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IS THERAPEUTIC GERMLINE EDITING VALUE-BASED HEALTHCARE? AN EARLY HEALTH TECHNOLOGY ASSESSMENT

abstract

Innovative healthcare technologies may raise ethical concerns which prevent their implementation for fear of unexpected or undesirable outcomes, even before they are introduced into usual clinical practice. Essential to innovation is therefore to analyze benefits and drawbacks from a multidisciplinary point of view (i.e., biomedical, social, financial). Value-based healthcare is currently the most comprehensive theoretical framework to evaluate the benefits of healthcare technologies on patients and society in the longer term. Technically, "the systematic evaluation of properties, effects and/or impacts of health technologies" must be performed by validated procedures of Health Technology Assessment (HTA), supported by early HTA procedures to retrieve preliminary evidence and expert opinions. The aim of this study is to perform an early HTA of germline editing technologies in order to estimate their impact on patients and society, in light of the recent, controversial debate which followed the germline gene editing of human embryos.

keywords

bioethics, designer babies, distributive justice, germline editing, value-based healthcare

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1. Introduction

Psychophysical functions and social capabilities are given special value as long as they allow people to achieve what they hold most important in life (Sen, 1993). This is why healthcare is considered a fundamental social right, at least in the European welfare tradition (European Commission, 2019). Today, advanced healthcare systems are challenged by financial and human constraints, more health expectations, more patients affected by chronic morbidities and constantly evolving technology and clinical practice (Organization for the Economic Cooperation and Development, 2015). As a result, they are asked to provide increasing quality of care at sustainable costs, and spend their resources more efficiently and wisely.
Efficiency is a technical assessment based upon the number of resources employed to achieve certain benefits. Wisdom is a value judgement upon which of these benefits matter most, given the impossibility of achieving them all (European Commission, 2019). When human and financial resources are no longer able to cope with endlessly growing demand, and room for further efficiency is reduced to the bone, investing in healthcare becomes a matter of distributive justice and value. Value-based healthcare (VBHC) is currently the most comprehensive approach to evaluate the benefits of healthcare technologies on patients and society in the longer term, as best value is determined by long-term benefits that can be shared by the maximum possible stakeholders (patients, funders, providers) (European Commission, 2019; Pennestrì *et al*., 2019).
Some researchers have questioned whether the introduction of new technologies really does benefit the patients they are designed for, as innovation should improve "outcomes that matter to patients" and solve real-world problems (Coffey & Coffey, 2019; Mangan, 2018; Finnegan 2017) rather than promote technological advancement itself (Kluytmans *et al*., 2019). Technically, "the systematic evaluation of properties, effects and/or impacts of health technologies and interventions" must be performed by validated procedures of the Health Technology Assessment (HTA) (World Health Organization, 2007). A complete HTA needs a certain technology (drug, medical device, surgical procedure) to have been previously tested in clinical trials or real-world settings, in order to compare different treatments and maximize the expected outcomes. However, some technologies raise ethical concerns which may prevent their implementation for fear of unexpected or undesirable outcomes (i.e, patient harm or the slippery slope) (Van der Burg, 1991), in which case it is essential to analyze the benefits and drawbacks before introducing them into routine clinical practice. For this reason, preliminary assessments or early-HTA (eHTA) have been developed to retrieve preliminary evidence and expert opinion before a full HTA can be performed (Kluytmans *et al*., 2019; Ijzermans *et al*., 2017).

A relevant part of this information is represented by the ethical and social issues associated with the introduction of a certain technology into current medical practice, which requires a consideration of values and philosophical reflection. The aim of this manuscript is to perform an eHTA of germline editing technologies in order to estimate their impact on individual patients and wider society, in light of the recent, controversial debates which followed the performance of germline gene editing of human embryos (Lander *et al*., 2019; Greely, 2019; Lavazza, 2019).
In section one, germline editing is described, together with a discussion of the opportunities which emerge upon the technology, their potential applications (distinguishing between therapeutic, cosmetic and enhancement germline editing), as well as key associated risks. Section two provides a multidisciplinary set of indicators used to perform an eHTA, via the introduction of the four dimensions of healthcare value (personal, technical, allocative and societal) and the nine dimensions of HTA (relevance of the technology, technical characteristics, safety, clinical effectiveness, cost and economic evaluation, ethical and legal analysis, social and organizational impact). In section three the economic, ethical, organizational and social dimensions of impact are developed, building on preliminary evidence of effectiveness, costs, and philosophical considerations of distributive justice.

2. From chance to choice - what is germline editing and why it is controversial?

The human animal has always been worried, and frustrated, by the corruption of its body (Silverstein, 1979). Innovative healthcare technologies have continually been developed to heal disease, slow down aging, and delay death. Among them, gene editing is the latest, promising attempt (Pennestrì, 2019). Behind this technology, however, lie ancient immunological mechanisms employed by some of the simplest living beings on earth (bacteria), to defend against even simpler, barely-living beings (viruses), for millions of years before mankind made its appearance.
Streptococcus pyogenes, responsible for sore throat, is one of these bacterial species. Among the viruses that attack bacteria are bacteriophages, or phages, parasites that "eat (from the Greek *phagein*) their host (bacteria)". Phages take advantage of a host organism's DNA replication to reproduce their own genes and preserve themselves, hijacking the host's biochemical cornerstone of life. In response, bacteria co-evolved an ingenious 'fingerprint scan' security system, CRISPR (a guide RNA able to identify the genetic sequences of the viral aggressor), and a scissor-protein, Cas9 (able to cut those sequences in order to prevent them from replication) (Le Rhun *et al*., 2019; Marraffini *et al*., 2016; Barrangou *et al*., 2007).
Interestingly to humans, this natural security system has the potential to defeat rare, deadly diseases which do not yet have effective therapy. This is the revolutionary idea that led American chemist Jennifer Doudna and French microbiologist Emmanuelle Charpentier to test CRISPR-Cas9 on humans (Jinek *et al*., 2012). Seven years and 11135 scientific publications after their brilliant, pioneering work, a bacterial defence mechanism became the State-of-the-Art genetic manipulation tool (Loureiro & da Silva, 2019). Doctors and scientists are performing stunning international trials to assess the safety of this complex engineering technique on living patients. CRISPR-Cas9 is being tested to treat lung cancer in China (Cyranoski, 2016), inherited blood disorders in Europe (European Hematology Association, 2017), and strengthen key components of the immune system in the United States (PennMedicineNews, 2019). Huntington's Corea (Vachey & Déglon, 2018), Cystic Fibrosis (Marangi & Pistritto, 2018), Duchenne Muscular Dystrophy (Lim *et al*., 2018) and Acquired-Immuno Deficiency Syndrome (AIDS) (Huang *et al*., 2017) may follow the same route. The greatest global health worry at the time of writing, the novel coronavirus SARS-CoV-2, can hopefully become another target (World Health Organization, 2020; Jamal Anjum Official, 2020).
Gene editing may *heal* disease if therapeutic genes are administered to a living patient (somatic

gene therapy). But gene editing may also *prevent* disease if mutations are performed on developing embryos (germline editing). Once embryos are generated from *in vitro* fertilization, they can be engineered with target adaptive mutations, such as strengthening the immune system or removing HIV receptors (Tebas *et al*., 2014); if the mutation occurs, it will not just be the newborn who will be covered against certain types of cancer and life-threatening viral infections, but that coverage will potentially be extended to its children, grandchildren, and any subsequent generations: the more embryos are subject to a certain therapeutic mutation, the earlier next generations will benefit.

If *adding therapeutic genes* was the breakthrough introduced by classical gene editing (that made bacteria produce insulin and fish glow like fireflies), *replacing corrupted genes* is technically more promising. Correlations between genes, psychosomatic traits and disease are generally difficult to capture, but more than a hundred monogenetic diseases have already been found (Tang *et al*., 2017). International fertility institutes already offer *in vitro* genetic selection in order to design the sex and eye colour of babies (The Fertility Institutes, 2020). The more humans can *reduce* their nature to genes (*that* disease, *that* somatic trait, *that* talent, or *that* psychological skill, is generated by *that* gene, or *that* sequence of genes), the more they are able to modify it.

A first clarification is needed here. Given that it is possible to modify genes, and that such modifications can be performed with different end goals in mind, the reasons behind performing such a surgeries is worth considering. Preventing Huntington's Chorea, Cystic Fybrosis, Muscular Dystrophy and AIDS can be considered *therapeutic* germline editing, being that the target of surgery is correcting disease. In contrast, choosing height, eye colour and skin colour has been called *cosmetic* germline editing, as a certain eye colour, skin colour or height are not diseases (Carroll, 2017). Empowering psychophysical skills beyond the "average function of the species" (Boorse, 1977) is *enhancing* germline editing, as the goal is to perform better than that average (i.e., by increasing strength, memory and attention) with no disabling infirmity occurring at baseline. The focus of this manuscript is on therapeutic germline editing, as 1) cosmetic gene selection is already performed by choosing – rather than modifying – embryos after *in vitro* fertilization, which makes germline editing a more complicated and implausible alternative as of now; 2) similar considerations apply to human enhancement, as cheaper, available drugs represent a widespread and affordable alternative to germline editing, although the effects cannot be transmitted from generation to generation (Frati *et al*., 2015; Outram, 2010; Glannon, 2006); 3) major scientific interest is currently focused on the prevention of non-curable disease, as the case of He Jiankui demonstrates (Greely, 2019).

In November 2018, the Chinese biophysicist announced that 22 human embryos generated by 8 couples with an HIV+ father had been modified, and two HIV-free female twins, Lulu and Nana, were born as a result (He, 2018). The goal was to test CRISPR-Cas9 technology directly on human embryos, in order to prevent the transmission of HIV from positive parents to the newborn. As a matter of fact, CRISPR-Cas9 is able to remove the cellular receptor that works as a target for the virus, performing a gene mutation (CCR5Δ32) which can be adaptive for the host. Other scientists were already working on this premise, but previous trials were performed on tripronuclear zygotes which could not initiate pregnancy. Moreover, these trials did not show promising results (Liang *et al*., 2015; Kang *et al*., 2016).

For Lulu and Nana, not only did the gene editing appear to have failed, but unexpected mutations occurred on target genes. Since the protocol was unclear (Greely, 2019) and the manipulation of regular human embryos is forbidden in China (Araki & Ishii, 2014), the scientist was fired from his University and has been recently sentenced to three years in prison (Sample, 2019). The Chinese scientific community was "opposed to any clinical

operation of human embryo genome editing for reproductive purposes in violation of laws, regulations, and ethical norms in the absence of full scientific evaluation" (Wang *et al*., 2019). The international scientific community, in turn, called for "a global moratorium on all clinical uses of germline editing, that is, changing heritable DNA (in sperm, eggs or embryos) to make genetically modified children" (Lander *et al*., 2019). The trial generated rich ground for a multidisciplinary assessment of the technology, as all dimensions of value were involved in the case.

3. Healthcare value from theory to practice

According to the European Commission's Expert Panel on Effective Ways of Investing in Health (EXPH), there are four pillars of value (European Commission, 2019).

1. Personal value: significantly improving patient wellbeing, quality of life and autonomy (i.e., restoring the functions that make patients' lives worth living, according to their preferences);
2. Technical value: reaching the desired result(s) using as few resources as possible (i.e., reducing pain with conservative treatment rather than major orthopaedic surgery);
3. Allocative value: equitable distribution of resources across patients (i.e., freeing up resources which can be invested in the treatment of other patients and diseases);
4. Societal value: extending the benefits of a certain treatment from patient to society (i.e., reducing the burden of disability, loss of productivity, and social fabric erosion).

Best value is when shared benefits are experienced by all the stakeholders involved in the process. Few technologies can meet all the requirements at the same time or to the same degree, but this approach still provides a useful framework to perform HTAs from a sustainable and longer-term perspective. To avoid wasting limited resources, the value of a certain treatment should not be reduced to its effectiveness in an ideal clinical trial, in ideal settings, or in the shortest possible time; rather, it should be assessed in real-world patients, living in a real-world society, over the longest possible span; otherwise, these resources are wasted, generating poor allocative and societal value. Therefore, providing VBHC is mandatory for healthcare systems based on the universal taxation of workers, as resources are shared and institutions are accountable for how they are spent (accountability for reasonableness) (Pennestrì, 2017; Daniels & Sabin, 2008).

The validated European Network for Health Technology Assessment (EuNetHTA) core model is currently employed to support healthcare planning from the assessment of public priorities to the adoption of certain technologies in single hospitals (Foglia *et al*., 2017; Radaelli *et al*., 2014; Kristensen et al. 2009). The assessment is based on nine dimensions, six of which are not strictly clinical (5-9):

1. Relevance (health problem and current use) of the technology;
2. Technical characteristics;
3. Safety;
4. Clinical effectiveness;
5. Cost and economic evaluation;
6. Ethical analysis;
7. Social aspects;
8. Legal analysis;
9. Organizational aspects.

The relevance of germline editing technologies was described in detail in the previous section, along with the current use of CRISPR in regular and irregular experimentation. Information about their safety and clinical effectiveness on human embryos is (partly) available only from He's trial and the following legal vicissitudes. Legally, the moratorium of international scientists places further warnings on a procedure already banned in much of Europe, United

States and China (National Academies of Sciences, 2017; Araki & Ishii, 2014). Ethical and social analysis can be retrieved from the philosophical debate on germline editing, which has formed the basis of books (Huxley, 1932), movies (Niccol, 1997) and philosophy (Buchanan *et al*., 2000) even before this technology was at hand. Today, the debate is also attracting the attention of civil society (The Associated Press-NORC Center for Public Affairs Research, 2018). The economic benefits of the procedure can be estimated on the basis of the cost of somatic gene editing already introduced in pioneer countries, such as the United States and Italy, compared to alternative treatments and in light of intergenerational benefits or harms. The organizational aspects derive in part from this dimension.

The need for temporary assessments is frequent in the rapidly evolving process of healthcare innovation, as demonstrated by the spread of eHTA frameworks (Kluytmans *et al*., 2019; Ijzermans *et al*., 2017). Distinct from traditional HTA (which evaluates the benefits of new technologies *after* they have been tested in clinical trials or applied in practice for some time), eHTA is performed *during* the early phases of development of a novel technology, when information is limited and evidence is lacking. The key idea is that earlier stages of experimentation (here represented by regular clinical experimentation with CRISPR somatic editing or germline editing on irregular experimental human embryos, and He's experimentation with germline editing on IVF embryos) enable the identification of barriers and facilitators *before* the technology is introduced into society, or adopting necessary precautions before major investments are made. The VBHC framework is adopted here to bring order to the economic, social, ethical and organizational dimensions, as it provides a clear framework that highlights their connections.

4. Is therapeutic germline editing value-based healthcare? An early health technology assessment

It is difficult to assess the benefits of a certain healthcare technology on a patient who is unable to provide a preference, to describe his/her experience, and to compare his/her wellbeing before and after applying that technology. Would a person agree to have his/her genes modified before being born? In order to overcome the consensus problem (Santas, 2019), two surrogate solutions are 1) to hypothesize how these modifications could be perceived by patients once performed, after birth, building on the preference, experience and sensitivity of a population interested to this question; 2) to evaluate whether the parents have a duty to protect their child from developing preventable disease or disability, at the early stage of embryos, in the absence of safer or less invasive alternative treatments (Benston, 2016).

4.1 Personal value

A preliminary answer to both questions is suggested by a University of Chicago survey that investigated the attitudes of 1,067 adult Americans towards "the technology that could be used to edit the genes of human embryos" (The Associated Press-NORC Center for Public Affairs Research, 2018). The majority of those surveyed was in favour of using gene editing to prevent disease or disability, while remaining strongly opposed the use of technology to change psychosomatic characteristics such as eye colour or intelligence. In both cases, there was a deep agreement among citizens regardless of party identification, education and religious preference.

The author agrees with this view, with the provision of some further clarification. On the one hand, it is reasonable to expect that a person who decides from a hypothetical original position (Rawls, 1971) would not choose to have a serious illness or disability that prevents him/her from living a life similar to that of the people he/she is surrounded by, characterized by comparable opportunities and substantial freedom. This is confirmed by the reactions of many people affected by disabilities or hereditary diseases after the introduction of the Abortion Act (1967) in the U.K., and later in other European countries, who have sued parents, doctors and hospitals for not interrupting pregnancy although they were aware of impending health conditions (Falzon, 2014). A few years after the introduction of the artificial

kidney, another "medical miracle" (the introduction of advanced screening and diagnostic technologies) presented people with the moral burden to "decide who could live and who should die" (Alexander, 1962). The argument of "wrongful birth" (or "wrongful pregnancy", "-conception", and "-life") is still frequent in worldwide law Courts, from the U.S. to Hong Kong (Tsang & Cho, 2018; Hale, 2001; Teff, 1985).
On the other hand, disability is a relative condition which depends on a number of psychological, social and environmental factors, as the "happy disabled" argument supports (Kamm, 2013). Disabled people can learn to cope with their impairment much better than a healthy person can imagine, as 1) patients affected by genetic diseases have never experienced complete health, and 2) even if they were healthy before a certain accident occurred, they show a capacity to cope with critical, sudden disabilities much better than one would expect, provided genuine love, spiritual and social support from the environment. Moreover, the disability of a few people may be interpreted as a lesson to help much higher numbers of healthy people appreciate what they do have in their life (Adams *et al.*, 2015; van Leeuwen *et al.*, 2012; Do Rozario, 1997), especially when the latter are mentally conditioned by perfectionism, healthism and healthcare consumerism, as more health and more expectations are increasingly associated with more frustration and wasteful expenditure (Davini, 2013; Gossen, 1854).
Halfway between the "happy-disabled" and the "wrongful birth" arguments, germline editing – once safe – could prevent severe disabilities and frequent abortions at the same time, allowing parents to choose in light of their sensitivity without any pressure from society. If germline editing is performed in safe conditions and no alternative treatment is available, the technology would provide better personal value in comparison with abortion, for the same outcome (preventing disease) is achieved while also preserving life. Theoretically, performing gene surgery after the embryo has been implanted (*in vivo*) would benefit the very same individual that has been conceived, providing the equivalent of somatic gene therapy before the child can suffer from the target disease. In this scenario, the personal value disclosed by the procedure would be achieved in the narrow sense of the definition.

4.2 Technical value

Technical value is given by the ability to obtain the desired results using as few resources as possible. To extinguish a match, a person can either blow or employ a Canadair. To get rid of an annoying fly, a person can either use a fly swatter or a bazooka. All these actions and technologies are very likely to reach the goal, but employing a Canadair or a bazooka adds no effectiveness and must be set against the considerable waste of human and/or financial resources.
With respect to healthcare, several treatments provide less trivial but still clear examples. Vaccinations reduce infectious disease mortality saving significant resources compared to hospitalization of patients in specialized units, providing higher technical value and additional allocative value, as more resources are freed up to invest in other treatments (i.e., beds in intensive care), and critical side-effects of drug misuse are reduced (i.e., antibiotic resistance). When a vaccine is not available, other preventive techniques can still provide high technical value. For instance, wearing a condom prevents HIV infection by saving significant resources compared to engineering the cells that offer entry to the virus, either through gene surgery or a bone marrow transplant (Gupta *et al.*, 2019; Hütter *et al.*, 2009). From a technical point of view, prevention is generally more valuable than cure. When prevention is not viable or sufficient, different treatments can still be compared. For instance, conservative antalgic therapy offers more technical value in the treatment of a certain degree of knee osteoarthritis compared to major orthopaedic surgery (i.e., total knee arthroplasty), even more so if the patient loves to kneel down to garden or to play with grandchildren nephews on the ground.

What is relevant here is not whether germline editing can prevent a fatal or non-fatal condition, but the presence of any effective alternatives. This is consistent with findings from a survey on American citizens' attitudes towards germline editing, which are equally in favor of using the technology for both the prevention of incurable, inherited fatal disease (such as Huntington's Korea and Cystic Fybrosis) and non-fatal inherited conditions such as genetic blindness. In the case of He, the experiment was conducted on embryos generated by couples with a HIV-positive father and HIV-negative mother. The scientist welcomed the birth of Lulu and Nana by calling attention to the resulting significant personal and social value, for example, 1) "Mark has HIV, discrimination in many developing countries makes the virus worse; employers fire people like Mark, doctors deny medical care, and even forcibly sterilize women"; 2) Mark "said that he never thought he could be a father, [while] now he has found a reason to live, a reason to work, a purpose" (He, 2018). These are the kind of problems that Lulu and Nana were expected to avoid thanks to editing technology, were it not for the fact that the surgery did not work and that the twins could suffer from critical health conditions (Xie *et al.*, 2019). Morally aggravated by being artificially induced, this highlights poor personal value (worse health), poor technical value (bad healthcare outcomes), poor allocative value (preventable healthcare expenditure will be employed to treat potential long term disease, i.e., following from irregular bone growth and development) and poor societal value (the impact of the associated disability on their family and society).

While taking these risks is acceptable when there is no alternative treatment at all, as the argument of compassionate care supports (Hyry *et al.*, 2015), safer prevention and treatment of HIV infection do already exist. First, a child can inherit HIV from the mother during pregnancy, delivery or through breast-feeding (vertical transmission). Transmission occurs in less than 1% of cases if adequate precautions are taken, from antiretroviral treatment for the woman in labour to caesarean delivery, neonatal prophylaxis and artificial milk feeding (Lega Italiana per la Lotta contro l'AIDS, 2019). Hence, vertical mother-to-child transmission can be prevented via many other alternatives before gene editing is performed on embryos, provided it works in the future.

Second, Anti-Retroviral Therapy (ART) has made HIV infection a non-fatal condition since 1996, preventing the virus from evolving into AIDS and guaranteeing patients a life expectancy roughly equivalent to the average population. When therapy is effective, people can have personal life plans including becoming parents and avoiding the risk of sexual transmission to a partner (Lega Italiana per la Lotta contro l'AIDS, 2019). When the treatment is funded by public resources, there is evidence of increased personal value (more health, freedom and better opportunities), allocative value (prevention of complications) and societal value (protection of other people) (Taramasso *et al.*, 2018). Although ART almost halved the average mortality after HIV-infection in Europe and the U.S., the difficulty of affording life-long therapy in limited-resources settings, the interaction of social and clinical conditions with adherence to therapy, and the side-effects associated with the alternative of bone marrow transplant (Xie et al., 2019; Haworth *et al.*, 2017; Zou *et al.*, 2013; Scanlon & Vreeman, 2013; The HIV-Causal Collaboration, 2010) still make prevention technically more valuable, but several effective alternatives exist that might be employed before germline editing. From a technical point of view, germline editing could be valuable only in the absence of more conventional, safer and cheaper alternatives.

4.3 Allocative value

In 2017, the U.S. Food and Drug Administration approved the first gene therapy against cancer, Kymriah® (tisagenlecleucel), to treat acute lymphoblastic leukaemia (ALL). A single therapy costs USD 470,000, is hardly covered by insurance, and is not effective on patients older than 25 years. In 2016, Agenzia Italiana del Farmaco approved the first gene therapy against Severe

Combined Immunodeficiency Syndrome (SCID), a rare paediatric disease that forces babies to live within blisters to protect them from common but lethal microorganisms (the so-called "bubble babies"). The therapy, called Strimvelis®, is administered via a single intravenous injection, and costs Euros 600,000 per patient.

Funding expensive drugs for rare diseases is a puzzling problem for many European healthcare systems (Wieseler, 2019; Jørgensen & Kefalas, 2013; McCabe *et al*., 2008), as public resources are always limited and tragic choices must frequently be made. For any treatment introduced into the basket of healthcare, another treatment is removed, delivered late, or covered by additional financial payments on part of the user, which seriously questions the consistency of universal health coverage in practice (Consorzio Universitario per la Ricerca Economica Applicata in Sanità, 2015; Costa *et al*., 2014; Bognar *et al*., 2014; Daniels, 2008). The administration of somatic gene therapy to a single patient can offer him/her a lot of personal value, allowing for an effective and complete recovery to the detriment of many other patients who are denied more conventional, cheaper, but effective treatments for more common diseases. Opting for this technology would then generate poor personal value to those who are denied care, poor allocative value to the funder, and poor societal value as a result of more people suffering direct or indirect burdens of disease. If it is immoral to give a blameless child a price for his life, it is probably equally immoral to neglect more common therapies for other hundreds of blameless children, in order to treat one affected by such a rare disease. As long as no ideal solutions are viable here, distributive justice becomes a question of comparing losses (Calabresi *et al*., 1978).

This is what makes germline gene editing financially attractive. Performing gene editing on a 8-cell embryo 3 days after fertilisation would theoretically transmit the mutation to all of the cells, tissues, organs, and systems it produces, and passes to subsequent generations, due to the staminal power of these cells. The price of one gene surgery would be an expensive lump sum, but entire populations could benefit from a single treatment, which produces high intergenerational allocative value. Add to that, if patients affected by genetic disease are children with very demanding needs, which cause a heavy burden to their carers (Reichman *et al.* 2007), germline editing would also generate high societal value. Consider therefore how many human and financial resources –no child left untreated – would be saved to assist patients affected by more common disabilities and diseases, their lives being equally worthy, which is optimal distributive justice for utilitarian philosophers and considerable allocative value (European Commission, 2019). Moreover, the institutional fragmentation of long-term care is today a major determinant of suboptimal outcomes, inappropriate prescriptions, extended waiting lists and rising health expenditure to the detriment of the most fragile people, among which patients affected by critical disabilities, genetic disease, and children with different degrees of incurable conditions (Lawless *et al*., 2020; Brewer, 2018; Altman *et al*., 2018). In this case, preventing the onset of such morbidities could add further, organizational benefits to increasingly complex and stratified healthcare systems.

Germline editing may also reveal unexpected benefits for the prevention of sudden public health emergencies such as the current COVID-19 pandemic. At the time of writing, no preventive or therapeutic treatments are available yet, although the virus had been isolated and a spike protein is paving the way for the creation of a vaccine (King, 2020). Personal hygiene, quarantine and individual protective equipment are the only viable solutions to reduce the spread, to the extent that apparently trivial and obsolete public health measures have made a return to paramount importance (Signorelli & Fara, 2020). CRISPR editing is being studied not just to rapidly diagnose SARS-CoV-2 infections, but even to engineer human cells in order to remove the target receptor of the virus as for the (HIV) CCR5Δ32 mutation, and with similar potential germline applications (Davies & Barrangou, 2020; Chekani-Azar *et al*.,

2020; Soni, 2020). Once the technology proves safe and effective, the remarkable regularity of viral epidemics (SARS 2003, H1N1 2009, MERS 2012, SARSCOV2 2019) (Zangrillo & Gattinoni, 2019) would be a further reason to consider germline gene editing valuable from an allocative point of view.

4.4 Societal value

The societal value of germline gene editing was already introduced in the previous three paragraphs, in which the prevention of genetic diseases and disability was associated with better opportunities for more patients and families. Not only patients affected by permanent impairment have reduced chances to find a job, if any, but their parents, relatives and carers may experience from the same problem. Indeed, people suffering from serious chronic disease or disability need to be assisted at home and/or frequently accompanied to one or more healthcare facilities. When care givers are not able to provide sufficient support on their own, i.e., because of incompatibility with work, they can be replaced or helped by social professionals. However, social professionals may not able to provide sufficient support in turn, i.e., because of long term care fragmentation or limited investments. When this is the case, increasing numbers of patients and families get into debt in order to access private support, or give up seeking treatment because long term care is too expensive or complicated to follow, meaning that even more clinical fragility is aggravated by the progressive erosion of the social fabric (Consorzio Nazionale delle Associazioni dei Malati Cronici & CittadinanzAttiva, 2015; Consorzio Universitario per la Ricerca Economica Applicata in Sanità, 2015; Regione Lombardia, 2014).

In that case, the individual and social burden associated with permanent physical impairment may offer a strong empirical reason to support therapeutic germline editing. However, there are normative counterarguments to be considered. First, if being disabled is associated with lower social opportunities, the solution may not necessarily be in preventing disability with gene editing technologies, but rather in educating society to include disabled patients, as the "stigmatization" or "right to disability" arguments claim (Conti, 2017; Benston, 2016). Second, the authorization of germline editing for the prevention of exceptional disabilities could gradually pave the way for the authorization of cosmetic germline editing to avoid discrimination of somatic diversity. Setting aside racism, beautiful people have better access to many social and employment opportunities, and beauty is a relative concept strongly associated with somatic traits (Little *et al*., 2011). In turn, the authorization of cosmetic germline editing to protect equal opportunities could gradually pave the way to the strengthening of psychosomatic skills in order to ensure optimal performance in an increasingly competitive society.

If psychosomatic enhancement was available to any citizen by drawing on shared financial resources, society would simply shift from one average of acceptable performance to another, more advanced, new average of acceptable performance, jeopardizing any competitive advancement (low personal and technical value) while also neglecting the risks of long-term, unpredictable side effects (low allocative and societal value). From a strictly biomedical point of view, even once the safety of germline editing has been demonstrated on a single patient, it will still be necessary to monitor the long-term effects of gene surgery on that patient and future generations (Araki & Ishii, 2014); from a holistic, psychosocial point of view, the theory of decreased marginal benefit clearly shows how – beyond a certain threshold of health – increasing expectations are associated with more healthcare expenditure and less satisfaction (Davini, 2013). If psychosomatic enhancement is funded by individual, private resources, progressive health inequalities would follow from financial (ability to afford treatment) or cultural inequalities (awareness of treatments and which genes to modify), extending the social determinants of health gap to subsequent familial generations (Buchanan *et al*., 2000).

In this way, deep health inequalities, decreased health satisfaction and potential harm to the next generations – which present an undesirable state of things – could gradually follow from an initial authorization of germline editing for the prevention of incurable disease or severe disability. This is known as the "slippery slope" argument (Gumer, 2019; Van der Burg, 1991). If psychosomatic enhancement is considered an abuse of germline editing, the use of these technologies should therefore be either completely prohibited (Gumer, 2019) or strictly regulated and limited to therapeutic applications (Xu, 2020).
Considering the slippery slope argument from an even longer perspective, the societal value of therapeutic germline editing may become even more controversial. Epidemics are known, in history, to have provided a rapid, though brutal solution to chronic problems of overcrowding, misery, lack of resources, and violent competition among populations, if not within the same families. During the golden age of medicine (Le Fanu, 2011), many countries learned to get rid of the scourge of infections that significantly reduced childhood mortality (Istat & Unicef, 2011), extending the average life expectancy (Le Fanu, 2011). Unfortunately for wealthy societies, today, a longer life expectancy hardly means a *healthier* life expectancy, since chronic comorbidity and degenerative disease multiply precisely due to aging and greater exposure to the side-effects of comfort (i.e., pollution, overeating, traffic accidents, poor physical activity, poor prevention, inappropriate medicalization and drug abuse) (Davini, 2013). Less brutally but more insidiously than the plague, tuberculosis or Spanish flu, the diseases of the "health [and wealth] epidemic" (Porter, 2011) reveal hidden pitfalls behind a determination to prolong life at all costs, raising fundamental questions about the reasonable goals of medicine and healthcare. Is the goal of medicine adding years to life, or life to years? Current CRISPR trials against aging (either directly, by addressing the molecular drivers of aging, or indirectly, addressing age-related disease) (Beyret *et al*., 2019; Chen *et al*., 2018) seem to favour the latter option. That being the case, suppose that germline editing works on regular human embryos with no side-effects on the newborn or subsequent generations; suppose that germline editing is able to prevent any (non-traumatic) disease and slow down or eliminate aging, transmitting extraordinary resistance against the physio-pathological mechanisms of human nature, generation after generation; even so, our invincible offspring will, at some point, be faced with more and more people living on a planet with fewer and fewer resources, and will continue to die because of the natural selection, fighting for food, shelter or water. If the potential benefits of germline editing are expected to obtain maximum value because of the transmission of benefit between generations, the risk of a slippery slope additionally makes the societal value of germline editing controversial from the longest possible perspective.

5. Conclusions

Aging societies, financial constraints and the progressive erosion of the social fabric mean that the wellbeing of individuals, the cohesion of society and the sustainability of welfare can no longer be considered within watertight compartments. The key to maintaining a fair and sustainable healthcare system is to identify which treatments provide greater value, to whom, and for how long. A multidisciplinary HTA is needed to answer these questions. Awaiting further clinical trials and developments of gene editing techniques on embryos, a useful framework to assess the social, ethical, economic and organizational implications of potential applications is provided by the value-based approach. Once safe, germline editing could prevent severe impairment and disability. Even though parents should be free from coercion, as there is no intrinsic moral evil in conceiving and living with disability, this intervention could provide better personal value to the newborn, as compared with abortion. Better social inclusion is a worthwhile cultural effort to avoid stigma and the risks that might follow either abortions or inappropriate germline editing. From a technical point of view, germline editing can generate significant value – once safe – in the absence of safer, cheaper or more

conventional treatments. In that case, germline editing would also generate significant allocative value. In terms of societal value, germline editing can benefit patients and society provided there is strict regulation against any inappropriate use. Overall, the value of germline editing technologies – once clinically safe – would lie in the prevention of serious disease and disability where safer, and cost-effective alternatives do not exist, maintaining the freedom of parents to choose whether or not to opt for treatment.

REFERENCES

Adams, R., Reiss, B., & Serlin, D. (2015). Disability. In R. Adams, B. Reiss & D. Serlin. *Multiculturalism in the United States: A comparative guide to acculturation and ethnicity* (pp. 5-11). New York, NY: New York University Press;

Alexander, S. (1962, November 9). They Decide Who Lives, Who Dies: Medical Miracle Puts Moral Burden on Small Committee, *Life*, 102-105;

Altman, L., Zurynski, Y., Breen, C., Hoffman, T., & Woolfenden, S. (2018). A Qualitative Study of Health Care Providers' Perceptions and Experiences of Working Together to Care for Children With Medical Complexity (CMC). *BMC Health Service Research*, 18(1), 70. Doi: 10.1186/s12913-018-2857-8;

Araki, M., & Ishii, T. (2014). International regulatory landscape and integration of corrective genome editing into in vitro fertilization. *Reproductive Biology and Endocrinology*, 108(12). Doi: 10.1186/1477-7827-12-108;

Barrangou, R., Fremaux, C., Deveau, H., Richards, M., Boyaval, P., Moineau, S., Romero, D. A., & Horvath, P. (2007). CRISPR provides acquired resistance against viruses in prokaryotes. *Science*, 315(5819):1709-12. doi: 10.1126/science.1138140;

Benston, S. (2016). CRISPR, a Crossroads in Genetic Intervention: Pitting the Right to Health against the Right to Disability. *Laws*, 5(1). Doi: 10.3390/laws5010005;

Beyret, E., Liao, H.-K., Yamamoto, M., Hernandez-Benitez, R., Fu, Y., Erikson, G., Reddy, P., & Izpisua Belmonte, J. C. (2019). Singe-Dose CRISPR/Cas9 Therapy Extends Lifespan of Mice with Hutchinson-Gilford Progeris Syndrome. *Nature Medicine*, 25(3), 419-422. Doi: 10.1038/s41591-019-0343-4;

Bognar, G., & Hirose, I. (2014). *The ethics of health care rationing. An introduction*. New York, NY: Routledge;

Boorse, C. (1977). Health as a Theoretical Concept. *Philosophy of Science Association*, 44(4), 542-573;

Brewerm A. (2018). "We Were on Our Own": Mother's Experiences Navigating the Fragmented System of Professional Care for Autism, Social Science and Medicine, 215,61-68. Doi: 10.1016/j.socscimed.2018.08.039;

Buchanan, A., Brock, D. W., Daniels, N., & Wikler, D. (2000). *From chance to choice. Genetics & Justice*. Cambridge: Cambridge University Press;

Calabresi, G., & Bobbitt, P. (1978). *Tragic Choices*. New York, NY: W W Norton & Co Inc.;

Carroll, D. (2017). Genome Editing: Past, Present, and Future. *Yale Journal of Biology and Medicine*, 90(4), 653-659;

Chekani-Azar, S., Gharib Mombeni, E., Birhan, M., & Yousefi, M. (2020). CRISPR/Cas9 gene editing technology and its application to the coronavirus disease (COVID-19), a review. *Journal of Life Science and Biomedicine*, 10, 1-9. Doi: 10.36380/scil.2020.jlsb1;

Chen, C.D., Zeldich, E., Li, Y., Yuste, A., & Abraham, C. R. (2018). Activation of the anti-aging and cognition-enhancing gene Klotho by CRISPR-Cas9 transcriptional effector complex. *Journal of Molecular Neuroscience*, 64(2), 175-184. Doi: 10.1007/s12031-017-1011-0;

Coffey, M.J., Coffey, & Coffey, C.E. (2019, June 12). Real-Time Pursuit of Outcomes That Matter to Patients. *NEJM Catalyst*. Retrieved from: https://catalyst.nejm.org/doi/abs/10.1056/

CAT.19.0651;
Consorzio Nazionale delle Associazioni dei Malati Cronici, & CittadinanzAttiva. (2015, December 2). *XIII Rapporto sulle politiche della Cronicità. È ancora pubblico accesso?* Retrieved from: https://www.cittadinanzattiva.it/comunicati/salute/6972-xiii-rapporto-sulle-cronicita-e-ancora-pubblico-accesso.html;
Consorzio Universitario per la Ricerca Economica Applicata in Sanità. (2015). *11° Rapporto Sanità – L'universalismo diseguale*, Roma. Retrieved from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwi6uIfp57_qAhUkx4sKHbOFCfEQFjAAegQIAhAB&url=https%3A%2F%2Fwww.creasanita.it%2Fimages%2Frapportosanita%2F11%2FXI_RapportoSanita.pdf&usg=AOvVaw2NcIQeriSDlNNxkVRCLTwF;
Conti, A. (2017). Drawing the Line: Disability, Genetic Intervention and Bioethics. *Laws*, 6, 9. Doi: 10.3390/laws6030009;
Costa, G., Bassi, M., Gensini, G. F., Marra, M., Nicelli, A. L., & Zengarini, N. (2014), *L'equità nella salute in Italia. Secondo rapporto sulle diseguaglianze sociali in sanità*, Milano: Franco Angeli;
Cyranoski, D. (2016, November 15). CRISPR gene-editing tested in a person for the first time. Nature. Retrieved from: https://www-nature-com.bibliosan.clas.cineca.it/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988;
Daniels, N. (2008). *Just Health. Meeting Health Needs Fairly*. Cambridge: Cambridge Univeristy Press;
Daniels, N., & Sabin, J. (2008). The Ethics of Accountability in Managed Care Reform. *Health Affairs (Milwood)*, 17(5), 50-64. Doi: 10.1377/hlthaff.17.5.50;
Davies, K., & Barrangou, R. (2020). COVID-19 and the CRISPR Community Response. The CRISPR Journal, 3, 66-67. Doi: 10.1089/crispr.2020.29092.rba;
Davini, O. (2013). *Il prezzo della salute. Per un sistema sanitario sostenibile nel terzio millennio*. Roma: Nutrimenti;
Do Rozario, L. (1997). Spirituality in the lives of people with disability and chronic illness: a creative paradigm of wholeness and reconstruction. *Disability Rehabilitation*, 19(10), 427-34. Doi: 10.3109/09638289709166568;
European Commission. (2019). *Expert Panel on Effective Ways of Investing in Health. Defining "value in value-based healthcare"*. Retrieved from: https://ec.europa.eu/health/expert_panel/sites/expertpanel/files/docsdir/024_defining-value-vbhc_en.pdf;
European Hematology Association. (2017, June 23). *European Hematology Association: Treating Sickle Ceel Disease and Beta-Thalassemia with CRISPR/Cas9 Gene Editing*. Retrieved from: https://www.prnewswire.com/news-releases/european-hematology-association-treating-sickle-cell-disease-and-beta-thalassemia-with-crisprcas9-gene-editing-630287013.html;
Falzon, C. (2014, June). *Wrongful Life & Wrongful Birth – Legal and Moral Issues*. doi: 10.13140/RG.2.1.2156.4649; Retrieved from: https://www.researchgate.net/publication/281372405_Wrongful_Life_Wrongful_Birth_-_Legal_and_Moral_Issues;
Finnegan, G. (2017, May 23). Outcomes that matter to patients derive more value from health budgets. *Science Business*. Retrieved from: https://sciencebusiness.net/healthy-measures/news/outcomes-matter-pa;
Foglia, E., Lettieri, E., Ferrario, L., Porazzi, E., Garagiola, E., Pagani, R., Bonfanti, M., Lazzarotti, V., Manzini, R., Masella, C., & Croce, D. (2017). Technology Assessment in Hospitals: Lessons Learned From an Empirical Experiment. *International Journal of Health Technology Assessment in Health Care*, 33(2), 288-296. Doi: 10.1017/S0266462317000356;
Frati, P., Kyriakou, C., Del Rio, A., Marinelli, E., Montanari Vergallo, G., Zaami, S., & Busardò, F. P. (2015). Smart Drugs and Synthetic Androgens for Cognitive and Physical Enhancement: Revolving Doors of Cosmetic Neurology. *Current Neuropharmacology*, 13(1), 5-11. Doi: 10.2174/15

70159X13666141210221750;
Glannon, W. (2006). Psychopharmacology and memory. *Journal of Medical Ethics*, 32(2), 74-78; doi: 10.1136/jme.2005.012575;
Gossen, H. H. (1854). *Entwicklung der Gesetze des menschlichen Verkehrs und der daraus fließenden Regeln für menschliches Handeln*, Braunschweig: Friedrich Vieweg & Sohn;
Greely, H.T. (2019). CRISPR'd babies: human germline genome editing in the "He Jiankui affair". *Journal of Law and the Biosciences*, 6(1), 111-183. Doi: 10.1093/jlb/lsz010;
Gumer, J. M. (2019). The Wisdom of Germline Editing: An Ethical Analysis of the Use of CRISPR-Cas9 to Edit Human Embryos. *The New Bioethics: a multidisciplinary journal of biotechnology and the body*, 25(2), 137-152. Doi: 10.1080/20502877.2019.1606151;
Gupta, R. K., Abdul-Jawad, S., McCoy, L. E., Ping Mok, H., Peppa, D., Salgado, M., Martinez-Pciado, J., Nijhuis, M., Wensing, A. M. J., Lee, H., Grant, P., Nastouli, E., Lambert, J., Pace, M., Salasc, F., Monit, C., Innes, A. J., Muir, L., Walters, L., Frater, J., Lever, A. M. L., Edwards, S. G., Gabriel, I. H., & Olavarria, E. (2019). HIV-1 Remission Following CCR5Δ32/ Δ32 Haematopoietic Stem-Cell Transplantation, *Nature*, 568(7751), 244-248. Doi: 10.1038/s41586-019-1027-4;
Hale, B. (2001). The value of life and the cost of living – Damages for wrongful birth. *British Actuarial Journal*, 7(5), 747-763;
Haworth, K. G., Peterson, C. W., & Kiem, H. P. (2017). CCR5-edited gene therapies for HIV cure: Closing the door to viral entry. *Cytotherapy*, 19, 1325-1338. Doi: 10.1016/j.jcyt.2017.05.013;
He, J. (2018, November 26). Lulu and Nana: Twin girls born healthy after gene surgery as single-cell embryos. Retrieved from: https://www.youtube.com/watch?v=th0vnOmFltc;
Huang, Z., Tomitaka, A., Raymond, A., & Nair, M. (2017). Current application of CRISPR/Cas9 gene-editing technique to eradication of HIV/AIDS, *Gene Therapy*, 24(7), 377-384. Doi: 10.1038/gt.2017.35;
Huxley, A. (1932). *Il mondo nuovo. Ritorno al mondo nuovo*. Milano: Mondadori (1998);
Hütter, G., Schneider, T., & Thiel, E. (2009). Transplantation of selected of transgenic blood stem cells – a future treatment for HIV/AIDS? *Journal of International AIDS Society*, 12(10). Doi: 10.1186/1758-2652-12-10;
Hyry, H. I., Manuel, J., Cox, M. T., & Roos, J. C. P. (2015). Compassionate use of orphan drugs. *Orphanet Journal of Rare Disease*, 10(100). Doi: 10.1186/s13023-015-0306-x;
Istituto Nazionale di Statistica (Istat), & United Nations International Children's Emergency Fund (Unicef). (2011). *La mortalità dei bambini ieri e oggi. L'italia post-unitaria a confronto con i Paesi in via di sviluppo*. Roma: Comitato Italiano per l'UNICEF Onlus;
Ijzermans, M.J., Koffijberg, H., Fenwick, E., & Krahn, M. Emerging Use of Early Health Technology Assessment in Medical Product Development: A Scoping Review of the Literature. *Pharmacoeconomics*, 35(7),727-740. Doi: 10.1007/s40273-017-0509-1;
Jamal Anjum Official. (2020, January 31). 4 ways to defeat Corona virus. Retrieved from: https://www.youtube.com/watch?v=1mx5_eV2nAM;
Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A programmable dual-RNA-guided DNA endonucleases in adaptive bacterial immunity, *Science*, 337(6096):816-821. Doi: 10.1126/science.1225829;
Jørgensen, J., & Kefalas, P. (2017). Annuity Payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *Journal of Market Access & Health Policy*, 5(1), 1355203. Doi: 10.1080/20016689.2017.1355203;
Kamm, F. M. (2013). *Bioethical Prescriptions: To Create, End, Choose, and Improve Lives*. New York, NY: Oxford University Press;
Kang, X., He, W., Huang, Y., Yu, Q., Chen, Y., Gao, X., Sun, X., & Fan, Y. (2016). Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *J Assist Reprod Genet*, 33(5), 581-588;

King, A. (2020, February 20). Detailed 3D coronavirus spike map offers hope for vaccine development [Royal Society of Chemistry]. Retrieved from: https://www.chemistryworld.com/news/detailed-3d-coronavirus-spike-map-offers-hope-for-vaccine-development/4011226.article;
Kluytmans, A., Tummers, M., van der Wilt, G. J., & Grutters, J. (2019). Early Assessment of Proof-of-Problem to Guide Health Innovation. *Value Health*, 22(5), 601-606;
Kristensen, F. B., Lampe, K., Chase, D. L., Lee-Robin, S. H., Wild, C., Moharra, M., Velasco Garrido, M., Palmhøj Nielsen, C., Røttingen, J.-A., Allgurin Neikter, S., Bistrup, M. L., & European Network for Health Technology Assessment. (2009). Practical Tools and Methods for Health Technology Assessment in Europe: Structure, Methodologies, and Tools Developed by the European Network for Health Technology Assessment, EUnetHTA. *International Journal of Technology Assessment in Health Care*, 25 Suppl 2, 1-8. Doi: 10.1017/S0266462309990626;
Lander, E. S., Baylis, F., Zhang, F., Charpentier, E., Berg, P., Bourgain, C., Friedrich, B., Keith Joung, J., Li, J., Liu, D., Naldini, N., Nie, J. B., Qiu, R., Schoene-Seifert, B., Shao, F., Terry, S., Wei, W., & Winnacker, E.L. (2019, March 13). *Adopt a moratorium on heritable genome editing*. Retrieved from: https://www-nature-com.bibliosan.clas.cineca.it/articles/d41586-019-00726-5;
Lavazza, A. (2019). Parental Selective Reproduction: Genome-Editing and Maternal Behavior as a Potential Concern. *Frontiers in Genetics*, 10, 532. Doi: 10.3389/fgene.2019.00532;
Lawless, M. T., Marshall, A., Mittinty, M. M., & Harvey, G. (2020). What Does Integrated Care Mean From an Older Person's Perspective? A Scoping Review. *BMJ Open*, 10(1), e035157. Doi: 10.1136/bmjopen-2019-035157;
Le Fanu, J. (2011). *The Rise & Fall of Modern Medicine*. London: Abacus;
Lega Italiana per la Lotta contro l'AIDS. (2019, June). *HIV e genitorialità*. Retrieved from: https://www.lila.it/it/vivere-con-hiv/592-hiv-e-genitorialita;
Le Rhun, A., Escalera-Maurer, A., Bratovic, M., & Charpentier, E. (2019). CRISPR-Cas in Streptococcus pyogenes. *RNA Biology*, 16(4), 380-389. doi: 10.1080/15476286.2019.1582974;
Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., Ly, J., Xie, X., Chen, Y., Li, Y., Sun, Y., Bai, Y., Songyang, Z., Ma, W., Zhou, C., & Huang, J. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, *Protein cell*, 6, 363-372;
Lim K. R. Q., Yoon C., & Yokota T. (2018). Applications of CRISPR/Cas9 for the Treatment of Duchenne Muscular Dystrophy. *J Pers Med*. 8(4). Pii: E38. doi: 10.3390/jpm8040038;
Little, A.C., Jones, B.C., & DeBruine, L.M. (2011). Facial attractiveness: evolutionary based research. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366(1571), 1638-1659. Doi: 10.1098/rstb.2010.0404;
Loureiro, A. & da Silva, G. J. (2019). CRISPR-Cas: Converting A Bacterial Defence Mechanism into A State-of-the-Art Genetic Manipulation Tool, *Antibiotics (Basel)*, 8(1), pii: E18. doi: 10.3390/antibiotics8010018;
Mangan, B. (2018, May 23). Value-based procurement: a users' guide to improving outcomes and delivering efficiencies in the UK. *MedTech Views*. Retrieved from: http://www.medtechviews.eu/article/value-based-procurement-users-guide-improving-outcomes-and-delivering-efficiencies-uk;
Marangi, M. & Pistritto, G. (2018). Innovative Therapeutic Strategies for Cystic Fibrosis: Moving Forward to CRISPR Technique. *Front Pharmacol*, 9, 396. doi: 10.3389/fphar.2018.00396;
Marraffini, L. A. (2016). The CRISPR-Cas system of Streptococcus pyogenes: function and applications. In Ferretti J.J., Stevens D.L., Fischetti V.A. (Eds), *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. Oklahoma City, OK: University of Oklahoma Health Sciences Center;
McCabe, C., Claxton, K., & Culyer, A. J. (2008). The NICE Cost- Effectiveness Threshold: What It Is and What That Means. *Pharmacoeconomics*, 26(9), 733-44. Doi: 10.2165/00019053-200826090-00004;

National Academies of Sciences. (2017). *Human Genome Editing: Science, Ethics, and Governance*. Washington DC: National Academies Press;
Niccol, A. (1997). *Gattaca*. United States: Columbia;
Organization for the Economic Cooperation and Development. (2015, September 24). Healthcare costs unsustainable in advanced economies withour reform. Retrieved from: https://www.oecd.org/health/healthcarecostsunsustainableinadvancedeconomieswithoutreform.htm;
Outram, S. M. (2010). The Use of Methylphenidate Among Students: The Future of Enhancement? *Journal of Medical Ethics*, 36 (4): 198-202; doi: 10.1136/jme.2009.034421;
Penn Medicine News (2019, November 6). Early Results from First-In-U.S. Trial of CRISPR-Edited Immune Cells for Cancer Patients Suggest Safety of Approach. Retrieved from: https://www.pennmedicine.org/news/news-releases/2019/november/results-first-us-trial-crispr-edited-immune-cells-cancer-patients-safety-of-approach;
Pennestrì, F. (2019). *Eppur si Muore. Vivere di più o vivere meglio?* Milano: Mursia;
Pennestrì, F., Lippi, G., & Banfi, G. (2019). Pay less and spend more – the real value in healthcare procurement. *Annals of Translational Medicine*, 7, 688. doi: 10.21037/atm.2019.10.93;
Pennestrì, F. (2017). L'essenziale a tutti. I nuovi livelli di assistenza fra sostenibilità ed equità. *Notizie di Politeia,* 128, 60-73;
Porter, R. (2011). *The Cambridge Illustrated History of Medicine*. Cambridge: Cambrigde University Press.
Radaelli, G., Lettieri, E., Masella, C., Merlino, L., Strada, A., & Tringali, M. (2014). Implementation of EuNetHTA Core Model in Lombardia: The VTS Framework. *International Journal of Technology Assessment in Health Care*, 30(1), 105-112. Doi: 10.1017/S0266462313000639;
Rawls, J. (1971). *A Theory of Justice*. Cambridge: The Belknap Press of Harvard University;
Regione Lombardia. (2014). *Indicazioni di policy per l'integrazione sanitaria, socio-sanitaria ed assistenziale. Policy paper*, Milano: Polis.
Reichman, N. E., Corman, H., & Noonan, K. (2008). Impact of Child Disability on the Family. *Maternal Child Health Journal*, 12(6), 679-83. Doi: 10.1007/s10995-007-0307-z;
Sample, I. (2019, December 31). Chinese scientists who edited babies' genes jailed for three years. Retrieved from: https://www.theguardian.com/world/2019/dec/30/gene-editing-chinese-scientist-he-jiankui-jailed-three-years;
Santas, G. (2019). CRISPR and the Ethics of Gene Editing: A Modest Framework for Discussion. *International Journal of Clinical Research & Trials*, 4, 138. Doi: 10.15344/2456-8007/2019/138;
Scanlon, M. L., & Vreeman, R. C. (2013). Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. *HIV/AIDS (Auckland)*, 5,1-17. Doi: 10.2147/HIV.S28912;
Sen, A. (1993). Capability and Well-Being. In M., Nussbaum & A. Sen (Eds), *The Quality of Life* (pp. 30-53). Oxford: Clarendon Press;
Signorelli, C., & Fara, G. M. (2020). COVID-19: Hygiene and Public Health to the Front. *Acta Bio-medica: Atenei Parmensis*, 91(3-S), 7-8. Doi: 10.23750/abm.v91i3-S.9507;
Silverstein, A. (1979). *The Conquest of Death. A controversial look on medicine and why we may be the last generation to die*. New York, NY: Macmillan;
Soni, S. (2020, May 21). COVID-19 and gene editing: ethical and legal considerations. *The Conversation*. Retrieved from: https://theconversation.com/covid-19-and-gene-editing-ethical-and-legal-considerations-138164;
Tang, L., Zeng, Y., Du, H., Gong, M., Peng, J., Zhang, B., Lei, M., Zhao, F., Wang, W., Li, X., & Liu, J. (2017). CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. *Molecular genetics and genomics*, 292(3), 523-533. doi: 10.1007/s00438-017-1299-z;
Taramasso, L., Demma, F., Bitonti, R., Ferrazin, A., Giannini, B., Giacomini, M., Beltramini, S., Sasso, E., Viscoli, C., & Di Biagio, A. (2018). How has the cost of antiretroviral therapy changed

over the years? A database analysis in Italy. *BMC Health Service Research*, 18, 691. Doi: 10.1186/s12913-018-3507-x;
Tebas, P., Stein, D., Tang, W. W., Frank, I., Wang, S. Q., Lee, G., Kaye Spratt, S., Surosky, R., T., Giedlin, M. A., Nichol, G., Holmes, M., C., Gregory, P. D., Ando, D., G., Kalos, M., Collman, R., G., Binder-Scholl, G., Plesa, G., Hwangm W-T., Levine, B., L., & Hune, C., H. (2014). Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV. *New England Journal of Medicine*, 370(10), 901-910. doi: 10.1056/NEJMoa1300662;
Teff, H. (1985). The action for "wrongful life" in England and the United States. *International Journal of Comparative Law Quarterly*, 34, 423-41;
The Associated Press-NORC Center for Public Affairs Research. (2018). Human Genetic Engineering. Retrieved from: http://apnorc.org/projects/Pages/Human-Genetic-Engineering.aspx;
The HIV-Causal Collaboration (2010). The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*, 24: 123-127. Doi: 10.1097/QAD.0b013e3283324283;
The Fertility Institutes (2020). Choose Your Baby's Eye Color. Takind advantage of the ever-expanding role of modern genetics. Retrieved from: https://www.fertility-docs.com/programs-and-services/pgd-screening/choose-your-babys-eye-color.php;
Tsang, C., & Cho, S. (2018 January 22). Wrongful Pregnancy: UK Courts continue to refuse compensation for such claims on public policy grounds. *Kennedys Law*. Retrieved from: https://www.kennedyslaw.com/;
Vachey, G. & Déglon, N. (2018). CRISPR/Cas9-Mediated Genome Editing for Huntington's Disease. *Methods Mol Biol*, 1780:463-481. doi: 10.1007/978-1-4939-7825-0_21;
Van der Burg, W. (1991). The Slippery Slope Argument. *Ethics*, 102, 42-65;
Van Leeuwen, C. M., Post, M. W., Westers, P., van der Woude, L. H., de Groot, S., Sluis, T., Slootman, H., & Lindeman, E. (2012). Relationships Between Activities, Participation, Personal Factors, Mental Health, and Life Satisfaction in Persons With Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation*, 93(1), 82-9. Doi: 10.1016/j.apmr.2011.07.203;
Wang, C., Zhai, X., Zhang, X., Li, L., Wang, J., Liu, D-P., & Chinese Academy of Medical Sciences. (2019). Gene-edited Babies: Chinese Academy of Medical Sciences' Response and Action. *Lancet*, 393(10166), 25-26. Doi: 10.1016/S0140-6736(18)33080-0;
Weiseler, B., McGauran, N., & Kaiser, T. (2019). New drugs: where did we go wrong and what can we do better? *The British Medical Journal*, 366, l4340. Doi: 0.1136/bmj.l4340;
World Health Organization (2020, January 30). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Retrieved from: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov);
World Health Organization (2007). Sixtieth World Health Assembly: Health technologies. Retrieved from: https://www.who.int/healthsystems/WHA60_29.pdf?ua=1;
Xie, Y, Zhan, S., Ge, W., & Tang, P. (2019). The Potential Risks of C-C Chemokine Receptor 5-edited Babies in Bone Development. *Bone Research*, 7(4). Doi: 10.1038/s41413-019-0044-0;
Xu, M. M. (2020). CCR5-Δ32 biology, gene editing, and warnings for the future of CRISPR-Cas9 as a human and humane gene editing tool. *Cell Bioscience*, 10, 48. Doi: 10.1186/s13578-020-00410-6;
Zangrillo, A., & Gattinoni, L. (2020). Learning From Mistakes During the Pandemic: The Lombardy Lesson. *Intensive Care Medicine*, 1-2. Doi: 10.1007/s00134-020-06137-9;
Zou, S., Glynn, S., Kuritzkes, D., Shah, M., Cook, N., Berliner, N., & NHLBI AIDS Blood Session Group. (2013). Hematopoietic Cell Transplantation and HIV Cure: Where We Are and What Next? *Blood*, 122(18), 3111-5. Doi: 10.1182/blood-2013-07-518316.