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Article Title: Non-invasive foetal sexing: medical test or a new tool for sex selection?

Year of publication: Forthcoming

Link to published article:

[http://www.radcliffe-](http://www.radcliffe-oxford.com/journals/J18_Diversity_in_Health_and_Social_Care/)

[oxford.com/journals/J18\\_Diversity\\_in\\_Health\\_and\\_Social\\_Care/](http://www.radcliffe-oxford.com/journals/J18_Diversity_in_Health_and_Social_Care/)

Publisher statement: This is a pre-copy-editing, author-produced PDF of an article accepted for publication in Diversity in Health and Care following peer review. The definitive version Osipenko, L. and Szczepura, A. (2011). Non-invasive foetal sexing: medical test or a new tool for sex selection? Diversity in Health and Care is available online at: [http://www.radcliffe-oxford.com/journals/J18\\_Diversity\\_in\\_Health\\_and\\_Social\\_Care/](http://www.radcliffe-oxford.com/journals/J18_Diversity_in_Health_and_Social_Care/)

## Debate Paper

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

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#### **What is known**

1. Certain countries which exhibit a preference for male offspring display worryingly skewed sex ratios at birth in favour of baby boys.
2. There has been widespread use of antenatal ultrasound to enable sex selective abortion in these countries, now illegal.
3. Non-invasive prenatal tests (based on foetal 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**

1. Direct-to-consumer marketing of non-invasive foetal DNA tests for social sex determination became available without sufficient consideration for technical performance.
2. Non-invasive foetal sexing is likely to impact sex selection practices in the Developing World and Asian Diaspora.
3. Corporate responsibility in marketing tests requires balancing of legitimate consumer needs versus unintended consequences.

## **Abstract**

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

At the same time, further developments in foetal DNA technology are making antenatal sex determination possible via a finger-prick 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 entirely.

Female foeticide, 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 foetal sex selection. Currently, mail-order foetal sexing, based on foetal 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.

**Key words:**

Prenatal testing; foetal sex determination; non-invasive diagnosis; sex selection; gender imbalance; son preference.

**Introduction**

Currently, expectant parents who wish to know their baby's sex have to wait for a second trimester ultrasound. While for most there may be no strong gender preference and this information simply satisfies their curiosity, there is research showing the existence of preferences for an offspring's sex 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 being used for sex selection, although originally marketed ostensibly to check the health of the foetus. Reports from India and China indicate worryingly skewed sex ratios at birth in favour of baby boys since ultrasound was introduced (The Economist, 2010; Lai-wan, 2006; Hudson and den Boer, 2005). 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 foeticide based on the widespread availability of this technology (Sheth, 2006; Jha *et al*, 2006; Aravamudan G, 2007). The "50 Million Missing" campaign launched in India in December 2006 seeks to reduce the loss of girls through foeticide (Banerji R, 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 ultrasound through limiting its antenatal use to licensed clinics, but with limited success. In the developed world, although no notable sex imbalance at birth has been reported for the majority populations, there is evidence of an effect beginning to emerge in South Asian communities in the UK and other countries.

In May 2007, a prenatal home-testing kit to detect a baby's sex early in pregnancy made headlines in the UK (see: [www.dna-worldwide.com](http://www.dna-worldwide.com)). This test

was marketed directly to prospective parents via the internet. Foetal sex testing simply required pregnant women to extract a few drops of blood from their finger tip and mail this to a commercial laboratory. The laboratory testing process exploited a new technique for tracing and analysing minute amounts of foetal DNA in maternal blood. This product followed an earlier one which was launched in the USA in 2005. Initially, public demand was reported to be high for this product, with more than 1,000 enquiries in the first 3 weeks (Hopkins, 2005; BMJ News, 2005). At the same time, several scientists working in the field voiced their concerns and recommended caution in terms of the reported accuracy of the test (Kaiser, 2005; Bianchi *et al*, 2006). The only research published using 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 foetal sexing has at first been driven by clinical need in families where a foetus 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 foetus was affected. However, wider marketing of NIPD foetal sexing tests direct to parents raises a number of concerns. At first sight, these may appear to be only significant in the developing world, but closer consideration shows 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 foetal sexing is still an emerging technology, more widespread discussion of its potential use is required.

### **Clinical drive for NIPD technology development**

Pregnant women whose child is at risk of a sex-linked disorder have, until recently, undergone invasive chorionic villus sampling (CVS) for foetal sexing from 11 weeks of gestation; however, this procedure carries a 1% risk of miscarriage. Non-invasive prenatal foetal sexing became possible following the

discovery of cell-free foetal DNA in maternal plasma (Lo, 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, foetal sexing using NIPD is currently available at a number of laboratories at a cost comparable to invasive CVS testing. NIPD not only offers psychological benefits for expecting parents if the test indicates the foetus 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 of maternal blood (2.5 ml - 5 ml).

Because the test relies on sex-dependent markers which are present only in males, the NIPD test will give a signal if a male foetus is present and, if no signal is observed, a foetus is assumed to be female. It is, therefore, highly dependent on detecting foetal DNA in the blood sample. In 2004, a National Institute of Child Health and Human Development consortium conducted NIPD foetal sexing tests in five US centres on samples from 20 pregnant women between 10 and 20 weeks of gestation; the recorded sensitivity (the ability to detect male DNA when the foetus was male) varied from 31% to 97% across centres (Johnson *et al*, 2004). More recently, a Dutch study of noninvasive foetal sex determination in maternal plasma reported results for 201 pregnant women (Scheffer *et al*, 2010). The test protocol allowed reporting of a female foetus only if the presence of foetal 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 not to contaminate the sample by male staff handling the test materials, which would lead to incorrect identification of a foetus as male.

Although NIPD testing is now being used clinically in women carrying an at risk foetus, the percentage of pregnancies at risk of sex-linked disorders is extremely low. A potentially much larger market exists world-wide for the social use of NIPD foetal sexing to enable parents to discover the sex of their baby early in pregnancy. High throughput laboratory NIPD processes have already been developed for detecting foetal rhesus (RhD) blood group which 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 (Finning and Chitty, 2008; Avent and Chitty, 2006; Hahn *et al*, 2008). To date, however, there have been no published large scale technical trials reporting test performance using finger-prick samples. Expert opinion suggests that the percentage of false negatives (i.e. foetus falsely identified as female) will be higher than for venous blood samples used for medical purposes (Personal correspondence with Prof. Tobias Legler, Universitätsmedizin Göttingen, Germany and Dr. Kirstin Finning, National Blood Service, Bristol, UK). A low signal, due to insufficient foetal DNA, would lead to failure to identify the presence of male DNA and therefore falsely conclude that the foetus is female. Sex-independent markers which can improve identification of female fetuses are needed to improve accuracy (Finning and Chitty, 2008).

### **Marketing of NIPD tests for foetal sexing**

Marketing of direct-to-consumer foetal 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 & Drug Administration, 2010). NIPD foetal sexing tests are not considered suitable for

regulation by the FDA or Federal Trade Commission because gender is not a clinical condition. This has theoretically made the path to market much easier with some companies stating correctly that their test is FDA cleared (e.g. IntelliGender, 2010).

Companies who offer NIPD foetal sexing generally offer testing for £150 to £200 (e.g. [www.babygendermentor.com](http://www.babygendermentor.com); [www.tellmepinkorblue.com](http://www.tellmepinkorblue.com); [www.nimblediagnostics.co.uk](http://www.nimblediagnostics.co.uk)). This includes the test kit and processing, making the technology affordable to a large number of people in both the developed and developing world. At present, however, there is no data available on when, in pregnancy, testing is taking place, the level of NIPD uptake in different countries, or accuracy rates based on finger prick samples. Available sources, such as comments on users' websites, suggest that women send their samples at around week eight 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 results were incorrect. An informal web-based poll which closed in September 2006 resulted in 97/151 incorrect results being reported (Baby Gender Mentor Results Poll, 2007). Following this, a class action lawsuit was filed in the USA suing the company for false advertising and altering their *money back* policy (What's New, 2007; Lawsuits & Legal News, 2010). The company filed for chapter 11 bankruptcy in December 2009.

More recently, other US companies which have started to offer a similar service are promising a more realistic 95.0% accuracy rate and include instructions for males not to handle the kit because this can contaminate the sample leading to incorrect identification of a foetus as male (e.g. Pink or Blue, 2010). 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. Pink or Blue, 2010). 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 ones for determining the sex of a foetus, tests for cystic fibrosis and for foetal Rh-negative blood incompatibility, all by analysing the mother's blood; the non-invasive foetal sexing test does not appear to be aimed at social sex determination (Sequenom, 2010).

### **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 (Zhu *et al*, 2009; Tao and Zhang, 2009; Ding and Hesketh, 2006). The introduction of various technologies has allowed prenatal foetal sex determination followed by selective abortion of a foetus of unwanted sex (Pallikadavath and Stones, 2006; Aravamudan G, 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 foetuses 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 (Dubuc and Coleman, 2007; George, 2006). 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 (Jha *et al*, 2006; Pallikadavath and Stones, 2006; George, 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 hold significantly less value than those of males. The reasons for male preference are similar in most cultures and have been well described in the literature (Hesketh and Xing, 2006; George, 2006; Lai-wan *et al*, 2006). In countries such as India and China, although improved health care and conditions for women have resulted in reductions 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 (The Economist 2010). In India, ratios below 800 females to 1,000 males in the age group 0-6 years 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). 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 foetal sex determination. In India, the Pre-natal Diagnostics Techniques (PNDT) Act came into force in 1996, making it a crime to reveal the sex of a foetus. In 2000, the Supreme Court passed orders to improve implementation resulting 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 foetal sex, but these actions have not proved successful. Although doctors have been prosecuted, few appear to be convicted (Mudur, 2006). The resulting surplus of men who are unable to find wives is reported to be already 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; Hudson and den Boer, 2005; Hesketh and Xing, 2006).

It appears that sex selection in these societies is not only exhibited 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 outnumber male deaths (Hudson and den Boer, 2005). This is the reverse of the pattern observed in the developed world where girls universally demonstrate higher survival rates. Explanations offered for this difference include child neglect, malnourishment, and more limited access to medical care for female children. Also, there is 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 mothers; in this way 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. While PGD provides complete accuracy in terms of foetal sex, it is a complicated and invasive method requiring in-vitro fertilisation (IVF) and hormone therapy preceding IVF. Not only is IVF expensive, it also has a conception success rate of only 25%-50% (Borini *et al*, 2008). This procedure has been allowed in Israel since 2005 as a means of 'family balancing' if there are already four children of the same sex in the family (Israeli, 2005). In other countries sex selection through PGD is available in private clinics for those 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 influence the gender of their next child, although their accuracy has been questioned (CBS News, 2004).

It is worth noting that parents can only hope to select a future child's sex but not its gender. Parents cannot predict the sexual orientation of their children when they become adults, or the possibilities 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 foetal sex when there is a suspicion of genital ambiguity on ultrasound (Finning and Chitty, 2008).

### **NIPD markets in India and China**

Currently, sex determination and sex selection practices in India and China represent a multimillion dollar business (George, 2006). NIPD technology for foetal 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 or ten times less than in the UK and USA respectively (Sen, 2008). Technical know-how and the required infrastructure already exist, in India and China, through the Special Non-Invasive Advances in Foetal and Neonatal Evaluation (SAFE) Network of Excellence which was funded by the European Commission Framework 6 Research Programme (2004-09) to speed up the development and implementation of NIPD tests. It is, therefore, reasonable to assume that this form of foetal 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 foetal sexing via Indian and Chinese laboratories.

Widespread availability will mean that parents in countries where sex selection is already being practiced via ultrasound clinics could order a test online, post a blood sample, and receive results without their medical practitioner being aware. Women may then present to a physician, who has 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 for non-surgical abortion at home during the first few weeks of pregnancy (e.g. <http://www.abortion-pill-online.com>).

## **NIPD markets in western countries**

In the western world, some communities, such as the Hispanics in the USA and South America and populations in certain European countries, appear to exhibit a slightly higher preference for girls, although this gender preference is dependent on the number and sex of existing children in the family (van Balen, 2006). Other migrant ethnic minority populations in the US, such as Asians and Arabs, show a preference for boys, although not to the same extent as 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; no such effect is 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 1,500 fewer girls were born to Indian mothers; there was a four-point increase in the sex ratio at birth for mothers born in India, attributable particularly to an increase at higher birth orders, mirroring findings reported for India (Dubuc and Coleman, 2007). No significant increase was observed for Pakistan-born and Bangladesh-born mothers, among whom male preference presumably also exists. However, no evidence was presented to show why these South Asian sub-groups differ.

While the western world has not shown any predisposition towards sex selection practice following the development of antenatal ultrasound, it does not mean that NIPD introduction 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 sex of their future baby before the second trimester ultrasound. Rationales given include a desire to “share the news”,

“decorate the room”, “buy baby clothes” and “to 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 foetus were 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 sex selection reasons. 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, 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 foetal 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; 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 boy 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 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, neither 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 companies 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 technology use 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; Hall and Marteau, 2006; Newiss, 2006; Thomas, 2007; Baldwin, 2006; Courtwright, 2008; Seavilleklein and Sherwin, 2007). Authors are now starting to address NIPD for foetal sexing with a number of potential ethical concerns being raised (Newson, 2008; Smith *et al*, 2006; Guetta, 2006; Hyett *et al*, 2005). However, commercial developments are moving ahead with NIPD tests now emerging for other foetal characteristics such as foetal RhD blood, status inherited single gene recessive disorders like haemoglobinopathies, and Downs syndrome. It is likely that these NIPD tests will initially be carried out 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 foetal sexing becomes

widespread. Key questions are: how to control their use 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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### **Funding**

This work is supported by the European Commission funds allocated to the SAFE Network of Excellence under the 6th Framework. Project Number: LSHB-CT-2004-503243.

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