**Has special interest been allowed to usurp the ethics process in prenatal diagnosis?**

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**Abstract**

Non-invasive prenatal testing (NIPT) is moving the goalposts for the attainable information to know whether a foetus has a genetic disorder such as Down syndrome (DS). NIPT not only misses fewer cases than first trimester combined screening (FTC), but also has less false positive results. Unlike with neural tube defect (NTD) where screening to detect affected pregnancies was welcomed, NIPT for trisomy has met surprising resistance. Special interest groups have been allowed to usurp influence beyond what is balanced in the discussions. The fear of parents of children with DS, that their children might be devalued, must not trump the right of autonomy of pregnant women to decide what is best for their own family and what they can cope with emotionally and economically. Society, however, must ensure that resources for caring for those with DS and other handicaps remain adequate. Here recent articles are reviewed.

**Introduction**

Every couple wants to give birth to a healthy child. It is impossible to imagine that a couple would want a child to have a disease or a handicap, and fortunately the vast majority of children are born healthy. Carrier-screening and prenatal diagnosis has long been established and the milestones well recognised. In the 1960s amniocentesis with karyotyping came into practice and later testing with alpha-fetoprotein (AFP) for NTD which subsequently was developed for maternal blood. In 1971 carrier-identification for Tay-Sachs disease was introduced, and 5 – 6 years later screening for thalassemia-carriers around the Mediterranean. The distressing condition of Tay-Sachs was almost eliminated based on carrier detection by a simple blood test, and carriers were advised not to marry. Today, genetic testing has replaced the blood test. Second trimester screening was introduced 25-30 years ago and first trimester combined screening with ultrasound and biochemical markers (FTC) about 20 years ago. Non-invasive prenatal testing (NIPT, also sometimes called NIPS) started on a large scale about 5 years ago. It can detect trisomy 21, 18 and 13 – Down syndrome (DS), Patau syndrome and Edwards syndrome, respectively – with high accuracy.

When DS is detected by genetic screening during pregnancy, the vast majority of prospective parents chose to terminate the pregnancy. Because of this high abortion rate, some groups argue that testing designed to identify foetuses with DS are discriminatory against people with this condition. Though this attitude in some ways is understandable, it is fallacy. (It is worth noting that cases of Edwards and Patau syndrome never enter into these discussions partly because they are rarer but mainly because 90 – 95 % are stillborn and 80 % of those born alive die within a year.) A more constructive view is that as fewer and fewer children with DS are born, the more secure is the funding for those that are. In many countries around the world, there is very little support from the public purse for these children, so the cost is born by the family. Here I review 11 recent studies that directly or indirectly address attitudes of pregnant couples to NIPT [1 – 11], only 2 of which [1, 7] are theoretical discussions.

**Recent studies on women’s perspectives on the ethical implications of NIPT**

A Delphi study from Canada was published in 2019 [1]. The Delphi method is a forecasting process using multiple rounds of questionnaires sent to a panel of experts. Several rounds of questionnaires are sent out to the group of experts, and the anonymous responses are aggregated and shared with the group after each round. Briefly, issues relating to prenatal diagnosis were discussed in 3 rounds with 61, 58 and 49 persons in each group. The paper presented details about the people involved. One group was “patients or disability rights advocates”, of which there were 17, 16 and 14. A specific subgroup of these were “association specific to Down syndrome” of 4, 4 and 4. In addition there were representatives of religions, 10, 9, and 6. Of these there were 2, 2 and 2 identified as Christians, 3, 3 and 3 as Muslim, 2, 2, and 1 as Jewish, and the rest were not well identified, certainly not described as Hindu or Buddhist. 67 – 69 % were born in Canada and 70 % spoke English and 26 % French. In this context, of Canada’s 36 million inhabitants, 39 % are Catholic, 20 % Protestant, 3 % Muslim and 1 % Jewish, while 60 % consider themselves primarily English-speakers and 22 % French-speakers, and their median age is 42 years [2]. Among “potentially influencing factors”, 23 % had a child with a disability and 86 % knew one; and 45 % had experienced prenatal screening, and 17 % had undergone prenatal diagnosis, though the study did not identify whether NIPT or FTC. Thus, though in some aspects the study members were representative of Canadians in general, in other aspects they were not.

Recently 3 papers were published that address not only the incidence of children born with DS but also the significant costs that affect the families [3, 4, 5]: one from South-Korea [3], one from Mexico [4] and one from the US [5]. Briefly, these studies can be summarised as follows.

The Korean study [3] compared the number of children born with DS between 2007 and 2016 and found that despite the increase in the average age of the mothers (a major risk factor for DS), the number of DS births was constant at about 5 per 10,000 live births. Four (4) different models were used to estimate the "deficit", ie the differences between observed and model-based frequency were more than 10 per 10,000 born in 2007 and 15 per 10,000 born in 2015. In addition, a comparative analysis for the cost of care needs between 2,301 DS children and 12,265 non-DS children was performed. The medical expenses for children with DS were about ten times higher than those for non-DS children and the direct costs to the families were about twice as high.

The authors concluded that because the total medical and private costs for children with DS are higher than for non-DS children, additional financial and welfare support is required for them. They asked that public policies should be implemented to provide adequate antenatal care to prevent the financial burden of medical care for infants and children with DS. It is hard not to believe that it is a softly spoken pronouncement for more and better prenatal diagnostics.

The Mexican study [4] did not focus as much on the number of births with DS, which had dropped significantly (from 11.5–15.5 in 2007 to 3.7–4.6 per 10,000 a year later), but instead emphasized the cost aspects which are burdensome in Mexico, where when the child reaches 5 years, costs are not covered by the general health and social services. It was estimated that the annual expenses for a child with DS accounted for 27 % of the available household expenses. On average, 33% of families with DS children had disastrous expenses, and 46% of families had to borrow money to pay for medical expenses.

A north-American study [5] between 1999 and 2013 from Boston and Montreal (2017) found that, overall, patients with DS incurred incremental medical costs directly to the family of $ 18,248 between birth and 18 years, while third-party payers (health insurance companies, etc) paid incremental costs of $ 230,043 during the same period.

According to these studies, the extra costs for a child with DS are extremely significant and hit families hard in countries such as Mexico and South Korea. In countries with tax-financed health care systems that increasingly are underfinanced and in deficit, sooner or later an increasing proportion of the costs will needs be passed on to the families. In this situation, a positive foetal diagnostic test will become a financial reality for the family. Nevertheless, these articles have not been discussed in the media. It is as if they never had been published. One is left with an impression that uncomfortable truths must not be allowed to enter the debate on prenatal testing.

Other recent papers are worth considering in this context. The first interim report on the Dutch Trident-2 study, which began on April 1st, 2017 and will continue until April 2023, has just been published [6]. In the Netherlands, the cost of foetal diagnosis is not covered, but those who entered the study received NIPT at the same price as FTC: 175 €. NIPT is performed with whole-genome sequencing at labs in Amsterdam, Maastricht and Rotterdam. In the first year, 42 % of all pregnant women chose NIPTs (73,239) while 4% chose KUB, and 52% did not participate. However, it was estimated that 3 - 5% underwent NIPT privately outside of Trident-2.

Almost 80% of those who opted for NIPT chose to be informed of more findings than trisomy 21, 18 and 13. This was unexpectedly high. The positive predictive values ​​were also unexpectedly high - 96% for trisomy 21, 98% for trisomy 18 and 53% for trisomy 13. That less than 50% of pregnant women undertook prenatal diagnostics considered the authors could be due to several reasons, such as cost, a negative attitude towards abortion and a positive attitude towards DS, and that the offer for testing focused on the right not to need to know. The article also covered the unusual trisomies and other chromosome anomalies.

A second Dutch article is from a group of medical ethicists and philosophers and clinical geneticists at Erasmus University in Rotterdam [7]. The article is an ethical discussion about whether it was justified to charge pregnant women (in whole or in part) for NIPT. Two reasons were discussed. One reason for payment was that it would slow down the adoption of NIPT. The second was that a payment would ensure that pregnant women made an informed choice.

The authors considered that the use of financial instruments to curb the use of a screening system violated the principles of screening. The whole point of screening is that as many as possible participate. In addition, it was considered that payment - unless only symbolic like the € 8.68 in Belgium - disproportionately affects the lower socio-economic groups, which conflicts with fair and equal access to prenatal diagnosis. They also felt that there was no evidence that payment would lead to better informed choices. Instead, external (ie financial) impact on pregnant women should preferably be avoided. In order to promote informed decisions, healthcare should instead invest in adequate counselling before prenatal diagnosis and when the results were communicated.

A further article was a German systematic review of whether there were studies on how pregnant women experienced prenatal diagnosis with NIPT [8]. Their search found 2007 unique articles and abstracts of which 99 were examined in detail, with the conclusion that 7 articles met the search criteria and requirements set. The studies, which ranged from relatively small to fairly large, consisted of 5 who had assessed anxiety, psychological distress and/or regret over decisions among women with validated instruments, while 2 studies had interviewed women or held focus groups. It was found that women's anxiety decreased when they received a message about low risk of trisomy. In addition, few women regretted their decision on whether to terminate or continue their pregnancy. However, they did not find any studies with long-term follow-up on the pregnant partner either.

The preferences of Canadian women, their partners and health-professionals regarding NIPT use and access has also been studied by the group that did the Delphi study described above [9]. They looked at 882 pregnant women, 395 partners and 184 health care professionals. Women and partners when asked if they were concerned that NIPT being covered as part of routine prenatal care could lead to increased pressure, the majority of women reported “no concern” whatsoever and only 1.8% reported “very concerned”. This suggests that the impact of public funding for NIPT would enhance autonomy in women’s decision-making. Almost 4 out of 5 pregnant women wanted NIPT to be the first-tier screening test instead of FTC because of better accuracy and earlier availability of results. Even more interesting, more than 2/3 of pregnant women preferred NIPT to amniocentesis as a diagnostic test after current screening, disregarding the possibility of false positives (and negatives, though the risk of those are minimal). Generally, women and their partners were willing to pay up to 499 Canadian dollars for NIPT ($100 – 499 was the most popular choice). In Ontario, the province that provides NIPT free for high-risk pregnancies, the willingness to pay between $100 – 499 was less than for Canada as a whole.

A different Canadian study had looked at women’s perspectives on the ethical implications of NIPT by using an adapted version of constructive grounded theory [10]. They interviewed 38 women who had had personal experience with NIPT and used an iterative process of data collection and analysis. They found that the participants overall were dissatisfied with NIPT only being offered to women with high risk and noted the cost of NIPT as a barrier to getting it. All participants in the study supported both early access to NIPT and access to NIPT for all women as the initial prenatal test. Restricting NIPT to only a few went against Canada’s commitment to universal care. It was the woman’s right to choose how to use the information about the health status of the foetus. It was her baby and not someone else’s, and others must not be allowed to limit her choice. At the same time, women feared that NIPT would be used for sex selection. The risk of sex selection was the major issue (not so surprising seeing that mainly female foetuses are aborted). The women were also critical of “frivolous” uses. The earlier availability of the results (compared with FTC) was seen as positive because it avoided the physical and emotional difficulties of later terminations. Many women also considered that governments should consider potential savings in long-term health-care costs and social support when affected pregnancies were terminated. Whatever the system paid for testing, the system would save down the line in the cost of care for disabled children and their hospital costs including intensive care, even if they only lived for a few weeks or months after birth.

A British team conducted a mixed methods study to assess women’s experience of being offered NIPT using validated measures of decisional conflict, decisional regret, and anxiety [11]. Clinical service preferences were also explored. Women with a DS screening risk >1:1000 were invited to take part in the study and offered NIPT, NIPT and invasive testing (for women with a risk above 1:150) or no further testing. A cross-sectional survey and semi-structured interviews were conducted at two time points; at the time of testing and one month following receipt of results (or equivalent for NIPT decliners). In total, 845 questionnaires and 81 interviews were analyzed. Decisional conflict occurred in a minimal number of cases (3.8%). However, none of the participants experienced decisional regret. Likewise, a questionnaire study was performed in the Netherlands of 682 pregnant women with elevated risk for fetal aneuploidy based on first-trimester combined (FTC) test (risk ≥1:200) or medical history, who were offered NIPT in the nationwide Dutch TRIDENT study [12]. Pre- and post-test questionnaires included measures on: experiences with NIPT procedure, feelings of reassurance, anxiety (State-Trait Anxiety Inventory, STAI), child-related anxiety (PRAQ-R), and satisfaction. The majority (96.1%) were glad to have been offered NIPT. Most women with a normal NIPT result felt reassured (80.9%) or somewhat reassured (15.7%). Levels of anxiety and child-related anxiety were significantly lower after receiving a normal NIPT result as compared to the moment of intake (*p* < 0.001). A study in Australia came to essentially similar conclusions, that NIPT was well received and women were reassured by a result indicating low risk [13].

These studies have shown that when a pregnant woman receives a message that her foetus does not have trisomy, she experiences the prenatal diagnoses process as positive [8, 9, 10, 11, 12, 13]. This is not surprising; it reflects human nature. In contrast, when the message is that of a trisomy, the women report substantial dissatisfaction with the process, complaining about a number of features. This too is not surprising. They are forced to make a decision. It is also reassuring that NIPT does not cause regret of the decision taken.

The Trident-2 study will build up a huge database of foetal genomes linked to pregnancy outcomes. New genetic hypotheses will be easily tested. It will also be possible to see how attitudes towards NIPT develops. With just 3 labs the Dutch will have gained a lot of experience. It feels like other countries have missed the bus to be part of this research. What is worse, by insisting on continuing with FTC, which misses significantly more trisomies than NIPT, and limiting access to prenatal diagnostics in the public sphere (unlike Belgium), they have created unequal care, something resented by participants in the studies described above.

**Discussion**

We have a situation today where one country, Belgium, moved the goalposts in 2017 when they introduced NIPT as the primary screening system at a nominal fee (8,68 €, ca 9 USD). Belgium is 50 % Catholic and 33 % non-religious [14]. The Netherlands have chosen to undertake a substantial study as part of an ordered introduction [6, 12]. This shows an overwhelming preference for NIPT and those pregnant also wish to learn as much as possible. The data base being established will enable the Netherlands to test and confirm or refute any hypothesis for a candidate genetic locus. The other countries of the world are not using NIPT as a first line test, only as a confirmatory test after the less accurate FTC has been performed, this in spite of FTC having a substantial false negative rate (that is misses cases), an illogical choice. Nevertheless, the coverage of NIPT by insurers in USA seems to be increasing. In addition, in all the countries without subsidised or free NIPT, there is a lot of private NIPT performed. The cost of this varies but is usually considerably higher than the lowest prices charged by reputable labs as judged by surveying the Internet. Nevertheless, in comparison to the lifecost of raising a handicapped child, it is a trivial amount, as illustrated by the Mexican, South-Korean and American studied [3 – 5].

No reputable discussant challenges that NIPT is a much better test than FTC for trisomy [15]. It has virtually no false negative rate, while FTC’s false negative rate is significant. Thus, NIPT does not miss a case. When NIPT does not find evidence for a trisomy the risk is essentially zero. This is simple message for midwives and obstetricians to communicate, and it is clear that they find this less stressful than the FTC results. NIPT also has a much lower false positive rate than FTC. This means that far less women need be subjected to amniocentesis or chorionic villous sampling (CVS), with the resultant reduced stress. (NIPT has a slightly lower positive predictive value for the rarer T13 and T18 than for T21.) If NIPT was a test for prostate cancer, it would have swept PSA from the stage. Yet, every time the superior NIPT is discussed, special interest groups are allowed to undermine its status, usually without raising the obvious: sex-selection (female foeticide).

Yet, when one considers how much fewer resources families in emerging economies have than South-Korea, Mexico, the USA, and most western European nations, the need for effective screening is even higher because of the costs to families and society. As the Canadian structured interview study [10] found, women not only expect NIPT to be available to all but they also consider it their own right to decide about how to proceed with a foetus with a handicap. Their big concern is sex-selection. It is not acceptable that others prevent those pregnant deciding the path forward for themselves and their family including the impact on any future children they might have. That those with children with DS may want more children with DS to be born to prevent discrimination is one view but who are they to order others to bear and care for any child with a handicap. Autonomy means the right of those pregnant to make that decision for themselves.

It is understandable that people who have to handle caring for children and/or relatives with handicaps register themselves for meetings about these conditions, including their prevention, and thus are overrepresented. Nevertheless, it is reasonable to ask why the organisers seem to let special interest groups and people with vested interests dominate this debate. Is it not high time to let the voice of the common people be heard? Indeed, that 7 – 10 % of those consulted in the Canadian Delphi study [1] could be representatives for DS interests seems out of proportion to that of the healthy population. In all handicap groups accounted for about 30% of the groups. Indeed, 25 % of the delegates had a child with a significant handicap. That almost 80% knew a handicapped child makes some sense in that they have experience of the issue.

It seems bizarre to discuss the cost-effectiveness of various forms of screening divorced from the costs of a handicapped child to the family and society, yet many (if not all) discussions about the cost-effectiveness of prenatal screening do not. It is fitting, as the Swedish State Medical Ethical Council (SMER) and the Swedish State Committee for Medical and Social Evaluation (SBU) in several reviews argue that society should provide good support for families and individuals with DS. SBU’s review of NIPT in 2015 [15] states – "From an ethical point of view it is extremely important that there is good social support for people with disabilities”, but they then go on and claim that “there is a potential risk that offering prenatal diagnostics of T13, 18 and 21 may be seen as devaluing and inducing discrimination of individuals with these trisomies.” The DS and other interest groups argue that this means that if a nation transfers costs to families and individuals then prenatal diagnosis must stop. DS interest groups also have a tendency not to declare a conflict of interest when commenting on prenatal diagnosis and its implications, a pernicious practice not uncommon among many and various interest-groups [16].

The infected debate around better screening for trisomy should be compared to the case of neural tube defect (spina bifida). In NTD, methods for prenatal screening were welcomed. Screening with alpha-fetoprotein (AFP) first in amniotic fluid and then in maternal blood was introduced several years before Laurence’s and Smithells’s groups [17 - 23] showed that supplementation of diet with folate could prevent neural tube defects. Ultrasound screening has now replaced AFP, and today very few babies are born with NTD in developed countries, although the condition is still a major health problem in many poorer countries. What is controversial today is that the so-called Groeningen Protocol allows for newborn with NTD to be euthanized [24]. The principle of screening and termination in NTD is seen as self-evident.

**Conclusion**

Already Smithells, Laurence and Lorber showed the huge negative impact NTD had on families, not just economical but psychological and social stress, including the high divorce rates and the damage to the oldest daughter who had to act as a second mother (reviewed in [23]). Developing nations do not have the resources of rich countries. At the same time, the use of cheap ultrasound to identify and selectively abort female foetuses shows how dangerous unregulated screening can be. It also illustrates how powerful the market place is even when the outcome is a disaster for society. That this occurs not only in nations such as China and India but also in rich countries like the USA [25] and Western Europe, at least among immigrants to those nations from areas where girls are not highly valued, illustrates the problems in society. Nevertheless, it is hard to see how screening to exclude births with untreatable congenital handicaps should not be seen as an improvement. At the same time, every effort to prevent sex-selected foeticide must be supported.

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