Ethical dilemmas of non-invasive prenatal genetic diagnosis using cell-free fetal DNA technology: An appraisal of the first ten years since its introduction in medical practice

Dilemas éticos del diagnóstico genético prenatal no invasivo, utilizando la tecnología de ADN fetal libre en células: una valoración de los primeros diez años, desde su introducción en la práctica médica

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Abstract

Introduction: In 2011 a non-invasive screening test based on the analysis of cell-free DNA (cf-DNA) in pregnant women's blood has been introduced into clinical practice and has rapidly revolutioned the world of prenatal genetic diagnosis (PGD).
Methods: A literature search to identify the articles published in the last 10 years focusing on blood cf-DNA and the ethical issues associated to it has been carried out.
Results: The literature review resulted in 26 articles matching the research criteria. The main ethical issues highlighted were concerns for informed consent, increase rate of abortion, disclosure of incidental genetic findings, and discriminatory practices for people with congenital diseases and disability.

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Conclusions: cf-DNA screening test should be limited to cases deemed strictly necessary to protect women and future children's health. Right of making individual choices should be respected but crucial remains to prevent discrimination, respect human dignity, and avoid the diffusion of a eugenic mentality.

Keywords: Prenatal Genetic Diagnosis (PGD), cell-free DNA, counseling, Down Syndrome, aneuploidy, termination of pregnancy.

1. Introduction

Prenatal Genetic Diagnosis (PGD) became part of medical practice in 1970 with the declared aim of allowing families who previously had children affected with severe congenital disorders to make «reproductive decisions» (through selective abortion). Already in those years, when the technology was invasive, consisting mainly of amniocentesis, chorionic villus sample and cordocentesis, an extensive and divisive debate on the appropriateness of PGD from a medical, ethical, philosophical, and legal point of view took place (1).

Nowadays, prenatal genetic diagnosis consists of non-invasive and invasive tests. Non-invasive tests (ultrasound, Tri-test, and most recently cell-free DNA) are screening tests and have a predictive value; this means that they are probabilistic and need to be confirmed by invasive tests (amniocentesis or chorionic villus sampling) which carry a small risk (0.5-1.5%) of miscarriage (2).

The cell-free DNA (cf-DNA) screening test was introduced in clinical practice in 2011 and it is based on the analysis of free circulating fetal fraction (FF) DNA naturally present in maternal blood during pregnancy. The FF is a percentage of the cell free fetal DNA in relation to the overall circulating free DNA in the maternal plasma which affects the sensitivity of the test. FF is around 10% (ranging from 6 to 20%) and can vary according to several factors such as gestational age, mother's weight, number of pregnancies, ethnicity and presence of fetal aneuploidy (2).

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At the present state of knowledge, cf-DNA is considered the most reliable screening test for trisomy 13, 18 and 21, and it is diagnostic in the determination of fetal gender and RhD genotype (3).

Cell free-DNA has revolutioned the field of prenatal diagnosis in the last 10 years and has suddenly reinvigorated and exacerbated the previous ethical debate about the appropriateness of PGD in routine clinical practice. This new non-invasive test arrives also in a different social, technological, and economic global texture with potential far reaching ethical, philosophical, and legal consequences (4) (5).

This paper, after an in-depth review of the literature on cf-DNA technology from a medical, ethical-philosophical, and legal point of view, will argue that cf-DNA screening test, in the way it is offered today in many Countries, is problematic and greatly contributing to the practice of selective abortion, creating new ethical dilemmas about the disclosure of incidental secondary findings from genomic sequencing, and generating a growing accepted eugenic mentality amongst the population. A possible solution on how to provide this test in an ethical way, taking the advantages that it offers without undermining human dignity is also discussed.

2. Literature review: Methodology and results

a) Methodology

A literature search to identify the articles published since 2010 (the year before the official introduction of cf-DNA screening test into clinical practice) focusing on prenatal genetic diagnosis (PGD), blood cf-DNA and the ethical issues associated to it has been carried out exploring the following databases: Pubmed, Science Direct, JSTOR, Web of Science (accessed via Open Athens) and Cochrane Library.

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The keywords utilised were prenatal genetic diagnosis, cell-free DNA, ethical aspects, Down syndrome, aneuploidy and termination of pregnancy. Only articles written in English were considered for the review. The PRISMA (Preferred Reporting Items for Systematic Reviews and Metanalysis) was used to screen and identify the relevant articles to include in the final review (6).

b) Results

A total of 168 articles were found in the five databases explored. 20 duplicates were immediately excluded leaving 148 articles in total which were screened for inclusion criteria (published from 2010, English language only, ethical issues on cf-DNA discussed); 121 of these articles were rejected after reading the abstracts as not fitting the inclusion criteria, leaving 27 final articles which were included in the literature review (1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30).

The geography of the publications included Europe, United Kingdom, North America, and Australia. Finally, the documents were also classified according to their quality assigning them a score (excellent, 1; good, 2; regular, 3) in several domains such as pertinence, reliability, content, upgrade, structure, design/style and availability.

3. Cell-free DNA screening: Problematisation

Analysing the first ten years of diffusion of this technology is extremely instructive and provide us with lessons for the future implementation of the screening amongst the population.

The first observation we can make, after an attentive review of the literature, is that the diffusion and utilisation of the test amongst pregnant women largely depended on whether the countries already had state-sponsored screening for Down syndrome and the other most common aneuploidies (trisomy 13 and 18) risk

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or not. In the former countries, cf-DNA was distributed mainly through national health systems and limited to «high risk» women as a second level screen for the three major autosomal aneuploidies. In countries without a national health system (US, Brazil, India etc.), instead, cf-DNA was distributed primarily as a consumer item with six for-profit companies investing a great deal of money –and holding the intellectual property of the technology (23)– and it was mostly regulated by market logics (7). In these countries cf-DNA was offered indistinctly to high and low-risk women, and users could decide whether they want to know only if the fetus had aneuploides, or additional information about other genetic anomalies and the fetus sex (8).

Although in some limited circumstances predictive tests can represent a useful therapeutic adjunct –for instance knowing that a woman is carrying a child with spina bifida and hydrocephalus will allow to plan the delivery and the immediate postnatal care avoiding major risks for the mother and the child– most of the genetic diseases detected by the prenatal test have no treatment available yet, hence the value of the test, beyond preparing psychologically the parents to the baby's disease serves often no purpose, other than giving the mother the choice of terminating the pregnancy (9) (10). Hence, the main consequence of allowing a widespread use of cf-DNA test outside the clinical contest, has resulted in a commercialisation of the technology with easy access on internet and usually without a proper informed prenatal counselling done by healthcare professionals (11).

Another important issue which emerges from the literature review is that websites and non-specialised centres offering the screening test, having the profit amongst their main aims, do not stress the probabilistic nature of the test and the possibility of false positives to the patients with the result of some unpleasant consequences of «normal fetuses» erroneously aborted (12) (13).

In addition, in countries with a «soft» abortion legislation this technology has been also utilised to selective abort fetuses based

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on gender (usually females), minor genetic diseases, or even on the probability that the fetus will develop a particular disease later in life. Undoubtedly, fetuses and embryos affected by Trisomy 21 have been the main target of selective abortion following the introduction of the cf-DNA test (14) with the extreme consequence of nearly 100% fetuses with Trisomy 21 aborted recently achieved in Iceland (15).

A common indication for cf-DNA test in the last 10 years has been the determination of the fetus sex. This can be achieved accurately from 7 weeks' gestation and the cf-DNA is considered diagnostic. Beyond strict medical reasons, such as congenital adrenal hyperplasia (where fetus sex determination is beneficial to start early treatment with dexamethasone in order to mitigate the «virilization» of the fetus), haemophilia and few other indications, testing for fetal sex, particularly in Asian countries including India and China, has been mainly used for sex selective termination of pregnancy (usually female fetuses) (8) and/or for family balancing purposes (16).

The main issue consistently highlighted by women who expressed regret for the choice made after taking the cf-DNA test is that the widespread diffusion of commercially produced tests does not provide adequate discussion with healthcare professionals to appropriately explain the advantages and the pitfalls of taking the test. It is clear that most of the patients and families did not understand –or were confused– about the meaning of statistical terms such as high specificity, sensitivity and positive predictive value (17). The «99% accuracy» advertised by the screening test providers led to false expectations and an overestimation of the reliability of the high-risk result (18).

4. Medical concerns

The standard assessment of risk in pregnancy includes obstetric risk factors (e.g., prior preterm birth delivery), woman's medical

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conditions such as diabetes, hypertension, anemia, substance use, prenatal screening for infectious diseases, and maternal blood group typing. These tests are considered in the best interest of the patients and are unquestionable and accepted by virtually all pregnant women as they are perceived as a measure to prevent and/or timely treat issues for the mother and the fetus (19).

However, when we move to PGD, the medical benefits for women and particularly fetuses become more blurred. These are mostly limited to high-risk pregnancies or women with previous severely genetic affected children. Thus, widespread indiscriminate use of Non Invasive Prenatal Test (NIPT) through cf-DNA testing does not seem, in the majority of cases, in the best interest of the mother and the fetus (20).

Literature review clearly shows that many «low risk» women who accepted the cell-free DNA testing and were told that their fetus had a high chance of a genetic anomaly, felt that this information produced emotional stress and heavily influenced their final decision about the pregnancy. Some of these women, in order to confirm the diagnosis, underwent invasive tests which carry around 1% risk of miscarriage and then opted for termination of pregnancy when the diagnosis was confirmed in nearly 67 % of cases; in the USA, over 6 % of women decided to terminate their pregnancy without any further diagnostic validation (18) (21). It appears, as highlighted by some commentators, that NIPT, allowing earlier and easy testing through a simple blood sample, has inevitably led to the «trivialization» of selective abortion (22).

Finally it is crucial to highlight that, although from a clinical point of view, cf-DNA is a reliable test for the classic trisomies (13, 18, 21) compared to the combined biochemical analysis and nuchal translucency measurement, it still has some pitfalls arising from the fact that the DNA analysed is a combination of maternal and fetal cf-DNA which derives from the placenta; therefore a result indicating a suspected aneuploidy might be also the result of other

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circumstances such as a vanishing twin, placental mosaicism or a maternal tumour (23).

5. Ethical and philosophical considerations

The main argument used in healthcare for offering NIPT is to increase «the reproductive autonomy» of pregnant women. However, analysing the existing literature, this does not appear to be necessarily the case. To increase reproductive autonomy, women should be well informed about the implications of taking the test and understand the scientific terminology such as predictive value, prevalence, incidence, etc. Several scholars have highlighted, instead, how poor is the informed consent process –if at all present– especially when the test is offered outside the clinical setting (24). Furthermore, although cell-free DNA screening has the potentiality to improve individual autonomy and reproductive rights, we should not ignore that its availability, depending to the pre-existing sociocultural variables, could, on the other hand, intensify pressure on women to make certain reproductive decisions (25).

It is well known that the perception and acceptance of children with disabilities varies in different countries. For instance, while in Chile, where is illegal to abort on the sole basis of a Trisomy 21 diagnosis, there is a great acceptance of these children and when adults they are very well integrated in the society, in Israel, on the other hand, there is a great public support to take NIPT because the very low acceptance of children with disabilities within the society. Other countries, such as India and China, have a long tradition of selective abortion on gender basis (26).

We need to wonder if some societies have exaggerated the negative aspects of disability till the point that today living with disability is not perceived anymore as a meaningful life. Many disability groups have raised their voice against what is perceived as a discriminatory practice. The paradox is that this happens in Western

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countries where there is a long tradition and activism against any form of discrimination. The greatest concern is that cf-DNA could represent, as in fact it already is in many aspects, just one of the gateways for a public acceptance of eugenic medicine (27) (28).

6. Legal aspects

Some legal aspects on the introduction of NIPT in the routine prenatal medical practice should also be examined. The first one is the implementation of cf-DNA technology in countries without a safe and/or legal access to abortion. In these circumstances, the NIPT may accentuate the risks women incur if they decide to terminate their pregnancy following a positive cf-DNA screening result through the use of illegal abortion methods, or exacerbate the «abortion tourism» in women with financial means as already happens in countries with restricted use of cf-DNA for sex selection (25).

Another concern is the involvement of commercial companies as future main providers of this technology, considering the massive investment done in the recent years in the cf-DNA testing, with the result of offering genetic screening for several conditions beyond the classical ones routinely used in clinicals setting (23). This will also inevitably produce an enormous amount of genetic incidental findings which will amplify the resonance of the existing ethical dilemmas (29, 30). For instance, in cases where a predisposition for hereditary tumours is found and the pregnancy is continued, scholars see this information as a potential infringement to the child's autonomy, also referred as «the right to an open future» with unforeseen legal consequences (31).

On the other hand, at the opposite, there has been a growing incidence of claims of «reproductive negligence», especially in the Anglo-Saxon jurisprudence where the concept of «quality of life» has been emphasised to the extreme, in terms of «wrongful life» involving children who have sued their parents, carers or the

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healthcare facilities because allowed them to come into existence with some disability, illness or genetic predisposition arising from artificial reproductive technology. There is a serious concern that NIPD could further expand this kind of lawsuits (32).

7. Bioethical analysis

The agents involved in the prenatal genetic diagnosis with cf-DNA are the pregnant women, the fetuses, the doctors, the screening test providers, the governments regulating the access to the technology and, the society at large. Utilising a personalist ethical approach, the principles at stake in our analysis are the principle of defence of physical life, the therapeutic principle and the principle of sociality and subsidiarity (33).

a) The principle of defence of physical life presupposes that the right to life precedes the right to health and the right to freedom which are nowadays considered in many places an absolute. Fetus dignity as a human subject remains even when this is a genetic carrier of a specific malformation or disorder.

This should be the foundation of any other ethical consideration: the embryo from the moment of fertilisation is a subject with his own genetic, biological, and personal identity. Biology unequivocally shows this as also does the highest metaphysical speculation (34, 35, 36). The concept has been extensively treated and clarified by the Congregation for the Doctrine of the Faith of the Catholic Church in several documents and stressed in virtually all popes encyclicals in the last 100 years (37).

b) The therapeutic principle. According to this principle, each technology or invasive intervention proposed to a patient must be justified. It must have a high chance of success and no other way to correct the condition. Considering, as stated above, that the therapeutic possibilities on genetic anomalies are still very limited nowadays, very often this technology is used as a method of selec-

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tive abortion on the presumption that the dignity of human life is measured with parameters of quality, usefulness, cost-benefit, and freedom of choice of the parents.

c) The principle of sociality and subsidiarity. Advocates of selective abortion support termination of pregnancy when the fetus has high chances of suffering from a severe illness on the consideration that this will represent a burden to the family and the society. Personalist approach refuses this cost-benefit mentality when it comes to human life. From an ethical point of view, the fact that a fetus might have a particular malformation or illness does not diminish his/her dignity, but on the contrary, according to this principle, to terminate its life constitutes an aggravation of the offence against the human dignity as it contravenes the principle of sociality and subsidiarity of providing assistance to the persons more in need. Society should not choose selective abortion but put in place a social welfare to help families who have to look after these children.

Therefore, using a personalist approach, we would consider the use of cf-DNA screening only in medically justified selected cases. This position is based on the fact that the embryo and the fetus are human subjects with the same dignity and right to life of any other human being. The *Evangelium Vitae* well summarises the position of the personalist approach, highlighting the cases in which prenatal diagnosis is considered morally licit: «when they do not involve disproportionate risks for the child and the mother, and are meant to make possible early therapy or even favour a serene and informed acceptance of the child not yet born» (37).

8. Possible solutions

From the analysis of the first ten years since its introduction into clinical practice, it seems necessary to revisit the indications for offering the cf-DNA screening test considering that the direct-

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to-consumer diffusion of the test has watered down the potential advantages –increase in parental information and possible reduction of severe hereditary disorders– which are overwhelmingly outweigh by the contra: women and families psychological stress, termination of pregnancy for minor fetal issues, gender discrimination and culture of stigmatization of fetuses with disabilities with a consequent increasing social pressure to abort these fetuses leading to legalised eugenic practices (8, 9, 10, 11, 23, 28).

Finally, non-invasive prenatal diagnosis is an extremely dynamic field with a rapidly developing technology, so it is paramount for governments to remain vigilant on the role of industry, including their aggressive global marketing strategies, on the future development of the test which can only exacerbate the already existing ethical grey areas of cf-DNA screening (7).

9. Conclusions

Non-invasive prenatal genetic diagnosis in most cases does not promote human life, instead it provides a threshold for a worthwhile human existence. The acceptance of cf-DNA in routine medical practice implies that the definition of preventive medicine should be widened to include not only promotion of health and life but also elimination of life. The public health rationale which labels NIPT as «reproductive choice» appears to be intimately associated with the ethical debate on abortion with eugenic connotations.

Although the principle of autonomy seems to justify the routine introduction of cf-DNA screening in medical practice, an exclusive focus on autonomy ignores the enormous pressure women experience in taking the test and terminate the pregnancy if a positive result for disability is identified. Furthermore, the reproductive autonomy rationale often overlooks the unequal socio-economic and political circumstances in which women take their decision, espe-

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cially in countries where abortion is illegal and there is lack of a safe access to the termination of pregnancy.

The literature review has also shown that most of the decisions on non-invasive prenatal testing arise from a lacking inform consent process, a culture of misinformation and misconceptions about disability often echoing a wrong idea of parenthood where perfect children must be guaranteed, and «the implicit premise that the value of a human being is based on their economic contribution to society» (27).

Disclosure

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Bibliographic references

1. Van El C, Henneman L. Chapter 14, Cell-Free DNA-Based noninvasive prenatal testing and Society. In: *Page-Christiaens* L, Klein H-G, editors. Non-Invasive Prenatal Testing (NIPT). *Academic Press.* 2018; 235-249. Available at: https://www.sciencedirect.com/science/article/pii/B9780128141892000141 https://doi.org/10.1016/B978-0-12-814189-2.00014-1

2. Alberry MS, Aziz E, Ahmed SR, Abdel-fattah S. Non invasive prenatal testing (NIPT) for common aneuploidies and beyond. *Eur J Obstet Gynecol Reprod Biol.* Mar 1, 2021; 258: 424-429. https://doi.org/10.1016/j.ejogrb.2021.01.008

3. Deans Z, Newson AJ. Ethical considerations for choosing between possible models for using NIPD for aneuploidy detection. *J Med Ethics.* 2012; 38(10): 614-618. https://doi.org/10.1136/medethics-2011-100180

4. Newson AJ. Ethical aspects arising from Non-Invasive Fetal Diagnosis. *Semin Fetal Neonatal Med.* Apr 1, 2008; 13(2): 103-108. https://doi.org/10.1016/j.siny.2007.12.004

5. Dickens BM. Ethical and legal aspects of noninvasive prenatal genetic diagnosis. *Int J Gynecol Obstet.* Feb 1, 2014; 124(2): 181-184. https://doi.org/10.1016/j.ijgo.2013.11.001
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009; 339. Available at: https://www.bmj.com/content/339/bmj.b2535 https://doi.org/10.1136/bmj.b2535
7. Löwy I. Non-Invasive Prenatal Testing: A diagnostic innovation shaped by commercial interests and the regulation conundrum. *Soc Sci Med.* May 20, 2020; 113064. https://doi.org/10.1016/j.socscimed.2020.113064
8. Dondorp W, Clarke A, De Wert G. Chapter 15, Ethics of Cell-Free DNA-Based Prenatal Testing for Sex Chromosome Aneuploidies and Sex Determination. In: Page-Christiaens L, Klein H-G, editors. Non-Invasive Prenatal Testing (NIPT). *Academic Press.* 2018; 251-268. Available at: https://www.sciencedirect.com/science/article/pii/B9780128141892000153 https://doi.org/10.1016/B978-0-12-814189-2.00015-3
9. Richardson A, Ormond KE. Ethical considerations in prenatal testing: Genomic testing and medical uncertainty. *Perinat Bioeth.* Feb 1, 2018; 23(1): 1-6. https://doi.org/10.1016/j.siny.2017.10.001
10. Benn PA, Chapman AR. Ethical challenges in providing Non-Invasive Prenatal Diagnosis. *Curr Opin Obstet Gynecol*. 2010; 22(2). Available at: https://journals.lww.com/co-obgyn/Fulltext/2010/04000/Ethical_challenges_in_providing_noninvasive.8.aspx https://doi.org/10.1097/GCO.0b013e3283372352
11. Kelly SE, Farrimond HR. Non-Invasive Prenatal Genetic Testing (NIPT). Public Health Genomics. 2012; 15(2): 73-81. https://doi.org/10.1159/000331254
12. Hall A, Bostanci A, Wright CF. Non-Invasive Prenatal Diagnosis using cell-free fetal DNA technology: Applications and implications. *Public Health Genomics.* 2010; 13(4): 246-255. https://doi.org/10.1159/000279626
13. Chan WV, Johnson J-A, Wilson RD, Metcalfe A. Obstetrical provider knowledge and attitudes towards cell-free DNA screening: Results of a cross-sectional national survey. *BMC Pregnancy Childbirth*. Jan 23, 2018; 18(1): 40. https://doi.org/10.1186/s12884-018-1662-z
14. Lewis C, Silcock C, Chitty LS. Non-Invasive Prenatal Testing for Down's Syndrome. *Public Health Genomics.* 2013; 16(5): 223-232. https://doi.org/10.1159/000353523
15. Dave McLean. Iceland close to become first country where no Down's Syndrome children are born. *Independent*. Aug 16, 2017; Available at: https://www.independent.co.uk/life-style/health-and-families/iceland-downs-syndrome-no-children-born-first-country-world-screening-a7895996.html
16. Bowman-Smart H, Savulescu J, Gyngell C, Mand C, Delatycki MB. Sex selection and Non-Invasive Prenatal Testing: A review of current practices, evidence, and ethical issues. *Prenat Diagn.* Mar 1, 2020; 40(4): 398-407. https://doi.org/10.1002/pd.5555

17. Lewis C, Hill M, Silcock C, Daley R, Chitty L. Non-Invasive Prenatal Testing for trisomy 21: A cross-sectional survey of service users' views and likely uptake. *BJOG Int J Obstet Gynaecol.* Apr 1, 2014; 121(5): 582-594.
https://doi.org/10.1111/1471-0528.12579
18. Gammon BL, Jaramillo C, Riggan KA, Allyse M. Decisional regret in women receiving high risk or inconclusive prenatal cell-free DNA screening results. *J Matern Fetal Neonatal Med.* Apr 17, 2020; 33(8): 1412-1418.
19. Uhlmann WR, Roberts JS. Chapter 3, Ethical issues in neurogenetics. In: Geschwind DH, Paulson HL, Klein C, editors. Handbook of Clinical Neurology. *Elsevier.* 2018; 23-36. Available at:
https://www.sciencedirect.com/science/article/pii/B9780444632333000038
https://doi.org/10.1016/B978-0-444-63233-3.00003-8
20. Grati FR, Bajaj K, Simoni G, Maggi F, Gross SJ, Ferreira JCPB. Chapter 28, Non-Invasive Prenatal Testing by Cell-Free DNA: Technology, biology, clinical utility, and limitations. In: Leung PCK, Qiao J, editors. Human Reproductive and Prenatal Genetics. *Academic Press.* 2019; 627-652. Available at:
https://www.sciencedirect.com/science/article/pii/B9780128135709000280
https://doi.org/10.1016/B978-0-12-813570-9.00028-0
21. Dobson LJ, Reiff ES, Little SE, Wilkins-Haug L, Bromley B. Patient choice and clinical outcomes following positive non-invasive prenatal screening for aneuploidy with cell-free DNA (cf-DNA). *Prenat Diagn.* May 1, 2016; 36(5): 456-462.
https://doi.org/10.1002/pd.4805
22. Stefanovic V. The importance of pre- and post-test counseling for prenatal cell-free DNA screening for common fetal aneuploidies. *Expert Rev Mol Diagn.* Mar 4, 2019; 19(3): 201-215. https://doi.org/10.1080/14737159.2019.1571912
23. Mozersky J, Ravitsky V, Rapp R, Michie M, Chandrasekharan S, Allyse M. Toward an ethically sensitive implementation of noninvasive prenatal screening in the global context. *Hastings Cent Rep.* 2017; 47(2): 41-49.
https://doi.org/10.1002/hast.690
24. Griffin B, Edwards S, Chitty LS, Lewis C. Clinical, social and ethical issues associated with Non-Invasive Prenatal Testing for aneuploidy. *J Psychosom Obstet Gynecol.* Jan 2, 2018; 39(1): 11-18.
https://doi.org/10.1080/0167482X.2017.1286643
25. Rolfes V, Schmitz D. Unfair discrimination in prenatal aneuploidy screening using cell-free DNA? *Eur J Obstet Gynecol Reprod Biol*. Mar 1, 2016; 198: 27-29. https://doi.org/10.1016/j.ejogrb.2015.12.023
26. Hill M, Johnson J-A, Langlois S, Lee H, Winsor S, Dineley B, *et al.* Preferences for prenatal tests for Down Syndrome: An international comparison of the views of pregnant women and health professionals. *Eur J Hum Genet.* Jul 1, 2016; 24(7): 968-975. https://doi.org/10.1038/ejhg.2015.249
27. Ravitsky V. The shifting landscape of prenatal testing: Between reproductive autonomy and public health. *Hastings Cent Rep.* 2017; 47(6): S34-40.

https://doi.org/10.1002/hast.793
28. Iltis AS. Prenatal screening and prenatal diagnosis: Contemporary practices in light of the past. *J Med Ethics.* 2016; 42(6): 334-339.
https://doi.org/10.1136/medethics-2016-103623
29. Kaneva V, Dimitrova I. Chapter 16, Should incidental findings arising from prenatal testing be reported indiscriminately to patients? In: Hostiuc S, editor. Clinical ethics at the crossroads of genetic and reproductive technologies. *Academic Press;* 2018; 367-384. Available at:
https://www.sciencedirect.com/science/article/pii/B9780128137642000167
https://doi.org/10.1016/B978-0-12-813764-2.00016-7
30. Donley G, Hull SC, Berkman BE. Prenatal Whole Genome Sequencing: Just because we can, should we? *Hastings Cent Rep.* 2012; 42(4): 28-40.
https://doi.org/10.1002/hast.50
31. Bredenoord AL, De Vries MC, Van Delden JJM. Next-generation sequencing: Does the next generation still have a right to an open future? *Nat Rev Genet.* May 1, 2013; 14(5): 306-306. https://doi.org/10.1038/nrg3459
32. Fox D. Reproductive negligence. *Columbia Law Rev.* 2017; 117(1): 149-241.
33. Sgreccia E. Personalist Bioethics: Foundations and applications. *National Catholic Bioethics Center* (Personalist Bioethics). 2012. Available at: https://books.google.co.uk/books?id=v4vuugAACAAJ
34. Miklavcic JJ, Flaman P. Personhood status of the human zygote, embryo, fetus. *Linacre Q.* May 1, 2017; 84(2): 130-144.
https://doi.org/10.1080/00243639.2017.1299896
35. Aristotle. *Metaphysics*. In p. 7.
36. Aristotle. *De Anima.* Vol. II. 2, 421a, 1-28 p.
37. *Evangelium Vitae* (March 25, 1995). John Paul II (Accessed on Dec 10, 2021). Available at: https://www.vatican.va/content/john-paul-ii/en/encyclicals/documents/hf_jp-ii_enc_25031995_evangelium-vitae.html