Non-Invasive Prenatal Testing: a New Tool for Sex Selections?*

Pruebas prenatales no invasivas: ¿una nueva herramienta para la selección de sexo?

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Abstract: Prenatal genetic screening through non-invasive prenatal testing (NIPT) or otherwise called cell-free DNA testing became commercially available for clinical use in late 2011. However early applications of NIPT, which included the determination of Rhesus D blood-group status and fetal sex, have started even before, after the presence of cell-free fetal DNA in maternal blood was described in 1997. The commercialization of tests to detect chromosomal aneuploidies has been rapid, and global marketing is steadily increasing. NIPT was introduced in the United States and Western Europe in late 2011, and currently the tests are rapidly becoming available in the Middle East, South America, South and Southeast Asia, and Africa. Apart from well known benefits of NIPT, which are high accuracy compared to standard screens or invasive tests and lack of harm to the fetus (potential miscarriage), noninvasive prenatal tests are also capable of disclosing fetal sex starting from 5-7 weeks of gestation. In fact, the ability to determine fetal sex early in the pregnancy without the need for invasive testing was perceived as "a bonus" for women. This raises multiple ethical and social implications related to dissemination and use of noninvasive tests in countries where abortions based on gender preference are common (China, India, now also in some Southeast European Countries (Albania, Montenegro), South Caucasus (Azerbaijan, Armenia, Georgia). The paper aims to discuss existing policy regulations/ guidelines that address use of noninvasive technologies with regards to fetal sex disclosure in countries with sex-selective practices.

Keywords: non-invasive prenatal testing; cell free DNA testing; fetal sex determination; sex selections

Resumen: Los exámenes genéticos prenatales mediante pruebas prenatales no invasivas (NIPT) o de también llamadas pruebas de ADN sin células, se comercializaron para uso clínico a finales de 2011. Sin embargo, las primeras aplicaciones de NIPT, que incluían la determinación del estado del grupo sanguíneo Rhesus D y el sexo fetal, comenzaron incluso antes, después de que se describiera la presencia de ADN fetal libre de células en sangre materna en 1997. La comercialización de pruebas para detectar aneuploidias cromosómicas ha sido rápida, y el marketing global está en constante aumento. NIPT se introdujo en los Estados Unidos y Europa Occidental a finales de 2011, y actualmente las pruebas están disponibles rápidamente en Oriente Medio, Sudamérica, Asia del Sur y Sudeste y África. Además de los beneficios bien conocidos de NIPT, que son de alta precisión en comparación con las pantallas estándar o las pruebas invasivas y la falta de daño al feto (posible aborto espontáneo), las pruebas prenatales no invasivas también son capaces de revelar el sexo fetal a partir de 5-7 semanas de gestación. De hecho, la capacidad de determinar el sexo fetal al principio del embarazo sin la necesidad de realizar pruebas invasivas fue percibida como "una ventaja" para las mujeres. Esto plantea múltiples implicaciones éticas y sociales relacionadas con la difusión y el uso de pruebas no invasivas en países donde los abortos basados en preferencias de género son comunes (China, India, ahora también en algunos países del sudeste de Europa (Albania, Montenegro), Cáucaso Sur (Azerbaiyán, Armenia, Georgia). El objetivo de este artículo consiste en discutir las regulaciones / directrices de políticas existentes que abordan el uso de tecnologías no invasivas con respecto a la divulgación del sexo fetal en países con prácticas selectivas de sexo.

Palabras clave: prueba prenatal no invasiva; prueba de ADN sin células; determinación del sexo fetal; selecciones de sexo

1. Introduction

Current discussions over non-invasive DNA tests mostly include issues about how to improve informed decision making process with the help of companies and clinical laboratories. The letters should develop clear and accurate consent forms that clinicians can use to order their services (Allyse, 2013). Some other legal and regulatory issues relate to potential "direct-to-consumer" nature of non-invasive tests which can lead to further ethical and legal implications. Unlike existing invasive methods, these tests can be offered remotely, which opens the door to their international provision and the heterogeneity of jurisdictions and law (Ibid.)

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Because most of the non-invasive tests currently offered globally are performed in laboratories based in US, China and Europe, only the laboratory accreditation/oversight mechanisms in US, China and Europe apply (Minear A. M., 2015). In Europe, two new Regulations were adopted on 5 April 2017, which regulate medical devices (including in vitro diagnostic medical devices). Although genetic testing in most developing countries generally occurs without national regulatory oversight, recent events in China highlight how regulatory issues can affect clinical implementation (Minear A. M., 2015). It should be mentioned that genetic testing in China (in particular non-invasive tests) has grown to be a business big enough to warrant the government's intervention. Chinese authorities, which appear to be most concerned about DNA-based prenatal testing, partly because of gender identification possibility that these tests can bring, came up with a ban on the provision of genetic tests to customers by domestic hospitals and a variety of medical and health institutions. The official ban was made through a cross-agency announcement posted on the website of the China Food and Drug Administration in 2014 (Chen, 2014). The statement specifically mentioned prenatal genetic testing, including sequencing-based tests, and added that regulating the use of such products is being done to "ensure the public safety of gene sequencing diagnostic products (Report, 2014).

As of March 2014, three different types of NIPT tests (Bambni, NIFTY, Harmony) have been provided in China by Berry Genomics, BGI and Ariosa Diagnostics accordingly (Chandrasekharan S., 2014).

2. Legal and ethical discussions over NIPT

Short content analysis of NIFTY website (niftytest.com) reveals the scope of information provided to future parents with regard to test application. In particular, website visitors can learn that NIFTY is aimed at screening for chromosomal aneuploidies, including trisomies 21, 18 and 13 (Down, Edwards and Patau syndromes accordingly), sex chromosome aneuploidies and deletion/ duplication syndromes from as early as week 10 of gestation. Meanwhile, *the website contains explicit information about the possibility to detect the sex of the fetus, considering it to be a test option as well*. Among advantages of the test, the website mentions high accuracy, large coverage and price competitiveness. For "expecting parents" website contains detailed information on how to have the test carried out step by step. In particular, "expecting parents" are advised to contact the company to learn about the local provider of the test in case they have no information on that. Meanwhile, those who know any local provider and are fully aware of the process and conditions of the test

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can directly apply for it. After providing blood sample they can get the test results only in 10 days. While it is still not very clear whether BGI owned NIFTY provides gender disclosure possibility also to Chinese providers, it is an issue that requires additional research. It should be mentioned that BGI was the first NIPT provider in China to react on the new regulation of Chinese government to control implications of genetic tests. In particular, in its statement BGI said that it "fully acknowledged the necessity to regulate [the] genetic testing industry" and was in the process of registering its tests according to new regulations (Report, 2014). Later, in 2014 the China Food and Drug Administration has approved next-generation sequencing-based products developed by BGI (Reporter, 2014).

Similar to NIFTY tests, Harmony prenatal tests provided by Ariosa Diagnostics, Inc (local distributor in China is Femina Healthcare) (Chandrasekharan S., 2014) advertise the possibility to detect the fetal sex both on their website (http://www.ariosadx.com/expecting-parents/) and on the relevant brochure. In particular, detection of fetal sex and/or X and Y chromosome conditions are provided as additional services. Interestingly, the Chinese/English website of Femina Healthcare does not mention about gender identification possibility when listing available NIPS tests. However, "fetal sexing" is introduced to website visitors as a prenatal diagnostic service starting from 7 weeks of gestation and in case of ultrasound diagnosis, starting from 11 weeks (http://www.feminahealthcentre.com/services/46-product-3). Considering the fact, that currently only BGI and Berry Genomics have been authorized to undertake genetic testing in China, it is unclear which gender identification method could be used to detect the fetal sex from 7 weeks of gestation in this case.

Meanwhile, the Chinese website of Berry Genomics (http://www.berrygenomics.com/bambnitest) does not provide information on the potential of Bambni test to determine the fetal sex. Despite having more complex website and providing very detailed information on various genetic tests provided by Berry Genomics (including Bambni and Bambni+), the content of the website is restricted with regard to gender disclosure information. Expecting parents can find useful information about who the tests are made for, what gene sequencing specific technology can detect and what the success/failure rates are.

While in India, according to Madan K. and Breuning M. H. (2014) companies in the United States have been providing DNA kits for home use, which have been freely available and widely used in the north-western states of Punjab and Haryana since 2006. Blood sample from a seventh week pregnant woman could be sent to the United States by post, and the result was known in 10 days (Madan, 2014).

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As of April 2014, two types of non-invasive tests are performed by medical institutions in India; NIFTY by BGI and NACE by Iviomics (Chandrasekharan S., 2014). A short content analysis of websites of Indian largest genetic labs and medical institutions (those providing genetic testing) was also conducted. For this purpose, websites of Sir Ganga Hospital, DNA Labs India, SRL Diagnostics, Srushti Fertility Center and Bangalore Fetal Medicine Center were observed.

The website of Sir Ganga Hospital, includes comprehensive information about the available genetic tests (both screening and diagnostic). It also details the test ordering process and specifies the response dates for each genetic test. One interesting finding is that along with the informed consent form for prenatal diagnostic tests for hospital (as indicated on the website[1]), there is a separate form for cases of prenatal sex selections. In particular future parents should declare that they understand that the sex of the fetus will not be disclosed to them. The breach of this understanding will make them liable to penalty as prescribed in the Prenatal Diagnostic Techniques Act (see later in the paper).

Similarly, DNA Labs India, which is considered number one ranked genetic testing laboratory in India, provides for detailed information on available non-invasive tests, pricing and online offers. According to the website costs of different non-invasive tests varies from 20,000 to 40,000 rupees (approximately 310 to 620 US dollars). DNA Labs India has 3000 collection centers and performs more than 5000 tests per day; including screening for trisomies, sex chromosome aneuploidies and deletion/duplication syndromes. [2] Being one of the largest providers of non-invasive tests in the country, DNA Labs India doesn't not mention about the gender disclosure potential of the tests on its website. Neither do SRL Diagnostics, Srushti Fertility Center and Bangalore Fetal Medicine Center.

In general, companies marketing NIPT in China and India state that they are compliant with national laws, but additional monitoring is needed to assess whether fetal sex information is ordered/reported and whether current laws adequately protect against the use of NIPT for determining fetal sex (Minear A. M., 2015). It should be recalled that both China and India have enacted relevant legislation prohibiting sex selections for non-medical reasons for already two decades.[3] Apart from the laws on Maternal and Infant Health Care and Population and Family Planning, China recently enacted an Order on the "Provisions on Prohibiting Fetal Sex Identification for Non-medical Needs and Sex-Selective Pregnancy Termination (National Health and Family Planning Commission, 2016)"[4]. The document is aimed at creating a national policy to ensure the implementation of the aforementioned laws. Similarly to the Chinese laws, Indian law on

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Pre-natal Diagnostic Techniques (Regulation and Prevention of Misuse) Act[5] prohibits use of prenatal diagnostic techniques and tests (explicitly mentioning diagnostic ultrasound machines) to acquire information on fetal sex. The use of non-invasive tests in India falls under the PCNDT act (Madan, 2014).

It should be mentioned, that additional research is necessary to understand how genetic institutions providing NIPS tests in China and India address this ban in practice. This is particularly important as the number of non invasive tests being carried out in China is rapidly growing. According to Mei, L., Tang, Q., Sun, B., & Xu, L. (2014) total number of non invasive tests carried out by BGI and Berry Genomics starting from 2010 was approximately 210,000. As of 2014, this was 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 (Mei, 2014). However, more robust research about the clinical use of NIPT technologies in China and India is necessary with a particular focus on gender disclosure issue. More information and guidance is also needed about how prenatal diagnosis of sex chromosome aneuploidies is provided, given their unavoidable relationship to fetal sex (Minear A. M., 2015).

Another concern is that currently many Chinese parents either visit Hong Kong or Shenzhen based clinics and hospitals or send a sample of pregnant woman's blood through agents, thus leading to growing number of reproductive tourists. The collection, processing and storage of the blood sample is, however, not thoroughly regulated neither by Chinese nor by Hong Kong legislation. Personal genetic data is considered "sensitive data" in both legislations[6] Until recently, China's data privacy framework has consisted of fragmented rules found in various laws, measures and sector- specific regulations. The comprehensive regulation of data protection provisions in the form of national- level legislation, i.e *Cyber Security Law* (the *CS Law*), came into effect on 1 June 2017. However, with the exception of a non-binding National Standard[7], none of the PRC data-related rules and regulations distinguish between *general* and *'sensitive'* (genetic) personal information. The National Standard states that when collecting sensitive personal information, an individual's express consent may be obtained (opt-in), whereas when collecting general personal information, tacit consent is sufficient. *Compliance* with the National Standard is *voluntary* and no penalty is imposed in the event of a breach. Meanwhile, the Hong Kong data protection legislation does not clearly separate the concept of sensitive personal data in the Ordinance. However, non-binding guidance issued by the PCPD[8] (in the context of biometric data) has indicated that higher standards should be applied as a matter of best practice to more sensitive personal data. To improve genetic data protection in these countries, legally binding legal

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acts need to be enacted so that uniform and coherent specifically genetic data protection practice can be established. The frameworks of the U.K. and the European Union recently adopted data protection regulations can serve as a good basis for this.[9, 10]

3. Conclusion

Being a relatively new technology, NIPT should be addressed more by academic societies, especially in countries like China and India, considering the additional ethical and legal issues it brings forward. Currently, several academic committees from U.S. and Europe have issued recommendations and guidelines on the use of non invasive prenatal tests. As mentioned, they mostly emphasize the informed decision-making process, "direct-to-consumer" nature of the tests, etc. However, there are several general recommendations that could lead to proper application of non-invasive tests in countries with sex selective issues. In particular, Allyse et al., (2013) have provided for best ethical practices for commercial test providers related to non-invasive prenatal tests. First and foremost, these practices include offering testing only through licensed clinicians and not directly to consumers. Implementing this recommendation can possibly lead to avoiding routinization of the tests. Because the commercial landscape and the types of these tests are rapidly growing, some experts suggest on developing NIPT using other techniques/ platforms for which kits can be purchased and the test can be run in house (Minear, 2015). According to the same source, NIPT is effective after complete understanding of the test by the offering physicians, its advantages and drawbacks and most importantly if it is accompanied with good pretest and posttest counseling. A recommended pretest counseling may be very useful in understanding the reasons for undertaking non-invasive tests and can possibly eliminate the number of tests aimed at gender disclosure. Besides, companies should do their best to comply with national and international regulation and laws regarding the results that can legally be returned to the patients.

Another recommendation is to design marketing and advertising materials that promote value-based decision-making and avoid advocating for specific actions based on the test results. Another recommendation is to filter out fetal sex information from the test result as long as NIPT is not directed at sex-chromosomal aneuploidies (Dondorp, 2015).

It should be mentioned that some of these recommendations were met by the Chinese government when it announced about the necessity to approve genetic tests. This surely could slow down the routinization process of all genetic tests in China. However, marketing of these tests still poses a problem with regard to specific information provided to consumers. It is

said that the best way to counteract improper use of information about fetal sex is to avoid its generation (Dondorp, 2015), which China is currently trying to do. In 2015, the Advertising law has been revised to prohibit sexually discriminatory content of advertisements.

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Notes

1. www.sgrh.com/UserFiles/Image/TestOrdering.pdf
2. https://dnalabsindia.com
3. Law of the People's Republic of China on Maternal and Infant Health Care, 1994
4. http://lawinfochina.com/display.aspx?id=21908&lib=law The order is yet available only in Chinese
5. The Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 (PNDT), amended in 2002
6. Cybersecurity Law of the People›s Republic of China, June 1, 2016
7. National Standard of Information Security Technology – Guideline for Personal Information Protection within Information System for Public and Commercial Services (promulgated 05 Nov 2012 and effective on 01 February 2013, GB/Z 28828-2012; the 'Guideline')
8. Non-binding Guidance of the Personal Data (Privacy) Ordinance (Cap. 486) ('Ordinance'), Hong Kong
9. Regulation (EU) 2016/679 of the EU and the Council, 27 April 2016
10. Directive (EU) 201/680 of the European Parliament and of the Council, 27 April 2016