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## Ethical and social implications of current prenatal genetic testing

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**Abstract:** A new prenatal genetic testing technique using cell-free fetal DNA in maternal plasma, the Non-Invasive Prenatal Test (or NIPT), was introduced in Japan in 2013. The NIPT is easy and safe but not definitive; it also has high sensitivity and specificity under certain conditions. In the near future, it could be used not only for detecting chromosomal aneuploidy, but also complete genome analysis of the fetus. However, termination of pregnancy is the only option for those wanting to avoid having a baby with a chromosomal anomaly or a genetic disease. Given this situation, this review explores the ethical and social issues surrounding prenatal genetic testing focusing on three points: 1) selective abortion as an ethical issue, 2) informed consent and decision making, and 3) alternative perspectives on prenatal testing.

**Key words:** Prenatal genetic testing, NIPT, Selective abortion, Women's decision making, Wrongful birth trial, Disability rights movement

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### Introduction

The new prenatal genetic testing technique using cell-free fetal DNA, the Non Invasive Prenatal Test (or NIPT), is a commercially available maternal blood test that was developed for use in the United States of America (US) in 2011 and has begun to be introduced in other countries. It was introduced in Japan in 2013 after careful consideration [1–3]. Prenatal tests previously used here fall into two groups: non-invasive but not definitive, such as maternal serum screening (MSS); or invasive but definitive, such as amniocentesis and chorionic villus sampling. The NIPT can be seen as a third category, non-invasive but with high sensitivity and specificity in high risk groups.

The presence of fetal DNA in human maternal plasma

was discovered in 1997 and later led to the development of the NIPT [4, 5]. The clinical validity of the NIPT has been confirmed for detecting fetal aneuploidies, including trisomy 21 (Down syndrome), 13 (Patau's syndrome) and 18 (Edwards' syndrome), as early as 10 weeks of gestation. While current invasive and definitive prenatal tests carry the risk of miscarriage (e.g., 0.3–0.5% for amniocentesis), the NIPT is easy and safe, and although it is not definitive, it has high sensitivity and specificity under certain conditions [6–8]. In addition, it can be performed at an earlier stage of pregnancy, giving women more time to make personal decisions.

The NIPT could be used for testing a potentially much broader range of abnormalities [9, 10]. In fact, use of the NIPT is expanding to include detection of sex chromosomal abnormalities, and whole genome analysis of the fetus with the NIPT seems to be possible in the near future. However, termination of pregnancy is the only option for those wanting to avoid having children with chromosomal anomalies. Therefore, the emergence of the NIPT has raised ethical and policy concerns about prenatal testing [1–3, 9–12]. This review explores the ethical and social issues surrounding prenatal testing, with a particular focus on the NIPT.

In Japan, only three percent of all pregnant women received MSS and/or amniocentesis tests in 2008, in contrast to England and Wales (over 80%) and Australia (more than 90%) [13]. The number of amniocentesis tests has been increasing in Japan [13]. In contrast, in the US, where MSS is widely used, the percentage of women undergoing amniocentesis among those giving birth has continued to decrease from 3.2% in 1989 to 1.7% in 2003, which may reflect the growing use of non-invasive screening tests [14]. In this context, Sago proposed the NIPT as a reasonable alternative to reduce the number of invasive procedures among pregnant women requesting prenatal screening for aneuploidy [15].

## The Impact of Prenatal Screening and Testing

The American College of Obstetricians and Gynecologists states that screening and invasive diagnostic testing for aneuploidy should be available to all women before 20 weeks of gestation regardless of maternal age [6]. Therefore, ultrasound scanning and MSS have been widely used to screen fetuses for chromosomal anomalies or spinal defects. In the United Kingdom (UK), the National Health Service offers its Fetal Anomaly Screening Program to all pregnant women [16]. France also has a screening policy for prenatal testing which is provided to all women without charge [17].

Several reports have compared the actual number of trisomy 21 births to the predicted number, calculating the number of pregnant women and their age, while others have calculated the abortion rate following positive prenatal testing results. Mansfield *et al.* reviewed medical papers published from 1980 to 1998, and recalculated the abortion rates in several countries following the detection of certain fetus malformations [18]. They concluded that in the UK, out of the 5035 cases of fetuses diagnosed with Down syndrome, 92 percent were aborted, as were 64 percent of the 204 cases diagnosed with spina bifida, and 84 percent of the 365 diagnosed with anencephaly [18]. Natoli *et al.* reviewed medical papers published from 1995 to 2011 and recalculated the ratio of abortions in the US, finding that abortion rates in the US varied from 50 to 85 percent [19]. Relevant factors were the age of the pregnant woman, ethnicity, and race. In addition, Natoli *et al.* concluded the abortion rate is decreasing in the US [19].

Considering the impact of prenatal testing from a different perspective, Egan *et al.* estimated that the rate of live births with Down syndrome declined in the US according to birth certificate data, despite an expected increase caused by delayed or extended childbearing [20]. Lin *et al.* also reported that the live birth rate of infants with Down syndrome per 100,000 live births decreased from 22.28 in 2001 to 7.79 in 2010 in Taiwan [21], demonstrating that screenings may be responsible for the marked decrease in the rate of live births [20, 21].

No similar report could be found for population shifts in children with Down syndrome in Japan. The number of cases and the rate of advanced-age pregnancy have gone up in recent years, which seems to have influenced the rate of amniocentesis testing [13]. Moreover, since the introduction of highly precise ultrasound diagnosis machines in clinics, fetal abnormalities found through ultrasound tests have increased. Sago *et al.* investigated the total number of NIPTs conducted for the year be-

tween April 2013 to March 2014, in Japan, and reported that 7,740 women underwent the NIPT, and among the 111 cases confirmed to involve fetal aneuploidy, 110 women opted to terminate their pregnancies [15]. Also, three women who tested positive for trisomy 21 opted to terminate their pregnancies without invasive, definitive diagnoses [15]. Lately, the Mainichi newspaper reported that the total number of NIPTs for the three years from April 2013 to December 2015 was 27,696 in the institutions of NIPT consortium in Japan. Among the 346 cases confirmed to involve fetal aneuploidy, 334 women opted to terminate their pregnancies (96.5%), while twelve woman opted to continue the pregnancy [22].

## What are the Ethical Questions Surrounding Prenatal Testing?

An ethical question relevant to prenatal testing, that is very often mentioned, is the question of abortion following a positive diagnosis of chromosomal aneuploidy or spinal defect [1–3, 9–12]. In some countries or areas, abortion is only allowed to save a pregnant woman's life or in the first trimester of pregnancy. Thus, there is a difference between the question of abortion itself and the question of having an abortion due to a fetal anomaly. The definition of what comprises ethical choices will vary with cultural, legal, and political conditions. Religious or personal opposition to abortion often affect people's attitudes toward prenatal testing. Is there any difference between having an abortion for socio-economic reasons and one in response to a positive result of anomalies by prenatal testing? Under Japanese legislation, abortion for economic reasons is legal, but an abortion following a positive result for prenatal testing falls into a gray zone [15, 23].

Press noted that "positive diagnosis raises questions as to what kind of life is worth living and who is entitled to decide" [24]. Thus, I will focus here on abortion following a positive result for a chromosomal anomaly.

Ethical issues of abortion following prenatal testing relate to the informed consent of prospective parents and their decision making abilities [25]. Prospective parents, especially mothers, face the difficulty of deciding whether to take the test or not and whether to terminate the pregnancy if a fetal anomaly is found [26–30]. Rothman showed in her incisive analysis that many women who had undergone amniocentesis and were waiting for the results considered their pregnancies as tentative because they knew that they could potentially terminate them [29]. Rapp wrote a rich ethnography of prenatal testing in the US [30]. She described people experienc-

ing prenatal testing from a range of perspectives, interviewing not only women undergoing prenatal testing, but also those who did not, along with the partners of these women, genetic counselors, lab technicians, and the parents of children with disabilities. She discussed a prodigious number of important case studies: for example, studies on how genetic counselors explain prenatal testing in scientific terms to pregnant women and how lab staffers determine test results. She also portrayed the women, who came from a diverse range of backgrounds, ethnicities, occupations, and races, as “moral pioneers” confronting difficult decisions [30].

Decision making on prenatal testing involves the principles of bioethics, which are usually defined as informed choice, nondirective counseling, and autonomy (or self-determination). However, these principles have been criticized as highly westernized [31–33] so that alternative models of decision making are being sought for different cultures. Another unique and important factor in prenatal testing is “individualization”. Munthe describes the phenomenon of individualization of prenatal testing as follows: Health services are increasingly outsourced to private contractors, thus transferring responsibility for health decisions to individual citizens [12]. Many clinicians and bioethicists assume that health conditions are the main cause of reduced survival rates among people with disabilities, largely ignoring the role of societal factors such as educational and employment discrimination [32–34].

The individualization of prenatal testing forces responsibility for decision making onto the affected women. As a consequence, “women who undertake prenatal testing are conflicted and then feel guilty, not only in the case of abortion but also after giving birth to ‘normal’ children” [35, 36].

### **Alternative Courses of Action for Societies in Which People Seek Prenatal Testing**

One of the reasons for emphasizing informed choice, non-directed counseling, and autonomy (or self-determination) for prenatal testing is the occurrence of several so-called “wrongful birth trials”. The plaintiffs, parents of children with chromosomal anomalies or congenital malformations, claimed that their doctors should have disclosed information about the fetus’s birth defect. As stated in the Harvard Law Review, “In a wrongful birth action, the parents of a child suffering from birth defects sues a health care provider for (1) failing to impart adequate information about their risk of producing a child with a serious defect, (2) failing to perform prenatal di-

agnostic procedures with due care, or (3) failing to accurately report the results of tests already performed” [37]. Many obstetricians and gynecologists in the US wish to avoid wrongful birth trials so they tend to ensure pregnant women are “well informed”.

What happens in the near future if the NIPT becomes a routine screening test? Press and Browner examined in their field work how maternal serum alpha fetoprotein screening became accepted as routine in the 1990’s in California [24]. Women they interviewed either believed that the alpha fetoprotein screening was good for the health of their fetus or did not care about the result of the test, thinking it was just another routine blood test [24].

De Jong *et al.* expressed concern that with the routinization of the NIPT, will come subtle pressure from healthcare providers and social environments to accept screening, leading women to feel the need to justify their non-participation, or fearing they will hold responsible if they have a child with a condition or handicap that “could have been prevented” [38].

Many studies have voiced concern that the widespread use of the NIPT would reinforce discrimination against people with disabilities. Furthermore, many have worried about whether the option not to be tested would remain if the NIPT become a routine screening test.

Saxton described the dilemma of people with disabilities. While some disabled people might consider the tests a kind of genocide, others might choose to use screening tests during their own pregnancies to avoid giving birth to a disabled child. But disabled people might also use the tests in ways that differ from those of women who share the larger culture’s anti-disability bias [39].

The National Down Syndrome Congress (the NDSC) in the US issued the “Recommendations on Prenatal Screening and Diagnosis” in 2010. They asked for improved regulation of informed consent and disclosure of information about prenatal screening and diagnostic testing for all women, enhanced training about Down syndrome for genetic counselors, obstetricians, pediatricians, and students in training, education and support for pregnant women and couples with positive screenings or diagnoses for trisomy 21, and monitoring of statistics on termination and non-termination rates for all fetuses with chromosomal anomalies, including trisomy 21 [40].

Parsons and Asch also expressed concern about prenatal testing from the perspective of the disability rights movement, stating, “if one thinks about the history of our society’s treatment of people with disabilities, it is not hard to see why people identified with the disability rights movement might regard such testing as dangerous”. They added, “for the members of this movement,

living with disabling traits need not be detrimental to an individual's prospects of leading a worthwhile life, nor to the families in which they grow up, nor to society at large" [33].

Skotoko *et al.* asked parents of children with Down syndrome how they felt about their lives so that such information could be shared with expectant couples during prenatal counseling sessions in the US [41]. He concluded that the overwhelming majority of parents surveyed reported they were happy with their decision to have a child with Down syndrome and indicated that their sons and daughters were great sources of love and pride [41]. Kosho also reported the results of a questionnaire to a trisomy 18 parental support group in Japan and showed that parents appeared to feel positive about caring for their children, and the children seemed to interact with parents and siblings as long as they lived, resulting in quality family time [42].

Japan has a long history of discussing prenatal testing from the perspective of concern for disabled rights and women's reproductive rights [32, 43]. Therefore, medical doctors and counselors in clinical genetic fields must consider the issues surrounding new prenatal testing techniques. I am deeply convinced that as a society, we need to decide what kind of life is worth living and who is entitled to decide. Finally, I would like to add if we try to understand how people with disabilities or disease lived in our society before prenatal testing became routine, it may help to nurture a better society.

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