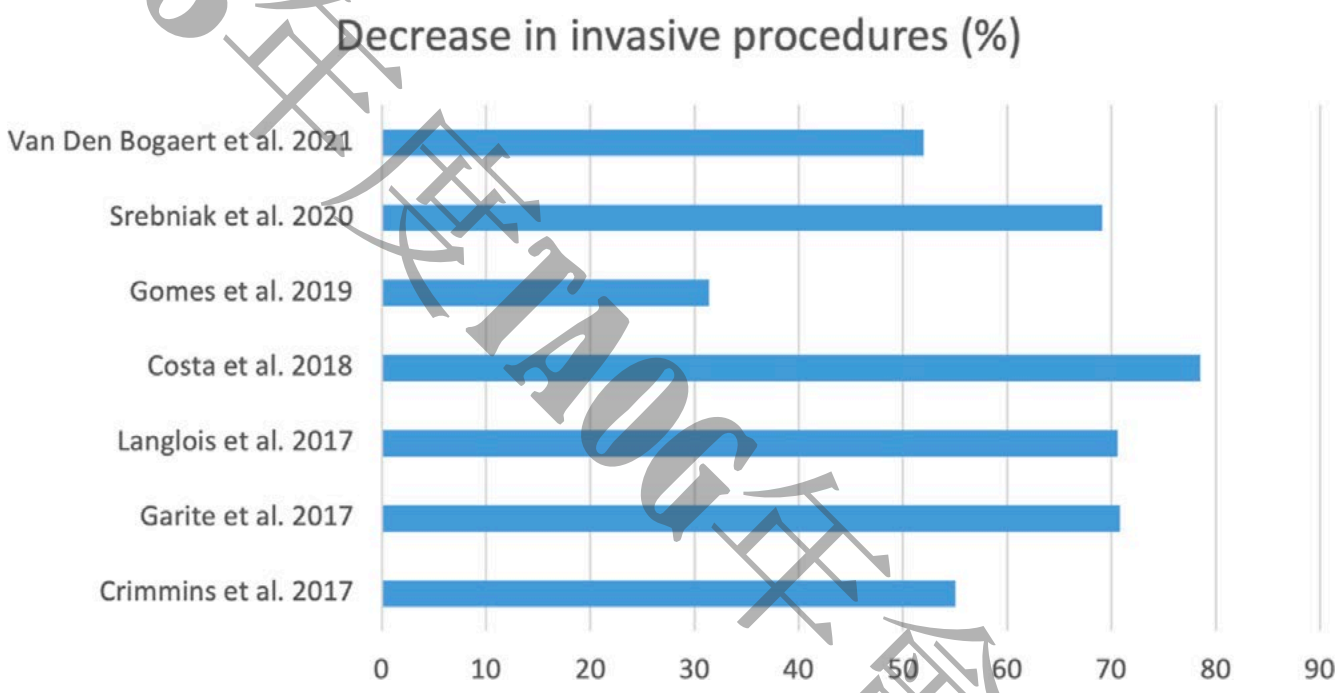
Take-home message

- NIPT has significantly reduced invasive procedures.
- It is important to understand the limitations of current genotyping technologies.
- The great mystery of placenta remains to be solved.



Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2023

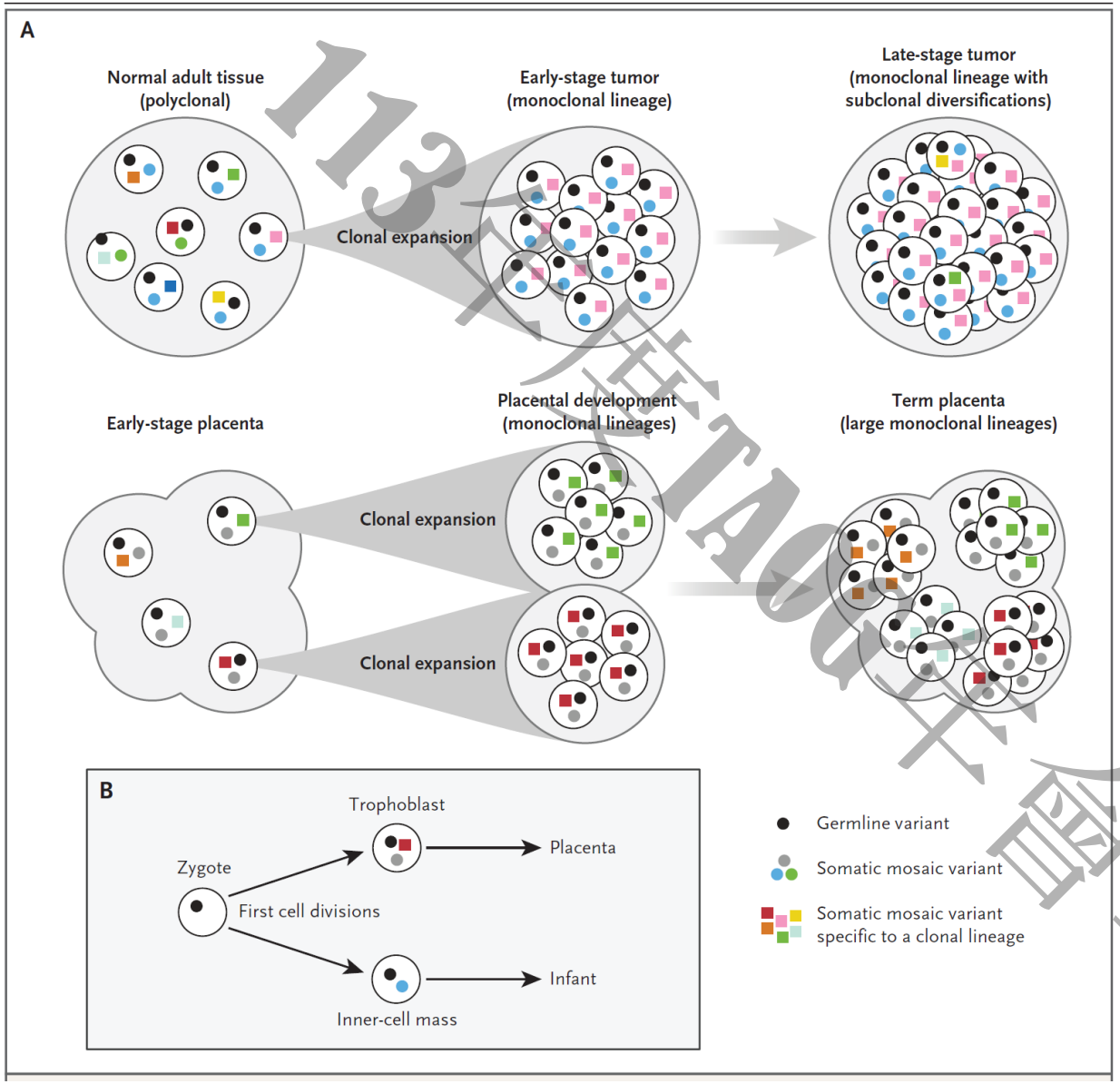
The information revealed by cell free DNA

- Cell free DNA 反應胎盤的狀態
- Cell free DNA 反應母親的狀態 (e.g. maternal constitutional mosaicism, maternal cancers, degenerating uterine myomas, various health conditions, etc.)

Extensive mutation of human placentas

- Clonal genetic mosaicism is a normal feature of the placenta
- Monoclonal outgrowths of trophoblasts were physically enormous, occupying a majority of each biopsy specimen and forming a patchwork of spatially confined outgrowths that must have arisen early in placental development

Tim H. H. Coorens et al. Inherent mosaicism and extensive mutation of human placentas. Nature 2022



Accrual of Somatic Variants in Context.

Joseph F. Costello, and Susan J. Fisher. The Placenta — Fast, Loose, and in Control. NEJM 2022

Implications of the study

- The genetic bottlenecks explain a high rate of confined placental mosaicism (aneuploidy detected only in portions of the placenta) that is estimated to affect approximately 2% of placentas.
- In this regard, it will be important to understand the range of “normal” and “abnormal” genomic changes in terms of pregnancy outcomes, which won’t be an easy task.
- The same issues will probably affect prenatal diagnoses made with the application of advanced sequencing methods to the analysis of free fetal DNA in maternal blood and biopsy specimens of chorionic villi.

Tim H. H. Coorens et al. Inherent mosaicism and extensive mutation of human placentas. Nature 2022

必也名正乎？

- Non-invasive prenatal diagnosis (NIPD)
- Non-invasive prenatal testing (NIPT)
- Non-invasive prenatal screening (NIPS)

New Prenatal Genetic Screens Pose Underappreciated Ethical Dilemmas

May 5, 2022

Noninvasive screens that look for abnormal fetal genomes often reveal hard-to-interpret results, raising challenging questions about selective abortion and eugenics

BY DANIEL NAVON

MANY THANKS FOR YOUR ATTENTION