Decision Tree for Human Germline Interventions

Q1 Is the human germline inviolable?

- *Yes* *P1a* → **C1** Renunciation of germline interventions
- *No* *P1b* → **Q2** May/should the goal of germline intervention be pursued?
  - *No* *P2b* → **C1** Renunciation of germline interventions
  - *Yes* *P2a* → **Q3** May/should research involving the destruction of human embryos in vitro be carried out?
    - *No* *P3b* → **Q4** May/should the results of embryo research be utilised even if one rejects such research oneself?
      - *No* *P4b* → **C3** Further development of the technology only without embryo research
      - *Yes* *P4a* → **C2** Allow embryo research
    - *Yes* *P3a* → **C2** Allow embryo research
      - *Only with 'surplus' embroys* *P3a.1*
      - *Also generate embryos* *P3a.2*
      - *Only as a last resort* *P3a.3*

C2 Allow embryo research → **Q5** May/should there be a transition to clinical research?

- *Return to Q5 when research has progressed* → **C4** Application moratorium → **Q5**
- *Definitely not* *P5b.2* → **C1** Renunciation of germline interventions
- *Not for the time being* *P5b.1* → **C4** Application moratorium → **Q5**
- **Cd1** *No positive answer without meeting the following conditions:*
  Fulfilment of minimum safety and efficacy requirements for the technology
  Appropriate planning, oversight and societal governance
  - *No* *P5b* → **Q5**
  - *Yes* *P5a* → **Q6.1** / **Q6.2** / **Q6.3**

Q6.1 May/should germline interventions be carried out to prevent hereditary disorders?

- *Yes* *P6.1a* → **C6.1** Germline interventions permissible to prevent hereditary disorders
- *No* *P6.1b* → **C5.1** No germline interventions to avoid monogenic hereditary disorders

Q6.2 May/should germline interventions be carried out to reduce the risk of disease?

- *Yes* *P6.2a* → **C6.2** Germline interventions permissible to reduce the risk of disease
- *No* *P6.2b* → **C5.2** No germline interventions to reduce the risk of disease

Q6.3 May/should germline interventions be carried out for enhancement purposes?

- *Yes* *P6.2a* → **C6.3** Germline interventions permissible for enhancement purposes
- *No* *P6.2b* → **C5.3** No germline interventions for enhancement purposes

Cd2 *No positive answer without meeting the following conditions:*
Fulfilment of minimum safety and efficacy and tolerability requirements for each application after the completion of clinical trials
Appropriate legal and societal governance for each application

Key:
- Q Question
- P Path/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**

Arguments

FUNDAMENTAL DECISIONS

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
Question 1 Is the human germline inviolable?	**Path/position 1a:** **Yes, the human germline is inviolable.** **P1a.A1** Protection of dignity should be afforded already to the human germline as such. **P1a.A2** The germline constitutes the naturally given basis of every developing human being and may not, therefore, be purposefully modified.	Human dignity Naturalness	**Path/position 1b:** **No, the human germline is not inviolable.** **P1b.A1** The germline, as such, cannot be the object or the substrate of the protection of dignity. **P1b.A2** The germline, as such, cannot be the object or the substrate of the protection of life and integrity. **P1b.A3** The human germline is constantly being altered as a consequence of natural processes and human action. Consequently, arguments in favour of naturalness lack conviction.	Human dignity Protection of life & integrity Naturalness
Question 2 May/should the goal of germline intervention be pursued?	**Path/position 2a:** **Yes, the goald of germline intervention may/ should be pursued.** **P2a.A1** Thorough and responsible research to develop gene editing technologies and assessing the safety and efficacy of germline interventions is ethically acceptable and may even be necessary to give couples with serious hereditary disorders a chance of conceiving a healthy child.	Freedom Non-maleficence & beneficence Justice Solidarity	**Path/position 2b:** **No, the goal of germline intervention may/ should not be pursued.** **P2b.A1** Germline interventions are a reproductive technology and not a procedure for treating or healing living individuals. The goal of having genetically related children is not imperative enough to justify imposing the associated risks of germline interventions on children and their offspring. **P2b.A2** In the vast majority of cases, the goal of conceiving a child free from serious hereditary disorders can be achieved by alternatives such	Freedom Non-maleficence & beneficence Solidarity

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
			as PGD or using donor gametes. Consequently, solidarity with couples wishing to have a child who does or does not have specific genetic predispositions, cannot mandate the development of corresponding germline modifications.	
			P2b.A3 Given the complexity of genetic and epigenetic processes, it is extremely unlikely that the risks could be reduced to an acceptable level in relation to the goals, even in the long term.	Non-maleficence & beneficence
			P2b.A4 The resources needed for germline interventions and the corresponding research could be put to better use in other ways.	Justice
BASIC AND PRECLINICAL RESEARCH				
Question 3 May/should research involving the destruction of human embryos in vitro be carried out?	**Path/position 3a:** **Yes, research involving the destruction of human embryos in vitro may/should be carried out.**		**Path/position 3b:** **No, research involving the destruction of human embryos may/should not be carried out..**	
	P3a.A1 Embryo research could provide critical insights to understand and reduce the risks for humans born in the context of later clinical applications of germline interventions.	Non-maleficence & beneficence	**P3b.A1** Human embryos deserve full protection from the very beginning and enjoy an unconditional right to live. Their use and destruction for research are without exception an inacceptable instrumentalisation.	Human dignity Protection of life & integrity
	P3a.A2 Commencing clinical trials without prior embryo research would be irresponsible.	Responsibility		
	Path/position 3a.1: **Embryo research may/should be carried out with surplus embryos and impregnated egg cells.**			
	Path/position 3a.2: **Embryos may/should also be generated for research.**			

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	P3a.1.A1 & P3a.2.A1 Early embryonic life in vitro demands respect and great care in its handling but does not yet enjoy the full protection of human dignity and therefore also not full protection of life and integrity.	Human dignity Protection of life & integrity		
	P3a.1.A2 & P3a.2.A2 When embryos are left over after fertility treatment and definitely no longer going to be used for this purpose it is better to donate them for research than to destroy them – provided the research goals are appropriate and the parents consent to the donation. Such use does not imply an inacceptable instrumentalisation of early human embryos.	Human dignity Non-maleficence & beneficence Freedom		
	P3a.2.A3 There can be a need to generate embryos for research, for example when many embryos with very similar features are needed to answer a scientific question, and when there are not enough surplus embryos that fulfill those criteria.	Non-maleficence & beneficence Freedom		
	P3a.2.A4 Full moral status and full protection of life and integrity of human life can only be justified later in development, so the instrumentalisation of earliest human life that is implied in the dedicated generation of human embryos for research can be acceptable if the research is important enough.	Human dignity Protection of life & integrity		
	Path/position 3a.3: Embryo research may/ should only be carried out as a last resort.			
	P3a.3.A1 Human embryos deserve full protection from the very beginning. Using and destroying them for research implies a principally unacceptable instrumentalisation.	Human dignity Protection of life & integrity		

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	P3a.3.A2 However, such an instrumentalisation can in exceptional circumstances be deemed justifiable if it is the only way to complete research that pursues very high-ranking, therapeutically relevant goals, after all other avenues for research have been exhausted. The acceptability of such embryo research would depend on safeguards to ensure that it will not create incentives to generate more surplus embryos for research.	Non-maleficence & beneficence Solidarity Justice Responsibility		
Question 4 May/should the results of embryo research be utilised even if one rejects such research oneself?	**Path/position 4a:** **Yes, the results of embryo research may/ should be utilised even if one rejects such research oneself.** **P4a.A1** Using such research results neither implies symbolic approval of embryo research abroad nor does it increase the number of embryos destroyed through such research. **P4a.A2** The use of such research results does not imply double standards since it is possible to honour a clear disapproval of embryo research through a local ban without having to declare such a ban as a mandatory norm that has to be shared and found convincing everywhere.	Protection of life & integrity Responsibility Justice Responsibility	**Path/position 4b:** **No, the results of embryo research may/should not be utilised if one rejects such research oneself.** **P4b.A1** Using research results that have been generated under conditions that one disapproves of is irresponsible or morally reprehensible (moral freeriding).	Responsibility Justice

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

The answer to this question depends less on fundamental arguments or ethical positions but hinges chiefly on the fulfilment of certain conditions. Any clinical trials of human germline interventions should only be approved, if the following conditions have been met for the specific application:

Cd1.1 The treatment in question must have been sufficiently tested in a suitable animal model and in models with human cells.

Cd1.2 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.

Cd1.3 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.

Cd1.4 Adequate civic participation procedures must have taken place beforehand, including in particular the relevant patient associations, to look at expectations, wishes, fears and assessments.

Cd1.5 There must be plausible and carefully determined criteria for participation in the trial that take into account the appropriateness of the opportunities and risks.

Cd1.6 A detailed research plan, containing the corresponding information, consent and oversight procedures in accordance with the established standards for clinical research must be available and have been approved by the competent governance bodies.

Cd1.7 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.

Cd1.8 The project would have to be registered with the international institution recommended by the German Ethics Council.

Cd1.9 The trial participants would need to have adequate insurance cover.

Cd1.10 Long-term accompanying research on possible individual, cultural and societal consequences of the respective interventions must be guaranteed.

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	Path/position 5a: **Yes, there may/should be a transition to clinical trials.**		**Path/position 5b1:** **No, there may/should be no transition to clinical trials for the time being.**	
	P5a.A1 Minimum safety and efficacy requirements for the technology have been met and appropriate planning, oversight and societal governance are in place.	All apply	**P5b1.A1** Minimum safety and efficacy requirements for the technology have not yet been met and/or appropriate planning, oversight and societal governance are not yet in place.	All apply
			Path/position 5b2: **No, there may/should definitely be no transition to clinical trials.**	
			P5b2.A1 Minimum safety and efficacy requirements for the technology have not been met and/or appropriate planning, oversight and societal governance are not in place. Either or both are not expected to be achievable with reasonable future efforts.	All apply

CLINICAL TRIALS

The answers to questions 6.1-6.3 do not only depend on fundamental arguments or ethical positions but also on the fulfilment of certain conditions. Any regular clinical application of germline interventions should only be permitted if the following conditions have been fulfilled for this specific treatment:

Cd2.1 There is evidence-based research on the mortality, morbidity, quality of life, etc. after germline interventions compared with alternative treatment scenarios.

Cd2.2 There is long-term monitoring of possible population effects.

Cd2.3 There is accompanying ethical and socio-empirical research to asses social impacts.

Cd2.4 There is health economics research to assess financing questions within the framework of statutory health insurance.

Cd2.5 There is ongoing communication and public participation.

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
Question 6.1 May/should germline interventions be carried out to prevent hereditary disorders?	**Path/position 6.1a:** **Yes, germline interventions may/should be carried out to prevent hereditary disorders.**		**Path/position 6.1b:** **No, germline interventions may/should not be carried out to prevent hereditary disorders.**	
	P6.1a.A1 The potential for a person to lead a life without impairments from a hereditary disorder is a high-ranking good.	Non-maleficence & beneficence Freedom	**P6.1b.A1** In most cases, PGD makes it possible to select an unaffected embryo without a need for genome editing. In the rare cases where this is not possible, it seems acceptable to deny the affected parents the fulfilment of their wish to have a genetically related child.	Freedom
	P6.1a.A2 Preimplantation genetic diagnosis is not possible or is rejected as an alternative in some cases.	Non-maleficence & beneficence Freedom		
	P6.1a.A3 Potential negative social effects could be minimised through appropriate legislation to ensure both fair access to germline therapies and support for those who decide against such interventions.	Justice Solidarity	**P6.1b.A2** The advantages that may arise from germline interventions for the few people for whom it has prevented a hereditary disorder cannot outweigh the disadvantages that are expected to arise from decreased justice and solidarity for families who still have to live with the disorder. This might be of special concern if the disorder becomes seen as an avoidable nuisance and burden to society.	Justice Solidarity
	P6.1a.A4 Withholding a sufficiently safe and effective germline intervention could imply a violation of the dignity and integrity of the future child, who would be denied access to an important therapeutic option. Parents and society bear responsibility for such a decision.	Human dignity Protection of life & integrity Responsibility	**P6.1b.A3** After a germline intervention, PGD will still be necessary in most cases to check for successful treatment. Embryos may still be discarded as a result.	Protection of life & integrity
	P6.1a.A5 Preimplantation genetic diagnosis involves the expectation that embryos that are affected by an undesirable trait will be discarded. It would be preferable to use germline intervention to offer a chance to live also to those embryos.	Protection of life & integrity	**P6.1b.A4** A decision for a germline intervention can also reduce the feedom of the future child, e.g. by making frequent checkups necessary.	Freedom
	P6.1a.A6 The decision about a germline intervention to prevent a hereditary disorder is covered by the reproductive freedom of the parents and will also increase freedom in the life of the future child.	Freedom	**P6.1b.A5** A germline intervention exceeds the classical doctoral mandate, so this cannot be used for justification. Nobody exists yet whose welfare would be affected by the intervention.	Non-maleficence & beneficence
			P6.1b.A6 It seems highly unlikely that the risks of germline interventions could ever be reduced to an acceptable level.	Non-maleficence & beneficence

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	P6.1a.A7 Reducing genetic disadvantages through germline interventions could contribute to fulfilling democratic societies' promise of equality.	Justice	**P6.1b.A7** Even the potential benefits of using germline intervention to prevent a hereditary disorder might be unclear for several reasons: 1. The genetic makeup offers limited information about the course a disease may take. 2. Some pathological gene variants confer health benefits to those who carry only one copy of them. 3. The assumption that germline intervention should permanently free a family from a disorder is an illusion since the mutation could always arise afresh or be reintroduced by future affected partners.	Non-maleficence & beneficence
	P6.1a.A8 Making such germline interventions possible and even publicly financing them could mean savings to the public health insurance system in the long run if fewer people needed lifelong expensive treament.	Solidarity		
Question 6.2 May/should germline interventions be carried out to reduce the risk of disease?	**Path/position 6.2a:** **Yes, germline interventions may/should be carried out to reduce the risk of disease.**		**Path/position 6.2b:** **No, germline interventions may/should not be carried out to reduce the risk of disease.**	
	P6.2a.A1 The people born after the intervention are also those who primarily benefit from it. It is highly plausible that they would consent to the intervention. They are therefore respected as ends-in-themselves.	Human dignity	**P6.2b.A1** Even the offer of germline therapy to reduce disease risks could lead to stigmatisation and discrimination of people with elevated disease risks. Reducing such people to „cost factors" could erode their status as ends-in-themselves.	Human dignity
	P6.2a.A2 The reproductive freedom of the parents and the freedom of the future person is protected by permitting such interventions.	Freedom	**P6.2b.A2** The benefits that might be expected from reducing disease risks cannot outweigh the disadvantages to be expected from negative effects on justice and solidarity or from one-sided allocation of resources to germline therapy.	Justice Solidarity
	P6.2a.A3 The risk of impaired self-determination or social participation when suffering from a disease like breast cancer or dementia is reduced, as is the psychological burden that comes with knowing about a significantly elevated disease risk. The burden of frequent	Non-maleficence & beneficence Human dignity	**P6.2b.A3** Especially with multifactorial diseases, germline interventions could lead to an inappropriate focus on genetic factors (genetic	Non-maleficence & beneficence Naturalness

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	or more invasive checkups or preventative measures can also be reduced. **P6.2a.A4** Reducing a disease risk to the population average increases justice. The potentially worrying costs and the risk of discrimination for those who cannot afford germline therapy can be limited. **P6.2a.A5** Decresasing solidarity with those who cannot or will not minimise disease risks through germline interventions is not seen as likely based on experiences with other disorders.	Justice Solidarity	reductionism). This could lead to unrealistic expectations of perfectability or to a neglect of more important factors such as nutrition or lifestyle.	
Question 6.3 May/should germline interventions be carried out for enhancement purposes?	**Path/position 6.3a:** **Yes, germline interventions may/should be carried out for enhancement purposes.** **P6.3a.A1** The individual right to shape one's self and the freedom of parents to shape their children according to their own views of a good life should both be safeguarded. This applies as long as the intended enhancement would be of benefit for the future person under any conceivable life plan. **P6.3a.A2** Concerns about justice and solidarity problems are valid but not reason enough to forbid enhancements. They merely point towards a duty of the state to monitor developments and to intervene with regulation if necessary. **P6.3a.A3** Given the openness and malleability of human nature there are no mandatory reasons why humans as cultural beings should not intervene in their own nature, even for enhancement purposes. Even a strong intuitive rejection	Freedom Justice Solidarity Naturalness	**Path/position 6.3b:** **No, germline interventions may/should not be carried out for enhancement purposes.** **P6.3b.A1** Enhancements mandated by the government to implement eugenic aims are to be rejected as violations of the taboo of impermissible instrumentalisation. **P6.3b.A2** Should genetic enhancements become a widespread social practice, this could lead to a slow change of mentality, leading to ideologies that consider anything possible and change human self-understanding for the worse. **P6.3b.A3** The reproductive freedom of parents could be restricted through social pressure and they could be saddled with problematic new responsibilities. **P6.3b.A4** The inner freedom of the child and his or her status as an end-in-oneself could be limited,	Human dignity Human dignity Freedom Responsibility Freedom Human dignity

Questions	Arguments	Related ethical concepts	Arguments	Related ethical concepts
	of changes to human features beyond the spectrum that is perceived as natural is by itself not a valid moral argument. **P6.3a.A4** If genetic enhancements turned out to be no more risky to future children than established educational methods, it is not plausible that the latter should be seen as imperative but the former as reprehensible. Offering such applications might rather become an – albeit weak – moral duty.	Non-maleficence & beneficence	especially if features are changed that affect this person's character or that would only benefit the child on certain lifepaths favoured by the parents. **P6.3b.A5** Germline interventions for enhancement purposes are certainly problematic when they transcend the natural border between the human species and others. Such steps outside the natural limits of a hyper-complex biological system come with unknown risks. **P6.3b.A6** Compared to medical interventions, enhancements are a morally lesser good. This means that they would have to satisfy especially stringent criteria for risk evaluation and avoiding damage. **P6.3b.A7** A broad enhancement practice could have negative implications for justice as long as such interventions have to be financed privately. There could also be a slow erosion of solidarity, or even a complete dissociation of individuals or groups from the rest of society.	Naturalness Responsibility Non-maleficence & beneficence Justice Solidarity

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