

Noninvasive prenatal testing in China: Future detection of rare genetic diseases?

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Summary

Noninvasive prenatal testing (NIPT) provides an innovative method to detect genetic conditions in fetuses using a maternal blood sample, thus avoiding the risk of miscarriage associated with traditional invasive procedures. Since 80% of rare diseases are genetic diseases, NIPT has the potential to detect rare genetic diseases early on and it has been used in many countries and regions. Since China has the world's largest population of patients with rare diseases, NIPT has been implemented in China since 2010. However, the regulations governing NIPT in China are weak and NIPT oversight and research are still lacking. Strict registration is needed to ensure the quality of NIPT, additional certification can help a developer/manufacturer of an NIPT test to compile clinical data and to improve innovation, and academic societies can provide committee opinions that are suited to the current situation in China. These efforts may improve regulations governing NIPT and NIPT oversight and research in China. With these improvements, NIPT may offer promise in terms of the early detection of rare diseases.

Keywords: Premarket notification, Laboratory Developed Tests (LDTs), Clinical Laboratory Improvement Amendments (CLIA), Committee opinion

On February 12, 2014, Ariosa Diagnostics, Inc. obtained licensure approval from New York for Harmony™ noninvasive prenatal testing (NIPT) (1). This testing uses fetal genetic material obtained from a maternal blood sample to carry out genetic sequencing in order to detect certain genetic conditions during pregnancy based on the discovery of free fetal DNA in maternal plasma (2). NIPT offers advantages compared to traditional invasive procedures. NIPT can be performed with a maternal blood sample, which means that it is not associated with a risk of miscarriage. This aspect also means that NIPT is better suited to screening (3). Therefore, NIPT is likely to serve as a tool to screen for genetic defects in fetuses without risking a miscarriage.

Since 80% of rare diseases are genetic diseases (4), any method that can help to detect genetic conditions

can be seen as a possible way to respond to rare diseases. Earlier diagnosis and treatment of diseases like phenylketonuria can mean a better prognosis (5-7). Therefore, prenatal testing is more likely to help improve the treatment of rare diseases than newborn testing, and this is especially true for rare diseases (5,6,8). As mentioned earlier, NIPT avoids the risk of miscarriage associated with traditional invasive procedures, and this aspect means that NIPT is more likely to detect rare genetic diseases early on. Currently, NIPT is focused on detecting genetic diseases such as Trisomy 21, 18, and 13, Turner syndrome, 22q11.2 deletion syndrome, and 1p36 deletion syndrome, all of which are rare genetic diseases.

China is a country with the world's largest population of patients with rare diseases (7), and China faces huge challenges in responding to rare diseases. Faced with these challenges, China has adopted several strategies to improve the healthcare of patients with rare diseases, including reimbursement of medical expenses for children with congenital heart disease and leukemia (9) and a new born screening program (5,10). As NIPT has matured, this technology has been marketed

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(11,12) (Table 1). NIPT has been implemented in China since May 2010, and most NIPT technology is from US companies (22). In China, NIPT can test for Trisomy 21, 18, and 13 just as NIPT in Europe can, but NIPT in the US can test for 4 more conditions (Turner syndrome, Triploidy detection, 22q 11.2 deletion syndrome, and 1p36 deletion syndrome). China has the largest number of tested samples, approximately twice the number in the US and 33 times that in Europe, which shows that China has a large market for NIPT.

However, regulations governing NIPT in China are still weak and NIPT management is still lacking. Since the first NIPT was carried out in China in 2010, approximately 210,000 samples have been tested without oversight because of the lack of regulations. Under these circumstances, the China Food and Drug Administration (CFDA) and National Health and Family Planning Commission of the People's Republic of China (NHFPC) jointly issued a "Notice on the enhanced clinical use of products related to genetic sequencing and increased oversight of genetic sequencing" on February 9, 2014 (23). This move indicates that the Chinese government has begun overseeing the market for NIPT-related products. On March 3, 2014, the NHFPC issued a "Notice regarding approval procedures for a pilot project involving clinical use of high-throughput genetic sequencing" (24) to improve the system for registration of genetic sequencing in China. These notices are mainly focused

on criteria and authority for registration. Regulations on how NIPT should be performed and maintaining its quality are still lacking.

The US government has experience overseeing NIPT that may be helpful: *i*) Strict registration is needed to ensure the quality of NIPT. In the US, a developer/manufacturer of an NIPT test must first obtain a 510(k) premarket notification (510k) from the US Food and Drug Administration (FDA) (25). The 510k requires an *in vitro* diagnostic test yield a certain number of positive results from among tested samples. Using Trisomy 21 as an example, Trisomy 21 has an incidence of 1/1000. Given a target of 100 positive results, at least 100,000 samples would have to be tested to meet the requirements of a 510k. This requirement ensures the quality of any NIPT test approved for a 510k. *ii*) Additional certification can help a test developer/manufacturer to compile clinical data and to improve innovation. Since obtaining the number of positive results required by a 510k is difficult, only one NIPT device has been approved by the FDA. Applying for Laboratory Developed Tests (LDTs) certification and Clinical Laboratory Improvement Amendments (CLIA) certification from the Centers for Medicare & Medicaid Services (CMS) (26) provide another way for a developer/manufacturer to certify an NIPT test without clinical data. LDTs and CLIA certification are focused more on the developer/manufacturer's knowledge, training and experience, reagents and materials

Table 1. Current state of NIPT in the United States, Europe, and China

Region	Company	Service	Diseases tested for	Date started	Number of samples tested	Ref.
United States	Sequenom	MaterniT21™ PLUS	Trisomy 21/ Trisomy 18/ Trisomy 13/ Turner syndrome/ 22q 11.2 deletion syndrome/ 1p36 deletion syndrome	October 2011	100,000 (as of April 16, 2013)	(13)
	Natera	Panorama™	Trisomy 21/ Trisomy 18/ Trisomy 13/ Turner syndrome/ Triploidy detection / 22q 11.2 deletion syndrome/ 1p36 deletion syndrome	Unknown	Unknown	(14)
	Verifi	Verifi®	Trisomy 21/ Trisomy 18/ Trisomy 13/ Turner syndrome	March 2012	Unknown	(15,16)
	Ariosa	Harmony Prenatal Test™	Trisomy 21/ Trisomy 18/ Trisomy 13/ Turner syndrome	May 2012	40,000 (as of November 13, 2013)	(17)
Europe	LifeCodexx	PrenaTest®	Trisomy 21/ Trisomy 18/ Trisomy 13	August 2012	Nearly 6,000 (as of August 22, 2013)	(18,19)
China	BGI	NIFTY	Trisomy 21/ Trisomy 18/ Trisomy 13	May 2010	109,582 (as of April 2, 2013)	(12,20)
	Berry genomics	BambniTest	Trisomy 21/ Trisomy 18/ Trisomy 13	April 2011	Over 100,000	(11,21)

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preparation, characteristics of operational steps, calibration, quality control, and proficiency testing materials, test system troubleshooting and equipment maintenance, and interpretation and judgment (26). This certification can help a developer/manufacturer that does not have enough tested samples to market a NIPT test, and most manufacturers of NIPT tests in the US currently have their NIPT products certified based on LDTs and CLIA. After the developer/manufacturer obtains CLIA certification, the Centers for Medicare & Medicaid Services (CMS) will conduct subsequent inspections on a biennial basis or with such frequency as necessary to ensure compliance, thus requiring the developer/manufacturer to maintain the quality of its test (27). And study has also indicated that LDTs and CLIA certification can improve innovation (28).

Research into NIPT in China is still lacking. With a new technology like NIPT, recommendations or official opinions should be provided by academic societies to give guidance on how NIPT should be used and where the cutting edge of research lies. As of this writing, however, there are no such recommendations or opinions in China been reviewed. Several opinions on NIPT have been issued by academic committees in places like the U.S., Europe, Canada, and Japan from December 2012 to May 2013 (29,30). These opinions include statements on the clinical use of NIPT, the limitations of current NIPT, who is eligible to undergo NIPT, and guidelines for medical staff. In order to enhance research into NIPT in China, academic societies of geneticists, obstetricians, gynecologists and specialists in maternal-fetal medicine should provide committee opinions that are suited to the current situation in China.

NIPT has potential in terms of detecting rare genetic diseases and it has been used in many countries and regions. China is a country with the world's largest population of patients with rare diseases patients, and China has implemented NIPT since 2010. However, NIPT oversight and research in China are still lacking. With the improvement of these aspects, NIPT may offer promise in terms of the early detection of rare diseases.

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