NIFTY®

Non-Invasive Prenatal Testing

Over 2,000,000 tests performed worldwide.
Validated by a study of nearly 147,000 pregnancies.

BGI

Not For Diagnostic Use.

NIFTY®

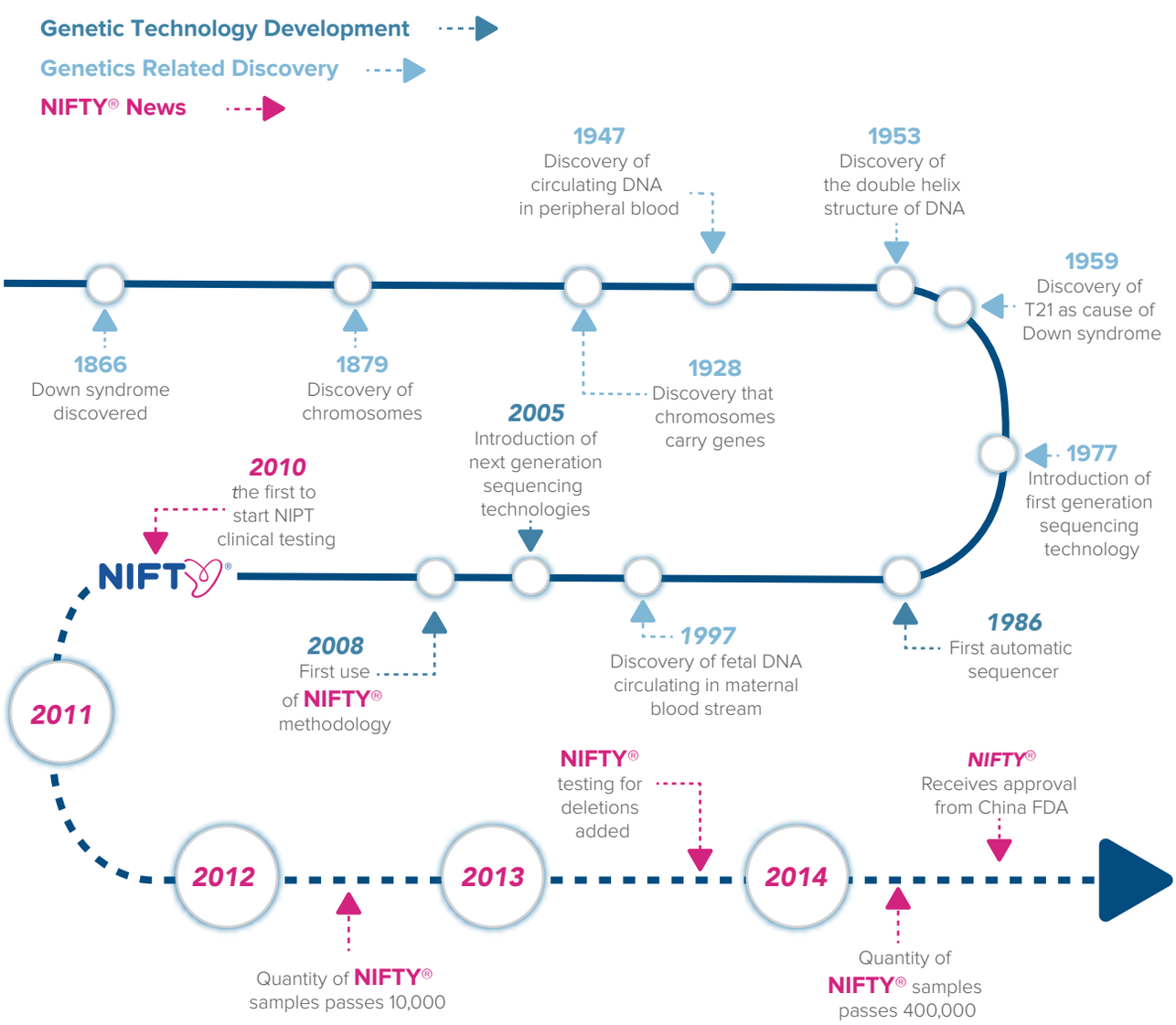
Introduction to NIFTY®

During the last decade, developments in the science of genetics and enormous advances in genetic technologies have altered our capability to understand diseases, make diagnoses and provide effective treatments. Transforming the world of prenatal testing, the advent of new DNA-based non-invasive prenatal testing (NIPT) has introduced a highly accurate screening strategy for fetal anueploidy.

The NIFTY® test (Non-Invasive Fetal TrisomY test) was the first NIPT to enter clinical testing in 2010 and was launched in Europe in the first quarter of 2013. Providing screening for the most common trisomies present at birth, as well as testing options for gender, sex chromosomal aneuploidies and chromosomal deletions, NIFTY® provides a significantly stronger risk indication than traditional screening procedures.

Up to date, over 2,000,000 NIFTY® tests have been performed worldwide. The NIFTY® test is brought to you by BGI.

TIMELINE

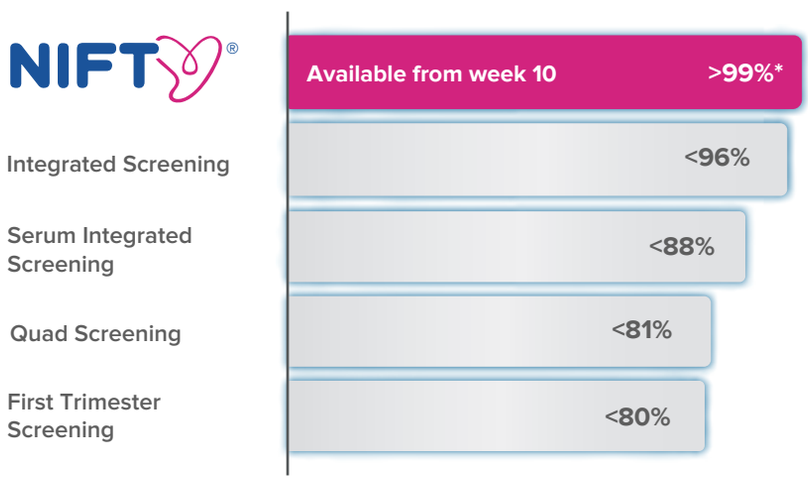


Why Non-Invasive Prenatal Testing?

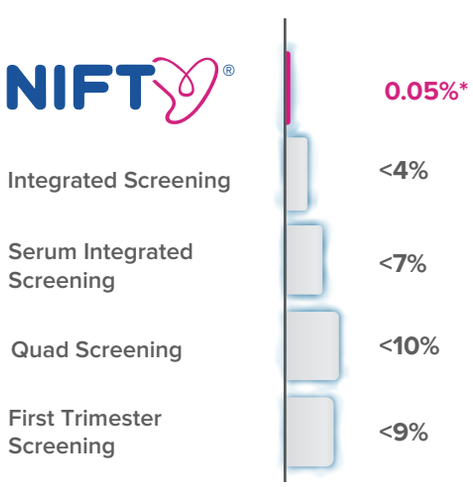
Many prenatal screening options already exist. However, compared to non-invasive prenatal testing (NIPT), traditional screening methods suffer from lower accuracy and higher false positive rates. Invasive diagnostic tests such as amniocentesis or chorionic villus sampling (CVS) are accurate but carry a 1-2% risk of miscarriage.

HOW DOES NIFTY® COMPARE TO TRADITIONAL SCREENING METHODS?

A Comparison of Detection Rates



A Comparison of False Positive Rates (FPR)



*Non-Invasive Prenatal Testing For Trisomy 21, 18 and 13 – Clinical Experience from 146,958 Pregnancies, Wei Wang et al, Journal of Ultrasound in Obstetrics and Gynecology

Introduction to Genetic Conditions Tested by NIFTY®

Trisomies

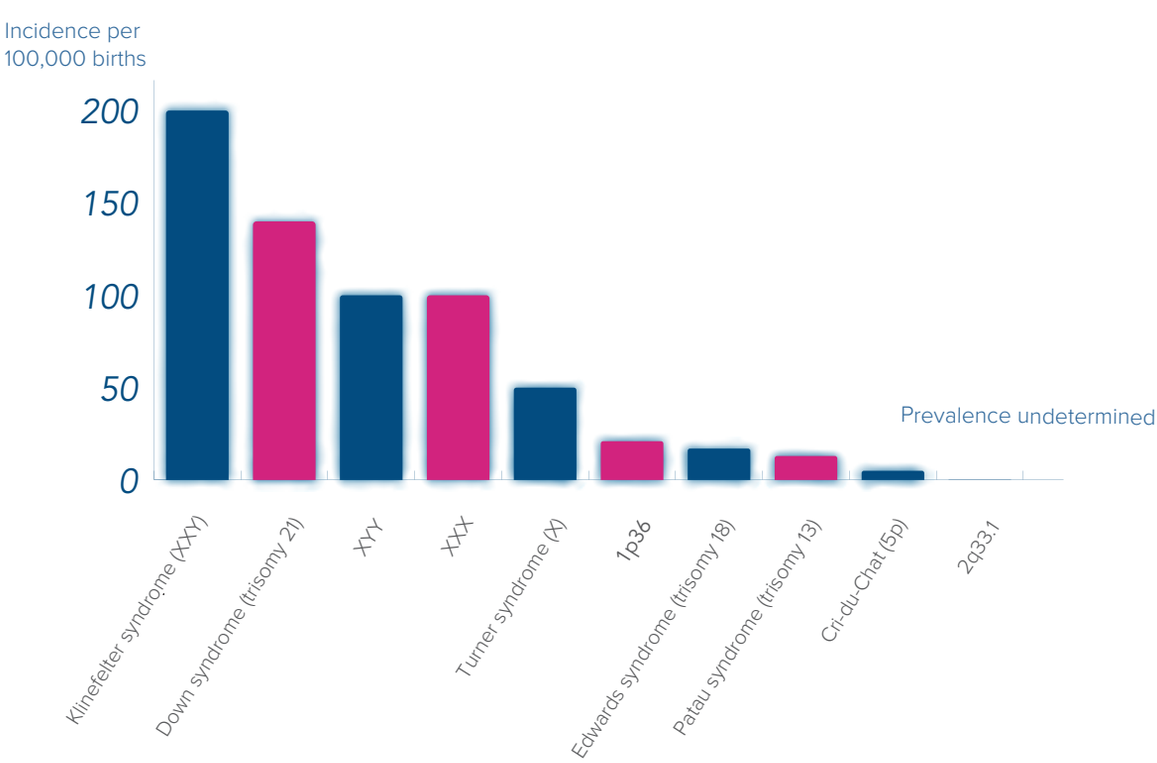
A trisomy is a type of aneuploidy in which there are three chromosomes instead of the usual pair. Trisomy 21 (Down syndrome), Trisomy 18 (Edwards syndrome) and Trisomy 13 (Patau syndrome) are the three most commonly occuring autosomal chromosome aneuploidies in live births. These chromosomal conditions are caused by the presence of an extra copy or partial copy of chromosome 21, 18 or 13 respectively. This additional genetic material can cause dysmorphic features, congenital malformation and different degrees of intellectual disability.

Deletion Syndromes

Deletion syndromes are defined as a group of clinically recognisable disorders characterised by a small deletion of a chromosomal segment. The size and position of the deletion determine which clinical features are manifested and how severe they are.
Clinical features of deletions can include developmental delays and intellectual disability, growth differences, behavioural problems, feeding difficulties, low muscle tone, seizures, dysmorphic features and a pattern of varying malformations.

Sex Chromosomal Aneuploidies

Sex chromosome aneuploidy is defined as a numeric abnormality of an X or Y chromosome, with addition or loss of an entire X or Y chromosome. Although most cases of sex chromosome aneuploidies are generally mild without intellectual disability, some have a well-established phenotype that can include physical abnormalities, learning delays and infertility.



> ISPD recognises that NIPT can be helpful as a screening test for women who are at high risk of Trisomy 21 with suitable genetic counselling. A positive test should be confirmed through invasive testing.
>
> **Source:** ISPD (International Society of Prenatal Diagnosis)

> The NSGC supports NIPT as an option for patients whose pregnancies are considered to be at an increased risk of certain chromosome abnormalities. Patients whose NIPT results are abnormal, or who have other factors suggestive of a chromosome abnormality, should receive genetic counselling and be given the option of standard confirmatory diagnostic testing.
>
> **Source:** NSCG (National Society of Genetic Counselors)

NIFTY® Test Overview

Test Options

Trisomies

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)

Additional Testing Options

Gender Identification

- Male/Female

Trisomies

- Trisomy 9
- Trisomy 16
- Trisomy 22

Sex Chromosome Aneuploidies

- Monosomy X (Turner syndrome)
- XXY (Klinefelter syndrome)
- XXX (Triple-X)
- XYY Karyotype

Deletion Syndromes

- 5p (Cri-du-Chat syndrome)
- 1p36
- 2q33.1
- Prader-Willi/ Angelman Syndrome (15q11.2)
- Jacobsen Syndrome (11q23)
- DiGeorge Syndrome II (10p14-p13)
- 16p12
- Van der Woude Syndrome (1q32.2)

NIFTY® Advantages

Largest capacity and coverage making NIFTY® price competitive against all other NIPT providers.

The only NIPT to offer testing services for deletion syndromes and sex chromosome aneuploidies at no extra cost.

Most validated NIPT on the market with a published study based on the outcomes of 112,000 pregnancies and over 2,000,000 NIFTY® tests carried out worldwide to date.

Test Information

- Twin Pregnancy (trisomies 21, 18 and 13)
- IVF Pregnancy
- Egg Donor Pregnancy

Tested Samples:**2,000,000**

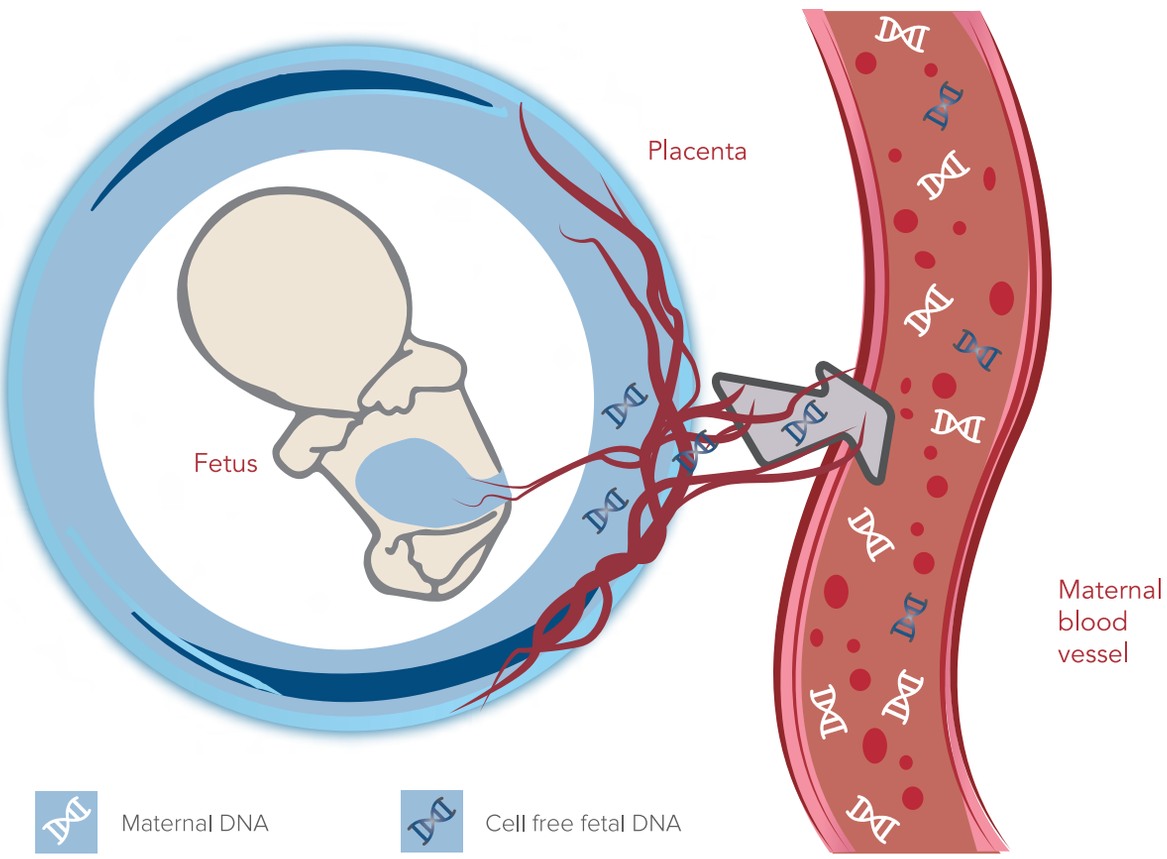
Turnaround time **10 working days**

Available from **week 10** of pregnancy

NIFTY® Methodology

Cell-Free DNA and Cell-Free Fetal DNA

Cell-free DNA fragments (cfDNA) are short fragments of DNA which can be found circulating in the blood. During pregnancy, cfDNA fragments originating from both the mother and fetus are present in maternal blood circulation. Cell-free fetal DNA (cffDNA) is present only as a minority component of the total cfDNA in maternal plasma, which poses a significant technical challenge for some NIPT detection methods.



How does NIFTY® work?

The NIFTY® test requires taking a small maternal blood sample of 10ml. cffDNA in the maternal blood is then analysed to detect for chromosomal abnormality. If aneuploidy is present, small excesses or deficits in counts of the affected chromosome will be detected.

NIFTY® effectively resolves the difficulty in measuring the small increments in the specific chromosome DNA concentration through use of massively parallel sequencing technology (MPS). This means NIFTY® sequences millions of fragments of both fetal and maternal DNA from each sample. Using whole genome sequencing technology and four different proprietary bioinformatics analysis pipelines, the NIFTY® test is able to analyse data across the entire genome and compare chromosomes in the tested sample against optimal reference chromosomes to accurately determine the presence of genetic abnormality.

As opposed to the 'targeted sequencing' methods employed by some other NIPT tests, the NIFTY® methodology allows for highly accurate results irrespective of the clinical symptoms of the patient, and a broader range of testing options including for trisomy, sex chromosomal aneuploidy and deletion syndromes.

The Test Workflow

1

Conduct pre-test genetic counseling and ensure patient provides informed consent for test

2

Discuss and fill in the NIFTY® Consent Form/Test Request Form with the patient

3

Conduct blood draw

4

Send scanned copies of Consent Form/Test Request Form and information sheet to BGI

5

Arrange collection of blood sample with courier

6

Send Consent Form/Test Request Form with blood sample to BGI laboratory

7

Receive results back in 10 working days

8

Conduct post test genetic counseling and provide drug guidance advice as required

Becoming a NIFTY® provider is a quick and simple process. Please contact us at info@niftytest.com to find out more about partnership opportunities.

Sample Requirements

Sample Type	Quantity	Requirements	Shipment
Plasma	2ml (4 tubes required)	Stored in 1.5ml Eppendorf tubes, and sealed with 1cm wide parafilm.	Stored at -80 ˚C, shipped with dry ice within one week.
Maternal Blood	10ml	Gently invert the tube ten times immediately after blood sampling.	Stored and shipped between 6~35 ˚C within 4 days. Keep the tubes upright during shipping.

Indications

To undergo the NIFTY® test, a pregnant woman should receive comprehensive information regarding non-invasive prenatal testing and non-directive advice on human genetics from a qualified health professional. The NIFTY® test is available from the 10th week of pregnancy.

The NIFTY® test is suitable for, but not limited to, patients who exhibit any of the following indications:

- Maternal age 35 years or older at delivery
- Contraindications for invasive prenatal testing, such as placenta prevaria, risk of miscarriage, HBV infection etc.
- History of a prior pregnancy with a chromosomal abnormality
- Fetal ultrasonographic findings indicating an increased risk of T21, T18 or T13
- Requires reassurance following previous screening result
- Received IVF Treatment or has previosuly suffered from habitual abortion

The NIFTY® test is not suitable for patients with the following indications:

- Maternal, fetal and/or placental mosaicism (mixtures of chromosomally normal and abnormal cells in the pregnancy)
- Mother or Father have chromosomal abnormality (translocation or inversion)
- Patients who have received a blood transfusion within one year prior to testing date
- Patients who have had transplant surgery
- Patients who have had stem cell therapy
- Vanishing twin syndrome (with developmental arrest identified has having occurred after week 8 of pregnancy and/or within 8 weeks of NIFTY® testing)

Clinical Validation

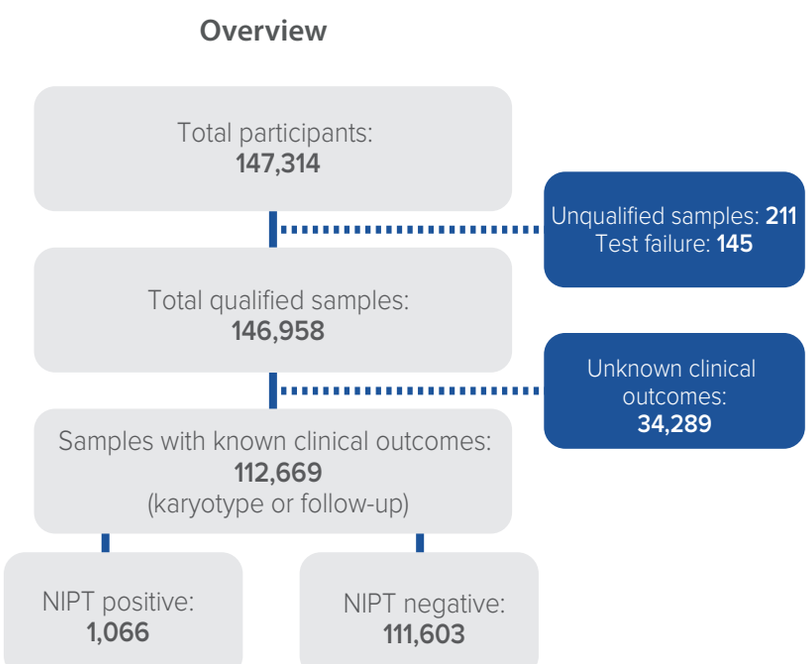
LARGE SCALE VALIDATION OF THE NIFTY® TEST

The NIFTY® test has been validated by the world's largest study on the clinical performance of NIPT to date.

Non-Invasive Prenatal Testing For Trisomy 21, 18 and 13 – Clinical Experience from 146,958 Pregnancies
Wei Wang et al, Journal of Ultrasound in Obstetrics and Gynecology

Overall Sample Total with Known Pregnancy Outcomes 112,669					
Trisomy	TP	Sensitivity	Specificity	PPV	NPV
T21	720	99.17%	99.95%	92.19%	99.99%
T18	167	98.24%	99.95%	76.61%	100%
T13	22	100%	96.96%	32.84%	100%
TOTAL	909	99.02%	99.86%	85.27%	99.99%

Samples were collected between Jan 2011 and Aug 2013. Study was published in the Journal of Ultrasound in Obstetrics and Gynecology.



Read all the NIFTY® test's published clinical data at www.niftytest.com/healthcare-providers/clinical-data/

NIFTY®

SAFE

Non-invasive with no risk of miscarriage

SIMPLE

Test from a small 10ml maternal blood sample as early as week 10 of pregnancy

ACCURATE

Proven >99% sensitivity based on a study of nearly 147,000 pregnancies*

TRUSTED

Over 2,000,000 NIFTY® tests carried out to date

* **Noninvasive Prenatal Testing for Trisomy 21, 18 and 13 - Clinical Experience from 146,958 Pregnancies** - Wei Wang et al, Journal of Ultrasound in Obstetrics and Gynecology

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Case Study

A 31 year-old pregnant woman had undergone traditional biochemical and ultrasonic fetal screening.The traditional screening assessed the risk of trisomy 21 to 1/510 corresponding to low risk. The woman was tested by NIFTY®, which identified her unborn child as being at a high risk of trisomy 21 (Figure 1). The presence of a third chromosome 21 was subsequently confirmed by karyotyping (Figure 2).

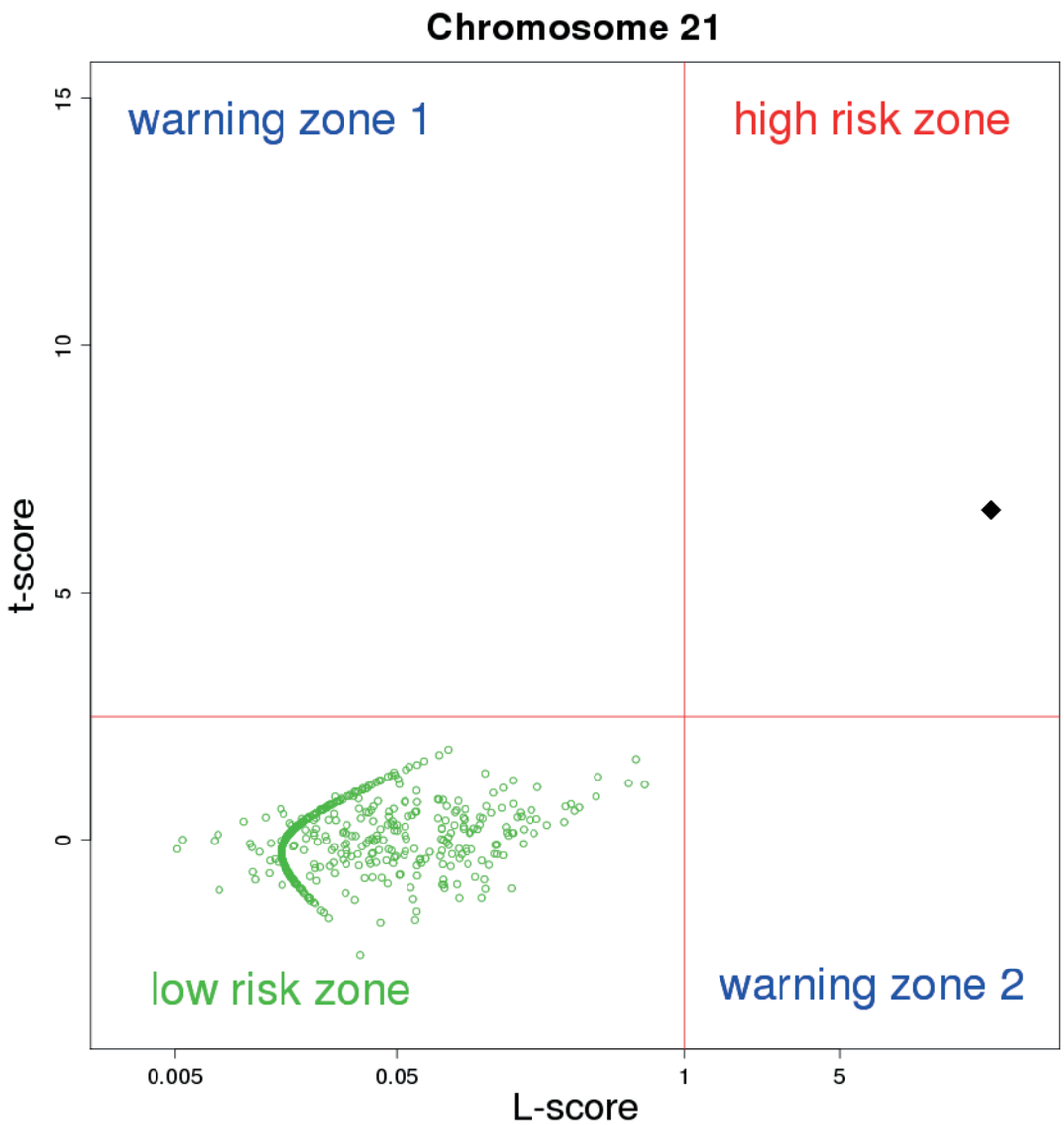

Figure 1. Scatter plot for the NIFTY® Test

Screening test: 1/510 (Low risk)

Sample ID: PDP10003761 **Age:** 31

NIFTY®: T21

Karyotyping: 47, XX, +21

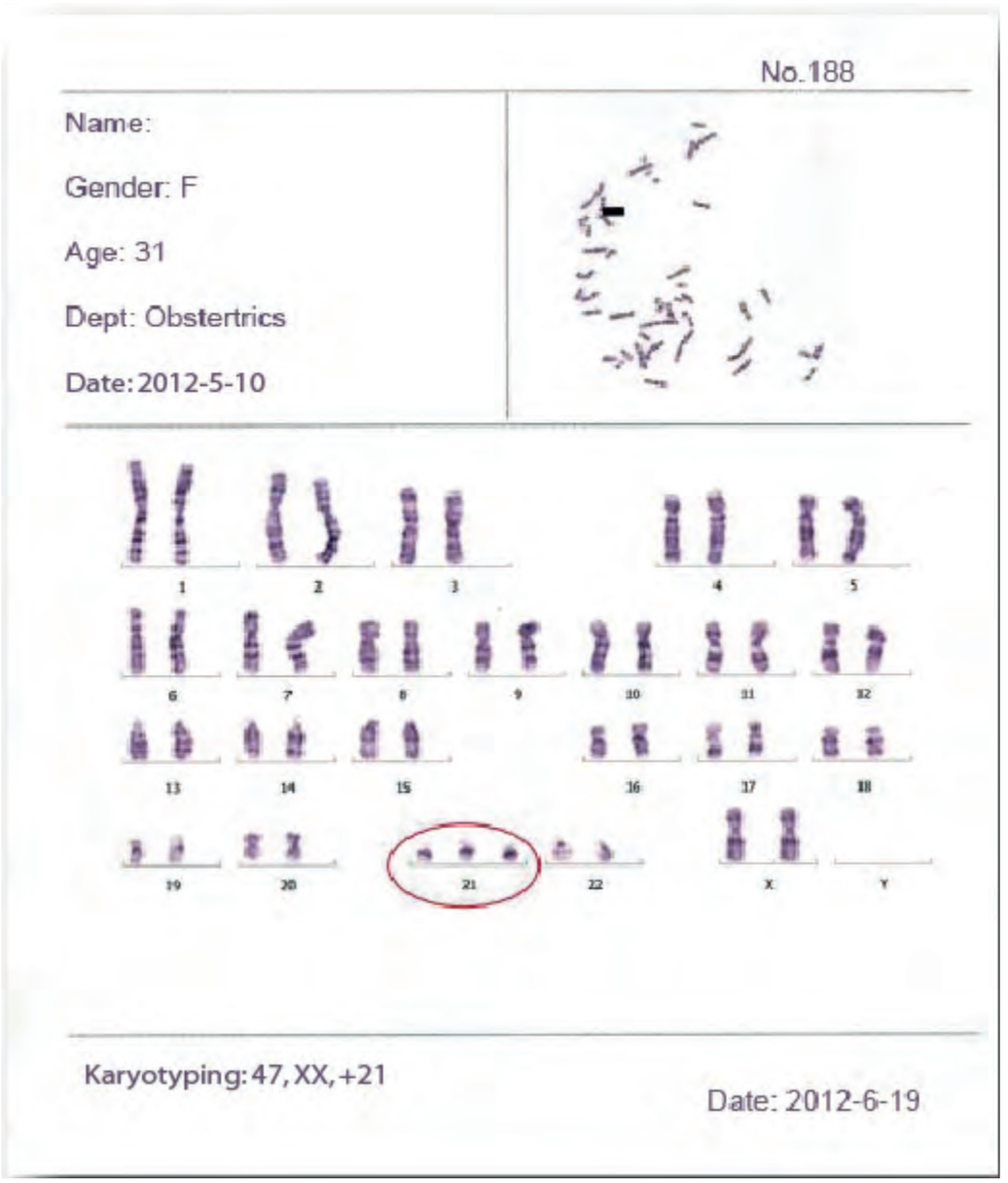

Figure 2. NIFTY® result was confirmed by Karyotyping

Publications

A: Methodology

1. Chiu RW, et al. ***Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study.*** *BMJ. 2011; 342:c7401, doi:10.1136/bmj.c7401.*

2. Chen EZ, et al. ***Non-invasive prenatal diagnosis of fetal trisomy 18 and trisomy 13 by maternal plasma DNA sequencing.*** *PLoS One. 2011;6(7):e21791. doi:10.1371/journal.pone.0021791.*

3. Dan S, et al. ***Prenatal detection of aneuploidy and imbalanced chromosomal arrangements by massively parallel sequencing.*** *PLoS One. 2012;7(2):e27835.*

4. Fuman Jiang, et al. ***Non-invasive Fetal Trisomy (NIFTY) test: an advanced non-invasive prenatal diagnosis methodology for fetal autosomal and sex chromosomal aneuploidies****. BMC Med Genomics. 2012 Dec 1;5:57.*

5. Yuan Y, et al. ***Feasibility study of semiconductor sequencing for noninvasive prenatal detection of fetal aneuploidy.*** *Clin Chem. 2013 May; 59(5):846-9.*

6. Chen S, et al. ***A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing. Prenat Diagn.*** *2013 Jun;33(6):584-90.*

B: Clinical validation

7. Lau TK, et al. ***Non-invasive prenatal diagnosis of common fetal chromosomal aneuploidies by maternal plasma DNA sequencing.*** *J Matern Fetal Neonatal Med. 2012 Aug; 25(8):1370-4.*

8. Dan S, et al. ***Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors.*** *Prenat Diagn. 2012 Dec;32(13):1225-32.*

9. Lau TK, et al. ***Clinical utility of non-invasive fetal trisomy*** *(NIFTY) test--early experience. J Matern Fetal Neonatal Med. 2012 Oct;25(10):1856-9.*

10. Lau TK, et al. ***Non-invasive prenatal screening of fetal sex chromosomal abnormalities: perspective of pregnant women****. J Maternal Fetal Neonatal Med. 2012 Dec;25(12):2616-9.*

11. Lau TK, Cheung SW, Lo PS, et al. ***Non-invasive prenatal testing for fetal chromsomal abnormalities by low-coverage whole-genome sequencing of maternal plasma DNA: review of 1982 consecutive cases in a single center.*** *Ultrasound Obstet Gynecol. 2014 Mar;43(3):254-64*

12. Yao H, Jiang F, Hu H, et al., ***Detection of Fetal Sex Chromosome Aneuploidy by Massively Parallel Sequencing of Maternal Plasma DNA: Initial Experience in a Chinese Hospital.*** *Ultrasound Obstet Gynecol. 2014 Mar 10. doi: 10.1002/uog.13361. [Epub ahead of print]*

13. Zhou Q, Pan L, Chen S, et al. ***Clinical application of noninvasive prenatal testing for the detection of trisomies 21, 18, and 13: a hospital experience.*** *Prenat Diagn. 2014 Jun 4. doi: 10.1002/pd.4428. [Epub ahead of print]*

C: Case study

14. Yao H, et al. ***Non-invasive prenatal genetic testing for fetal aneuploidy detects maternal trisomy X.*** *Prenat Diagn. 2012 Nov;32(11):1114-6.*

15. Choi H, et al. ***Fetal aneuploidy screening by maternal plasma DNA sequencing: 'false positive' due to confined placental mosaicism.*** *Prenat Diagn. 2013 Feb;33(2):198-200.*

16. Pan M, Li FT, Li Y, et al. ***Discordant results between fetal karyotyping and non-invasive prenatal testing by maternal plasma sequencing in a case of uniparental disomy 21 due to trisomic rescue.*** *Prenat Diagn. 2013 Jun;33(6):598-601.*

17. Lau TK, Jiang FM, Stevenson RJ et al. ***Secondary findings from non-invasive prenatal testing for common fetal aneuploidies by whole genome sequencing as a clinical service.*** *Prenat Diagn. 2013 Jun;33(6):602-8.*

18. Gao Y, Stejskal D, Jiang F, Wang W. ***A T18 false negative result by NIPT in a XXX, T18 case due to placental mosaicism.*** *Ultrasound Obstet Gynecol. 2013 Nov 1.*

D: Twins study

19. Huang X, et al. ***Non-invasive prenatal screening of fetal Down syndrome by maternal plasma DNA sequencing in twin pregnancies.*** *J Matern Fetal Neonatal Med. 2013 Mar;26(4):434-7.*

20. Jing Zheng. et al. ***Effective Non-invasive Zygosity Determination by Maternal Plasma Target Region Sequencing.*** *PLOS ONE. 2013: 8 (6) :e65050*

Brochure information from multiple sources, held on record.

BGI was founded in 1999 as a nonprofit research organization to support the Human Genome Project. Over the years, BGI has grown into a multinational genomics company with significant global operations, including sequencing laboratories based in the US, Europe, Hong Kong and mainland China.

BGI offers a wide portfolio of transformative genetic testing products across major diseases, enabling medical providers and patients worldwide to realize the promise of genomics-based healthcare. BGI's services and solutions are available in more than 50 countries around the world.

www.niftytest.com

Brought to you by:

BGI

Information is for qualified healthcare professionals only.

Information is not meant to substitute qualified medical advice and is for reference only.

The NIFTY® test screens for the specific genetic conditions listed on the testing panel (as selected for testing by the patient). The purpose of the NIFTY® test is to identify pregnancies as more likely to be affected by one of the listed genetic conditions. If the test result returns as high risk, further confirmatory diagnostic testing should be performed for final diagnosis of any condition by a qualified healthcare professional.

Any patient treatment plans should only be recommended and provided by a qualified healthcare professional.

BGI recommends that non-directive genetic counseling and guidance always be provided to patients prior to undertaking any genetic testing and when reviewing results with the patient.

Accuracy of genetic testing may be affected by certain clinical factors. Therefore, test results should always be interpreted in the context of other clinical and family information of the patient.

Informed consent should always be obtained from the patient prior to testing.

NIFTY®

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