Down Syndrome

Chapter 3

Noninvasive Prenatal Genetic Tests and Down Syndrome

Fermín J. González-Melado[1]*; Maria Luisa Di Pietro[2]

[1]Pontifical University of Salamanca, Spain

[2]Catholic University of the Sacred Heart, Italy

*[*]**Correspondence to: Fermín J. González-Melado,** Pontifical University of Salamanca, Spain*

Email: fjgonzalezme@upsa.es

Abstract

The use of techniques of analysis of fetal nucleic acid present in maternal peripheral blood for noninvasive prenatal genetic tests (NIPGT) is a reality in clinical practice in the case of certain diseases. In the coming years, it will become part of routine prenatal screening and diagnostic techniques for fetal diagnosis. A bioethical reflection on the possible difficulties and problems of the use of these techniques is necessary. On one hand, these techniques will result in reduced costs of screening, an increase in the number of disabled fetuses detected, and a decrease in the number of indirect abortions caused by invasive techniques. On the other hand, the widespread use of NIPGT could decrease the autonomy of women in the decision-making process; health authorities could use NIPGT as a means of eugenic prevention of genetic diseases, for example, in Down syndrome cases; and finally, NIPGT could increase the image of the disabled person as an individual that has to be excluded from society. For this reason, physicians play an important role in the process of pre-diagnosis and post-diagnosis genetic counseling. As a result, we conclude that the use of NIPGT to diagnose the existence of genetic diseases in the fetus in order to decide-in the case of a positive result-whether or not to perform an abortion implies and includes in itself the conditions that characterize a negative moral assessment.

1. Introduction

In October 2011, the results of an international clinical validation study on sequencing fetal DNA present in maternal blood in order to detect fetuses with Down syndrome were published [1]. The study establishes the necessary guarantees for the use of these tests for pregnant women with a high risk of giving birth to a baby with Down syndrome, before other more invasive tests such as amniocentesis or chorionic villus sampling are performed. Tests such as these have reopened the debate on the use of prenatal diagnosis for sex-selective abortion or eugenic abortion of children with Down syndrome [2,3]. Many critical voices have been raised calling for caution on the use of noninvasive prenatal genetic tests (NIPGT) through the analysis of fetal nucleic acids in the mother's blood [4]. But what are these tests really? How reliable are they? What are the ethical implications? In this chapter, we will attempt to answer these questions. In the first part, we briefly discuss the latest research on NIPGT techniques, as well as their current and future applications. In the second part of the paper, we will show the relationship between prenatal diagnosis and eugenics, illustrating it with the specific example of NIPGT for children affected by Down syndrome. We will also present some arguments against the use of NIPGT. Finally, we will introduce pre-test and post-test genetic counseling as a possible solution, concluding with an ethical evaluation of NIPGT.

2. Noninvasive Prenatal Genetic Tests

The current methods of noninvasive prenatal diagnosis (ultrasonography, serum biomarker testing) essentially measure epiphenomena that are associated with certain diseases (e.g., trisomy 21). As such, these methods do not directly diagnose disease. For direct prenatal diagnosis, invasive tests (amniocentesis, chorionic villi sampling, cordocentesis) are performed to collect fetal tissue that holds the cytogenetic and molecular information for prenatal genetic diagnosis. These invasive techniques, however, carry a risk of fetal loss, estimated between 0.5 and 3 percent. Both invasive and noninvasive techniques have limitations (e.g., the window of time in which these tests can be performed), which have led researchers to seek new methods of NIPGT, particularly the genetic study of the fetus from maternal blood analysis [5]. There are two different approaches to NIPGT: 1) the study of circulating fetal cells in maternal blood, and 2) the study of circulating free fetal nucleic acids (fetal DNA and fetal RNA) in maternal blood.

2.1 Fetal cells present in maternal blood

In 1997, D.W. Bianchi and colleagues determined the presence of a single fetal cell (erythroblast) per milliliter of maternal blood [6]. Further study of methods of isolation, enrichment, and analysis of fetal cells allowed them to develop various prenatal diagnostic tests such as fetal sex determination, determination of mosaicism confined to the placenta, fetal aneuploidy detection, and the diagnosis of various diseases with Mendelian inheritance [7]. At

present, the use of fetal cells in maternal blood has faded into the background within NIPGT due to the discovery of fetal nucleic acids (DNA and RNA) freely circulating in maternal blood. To be sure, some groups are still working on the study of fetal cells, and some have managed to identify the chromosomic aneuploidies in fetal cells present in maternal blood [8]. In spite of this recent success, however, most current studies in the field of NIPGT focus on the use of free fetal nucleic acids circulating in maternal blood.

2.2 Fetal DNA and Fetal RNA in maternal blood

2.2.1 Fetal DNA in maternal blood

In 1997, Doctors Y.M. Lo and N. Corbetta showed the existence of free circulating fetal DNA in the maternal blood stream. Their study was based on the detection of Y chromosome sequences in the plasma and serum of pregnant women with a male fetus [9]. This new discovery represented a breakthrough in the field of noninvasive prenatal diagnosis because the proportion of free fetal DNA in the plasma/serum of pregnant women was higher than the DNA present in fetal cells from the mother's bloodstream [10]. Free fetal DNA coexists with maternal DNA in the mother's blood. Through the study of in vitro fertilization (IVF) pregnancies, there is a known correspondence between the earliest gestational age at which the presence of fetal DNA is detected in maternal blood and the eighteenth day after embryo transfer. From that moment, the presence of fetal DNA in maternal plasma becomes more noticeable as the pregnancy progresses, representing approximately 3 percent of the total DNA present in maternal plasma during the early stages of pregnancy and 6 percent at term [11]. Free fetal DNA in maternal plasma has a halflife of less than twenty minutes [12]. Recent studies show that fetal DNA is detectable up to forty-eight hours after birth and disappears after this period of time [13].

Some pathological situations, however, have been identified that result in an increase in the amount of fetal DNA in the total maternal plasma: preeclampsia or intrauterine growth retardation, trisomy 21, trisomy 13, polyhydramnios, spontaneous abortions, preterm labor, hyperemesis gravidarum, and pregnancy with invasive placenta [14]. However, there has not been a significant increase in circulating fetal DNA in maternal plasma in cases of IVF pregnancies, fetuses with trisomy 18, nor in cases of tobacco use during pregnancy [15].

2.2.2 Fetal RNA in maternal blood

Years after the discovery of fetal DNA in maternal blood, the existence of free fetal mRNA in maternal plasma was demonstrated [16]. Several studies reported the detection of different mRNA molecules originating in the placenta, supporting the hypothesis that the placenta is the main source of fetal nucleic acids in maternal blood [17]. Free fetal mRNA can be found in maternal plasma from the beginning of pregnancy [18]. For example, mRNAs of human placental lactogen (hPL) and β subunit of human chorionic gonadotropin (hCG) have been

detected at the fourth week of pregnancy. In addition, the concentrations of different types of mRNA in maternal plasma are correlated with variations in the corresponding known protein products according to gestational age. This fact indicates that the measure and monitoring of placental mRNA in maternal plasma can provide a new method for NIPGT, providing knowledge of the physiological and pathological characteristics of the fetus [19].

Currently, there are various working tests that have been made from the analysis of fetal DNA and fetal RNA in maternal plasma (see **Table 1**). NIPGT has thus appeared as a new diagnostic tool.

Table 1: Applications of the analysis of free fetal nucleic acids present in maternal blood.

Free fetal nucleic acids	Disease	Techniques	Status
Fetal DNA for fetal sex determination	Duchenne's muscular distrophy	Real-time PCR	In clinical practice for detection of male fetuses
	Hemophilia,		
	Becker's muscular distrophy		
	Congenital adrenal hyperplasia		
	Norrie's disease		
	Retinoschisis		
	Retinitis pigmentosa linked to chromosome X	Automated sequencing + restriction analysis	
Fetal DNA for the diagnosis of fetal Rh factor	Fetal Rh determination in maternal plasma from pregnant women with negative Rh	Real-time PCR	In clinical practice
Fetal DNA for the diagnosis of monogenic diseases	Achondroplasia	PCR + restriction analysis MALDI-TOF MS	Validating techniques to implement in clinical practice
	β-thalassemia	Allele specific real-time PCR Mass spectrometry Size fractionation + PNA-clamping PCR	
	Congenital adrenal hyperplasia	PCR fluorescence SNPs	
	Huntington's chorea	QF- PCR	
	Cystic fibrosis	Restriction analysis Minisequencing	
	- Hb Lepore	Alle specific reall-time PCR	
	- Myotonic dystrophy	Nested PCR	
	- Retinal dystrophies	Automated sequencing HPLC	
	- Propionic acidemia	Minisequencing	
Fetal mRNA	- Preeclampsia	Real-time PCR	Clinical trials
	- Gestational trophoblastic disease		
	- Fetal growth		

Abbreviations: PCR: Polymerase chain reaction; FQ-PCR: Quantitative fluorescence polymerase chain reaction; MALDI-TOF MS: Matrix-assisted laser desorption/Ionization time-of-flight spectometry of mass dHPLC: Denaturing high- performance liquid chromatography; PNA-Clamping PCR: Peptide nucleic acid mediated clamping PCR

One of the major objectives of NIPGT is to diagnose fetal aneuploidies, such as Down syndrome (trisomy 21), Patau syndrome (trisomy 13), or Edwards syndrome (trisomy 18) [20]. The coexistence of fetal DNA and maternal DNA in maternal blood, together with the fact that the majority of aneuploidies have a maternal origin, has made the distinction between fetal and maternal chromosomes more difficult. This has long represented a major obstacle for the use of NIPGT for detection of aneuploidies. Various techniques are currently being developed to overcome this limitation (see **Table 2**).

Table 2: Different mechanisms of NIPGT for the detection of trisomies.

***The studies of allelic ratio analysis of single nucleotide polymorphisms* (SNP)**	Consist in the analysis of placenta mRNA (RNA-SNP) and the studies of methylated DNA markers.[a]
The next-generation sequencing	Uses the methods of molecule quantification such as massive parallel genomic sequencing. These requirements can be achieved only through the use of expensive equipment and relatively complex bioinformatics methods.[b]
The epigenetic-genetic chromosome-dosage approach (EGG)	The measurement of the ratio concentrations of specific markers methylated fetal DNA from chromosome 21 and specific markers of fetal DNA from a reference chromosome.[c]

[a] Y.M. Lo et al., "Digital PCR for the Molecular Detection of Fetal Chromosomal Aneuploidy," Proceedings of National Academy of Sciences of U.S.A. 104 (2007): 13116–13121.

[b] R.W. Chiu et al. "Non-invasive Prenatal Assessment of Trisomy 21 by Multiplexed Maternal Plasma DNA Sequencing: Large Scale Validity Study," British Medical Journal 342 (2011): c7401; G.E. Palomaki et al., "DNA Sequencing of Maternal Plasma to Detect Down Syndrome: An International Clinical Validation Study," Genetics in Medicine 13 (2011): 913–920.

[c] M. Zhang et al., "Non-invasive Prenatal Diagnosis of Trisomy 21 by Dosage Ratio of Fetal Chromosome-Specific Epigenetic Markers in Maternal Plasma," Journal of Huazhong University of Science and Technology [Medical Sciences] 3 (2011): 687–692.

In the last years, NIPGT research has focused on the location of genetic markers (both DNA and RNA) that reveal the presence of fetuses affected by Down syndrome. If we analyze the fetal chromosome constitution, we can see that 20 percent of fetuses born alive with a viable chromosomal aberration are carriers of trisomy 21 [21]. In other words, the highest percentage of birth defects in individual live births is due to Down syndrome. Thus prenatal diagnosis techniques have focused on the detection of trisomy 21 fetuses.

In October 2011, the results obtained from an analysis of 4,664 pregnancies with a high risk of carrying a fetus with Down syndrome were presented. They quantified the DNA sequences present in the maternal blood by parallel genomic sequencing mass, that is, they sequenced thirty-six million nucleotides of each DNA fragment to determine its specific chromosomal origin. If a fetus has a third chromosome 21, it is assumed that the percentage of fragments from chromosome 21 will be slightly higher than expected (compared with other chromosomes). The sensitivity and specificity of the test reached 99 percent. It is able to detect 98.6 percent of fetuses with Down syndrome with a false positive rate of 0.2 percent. Healthy

children are detected with an effectiveness of 99.8 percent and a false negative rate of 1.4 percent. The authors believe that this technique could be applied in clinical practice for women at high risk of carrying a fetus with Down syndrome and avoid (in 96 percent of cases) losses associated with invasive diagnostic tests. Invasive tests would be necessary only to confirm the positive diagnosis of an NIPGT [22].

3. The Relationship Between Prenatal Diagnosis and Eugenic Abortion

The current historical and cultural situation is strongly characterized by an abortion mentality [23]. In such a context, any legitimate diagnostic and therapeutic benefits from NIPGT risk being over shadowed by its use as a new first line tool of eugenic selection for abortion. The fact that many of the diseases diagnosed through NIPGT have no therapeutic treatment means that abortion is considered the only "treatment" for a disease positive result. In such uses of prenatal diagnosis (PD), the purpose of medicine is altered, and the meaning of the word "prevention" distorted. "The binomial PD/abortion is seen as the only prevention for genetic diseases diagnosed in the embryo" [24].

Over the last twenty years, popularity of this idea has expanded significantly and has led to a broad social consensus in many countries about the legitimacy of abortion, especially in cases of fetal malformation [25]. The good health of the child, the so-called *healthy child*, is assumed to be a categorical imperative within the "quality of life" ideology and leads to eugenic behavior in the search of the perfect child: the so-called *perfect child syndrome* [26].

This eugenic mentality and its relation to invasive genetic prenatal diagnosis have been clear from the outset. The first scientist to culture fetal cells from amniotic fluid, N.M. Macintyre, suggested that in order to prevent the birth of a seriously disabled child and the emotional and economic destruction of the family, abortion would be the better of two unhappy choices [27]. That year the World Health Organization defended the same thesis in a report on the prevention, treatment, and rehabilitation of genetic disorders: "In a world that views population growth as an important problem and is increasingly concerned with the quality of human life, it will be taken for granted that children should be free of genetic disease" [28].

The next year H.D. Aiken ended his speech at a conference on the ethical issues in human genetics by making the right to biological survival dependent on a certain quality of life. He recognized the right of parents to accept a child lacking the ability to have a meaningful human life. However, in cases where this care seriously damages the welfare of others, he argued that this right must give way to other stronger demands [29].

This mentality prevailed first among health professionals before gradually entering into the rest of society. In 1983, the Journal of the American Academy of Pediatrics published an article on a program at the University of Oklahoma Health Science Center in which twenty-

four infants with birth defects in the spine had been left to die as a result of a specific decision to not apply therapeutic treatment [30]. In this regard, the testimony of a Canadian scholar and teacher, Eaunes G. Nisbet, is significant. Nisbet, in a 1989 review of a book about evolution, asserted, "I teach a huge introductory class in Earth science, a thorough cross-section of North American humanity. Recently the creationists have become rare. More open-minded fundamentalists are common, but they are thoughtful and willing to be convinced by theological reason and scientific evidence.… More disturbing is the new incarnation of eugenicists: those who believe that medicine has a duty to abort all genetic failures" [31].

This procreative perfectionism is strongly presented today by the new liberal eugenics as a parental duty [32]. In the words of Julian Savulescu, "couples (or single reproducers) should select the child, of the possible children they could have, who is expected to have the best life, or at least as good life as the others, based on the relevant available information" [33].

Genetic prenatal diagnosis has become part of the "relevant available information" that leads parents to decide whether the expected child is worthy of life or not [34]. In the last ten years, we have gone from the acceptance of eugenic abortion as the lesser evil to an approach that sees eugenic abortion as a "moral duty" of parents [35]. Savulescu insists, "we have an obligation to try to manipulate these characteristics to give an individual the best opportunity of the best life" [36]. It follows that in this duty to create the best possible children, we must begin by eliminating those who are disabled.

4. NIPGT for Children with Down Syndrome

A clear example of eugenic tendencies can be found in the abortion statistics after a positive prenatal diagnosis for Down syndrome. In France, the United Kingdom, Spain, and Italy, the number of abortions of fetuses affected by Down syndrome detected by prenatal diagnosis is around 90 to 95 percent [37]. A 2009 study in the *British Medical Journal* recorded data on prenatal diagnosis and abortion for Down syndrome fetuses in England and Wales from 1989 to 2008. The article highlights that the use of NIPGT during the first gestational weeks would increase the number of abortions of Down syndrome fetuses. In particular, the article cites the tests based on the presence of fetal mRNA in maternal blood as an appropriate tool for the detection of Down syndrome fetuses [38].

In eighteen European countries, the implementation of screening policies has a measurable impact on the frequency of prenatal detection of Down syndrome:

In 2004, the majority of countries had moved from solely offering older mothers a diagnostic test to having some form of Down syndrome screening in place, with over half having an official country-wide policy or recommendation for first or second-trimester screening.

Having a screening policy in place had a measurable impact on prenatal detection rates for Down syndrome; the registry areas in countries offering primarily first-trimester screening had a significantly higher detection rate than those using a mixed first or second trimester screening policy; those with some screening but no national screening policy in place were significantly less likely to detect a Down syndrome case prenatally [39].

A recent report suggests that the emergence of tests based on NIPGT will drive down the per child costs of detecting Down syndrome [40]. For these screening policies, based on the implementation of genetic tests in the first trimester, the use of NIPGT appears to be a policy priority for the future.

This prospect has already raised critical considerations of the ethical, legal and social issues related to the implementation of NIPGT [41]. A bioethical reflection on the possible difficulties and problems that arise from the use of these techniques is necessary.

5. Arguments Against Use of NIPGT

Several authors have clearly opposed the use of prenatal diagnosis for eugenic purposes [42]. Here we offer some of these arguments in order to show the negative effect that a widespread introduction of NIPGT would produce in the context of a eugenic mentality.

The first argument is referred to as the *expressivist argument*. The essential point of this argument is that selective abortion following prenatal diagnosis expresses a set of discriminatory attitudes toward disabled people. If we apply this argument to NIPGT, we see that NIPGT reinforces the medical model that holds disability itself as a problem to be solved. NIPGT tests for incurable genetic diseases for which the only possible "therapy" is abortion. Little or no value is given to the life of the person with the genetic disease, and thus abortion appears as the obvious solution to a negative test result. In this sense, NIPGT supports and reinforces a reductionist conception of the person. Here, as in other instances of unjust discrimination, one particular feature is made the central criterion of the person's value. NIPGT tests will send the message that it is not necessary to consider the whole person [43]. Through NIPGT, the person is reduced to the particular, *perceived-to-be-undesirable* trait. In other words, just as prenatal sex selection is morally problematic because it reinforces discriminatory attitudes toward women, selective abortion of disabled human beings based on NIPGT becomes a great insult: "some of us are 'too flawed' in our very DNA to exist; we are unworthy of being born" [44].

The second objection to consider is the *parental attitude argument*. In rejecting a child who would otherwise be desired, because they believe the child's disability will decrease their experience of parenthood, parents are saying that they are unwilling to accept any significant deviation in their dreams of parenting that the child's characteristics may cause. A further

challenge is posed by the fact that genetic tests such as NIPGT allow for a diagnosis with a high degree of accuracy at a very early stage of pregnancy. At present, techniques of genetic prenatal diagnosis through amniocentesis or chorionic villus sampling are used at the end of the first trimester or middle of the second. It is well established that the future use of NIPGT during the first gestational weeks would increase the number of abortions of Down syndrome fetuses. NIPGT may well come to support the fantasy and fallacy that "parents can ensure or create perfection" for their children [45]. In fact, it should be the opposite: good parents are those who care about raising the child they have received. They value the relations that can be developed between them, and not the traits that the child possesses. It should be noted, however, that the earlier diagnosis potential that tests such as NIPGT bring could also serve to "provide a period in which a couple would be free to accept a child with medical problems" [46].

A third argument is the *argument against misinformation* [47]. The decision to abort a child as a result of a prenatal diagnosis is often based on ignorance of what a life with a disability is like, both for the child and the parents. Many decisions are based on an existing prejudice in our society according to which people with disabilities live in slow agony and frustration, and that most marriages break up under the stress of having a child with a disability. Unfortunately, NIPGT-a simple blood test-can seem an easy means of avoiding these perceived negative consequences. In fact, many laboratories are now offering NIPGT via the Internet. The prices are still high, but these tests will reduce their cost and expand the number of genetic diseases diagnosed. Such "commercialization" of testing could remove prenatal diagnosis from the oversight and standards of the medical field, particularly those concerning how medical information is communicated and used. This could lead to an undesirable situation from a bioethical point of view: a pregnant woman might not be made aware, in a full and complete manner, of the implications of the genetic information that she receives about her child. As a consequence, she would not be able to give a truly informed consent to the completion of the analysis. It will be necessary, therefore, to ensure that NIPGT be practiced only in a medical context. It is necessary that parents receive genetic counseling that is complete and truly informed, especially in terms of helping parents get good information about living with a child with disabilities as well as how the illness will affect their family.

Another objection is presented as *the argument of limited parental self-determination*. Takamichi Sato explains this argument in connection with the use of prenatal diagnosis for selective abortions [48]. In order to satisfy the parents' right to know, complete and accurate information is necessary. This is a basic prerequisite for the decision-making process. Misinformation is a manipulation of the decision-making process and, therefore, of the parents' self-determination. In the prenatal diagnosis process, however, complete and accurate information is difficult to attain, in part because the moment test results reveal the possibility

of a disability, medical efforts are too often focused on preparing for an abortion rather than preparing for real life with a disabled child. But also the right to self-determination of the parents has a limit: the fetus's right to survive. Sato explains this with a legal example: In Germany, and also in Japan, it is illegal to tell parents the sex of a fetus before a certain gestational age, precisely in order to prevent abortion on the grounds of sex selection [49]. Such a legal limit suggests that the right of self-determination is not an absolute moral right.

The final argument against the use of prenatal diagnosis for eugenic purposes is *the right to life argument* [50]. The first element of the ethical assessment made by the Magisterium of the Catholic Church concerning the moral use of prenatal diagnosis techniques is that such techniques not be used as a hypothetical first step toward procuring an abortion. On this point, the Catholic Church has presented an articulate and organic treatment whose culmination is in the formulation found in the Congregation for the Doctrine of the Faith's document Donum vitae [51]. This argument continues and deepens in Pope John Paul II's encyclical Evangelium vitae, where the ethical assessment focuses not only on prenatal diagnosis techniques themselves, but also on the eugenic mentality often associated with the techniques [52]. The encyclical also examines and assesses the behavior of the various subjects involved in the prenatal diagnosis process: from the mother who has the abortion, to any person who proposes or advises an abortion based on the results of prenatal diagnosis. This includes both the health-care worker who counsels abortion, as well as the authorities and organizations that promote and support this step. Here, we can also see a condemnation of the use of mass screening tests by health authorities in order to eliminate fetuses who carry congenital malformations. Both Donum vitae and Evangelium vitae, as well as the more recent instruction from the Congregation for the Doctrine of the Faith Dignitas personae, explicitly include texts condemning these practices [53].

As we have seen, the implementation of screening policies, particularly during the first trimester, increases the frequency of prenatal detection of Down syndrome. Furthermore, NIPGT presents itself as a preferable alternative to current methods of screening. NIPGT works without the risk of indirect abortion that is present in amniocentesis and fetal chorionic villus sampling. NIPGT is cost effective, reducing the overall costs associated with Down syndrome fetus detection. Finally, NIPGT will detect trisomies as early as seven weeks gestation. Without due controls, NIPGT could easily be used as a eugenic tool for the prevention of genetic disease.

The strong cautionary evaluation of prenatal diagnosis techniques seen in the Magisterium is ultimately based on respect for the life, health, and human dignity of the embryo from conception. We could summarize the nucleus of this assessment in the following points: 1) recognition of the embryo's human dignity from the moment of conception; 2) the absolute right of the embryo to life as the first and fundamental right of every human being [54] an

absolute right, not to be subordinated to any condition, not even to health; 3) any behavior in relation to the embryo or the fetus that constitutes exploitation, that is, using the fetus as a means to achieve ends foreign to his true good, is completely unacceptable. An example of such exploitation most certainly would include killing a child with a disorder as a means to eliminating the disorder, disregarding the child's true good.

6. The Importance of Pre-test and Post-diagnosis Counseling in NIPGT

If NIPGT does become commonplace, providing sound genetic counseling to expectant parents will be crucial. Understanding complex and sometimes ambiguous genetic information is no easy task. Many people do not even know the difference between "risk" and "diagnosis." Sometimes the quantity of information that parents receive is so large that they cannot process it all, and thus they look for health-care providers to guide them through understanding the information. A mother's autonomy depends on the development of a truly informed consent. NIPGT could easily compromise such consent. "In the case of Down syndrome screening, where the technology would replace a probabilistic test with a single highly predictive test, the main ethical challenges to implementation are safeguarding patient autonomy and ensuring informed consent" [55]. For all these reasons, the role of physicians together with well implemented pre-test and post-diagnostic counseling take on a crucial importance.

6.1. Pre-test counseling in NIPGT

Traditionally, pre-test counseling focuses on two elements: the explanation of invasive prenatal diagnosis procedures, and the achievement of informed consent for execution of the diagnostic procedure. If the risk of fetal loss during the diagnostic test were eliminated, it would seem that pre-test counseling could be limited simply to obtaining informed consent for completion of NIPGT. However, the choice whether or not to conduct the NIPGT itself should be made by the woman only after receiving notification of the ramifications and implications of the test. It is important to highlight that the physician or genetic counselor must not impose a choice on the woman, but only help her to make a decision, avoiding any form of pressure that might determine her choice. For this, it must be clearly communicated in the course of the counseling session what difficulties the woman will encounter, the methodology of the test used, the nature of the diseases to be detected, and the degree of certainty of the results.

At an ethical level, the duties of professional deontology require 1) informed consent prior to NIPGT, which necessitates, as we have indicated, a complete and rigorous disclosure of information; and 2) strict quality control at the level of the techniques used by the laboratories involved in NIPGT. There is currently a wide range of reliability in the tests depending on the use of one technique or another as well as the use of one or multiple genetic markers.

6.2. Post-test counseling in NIPGT

Some studies show that information currently given to mothers upon the detection of trisomy 21, particularly during the first trimester of pregnancy, does not offer the pregnant woman a good understanding of the current or future health prospects of her child. Only with such information, however, can the parents exercise real autonomy and make decisions that respect ethical principles [56]. At the same time, as the techniques of genetic testing advance, there is a need for skilled and qualified counselors to transmit the resulting genetic information to parents.

In most cases, the NIPGT test returns negative for the detection of trisomies, bringing a sense of psychological relief for the woman. However, when the test returns positive, meaning the fetus has a genetic problem, medical personnel are presented with a unique opportunity to assist the woman. In such situations, the counselor cannot allow a woman to become dependent on his advice, but must present pertinent information so that a responsible decision can be made. The counselor must sincerely endeavor to inform the woman, without exaggerating or diminishing the severity of the disease's anticipated impact on the life of the family. Counselors must allow the woman the time necessary for calm reflection, providing answers for her thoughtout questions, and helping her work toward alleviating her feelings of anxiety. There are signs that, by improving the scientific and human quality of information during the decision-making process about a genetic disease, there is a statistically significant trend in recent years, for the woman to elect continuation of pregnancy and to reject abortion [57]. E. Parens and A. Asch have pointed out this principle of injustice by stating, "Ignorance is one of the primary sources of the discrimination suffered by people with disabilities" [58].

7. Bioethical Reflection on NIPGT

The efforts of science and technology to find genetic markers of disease and to develop techniques that can make a method of prenatal diagnosis more sensitive and specific are, in themselves, good. As such, the techniques of NIPGT that have been developed may be evaluated positively. We believe that it is licit to do research in order to find genetic markers that would establish a correct and efficient method for the prenatal diagnosis of fetuses carrying a particular genetic disorder. We believe it is licit to make an NIPGT available to all pregnant women who are in a high risk situation, defined on the basis of medical and ethical criteria, without compromising the integrity of the fetus, because it will allow the treatment of those disorders and, therefore, the pursuit of the good of the child. Still, *the positive moral assessment of the clinical application* of this new diagnostic technique, satisfying all the requirements for the successful execution of the method, *depends on the conditions that precede and accompany it.*

The first condition is that *the purpose* for which the method is applied *has to be good*.

Unfortunately, in much of the research there is evidence, albeit not always explicit, that the end is eugenics: not allowing the birth of subjects affected by genetic and chromosomal disorders, in particular, individuals affected by Down syndrome. This eugenic aim is supported by reports that emphasize the need for implementing NIPGT in order to increase detection and abortion of fetuses with Down syndrome, and to decrease the detection/cost rate [59]. There is a eugenic trend in the application of prenatal diagnosis in developed countries, with the exception of Japan [60].

The second condition is that *it will do no harm*. Three subjects can potentially suffer the consequences of this new diagnostic method: women, children, and society. For the woman who is told that she has a high risk of having a child with a genetic disease, and to whom prenatal diagnosis is proposed, a period of profound psychological suffering begins that will affect the whole family. Especially distressing is the waiting period after completion of amniocentesis for the required growth of cell cultures. This period of anxiety will be significantly reduced with the use of NIPGT techniques where results may be available within twenty-four to forty-eight hours. In most cases, she will get a negative result. However, this does not exclude the possibility that the child might be affected by other genetic diseases for which the appropriate markers have not yet been identified.

For the child in the womb, the use of NIPGT techniques eliminates the risk of indirect abortion, safeguarding the child from the harm associated with invasive tests: Data from indirect abortion studies is highly variable, ranging from one indirect abortion for every four fetuses with Down syndrome identified, to studies (greater in number) that recognize one indirect abortion for every Down syndrome fetus identified [61]. However, the use of NIPGT technology in the context of a liberal eugenic mentality will reinforce the image of the disabled person as an individual to be excluded from society, thereby causing harm to the child. Furthermore, the earlier diagnosis promised by NIPGT is considered a factor that will enable a greater number of direct eugenic abortions. As the Congregation for the Doctrine of the Faith notes in the Declaration on Procured Abortion: “It is true that the evolution of technology makes early abortion easier and easier, but the moral evaluation is in no way modified because of this” [62].

For society, NIPGT can lead to serious harm owing to its ability to reinforce an underlying societal mentality of liberal eugenics. As disability advocates will note, prenatal diagnosis is morally problematic for at least two reasons. First, selective abortion expresses negative or discriminatory attitudes not only about the disease but also about those who have it. And second, prenatal diagnosis establishes intolerance toward diversity, not only in society but also in the family and, ultimately, this can affect the attitudes of parents toward their children [63]. In fact, the number of geographical areas or social strata in which, for example, there are no children with Down syndrome is increasing. Social pressure against the genetically damaged

may not represent an ideology of racial superiority, but it does reveal several tendencies of the pragmatic and hedonistic culture in which we live. The social reluctance to accept visible genetic disabilities, the aspiration for the perfect child, the intolerance shown to the suffering of self and others, and the economic rationality that rejects the added cost of a genetic disease are some of the symptoms of discriminatory attitude in our Western societies.

8. Conclusion

The rapid development of genetic engineering and the globalization of information should prompt us to reflect more thoroughly on the ways in which new techniques of prenatal diagnosis are applied in the daily practice of medicine. The use of techniques of analysis of fetal nucleic acid present in maternal peripheral blood for NIPGT is a reality in clinical practice in the case of certain diseases. In the coming years, it will become part of routine fetal screening. In this paper, we have offered a bioethical reflection about the possible difficulties and problems of the use of these techniques. Two questions present themselves.

Should we diagnose any chromosomal abnormality? The answer depends on the diagnostic intention. The goal of prenatal diagnosis need not simply be to determine if abortion is necessary. NIPGT could empower parents by offering knowledge of their child's disability and time to prepare, particularly in the setting of a genetic disease of considerable impact. Many parents who discover that they have a child affected by Down syndrome choose not to terminate, but are empowered by the information and the time for preparation that early screening gives them. In this sense, NIPGT has a positive moral assessment.

It is the relation between prenatal diagnosis and eugenic abortions that converts NIPGT into a problematic tool from a moral point of view. The widespread use of NIPGT could, in fact, decrease the autonomy of women in the decision-making process. The use of NIPGT techniques will result in reduced costs of screening, an increase in the number of disabled fetuses detected, and a decrease in the number of indirect abortions caused by invasive techniques. These properties of NIPGT are well-known by those health authorities that may use policies of extensive NIPGT screening as a means of eugenic prevention of genetic diseases, particularly Down syndrome. NIPGT cannot be used as a justification that leads parents to decide whether the expected child is worthy to live or not.

Should fetuses with genetic defects be regularly aborted? The answer has to be no. "Dignity" cannot be established at the molecular level. This should be clear to all. As time unfolds, the detection methods of chromosomal abnormalities from NIPGT will become more effective. In addition to trisomies 13, 18, and 21, more and more fetal chromosomal imbalances will become diagnosable. Given that many of the diagnosed diseases do not have a therapeutic treatment, abortion is often considered as a preventive treatment. Eugenics wrongly identifies the disease with the patient's life, the part with the whole. While a disease does not deserve

to be respected, this rejection must never be erroneously manifested in social rejection of the patients suffering the disease, extolling abortion as a priority solution and abandoning the challenge of trying to find a cure consistent with the value of the life of the person. This is what some have called "handicapphobia" [64]. The use of NIPGT in this direction is in contrast to the first principle of medical ethics and, indeed, all ethics: *primum non nocere*, first do no harm. NIPGT could reinforce the image of the disabled person as an individual to be excluded from society. For this reason, physicians must play an important role in the process of pre-diagnosis and post-diagnosis genetic counseling. NIPGT will change our medical routine over the next few years, and it will depend on the medical community's utilization of NIPGT as to whether it will remain a diagnostic tool or become a eugenic one.

In conclusion, we can say that the use of NIPGT techniques to *diagnose the existence of genetic diseases in the fetus in order to decide*, when the result is positive, *whether or not to perform an abortion*, implies and includes in itself the conditions that characterize a *negative moral assessment*. On the other hand, when NIPGT is used to diagnose genetic diseases that do have treatments (whether immediately after birth or even in utero), and without an abortive intention in the event of a positive test result, i.e., when it is *for the true good of the child*, the moral assessment can be positive.

9. References

1. G.E. Palomaki et al. "DNA Sequencing of Maternal Plasma to Detect Down Syndrome: An International Clinical Validation Study," Genetics in Medicine 13 (2011): 913–920.

2. J. Mozersky, V. Ravitsky, R. Rapp, M. Michie, S. Chandrasekharan and M. Allyse, "Towards an ethically sensitive implementation of non invasive prenatal screening in the global context, Hastings Center Report 47 (2017):

3. F.J. González-Melado and M.L. Di Pietro, "Noninvasive Prenatal Genetic Diagnosis and Eugenic Aims", The Linacre Quaterly 79 (2012) : 282-303.

4. D. Schmitz, H. Wolfra, and N. Christian, "No Risk, No Objections? Ethical Pitfalls of Cell-Free Fetal DNA and RNA Testing," British Medical Journal 339 (2009): 165; D. Schmitz, C. Netzer, and W. Henn, "An Offer You Can't Refuse? Ehtical Implications of Non-invasive Prenatal Diagnosis (NIPD)," Nature Review Genetics 10 (2009): 515; A. Jong, W.J. Dondorp, and S.G. Frints, "Non-invasive Prenatal Diagnosis for Aneuploidy Toward an Integral Ethical Asessment," Human Reproduction 26 (2011): 2915–2917.

5. Y.M. Lo, "Noninvasive Prenatal Detection of Fetalchromosomal Aneuploidies by Maternal Plasma Nucleic Acid Analysis: A Review of the Current State of the Art," British Journal of Obstetrics and Gynecology 116 (2009): 152–157.

6. D.W. Bianchi, et al., "PCR Quantitation of Fetal Cells in Maternal Blood in Normal and Aneuploid Pregnancies," American Journal of Human Genetics 61 (1997): 822–829.

7. M. Rodriguez de Alba et al., "Prenatal Diagnosis on Fetal Cells Obtained from Maternal Peripheral Blood: Report of 66 Cases," Prenatal Diagnosis 19 (1999): 934–940; I. Hromadnikova et al., "Non-invasive Fetal Sex Determination on Fetal Erythroblasts from the Maternal Circulation Using Fluorescence in Situ Hybridisation," Fetal Diagnosis Therapy 17 (2002): 193–199; D.W. Bianchi et al., "Fetal Gender and Aneuploidy Detection Using Fetal Cells in Maternal Blood: Analysis of NIFTY I Data. National Institute of Child Health and Development Fetal Cell Isolation Study," Prenatal Diagnosis 22 (2002): 609–615; F.Z. Bischoff et al., "Detection of Low-Grade Mosaicism in Fetal Cells Isolated from

Maternal Blood," Prenatal Diagnosis 15 (1995): 1182–1184; M. Rodriguez de Alba et al., "Prenatal Diagnosis on Fetal Cells from Maternal Peripheral Blood in Cases of Confined Placental Mosaicism," Prenatal Diagnosis 20 (2000): 264–265; S. Elias et al., "First Trimester Prenatal Diagnosis of Trisomy 21 in Fetal Cells from Maternal Blood," Lancet 340 (1992): 1033; M. Rodriguez de Alba et al., "Prenatal Diagnosis on Fetal Cells from Maternal Blood: Practical Comparative Evaluation of the First and Second Trimesters," Prenatal Diagnosis 21 (2001): 165–170; A. Saker et al., "Genetic Characterisation of Circulating Fetal Cells Allows Non-invasive Prenatal Diagnosis of Cystic Fibrosis," Prenatal Diagnosis 26 (2006): 906–916.

8. M. Borgatti et al., "New Trends in Non-invasive Prenatal Diagnosis: Applications of Dielectrophoresis-Based Labon-a-Chip Platforms to the Identification and Manipulation of Rare Cells," International Journal of Molecular Medicine 21 (2008): 3–12; G. Calabrese et al., "Detection of Chromosomal Aneuploidies in Fetal Cells Isolated from Maternal Blood Using Single-Chromosome Dual-Probe FISH Analysis," Clinical Genetics 82 (2012): 131– 139.

9. Y.M. Lo and N. Corbetta, "Presence of Fetal DNA in Maternal Plasma and Serum," Lancet 350 (1997): 485–487.

10. Y.M. Lo et al., "Quantitative Analysis of Fetal DNA in Maternal Plasma and Serum: Implications for Noninvasive Prenatal Diagnosis," American Journal of Human Genetics 62 (1998): 768–775.

11. Ibid.

12. T.W. Lau et al., "Fetal DNA Clearance from Maternal Plasma Is Impaired in Preeclampsia," Clinical Chemistry 45 (2002): 2141–2146.

13. A. Bustamante-Aragones, ADN fetal en plasma materno: nuevas estrategias para el estudio de mutaciones de herencia paterna y diagnóstico prenatal no invasivo del sexo fetal (Tesis doctoral europea. Fundación Jiménez Díaz-Capio, CIBERER, Madrid 2008).

14. Lo, "Noninvasive Prenatal Detection of Fetalchromosomal Aneuploidies"; Y.M. Lo et al., "Quantitative Abnormalities of Fetal DNA in Maternal Serum in Preeclampsia," Clinical Chemistry 45 (1999): 184–188; M. Smid et al., "Correlation of Fetal DNA Levels in Maternal Plasma with Doppler Status in Pathological Pregnancies," Prenatal Diagnosis 26 (2006): 785–790. Y.M. Lo et al. "Increased Fetal DNA Concentrations in the Plasma of Pregnant Women Carrying Fetuses with Trisomy 21," Clinical Chemistry 45 (1999): 1747–1751; X.Y. Zhong et al., "Fetal DNA in Maternal Plasma Is Elevated in Pregnancies with Aneuploid Fetuses," Prenatal Diagnosis 20 (2000): 795–798; C.J. Jorgez et al., "Elevated Levels of Total (Maternal and Fetal) Beta-Globin DNA in Maternal Blood from First Trimester Pregnancies with Trisomy 21," Human Reproduction 22 (2007): 2267–2272; T. Wataganara et al., "Maternal Serum Cell-Free Fetal DNA Levels Are Increased in Cases of Trisomy 13 but Not Trisomy 18," Human Genetics 112 (2003): 204–208; X.Y. Zhong et al., "High Levels of Fetal Erythroblasts and Fetal Extracellular DNA in the Peripheral Blood of a Pregnant Woman with Idiopathic Polyhydramnios: Case Report," Prenatal Diagnosis 20 (2000): 838–841; A.Yin et al., "Correlation of Maternal Plasma Total Cell-Free DNA and Fetal DNA Levels with Short Term Outcome of First-Trimester Vaginal Bleeding," Human Reproduction 22 (2007): 1736–1743; T.N. Leung et al., "Maternal Plasma Fetal DNA as a Marker for Preterm Labour," Lancet 352 (1998): 1904–1905; A. Farina et al., "High Levels of Fetal Cell-Free DNA in Maternal Serum: A Risk Factor for Spontaneous Preterm Delivery," American Journal of Obstetrics Gynecology 193 (2005): 421–425; A. Sekizawa et al., "Cell-Free Fetal DNA Is Increased in Plasma of Women with Hyperemesis Gravidarum," Clinical Chemistry 47 (2001): 2164–2165; A. Sekizawa et al., "Increased Cell-Free Fetal DNA in Plasma of Two Women with Invasive Placenta," Clinical Chemistry 48 (2002): 353–354.

15. P.D. Pan et al., "Cell-Free Fetal DNA Levels in Pregnancies Conceived by IVF," Human Reproduction 20 (2005): 3152–3156; N.B. Tsui et al., "Non-invasive Prenatal Detection of Fetal Trisomy 18 by RNA-SNP Allelic Ratio Analysis Using Maternal Plasma SERPINB2 mRNA: A Feasibility Study," Prenatal Diagnosis 29 (2009): 1031– 1037; Cf. O. Lapaire et al., "Maternal Smoking: Effect on Circulating Cell-Free Fetal and Total DNA Levels in Maternal Plasma from the Second Trimester," Obstetrics and Gynecology 110 (2007): 1358–1363.

16. L.L. Poon et al. "Presence of Fetal RNA in Maternal Plasma," Clinical Chemestry 46 (2000): 1832–1834; L.L. Poon et al., "Circulating Fetal RNA in Maternal Plasma," Annals of the New York Academy of Sciences 945 (2001): 207–210.

17. E.K. Ng et al., "mRNA of Placental Origin Is Readily Detectable in Maternal Plasma," Proceedings of the National Academy of Sciences of U.S.A. 100 (2003): 4748–4753; C.B. Oudejans et al., "Detection of Chromosome 21-Encoded mRNA of Placental Origin in Maternal Plasma," Clinical Chemistry 49 (2003): 1445–1449; A.T. Go et al., "Detection of Placental Transcription Factor mRNA in Maternal Plasma," Clinical Chemistry 50 (2004): 1413– 1414; N.B. Tsui et al., "Systematic Micro-Array Based Identification of Placental mRNA in Maternal Plasma: Towards Non-invasive Prenatal Gene Expression Profiling," Journal of Medical Genetics 41 (2004): 461–467.

18. W.K. Chiu et al., "Time Profile of Appearance and Disappearance of Circulating Placenta-Derived mRNA in Maternal Plasma," Clinical Chemistry 52 (2006): 313–316.

19. Lo, "Noninvasive Prenatal Detection of Fetalchromosomal Aneuploidies"; Ng et al., "mRNA of Placental Origin Is Readily Detectable in Maternal Plasma"; Oudejans et al., "Detection of Chromosome 21-Encoded mRNA of Placental Origin in Maternal Plasma"; Go et al., "Detection of Placental Transcription Factor mRNA in Maternal Plasma"; Tsui et al., "Systematic Micro-Array Based Identification of Placental mRNA."

20. Palomaki et al., "DNA Sequencing of Maternal Plasma to Detect Down Syndrome." E.Z. Chen et al., "Noninvasive Prenatal Diagnosis of Fetal Trisomy 18 and Trisomy 13 by Maternal Plasma DNA Sequencing," PLoS ONE 6 (2011): e21791, 1–7.

21. The second one is trisomy 18 or Edwards syndrome (1, 93 percent); Cf. N. Jouvé, "Defectos Congenitos y Discapacidad," Cuadernos de Bioética 20 (2009): 407–422.

22. Palomaki et al., "DNA Sequencing of Maternal Plasma to Detect Down Syndrome."

23. D.I. Bromage, "Prenatal Diagnosis and Selective Abortion: A Result of the Cultural Turn?" Medical Humanities 32 (2006): 38–42, where it establishes a relationship between postmodernity (with its aim in stetic perfectionism) and the increase of prenatal diagnosis and eugenics abortions.

24. M.L. Di Pietro, "Diagnóstico Prenatal y Consejo Genético," in Diccionario de Bioética, ed. C.S. Vázquez, Monte Carmelo, and Burgos (2006), 240–248.

25. Cf. W. Lenhard, et al., "Attitudes of Mothers Towards Their Child with Down Syndrome before and after the Introduction of Prenatal Diagnosis," Intellectual and Developmental Disabilities 45 (2007): 98–102.

26. M.L. Di Pietro and Z. Serebrovska, "Prenatal Noninvasive Genetic Diagnosis: Clinical and Ethical Aspects," Medicina e Morale 56 (2006): 1125–1145.

27. N.M. Macintyre, "Professional Responsibility in Prenatal Genetic Evaluation," Birth Defects (Original Article Series) 8 (1972): 35, quoted in Italian by M.L. Di Pietro and A.G. Spagnolo, "Famiglia e Diagnosi Prenatale," La Famiglia 21 (1987): 57–66.

28. World Health Organization, "Genetics Disorders: Prevention, Treatment and Rehabilitation," WHO Technical Report Series 497 (1972): 1–46.

29. H.D. Aiken, "Life and the Right to Life," in Ethical Issues in Human Genetics, eds. B. Hilton et al. (New York: Plenum Press, 1973), 173 (translation from the Italian version that apeared in A. Serra, "La diagnosi prenatale di malattie genetiche," in Ingegneria genetica e biotecnologie nel futuro dell'uomo, eds. E. Sgreccia and V. Mele (Milano: Vita e Pensiero, 1992), 191–209.

30. R.H. Gross et al., "Early Management and Decision Making for the Treatment of Myelomeningo-Cele," Pediatrics 72 (1983): 450–458.

31. E.G. Nisbet, "Monster on the Loose," Nature 339 (1989): 267–268.

32. N. Agar, Liberal Eugenics: In Defence of Human Enhancement (Oxford: Blackwell Publishing, 2004), 5–6.

33. Cited by J. Glover, Choosing Children: Genes, Disability and Design (New York: Oxford University Press, 2006),

54.

34. From a scientific context, it is making claims about the reduction of a woman's risk age and modification of general criteria about risk pregnancy. See B.F. Grandall, T.B. Lebherz, and K. Tabsh, "Maternal Age and Amniocentesis: Should This Be Lowered to 30 Years?" Prenatal Diagnosis 6 (1986): 237–242; B.A. Goodwinn and C. Huether, "Revised Estimates and Projections of Down Syndrome Births in the United States, and the Effects of Prenatal Diagnosis Utilization, 1970–2002," Prenatal Diagnosis 7 (1987): 261–271.

35. This point is clearly defended by transhumanism (humanity-plus). Cf. C.W. Brock, "Is Selection of Children Wrong?" in Human Enhancement, eds. J. Savulescu and N. Bostrom (New York: Oxford University Press, 2009), 251–276; See also P. Singer, "Parental Choice and Human Improvement," in Savulescu and Bostrom, Human Enhancement, 277–289.

36. J. Savulescu, "New Breeds of Humans: The Moral Obligation to Enhance," Reproductive Biomedicine Online 10 supp 1 (2005): 36–39.

37. P.A. Boyd, et al., "Survey of Prenatal Screening Policies in Europe for Structural Malformations and Chromosome Anomalies, and Their Impact on Detection and Termination Rates for Neural Tube Defects and Downs Syndrome," British Journal of Obstetrics and Gynecology 11 (2008): 689–696.

38. J.K. Morris and E. Alberman, "Trends in Down's Syndrome Live Births and Antenatal Diagnoses in England and Wales from 1989 to 2008: Analysis of Data from the National Down Syndrome Cytogenetic Register," British Medical Journal 339 (2009): b3794.

39. Boyd et al., "Survey of Prenatal Screening Policies in Europe."

40. J. Gekas, et al., "Comparison of Different Strategies in Prenatal Screening for Down's Syndrome: Cost Effectiveness Analysis of Computer Simulation," British Medical Journal 338 (2009): b138, 1–10.

41. R. Collier, "Prenatal DNA Test Raises Hopes and Worries," Cananadian Medical Association Journal 180 (2009): 705–706; D. Schmitz, H. Wolfram, and N. Christian, "No Risk, No Objections? Ethical Pitfalls of Cell-Free Fetal DNA and RNA Testing," British Medical Journal 339 (2009): 165; editorial, "Le dianostic prénatal non invasif: est-ce pour demai? Quelles conséquences pour notre pratique?" Gynécologie Obstétrique & Fertilitè 38 (2010): 435–438; D. Schmitz, C. Netzer, and W. Henn, "An Offer You Can't Refuse? Ethical Implications of Noninvasive Prenatal Diagnosis (NIPD)," Nature Review Genetics 10 (2009): 515.

42. E. Parens and A. Asch, "The Disability Rights Critique to Prenatal Genetic Testing. Reflections and Recommendations," Hasting Center Report 29 supp (1999): s1–s22; Prenatal Testing and Disability Rights, eds. E. Parens and A. Asch (Washington, D.C.: Georgetown University Press, 2000); S. Shimazoho, "Reasons Against the Selection of Life: From Japan's Experience of Prenatal Genetic Diagnosis," in Savulescu and Bostrom, Human Enhancement, 291–313.

43. A. Asch, "Reproductive Technology and Disability," in Reproductive Laws for the 1990s, eds. S. Cohen and N. Taub (Clifton, NJ: Humana Press, 1989), 69–124.

44. M. Saxton, "Disability Rights and Selective Abortion," in Abortion Wars: A Half Century of Struggle, ed. R. Solinger (Berkeley: University of California Press, 1997), 374–395.

45. Asch, "Reproductive Technology and Disability."

46. Congregation for the Doctrine of Faith, instruction Dignitas personae (2008), n. 22.

47. Parens and Asch, "The Disability Rights Critique to Prenatal Genetic Testing"; Parens and Asch, Prenatal Testing and Disability Rights; Shimazoho, "Reasons Against the Selection of Life."

48. Shimazoho, "Reasons Against the Selection of Life."

49. Ibid.

50. Ibid.

51. Congregation for the Doctrine of the Faith, instruction Donum vitae (1987), I, n. 2.

52. Pope Blessed John Paul II, encyclical Evangelium vitae (1995), n. 63.

53. Congregation for the Doctrine of the Faith, Donum vitae, I, n. 2; also John Paul II, Evagelium vitae, n. 63. The Congregation for the Doctrine of the Faith's instruction Dignitas personae, n. 2, also presents this idea: "At the same time, however, there are also persons in the world of philosophy and science who view advances in biomedical technology from an essentially eugenic perspective"; ansd in n. 22, when making an assessment of preimplantation diagnosis, quoting Jopn Paul II, Evangelium vitae, n. 63.

54. Congregation for the Doctrine of the Faith, Donum vitae, I, n. 1, quoting Vatican Council II, Pastoral Constitution on the Church, Gaudium et spes (1965), n. 51: "Therefore from the moment of its conception life must be guarded with the greatest care while abortion and infanticide are unspeakable crimes." Cf. Pope Blessed John Paul II, Charter of the Rights of the Family (1983), n. 4, when he said: "Human life must be respected and protected absolutly from the moment of conception." John Paul II, Evangelium vitae, n. 62. 55. C.F. Wright and L.S. Chitty, "Cell-Free Fetal DNA and RNA in Maternal Blood: Implications for Safer Antenatal Testing," British Medical Journal 339 (2009): 161–164.

56. R. Favre et al., "How Important Is Consent in Maternal Serum Screening for Down Syndrome in France? Information and Consent Evaluation in Maternal Serum Screening for Down Syndrome: A French Study," Prenatal Diagnosis 27 (2007): 197–205; R. Favre et al., "What About Informed Consent in First-Trimester Ultrasound Screening for Down Syndrome?" Fetal Diagnosis Therapy 23 (2008): 173–184.

57. S.M. Christian et al., "Parental Decisions Following Prenatal Diagnosis of Sex Chromosome Aneuploidy: A Trend Over Time," Prenatal Diagnosis 20 (2000): 37–40.

58. Parens and Asch, "The Disability Rights Critique to Prenatal Genetic Testing"; Parens and Asch, Prenatal Testing and Disability Rights.

59. Morris and Alberman, "Trends in Down's Syndrome Live Births and Antenatal Diagnoses"; Gekas et al., "Comparison of Different Strategies in Prenatal Screening for Down's Syndrome."

60. D. Sicard, "La france au risque de l'eugenisme," Le Monde, March 2, 2007, http://www.lemonde.fr/planete/article/2007/02/03/la-france-au-risque-de-l eugenisme_863262_3244.html; A. Sasaki et al., "Low Prevalence of Genetic Prenatal Diagnosis in Japan," Prenatal Diagnosis 31 (2011): 1007–1009.

61. The editorial of the British Medical Journal is interesting: "In others words, somebody needs to decide what is more important to avoid-the unexpected birth of a baby with Down's syndrome or the loss of a healthy baby as a consequence of an invasive test (amniocentesis or chorionic villus sampling) triggered by a false positive test," Z. Alfirevic, "Prenatal Screening for Down's Syndrome. A Range of Options that Provide a Reliable and Reproducible Result Is Essential," British Journal of Medicine 338 (2009): 421–422.

62. Sacred Congregation for the Doctrine of the Faith, Declaration on Procured Abortion (1974), n. 17, http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_19741118_declarationabortion_en.html.

63. Parens and Asch, "The Disability Rights Critique to Prenatal Genetic Testing"; Parens and Asch, Prenatal Testing and Disability Rights.

64. Sicard, "La france au risque de l'eugenisme."