Non-invasive Prenatal Test as Primary Screening for Down Syndrome

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The performance of non-invasive prenatal testing (NIPT) is superior to that of current Down screening methods in both high- and low-risk pregnancies. On the other hand, concern over loss of benefits from current screening strategy for Down syndrome after its replacement by NIPT is not substantiated. The ethical principles of equity and reproductive autonomy also favour NIPT for universal screening. A preliminary analysis showed that the current Down screening strategies in the Hospital Authority could be replaced by NIPT without increasing the expense per case of trisomy 21 diagnosed from a societal perspective. In fact, the use of NIPT as a primary screening test for all pregnant women has been endorsed by the International Society of Prenatal Diagnosis.
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Introduction

Non-invasive prenatal testing (NIPT) can be used as a first-tier screening test or a second-tier test for cases screened positive using conventional screening methods. There are three main concerns using NIPT as a universal first-tier test: (1) the test performance in a low- or mixed-risk obstetric population; (2) potential loss of other benefits offered by the current Down screening programme; and (3) the relatively high cost of NIPT.

Test Performance in the General Obstetric Population

NIPT has an excellent performance in a routine obstetric population. Since the first study in low-risk women in 2012, there have been at least 13 large studies, each with more than 1000 women, on the performance of NIPT for Down syndrome screening in a low-risk obstetric population[1-13]. The total number of women studied exceeds 123,000. All studies showed that the rate of indeterminate results is extremely low (1.2-4.8% on first sample and 0.0-1.9% after redraw). The detection rate is >99.9%, comparable with that in the high-risk group. The false-positive rate was ≤0.3%, comparable with that in the high-risk group, and much lower than that of current screening strategies (false-positive rate, 4%)[1-13]. The positive predictive value ranges from 46% to 91%, again many fold higher than that of current methods (positive predictive value, 4.2%)[1-13]. It is no longer justifiable to offer pregnant women a test that has a poor positive predictive value and a high false-positive rate[14].

Loss of Other Benefits of Current Down Screening Programme

The current Down screening programme sometimes detects other unrelated chromosomal abnormalities. Some are worried that these may be missed by targeted NIPT. Nonetheless, these conditions do not fulfil the criteria for screening. Many of them are randomly distributed and are not more common with a positive Down screening result. They are picked up simply due to the higher false-positive rate of the current Down screening programme and therefore more invasive diagnostic procedures are performed. It is the downside, and not an additional benefit, of current Down screening methods.

Atypical autosomal aneuploidies are rare after 12 weeks because they are lethal beyond the first trimester. Why bother then? The phenotypes of sex chromosome abnormalities and other autosomal aberrations are variable, usually mild. Findings of unclear significance sometimes arise secondary to a false-positive Down screening result. These conditions cause complex counselling issues, especially in the absence of ultrasound abnormalities. They unnecessarily overload the highly sought genetic counselling service. There are significant ethical issues as well. Adequate pretest counselling is impossible given the

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multitude of possibilities associated with a false-positive Down screening result. It poses potential psychological harm to the woman due to unpreparedness, anxiety, and shock. Knowing more is not necessarily a blessing. To avoid this pitfall, the UK National Screening Committee has wisely recommended quantitative fluorescent polymerase chain reaction confirmation of a positive Down screening result[15].

Coupled with maternal characteristics, blood pressure, and uterine artery Doppler, the current Down screening programme has the potential to predict development of pre-eclampsia and small babies. Nonetheless, the need for multiple markers means individual markers are not good enough. Replacing the current programme with NIPT, only the biochemical markers are lost. This is acceptable since biochemistry is not a good marker.

Ultimately, nothing is missed switching to targeted NIPT and it helps to alleviate the problems caused by the much higher false-positive rate of current screening methods. Nonetheless, NIPT is not a substitute for quality prenatal ultrasound, instead the two are complementary.

Cost

Two recent studies from the US examined the cost of replacing current screening strategies with NIPT from a societal perspective, i.e. taking into consideration the lifetime cost of the birth of an affected child. In one[16], if NIPT cost was ≤US$744, conventional Down screening strategies could be replaced by NIPT without increasing the total health care expenditure. NIPT in this analysis reported trisomies 13 and 18 and Turners syndrome, as well as trisomy 21. Another study[17] showed that if NIPT cost was ≤US$665, first trimester screening (FTS) could be replaced by NIPT without increasing the societal cost per trisomy case diagnosed. If NIPT cost was ≤US$543, then FTS could be replaced without an increase in total cost. In this study, NIPT reported trisomies 13 and 18 as well as trisomy 21. To date, no cost-effective analysis can address the psychological and non-monetary benefits of NIPT.

A preliminary analysis was carried out to assess the differential performance and cost-effectiveness of replacing the current Down screening strategy in the Hospital Authority with NIPT. The unit NIPT cost per case of trisomy 21 diagnosed was reported to be no higher than that of the current Down screening programme. The cost from a societal perspective is calculated by taking into account the lifetime cost of the birth of an affected child, and includes the difference in direct medical and educational costs between a Down syndrome child and an average individual in addition to the indirect costs of lost productivity due to morbidity and mortality associated with Downs. NIPT outperforms the current screening strategy (Table 1[18,19]). When NIPT charge was US$160-300 (a range reported taking into account the variation in lifetime cost estimate of an affected child), the expense per case of trisomy 21 diagnosed was not increased (Table 2[16,18,20]).

The market price of NIPT has already reduced to US$300 and was lower in 2014[21,22]. It was recognised that, in Hong Kong, the test could be offered at <HK$2000 (US$250) with the provider already making a good profit. These providers and their intermediates (such as private doctors and hospitals) are making a huge profit by offering the test at HK$8000[23]. One major NIPT provider from China has conceded that profit was made by offering NIPT at around US$160 (personal communication). Therefore, replacing current screening strategies with NIPT at no additional cost is economically feasible.

Further fall in NIPT cost is expected for good reasons. The principal reason is advances in technology. Chromosome-selective sequencing, semiconductor sequencing, and microarray-based analysis all have good potential to reduce costs compared with massively parallel sequencing. Revolutionary third-generation sequencing, or nano-sequencing will soon be available. The second reason is the economics of scale attributed to increasing uptake of NIPT. The third reason is price negotiation with government participation, through incentive structure, regulations, and reimbursement policies. The fourth is competition. Today, there are at least 13 NIPT providers worldwide. Three more are forthcoming in the US. The competition is keen. Almost all NIPT providers in the US are embattled in lawsuits over enforcement and infringement of patents. In a recent case, the court invalidated the "540 patent" and denied Sequenom's request for an injunction against Ariosa Diagnostics (San Jose, California)[24]. Nonetheless, even if not invalidated, the "540 patent" will expire by 2017, paving the way for further reductions in NIPT cost.

Ethical Considerations

From an ethical point of view, there are also strong grounds for NIPT for all (equity of access) and not just for a select few. If NIPT is an important and beneficial technology, it should be available to all patients[25]. When NIPT is used as a second-tier test, the risk cut-offs to define high-risk groups eligible for NIPT differ widely in different studies. The eligibility for NIPT as a secondary test is

Table 1. Clinical performance of non-invasive prenatal test as first-tier test versus that of current screening strategy in the Hospital Authority (assuming 50,000 deliveries/year)

Clinical performance	First-tier non-invasive prenatal test	Current screening
Detection rate[18]	99%	93%
False-positive rate[18]	0.3%	5%
No. of trisomy 21 fetus/year[19]	117	117
Screening positive	116	109
No. of invasive tests*	266	2603
Procedure-related loss[19]	2	23

* No. of invasive tests = ([Total No. of annual deliveries (assumed 50,000) – No. of trisomy 21 fetus/year] x false-positive rate) + No. of screen-positive cases

Table 2. Cost analysis

Item	Unit cost (HK$)
Serum assay[18]	220
Invasive procedure[18]	1900
Polymerase chain reaction*	900
Karyotyping*	1600
Human capital†	54,350
Ultrasound machine‡	0.8 million
Lifetime cost of affected child[16,20]	5.3-11.7 million
Non-invasive prenatal test cost to keep expense per case of trisomy 21 diagnosed constant from a societal perspective§	1250-2340 (US$160-300)

* Data from Tsan Yuk Hospital Prenatal Diagnosis Laboratory

† Mean monthly salary of specialist midwife responsible for nuchal translucency scanning and pretest counselling (salary quoted from Hospital Authority vacancy for advanced practice nurse)

‡ Philips IU22 ultrasound machine

§ First-trimester ultrasound for nuchal translucency is retained after implementing universal non-invasive prenatal test

subject to manipulation. This has raised significant ethical concerns.

In a civilised society, free choice is highly valued. If the government is unable to or hesitates to offer the benefit of NIPT for all, a publically funded coupon will be a much better choice than a centralised service offering an inferior/less optimal test[23].

Acceptance of Universal Non-invasive Prenatal Test

We are not alone in the pursuit for NIPT for all. In a recent survey of members of the American College of Obstetricians and Gynecologists (ACOG), the majority (79.1%) were of the view that NIPT should be offered to all patients, similar to current Down syndrome serum and ultrasound screening[26]. In the Netherlands, replacement of FTS by NIPT is favoured by 72% of health care professionals. The majority found NIPT easier to explain to patients than conventional screening[27].

Endorsement by Major Professional Bodies

In 2015, the ACOG and International Society of Prenatal Diagnosis (ISPD) revised their guidelines to keep up with the rapid developments in the field. The ACOG, in conjunction with the Society for Maternal-Fetal Medicine in the US, stated that any patient may choose NIPT as a screening strategy for common aneuploidies regardless of her risk status[28]. In 2015, the ISPD also considered it appropriate to offer NIPT as a primary test to all pregnant women[29]. The European Society of Human Genetics and American Society of Human Genetics also released their joint statement in 2015 in support of universal NIPT[30].

Conclusion

NIPT has superior efficacy to conventional screening for all pregnant women. The replacement of the current Down screening strategy with universal NIPT can potentially be achieved without adding to the overall cost from a societal perspective. The next question will be how to maximise its benefits to pregnant women in the local setting.

Declaration

The author has disclosed no conflicts of interest.

References

1. Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol* 2012; 207:374.e1-6.
2. Dan S, Wang W, Ren J, 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; 32:1225-32.
3. Song Y, Liu C, Qi H, Zhang Y, Bian X, Liu J. Noninvasive prenatal testing of fetal aneuploidies by massively parallel sequencing in a prospective Chinese population. *Prenat Diagn* 2013; 33:700-6.
4. Gil MM, Quezada MS, Bregant B, Ferraro M, Nicolaides KH. Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. *Ultrasound Obstet Gynecol* 2013; 42:34-40.
5. 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; 34:1061-5.
6. Lau TK, Cheung SW, Lo PS, et al. Non-invasive prenatal testing for fetal chromosomal abnormalities by low-coverage whole-genome sequencing of maternal plasma DNA: review of 1982 consecutive cases in a single center. *Ultrasound Obstet Gynecol* 2014; 43:254-64.
7. Jackson J, Hamar B, Lazar E, et al. Nuchal translucency measurement plus non-invasive prenatal testing to screen for aneuploidy in a community-based average-risk population. *Ultrasound Obstet Gynecol* 2014; 44:491.
8. Willems PJ, Dierickx H, Vandenakker E, et al. The first 3,000 non-invasive prenatal tests (NIPT) with the Harmony test in Belgium and the Netherlands. *Facts Views Vis Obgyn* 2014; 6:7-12.
9. Pergament E, Cuckle H, Zimmermann B, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstet Gynecol* 2014; 124:210-8.
10. Dar P, Curnow KJ, Gross SJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am J Obstet Gynecol* 2014; 211:527.e1-17.
11. Bianchi DW, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med* 2014; 370:799-808.
12. Quezada MS, Gil MM, Francisco C, Oròsz G, Nicolaides KH. Screening for trisomies 21, 18 and 13 by cell-free DNA analysis of maternal blood at 10-11 weeks' gestation and the combined test at 11-13 weeks. *Ultrasound Obstet Gynecol* 2015; 45:36-41.
13. Zhang H, Gao Y, Jiang F, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies. *Ultrasound Obstet Gynecol* 2015; 45:530-8.
14. Van Lith JM, Faas BH, Bianchi DW. Current controversies in prenatal diagnosis 1: NIPT for chromosome abnormalities should be offered to women with low a priori risk. *Prenat Diagn* 2015; 35:8-14.
15. NHS fetal anomaly screening programme. Screening for Down's syndrome: UK National Screening Committee policy recommendations 2011-2014 model of best practice. Available from: http://www.fetalanomaly.screening.nhs.uk. Accessed 8 Nov 2014.
16. Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M. An economic analysis of cell-free DNA non-invasive prenatal testing in the US general pregnancy population. *PLoS One* 2015; 10:e0132313.
17. Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. *J Matern Fetal Neonatal Med* 2015; 29:1160-4.
18. Sahota DS. Noninvasive testing for fetal aneuploidy: a Hong Kong perspective. *AJOB Empir Bioeth* 2015; 6:106-10.
19. Sahota DS, Leung WC, Chan WP, To WW, Lau ET, Leung TY. Prospective assessment of the Hong Kong Hospital Authority universal Down syndrome screening programme. *Hong Kong Med J* 2013; 19:101-8.
20. Walker BS, Nelson RE, Jackson BR, Grenache DG, Ashwood ER, Schmidt R. A cost-effectiveness analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States. *PLoS One* 2015; 10:e0131402.
21. Han J, Zhen L, Pan M, et al. Uptake of non-invasive prenatal testing in Chinese women: money matters. *Eur J Obstet Gynecol Reprod Biol* 2015; 195:100-2.
22. Neyt M, Hulstaert F, Gyselaers W. Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis. *BMJ Open* 2014; 4:e005922.
23. Minear MA, Lewis C, Pradhan S, Chandrasekharan S. Global perspectives on clinical adoption of NIPT. *Prenat Diagn* 2015; 35:959-67.
24. Chandrasekharan S, McGuire AL, Van den Veyver IB. Do recent US Supreme Court rulings on patenting of genes and

genetic diagnostics affect the practice of genetic screening and diagnosis in prenatal and reproductive care? *Prenat Diagn* 2014; 34:921-6.

25. Vanstone M, King C, de Vrijer B, Nisker J. Non-invasive prenatal testing: ethics and policy considerations. *J Obstet Gynaecol Can* 2014; 36:515-26.
26. Benn P, Chapman AR, Erickson K, et al. Obstetricians and gynecologists' practice and opinions of expanded carrier testing and noninvasive prenatal testing. *Prenat Diagn* 2014; 34:145-52.
27. Tamminga S, van Schendel RV, Rommers W, et al. Changing to NIPT as a first-tier screening test and future perspectives: opinions of health professionals. *Prenat Diagn* 2015; 35:1316-23.
28. American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 640: cell-free DNA screening for fetal aneuploidy. *Obstet Gynecol* 2015; 126:e31-7.
29. Benn P, Borrell A, Chiu RW, et al. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. *Prenat Diagn* 2015; 35:725-34.
30. Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. *Eur J Hum Genet* 2015: 23:1438-50.