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Ethical issues in genetic counseling

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Genetics has made great progress in the past decades, and prenatal diagnosis, predictive genetic testing, and genetic counseling have drawn the limelight of public attention. Because the subject of genetic counseling is of crucial consequence for both the short and long term, its ethical aspects are paramount. The question is whether mankind is mature enough to use this extraordinary knowledge in the right way for the benefit of the society. In the center of ethical questions is the comprehensiveness of information provided to the couples or patients and counseling them about results and making informed educated decisions. In addition, it is crucial how sensitive personal information is treated and whether and how it should be made public.

Genetic counseling

Genetic counseling is a field of professional expertise that includes diagnosis, provision of information, and consultation with individuals about their genetic make-up and chances of bearing a child with an anomaly or other detectable problem. Before the era of modern genetics, genetic counseling was based on empirical observations of the higher frequency of particular diagnoses in certain families. It was about 150 years ago when the first scientific observations were made by Gregor Johann Mendel,

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which led to the biological understanding of the inheritance of human traits [1]. This was followed by revolutionary progress in the science of genetics in the 20th century that became an integral part of modern genetic counseling [2]. Recently, technological advances have enabled the rapid development of a broad range of methodologies supporting prenatal and preimplantation genetic diagnoses [3,4]. These new methods are aimed at diagnosing the genetically affected fetus at a time during gestation when parents may request the termination of pregnancy that is permitted by applicable law. This chapter discusses various ethical challenges of genetic counseling, especially those generated by the rapid progress in genetics and the use of novel methodologies.

The evolution of genetic counseling

Genetic counseling was developed by two occupational groups [5]. The early pioneers were biologists and geneticists working in natural sciences, and then medical doctors, mainly pediatricians and obstetricians, took control over the field. Human genetics pioneers were mainly self-trained biologists and geneticists who worked within academic departments isolated from other medical disciplines. Their high standing as scientists was derived from working in areas involving mysteries and elements considered sacred by the society. They dealt with population genetics and were more often interested in the effects of genetics on human evolution than on individuals [6].

Classical genetic counseling aimed at helping families with emotional support and by disclosing and discussing the causes of hereditary problems, the risks of recurrence, the possibilities for prevention, and other options [7–10]. The family history and pedigree were the only basis for providing risk assessment, education, and psychosocial support for patients referred to genetic evaluation and counseling [11–15]. Very often, no reliable estimates for recurrence risk were available. In many instances, the classical options included contraception, sterilization, adoption, or heterologous insemination by a donor [11,15–20].

In the beginning of the 20th century, genetic counseling offered premarital, preconception, and postconception heredity counseling, which consisted of an interview along with pedigree taking. The recurrence risk estimate was presented and highly directive advice was provided on whether or not to marry or reproduce [21]. This approach fit well with the interest of the eugenics movement in decreasing the prevalence of harmful traits and increasing the prevalence of desirable traits [22,23]. Indeed, the use of the term “genetic counseling” was interchangeable with “eugenics counseling” even into the late 1960's [24].

Subsequently, the discipline of genetic counseling emerged, and the concern about the future of the gene pool was replaced with an emphasis on the prevention of the birth of individuals who might have severe birth defects. Key medical discoveries in the study of hereditary diseases and cytological and chromosomal genetics widened the clinical applications of human genetics [25], which led to the cataloguing of more than 9,000 monogenic disorders and traits since the 1950's [26,27]. This catalogue was first published in the form of a book in 1966 [26]. Then, a comprehensive online database of genetic conditions and their patterns of inheritance (Online Mendelian Inheritance in Man, OMIM) was established, which also contains a compendium of human genes [27]. The OMIM database also cites the seminal papers on genetic conditions, including history, clinical findings, diagnosis, biochemical features, pathogenesis, animal models, mapping, molecular genetics, population genetics, inheritance, and clinical management.

Using this rich source of information, genetic counseling currently provides two major services: (1) it assesses whether diseases of a newborn, older child, or adult are hereditary; makes a diagnosis; and provides information about the possible treatments and (2) it counsels during pregnancy concerning the occurrence and/or recurrence of hereditary diseases in a family or those materializing in pregnancy by using prenatal diagnostic tools to ensure the birth of a healthy offspring [28].

Prenatal genetic counseling

Prenatal genetic counseling relies on the availability of an increasing number of prenatal diagnostic methods together with the widening knowledge in molecular genetics and the consequent improved understanding of genetically determined diseases at many levels [29]. The fetal phenotype can be

examined by ultrasound for malformations or growth retardation or by cell biochemistry for metabolic disorders. The fetal genotype can be examined by cytogenetic analysis for chromosome disorders or by PCR, microarray, or sequencing for the identification of gene mutations. It is expected that genetic disorders with no currently available diagnosis and known cause will soon be understood at the biochemical or gene levels, and many presently "unmapped" disease genes will be identified in the near future [30]. Prenatal genetic counseling also examines the pattern(s) of inheritance for the genetic conditions, keeping in mind that there can be factors such as variable expressivity, reduced penetrance, heterogeneity, and mosaicism with genetic conditions that can affect the interpretation of the pedigree [31,32].

The increased availability of prenatal diagnostic methods has stimulated the development of screening for genetic diseases. The implementation of these screening methods in prenatal genetic counseling aimed at the early diagnosis of congenital defects, mental retardation, or genetic disorders at a point where parents may still be able to legally request the termination of pregnancy [33]. Certain screening methods (e.g., biochemical assays, ultrasound) can only be applied during pregnancy [30]. Patients at particular risk may be identified without testing (e.g., advanced maternal age) or identified after specific testing (e.g., for hemoglobinopathies, thalassemia) before pregnancy.

Preconception genetic counseling should be considered in the clinical settings of advanced maternal age, a previous fetus or child with a genetic disorder, a parent with a genetic disorder or trait, family history of a genetic disorder, maternal genetic disorders that pregnancy may aggravate or that may threaten fetal health and survival, history of infertility, consanguinity, and environmental exposures that threaten fetal health. After identifying specific risks, preconception genetic counseling should present options, including the decision not to have children, adoption, assisted reproductive technologies, carrier detection tests, presymptomatic diagnosis and predictive genetic testing, preimplantation genetic diagnosis, and folic acid supplementation in periconceptional period.

Ethical issues in prenatal genetic counseling

Although prenatal genetic counseling and testing are originally aimed at diagnosing the genetically affected fetus at an early time-point, the demands of the modern society sometimes point to the need for healthy, "perfect" babies [34]. In addition, the application of prenatal genetic testing and counseling raises several *ethical questions for consideration*:

- Prenatal diagnosis should not be withheld for social or financial reasons.
- Thorough counseling must be provided and informed consent should be obtained for all procedures.
- The attitude of the woman toward abnormal results of prenatal diagnosis should be ascertained in advance; however, she should be provided with the diagnosis even if she had refused to agree to pregnancy termination in advance.
- The results of prenatal diagnosis should be kept in strict confidence, so the information on disease could not be used for the justification of withholding normal medical services.
- To support voluntary decision-making, the pregnant woman should not be put under pressure to reach any specific decision after obtaining abnormal prenatal diagnosis.
- Diagnostic tests are generally performed for the benefit of the person affected by the disease while avoiding any harm that might be greater than the expected benefits. However, invasive prenatal diagnostic methods may harm the fetus, although the benefits are not always clear.
- The question who is the beneficiary of prenatal testing, the pregnant woman, the fetus, or both? Some people believe that mostly it is the woman; however, this is not always true. Frequently, prenatal testing is for the benefit of the fetus to not be born with severe congenital disorder ultimately resulting in death or life-long suffering. Therefore, the tested disorder should be severe or incompatible with life and relevant to the welfare of the fetus. Societal consensus would be helpful but challenging to achieve. The ethics of genetic counseling therefore remain a central guiding consideration.
- The pregnant woman should understand that some detected disorders are treatable and not expected to affect the child's future quality of life [35]. However, in most cases prenatal diagnosis does not detect treatable conditions of the fetus; treatment is available for only a few diagnoses. For

example, fetal anemia due to isoimmunization can effectively be treated, some immunodeficiency conditions can be cured by bone marrow transplantation, and fetal hemophilia can warrant physicians to avoid procedures during obstetric management, which may harm the fetus (e.g., scalp sampling). However, fetal therapy is not expected to be available in the near future for treating chromosome aberrations; thus, pregnancy termination will remain an important option.

- Termination of pregnancy can sometimes prevent the birth of a child with a congenital disability. The ethics of termination for such conditions is controversial [36]. For example, for some, life with Down syndrome is considered worth living, meaning that selective termination would not constitute benefit or avoidance of harm for that child. For others, termination of pregnancies involving trisomy 21 is readily accepted and even encouraged. Then there is the question of how families that decline testing or accept the birth of a child with Down syndrome will deal with a society that is less welcoming and supportive of intellectually disabled children [36]?

Nondirective or directive counseling

Because of the above-mentioned key ethical issues, it is critical how genetic counselors give information and advice for the couples. Pregnant women and their partners will base their decision on the information and advice given by these professionals in the light of their own individual circumstances and attitudes [35,37,38]. Counseling can follow two principles: the more widely used nondirective genetic counseling and directive genetic counseling [39–42].

Despite patients generally expecting and even demanding a decision-shaping process closely guided by physicians, there is a widespread support among genetic counselors for the nondirective method and neutrality in genetic counseling [43,44]. In a nondirective approach, information is presented with no bias and no recommendations about continuation of pregnancy. This approach arises from concerns about early abuses by the eugenics movement of the right to privacy and autonomy in reproductive decisions. In addition, nondirective counseling is more widely accepted and more easily defendable in the current era affected by professional liability.

Using the nondirective method, the counselors have to thoroughly describe the disease in question and the possible risks and prognosis; inform the patient about the risk of occurrence and/or recurrence, the consequences, the available choices, and the purpose and nature of the intervention; and describe and offer diagnostic alternatives. These have to be provided in a fashion that patients seeking counseling can understand the basic facts to avoid fear and anxiety that can be promoted by an opinion expressed in mystical, complicated sentences that are incomprehensible to almost all patients. Then the pregnant woman and those she wants involved have to make decisions, with counselors leaving to patients whether they intend to use an intensive interactive process with the counselors to arrive at their final decision [28,39,41,45].

Discussions on the desirability and practicality of nondirective and value-neutral counseling have questioned whether it would ever be possible to achieve such a counseling [46–48]. Moreover, empirical studies have shown that the practice of genetic counseling is not characterized as uniformly nondirective [42]. Genetic counselors always have the freedom and power to influence clients by selecting to discuss one aspect of a situation while ignoring or downplaying another, and genetic counseling sessions are always context dependent. For example, the information on Down syndrome included in a preamniocentesis counseling session can differ considerably from that given in a session concerning a neonate with Down syndrome [49].

A literature review provides no evidence that a nondirective approach benefits the clients [50], and another showed the lack of association of nondirectiveness with client satisfaction, fulfillment of client expectation, and self-reported client anxiety and concern [42]. Some patients may welcome directiveness as they reported a higher perceived risk associated with more neutral counseling. In addition, the majority of individuals with certain genetic diseases would like to know the opinion of the genetic counselor with regard of undergoing termination of pregnancy after a positive prenatal diagnosis result.

As a result, a partnership model has evolved that incorporates high levels of both provider and patient participation in decision-making [51], which acknowledges patients' needs, desire, and role in decision-making without advocating physicians to abdicate their role in providing recommendations when patients would welcome them. In this model, patients are assisted in reaching an informed and

autonomous decision that meets their preferences and needs in the decision-making process. In addition, supportive counseling by social workers and clinical psychologists affiliated with prenatal genetic counseling centers can help consultants in their decision-making process.

Factors influencing decision-making

The woman's decision will depend on a number of factors such as optimistic or pessimistic attitudes, ethical and religious principles, level of education, social circumstances, and previous experience with the disease. One compelling argument is when a couple declares that they do not want to undergo another tragedy. Often couples coming for genetic counseling are full of fears and anxiety, burdened with the memory of one or more affected or dead child. Thus, couples appreciate the opportunity for a counseling session and discussion [12,42,47,52,53], and the offer for prenatal diagnosis will be accepted by most of them [54,55].

The personality of the counselor is of importance. The content and clarity of the information and how this information is imparted are very critical, in addition to the manner in which the couple's questions, fears, and problems are addressed. Because decision-making is very difficult and painful for some couples and decisions will often have lifelong consequences, the counselor should help the couple to the best of his or her ability. It is essential for the counselor to present clear and full description of the relevant disorder and answer all questions honestly and promptly. A good and harmonious relationship is necessary between the counselor and the couple for the proper help and management. The counselor-family relationship, which deepens in the course of counseling, greatly depends on the character of the individual physician.

The option of further pregnancies includes the option of prenatal diagnosis, which in turn, includes the option of pregnancy termination. Most couples in at-risk situations will have a healthy child and only a few will go through the trauma of one or several terminations. Couples identified by screening as “high risk” may be at high risk (~25%) in cases of monogenic traits, at a lower risk (~10%) if identified through positive biochemical tests, or at relatively low risk (~1%) if identified by maternal age [56]. The designation of “high risk” should therefore be used carefully and explained. The decision on pregnancy testing and termination must be the couple's own, and the counselor's duty is to support and to inform but not to persuade.

Despite the information from the counselors, some couples refuse the idea of interrupting pregnancy for religious or other reasons. Regarding this situation, the question arises whether anybody has the right to insist on the birth of a child who will suffer from an undoubtedly incurable disease and also severely burden public finances. There is no doubt that the right to make individual decisions must be respected and that genetic diseases do not threaten the health of other people and endanger society directly unlike some infectious diseases [57–59]. Given the uncertainty and high variability of the social dimensions of the birth of an affected child, such circumstances should play no role in genetic counseling.

Prenatal testing

The neonate is no longer our youngest patient. Fetal medicine has emerged as a scientific discipline, and the fetus and its chromosomes, enzymes, and individual genes can be examined *in utero*. The currently used prenatal tests include amniocentesis, chorionic villus sampling, cordocentesis, noninvasive biochemical, genetic tests, and especially ultrasound, which enables recognizing major fetal anatomical defects [1]. These prenatal screening and diagnostic methods have demonstrated revolutionary progress and have become indispensable components of modern obstetrical care. Screening tests have been able to lower the anxiety of some patients, but it was prenatal diagnostics that made the real breakthrough in the practice of genetic counseling. There is an inevitable necessity during counseling to explain the differences between screening tests and diagnostic methods because society mistakenly confuses the two and attributes equal importance to them. This can result in erroneous decisions in the daily routine practice because many patients regard the reassuring results of the screening tests as negative diagnosis. However, screening tests are only performed to assist in identifying those who face a higher than average risk of certain pathological conditions and who therefore

should be offered diagnostic evaluation. Of importance, certain procedures may serve as screening methods in some cases, although they can have a diagnostic value in association with a given disease (e.g., ultrasonography).

Ultrasound

Ultrasonography is a widely used tool for the detection of fetal anomalies, and fetal ultrasound screening has become routine practice in many countries [60,61]. Novel developments include high resolution and transvaginal probes and 3D/4D technology, which enable the visualization of the embryo as early as 5 weeks gestation [62]. The establishment of accurate gestational age, the detection of fetal anomalies and multiple gestations, the accurate determination of chorionicity, and the use in postdate pregnancies and labor induction are proven benefits of routine ultrasound. However, controversy exists regarding the practice of routine obstetric ultrasound with objections to its use that inadequately addresses the central ethical principles of beneficence and respect for autonomy. The putative harms involve a theoretical risk of fetal damage from ultrasound exposure and false-positive diagnoses yielding unnecessary interventions and potential maternal anxiety. However, no *in vivo* data exist to suggest that diagnostic two-dimensional ultrasound, performed skillfully and within reasonable time constraints, is harmful. Thus, the benefit/risk calculus of routine prenatal ultrasonography supports its use and fulfillment of ethical principles of beneficence and respect for patient's autonomy [61].

During the last two decades, ultrasound screening has frequently led to situations characterized by clinical uncertainty due to the disclosure of soft markers (minor anatomical variations) in the fetus. Ethical challenges have thus emerged as a direct result of advancing medical technology, and healthy fetal lives have been lost due to invasive diagnostic testing aimed at resolving this clinical uncertainty. Ultrasound examiners have warned against a policy of disclosing all findings of soft markers to expectant parents, but no exploration of the disclosure of fetal soft markers has yet been published [63].

Biochemical markers

Given the advances in prenatal screening, maternal age should no longer be used as a solitary indicator for offering women invasive procedure for karyotyping. Prenatal screening using maternal serum biomarkers in midtrimester is a mature clinical process and maintains an important role in obstetrical care. The quad marker test involves the assessment of AFP, hCG, inhibin-A, and unconjugated estriol to assign a numerical risk for having a fetus with Down syndrome. With the advent of first trimester ultrasound (i.e., nuchal translucency) and serum biomarkers (PAPP-A, free-hCG), it is probable that a proportion of pregnant women will seek earlier screening and that, depending on their choice, the volume of second trimester screening might decline. However, new tests that integrate first- and second-trimester markers into a single risk estimate that is reported in the second trimester show major promise and provide the best possible screening performance. For women having this integrated test and for those who present for prenatal care later than the first trimester, the second trimester biomarkers will continue to be an important resource [64].

In decision-making about risk assessment for chromosomal anomalies, clinicians should be guided by transparency about such risk assessment. It is now well established that first trimester screening, for which nuchal translucency and biochemistry are accepted as the standard, is a reliable tool for the risk assessment of the risk of trisomy 21. First trimester risk assessment is thus medically reasonable and should be offered for all pregnant women being evaluated for prenatal care in the first trimester. The concept of risk assessment should be clearly explained, with emphasis that risk assessment is not diagnosis. To respect the patient's autonomy when making the offer, however, the physician or counselor should not express or imply any expectation for the acceptance of risk assessment and should not imply that either refusal or choice of invasive diagnosis is any less acceptable than accepting risk assessment. An algorithm has been offered to guide the process of decision-making from risk assessment to diagnostic measures [38].

Prenatal genetic testing

The completion of the *Human Genome Project* in 2001 was an incredible accomplishment [65,66], leading to the continuing identification of genes associated with human disease. The development of new technologies has made it possible to study these genes, search for disease-causing mutations, and develop genetic tests [67]. Genetic testing has the potential to offer dramatic benefits for patients and their families, both clinically and psychologically. The array of benefits begins with the clarification of diagnosis and prognosis, which assists in decision-making about clinical care. Genetic testing for familial mutations is available by predictive, carrier, and prenatal testing, all of which provide risk assessment for family members of an affected patient to assist them in making complex personal, medical, and reproductive decisions. In addition, there are a multitude of genetic tests available to those with no family history of genetic disease, which can provide information about potential reproductive or future health risks.

The process of ordering genetic testing can be complex and often bewildering for healthcare professionals because of the challenges related to test selection, laboratory choice, standards of practice, and ethical issues. In general, genetic counselors receive requests for genetic testing for disorders for which gene identification has only recently been reported in the scientific literature. Often these requests arrive from primary care providers, but they also increasingly come from family members who follow scientific research on the particular genetic disease that has been diagnosed in their family. The immediacy with which peer-reviewed research findings are available on public internet sites speeds this process [31].

Historically, the broad categories of genetic tests have been cytogenetic tests, molecular tests, and biochemical tests. Generally, cytogenetic tests detect changes in chromosome number, structure, and arrangement. Molecular tests look for changes in DNA sequence, epigenetic modifications, deletions, and duplications. Biochemical tests detect changes in gene products, such as changes in levels of enzymes, proteins, and metabolites. Evolving technologies have led to considerable overlap between these categories of genetic tests as there are cytogenetic tests that actually use molecular/DNA methodologies, such as FISH (fluorescent *in situ* hybridization) and chromosomal microarray analysis (CMA, also known as comparative genomic hybridization). Genetic tests have different clinical applications, and these influence the specific technology selected [31].

Advances in technology and genetic knowledge are likely to enhance the importance of prenatal testing in future obstetric practice. Because of the complexity of the aspects associated with prenatal genetic testing, it will increasingly be necessary for providers to understand the ethical, legal, and social issues that affect the use of prenatal genetic testing. The most important of these include the provider's duty to obtain informed consent from and offer prenatal genetic counseling to patients, the standards for establishing negligence, and genetic discrimination [68]. With the clinical introduction of new genetic tests, issues of patient education, result interpretation, and genetic counseling must be anticipated and strategies must be adopted to allow the implementation of the testing with maximum benefit and minimum risk [69,70]. Currently, it seems doubtful that patients can adequately be counseled for routine prenatal microarray in most cases because of the low level of current knowledge on the natural history and range of clinical variability associated with most submicroscopic copy number variants [71].

Noninvasive prenatal genetic testing

The seminal discovery by Lo et al. 20 years ago described that cell-free fetal DNA (cffDNA) is present at considerable concentrations in the maternal circulation [72]. It is primarily derived from the placenta, can be detected in maternal serum from the 7th week in an increasing concentration as pregnancy progresses, comprising 3-13% of total cell-free maternal DNA, and can be used to determine the genetic characteristics of the fetus [72–74]. Although a recent meta-analysis suggested that invasive tests (i.e., amniocentesis and CVS) have only minimal procedure-related risks of miscarriage (0.11% and 0.22%, respectively), obtaining information noninvasively about a conceptus at an early stage is continuing to be the holy grail of prenatal diagnosis [75,76]. The use of cffDNA in maternal blood for the detection of fetal RhD antigen status, gender, single-gene disorders, and common

chromosomal aneuploidies is now well established [73,77–79], although cffDNA-based noninvasive prenatal testing (NIPT) for fetal aneuploidies is considered a screening and not a diagnostic tool [78,79]. The rise of massively parallel sequencing (MPS) has enabled NIPT to test for chromosomal aneuploidies with unparalleled robustness. In addition, MPS-based NIPT tests for microdeletions, microduplications, and single-gene disorders have also been developed, and the number of these applications has steadily been increasing.

Current NIPT methods implicated in clinical practice include shotgun MPS (s-MPS), targeted MPS (t-MPS), and single nucleotide polymorphism (SNP)-based targeted MPS [78,80]. s-MPS relies on the simultaneous random sequencing of millions of genome-wide fetal and maternal genomic fragments. Then sequence reads are mapped to chromosomes, and bioinformatics algorithms are utilized to calculate normalized values for each chromosome. In case of fetal trisomy, there is a relative excess of reads for a given chromosome, whereas fetal monosomy is accompanied with a deficit in the observed distribution of reads of chromosomes compared to the expected distribution of reads for euploid cases. Because the fetal fraction of cell-free DNA is low in most cases and the excess or deficit of DNA fragments is small, large numbers of sequence reads are necessary for the analysis. t-MPS focuses on the analysis of certain loci on selected chromosomes (e.g. 13, 18, 21, Y). The selected genomic regions are first enriched by hybridization-based capture and then amplified by highly-multiplexed PCR. The amplified regions are then massively parallel sequenced. Patient-specific risk scores for trisomies are then generated by statistically adjusting the results for the fetal fraction of cell-free DNA combined with maternal and gestational ages. The *SNP-based targeted sequencing* relies on DNA polymorphic differences between the pregnant woman and fetus. Using buffy coat (maternal DNA) and maternal plasma (maternal and fetal DNA) samples, multiplex PCR amplification of ~20,000 SNPs is performed followed by MPS. After considering chromosomal SNP positions and the possibility of recombination, a maximum likelihood is calculated for each option, and the results are presented as risk scores.

The efficacy of NIPT for common autosomal trisomies exceeds that of conventional screening; however, discordance may still exist between NIPT results and fetal karyotype because of fetal and/or placental mosaicism, maternal karyotype abnormality, insufficient sequencing read numbers due to low fetal fraction, and a vanishing twin. NIPT methods are not equivalent in detecting chromosomal abnormalities [78]: s-MPS and t-MPS involve greater sequencing depth and have greater efficacy when fetal fraction is low or when testing for small copy number variations (CNVs). t-MPS can possibly have greater sequencing depth for chromosomes of interest while requiring lesser DNA sequencing (lesser by an order of magnitude) and lower cost than s-MPS. The advantages of the SNP-based method include the need for less cffDNA, the exclusion of maternal imbalances, the identification of additional haplotypes indicative of undetected multiple pregnancies, the detection of parent of origin of aneuploidy, diandric triploidy, nonpaternity, consanguinity, uniparental disomy, and genetic abnormalities such as short insertions/deletions/aberrations that cause Mendelian disorders [76].

Because of the continuing developments in sequencing technologies and the reduction in sequencing costs, NIPT has been playing an increasingly important role in prenatal testing and risk stratification of fetal conditions and likely will become the standard of care. As summarized by the American College of Obstetricians and Gynecologists Committee Opinion "Noninvasive Prenatal Testing for Fetal Aneuploidy," cffDNA testing should be an active, informed choice and not part of routine prenatal laboratory testing [81]. It should be emphasized to patients that NIPT is a screening and not diagnostic test and does not replace the accuracy and diagnostic precision of prenatal diagnosis with CVS or amniocentesis. Additional practicalities to be considered have to include pretest counseling about the scope and accuracy of NIPT, the interpretation of results when there is a low fetal fraction of cffDNA, and follow-up studies for positive test results.

Preimplantation genetic diagnosis and screening

Preimplantation genetic diagnosis (PGD) has been developed since 1989 primarily for the identification of aneuploidies and other genetic disorders or defects in human zygotes and pre-embryos created by *in vitro* fertilization (IVF) prior to their implantation for gestation [82]. As an alternative to traditional prenatal genetic diagnosis, PGD is an attractive way of preventing genetic diseases, currently making it possible to select against more than hundred different genetic diseases. PGD can

overcome the most sensitive issue in avoidance of genetic disease, the need for termination of the affected fetuses, by the selective destruction of extracorporeal human pre-embryos and the selection of chromosomally normal pre-embryos for embryo transfer [3]. As a matter of general principle, prevention of the birth of a genetically or otherwise diseased or disabled child is a morally legitimate goal. Nonetheless, strong moral objections have been made to the use of PGD to determine conditions that cannot plausibly be called "diseases," such as sex and the absence of desirable physical, mental, or social characteristics.

The selection of an embryo's sex using PGD is performed for two reasons: (1) preventing the transmission of sex chromosome-linked genetic disorders and (2) achieving gender balance in a family with more than one child or the preferred birth order of children by sex or providing a parent with a child of the sex he or she prefers to raise. Although little ethical debate exists regarding the former point, the latter is the subject of heated ethical disagreement [83].

Another area of intense debate is on creating a tissue-matched child, a *savior sibling*, who can serve as a compatible stem cell donor to save a sick sibling in need of a hematopoietic stem cell transplant [84]. Fertilized zygotes are tested for genetic compatibility and for genetic diseases, and then only zygotes that are HLA-matched with the existing child and free of the disease are implanted, so the couple can avoid the uneasy decision of terminating the pregnancy if the fetus is a nonmatch and/or having another child in the hope of the next one will be tissue compatible. A *savior sibling* may be the solution for monogenic diseases such as Fanconi anemia and beta-thalassemia or for cases of childhood leukemia. Many have opposed the use of PGD for this purpose as it is also associated with conflicting interests including religion, ethics, and legal regulation. Some jurisdictions have created legal frameworks to regulate the use of this technology, mostly based on the model of the UK's Human Fertilisation and Embryology Authority, which ruled that it is lawful to use PGD for the creation of savior siblings. It is fundamental to have such legal frameworks to be established everywhere to adequately regulate the use of PGD and guard against misuse of the technology. From an ethical perspective, arguments for or against the creation of savior siblings are based on key issues including the commodification and welfare of the donor child. One of the major ethical arguments against the use of this technology is the possible exploitation of the child, such as the potential adverse psychologic effects on a child born not for itself but to save another.

Termination of pregnancy because of genetic indications

Challenging moments of genetic counseling arise when a decision has to be made on the disposition of a pregnancy. The goal of nondirective counseling is to inform the patient about the option of termination of pregnancy when a fetal anomaly has been diagnosed. From the pregnant women's point of view, these can be ethically challenging decisions.

The moral status of the fetus (i.e., whether there is an ethical obligation to protect the fetus is such a strength as to override respect for the autonomy of the pregnant woman) is at the center of debates, not only within professional circles but also as a political issue. The Roman Catholic Church has a well-defined attitude in this regard, which can stir a lot of debates even within that faith community. The Church does not accept termination of pregnancy as a legitimate option, with only a few exceptions. These do not include the diagnosis of a fetal anomaly. Nonetheless, it is ethically obligatory to present the results of prenatal diagnosis to Catholic patients and counsel them nondirectively. Nondirective counseling in this context includes refraining from making any assumptions about whether Catholic patients will accept the Church's position.

The weight of ethical challenges of the decision about termination can depend on the gestational age of the pregnancy. Decisions about severe conditions detected in the first trimester are easier for some women [85]. However, most diagnoses are made in midtrimester, and by this time, a close relationship may have developed of the expectant woman toward her fetus. The need for making a decision can become more ethically challenging. In such situations, the counselors' task is nondirective: provide with her the relevant facts, help her considering these facts calmly and thoughtfully, and encourage her to developing an informed view about the future of an effected child. If the woman opts to continue her pregnancy, she will need to be briefed on what sort of aid she can rely on including medicine, social services, and family care. Women who decide to terminate the

pregnancy should be accurately informed about the procedure so that they can make an informed decision about it. It must be stressed that upon opting the termination of pregnancy, the procedure should be initiated as early as possible, especially when legal limits are being approached. The methods used for midterm abortions vary from country to country [85]. Third trimester abortion is justified if the fetus will be unable to survive after birth even with intervention and the woman requests termination of pregnancy [86,87].

Multifetal pregnancy reduction (MFPR) has become a well-established and integral part of dealing with multifetal pregnancies, especially those resulting from assisted reproduction. Accumulating evidence has provided data on the risks and benefits of this procedure and also an understanding that the risks increase with the starting and finishing number of fetuses in multifetal pregnancies [88].

Regardless of the method of termination, a major goal is to get the procedure done within the shortest possible time and in the least intrusive and safest way. The patient may want to get back to her home as soon as possible to be able to deal with the tragedy with her loved ones. Importantly, access always must be made available to post-termination counseling to help her and her family to cope and plan [28,39].

Post-termination fetopathology

Prenatal diagnosis of fetal anatomy by ultrasound in late first and early second trimesters has become a key factor leading to the termination of pregnancies. Even in centers with a high rate of accurate prenatal ultrasound scans, a considerable percentage of fetuses with reliably diagnosed anomalies have additional defects, which cannot be recognized by ultrasound. Fetopathology is the specialty concerned with causes and mechanisms of reproductive loss. At the post-termination autopsy, fetopathologists focus on tiny anatomic details to find these additional defects and help refining pretermination diagnosis. It should be emphasized that the placenta should be submitted to the pathologist following all terminations and pregnancy losses so that pathologists can evaluate it in the context with clinical history and postmortem fetal findings. The precise description of clinically suspected anomalies, the fine details of dysmorphic features, and the final diagnosis are essential for the correct estimation of recurrence risk to guide surveillance in subsequent pregnancies. Discussion about postmortem findings at regular fetal pathology/dysmorphology meetings is also recommended for education purposes as part of a multidisciplinary approach. In these ways, fetopathology can serve to improve the quality of care for individual and public health [89,90].

Ethical challenges of genomics for perinatal medicine

It is often important to take into account both the genotype (genetic makeup) and the associated phenotype (observable traits, characteristics, and symptoms) in genetic testing. In an “ideal” genetic test, there is a one-to-one relationship between the genotype and phenotype. However, a genetic test may be able to accurately identify changes in genotype, although it can be limited in its ability to predict phenotype, particularly the type and severity of symptoms, age of onset, and disease course. This limitation in predicting outcome can particularly be challenging and requires that genetic counselors use a wide variety of critical thinking, educational and counseling skills in discussing these testing issues with the patients. Because genetic testing is now widely available for diagnostic confirmation, predictive testing, carrier, and fetal risk assessment, genetic counselors have a key role in the evaluation and explanation of the limited clinical usefulness of these tests as they work with patients and their families to assess the medical and personal benefits and the risks of undergoing testing.

Genetic counselors' critical thinking and assessment skills are needed for determining whether genetic testing is clinically indicated and for selecting the type of genetic test and appropriate laboratory. Genetic counselors must be knowledgeable about the test validation procedures and laboratory variability. Their thorough consideration of the clinical utility of the genetic test and patient-focused genetic counseling should precede the use of any genetic test. To appropriately select a diagnostic laboratory for their patients, genetic counselors must know the rapidly evolving standards by which clinical laboratories are certified, the laboratories' accreditations, professional guidelines, participation

in proficiency testing, experience with the particular test being considered, the specific technology utilized, and the increasing involvement and oversight of government agencies and interested entities from the private sector. These considerations are especially important before the utilization of new technologies, which may have a higher likelihood of inconclusive test results, or before the use of genetic tests, which may have outcomes directly influencing medical interventions.

Because genetic counselors play a key role in ensuring that their patients receive optimal genetic testing, they should continue to actively participate in research aimed at evaluating the impact of genetic testing outcomes and work with other stakeholders in defining enhanced oversight of genetic testing and global practice guidelines for the appropriate use of genetic tests [43,91–93]. The *"Budapest Declaration"* of the *International Academy of Perinatal Medicine* in 2007 [67] offered the ethical framework for genomics in prenatal testing and counseling, emphasizing that "ethics is an essential component of genomic assessment of the fetus. Perinatologists have resources in medical ethics adequate to guide them in leading responsible change. These resources include the ethics of informed consent, the enhancement of patient autonomy, protection of professional integrity, fiduciary responsibility to pregnant and fetal patients, and advocacy for access to fetal genomic assessment." The challenges of responsible innovation in prenatal screening with NIPT were recently addressed by the *position document of the joint European Society of Human Genetics and the American Society of Human Genetics* published in 2015 [94]. This provides with recommendations regarding responsible innovation in NIPT, emphasizing that "NIPT has the potential of helping the practice better achieve its aim of facilitating autonomous reproductive choices, provided that balanced pretest information and non-directive counseling are available as part of the screening offer." Furthermore, "This document argues for a cautious expansion of the scope of prenatal screening to serious congenital and childhood disorders, only following sound validation studies and a comprehensive evaluation of all relevant aspects." Moreover, "in countries where prenatal screening is offered as a public health program, governments and public health authorities should adopt an active role to ensure the responsible innovation of prenatal screening on the basis of ethical principles."

Predictive genetic testing and presymptomatic diagnosis

Human genome projects

After the "*Human Genome Project"* provided researchers with the reference sequence of the human genome [65,66], genomics research has been accelerated with the "*1000 Genomes Project."* This created the largest public catalogue and global reference for human variations and genotype data by reconstructing the genomes of 2,504 individuals from 26 populations [95]. China's BGI, the world's largest genomics research company first announced the sequencing of a million human genomes, and then the US president announced the *"Million Genomes Project."* Despite these large sequencing efforts, the first genome "millionaire" is the company 23andMe, which has surpassed processing the millionth customer-submitted genomic sample in 2015. Because of the increasing number of these "million genome projects," it has recently been suggested that several billion human genomes may be sequenced by 2024 at the current rates of sequencing, which raises serious questions about medical, ethical, and legislative aspects of these advancements in genomics.

Genetic testing for late-onset diseases

Predictive (susceptibility) testing is the use of a genetic test that identifies healthy individuals who may have inherited a genetic predisposition that puts them at an increased risk of developing a multifactorial disease (e.g., Alzheimer disease, cancer) but who may never develop the disease in question [96]. It is sometimes called "*predisposition testing*" in case of testing mutations with less than 100% penetrancy. *Presymptomatic diagnosis* refers to the identification of healthy individuals who may have inherited a gene for a late-onset monogenically inherited disease and may develop the disorder if they live long enough (e.g., Huntington disease) [97,98]. Microarrays could potentially include probes for an extended spectrum of mutations and polymorphisms for a large set of late-onset diseases, dramatically complicating an already controversial genetic and social counseling problem [99].

The hope underlying such tests, which differ in fundamental ways from conventional medical diagnostic tests, is that early identification of individuals at risk of a specific condition will lead to reduced morbidity and mortality through targeted screening, surveillance, and prevention. However, the clinical utility of predictive genetic testing for different diseases varies considerably. Predictive genetic tests inform us only about a future condition that may develop. The identified risk is sometimes high but always contains a substantial component of uncertainty, not only regarding whether a specific condition will develop but also regarding when it may appear and how severe it will be. Predictive genetic tests often carry another element of uncertainty on that the interventions available for individuals at risk are often untested and recommendations may be based on presumed benefit rather than observed outcomes. These uncertainties contrast with the presentation of predictive genetic testing in the media, which often fosters an illusion that genetic risk is highly predictable and determinative. In fact, inherent uncertainties in most genetic tests represent a major limitation to their clinical utility.

As an example, some breast and ovarian cancers result from the inheritance of mutations in the *BRCA1* or *BRCA2* genes. Predictive genetic testing for breast and ovarian cancer, such as for hereditary non-polyposis colon cancer, can be useful to identify those at increased risk. In both breast and ovarian cancers, however, the utility of such a test is limited because of considerable uncertainty about the predictive value. A woman carrying a mutation in the *BRCA1* or *BRCA2* gene may develop breast cancer, ovarian cancer, breast and ovarian cancers, or no cancer at all. Penetrance estimates range from 36% to 85% for breast cancer and 10-44% for ovarian cancer. Moreover, the age at which cancer may occur is widely variable. These uncertainties probably reflect a combination of factors, including the environment, modifying genes, the nature of a woman's specific mutation, and purely stochastic processes.

Whereas conventional diagnostic testing rarely has medical importance for anyone other than the person tested (except in cases of communicable diseases), predictive genetic testing typically has direct implications for family members of the patient. Although concerns for relatives may be an important motivating factor for a patient's desire to undergo such testing, some family members may resist participating in testing because they would rather not have information about their genetic risk. The utility of a predictive genetic test will therefore depend on whose point of view is considered. These concerns can heavily be affected by other factors such as the media and the increasing amount of information available online about direct-to-consumer (DTC) genetic tests.

Legislation and government regulations of predictive genetic testing

Predictive genetic testing for breast cancer got into a major focus due to the *"Angelina Jolie effect,"* with the decision of the actress to have genetic testing for the *BRCA1* gene and subsequently undergo risk-reducing mastectomy. This induced a dramatic and immediate increase in traffic to the U.S. National Cancer Institute's online resources on genetics of breast and ovarian cancer and preventive mastectomy. In addition, there was an immediate, global and long-lasting increase in referrals for BRCA1/2 testing and risk-reducing mastectomy [100,101].

With the availability of inexpensive genetic testing, several commercial companies pursued a niche market for personal genetic testing and have started to offer DTC genetic tests. These are ancestry, diagnostic, preconceptional carrier, nutrigenomic, or pharmacogenomic tests and those indicating a predisposition to common disorders or profiling a risk to addiction. Companies selling these argue that individuals have a fundamental right to access information about their genetic information and market these tests by offering consumers the ability to monitor or improve their health conditions. They also argue that these tests guarantee better privacy than those provided inside the traditional healthcare systems. Autonomy, convenience, empowerment, prevention, and privacy are the major marketing keywords of these DTC tests. However, several criticisms have been made about the provided services. These include the operation of most companies without the involvement of healthcare professionals, the lack of individualized medical supervision, the doubtful quality of pre- and post-test information provision and genetic counseling, and the inappropriate genetic testing of minors. In addition, there are concerns regarding the limited predictive value,

clinical validity, and utility of various DTC tests and the lack of respect for privacy and the potential burden on public health care resources [102].

Because of these concerns, professional organizations and governmental agencies in Europe have published statements to educate and warn consumers about DTC genetic tests, including recommendations to ensure test service quality, provision of pre-test information and genetic counseling, and individualized medical supervision. Commonly, legislation in many countries specified that genetic tests should be offered only under medical supervision and with genetic counseling and that individuals should be given the opportunity to make their decisions freely based on adequate information about the limitations of DTC genetic tests and their implications. In the US, the American Medical Association suggested to the American Food and Drug Administration (FDA) that "genetic testing, except under the most limited circumstances, should be carried out under the personal supervision of a qualified health-care professional, and provide individuals interested in obtaining genetic testing access to qualified health-care professionals for further information" [102].

The DTC genetic testing debate reached its peak in November 2013 when the FDA instructed 23andMe to discontinue marketing and sale of their Personal Genome Service until it receives FDA marketing authorization [103]. As it is one of the largest DTC genetic testing companies that lead the field, the FDA's action had huge implications. Responses have either supported the FDA's action for the protection of consumers from potentially invalid information or insisted that the FDA's action violates the rights of individuals to receive information and undermines democratization of health care. However, DTC genetic tests have finally been accepted in the regulatory and medical communities. In 2015, the FDA reclassified carrier tests as Class II devices and approved 23andMe's carrier test for Bloom syndrome. Moreover, the National Society of Genetic Counselors' revised its position that people have every right to pursue DTC genetic testing with the warning that DTC companies have a responsibility to offer consumers easy access and/or referrals to appropriate resources and qualified genetics professionals. Experts agree that given the promise of precision medicine and the potential for genetic information to inform decision-making from preventive medicine to drug and therapy response, DTC genetic testing would represent a good path forward through an expert physician intermediary [103]. However, considering the likely rapid dissemination of predictive tests, there is an urgent need to develop a thorough and detailed legal framework. Prohibition cannot be allowed because it would deprive the individual of rather important information. Proper regulation would eliminate the situation of diametrically opposed interests among the parties and would make them interested in wide-ranging examinations.

Ethical challenges regarding predictive genetic testing

A study that explored women's decision-making preferences with regard to genetic testing for susceptibility to breast cancer found that most women wanted to hear their providers' recommendation about testing [104]. Women still wanted to make their own decisions either by choosing to follow the provider's recommendation or by vetoing it. If a provider did not give an expert recommendation, women believed that either the provider was not fulfilling its duty or they were not getting their money's worth. It has been suggested that concerns about autonomy should shift from focusing on whether the decision was made voluntarily to whether the decision-making process was entered voluntarily. Such a shift would preserve autonomy and empower patients as they are able to play their preferred role in decision-making.

Genetic screening is changing from Mendelian disease ascertainment to predictive testing. In parallel, we are also learning that phenotypes of even simple Mendelian disorders are influenced by complex genetic and environmental factors and genotypes rarely predict phenotypes [105], which have significant ramifications for counseling. For single-gene disorders with high penetrance, the information derived from such testing may be relatively easy to interpret and apply. For complex diseases, however, the populations studied and their demographic characteristics are extremely important for extrapolation to counseling of individual patients [106].

Several ethical concerns and questions arose with genetic counseling of predictive genetic testing. Do we have an ethical obligation to inform the patient about the existence of untreatable disease before

symptoms appear? Is it necessary to do so? Is this individual ill at all? Can or need populations to be screened for certain diseases? Indeed, the development of some diseases might be slowed down if changes in lifestyle were implemented. The knowledge, however, that the development of severe disease is inevitable in a later stage of one's life could put a heavy burden on a patient's everyday life and might even change an individual's personality. Living with the knowledge that one is expected to develop a malignant tumor by the age of 30–40 years is difficult [107–109]. Possessing the relevant information might result in more careful diagnostic examinations, which should have a substantial effect on the life expectancy [30].

At the same time, there are several questions raised about the person who is entitled to know the information. Is the individual affected and/or the relatives? One might think that only the individual affected should be entitled, but with the disease in question being a genetic one, are the relatives not affected too? Do they not have the right to know their risk? Is the parent obliged to tell his or her child? Can the child request the performance of a predictive test [110]? Can the parent make a decision on whether the examination should be performed for her minor child [111]?

It is also important that susceptibility testing and presymptomatic diagnostics in the absence of therapeutic options should be available only if certain conditions are met. It is pivotal to provide thorough information for the individual about the limits of testing that will contribute to enhancing the pathography and informing the family because in many cases, it is impossible to predict the onset and seriousness of a particular disease and its symptoms. Awareness of susceptibility could induce a change in lifestyle, which could prevent or postpone the development of a disease. If a disease is inevitable, the individual will have the chance of planning for his/her short life, as in the case of Huntington disease. Such genetic information can influence plans for marriage and having children [30]. The problem is further complicated by the shortcomings of available predictive genetic tests that carry a factor of serious uncertainty about whether a disease will develop and if it does, when exactly and to what extent. Given the onus of this information, if there is no medical advantage concerning prevention or treatment, these examinations can best be postponed until adulthood, when the individual is able to make decisions on crucial aspects of his own life.

Another important question is how likely it is that nondirectiveness will or should be upheld in the era of predictive testing for common adult-onset disorders. For several reasons, it is likely that most clients seeking genetic counseling in conjunction with predictive testing will be given directive counseling. This is because genetic counseling and testing will increasingly move into the primary care arena and will be provided by nongeneticists, and there is a perception on the part of nongeneticist physicians that patients want direction.

Summary

Genetics has made impressive progress in the past decades and in prenatal diagnosis. Because the subject of genetic counseling is of crucial consequence for both short and long terms, its ethical aspects are paramount. The question is whether mankind is mature enough to use this extraordinary knowledge in a responsible way for the benefit of patients and society. There is ethical consensus that patients should be provided with reliable, comprehensive information and counseled with the goal of the pregnant woman and those she wants to be involved to make an informed and voluntary decision. The results should be kept private, consistent with applicable law. Government oversight should be based on these ethical considerations.

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Conflict of interest

None.

Practice points

- Genetic testing offers dramatic benefits for patients and their families including the clarification of diagnosis and prognosis and assisting in decision-making about clinical care.
- Because of the complexity of aspects associated with genetic testing, it is increasingly necessary for providers to understand the ethical, legal, and social issues affecting genetic testing.
- New technologies have opened up the possibility of screening pregnant woman and fetuses for many genetic diseases and traits through prenatal, preimplantation, and predictive genetic tests, also dramatically increasing ethical concerns.
- Key questions in ethics of genetic counseling include those about the comprehensiveness and the way of counseling and whether and how sensitive personal information is treated and being made public.
- Nondirective genetic counseling is preferred for assisting patients in reaching an informed and autonomous decision on genetic testing appropriate for their life situation.

Research agenda

- To promote the understanding of providers of the ethical, legal, and social issues affecting genetic testing.
- To support the establishment of proper legislations for novel genetic tests and enable genetic counseling for direct-to-consumer genetic tests.
- To ensure comprehensive ways of genetic counseling and treatment of sensitive personal information.
- To advocate nondirective genetic counseling to patients and couples for reaching an informed and autonomous decision.

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