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DO FAIR AND JUST SYSTEMS REQUIRE COMPENSATION FOR THE DISADVANTAGES OF THE NATURAL LOTTERY? A DISCUSSION ON SOCIETY'S DUTIES ON THE PROVISION OF GENE THERAPY

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ABSTRACT

Genetic diseases have been thought to be acquired as a result of sheer bad luck. However, recent advances in medical science have demonstrated the mechanisms of genetic disorders, which enable us to intervene with their occurrence and treatment. Today, gene therapy, once considered too risky, has become safer and can save the lives of patients with previously untreatable and lethal genetic diseases. However, the positive expectations from gene therapy are overshadowed by their extremely high prices. Thus, the duty of society in the provision of gene therapies has been frequently discussed. The discussions mainly focus on how to meet the genetic treatment needs of patients without violating the notion of justice and fairness in society. This study discusses the theoretical grounds for society's duty to compensate for genetic disease patients' disadvantages by providing them with appropriate genetic treatment. The main question is whether a fair and just system requires society to provide available lifesaving gene therapy to patients in need. The discussion is constructed on the crucial notion of the fair equal opportunity principle in a just system and the plausibility of including disadvantages emerging from bad luck in the natural lottery in the domain of justice.

Keywords: Capability approach; Distributive justice; Ethics; Gene therapy; Rare disease.

INTRODUCTION

Case 1. Three-year-old Baby X is brought to an emergency service with severe abdominal pain. Her physical examination show fat deposits under her skin and severe hepatosplenomegaly. The doctors' first diagnosis was acute pancreatitis and further tests showed that she had lipoprotein lipase deficiency (LPLD), a genetic metabolic disorder that disrupts the normal breakdown of fats in the body due to a deficiency of the lipoprotein lipase enzyme. Lipoprotein lipase deficiency is inherited in an autosomal recessive pattern, which means that the parents of an LPLD patient carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. The disorder in Baby X's fat metabolism results in her blood having a milky appearance and causes a massive accumulation of fat in her tissues and increases plasma triglycerides. The doctors tell the family that if Baby X remains untreated, she will experience several acute pancreatitis attacks that would damage her pancreas and may be life-threatening. A lifetime of adhering to a diet restricted of fats was the only advice doctors could provide for Baby X. However, doctors warned the family to be aware of abdominal pain, as dietary restrictions usually fall short of avoiding acute pancreatitis attacks, as well as other health risks such as depression, memory loss, mild intellectual decline and dementia, which Baby X may suffer from in the near future.

Case 2. Six-month-old Baby Y has been admitted to a pediatric service due to repeated and severe infections. First it was pneumonia, accompanied by a high fever and cyanosis that turned Baby Y purple due to oxygen deficiency. He developed a widespread skin rash accompanied by chronic diarrhea. Doctors also observed developmental delays, which alerted them regarding a possible genetic disorder. Several tests were administered and finally Baby

Y was diagnosed with adenosine deaminase (ADA) deficiency, a genetically inherited disorder that causes severe combined immunodeficiency (SCID) by destroying the immune system. Babies with a lack of immune protection from any kind of microorganism are susceptible to repeated and persistent infections that can be very serious or life-threatening. Doctors said that without treatment, these babies usually do not survive past the age of 2. The treatment options include early diagnosis and treatment for the infections and intravenous immunoglobulin injections. Bone marrow and stem cell transplantations are investigated with high prospects of effectiveness. However, the long term prognosis depends on the severity of the disease and the timing of the diagnosis. Severe and underdiagnosed babies typically do not survive past the age of 2.

Patients such as Baby X and Baby Y are destined for very restricted lifestyles, if not premature death. Research on genetic disorders such as LPLD and ADA-SCID aim to develop treatments for these kinds of genetic diseases that have high rates of morbidity and mortality. Alipogene tiparvovec (brand name Glybera), is a gene therapy product indicated for the treatment of LPLD, which was approved for use in the European Union on March 8, 2004 [1], and to date has only successfully treated one patient. After Glybera, Strimvelis was the second gene therapy approved by European Medicines Agency (EMEA) for the treatment of ADA-SCID [2]. It was the first instance of marketing approval for an *ex vivo* gene therapy in Europe, paving the way for the next generation of advanced medicinal therapy products [3]. Following these interventions, the number of approved gene therapy medicines increased in a short period time. By the end of December 2017, there were four gene therapies approved by the Food and Drug Administration (FDA) in the United States: Imlygic (talimogen elaherparepvec), a genetically modified oncolytic viral therapy indicated for the local treatment of melanoma [4]; Kymriah (tisagenlecleucel), the first gene therapy drug approved to treat leukemia [5]; Yescarta (axicabtagenecilo-leucel), a gene therapy for lymphoma [6]; and Luxturna (voretigeneneparvovec-rzyl), the first gene therapy to treat a rare inherited disease, retinal dystrophy [7].

There is no doubt that Glybera and subsequently approved gene therapies have made giant strides forward for patients such as Baby X and Baby Y to have a normal life-span, which was only a remote possibility before. These interventions showed that gene therapy, once considered too risky, is safe and can save the lives of patients with previously untreatable lethal diseases. However, the positive expectations from gene therapy are overshadowed by their extremely high prices. The unit price of Glybera was approximately €1 million per patient [8] and it has only been used to treat one patient [9]. Glybera's market authorization holder did not apply for the renewal of its license and in only 5 years, Glybera's status has changed from being a miracle cure to a commercial disaster, at least for the company.

The incredible potential of gene therapy implies that the share of gene therapy drug spending in total pharmaceutical budgets will likely increase even more in the coming years. These economic concerns drive discussions about society's duty to provide these treatments to those in need. These discussions mostly focus on how to meet the needs of genetic disease patients without violating the notion of justice and fairness in society. Disorders or diseases of a genetic origin have been considered a result of bad luck in the natural lottery, and therefore, have been excluded from the domain of justice for centuries. However, the novel genetic knowledge that we have acquired and the interventions that gene therapy make possible, require that we reconsider the appropriateness of this exclusion.

This study discusses the theoretical grounds for society's duty to provide available gene therapies to patients in need in order to compensate for their disadvantages. The main question is whether a fair and a just system requires that society provide available lifesaving gene therapies to those in need. This article discusses the plausible answers to this question in the domain of justice and fairness. The discussion is constructed around the crucial role of the notion of the fair equal opportunity principle in a just system and the plausibility of including disadvantages emerging from bad luck in the natural lottery in the domain of justice. The discussion proceeds with particular interest in the distinction between genetic diseases and other consequences of the natural lottery, such as personal traits and features.

Justice and the Fair Equal Opportunity Principle. Theories on justice set forth principles in order for society to have a fair fundamental structure. This fair structure enables individuals in that society to make and realize their own life plans depending on their own concepts of the "good life." Individuals require some primary goods in order to fulfill this end. These primary goods can be natural or social in source. Income, welfare and equal opportunity constitute some of the primary social goods, whereas intelligence, vigor, and imagination are among the primary natural goods. John Rawls' [10] theory of justice is one of the most influential contemporary theories in this domain. His theory states that a fair social system requires the establishment of institutions to distribute *the social primary* goods due to principles of justice and fairness, and these principles are determined in a hypothetical situation. In this hypothetical situation, rational individuals are behind a veil of ignorance and do not have any information regarding their social status, gender, age, ethnicity, abilities, level of intelligence, and level of education. The veil

of ignorance guarantees the objectivity and impartiality of fundamental principles of justice. Rawls [10] puts forth that rational individuals will agree on two fundamental principles of justice in the hypothetical original position: *1)* Every individual should have equal liberty and fundamental rights. Political liberties, liberty of conscience, freedom of speech and gathering, freedom of expression, self-respect, the right to personal integrity, the right to property, the right to not be arrested arbitrarily, and freedom of thought are addressed in this principle. *2)* Social inequalities should be avoided by the difference principle and every individual should have an equal opportunity to apply for positions in institutions with responsibility and authority for the administration. Rawls [10] thinks that the difference principle, which frankly states that "the *inequalities* of income and welfare are considered to be fair if and only if these inequalities are for the benefit of the worst off," would ensure fairness in society. The difference principle implies that the social primary goods do not have to be distributed in *absolute equality*; on the contrary, they should be allocated in a way that maximizes the benefit of the worst-off groups in society [11].

In addition to John Rawls [10], many other contemporary theorists have considered establishing equal opportunity as a crucial factor for a just system and to require compensation for the disadvantages hindering individuals from having this equal opportunity. However, the discussion regarding the extent of this compensation has not reached an end [12]. It is plausible to say that there is unanimity regarding the elimination of legal barriers to provide equal opportunity for people with similar talents or qualifications, and that there is a high degree of consensus about avoiding informal barriers such as discrimination based on ethnic identities, gender orientations, or religions. The discussion aggravates when compensation for disadvantages resulting from bad luck in the *social or natural lottery* is suggested. Equal opportunity clearly demands that positions and posts should be open to all applicants and that the selection of applicants should be based on appropriate criteria relevant to performance, and that the most qualified applicant should be offered the position [13]. However, this perspective does not necessarily ensure that all people enjoy equal opportunity in practice, as acquiring the merits and capabilities required for a particular position or post greatly depends on an individual's initial starting point in life. The social, cultural, and economic factors in which an individual is born may enhance or impair their chances to develop the required talents or abilities. Rawls' [10] difference principle endorses this perspective and requires that society compensate for disadvantages resulting from socioeconomic status, religion, ethnicity, or any other factor beyond individuals' control or choice.

Apart from Rawls' [10] theory of justice and the difference principle, there is another argument that supports compensation for disadvantages resulting from bad luck in the social lottery. This argument emphasizes the core position of individual responsibility and puts forth that if a disadvantage is as a result of an individual's own behavior, then it is not society's responsibility to compensate for that disadvantage [14]. However, if the disadvantages *happen to find* an individual due to bad luck in the natural lottery, then justice requires that society eliminate these disadvantages. The natural lottery is beyond individuals' control. No one can choose their nationality, religion, ethnicity, or socio-cultural environment [15]. The individual responsibility argument is endorsed by the sheer bad luck perspective, which implies that equal opportunity can be achieved if the inequalities in talents and abilities as well as means resulting from an initial social position are compensated for. This perspective suggests establishing a compensation mechanism to allocate resources in such a system in order to provide fair distribution, and that fairness is realized if every individual has access to resources that they require in order to achieve equal opportunity [12].

Can We Use the Same Arguments to Justify the Plausibility of Compensating for Natural Primary Goods? It is apparent that the results of the natural lottery are not limited to social disadvantages. Primary natural goods such as intelligence, imagination, vigor, and health are also gifted or deprived by the same lottery. Unlike social primary goods, the inequalities between human beings originating from natural factors have been excluded from the domain of justice since Plato. There can be two reasons for this. First, theories of justice aim to establish a just system through structures and terms of implementation for institutions. Social institutions and social structures have no impact on the inequalities emerging from the natural lottery of primary natural goods; if the social system and institutions have no effect on the occurrence of a disadvantage, it is beyond the scope of justice.

The second reason relies on the fact that knowledge about how the natural lottery occurs and how the results of the natural lottery lead to disadvantageous consequences have been lacking until recently. The multifactorial unknown etiology of the disadvantages emerging from the natural lottery leaves us ignorant about how to annihilate or correct them. Therefore, the lack of knowledge about the causes and means to rectify these disadvantages could have contributed to excluding the disadvantages arising from the natural lottery from the domain of justice.

Contemporary science has changed this ignorance to some extent and has proven that some personal qualifications and diseases do result from genetic factors. A low intelligence quotient, defects in phenotype, or even some

social behavior disorders have been proven to emerge from our genes. As a result, knowledge of the inner workings of the natural lottery are no longer a mystery. Thanks to genetics, our knowledge of diseases with genetic origins has increased. For example, we now know that Down syndrome is a result of trisomy 21 and that LPLD is a rare autosomal recessive inherited disease caused by mutations in the lipoprotein lipase gene. Moreover, the increase in our genetic knowledge has provided medical means to intervene in the natural lottery and to avoid or undo the results of sheer bad luck by means of gene therapies.

Although today, gene therapy is still considered experimental, the prospects of replacing a mutated gene that causes disease with a healthy one, deactivating a mutated gene, introducing a new gene into the body to combat a disease, or scanning intrauterine fetuses for gene disorders, are more promising than ever. This new idea of knowing how the natural lottery works and having the means to remove the disadvantages of a genetic origin urges us to reconsider the on-going assumption of excluding natural factors from the domain of justice, and to provide a new status for curable or preventable disadvantages stemming from the natural lottery. Referring to the discussion in the previous section, this new status can be defended on two grounds. The first is fair equal opportunity. As it has been established that equal opportunity is considered crucial for justice [12] and that some form of compensation for disadvantages hindering individuals from having equal opportunity is required, and since it is indubitable that genetic diseases cause disadvantages for individuals that prohibit them from enjoying equal opportunities, justice requires compensation for such disadvantages. It is plausible to think that this argument was not developed when equal opportunity was first discussed because it was not possible to intervene in the consequences of the natural lottery. The only option was to accept them as bad luck and to focus on the disadvantages that we are able to mitigate or compensate for.

The second ground is individual responsibility. Since genetic disease is a consequence of bad luck in the natural lottery and an individual has no inducements to have a genetic disorder, and as justice requires that society eliminate the disadvantages emerging from bad luck in the natural lottery in which the individual has no inducement, then it follows that genetic diseases should be considered in the purview of justice. Interventions to prevent or cure genetic diseases should be considered as part of the compensation mechanism to allocate resources to provide fair distribution, and that fairness is only realized once every individual has access to the resources that they require to achieve equal opportunities [12].

The Limits of Compensation: Genetic Diseases and Personal Variations. The disadvantages of the natural lottery are not limited to genetic diseases. Being shorter than the average person, extreme shyness, an introverted personality, or even having ears that stick out, are consequences of the natural lottery. It can be argued that these features cause disadvantages when applying for positions or posts. A person who is extremely shy and has difficulty speaking in front of a jury or significantly short when compared to other candidates, would face difficulties in enjoying equal opportunity. In such cases, it is not only genetic diseases but also several negative features or personality traits that have the potential to endanger equal opportunity. Additionally, individuals with these features or personal traits do not have any responsibility in having them. Therefore, it is plausible to say that the two theoretical grounds, *equal opportunity and individual responsibility*, apply to all disadvantages emerging from the natural lottery and that they should also be compensated for in a just system. If we are justifying the right to access to health services, gene therapy in our case, to ameliorate the genetic disadvantages of an individual so that they may enjoy a normal opportunity range and fair equal opportunity, then we should also agree to provide these services to, for example, shy people.

Although the broad implications of our discussion seem plausible on theoretical grounds, there are strong counter arguments against them. First, variations in phenotype and personality together with talents and abilities are among the features that make a person unique. These variations should be considered normal and necessary for the genetic plurality of the human species. This variation and uniqueness might restrain an individual's opportunities to be appointed to some positions or posts, but may enhance their chances in others. For example, an introverted person might be disadvantaged if seeking a career in the media sector, but may enjoy a good career in writing. Another example would be that your physical appearance might not be a huge disadvantage if your brain functions like that of Stephen Hawking.

The second argument is that the disadvantageous nature of these features or traits is not absolute or universal. Their value in terms of being advantageous varies over time and according to different cultures. For example, a big body with strong muscles was certainly an advantage in the Stone Age, but contributes little to a career as a nuclear scientist. Likewise, being humble and taciturn might be considered a sign of self-containment and maturity in Eastern cultures, but people with these features might be considered too obscure and insignificant in Western societies. On the other hand, genetic diseases form health conditions with severe morbidity and mortality risks regardless

of the time and culture they occur in. There is no occasion that ADA or LPLD would be considered an advantage. Moreover, the genetic disorder behind genetic diseases cannot be considered as variations in normal human genomes, as their consequences are incompatible with life.

The third argument comes from science. The direct causal relationship between genetics and the presence of these features or traits is not defined. On the contrary, our current knowledge suggests that several phenotypic variations as well as personality traits result from multiple factors. Hereditary factors together with environment, nutrition, education, and cultural and religious customs play a crucial role in their presence. Therefore, it is not possible to predetermine their occurrence in the future. Moreover, the means to "cure" them is limited and has no resemblance to the certainty and scientificity of gene therapy. Thus, it is not plausible to form a comparison between them.

Conclusions. The vast improvements in genetics have enabled us to intervene in genetic diseases, something that was considered to be a result of bad luck in the natural lottery, and was excluded from the domain of justice in this respect. Contemporary theories on justice require that society compensate for the disadvantages of individuals so that they may enjoy equal opportunities, which is considered crucial for a fair and just system. The high rates of mortality and morbidity of genetic diseases create concrete disadvantages for these patients to enjoy fair equal opportunities. From this perspective, the fair equal opportunity principle requires that society provide available genetic treatment to those in need in order to compensate for the disadvantages that result from genetic disease. This view brings a new context to the domain of justice by including disadvantages resulting from bad luck in the natural lottery. However, genetic diseases are not the sole element in the set of disadvantageous results of the natural lottery. Personal traits and features that might have some negative impact on enjoying fair equal opportunity are also included in this set. Thus, we need to draw a line in order to avoid a slippery slope and to hold society responsible for correcting any variation in human beings that has the potential of hindering the realization of a person's life plans. The high rates of mortality and morbidity of genetic diseases create an *absolute and universal disadvantage* for any individual who is unlucky enough to have them, whereas the disadvantageous qualification of personal traits or features are relative to certain times and cultures. Moreover, personal traits and features are considered as normal variations in the human species with no requirement for a cure, whereas genetic diseases are disorders that are not compatible with life unless cured. Thus, it is plausible to say that society's duty to compensate for genetic diseases can be justified due to the fair equal opportunity principle; however, this does not apply to the compensation of any variation emerging from the natural lottery.

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