

## Debate paper

# Non-invasive fetal sexing: medical test or a new tool for sex selection?

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### What is known on this subject

- Certain countries that exhibit a preference for male offspring display worryingly skewed sex ratios at birth in favour of baby boys.
- There has been widespread use of antenatal ultrasound scanning to enable sex-selective abortion in countries such as India and China, which is now illegal.
- Non-invasive prenatal tests (based on fetal DNA in maternal blood) are currently used (for clinical purposes) in a small number of women whose babies are at risk of a sex-linked disorder.

### What this paper adds

- Direct-to-consumer marketing of non-invasive fetal DNA tests for social sex determination became available without sufficient consideration for technical performance.
- Non-invasive fetal sexing is likely to affect sex selection practices in the developing world and Asian diaspora.
- Corporate responsibility when marketing tests requires the balancing of legitimate consumer needs against unintended consequences.

## ABSTRACT

Recent scientific developments in prenatal testing, based on fetal DNA in maternal blood, now allow non-invasive fetal sexing in pregnancies at risk of a sex-linked disorder. In such cases, these novel non-invasive tests can improve prenatal care by avoiding the need for invasive procedures such as amniocentesis, with their associated risk of fetal loss. The tests available for medical use are characterised by high levels of accuracy (> 99%) and early fetal sex determination (from week 7 of gestation). Many countries now offer families at risk of a sex-linked disorder this new form of clinical fetal sexing.

At the same time, further developments in fetal DNA technology are making antenatal sex determination possible via a fingerprick sample mailed anonymously to a commercial organisation. Direct marketing to future parents of such non-invasive tests for social sex determination will bypass a woman's physician. This could allow termination based on sex selection while women ostensibly present to physicians, who will have no access to the test result, for a termination on social grounds.

If test results are available at 7 weeks gestation, online purchase of products for non-surgical abortion at home early in pregnancy could also enable some parents to bypass a health system altogether.

Female feticide, linked to son preference and widespread ultrasound diffusion, has already led to significant gender imbalances in India and China. Certain ethnic minority communities in the west are also now displaying evidence of fetal sex selection. Currently, mail-order fetal sexing, based on fetal DNA in maternal blood, is still an emerging market. However, before any widespread diffusion, discussion about the implications of this new technology and associated issues is important and timely. This article considers evidence of technology development, existing demographic and social changes, corporate responsibility in product marketing, and the role of community engagement and education.

**Keywords:** fetal sex determination, gender imbalance, non-invasive diagnosis, prenatal testing, sex selection, son preference

## Introduction

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Currently, expectant parents who wish to know their baby's gender have to wait for a second-trimester ultrasound scan. While for most there may be no strong gender preference and this information simply satisfies their curiosity, research has shown the existence of preferences for an offspring's gender in certain populations. Traditionally boys are favoured over girls in China, South Asia and Arab countries (Hudson and den Boer, 2005). There is also evidence of antenatal ultrasound scans being used for sex selection, although originally marketed ostensibly to check the health of the fetus. Reports from India and China indicate worryingly skewed sex ratios at birth in favour of baby boys since ultrasound was introduced (Hudson and den Boer, 2005; Lai-wan *et al*, 2006; Anonymous, 2010). In both countries it appears that female infanticide, which previously occurred on a relatively small scale, has been replaced by large-scale sex-selective abortion or female feticide based on the widespread availability of this technology (Jha *et al*, 2006; Sheth, 2006; Aravamudan, 2007). The '50 Million Missing' campaign, which was launched in India in December 2006, seeks to reduce the loss of girls through feticide (Banerji, 2006). The extent to which sex selection is driven by family or cultural preferences and the extent to which it is a result of the availability of suitable technology may be debatable, but there is clearly a relationship between the two. Both India and China have introduced legislation to attempt to control the availability of ultrasound scanning by confining antenatal use to licensed clinics, but have met with limited success. In the developed world, although no notable sex imbalance at birth has been reported for the majority populations, there is evidence that an effect is beginning to emerge in South Asian communities in the UK and other countries.

In May 2007, a prenatal home-testing kit for detecting a baby's sex early in pregnancy made headlines in the UK ([www.dna-worldwide.com](http://www.dna-worldwide.com)). This test was marketed directly to prospective parents via the Internet. Fetal sex testing simply required pregnant women to extract a few drops of blood from their fingertip and then post this to a commercial laboratory. The laboratory testing process exploited a new technique for tracing and analysing minute amounts of fetal DNA in maternal blood. This product followed an earlier one which was launched in the USA in 2005. Initially, public demand for this product was reported to be high, with more than 1000 enquiries during the first three weeks (Hopkins Tanne, 2005). At the same time, several scientists working in the field voiced their concerns and recommended caution with regard to the reported accuracy of the test (Kaiser, 2005; Bianchi *et al*, 2006). The only research that had been published

which had used dried drops of maternal blood had suggested that this was less reliable than fresh blood (Bischoff *et al*, 2003; Jorgez *et al*, 2006).

The development of new non-invasive prenatal diagnostic (NIPD) tests for fetal sexing was initially driven by clinical need in families where a fetus is at risk of a sex-linked disorder. In these cases, a non-invasive test could improve clinical care considerably because women would otherwise have to undergo invasive amniocentesis or chorionic villus sampling (CVS) to identify whether their fetus was affected. However, wider marketing of NIPD fetal sexing tests direct to parents raises a number of concerns. At first sight, these may appear to be significant only in the developing world, but closer consideration shows that they are also potentially relevant to certain ethnic minority communities in the west. This paper explores some of the issues associated with the technical development and direct marketing of NIPD tests. Because NIPD for fetal sexing is still an emerging technology, more widespread discussion of its potential use is required.

## Clinical drive for NIPD technology development

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Pregnant women whose child is at risk of a sex-linked disorder have, until recently, undergone invasive chorionic villus sampling (CVS) for fetal sexing from 11 weeks of gestation. However, this procedure carries a 1% risk of miscarriage. Non-invasive prenatal fetal sexing became possible following the discovery of cell-free fetal DNA in maternal plasma (Lo *et al*, 1997). Subsequent test development and clinical trials have demonstrated the accuracy of small-scale testing in individual pregnancies at risk of sex-linked disorders (Avent and Chitty, 2006; Hahn *et al*, 2008). As a consequence, in the UK and other European countries, fetal sexing using NIPD is currently available at a number of laboratories at a cost comparable to invasive CVS testing. NIPD offers not only psychological benefits for expectant parents, if the test indicates that the fetus is not prone to a sex-linked disorder, but also the possibility of earlier termination if it is prone to a serious disorder (e.g. haemophilia or Duchenne/Becker muscular dystrophy), and better management of *in utero* treatment in other cases (e.g. congenital adrenal hyperplasia, a genetic disorder that causes girls to develop abnormal male-like characteristics, which can be treated with a steroid if identified early in pregnancy). Sex determination for such clinical purposes is based on a venous sample (2.5–5 ml) of maternal blood.

Because the test relies on sex-dependent markers which are present only in males, the NIPD test will give a signal if a male fetus is present, so if no signal is observed, the fetus is assumed to be female. It is therefore highly dependent on detecting fetal DNA in the blood sample. In 2004, a National Institute of Child Health and Human Development consortium conducted NIPD fetal sexing tests in five US centres on samples from 20 pregnant women between 10 and 20 weeks of gestation. The recorded sensitivity (i.e. the ability to detect male DNA when the fetus was male) ranged from 31% to 97% across centres (Johnson *et al*, 2004). More recently, a Dutch study of non-invasive fetal sex determination in maternal plasma reported results for 201 pregnant women (Scheffer *et al*, 2010). The test protocol allowed reporting of a female fetus only if the presence of fetal DNA was confirmed. Using this protocol, the test was able to produce conclusive results in 189 cases, and all of those results were correct. Because trace amounts of DNA are being detected, great care is required to avoid contamination of the sample by male staff handling the test materials, which would lead to incorrect identification of a fetus as male.

Although NIPD testing is now being used clinically in women carrying an at-risk fetus, the percentage of pregnancies at risk of sex-linked disorders is extremely low. A potentially much larger market exists worldwide for the social use of NIPD fetal sexing to enable parents to discover the gender of their baby early in pregnancy. High-throughput laboratory NIPD processes have already been developed for detecting the fetal rhesus (RhD) blood group, and these could be adapted for mass screening (Finning *et al*, 2008). Based on the results of published clinical trials, medical sexing should have an accuracy rate of 99.8–100% if this laboratory protocol is followed (Avent and Chitty, 2006; Finning and Chitty, 2008; Hahn *et al*, 2008). To date, however, there have been no published large-scale technical trials reporting test performance using fingerprick samples. Expert opinion suggests that the percentage of false negatives (i.e. cases where the fetus is falsely identified as female) will be higher than for venous blood samples used for medical purposes (Professor Tobias Legler, Universitätsmedizin Göttingen, Germany and Dr Kirstin Finning, National Blood Service, Bristol, UK, personal communication). A low signal, due to insufficient fetal DNA, would lead to failure to identify the presence of male DNA, and therefore to the false conclusion that the fetus is female. Sex-independent markers which can improve the identification of female fetuses are needed to improve accuracy (Finning and Chitty, 2008).

## Marketing of NIPD tests for fetal sexing

Marketing of direct-to-consumer fetal DNA tests for sex determination should be set within the context of an increased trend towards direct test marketing. Recent technological developments have produced a range of tests that can either be completed entirely in the home, or that involve self-collection of blood, saliva, urine or other specimens which are shipped directly to the manufacturer or a reference laboratory for rapid turn-around. In the USA, the Food and Drug Administration (FDA) has cleared a range of over 500 different clinical tests for home use and over-the-counter purchase in pharmacies (US Food and Drug Administration, 2010). NIPD fetal sexing tests are not considered suitable for regulation by the FDA or the Federal Trade Commission because gender is not a clinical condition. This has theoretically made the path to marketing them much easier, with some companies stating correctly that their test is FDA cleared (e.g. IntelliGender, 2010).

Companies who offer NIPD fetal sexing generally charge £150 to £200 for testing (e.g. [www.babygendermentor.com](http://www.babygendermentor.com), [www.tellmepinkorblue.com](http://www.tellmepinkorblue.com) and [www.nimbleiagnostics.co.uk](http://www.nimbleiagnostics.co.uk)). This includes the test kit and processing, making the technology affordable for a large number of people in both the developed and developing world. At present, however, there are no data available on the stage of pregnancy when testing is taking place, the level of NIPD uptake in different countries, or accuracy rates based on fingerprick samples. Available sources, such as comments on users' websites, suggest that women send their samples at around week 8 of gestation. Users' website comments following the launch of the first test in the USA also indicated that there appeared to be problems with test performance. This test was initially marketed as 99.9% accurate, with a 200% refund offered if the results were incorrect. An informal Internet-based poll which closed in September 2006 resulted in 97/151 incorrect results being reported ([In-Gender.com](http://In-Gender.com), 2007). Following this, a class action lawsuit was filed in the USA suing the company for false advertising and altering their money back policy ([BabyGenderInvestigation.com](http://BabyGenderInvestigation.com), 2007; [LawyersandSettlements.com](http://LawyersandSettlements.com), 2010). The company filed for chapter 11 bankruptcy in December 2009.

More recently, other US companies which have started to offer a similar service have promised a more realistic 95% accuracy rate, and include instructions to males not to handle the kit because this can contaminate the sample, leading to incorrect

identification of a fetus as male (e.g. [www.tellmepinkorblue.com](http://www.tellmepinkorblue.com)). Some companies also provide a clear statement that they will not market the product to India or China, explaining that 'due to the high incidence of gender selection in China and India, it is our policy not to service these countries. No exceptions can be made' (e.g. [www.tellmepinkorblue.com](http://www.tellmepinkorblue.com)). In contrast, other companies appear to offer a service anywhere in the world.

The potential market for non-invasive tests for social sex determination encouraged other companies to start offering NIPD tests, who subsequently suspended marketing (e.g. DNA Worldwide (UK) and Paragon Genetics (Canada)). It is unclear whether this was due to technical problems, fear of jeopardising the company's image, or other reasons. Recently, in February 2010, a further company has launched a battery of NIPD tests, including tests for determining the sex of a fetus, for cystic fibrosis and for fetal Rh-negative blood incompatibility, all by analysing the mother's blood. The non-invasive fetal sexing test does not appear to be aimed at social sex determination ([www.sequenom.com/Home](http://www.sequenom.com/Home)).

## Sex selection practices

For centuries, sex selection was practised in the form of infanticide in certain societies and cultures. However, it is now acknowledged that a preference for sons can affect the sex ratio in a country's population where there is widespread access to prenatal sex-selective technology and a reduced fertility rate, either by choice as in India (Jha *et al*, 2006), or by coercion as in China (Ding and Hesketh, 2006; Liu and Zhang, 2009; Zhu *et al*, 2009). The introduction of various technologies has allowed prenatal fetal sex determination followed by selective abortion of a fetus of unwanted sex (Pallikadavath and Stones, 2006; Aravamudan, 2007). Ultrasound, which is relatively inexpensive, has been most frequently utilised in the developing world, particularly in countries such as India and China (Hesketh and Xing, 2006). However, there is some evidence of the use of more invasive and expensive procedures such as amniocentesis for sex determination, although these are ostensibly available primarily for genetic testing (Sharma, 2008). It appears that, in India, male fetuses may be kept following such a procedure even if there is evidence of a genetic problem (Hudson and den Boer, 2005). Data from India also show that sex selection practices are more common in higher birth orders, especially if other children in the family are girls (George, 2006; Dubuc and Coleman, 2007). Currently, although sex selection appears to be practised across all class and income groups in India, there is evidence of more extensive

use in the economically advantaged or educated middle classes than in lower-income rural populations (George, 2006; Jha *et al*, 2006; Pallikadavath and Stones, 2006). There is also a link between decreasing fertility and increases in sex selection practices (Hudson and den Boer, 2005).

In general, sex selection, which almost universally favours males, is found in societies where the lives of females are held to be of significantly less value than those of males. The reasons for male preference are similar in most cultures, and have been well documented in the literature (George, 2006; Hesketh and Xing, 2006; Lai-wan *et al*, 2006). In countries such as India and China, although improved healthcare and conditions for women have resulted in a reduction in female mortality, these advances have been offset by a huge increase in the use of sex-selective abortion, which became available in the mid-1980s (Anon., 2010). In India, ratios below 800 females to 1000 males in the 0–6 years age group are now recorded in some areas, and it has been estimated that, due to sex selection based on prenatal detection, 40–50 million women are 'missing' (George, 2006). In China, this figure could be as high as 80–100 million (Hudson and den Boer, 2005). The numbers continue to grow, and all the projections are that the gender gap will continue to increase over the coming decades. India, South Korea, China and most European countries have laws banning fetal sex determination. In India, the Prenatal Diagnostics Techniques (PNDT) Act came into force in 1996, making it a crime to reveal the gender of a fetus. In 2000, the Supreme Court passed orders to improve implementation, which resulted in most ultrasound clinics being registered. In 2003, a further amendment added pre-conception sex selection. Governments have also financed multiple campaigns to encourage families to have girls, promised financial rewards, and prosecuted physicians who report fetal gender, but these actions have not proved successful. Although doctors have been prosecuted, few of them appear to have been convicted (Mudur, 2006). The resulting surplus of men who are unable to find wives is already reported to be creating social problems such as an increase in the trafficking of women, selling them into marriage, and forcing increasingly younger girls into marriage (Hudson and den Boer, 2002, 2005; Hesketh and Xing, 2006).

It appears that sex selection in these societies is not just manifested in practices such as prenatal testing and abortion. There is evidence that in India and China the deaths of females up to the age of 35 years outnumber male deaths (Hudson and den Boer, 2005). This is the reverse of the pattern observed in the developed world, where girls universally have higher survival rates. The explanations that have been offered for this difference include child neglect, malnourishment, and more limited access to medical

care for female children. There is also some evidence from China and India that where women themselves choose not to have a baby girl, this is so that their female child will not suffer in life as much as their mother has done. Thus women are trying to protect their unborn children from the fate of being a woman in their society (Hudson and den Boer, 2005).

In addition to prenatal testing, pre-conceptual sex selection through pre-implantation genetic diagnosis (PGD) has also been utilised in some societies. Although PGD provides complete accuracy in terms of identifying fetal sex, it is a complicated and invasive method that requires *in-vitro* fertilisation (IVF), and hormone therapy preceding IVF. Not only is IVF expensive, but it also has a conception success rate of only 25–50% (Borini *et al*, 2008). This procedure has been allowed in Israel as a means of ‘family balancing’ if there are already four children of the same gender in the family (Israeli, 2005). In other countries, sex selection through PGD is available in private clinics for those who are willing to undergo the procedure. Sperm sorting, a much simpler method of pre-conceptual sex selection, is not widely used because it is associated with a low success rate (Sutton, 2002). Other methods have been marketed openly for sex selection (e.g. GenSelect). These are based on ‘modifying the body chemistries of both mother and father’ to help parents to influence the gender of their next child, although the accuracy of these methods has been questioned (CBS News, 2004).

It is worth noting that parents can only hope to select a future child’s gender, not its sexuality. Parents cannot predict the sexual orientation of their children when they become adults, or the likelihood of them becoming transgender individuals (Seavilleklein and Sherwin, 2007). Although cases when sex differs from gender are rare, NIPD technology may be a useful tool for confirming fetal sex when there is a suspicion of genital ambiguity on ultrasound (Finning and Chitty, 2008).

## NIPD markets in India and China

At present, sex determination and sex selection practices in India and China represent a multi-million-dollar business (George, 2006). NIPD technology for fetal sexing could be easily developed in laboratories in these countries at a lower cost than in the west. In India, laboratory testing following amniocentesis costs four times less than in the UK and ten times less than in the USA (Sen, 2008). Technical know-how and the required infrastructure already exist in India and China, through the Special Non-invasive Advances in Fetal and Neonatal Evaluation (SAFE) Network of Excellence which was funded by the European

Commission Framework 6 Research Programme (2004–2009) to speed up the development and implementation of NIPD tests. It is therefore reasonable to assume that this form of fetal sexing could also eventually be performed at a far lower cost than in Europe or the USA. This would allow widespread diffusion of non-invasive fetal sexing via Indian and Chinese laboratories.

Such widespread availability will mean that parents in countries where sex selection is already being practised via ultrasound clinics could order a test online, post a blood sample to the laboratory, and receive the results without their medical practitioner being aware of this. Women may then present to a physician, who will have no access to the test result, for a termination, ostensibly on social grounds. Alternatively, because the NIPD test allows for early termination, products could be purchased online (e.g. [www.abortion-pill-online.com](http://www.abortion-pill-online.com)) for non-surgical abortion at home during the first few weeks of pregnancy.

## NIPD markets in western countries

In the western world, some communities, such as the Hispanic community in the USA and South America and populations in certain European countries, appear to exhibit a slightly greater preference for girls, although this gender preference is dependent on the number and gender of existing children in the family (Van Balen, 2006). Other migrant ethnic minority populations in the USA, such as the Asian and Arab communities, show a preference for boys, although not to the same extent as has been reported in their home countries (Van Balen, 2006). More recently, male-biased sex ratios have been documented among US-born children of Chinese, Korean and Asian Indian parents, with the male bias particularly evident for later children. If there was no previous male child, sons outnumbered daughters by 50% (Almond and Edlund, 2008). In Norway, a recent study reported significantly lower female-to-male sex ratios in higher-order births to mothers of Indian origin who gave birth after 1987, whereas no such effect was observable for parents of Pakistani origin (Singh *et al*, 2010). In England and Wales, a similar study has reported that between 1990 and 2005 almost 1500 fewer girls were born to Indian mothers. There was a 4-point increase in the sex ratio at birth for mothers born in India, which was attributable in particular to an increase at higher birth orders, mirroring findings reported for India (Dubuc and Coleman, 2007). No significant increase was observed for mothers born in Pakistan or Bangladesh, among whom male preference presumably

also exists. However, no evidence was presented to show why these South Asian subgroups differ.

Although the western world has not shown any predisposition towards sex selection practice following the development of antenatal ultrasound, this does not mean that the introduction of NIPD will not be pursued as a business opportunity. There is currently no firm evidence that NIPD test kits are being purchased for sex selection in the west. Instead, online forum comments ([www.in-gender.com](http://www.in-gender.com)) suggest that they are being used for social reasons, with parents purchasing kits because they want to know the gender of their future baby before the second-trimester ultrasound scan. Rationales that are given include a desire to 'share the news', 'decorate the room', 'buy baby clothes' and 'bond with their future child.' It is perhaps not surprising that women are not prepared to discuss sex selection in an open online forum. However, comments from a small number of women suggest that they might consider a termination if the fetus was of the 'same sex as previous children in the family.'

In the UK, most terminations (89%) are carried out before 13 weeks of gestation (Department of Health, 2007). If sex determination through ultrasound is performed in the second trimester, this makes it more difficult to contemplate abortion for the purpose of sex selection. However, there is anecdotal evidence that some pregnant Indian-born women, under family pressure to have sons, are travelling to India to abort their unborn daughters (BBC Press Office, 2007). In contrast, since the new NIPD test can be performed as early as 7 weeks of gestation, parents who order an NIPD kit would be able to make an appointment at a clinic to terminate the pregnancy for 'social reasons' without leaving the country.

## Key issues for NIPD fetal sexing

A number of issues need to be addressed in advance of the widespread availability of accurate NIPD technology. Cultural and perceived economic reasons cannot be underestimated as continuing drivers for sex selection, and both will be difficult to change in both host and immigrant communities living in the west. Studies are necessary to understand whether public education campaigns can be effective in the west. In India it appears that education of women does not have a noticeable impact on attitudes towards sex selection, as males continue to be preferred as better providers for their parents in old age (Hudson and den Boer, 2005). Nevertheless, change is possible. In South Korea, for instance, the trend of male preference has been reversed with the growth in economic prosperity (Lee, 2007). Important factors appear to include men

moving to the cities for higher-paying jobs and leaving their parents behind, combined with the rising income of older Koreans, which allows them to save money for their retirement. Although such changes have been influential in a small country like Korea that is experiencing an economic boom, it is uncertain whether in much larger territories, such as China and India, economic improvement will shift the paradigm of son preference. The extent to which behaviour is carried over after immigration in different population groups is not clear, nor are the reasons for any differences. More research is needed to assess the attitudes of first- and second-generation ethnic minority women and families in the west, especially those going through a third or fourth pregnancy. Last, but perhaps most importantly, a dialogue should be initiated with the companies that are marketing non-invasive tests for social sex determination. More transparency is required in terms of where test markets are being developed and how corporate responsibility can be encouraged in the marketing of these tests so that legitimate consumer needs are met without the danger of unintended consequences.

In the literature, discussion to date related to the use of technology in sex selection has primarily focused on PGD and sperm sorting when considering the western world, and the use of ultrasound in the developing world (Sutton, 2002; Baldwin, 2006; Hall and Marteau, 2006; Newiss, 2006; Seavilleklein and Sherwin, 2007; Thomas, 2007; Courtwright, 2008). Authors are now starting to address NIPD for fetal sexing, with a number of potential ethical concerns being raised (Hyett *et al*, 2005; Guetta, 2006; Smith *et al*, 2006; Newson, 2008). However, commercial developments are moving ahead, with NIPD tests now emerging for other fetal characteristics, such as fetal RhD blood, status-inherited single gene recessive disorders such as haemoglobinopathies, and Down's syndrome. It is likely that these NIPD tests will initially be performed under the direction of a physician. However, with the increased trend towards marketing home testing kits, combined with parents' interest in the health of their unborn child, it is not impossible that such NIPD tests may also eventually be marketed direct to parents.

## Conclusions

The broad socio-economic issues outlined above need to be addressed before direct-to-consumer marketing of NIPD tests for fetal sexing becomes widespread. Key questions are how to control the use of these tests in the developing world, how to influence their use in the Asian diaspora, what means will encourage corporate responsibility, and how to maximise community engagement in the process.

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#### CONFLICTS OF INTEREST

None.

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