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REVIEW ARTICLE

IGF-1 biomarker testing in an ethical context

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***Abstract*:** As we have come to know, there is a connection between cancer biomarkers and genes, along with their susceptibility to a particular disease, all of which have an obvious impact on the clinical practice and development of genetic testing. In any cancer disease, the diagnosis and treatment should be related to the investigation of specific biomarkers (generally antigens and proteins) and their corresponding genes. The study of different antigens such as alpha-fetoprotein, insulin-like growth factor I (IGF-I), insulin-like growth factor II, vascular endothelial growth factor, and epidermal growth factor, as well as their presence in neoplastic cells have demonstrated that IGF-I is an essential target for gene testing and therapeutic purpose. An over-expression of the IGF-I gene in mature tissues is a sign of neoplastic processes, *e.g.* brain or breast malignancy. A lot of questions have arisen regarding the ethics of gene testing, particularly concerns on the selection of patients for specific growth hormone/insulin-like growth factor I (GHIIGF-I) testing. Evidently, our current society is involved in a process of geneticization – the redefinition of individuals in terms of genetic codes. As such, we should take extreme care when making ethical judgments based on "scientific evidence" derived from genetic testing (typically those involving different biomarkers such as DNA, RNA, chromosomes, and proteins) in relation to genetic abnormalities that could predict current or future diseases. In this situation, the understanding of bioethics is of utmost importance.

***Keywords*:** cancer; biomarkers; IGF-I; gene testing; bioethics

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Introduction

After demonstrating the convergence between ontogenesis and oncogenesis using alpha-fetoprotein (AFP) as a new biomarker of neoplastic development[1,2], the phenomenon was confirmed using another cancer biomarker–insulin-like growth factor I (IGF-I)[3,4], precipitated by the development of IGF-I testing[5,6] and the establishment of cancer gene therapy by applying the anti-IGF-I approach[7]. Using the IGF-I biomarker, which plays an important role in cancerology[7] as an example, this review describes the common ethical problems faced by genetic testing.

A biomarker or molecular marker is defined by the National Cancer Institute (NCI) as "a biological molecule found in blood, other body fluids, or tissues (including RNA and microRNA) that is a sign of a normal or abnormal process, or of a condition or disease." Biomarkers – especially those associated with genetic mutations or epigenetic alterations – help to identify early

stages of cancer, patient prognosis, treatment options, and response to therapy[8-14]. New array-based technologies such as comparative genomic hybridization arrays (CGH), single nucleotide polymorphism (SNP) arrays, and protein arrays, among other things, are powerful tools when identifying biomarkers. In fact, cancer studies using this kind of technology have identified genes that are involved with the initiation, promotion, progression, and treatment response of cancer, as well as improved the understanding of the biological characteristics of cancer cells. Finally, changes in micro RNA (miRNA) expression can also be a biomarker, *e.g.* an increase in *miR-206* and *miR-221* gene expression or a down-expression of the *miR-125b* and *let-7* genes[13,14].

As far as biomarkers are concerned, related genetic testing constitutes an important domain in clinical laboratory diagnostic. In this context, possible patents that are related to genetic testing should be discussed. The idea of patenting genes may seem absurd—as the "invention" is prior to the inventor, yet it is a reality. The United States, just 15 years ago, had at least 48 private companies with a minimum of three patents in class 435/6 (molecular biology involving nucleic acids)[15]. As of today, the genes of plants, animals, and humans have been patented[16,17]. While there is a scientific basis to patenting a method derived from the knowledge of one gene, it is contentious to patent a gene itself. If the human genome is (in a symbolic sense) a heritage of humanity (UNESCO, 1997)[18], then it is common property. In addition, there is great concern that gene sequence patents may hinder future biotechnological innovations in the medical field[19]. Under these circumstances, understanding bioethics is a priority. Jean Dausset, winner of the 1980 Nobel Prize of Medicine said in a personal correspondence with co-author Trojan J (unpublished, 2000): "Bioethics is an extremely important event in human consciousness. This stems from the extraordinary gap between concepts and technology due to the dazzling advances in biology and genetics."

IGF-1 biomarker

Certain antigens, which behave as oncoproteins, are present in normal fetal/neonatal development but are absent from mature tissues. Among them, serum albumin, transferrin, AFP[2], growth hormones such as epithelial growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-beta), and especially IGF I and II [20,21] reappear in neoplastic developing tissues[3,4,6,22] such as in brain, liver, prostate, ovarian, colon, and uterus cancers[23-27].

Comparative studies of different antigens such as AFP, IGF-I, IGF-II, VEGF, and EGF present in neoplastic cells[6,7,28] have demonstrated that IGF-I constitutes an important target for genetic testing and therapeutic purpose. The arrest of IGF-I expression diminishes or stops neoplastic development[7,29,30] due to the consequential apoptosis and anti-tumor immune response (MHC-I)[31-33]. These two phenomena, which play an important role in the mechanism of IGF-I, are barely present (if not non-existent) in other oncoprotein and growth factor mechanisms such as EGF, VEGF, or TGF-beta[34-37]. In terms of the growth factors involved in both ontogenesis and carcinogenesis, IGF-I may be a highly promising therapeutic and diagnostic target (400 publications/year). Similar to AFP, IGF-I is involved in tissue development and differentiation, especially in the development of the nervous system[1,38,39] as a mediator of growth hormone, thyroid stimulating hormone (TSH), and glucose metabolism, acting locally with autocrine/paracrine and has a predominant role compared to other growth factors[20,39-45].

According to Baserga[46], IGF-I is one of the most important growth factors that is related to normal and neoplastic differentiation, and its overproduction is considered to be a participating factor in cancer development[33,44,47,48]. IGF-I has been reported to block a number of apoptosis pathways (IRS/PI3K/AKT/Bcl, GSK3, Ca^{2+}, or caspases)[46,49-54]. Moreover, the mechanism of IGF-I depends on its receptor – IGF-I-R, which plays a predominant role in tumor growth processes[43,47-49,55]. IGF-I constitutes the first step of the following signal transduction pathway: IRS/PI3K-PKC/PDK1/AKT-Bcl2/GSK3/GS[56,57]. The elements of the aforementioned IGF-I-related transduction pathway were also considered as targets for diagnostic and therapeutic purposes[37,39,54,56,58-68]. The measurement of IGF-I and insulin-like growth factor-binding protein (IGFBP-3) often serves as first-line testing in children with growth disorders. The role of acid-labile subunit (ALS) as a screening parameter for homozygous or heterozygous mutations of the *ALS* gene has been recently determined[69]. The relationship between IGF-I and IGF binding proteins are being introduced in clinical diagnostics as one of the indicators of precancerous development[70]. The serum level of IGF-I (considered as a marker) was introduced in the diagnostic of breast cancer[71-73], prostate cancer[74,75], colorectal cancer[76-78], lung cancer[79-80], and pancreatic cancer[77,81].

The substantial individual variability in the circulating levels of IGF-I and binding proteins (especially IGFBP-3) may be important in determining the risk of developing

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malignant prostate, breast, colorectal, lung, and liver tumors[82-84]. Since the introduction of IGF-I in the 1990s as a breast cancer biomarker, another new biomarker – mammaglobin, a protein that is a member of the globin secreting family and contains lypophilin B was recently proposed for clinical diagnostic[14]. As far as the relationship between cancer and depression is concerned, elevated IGF-I serum levels have been found to be significantly associated with depression. This suggests that IGF-I signaling could play a role in the pathophysiology of depression and could possibly influence the response to antidepressant treatment[85].

Genetic engineering

Molecular biologists consider that the processes of living beings adhere to the laws of physics, chemistry, and protein chemistry[1,86-88]. However, life is characterized by high variability; especially when it comes to brain development, as demonstrated by the murine model of neoplastic central nervous system (CNS) development[22]. Major advances in molecular biology have led to the sequence hypothesis, from nucleotides to amino acids, which is consistent but independent of the laws of physics and chemistry[89]. Yet, should our fate be sealed by our genes and reduced to physics and chemistry? We should therefore take extreme care in making or accepting ethical judgments based on "scientific evidence"[90].

Molecular biology has allowed genetics to evolve a structure-function relationship. These findings generate deep questions about how biological structures operate, manage, and affect evolution[72,78,88,91,92]. Although molecular biology must always be consistent with physical and chemical processes, it cannot be derived from physics and chemistry alone[88,93]. Our knowledge of molecular and cellular biology techniques such as recombinant DNA and cloning has led to the development of a new domain – biotechnology. Biotechnology includes methods ranging from genetic engineering and genetic mapping to tissue culture hybridomas and genetically engineered vaccine. Genetic engineering has allowed the isolation and manipulation of genes to take place. Its impact has been particularly important as it has led to the creation of transgenic animals used as experimental models for research and the observation of genetic diseases, and to the creation of organic substances for therapeutic purposes through the process of enabling or disabling of a gene[6,27,94-97].

The creation in the early 1990s of a new medical domain, termed gene therapy, has become the most important revolution in the treatment of different diseases such as cancers, infections, and fetal diseases. Gene therapy is the logical consequence of genetic testing as both target the same gene and its related protein. The first gene therapy case approved in the United States took place in 1990 at the National Institute of Health (NIH)[98]. W. F. Anderson developed a treatment for his patient with a genetic defect that resulted in adenosine deaminase deficiency-severe combined immune deficiency (ADA-SCID). The effects were only temporary but successful nonetheless. In the same regard, the first stem cell gene therapy by C. Bordignon *et al.* was performed in 1992 at the Vita-Salute San Raffaele University, Milan, Italy, using hematopoietic stem cells as vectors to deliver genes intended to correct hereditary diseases[99]. Clinical trials resumed following regulatory review of the protocol in the United States, the United Kingdom, France, Italy, and Germany.

The first cancer gene therapy was introduced in 1992/93 at Case Western Reserve University (CWRU), Cleveland using the IGF-I antisense approach for the treatment of glioblastoma multiforme (GBM), the most common of human brain tumor whose outcome is always fatal[7] and the protocol was approved by NIH in 1993 and FDA in 1994. The modified strategy, using anti-gene (antisense/triple helix) anti IGF-I technology, has shown promising results in clinical trials; the median survival of glioblastoma patients reached 21 months and in some cases, reaching up to three to four years. This strategy was also proven to be efficient in the treatment of six different cancer diseases (as reported by the NATO Science program on cancer gene therapy: USA, France, Poland, Germany; 2002–2007)[27,39].

To target specific genetic defects, different kinds of molecules (antibodies, antisense oligodeoxynucleotides, antisense cDNAs, short peptides, and other small molecules) have been employed. The antisense technology has become one of the important anti-cancer approaches used in the last 10 years in preclinical and clinical studies of tumors, including GBM[39,68,100]. However, genetic engineering presents a certain level of risk to the environment, plant and animal species, and especially mankind owing to the lack of knowledge concerning the effects induced by genetic manipulations in organisms. For this reason, NIH and the Food and Drug Administration (FDA) generally avoid gene therapy protocols that propose adenoviral or retroviral vectors, suggesting instead the use of episomal vectors, which present a small risk of incorporating DNA derived from genetic engineering manipulation into the human genome[101].

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Genetic testing

Genetic testing involves analyzing DNA, RNA, chromosomes, proteins, and metabolite abnormalities that could predict current or future diseases[102,103]. In medicine, there is a tendency of using a genetic model to explain a particular disease, thus increasing the influence of genetic technologies in clinical practice[104]. The criteria which determines "who should be tested" depends on the type of disease; however, it is recommended that test subjects have a family history of at least three generations[105]. This effectively identifies high-risk individuals who would benefit from genetic testing and appropriate prophylactic measures, as well as early therapy, according to the 1996 report from the American Society of Clinical Oncology[106].

Genetic testing involves analyzing detailed family history, determining the type of test, and interpreting the results. Knowledge on available treatments and preventive measures is important for genetic counseling, which is an essential component in ensuring adequate data collection of family history, risks, and the selection of appropriate tests. Genetic counseling should be offered to all patients before and after genetic testing. Genetic tests have psycho-social implications owing to the risk of improper handling of information by insurers, as well as the loss of privacy and the potential to generate anxiety and/or depression in the patient and their family[107,108]. The use of genetic testing has improved the survival rate of people at risk. Advances in genetics and genetic testing are increasing rapidly, hence implying a greater responsibility in the management of patients undergoing predictive or diagnostic tests. As genetic testing involves patients and their family members, clinicians must be well-informed of the medical indications for genetic testing and the different available examinations, as well as having the ability to analyze and interpret the results.

IGF-1 gene test

There is a connection between genes and their susceptibility to certain diseases. Certain genes are related to different pathologies such as cancer, diabetes, hypertension, and obesity, among other things[109]. Some of these data have an impact on clinical practice, generating the availability of genetic tests. For example, knowledge of the genes responsible for colorectal cancer has resulted in improved genetic testing, management, and early treatment of the disease[110]. As far as the gene-disease relationship is concerned, we need to think of genes as structures that induce protein synthesis and therefore, they are potential tissue markers. As far as the *IGF-I* gene is concerned, an over-expression of the *IGF-I* gene in mature tissues is a sign of neoplastic processes, especially brain tumors[111] (**Figure 1**), and also a sign of other neural pathologies such as Huntington disease[111] (unpublished data) (**Figure 2**) or depression[112]. On the contrary, the deletion of the *IGF-I* gene is associated with reduced brain growth and mental retardation[42,113].

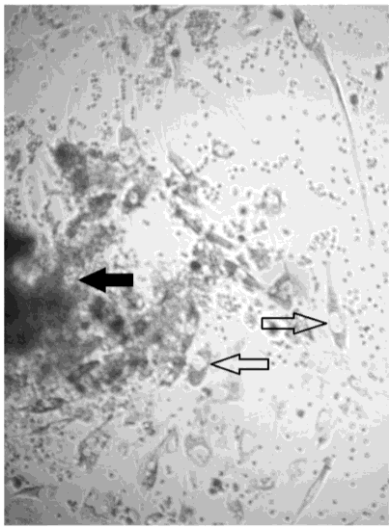

Figure 1. *In vitro* staining of IGF-1 biomarker in glioma cell culture; sixth day of culture established from human glioblastoma biopsy. Note the cells (empty arrows) proliferating from compact tissue of biopsy (black arrow). The tissue and cells are stained for IGF-1 using anti IGF-1 antibodies applied in immunoperoxidase technique (note the dark cytoplasm)[1].

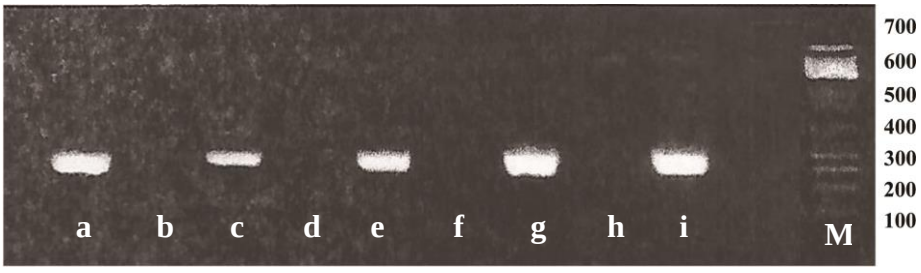

Figure 2. IGF-1 genetic testing in nervous system diseases using PCR technique[118]. Solid tumor of glioblastoma (a); Blood samples removed from glioblastoma patients (c, e); Blood samples removed from patients with Huntington disease[119] (g, i); Blood samples removed from healthy patients (b, d, f, h); Marker (M): PCR markers, Promega Corporation. Note the 200–300 bp of positive bands (a, c, e, g, i).

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Molecular testing could be useful in congenital malformations involving the central nervous system, which continue to be a major cause of infant death in the Western world; the incidence of malformations being higher in children with intrauterine growth retardation. Primary malformations go hand-in-hand with genetic intrinsic diseases[114], and the increase of intracytoplasmic IGF-I is associated with CNS malformations[115]. IGF-I function is parallel to the commonly used AFP marker, which becomes useful in the molecular diagnostics of neonatal malformations and tumor diseases[116]. These observations have enabled the testing of IGF-I as an oncoprotein and genetic marker. As a result of the "IGFs and Cancer" Symposium (held in Halle, Germany; September 15–17, 2000), an increased IGF-I serum level and an increased *IGF-I* gene expression in mature tissues have been viewed as a putative diagnostic marker for biological activity in different tumors as 17 different tumors are believed to express the *IGF-I* gene[82].

There is a convergence between normal embryo/fetal development and neoplastic development, more specifically the neoplastic brain development[1,117]. According to the theory of evolution, life is derived from amino acids; therefore, life can be altered by the imbalance that is related to protein presence. Diagnosis and treatment should logically be related to the investigation of proteins or growth factors (specific antigens) and their corresponding genes; firstly, by using gene testing for diagnosis[5,118,119] (**Figure 2**) and subsequently, targeting specific genes through special therapy such as cancer gene therapy[7,120] (**Figure 3**). Two promoters control IGF-I expression [42,121], with a low serum level of IGF-I being related to the IGF-I first promoter activity (*i.e.*, nucleotide sequence changes), as demonstrated in children with growth disorders presenting normal level of growth hormone (GH)[118]. The last data showed that testing the IGF-I first promoter region using polymerase chain reaction/single-strand conformation polymorphism (PCR/SSCP) analysis could be useful in the diagnosis of growth disorders[118].

In another study of genetic screening, which looks into the criteria of short children, the genetic analysis of these children with normal birth size has led to the detection of a SHOX or IGF1R genetic variant in 6% of short children[122]. According to Wit[123], if no obvious candidate gene can be determined in short children's genetic testing, a whole genome approach can be taken in order to check for deletions, duplications and/or uniparental disomy, or whole exome sequencing. Curiously, IGF-I plays also a role in the control of eye growth; IGF-I polymorphisms are associated with myopia (IGF-I genotyping was performed with selected tag single nucleotide polymorphisms)[124]. In recent studies regarding prostate cancer survival, IGF-I pathway genetic polymorphisms, in parallel with the circulating levels of IGF-I and IGFBP-3, have demonstrated that *IGF2-AS* and somatostatin receptor 2 (*SSTR2*) genes are primarily associated with pancreatic cancer mortality. Therefore, the testing of these two genes may be important in determining the survival of pancreatic cancer patients[125]. Moreover, the genetic variation in the *IGF-I*, *IGFBP-3*, and *SSTR-2* genes (wherein SNPs were genotyped) seems to influence the circulating levels of IGF-I and IGFBP-3 in prostate and breast cancers[126].

Moreover, genetic association and sequencing of the insulin-like growth factor 1 gene in bipolar disorder patients (via haplotype association and a gene test with wide significance of permutation testing for all markers genotyped IGF-1) implicate *IGF-1* as a candidate gene that causes genetic susceptibility to this psychiatric disease[112]. The study of IGF-I genetic variation in GH/IGF-1/insulin signaling pathway has demonstrated a potentially new human longevity loci[127]. We need to underline that there is a strong relation between genetics, signal transduction pathway, and metabolism. Gene coding for IGF-I and other growth factor-induced signaling, in particular the PI3K/AKT/mTOR pathway and in relation with rapamycin, promotes anabolism and suppresses

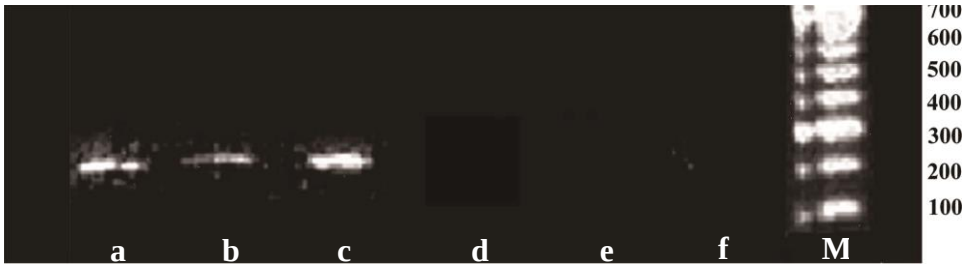

Figure 3. IGF-1 gene testing in cancer diseases. RT-PCR technique[120]. Parental cultured cells derived from (a) glioblastoma, (b) hepatocarcinoma, (c) ovary cyst-adenocarcinoma. Absence of *IGF-1* expression (d, e, f) in the same cells transfected with antisense anti IGF-1 vector (cell "vaccines"). (M): Marker. Note the 200–300 bp positive bands (a, b, c). The parental and transfected cells illustrate the passage from gene testing to gene therapy, respectively.

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catabolism to produce energy and macromolecules, respectively[128]. The interruption of any of these metabolic effects renders the growth factor ineffective.

Cancer is a prime example of a common human disease with genetically-defined, pathological metabolic perturbations[129-131]. For cancer, enzyme mutations may function as oncogenes. Genomic sequencing of tumors expressing IGF-I, especially gliomas[132,133], has identified mutations in two isoforms of $NADP^+$-dependent isocitrate dehydrogenase (IDH1 and IDH2). Tumor tissue and cell lines expressing mutant IDH1 or IDH2 produce large quantities of the (D)-2-hydroxyglutarate (2-HG) metabolite. This metabolite is produced from the NADPH-dependent reduction of α-ketoglutarate to 2-HG. The presence of 2-HG in these tumors mirrors one of the best established connections between inborn errors of metabolism (IEM) and cancer.

Bioethics

As far as bioethics and gene testing are concerned, the connection between genes and their susceptibility to certain diseases should be discussed. An increase in *IGF-I* gene expression has been viewed as a "sign" of potential tumor development in tested patients[70,82-84]. The question is: Should this type of test (which does not guarantee the appearance of cancer) be communicated to patients, relatives, or insurance companies? Another example of ethical issues for parents and physicians is the case of genetic testing in short children: Who decides if genetic testing is appropriate for this type of "pathology"?[134]. These ethical questions also concern patients who are selected for specific genetic testing of the GHIIGF-I axis, based on previously obtained clinical and biochemical assessments of growth deficiencies[135].

On November 11, 1997, the United Nations' Educational, Scientific, and Cultural Organization (UNESCO) adopted the Universal Declaration on the Human Genome and Human Rights. The text refers to the need of educating the society on bioethics and institutionalizes the presence of bioethics committees in the decision making process. Thus, the 186 countries involved in UNESCO recognized the need to: (a) promote education in bioethics, at all levels; (b) let individuals and society know of their collective responsibility in defending human dignity in topics related to biology, genetics, and medicine; (c) encourage open social and international debate, as well as ensuring freedom of expression involving the different currents of thought, should it be socio-cultural, religious, or philosophical; and (d) promote the creation (at the appropriate levels) of independent interdisciplinary and pluralistic bioethics committees. With respect to the function of the different committees, bioethical issues such as human genetic manipulation (human DNA, cells, individuals, and populations), human reproduction and embryology (the human embryo as the beginning of life and individualization, as well as assisted reproduction, embryo research and cloning), and genetically modified organisms (microorganisms released into the environment, with potential to evolve into transgenic animals and plants) should be handled appropriately.

Genetic testing comes with benefits as well as limitations. Individuals with "normal" genetic test results could experience relief whereas "abnormal" results may affect not only the patient, but also their family members. Informed carriers do benefit from knowing the risks associated with their disease, yet could still experience anxiety and guilt owing to possible transmission to the next generation[136], along with the loss of privacy, and genetic discrimination from insurers and employers[137,138]. Several insurance companies use the results of genetic testing in prenatal care to formulate insurance contracts, as well as to implement new policies and to derive concepts of health and disease, disorder, and abnormality[104]. Genetic testing can potentially impose a bias on human beings, conveniently forgetting that every person including newborns are protected by the law, as stated in Article 6 of the Universal Declaration of Human Rights (UDHR): "Everyone has the right to recognition everywhere as a person before the law."

The field of bioethics has evolved dramatically in recent years, and several major developments have transpired with regard to the niche area of biomedical sciences[139,140]. It would be a terrible mistake to think of genes as "genes of a particular factor"[141]. Perhaps the best example of "genes of a particular factor" is the gene of intelligence[142], the gene of schizophrenia[143], the gene of homosexuality[144], and the gene of a particular behavior, among other things. The growing impact of genetic concepts in popular culture has been linked to "genetic essentialism", the belief that human beings in all their complexity are products of a molecular model[145]. To identify and analyze the cultural processes involved in biomolecular life sciences, it is important to clarify the concept of "geneticization".

The concept of "geneticization" tries to describe the mechanisms of interaction between medicine, genetics, society, and culture[146]. We can define geneticization as the socio-cultural interpretation and explanation of human beings using the terminology and concepts of genetics; a process of not only seeing health and disease as what they are, but also to observe all human behaviors and social interactions through the prism of biomolecular

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technology[147]. Genetic technology should not be regarded simply as a new technology that is available to enrich the knowledge of responsible autonomous consumers, but also as a tool capable of transforming our understanding of human existence. More than a field of science, genetics is a way of thinking – an ideology where "genetics is the answer"[148].

Our society is clearly involved in the process of geneticization[147]. This process involves a redefinition of individuals in terms of genetic codes (DNA). Disease, health, and body are explained in terms of molecular biology[145]. It seems that the meaning of DNA is similar to that of the "immortal soul" as described in Christian theology. An example of the process of geneticization is the research programs and genetic counseling for β-thalassemia patients[104]. Case in point, individuals in Cyprus may only marry if they have a certificate proving their participation in genetic research. The discussion on bioethics of geneticization should involve a moral dimension. The concept of geneticization can actually produce a change in focus; we can direct the attention of our society to the different dimensions of genetic technology, which is usually neglected in bioethical analysis.

Conclusion

Progress in the field of molecular biology, medicine, and related disciplines has changed our perception of life and death, and influenced our bioethical decisions. Through the knowledge of the human genome, one can easily see the body as a machine made of multiple interchangeable parts[149]. The danger is that simplistic models of the body can override the science of life, interfering with its most sophisticated and complex mechanisms[150]. Molecular advances have extended the possibilities of genetic testing, establishing a new category of "potential patients". What is needed here is a redefinition of the concept of disease, focusing not only on clinical symptoms and genetic abnormality, but also on the increased risk of adverse individual consequences[151].

The rapid advances in genetics have had an undeniable impact on society; the consensus, therefore, is that bioethics and biomedicine must always be accompanied by bio-criticism. Bioethics is no longer an issue debated only in developed countries or an issue dealt exclusively by large corporations[120]. A number of discoveries that could revolutionize the economy and change our way of life[7,94,119,152] have repercussions on new forms of diagnosis (*e.g.*, genetic testing) and therapies (*e.g.*, gene therapy), with the latter being associated with ethical considerations. In fact, although somatic gene therapy is included in current clinical treatment, fetal gene therapy remains a subject of ethical interrogations in Western medicine.

Author contributions

All authors, in accordance to their respective specialties, have contributed to the preparation and final corrections of this manuscript.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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