



Intervening in the Human Germline

OPINION · EXECUTIVE SUMMARY & RECOMMENDATIONS

9 May 2019

The full text of the Opinion as well as all publicly available information and documentation of the German Ethics Council accompanying the work on interventions in the human germline are available at <https://www.ethikrat.org/en/topics/medizin-und-gesundheit/interventions-in-the-human-germline>.

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>> EXECUTIVE SUMMARY

Introduction

- 1) Molecular instruments that permit the targeted modification of the genomes of living organisms are developing rapidly. As a result, the possibility of intervening more easily and precisely in the human germline is drawing closer and closer.
- 2) This raises the question whether the previous categorical rejection of germline interventions can be upheld or whether it must undergo a new ethical assessment. An assessment of this nature must include a broad spectrum of very different aspects. They range from parents' wishes over the anticipation of the needs of future children to social concerns and our understanding of what it means to be human.
- 3) In September 2017, the German Ethics Council issued an ad hoc recommendation calling for a broad social debate on human germline interventions. This Opinion is the Council's contribution to this

debate. In it, the Council discusses the relevant ethical concepts that offer orientation on the different application scenarios for germline interventions. In the concluding summary, it outlines decision paths that set out the different lines of argumentation.

- 4) The alleged birth of genetically modified twin sisters in China at the end of 2018 underlines the urgent need to reach an understanding on how to responsibly handle the issue of human germline interventions, even if their introduction into medical practice is still a long way off given the current state of technology. A global consensus at least on the minimum ethical requirements seems indispensable no matter how difficult this might be to achieve.

Scientific and medical foundations

- 5) The information on the structure and the function of all cells in an organism is passed on from generation to generation through DNA (deoxyribonucleic acid) in the cell nucleus. Individual meaningful segments of DNA, which code for a certain protein, for example, are called genes. Their activity is determined by a complex interplay of interactions with the products of other genes and with external factors, many aspects of which are far from being fully understood.
- 6) The human genome is predominantly organised as chromosomes consisting of two long DNA strands wound into a double helix. The human genome consists of 23 pairs of chromosomes. A child inherits one chromosome of each pair from its mother and one from its father.
- 7) The gene copies inherited from a mother and a father often differ slightly from one another. In these cases, the child is heterozygous for this gene. If it carries two identical copies of a gene on both

chromosomes, it is homozygous for that gene. It can then pass on only this gene variant to its offspring.

- 8) New gene variants are created by mutations, for example due to environmental influences such as radiation or chemicals or during normal cell metabolism, when copying DNA before cell division, and through errors in repairing damage of this kind to DNA. Variants that cause disease or significantly increase the risk of disease are rare compared to more neutral variants.
- 9) If mutations affect cells from which eggs and sperm are later produced, they have reached the germline and can thus be passed on to offspring. The germline connects an individual with all his or her descendants via his or her own gametes and with his or her ancestors via the gametes from which he or she first originated. The germline includes not only the gametes but also all their precursor cells, including the cells of the early embryo.
- 10) Some mutations stop the proteins encoded by a gene from being produced or lead to them being produced only in an altered form or quantity. This can cause disease or impact the risk of disease.
- 11) Diseases caused by mutation in a single gene are referred to as monogenic disorders. Some of them only occur when both gene copies carry the mutation – they are recessive. Other mutations act in a dominant way: The affected person already becomes ill if only one of the two gene copies carries the mutation.
- 12) If the occurrence of a disease depends on several gene sites or if environmental influences also play a role, it is referred to as a polygenic or multifactorial disorder. Many common diseases are multifactorial disorders.

- 13) The distinction between the monogenic, polygenic and multifactorial inheritance of genetic susceptibility and other traits is something of an idealisation. The phenotypic impact of individual gene variants is always influenced by other genetic and non-genetic factors.
- 14) Genome editing is the term used for techniques that can be used to make targeted changes to previously defined parts of the genome. There are several molecular approaches and tools that can be used to pursue this goal. CRISPR-based techniques (CRISPR: clustered regularly interspaced short palindromic repeats) have attracted particular attention in recent years.
- 15) Genome editing approaches precisely modify a target sequence in the DNA, either through a cut or through biochemical modification. Cuts can lead to the removal of DNA fragments, to the insertion of new DNA fragments at a cutting site, or to a combination of both.
- 16) During the repair of cut sites, errors can occur that cause DNA fragments to be incorrectly reassembled or completely deleted. These unintended effects at the target site are also referred to as on-target effects. If the DNA is also cut at other sites in the genome that are similar to the actual target sequence but are not themselves the target of the intervention, this is referred to as an off-target effect.
- 17) It is difficult to predict the clinical consequences of these unintended modifications, especially when it comes to the genome editing of germline cells. One of the reasons for this is that most genes assume different functions in different tissues, at different stages of development, or even in different signalling cascades within one and the same cell.
- 18) The prerequisite for any clinical application of genome editing in germline cells is that undesirable side effects can largely be ruled out and that the desired gene alterations can nevertheless be precisely

achieved. Extensive research is being carried out to improve the accuracy of the methods and to reliably detect side effects in the genome.

- 19) Ensuring that a prospective child carries a desired gene variant in the nucleus of all its cells from the beginning of its development is currently only possible with preimplantation genetic diagnosis (PGD) and the selection of only those embryos that already have the desired trait. This technique does not involve any direct modifications to the DNA in the cell nucleus.
- 20) Direct germline interventions in the nuclear genome presuppose that genome editing tools can reach germline cells and unfold their action there. In principle, this could happen in already existing embryos, in gametes or in germline stem cells. Each of these options is associated with different difficulties, opportunities and risks.
- 21) Intervening in the genome of existing embryos frequently leads to mosaicism, where not all cells of the resulting organism are altered in the same way. This is because genome editing tools, even if they are injected at the single cell stage, do not spread fully or become fully effective until after the first cell divisions have begun. The intended processes of molecular change may then differ from cell to cell. Some cells may not be reached at all. Mosaicism cannot be reliably ruled out with PGD, as it can only examine individual cells.
- 22) Directly treating gametes prior to fertilisation might be one way of reducing or avoiding mosaicism. However, the special structure of mature gametes and their genomes poses its own challenges to the use of genome editing. Here, too, the success of the intervention cannot be verified before the embryo is created, since the mature gamete cannot be genetically examined after treatment without it being destroyed in the process. In addition, it might be that gametes that are not affected by an undesired gene variant would also be treated because they could not be identified prior to treatment.

- 23) Definite proof that a germline intervention has produced the desired result with no undesirable side effects could only be furnished if the procedure were to be performed in cells that can be genetically tested before they are used to create an embryo. This would be possible, for example, if viable human gametes could, in future, be obtained from cultured germ cell precursor cells or in stem cells generated from re-programmed body cells. This has already been done in animal experiments, but not yet in humans.
- 24) With the techniques available at the present time, germline interventions would not be reversible in the first generation. However, germline interventions could theoretically be reversed in the offspring of a genetically modified human by using genome editing again at the beginning of their development to undo the original edit.
- 25) Genome editing is still a very young field of research, which is why the basic techniques obviously still require considerable study and further development. Both the research objectives and the experimental systems available for each project may be of relevance for later ethical assessment.
- 26) Basic research, application-oriented preclinical research and clinical trials all have different research objectives. Basic research focusses on elucidating previously unknown mechanisms, structures or functional contexts not primarily in conjunction with a concrete application perspective. Application-oriented preclinical research examines the question of whether and, if so, how interventions in the germline could be carried over into practice but confines itself to non-human systems or research on human cells in vitro. Allowing genetically modified germline cells or embryos to develop into human beings should only be considered within the framework of clinical trials in order to determine the safety and efficacy of these interventions.

- 27) The experimental approaches that can be considered for research on germline interventions encompass research on animal and human cell cultures, but also on laboratory animals, synthetic human entities with embryo-like features (SHEEFs) and early human embryos in vitro.
- 28) Should the technologies mature, germline interventions would probably be used, for the foreseeable future, primarily in the context of pioneering clinical applications in reproductive medicine. For these applications, at least three conceivable goals can be identified: firstly, the prevention of genetic disorders; secondly, the reduction of disease risks, and thirdly, the optimisation of certain traits or abilities (enhancement).
- 29) The avoidance of monogenic disorders is a frequently mentioned potential field of application for germline interventions. In these cases, it can be assumed that the successful correction of a single disease-causing mutation in germline cells would lead to a child not being clinically affected by this disorder.
- 30) Whether such an intervention could ever be considered appropriate in practice would probably also depend on whether clinically proven alternatives such as PGD, which may be less risky for the child, are available. There are few cases in which this is definitely not the case – for example, if both parents themselves are clinically affected by a recessively inherited metabolic disease like cystic fibrosis. In this case, both parents carry a disease-relevant variant on both gene copies and all their children would inevitably also be clinically affected.
- 31) Normally, however, depending on the specific inheritance pattern and genetic status of both parents, between 25 and 75 percent of their offspring will not be clinically affected by the disease. If affected parents fulfil their wish of having genetically related children, PGD permits the selection of unaffected embryos. If germline interventions

were to be used instead in such cases, they would also have to be performed on potentially unaffected embryos, as it would not be possible to determine in advance which gametes carry the pathological gene variant.

- 32) In contrast to monogenic disorders, the risk of polygenic or multifactorial diseases is determined by a complex interaction between several genetic determinants (polygenic) or additional external factors, for example environmental influences (multifactorial).
- 33) There are only two cases in which an intervention in the germline to prevent polygenic and multifactorial diseases would have any chance of success: either a single gene would make such a major contribution to the overall disease risk that its modification would have a clearly preventive or mitigating effect. Or, it would be possible to simultaneously modify several gene variants that influence the risk of disease resulting in the overall risk being markedly reduced.
- 34) The correction of a germline mutation in the Breast Cancer 1 (BRCA1) gene could, for example, reduce the breast cancer risk of a woman affected by this form of familial breast cancer from about 75 percent to the level of the general female population of about 12 percent.
- 35) In contrast, in late onset Alzheimer's disease most genetic risk factors known to date only slightly increase the risk of developing the disease. One exception is the apolipoprotein E-4 gene variant. A single copy of this triples the disease risk. If two alleles are present, the risk increases 15-fold.
- 36) The use of genetic interventions to "improve" or extend certain physical, mental or personality functions or traits of healthy individuals is likewise referred to as genetic enhancement. In the narrower sense, this can be understood as an attempt to produce or enhance certain

desired traits in offspring that are not directly related to a disease. However, the dividing line between this use and therapeutic or preventive medical measures is by no means unproblematic.

- 37) The spectrum of potential enhancements is very broad and very complex. Interventions could be initiated at a single gene site, for example to increase athletic performance by altering the erythropoietin receptor gene, a certain variant of which leads to increased red blood cell production. In contrast, many other target traits such as intelligence or longevity are multifactorial and extremely complex. This means that the chances of success of germline interventions would be much more uncertain in their case.
- 38) In summary, it can be stated that interventions in the human germline are already hampered at the technical level by numerous major obstacles. The chances of overcoming them are still largely in the realm of speculation. The estimation of the interactions and long-term effects associated with germline interventions are unclear, too. Before any clinical intervention in the human germline could be carried out, the risks would have to be reduced to an acceptable level.
- 39) The weighing up of what is considered an acceptable level may also depend on the urgency of the parental desire for a child not affected by a specific affliction and the alternatives available for its treatment. However, the more complex the genetic component of a phenotype is and the more non-genetic factors play a role in its development and manifestation, the more difficult it would be to predict the effects of germline interventions, including undesirable consequences.

The legal framework

- 40) The legal norms for germline interventions in international and supranational law vary. Article 13 of the Oviedo Convention generally

prohibits any intervention seeking “to introduce any modification in the genome of any descendants”. However, it has not yet been ratified by a number of states, including the Federal Republic of Germany.

- 41) Article 24 of the Universal Declaration on the Human Genome and Human Rights of UNESCO states that interventions in the human germline “could be contrary to human dignity”. However, no explicit violation of human dignity is identified nor is a prohibition of germline intervention explicitly stated. Rather, the International Bioethics Committee is simply charged with the task of reviewing the situation. At the beginning of October 2015, the International Bioethics Committee called on the member states to adopt a joint moratorium on germline alteration by genome editing.
- 42) According to Article 3 para. 2 of the Charter of Fundamental Rights of the European Union, eugenic practices are not generally permissible. This can also be applied to germline interventions. However, therapeutic applications might be excluded. The Directive on the legal protection of biotechnological inventions of the European Parliament and of the Council of the European Union states that there is “a consensus within the Community that interventions in the human germline and the cloning of human beings offends against *ordre public* and morality”.
- 43) The legal situation in the various national legal systems is complex. It ranges from an explicit prohibition of interventions in the genetic makeup of human gametes and embryos in the Swiss Federal Constitution, the regulation of the permissibility of certain research projects on embryonic stem cells in Israel, a strict licensing procedure for research on human embryos in Great Britain to attempts in the USA to regulate research by means of the allocation of research funds, and selective state control in China.

- 44) The Embryo Protection Act (ESchG) of 1990 prohibits germline modifications for the purpose of reproduction in Germany. Beyond this, however, there are no explicit rules for dealing with this issue. The Basic Law, for instance, contains no explicit provisions on germline intervention.
- 45) The EschG does not explicitly cover many of the newer technical possibilities from the recent and most recent past. Since it is designed as a penal law, it cannot cover such new developments because of the principle “no criminal offence without law” (Article 103 (2) of the Basic Law), nor can it do so by analogy.
- 46) It is in this context that that the prohibitions regulated in the ESchG are to be understood. According to Section 5 ESchG it is punishable both to artificially alter the genetic information of a human germline cell and to use a human gamete with artificially altered genetic information for fertilisation. Moreover, the ESchG prohibits the production and use of human embryos for research purposes, including the testing and development of germline intervention techniques.
- 47) However, the prohibition of the artificial modification of the genetic information of a human germline cell does not apply if the process takes place in vitro and it is ruled out, at the same time, that the modified gamete will be used for fertilisation. Nor does it apply if the nucleus of an unfertilised egg cell is replaced by the nucleus of another egg cell or by the nucleus of a somatic cell. If gametes were artificially produced from previously genetically modified body stem cells and used for fertilisation, this would not fall under the ban either.

Outline and application of relevant ethical concepts

- 48) The German Ethics Council sets out those substantial normative and evaluative ethical concepts that provide, in its view, decisive and indispensable orientation for any ethical assessment of germline interventions. In so doing, it seeks to avoid two forms of problem reduction: on the one hand, the reduction of the ethical assessment to purely quantitative considerations of opportunities and risks, and on the other hand, any attempts to solve the problems at hand by exclusively referring to procedural strategies.
- 49) Using probability calculations, risk can be defined as a function of the extent of harm and the probability of its occurrence. However, numerical considerations of risks and opportunities reach their limits when a quantitative assessment is either impossible or inappropriate on ethical grounds. A pragmatic hurdle to the quantitative assessment of opportunities and risks would be, for example, that this involves interfering with an extremely complex system, the functionality of which has only been understood to a limited degree up to now. This limits the possibilities of reliably predicting the opportunities and risks of germline interventions.
- 50) In addition, the quantitative weighing up of certain moral goods appears to be fundamentally unacceptable, which means they impose ethical limits to any consideration of opportunities and risks. This is the case, for example, where human rights are concerned. This results in opportunity-risk considerations being subjected to deontological constraints, i.e. they are constrained by moral goods that are resistant to trade-offs. The consequence is that certain options for action may not be chosen even if their execution would lead to “the greatest happiness of the greatest number”, but would run counter to those moral goods that are resistant to trade-offs.

- 51) Human dignity has shaped bioethical discussions for many years and also represents an essential ethical concept for the debates on germline intervention. Its importance has undergone considerable changes since antiquity. In modern use, “human dignity” stands for that value which is resistant to any trade-offs and which is due to man as such and independently of all social provisions: man is regarded as an “end in himself”. This results in the ethical-philosophical and common jurisprudential prohibition of the “complete instrumentalisation” of any human being.
- 52) Views differ considerably when it comes to determining those entities to which human dignity could be attributed (impregnated eggs, embryos, born humans). These differences of opinion are, in turn, closely linked to the question of the necessary decoupling or coupling of the protection of dignity and the protection of life.
- 53) In the case of germline interventions, the question arises as to whether they completely instrumentalise future persons, assign them a legally devalued status and thereby violate their dignity. Conversely, however, the question also arises as to whether the renunciation of germline intervention, which could spare the people concerned severe suffering, would not violate their human dignity, too.
- 54) Because germline interventions affect future people or generations beyond the directly affected subjects, a “dignity of the human species” is occasionally postulated. This would make the human genome the object of protection of human dignity with the consequence that germline interventions would not be permissible. Occasionally, reference is also made to an “ethical self-understanding” of the species. Although this does not assign an independent dignity to the human species as such, it does consider the conditions of symmetry that exist between all human beings as equals which is violated when some people carry out targeted interventions in the genome of others.

- 55) In all interpretations of human dignity, however, the argumentative recourse to collective goods such as the genome, humanity or the human species must not undermine the formative individual core content of the guarantee of human dignity. A clear distinction should, therefore, be made between the human dignity of the individual – which is, constitutionally speaking, resistant to any critical weighing up – and any concepts of the “dignity of the human species” that are more open to critical appraisal.
- 56) The ethical concept of protection of life and integrity refers to the right of every human being to life and physical integrity irrespective of his or her performance. This right cannot be challenged on ethical or legal grounds. Beyond the basic prohibition of killing, it also encompasses the opportunity to access medical assistance (in the sense of a weak claim to basic health care).
- 57) Whether and to what extent protection of life and integrity already applies before birth, i.e. to human embryos and fetuses as well, is, however, a subject of controversy. This controversy is also reflected in the discussion as to when human life is accorded human dignity *in a comprehensive sense*. It leads back to fundamental anthropological and philosophical-ethical differences in the evaluation of human development. These differences also imply different assessments of the legal regulations applicable in Germany. This debate is of crucial importance when discussing the permissibility of embryo research.
- 58) More recently, there has been some discussion of whether this conflict could be avoided by not using human embryos with normal development potential for research but instead embryos with a built-in developmental stop or SHEEFs from which no viable human beings can develop. This would allow, where appropriate, further research on and improvement of the use of genome editing methods in the human germline, and the laying of the groundwork for possible clinical applications without destroying human embryos.

- 59) However, such entities cannot completely avoid the problems posed by questions of moral status. On the contrary, they reiterate the importance of the question as to which characteristics are to be deemed necessary and constitutive for full protection of life and integrity. The similarities between these entities and “ordinary” embryos must be large enough for the knowledge gained from the former to be transferable to the latter. But the more similar and scientifically meaningful the alternatives are, the more likely it is that their morally significant proximity to embryos with full developmental potential will increase.
- 60) The concept of protecting life and integrity must not be reduced to the question of the status of embryos or embryo-like entities. The life and integrity of human beings can also be endangered by failing to take certain measures. For this reason, the protection of life and integrity can, if necessary, demand certain actions – for example, to ward off diseases or disease risks and to promote health.
- 61) Freedom, as an ethical concept, initially encompasses both negative and positive freedom. Negative freedom refers to the absence of external constraints. Positive freedom is the condition of a self-determined orientation towards one’s own way of life, the meaningfulness of which one clearly accepts and which one adopts when executing one’s actions. The biographical realisation of negative and positive freedom always depends on external conditions – especially on the (free) actions of others.
- 62) Every research project, application or control of germline interventions affects the freedom of many stakeholders in many respects: freedom of research; in the event of a future maturity for application, the professional freedom of physicians; freedom of reproduction of those who consider germline interventions in their future children; and the freedom of those future individuals who carry the intentionally

altered genetic material and whose way of life has thus been affected in a specific manner.

- 63) The ethical concept of naturalness is mainly founded on two basic types of arguments. The first type refers to the germline as a symbolic “heritage of mankind” which imposes fundamental limits on human creative will. The second type refers to a presumed uncontrollability of the consequences of germline interventions, given the complexity of biological systems produced over millions of years in the course of evolution. However, the argument of naturalness is often used as a placeholder to articulate a vague unease about the mechanisation of the world.
- 64) Objections to arguments based on the concept of naturalness refer firstly to the concept’s extraordinarily broad spectrum of meaning, which ranges from originality and normality to complex philosophical ideas and thus allows very different interpretations. Secondly, reference is made to man as a cultural being whose “nature” consists precisely in changing his naturally predetermined conditions of life and action and adapting these to his or her cultural needs.
- 65) However, the reference to the ethical concept of naturalness also appears in another, primarily freedom-driven argument. According to this argument, a natural mode of development offers the most effective protection against any manipulative interests of third parties.
- 66) The ethical concepts of non-maleficence and beneficence are used both to criticise and to advocate interventions in the human germline. Beneficence refers to the opportunities offered by germline interventions to affected persons or humankind as a whole. The principle of non-maleficence, on the other hand, is based on the assessment and evaluation of risks.

- 67) Consequently, the consideration of these two ethical principles often takes the form of a risk-opportunity analysis. This, however, will not suffice if it is based on a purely objective quantitative analysis. Consequently, other relevant ethical concepts and the qualitative dimension of non-maleficence and beneficence must be taken into account. The latter depends on the respective perspectives of the various entities and groups involved in this process.
- 68) The ethical concept of justice demands that every person in society is actually guaranteed his or her due. Germline interventions will presumably change the network of relationships between the members of a society. Opinions differ whether these changes would tend to have negative or positive effects.
- 69) In principle, the question arises as to the extent to which and under what conditions certain attempts to modify gene variants deemed disadvantageous could actually lead to more or less justice. Political justice focuses, for example, on the extent to which the individuals and groups concerned are involved in the decision-making processes on germline interventions. Social justice focuses on the allocation of resources, i.e. on the just distribution of opportunities and risks or of the advantages and burdens of germline interventions respectively, as well as on their further research and development.
- 70) The effects of germline interventions on the allocation of resources and on the internal cohesion of societies are also regularly discussed in the context of the ethical concept of solidarity. “Solidarity” encompasses prosocial actions, inclinations and regulations that are intended to support others.
- 71) Overall, solidarity arguments can be applied to three areas, using partly different solidarity concepts: firstly, to research objectives and the organisation of research on germline interventions; secondly, to the solidary financing of healthcare, and thirdly, to socio-moral effects of

germline interventions on the cohesion of society and socio-cultural patterns of interpretation.

- 72) With reference to solidarity, one can argue both against and in favour of the application of germline interventions. There is potential for agreement on the demand that the practice and the objectives of current research should always be evaluated or aligned with a view to the social benefit and social goods. For individual application scenarios this leads on to the question of whether and, if so, how these should be integrated into the solidarity-based structure of the welfare state.
- 73) The ethical concept of responsibility is relevant to the normative relationships between stakeholders, their actions and the institutions to which the former are personally accountable. In the context of germline interventions, it is this very aspect of an anticipatory “responsibility for the future” that is as urgent as it is difficult to determine due to the complexity of the possible long-term consequences of today’s interventions in the human germline.
- 74) Different obligations may conflict with each other. In the case of germline interventions, for example, this can impact the responsibility for present and future generations. In such cases, a distinction must be made between the existence of an obligation and the degree to which it is binding in order to determine gradual differences in obligation. Responsibility towards members of future generations may, in principle, be unlimited but it is particularly binding for close generations for good reasons.
- 75) The briefly outlined ethical concepts that offer orientation when evaluating germline interventions only unfold their full potential when applied to specific scenarios. In this Opinion, this is the case for research on germline interventions and for three potential fields of application.

- 76) Before germline interventions can be applied in the context of human reproduction, there is almost unanimous agreement that extensive research must still be undertaken. Since, given the current state of the available technologies, a transition to clinical trials is still unanimously rejected at the present time, the German Ethics Council has concentrated its analysis on the application of ethical concepts that offer orientation in the context of basic and preclinical research.
- 77) General conditions for the transition to clinical research are taken into account when discussing possible clinical applications of germline interventions.
- 78) The question of the social embedding of research is equally relevant. This concerns both a broad public discourse on basic and preclinical research and research into the possible societal effects of clinical applications.
- 79) In basic and preclinical research, human dignity as an ethical concept is applied on the one hand to the question of whether and to what extent research on human embryos implies an impermissible instrumentalisation that would be considered a violation of human dignity. The answers to this question vary depending on the position adopted regarding the moral status of the embryo.
- 80) Human dignity also plays a role with regard to the research objective of improving the living conditions of people born after germline interventions or of humanity as a whole. Although human dignity does not justify a claim to an optimum of research or research benefits, it does, however, possibly offer protection against the general exclusion of relevant research.
- 81) When applying the ethical concept of protecting life and integrity, a distinction must be made between at least four positions: the categorical rejection of all embryo research, its exceptional approval as a

last resort, its general approval – but limited to surplus embryos and certain conditions, and its approval including the specific creation of embryos for research purposes.

- 82) The ethical concept of freedom is important in the context of research in several respects. They refer to freedom of research and to the freedom of persons who donate gametes or embryos for research purposes – perhaps in the context of reproductive interventions – but also with the freedom of future individuals who could benefit from the progress made through research. The scope of the rights to freedom involved largely depends on whether human dignity and the protection of life and integrity can demand or legitimise restrictions on research.
- 83) The ethical concepts of non-maleficence and beneficence in preclinical research are mainly concerned with the potential contribution of this research to a better assessment and the optimisation of the opportunities and risks of germline interventions. Beyond the above-mentioned problems of research on embryos, the risks that arise for donors of gametes and embryos are also relevant in this context.
- 84) With regard to research on germline interventions, it can be deduced from the ethical concepts of justice and solidarity that everyone should have the chance to benefit from such research in the mid- or long-term. Basic research and preclinical research should already be as transparent and participatory as possible, accompanied by an appropriate and broad societal discourse. Their goals should serve the common good.
- 85) Research on germline interventions touches on a broad spectrum of responsibilities. However, it is not easy to draw the line between the responsibility of individual researchers and collective responsibility. For this reason, it is essential that science and society engage in an

appropriate discourse process on these issues, also when it comes to specifying the respective responsibilities

- 86) The results of such processes can also impose limits on freedom of research beyond the question of the general permissibility of embryo research and the concrete prerequisites for clinical trials, for example if there were to be indications of undesired side effects of research. These may include stigmatisation or anti-solidarity effects in society or an overall negative assessment of the expected opportunities and risks. However, restrictions based on such concerns may only be justified if these effects cannot be countered in any other way.
- 87) If further developments in basic and preclinical research are sufficiently positive, the question may arise one day whether, after careful consideration of the relevant ethical principles that apply to research, a transition to clinical trials leading to the birth of genetically modified humans might be justifiable and whether, ultimately, the transition to regular application would then appear to be justifiable. This question may only be answered on a case-by-case basis and will have to be oriented towards the established rules and regulations for first-in-human trials.
- 88) The application scenarios analysed in the further course of the Opinion presuppose in each case – counterfactually – that these basic prerequisites have been met by appropriate research. The central question is whether certain applications might, in principle, be acceptable from a philosophical and ethical perspective. This is relevant for the specific decisions that may be pending in the future both when considering the transition *to* clinical research and when considering the transition to regular clinical application that may follow *after* such clinical studies have been successfully completed.
- 89) The *avoidance* of monogenic hereditary diseases is often referred to as the most realistic and most likely goal for the application of germline

interventions. Since these diseases are predominantly determined by mutations of a single gene, a germline intervention would have to be applied to only one gene in order to avoid them. Due to their often severe progression, their prevention is additionally classified as medically compelling.

- 90) There are already possibilities for most affected persons to avoid the birth of an affected child, for example with the help of PGD or germ cell donations. However, potential parents may reject such options in principle. It is also possible that PGD may not be an option because, for example, all of a couple's embryos would be clinically affected by the disease.
- 91) In its analysis, the German Ethics Council considers a hypothetical case in which both parents are affected by cystic fibrosis and wish to have a child together. In this case, a germline intervention would be the only way for the parents to have a healthy child who is genetically related to both partners. They could, for example, participate in a first-in-human trial on germline interventions if previous research had shown the technique to be sufficiently safe and effective.
- 92) In such a case, the ethical concept of human dignity does not argue against such an intervention. It is not evident that the parents' interest would imply an instrumentalisation of the future child that would impair human dignity. Rather, the withholding of a possible germline intervention could be interpreted as a violation of the future child's dignity, since the child would be unable to benefit from an important therapeutic possibility.
- 93) The application of the ethical concept of protecting life and integrity leads to similar results. From it can be derived a limited right for a future child to be protected against illness or disease risks. This would mean that failing to undertake such interventions would at least have to be justified. This applies not only to the specifically affected future

individual, but also with regard to the (not prevented) effects on future generations.

- 94) The ethical concept of freedom becomes relevant with regard to the reproductive freedom of parents who want to have a child who is genetically related to both of them. The freedom of the future child may be negatively affected by the risks of the intervention and the need to undergo lifelong check-ups. On the other hand, the avoidance of the disease also opens up new possibilities of freedom compared to living *with* the genetic condition.
- 95) Arguments based on the ethical concept of naturalness are of minor importance in the given application scenario. Hardly anyone will consider the accidental, “natural” presence of the cystic fibrosis gene as an aspect of human nature that is worth preserving.
- 96) On the other hand, non-maleficence and beneficence can be referred to in many ways. Both the carrying out and the failure to carry out the germline intervention are associated with opportunities and risks, the extent and quality of which can only be assessed to a limited extent and require careful consideration in each individual case.
- 97) The ethical concept of justice is linked to considerations about freedom if one sees the compensation for genetically conditioned disadvantages by germline intervention as an opportunity to fulfil the promise of equality of democratic societies and to increase individual opportunities for freedom. But questions of political justice also play a role when it comes to the participation of those affected in the decision-making process. Questions of fair access and distribution also arise with regard to the assumption of costs for such interventions by statutory health insurance.
- 98) Questions of financing are likewise relevant with respect to the ethical concept of solidarity. From the point of view of a solidary community,

there could be good reasons to support or even demand germline interventions for members with a cystic fibrosis mutation, either as an offer of help or out of a desire to reduce the costs for the entire community. The availability of germline interventions could, however, reduce solidarity with those already affected and lead to stigmatisation and discrimination of those who decide against such an offer.

- 99) Finally, responsibility towards persons who are affected in the future must be taken into account. If the technology were one day to be sufficiently safe, effective and tolerable, there could be a responsibility towards future children and their offspring to prevent their suffering by taking advantage of these interventions and allowing or financing them. An appropriate assumption of responsibility would include the duty to clarify the positive and negative consequences outlined above in the best possible way and to reach a decision on the permissibility of the intervention.
- 100) Overall, for the ethical assessment of germline interventions in monogenic hereditary diseases – assuming sufficient safety and efficacy of the technology – no categorical reasons for prohibiting such interventions can be derived from the application of the ethical concepts. Rather, the ethical concepts of the protection of life, of freedom and of beneficence suggest for some a duty to permit such interventions. Against this backdrop, considerations of non-maleficence, justice and solidarity do not provide any substantial arguments against the interventions.
- 101) Sceptics, on the other hand, are of the opinion that the technology in question is unlikely to acquire the necessary degree of perfection. Together with the view that germline interventions overstretch the field of normal medical action and could lead to a problematic expansion of the understanding of parental responsibility, this argumentation leads to the rejection of germline interventions even when it comes to avoiding a monogenic hereditary disease such as cystic fibrosis.

- 102) In contrast to the application scenarios for germline interventions in monogenic diseases, the probability of developing a disease that is caused by several genes (polygenic) or other, non-genetic factors (multifactorial) could generally only be *reduced* by germline intervention and not completely *avoided*.
- 103) The contribution of individual genes to the probability of disease does, however, vary greatly. At one end of this spectrum, hereditary breast and ovarian cancer are examples where the risk mainly stems from individual gene variants. A hypothetical case study features a woman with a BRCA1 mutation who has a 75 percent lifelong risk of developing breast cancer and a 45 percent risk of developing ovarian cancer. The probability of passing on the mutated BRCA1 gene copy to a child is 50 percent. This is what the future mother wishes to rule out with the help of a germline intervention.
- 104) The ethical concept of human dignity does not provide any indications of an improper instrumentalisation of the future child in this case, either. That the provision of a disease-risk reducing germline intervention is *called for* with a view to human dignity is less clear than when it comes to the certain avoidance of a monogenic hereditary disease. However, there might be a case for violation of human dignity if persons with a certain genetic disposition would have to expect stigmatisation and discrimination. Then germline interventions to reduce the risk of disease could be considered ethically called for because and insofar as they could prevent such occurrences.
- 105) With regard to risk-associated gene variants, the ethical concept of naturalness is regarded as even more problematic than in the case of monogenic hereditary diseases. The more disease-associated gene sites are involved, the more difficult it is to distinguish “natural” from pathological genetic make-up. In any case, from a developmental biology point of view, there is no clear standard for the natural genetic make-up of humans.

- 106) However, the ethical concepts of non-maleficence and beneficence continue to be relevant. People who bear an increased genetic risk for a disease and are aware of this may not yet be ill. But even the prognosis can have an effect on a person's attitude to life, his or her life planning, his or her physical self-image and, possibly, on working and insurance conditions. One can, therefore, describe these individuals as "healthy ill". If the disease is dangerous, the risk is high and its prevention is either impossible or invasive and stressful, there may be a duty to offer germline interventions on the grounds of non-maleficence and beneficence.
- 107) In the case of germline interventions to reduce disease risks, the status of the "healthy ill" raises questions of justice when it comes to whether and when such measures should be financed by the statutory health insurance system. It is difficult to determine the degree of risk that justifies financing on the grounds of justice.
- 108) The greater the stigmatisation and discrimination potential of a genetic predisposition, the more important become questions of solidarity with the individuals affected. This alone would not result in a moral imperative to eliminate such diseases by means of germline interventions. It would rather be a matter of structuring the society of the future in such a way that even the "healthy ill" can lead a good, existentially secure life.
- 109) In summary, the ethical assessment of a germline intervention in the case of hereditary breast cancer remains undecided even if a sufficiently effective and low-risk technique were to be available.
- 110) At the other end of the spectrum of genetically (co-)induced diseases, the disease risk is determined by an array of genetic and non-genetic factors. This can be illustrated using the example of late onset Alzheimer's disease, for which in most cases no clear genetic cause can be determined.

- 111) Nevertheless, scenarios are conceivable in which germline intervention to reduce the risk of Alzheimer's disease could become of interest to people who wish to have children. The hypothetical case study considered in the Opinion is based on potential parents who have both tested positive for the 11 gene variants that together increase the risk of late onset Alzheimer's disease by up to 20 times. The couple wishes to have the risk variants at all 11 affected gene sites corrected by germline intervention.
- 112) In this example, the application of the relevant ethical concepts basically leads to the same results as in the example of breast cancer. However, the specific disease risk of a future child can be predicted less clearly here due to the combinatorial possibilities between many gene sites. It will probably remain lower than in the previous example due to the greater contribution of non-genetic factors. This weakens the arguments for the urgency of a germline intervention and strengthens those for foregoing germline interventions or promoting other preventive measures.
- 113) Possible future applications of germline interventions also include scenarios of improving or enhancing certain features. Their potential spectrum is broad and diverse and it is difficult to distinguish them from therapeutic and preventive measures.
- 114) Challenges also arise from the question of whether and on what basis genetic enhancements should be considered ethically different from the improvement of physical, mental or character traits by means of traditional measures such as education. The latter are considered not only morally permissible, but even desirable or necessary.
- 115) In this context the ethical concept of human dignity is used in a prominent argument in order to examine the possibility of illegitimate instrumentalisation of the future child. An illegitimate instrumentalisation would be assumed if the traits of the child were partially altered

in such a way that they predispose it to a certain personality, a certain character or certain behaviours that serve parental goals or motives. The child would then be restricted in experiencing free self-determination and drawing up his or her own life goals and plans.

- 116) Another subject of controversy is whether a growing use of germline interventions for enhancement purposes could lead to the revival of eugenic or stigmatising attitudes and thus affect the human dignity of entire social groups. This could then also affect a dimension of human dignity that is linked to human self-understanding and the ethics associated with it: An imbalance could arise between parents, who make genetic decisions, and future children, who are determined genetically by their parents, that collided with the basic prerequisites of a democratic society as a society of members with equal rights and duties. At best, such decisions by parents could be compatible with these prerequisites if the (subsequent) consent of the children concerned could almost certainly be assumed.
- 117) Such fears do not justify a categorical ban of genetic enhancements, but they do emphasise an obligation on the part of the state to monitor such developments and, if necessary, take corrective action if germline interventions are to be permitted.
- 118) The ethical concept of freedom can be applied to questions related to enhancement both with a view to the freedom of the parents to shape their own children according to their own ideas and with a view to safeguarding the child's autonomy as a future person, i.e. to independently shape his or her own self. This consideration may lead to the conclusion that improvements may be permissible if they constituted a gain for every conceivable life plan of the future person, but not those that are intended to achieve highly specific abilities or qualities that might restrict the child in shaping his or her own life.

- 119) The ethical concept of naturalness takes on more relevance in the case of enhancement questions as these are particularly aimed at specific deviations from the norm that extend as far as the introduction of, for example, alien or artificial gene variants that do not normally occur in humans. This raises questions about the significance of naturalness per se as well as about the additional risks of deviating from evolved traits.
- 120) The dual determination of the non-arbitrariness and the flexibility of human nature does not, however, furnish any clear arguments against enhancement interventions either. The warning against a shift in the structure of society by certain delimitations of human biology, however, seems plausible to many.
- 121) With regard to non-maleficence and beneficence, it is often assumed that an opportunity-risk assessment will yield significantly less favourable outcomes when applied to enhancement interventions than when applied to therapeutic or preventive interventions. Possible risks of a germline intervention are more difficult to justify for the mere improvement of the normal condition.
- 122) The ethical concept of justice indicates that genetic enhancements, even if they were practicable and permissible, would have to remain a private financial matter for the foreseeable future. The coverage of costs by the public health system should be ruled out, since it cannot simply extend its responsibility to treatments that are defined precisely in contrast to therapy and medical prevention. It would be conceivable to finance enhancements indirectly (e.g. through tax deductibility) at some point in the future. But as long as this is not the case, a social practice of permitted germline enhancements could further widen the gap between rich and poor and exacerbate social inequality of opportunity.

- 123) Likewise, many see the danger of a creeping change of attitudes in society, which could undermine conditions of political justice, but also solidarity-based support. This would be the case if, at some point, coercive pressure were to be exerted to have enhancements carried out on one's own children in order to guarantee their later competitiveness in the best possible way. In a liberal society, however, the option must be upheld of being able to refuse interventions in the genome of one's own children without having to fear disadvantages for their later lives. This justifies an obligation on the part of the state to monitor and, if necessary, intervene.
- 124) In the case of enhancements, the ethical concept of responsibility is often related to the genetic constitution of future generations, with a view to both negative and positive consequences. On the other hand, it is argued that individual genetic changes would have scarcely any impact at the population level. The assumption of such a future responsibility is, therefore, exaggerated.
- 125) In summary, it can be observed that enhancements that would direct reproductive behaviour for collective purposes in a totalitarian manner by the state are clearly prohibited if the relevant ethical concepts that offer orientation are taken into account. In the case of individual decisions on enhancements by parents, such interventions would be inadmissible if they sought to enhance traits that only appeared meaningful in special life plans envisaged by the parents for their child.
- 126) Beyond these cases, the assessment is less clear. The concern about negative social effects of enhancements, namely the aggravation of justice problems and the emergence of cultural patterns of interpretation characterised by a lack of solidarity, are predominantly deemed to be important. For some, however, this does not justify any prohibitions, but merely an obligation on the part of the state to monitor such developments and, if necessary, to take regulatory countermeasures if the phenomena in question can actually be proven.

>> RECOMMENDATIONS AND DECISION PATHS

This Opinion has set itself the task of reconstructing and assessing the main facets and arguments of the complex debate surrounding the ethical evaluation of germline interventions. It seeks to present these arguments in a comprehensible manner and make them accessible to public and international debate. There have been repeated calls for this debate, not least by the German Ethics Council itself. To this end, the main paths on the road to conceivable decisions on basic and preclinical research on the one hand and clinical applications on the other are depicted in a *decision tree* (see book cover) and summarised below. With this tree it is possible to illustrate at which points decision paths take different forks in the road, i.e. where ethical concepts are interpreted differently and can thus be used to justify differing conclusions about what the next steps should be. An understanding of these main forks in the argumentation helps to throw light on the different possible positions and on the ensuing consequences in a clear and transparent manner.

However, prior to this, a number of conclusions are presented that have been shown to be capable of achieving a consensus in the German Ethics

Council. They can be seen as overarching recommendations irrespective of how the possible use of germline interventions is evaluated overall (and, perhaps, controversially).

Overarching conclusions and recommendations

1. The ethical analysis does not lead to any categorical inviolability of the human germline.
2. The assessment of the permissibility of germline interventions should not be reduced to a mere risk and opportunity analysis. Rather, it should be based on the ethical concepts of human dignity, protection of life and integrity, freedom, non-maleficence and beneficence, naturalness, justice, solidarity and responsibility.
3. The prerequisite for permissibility is, in any case, a sufficient degree of safety and efficacy of such interventions.
4. The German Ethics Council calls for an international moratorium on the clinical application of germline interventions in humans, and recommends that the German Bundestag and the Federal Government work towards a binding international agreement, preferably under the aegis of the United Nations.

This moratorium should firstly create a forum for a transparent process of discussion and evaluation of the possible goals of germline interventions in humans to determine in which cases and under what conditions germline interventions are to be classified as expedient and legitimate in future.

Secondly, it should allow time for careful basic and preclinical research, prevent premature application and classify any such application as a serious violation of both good scientific practice and general rules of good human coexistence.

Thirdly, it should create an arena for the elaboration of suitable instruments for international regulation.

The moratorium should undergo transparent regular review.

5. There is likewise agreement within the German Ethics Council that basic research without recourse to human embryos in vitro should be promoted with a view to gaining a deeper understanding of the effects of germline interventions in order to improve the level of knowledge about their safety and efficacy. This includes research involving synthetic human entities with embryo-like features provided they do not have embryo status.

6. Furthermore, the German Ethics Council recommends setting up an international agency that would be entrusted with at least two fundamental tasks:

Firstly, it should draw up and establish global scientific and ethical standards for research on and the practice of germline interventions in humans. It should monitor compliance with these standards wherever such research or practice is permissible. The register that is currently being put in place by the World Health Organisation could be one of the necessary foundations for this task.

Secondly, a standing committee should be set up within this agency to address the scientific, medical, ethical, legal, societal and political implications of germline interventions in humans, to set out possible solutions to the problems that arise and, in this way, to make a contribution to transparency and awareness-raising amongst the public at large.

7. This agency must be able to build on a broad national and international debate. The German Ethics Council, therefore, reiterates the demand formulated in its ad hoc recommendation of 29 September 2017 for the promotion of a global societal discourse on germline interventions. All relevant societal groups must be involved in this international exchange on appropriate ethical standards for the

assessment of possible future applications. An international conference hosted by the United Nations or the World Health Organisation would send out a welcome signal for such a development on the global level, too.

It goes without saying that public debate and awareness-raising must be stepped up in Germany, too. Various tried-and-tested formats of participation should be encouraged. The exchange of information should be ensured not just by the scientific community but also by public bodies. The German Ethics Council recommends that the Federal Government launch a structured civic discourse.

Decision paths

Although there is consensus within the German Ethics Council on the above-mentioned overarching recommendations, the concrete ethical evaluation of germline interventions may vary and even take on a controversial note, depending on the interpretation of the relevant ethical concepts and the application context. One and the same ethical concept can be interpreted very differently with regard to individual questions and individual application scenarios. As outlined in the Executive Summary and extensively addressed in the long version of this Opinion, the spectrum of the underlying arguments is highly detailed and nuanced. Nonetheless, some clear positions can be formulated and depicted as paths in a decision tree (see book cover). These paths touch on both basic and preclinical research on germline interventions and their clinical application. The questions (Q) take on a key or course-setting role in the decision-making processes, which means that the direction taken by the next sections of the paths will be determined by whether the answer to them is *yes* or *no*. Each section of these paths or each position (P) leads to further questions and, possibly, to specific consequences (C) that arise from a particular decision.¹

1 Courses of action are not formulated with any claim to completeness but are exemplary in nature. For each one key examples are given.

Most of the questions in the decision tree are geared towards whether an action *may* and also whether it *should* be carried out. *May questions* escalate ethical problems, thereby creating clarity and transparency. In some decision-making situations, however, they may conceal important nuances that are only revealed by the answer to the question whether an action which *may* be carried out, i.e. which is not prohibited, *should* also be carried out. Anyone who believes an action to be not only permissible but even necessary will answer this question in the affirmative. Conversely, anyone who does not want an action to be prohibited but nonetheless believes that it *should* not be carried out, will answer *no*, perhaps because there are more suitable alternatives that should be given preference in the weighing up process. Certain *should questions*, which thus go beyond the *may questions* sometimes facilitate a decisive differentiation when it comes to ethical orientation. Where such a distinction is relevant, the text emphasises this below.

Decision paths in the field of preclinical research

Question 1: Is the human germline inviolable?

Any reflections on germline interventions begin with the fundamental question whether the human germline may be interfered with *at all* or whether it is categorically inviolable and, therefore, basically precluded from any genetic engineering intervention (Q1). The answer of the German Ethics Council is a unanimous *no* to this categorical inviolability (P1b). It bases its answer more particularly on the following reasons: The germline, as such, cannot be the object or the substrate of the protection of dignity or life. Both must refer to concrete or, at least, potential persons. Furthermore, whilst direct interventions always require special justification and verification, the germline is nonetheless constantly being altered as a consequence of natural processes and human action. Consequently, *prima facie* arguments in favour of naturalness lack conviction (ethical concept naturalness).

- If the answer to the question 1 is *no* (P1b), this leads to the next question (Q2).

Possible reasons that may lead to a divergent position (P1a) are also mentioned here in order to support a substantial normative debate (see section 5.1). The view that the protection of dignity should be afforded already to the human germline as such (ethical concept human dignity) could back a categorical inviolability. Or it could be argued that the germline constituted the naturally given basis of every developing human being and may not, therefore, be purposefully modified (ethical concept naturalness). This position leads to several potential courses of action. They may include upholding existing prohibitions on research into germline interventions and their application or the more precise detailing or tightening of these prohibitions, for instance in the German Embryo Protection Act. Equally, there could be moves to secure the corresponding prohibitions through globally valid agreements.

- If the answer to question 1 is *yes* (P1a), this leads directly to the first consequence (C1): Germline interventions are ruled out.

Question 2: May/should the goal of germline intervention be pursued?

It does not necessarily follow from the conviction that the human germline is not, in principle, inviolable that germline interventions may or should be undertaken. There could be other reasons that fundamentally contest the legitimacy of this goal (*may*) or at least advocate the ethically mandated renunciation of this goal (*should not*). The second question (Q2) examines whether this is the case.

A large majority in the German Ethics Council is of the opinion that there are no further fundamental reasons for not pursuing the development of germline interventions in humans, and it gives an affirmative response to question 2 (P2a). In its opinion none of the ethical concepts suggests that germline interventions are, in principle, ethically reprehensible. On the contrary, arguments drawn from the ethical concepts of freedom, non-maleficence and beneficence, justice and solidarity advocate thorough and

responsible research into the opportunities and risks of the new technology. Some people even feel that the further pursuit of the goal of germline interventions is necessary because it can give couples with serious hereditary diseases a chance of conceiving a healthy child. Consequently, it is their belief that it is ethically justified and, where appropriate, necessary to drive research that looks into the opportunities for developing these technologies and assessing the safety and efficacy of germline interventions.

→ If the answer to question 2 is *yes* (P2a), this leads to the third question (Q3).

By contrast, a few members of the German Ethics Council are of the opinion that, for other fundamental reasons, interventions in the human germline may or at least should not be undertaken (P2b). Their stance is based on serious doubts that germline interventions can achieve any meaningful objectives at all, regardless of the individual application scenario. This draws firstly on the underlying reflection that germline interventions are not a procedure for treating or healing living individuals who have a disease. Ultimately, they pursue the goal of fulfilling a parent's wish for genetically related children who do or do not possess specific genetic traits. In their opinion germline intervention can be considered solely a reproductive technology. The goal of having genetically related children might be legitimate but, given the outlay required and the potential risks of germline interventions, it is seen as not imperative enough in any of the application scenarios discussed to justify imposing the associated risks on children and their offspring. It should not, therefore, be generally assumed that a germline intervention was permitted or even necessary with reference to the ethical concepts of beneficence or freedom.

Furthermore, when it comes to the goal of preventing serious hereditary diseases, it should be borne in mind that, in the vast majority of cases, PGD alone and, in the rare exceptional cases in which it was not possible, sperm or egg donation (although the latter is currently prohibited in Germany) would involve less outlay when it came to achieving this goal. Consequently, solidarity with couples wishing to have a child who does or

does not have specific genetic predispositions, could not impose the development of corresponding germline modifications.

Another fundamental objection is that, given the complexity of genetic and epigenetic processes, it is thought to be extremely unlikely that the risks could be reduced to an acceptable level in relation to the goals, even in the long term.

Finally, with reference to social justice the argument is advanced that the resources needed for germline interventions and the corresponding research could be put to better use in other ways.

If, against the backdrop of these arguments, the fundamental renunciation of the further pursuit of germline interventions is advocated, then one potential course of action might be to invest in those research activities and therapeutic applications which reduce or even eliminate genetically induced burdens on people without germline interventions. Similarly, recourse could be made to alternatives such as adoption or sperm donation.

Independently of this, reference is made in this context to the option of approving egg donation.

→ If the answer to question 2 is *no* (P2b), this leads back to the ruling out of germline interventions (C1).

Question 3: May/should research involving the destruction of human embryos in vitro be carried out?

If germline interventions are not ruled out from the very outset, this leads to the stage of basic and preclinical research. This stage encompasses both scientific endeavours to improve the reliability of genome editing techniques and the investigation of concrete opportunities of germline interventions in preclinical model systems. This then raises a further question, the alternatives of which are also a subject of contention within the German Ethics Council. May research be carried out on viable embryos in vitro? Such research involves early human embryos, the development of which is interrupted after a limited period of time (currently maximum 14 days as a rule) and which are then subsequently discarded. The respective

interpretation of the ethical concept of protection of life and integrity is particularly important when it comes to answering this question.

Most Council members answer *yes* to the permissibility of research involving early human embryos in vitro (P3a). If the increased knowledge that can be obtained through embryo research can significantly reduce the risks for humans born in the context of a later clinical application, they even believe that embryo research is necessary and, therefore, give an affirmative answer to question 3 also along the lines of “should” (ethical concepts non-maleficence and responsibility).

Proponents of this position might argue that the use of germline interventions to induce the birth of a human being should, in any case, be preceded by the corresponding research on early human embryos in vitro in order to assess the opportunities and risks of the intervention.

→ If the answer to question 3 is *yes* (P3a), embryo research would have to be permitted in Germany. This consequence (C2) encompasses the corresponding statutory amendments.

There are, however, major differences in the arguments advanced in this respect and the resulting conditions under which embryo research is deemed to be acceptable. They lead to different positions:

Two of them (P3a.1 and P3a.2) are in agreement that early embryonic life in vitro demands respect and great care in its handling but does not yet enjoy the full protection of human dignity (ethical concepts human dignity and protection of life and integrity).

Of the majority of Council members who answered “yes” to question 3, a majority again backs the fundamental legitimacy of embryo research but wishes to allow it solely in what are known as surplus embryos, i.e. embryos created during fertility treatment but which are definitely no longer going to be used for this purpose (P3a.1). The precondition for the use of these embryos for research purposes would be the consent of the couples from whom the gametes originated. Another option would be the further development of surplus impregnated eggs into embryos. The release for research purposes of impregnated eggs, whose fertilisation process has begun

but has not yet been completed, would have to be evaluated in the same way as the release of embryos after completed fertilisation. In both cases we are dealing with early human life which was originally produced for reproductive purposes but which cannot or should no longer be used for this purpose. In contrast, the express generation of embryos for research is ruled out as not permissible according to this position.

- This position (P3a.1) leads to consequence 2 – the approval of embryo research – but only for surplus embryos and impregnated egg cells.

In contrast, a minority of the Council members who answered “yes” to question 3 do not rule out the express generation of embryos from egg and sperm cells donated specifically for research purposes (P3a.2). They argue in favour of the permissibility of this option provided the persons from whom the germ cells originate have expressly agreed to their use for these purposes.

- This position (P3a.2) also leads to consequence 2 – approval of embryo research – including approval of the express generation of human embryos for research purposes.

According to a stricter variant, to which one member of the German Ethics Council also subscribes, the permissibility of embryo research is, in principle, *rejected* on the basis of the same arguments as presented in position 3b. However, certain circumstances are recognised under which this research should be permissible by way of exception and as a last resort (P3a.3). Certain germline modification applications pursue such morally high-ranking goals that ultimately the categorical prohibition of embryo research could become porous (ethical concepts protection of life and integrity, beneficence and solidarity). This position would likewise permit embryo research only in the case of surplus embryos generated by reproductive medicine. It would, however, also require that, for as long and as far as possible, priority was to be given to alternative research methods. Furthermore, it ties this

exception to a key date by which the surplus embryos must have been generated, similar to the Stem Cell Act. This key date rule is intended to thwart incentives for the generation of additional surplus embryos.

- Approval of embryo research only as a last resort (P3a.3) likewise leads to consequence 2 – the approval of embryo research. At the same time, it does impose strict conditions on this approval.

Others again, including a minority of Council members, strictly *reject* the permissibility of any embryo research (P3b). For them, every embryo created enjoys full protection of dignity from the very outset. This rules out any illegitimate instrumentalisation through research, and this protection includes an unconditional right to life (ethical concepts human dignity, protection of life and integrity). For them, the further development of the technology for interventions in the human germline is permissible *only if it takes place without* embryo research. Any necessary preclinical research would have to be restricted to alternative research subjects (for instance animals, cell cultures or SHEEFs). With reference to the ethical concept of protection of life and integrity, researchers should content themselves with the possibilities for expanding knowledge through these experiments and try to take the technology to a level of maturity deemed sufficient to progress to clinical research on germline interventions without embryo research. Nonetheless, this raises another ethical question: A decision must be taken on how to handle knowledge generated in other countries through embryo research.

- If the answer to question 3 is *no* (P3b), this takes us straight to the fourth question (Q4).

Question 4: May/should the results of embryo research be utilised even if one rejects such research oneself?

There are good scientific reasons for the assumption that molecular, cell and developmental biological processes in conjunction with a genetic modification to the human germline could be understood more easily if

they were also researched in viable human embryos. That explains why this research is permissible in many countries. This type of knowledge is, therefore, already being generated. If one backs position 3b, then one also has to decide whether one would be willing to declare the use of such knowledge as permissible and whether one would be willing to build further research in one's own country also on the contribution made to germline intervention technologies by embryo research elsewhere, even though one believes it is right to prohibit such research on ethical grounds.

The answer given to this question may be *no*, as is the case for some Council members, who base this on the view that the use of third party research findings which have been obtained under conditions deemed to be unacceptable, would be morally reprehensible or irresponsible ("free riding" accusation, ethical concepts justice, responsibility). If one supports this view (P4b), then one would either have to provide evidence, on the threshold to clinical research, that the findings obtained without embryo research are sufficient to justify the transition to the first clinical trials or – if this is not possible – to refrain from germline interventions (C1)

- If the answer to question 4 (P4b) is *no*, this leads to consequence 3 according to which further research on germline interventions is only to be carried forward without embryo research, and no recourse may be made to the embryo research findings of others either.

However the answer to question 4 can also be in the affirmative, as is the case for some other Council members. They argue that the use of research findings of third parties neither constitutes symbolic approval of embryo research outside Germany nor does it lead to an increase in the number of embryos destroyed abroad (P4a, ethical concepts protection of life and integrity, justice). The accusation of expressive moral dissonance ("double standards") can be countered by the fact that the rejection of embryo research within a specific population can be recognised through a prohibition without declaring this prohibition to be a genuinely moral (compelling) norm which everyone would have to share and deem plausible (ethical concept responsibility).

- If the answer to question 4 is *yes* (P4a), this means refraining from direct embryo research but does not rule out using the research findings of others obtained by using human embryos.

Irrespective of the path along which research in the preclinical phase progresses, the question will crop up at some point in the future as to whether research can move on to the clinical stage.

Question 5: *May/should there be a transition to clinical research?*

This question requires examination of whether, within the framework of basic and preclinical research, certain minimum safety and efficacy requirements regarding germline interventions in humans are met and whether, consequently, fundamental safety concerns or basic doubts about the usefulness of germline interventions have been sufficiently dispelled to justify the transition to clinical research (with the goal of reproduction) for individual scenarios.

At the time of publication, the answer to this question is unanimously “no” within the German Ethics Council and overwhelmingly “no” on the international stage (P5b.1). Globally, there is almost a comprehensive consensus that this technology is, in any case at the present time, still so immature that major tasks for basic and preclinical research have yet to be resolved.

- If the answer to question 5 is *currently no* (P5b.1), this has the consequence that a transition to clinical trials can for now be ruled out as impermissible (C4). For this reason the German Ethics Council unanimously recommends at this point in time a moratorium on applications (see recommendation 4).

However, there are some doubts whether, given the complex nature of inheritance processes, adequate safety and appropriate risk minimisation will *ever* be achievable.

- ➔ If, after the full exploitation of justifiable research efforts, the answer to question 5 becomes a *definitive no* (P5b.2), this leads to a permanent renunciation of germline interventions (C1).

If, on the other hand, in the light of future progress in preclinical research, the conclusion is one day reached that a suitable application scenario has been identified and the minimum safety and efficacy requirements regarding germline interventions have been sufficiently met, then the answer to question 5 will be yes and a transition to clinical research could, in principle, be considered.

- ➔ If the answer to question 5 (P5a) is *yes*, this paves the way for a transition to clinical trials and to questions 6.1-6.3, but only if certain conditions outlined in the following section are met.

Decision paths in the transitions to clinical application

A positive answer to question 5 marks the beginning of all decision paths in the field of clinical application in the context of human reproduction. This comprises at least two parts which are also arranged in chronological order: firstly, clinical trials in which an application is clinically tested for the first time, and secondly, the transition to regular clinical application which can only be considered if the clinical trials prove successful.

Prior to commencing clinical trials, the minimum safety and efficacy requirements of the technology to be used must be ensured, and appropriate oversight procedures and accompanying governance structures put in place for the intended clinical research (Cd1):

- » The treatment in question must have been sufficiently tested in a suitable animal model and in models with human cells.
- » It must be possible to assess the opportunities and risks arising from the application in humans in a transparent and expert-based manner, also with a view to any late onset traits.

- » The choice of a concrete application must also be backed by the reasoning that there are no alternative, less risky and effective treatments for this condition.
- » Adequate civic participation procedures must have taken place beforehand, including in particular the relevant patient associations, to look at expectations, wishes, fears and assessments.
- » The selection of the trial population will have been carefully checked for plausibility in an appropriate risk-benefit ratio.
- » A detailed research plan, containing the corresponding information, consent, supervisory and control mechanisms in accordance with the established standards for clinical research will be available and will have been approved by the competent governance bodies.
- » The organisation carrying out the trial undertakes to continue the scientific support for future persons born following germline interventions for an appropriately long trial period after their birth.
- » The project would have to be registered with the international institution recommended by the German Ethics Council (see recommendation 6).
- » The trial participants will have adequate insurance cover.
- » Long-term accompanying research on possible individual, cultural and societal consequences of the respective interventions is to be guaranteed.

The transition to regular clinical application, in turn, presupposes that, after completion of the clinical trials, the minimum safety, efficacy and tolerability requirements will be deemed to have been met and that the requirements in terms of their appropriate legal and social design and support will have been clarified and compliance ensured (Cd2). This also includes criteria for the practical design of the concrete clinical application, including guidance about to whom it may be offered, when and under which conditions, which societal processes may have to accompany the introduction of a specific treatment option and how, where appropriate, it should be financed. Here, too, some further fundamental conditions can be

formulated which should be met for the transition to the regular application of germline interventions:

- » evidence-based research on mortality, morbidity, quality of life, etc. after germline interventions compared with alternative treatment scenarios;
- » long-term monitoring of possible population effects;
- » accompanying ethical and socio-empirical research on the assessment of the social impact;
- » health economics research on assessing the financing questions within the framework of statutory health insurance;
- » ongoing communication and public participation.

Whether some of these criteria for the transitions to the two stages of clinical application can be regarded as having been met in a concrete case, will depend on the specific objectives pursued, the methods to be used and the current empirical state of play. Both in the weighing up of the opportunities and risks and in the application of ethical concepts, this can lead to different results. Although the concrete weighing up can thus ultimately only be undertaken for each individual case of application and with due consideration of the empirical findings available at that time, a generalisation of the ethical criteria for the evaluation of each of the three clinical application contexts examined in Chapter 4 is possible for both stages of the transition to clinical application.

As a result, the last question makes the permissibility of certain germline interventions dependent on the premise that the conditions for the transition to clinical trials and then to regular application have been fulfilled. At the time of publication of this Opinion, this question can be raised and answered on a general level for the three clinical application contexts developed in Chapter 4.

Question 6.1: May/should germline interventions be carried out to prevent hereditary disorders?

Monogenic hereditary disorders, such as cystic fibrosis, constitute a first area of clinical application. The question whether genetic predispositions to these disorders may be corrected through germline interventions – if this is possible – is answered in the affirmative by the vast majority of the members of the German Ethics Council for the following reasons (P6.1a): The prospect of an individual being able to lead his or her life without being restricted/burdened by a monogenic hereditary disorder is a high-ranking good. Its worthiness of protection results in particular from the ethical concepts of freedom, non-maleficence and beneficence. Or: The alternative, PGD, is not possible in some cases, for example if both partners carry the gene or only a few eggs can be harvested from the woman for fertilisation because of her age. Or: Possible negative effects from the angle of social justice or solidarity can be minimised through corresponding statutory provisions. For example, equal access to cost-intensive therapy (ethical concept justice) would have to be ensured as would the willingness to support the refinancing of lifelong cost-intensive treatment for those individuals whose parents did not undertake a genetic correction by means of germline intervention (ethical concept solidarity).

Nevertheless, it would have to be examined in each individual case whether the conditions outlined above (Cd1 and Cd2) have been met. In the case of the transition to regular application, the extent to which these clearly therapeutic applications could be financed through statutory health insurance would also have to be clarified.

- If the answer to question 6.1 is *yes* (P6.1a), this leads to the consequence 6.1 according to which germline interventions to avoid monogenic hereditary disorders are, in principle, permissible if the above conditions are met – provided the conditions for the transition to clinical trials (Cd1) and a subsequent transition to regular application (Cd2) can be met in each individual case.

One can, like a minority of the members of the German Ethics Council, *negate* the legitimacy or, at least, the usefulness of avoiding genetic predispositions to monogenic hereditary disorders through germline interventions (P6.1b). The following reasons could be given: PGD is necessary also in the case of germline therapy – at least as long as it is not possible to undertake both the intervention and its verification in cell lines. In most cases, PGD will permit the selection of clinically unaffected embryos even without germline intervention. This means that a germline intervention would only make sense in the very rare constellations in which this is not possible (for instance because both parents pass on the disorder homozygously). In these clearly foreseeable constellations it would, however, be reasonable to expect parents to abandon their wish for genetically related children in favour of parenthood through sperm donation or adoption (ethical concept freedom). Or: The advantages that may be gained from a less stressful life thanks to the prevention of the disorder by germline therapy for a few individuals cannot counterbalance the disadvantages from deficits in justice and solidarity that may arise for individuals who suffer from these disorders now or in the future (ethical concepts justice and solidarity).

- ➔ If the answer to question 6.1 is *no* (P6.1b), this means that germline interventions are not permissible for the purpose of avoiding monogenic hereditary disorders (C5.1).

Question 6.2: May/should germline interventions be carried out to reduce the risk of disease?

Given the broad spectrum of complex disease risks, which extends from almost monogenic burdens such as hereditary breast cancer to multifactorial causes such as late onset Alzheimer's disease, the German Ethics Council has refrained from a general vote on this question. Both the opportunities offered by such germline interventions and the risks and technical difficulties associated with them, very much depend on where a concrete risk of disease would fall in this spectrum. The factors on which a decision could be based include the likelihood of sufficiently safe and efficacious applications, the extent of risk minimisation that can be expected at best and the

alternative prevention and treatment approaches available. The higher the number of target sites in the genome that are to be treated simultaneously, the lower the contribution of an individual gene to the risk and the more complex the interaction with other factors, the less likely are the chances of a positive assessment. For the purposes of a provisional exploration of this topic, supporting and sceptical arguments are presented below.

The following reasons can be put forward to support an affirmative answer to the question whether genetic disease risks may be reduced with the help of germline interventions (P6.2a):

Germline interventions will mainly benefit those individuals whose genetic make-up is to be modified. This will preserve their concept of being an end in themselves. The potentially significant benefit of an intervention allows the counter-factual assumption that they would agree to the intervention (ethical concept human dignity). Both the reproductive freedom of parents and the real freedom of future persons are preserved and secured in the long term (ethical concept freedom). The danger of losing self-determination and social participation as a consequence of a disease such as breast cancer or dementia or being considerably psychologically burdened already by knowledge of the elevated genetic risk, is reduced (ethical concepts human dignity, non-maleficence). Similarly, burdens due to more intensive or more frequent health check-ups can be avoided. Reducing the risk of illness to the risks of the general population secures or increases equal opportunities. The potentially high initial costs, which may be considered problematic in terms of theoretical justice, the danger of discrimination and the exclusion of persons who cannot afford the therapy in question, can all be limited (ethical concept justice). Based on experience with other disorders, there are no grounds for fears that society will be less willing to support those individuals whose risks of disease have not been minimised by germline intervention (ethical concept solidarity).

In order to verify or confirm these assessments, increased research could be advocated to realistically estimate the relevant risk minimisation through germline interventions. Similarly, an evidence-based comparison with other ways of preventing and treating diseases would also be necessary, as would monitoring for adverse effects. Strict requirements could

likewise be put in place for the transition to clinical application, such as correspondingly robust evidence of a risk minimisation with a relevant impact on the quality of life, at least to the risk level of the population at large. Consideration should also be given to health economics research to assess the funding questions within the framework of statutory health insurance.

- If the answer to question 6.2 is *yes*, germline interventions are also to be deemed permissible in principle to minimise the risk of disease (C6.2) – provided that the conditions for the transition to clinical trials (Cd1) and a subsequent transition to regular application (Cd2) have been met.

The following reasons can be presented that argue against a minimisation of disease risk through germline therapy (P6.2b):

Even if such germline interventions do not directly violate the dignity of the persons concerned, societal attitudes about the burden to society generated by the financial follow-up costs of an illness, could create tendencies to reduce those persons who may still suffer from that illness in the future to a mere “cost factor” and, by extension, to their “objectification”. This would de facto erode the recognition of their status of being an end in themselves (ethical concept human dignity). The gains in freedom or self-determination, social participation etc. that may be derived from minimising the risks of illness do not outweigh the disadvantages that arise from negative justice and solidarity effects, such as discrimination against those individuals who cannot undergo germline modifications or the one-sided allocation of resources (ethical concepts justice and solidarity). Particularly in the case of multifactorial diseases like dementia, minimising the risks of disease through germline interventions can promote a focussing on genetic factors (risk of “genetic reductionism”). As a result, far more powerful factors such as nutrition or lifestyle could be neglected (ethical concepts non-maleficence and beneficence). Germline interventions in the case of multifactorial disease risks can only minimise these risks to a limited degree. However, they could nurture unrealistic expectations of perfectibility (ethical concept naturalness).

Against the backdrop of these arguments, research on and investments in other methods of minimising the risk of disease would be the preferred option.

→ If the answer to question 6.2 is *no* (P6.2b), this leads to the ruling out of germline interventions to minimise the risk of disease (C5.2).

Question 6.3: May/should germline interventions be carried out for enhancement purposes?

A third area of clinical application comprises germline interventions that serve to improve specific traits (enhancement). Here, too, the spectrum of imagined interventions ranges from those that focus on a single gene site to interventions at various gene sites where the interactions between genetic and other factors will probably still continue to be poorly understood for the foreseeable future.

The evaluation also depends on several factors, for instance the objectives pursued, the anticipated level of risk and environmental influences. The more complex the causes of the trait to be modified are and the less urgent the reasons for its modification, the more likely objections to any intervention will be. For many Council members, an evaluation of enhancement applications very much hinges on these aspects. A blanket affirmative or negative response to the question of permissibility would, therefore, be inappropriate. For the purposes of a provisional exploration of this topic, supporting and sceptical arguments are presented below.

The following reasons can be given in favour of enhancement options (P6.3a): The individual right to shape one's own body and personality and also the parent's right to freedom when it comes to shaping their own children in line with their own ideas of a good life must be guaranteed (ethical concept freedom). The concerns regarding the ethical concepts of solidarity and justice, i.e. the fears of an aggravation of injustice and the emergence of anti-solidary interpretation patterns, are deemed to be important but are not sufficient reasons to prohibit enhancement. They merely justify an obligation for the state to monitor such developments and, where necessary, introduce regulatory counter-measures.

In order to defuse such fears, increased research could be called for to realistically assess the health risks and social impacts, or particularly stringent conditions could be demanded for the transition to clinical application. Some thought would also have to be given to the economic dimension, be it the explicit exclusion of enhancement measures from statutory health insurance or – if they were to be desired by society as a whole – their funding from tax revenues.

- ➔ If the answer to question 6.3 is *yes*, germline interventions for enhancement purposes would also be permissible provided they meet the above-mentioned criteria for the transitions to clinical application (C6.3).

The permissibility of enhancement can also be negated (P6.3b). The following reasons can be presented to back this position: All state-controlled enhancement interventions for the widespread enforcement of eugenic goals are to be rejected as they constitute a violation of the prohibition of instrumentalisation on the grounds of the ethical concept of human dignity. As far as purely private enhancements are concerned, their permissibility could encourage a creeping shift in attitude towards ideologies of “feasibility” of the human condition, they could reinforce prevailing social stereotypes, and generate new dominant cultural patterns of interpretation which could have a negative impact on entire sections of the population (ethical concept human dignity). Furthermore, free decisions of parents about their reproductive decisions could be restricted by societal pressure or new and problematic forms of responsibility could be imposed on them (ethical concepts freedom and responsibility). The inner freedom and the concept of being an end in itself of a child who has been modified, could also be affected if traits were changed that (co-)determine his or her future character (ethical concepts freedom, human dignity). Enhancement goals are often accorded lower moral priority than medical interventions. Consequently, particularly strict criteria are advocated for risk assessment and non-maleficence (ethical concept non-maleficence). In addition, attention is drawn to the negative consequences for distributive, political

and participatory justice. There are likewise fears of a creeping erosion of the willingness to support solidarity in society (ethical concepts justice, solidarity).

Should these concerns lead to demands for blanket prohibitions of germline interventions for enhancement purposes, and if therapeutic and preventive germline interventions were to become feasible and permissible one day, then there would have to be an even more cautious determination of how to draw the boundaries between therapeutic, preventive and enhancing interventions. Nonetheless, the following conclusion applies:

- If the answer to question 6.3 is *no* (P6.3b), the consequence is that germline interventions for enhancement purposes are rejected (C5.3).

Final remarks

The above considerations clearly show that it can be difficult to differentiate between the conceivable application contexts. Furthermore, the range of complexity of the respective applications and the related opportunities and risks can vary considerably. For these reasons, a serious ethical evaluation of germline interventions – if one considers them to be ethically justifiable at all – can only be undertaken on a case-by-case basis and with reference to the respective relevant ethical concepts.

In principle, the less obvious any medical need is, the stricter the safety and efficacy requirements and, by extension, the innocuousness requirements for germline interventions will have to be. It is almost impossible to estimate and is doubtful in many respects whether acceptable minimum standards can ever be met at all, for any application, given the current state of technology development. Even if germline interventions were then in principle considered ethically legitimate, the demand would be, at least for pioneer applications, that the associated risks and uncertainties should only be tolerated to prevent severe disorders for which there are no alternative treatments.

Should such pioneer applications prove successful and their further technological development look promising, there are likely to be demands for an extension of treatment options to encompass less serious diseases, the mere minimisation of disease risks and, ultimately, enhancements. These developments may never happen. However, should they become reality, the German Ethics Council deems the path set out in this Opinion of cautiously weighing up the opportunities and risks based on the outlined ethical concepts, to be absolutely essential.

Members of the German Ethics Council

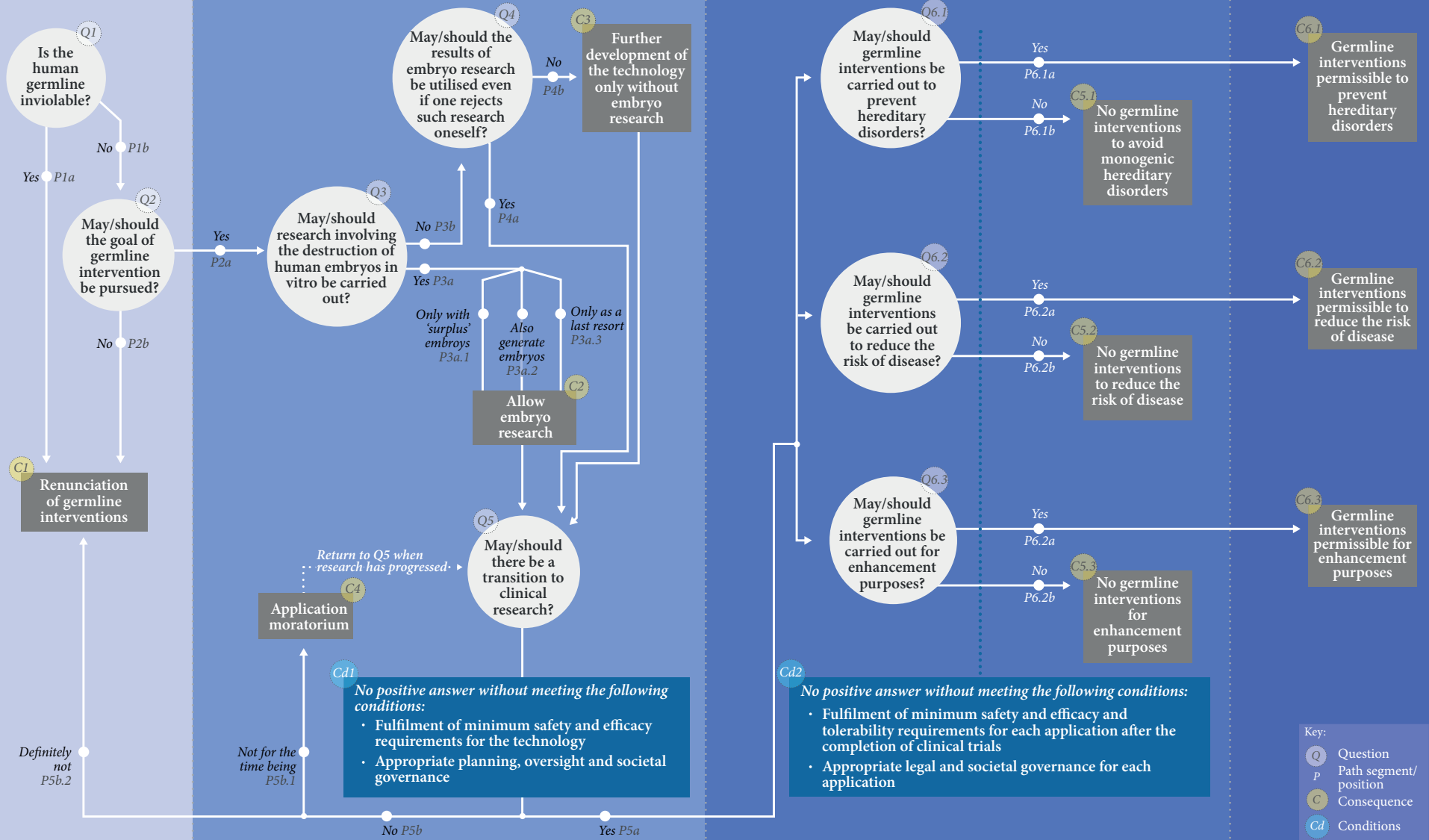
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Decision Tree for Human Germline Interventions



Key:

- Q Question
- P Path segment/position
- C Consequence
- Cd Conditions

Ethical concepts to be considered at each step: human dignity, protection of life and integrity, freedom, non-maleficence and beneficence, naturalness, justice, solidarity and responsibility

FUNDAMENTAL DECISIONS

BASIC & PRECLINICAL RESEARCH

CLINICAL TRIALS

CLINICAL APPLICATION