Framing the ethical and legal issues of human artificial gametes in research, therapy, and assisted reproduction: A German perspective

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Abstract

Recent results from studies on animals suggest that functional germ cells may be generated from human pluripotent stem cells, giving rise to three possibilities: research with these so-called artificial gametes, including fertilization experiments in vitro; their use in vivo for therapy for the treatment of human infertility; and their use in assisted reproductive technologies in vitro. While the legal, philosophical, and ethical questions associated with these possibilities have been already discussed intensively in other countries, the debate in Germany is still at its beginning. A systematic and detailed analysis of the legal framework in Germany is provided with regard to the three possibilities, including the applicable statutory laws as well as the constitutional law. The question emerges as to whether the statutory laws as well as the constitution justify a distinction to be made between embryos of artificial and natural origin. This question is subject to philosophical analysis, discussing the distinction between person and thing, dignity and price, personality and property, and nature and technique. As a result, the criterion of naturalness alone may not be sufficient to differentiate between embryos of natural and artificial origin, and other criteria need to be identified.

KEYWORDS

artificial germ cells, artificiality, ethics, human embryo, law, naturalness, pluripotent stem cells

1 | INTRODUCTION

Ten years after the seminal study by Yamanaka describing a set of four transcription factors that enables reprogramming of differentiated somatic cells into induced pluripotent stem cells (iPSCs), the field of stem cell research has made great progress towards potential clinical applications. At first sight, the major ethical and legal issues surrounding the destructive exploitation of human embryos for research and therapy by using human embryonic stem cells (ES cells) could be overcome, but other ethical issues have emerged. This applies particularly to the complex normative assessment of potential applications of human iPSC-derived artificial gametes for research and therapy. This article sets out to delineate the scientific and reproductive use of human artificial gametes as well as legal and ethical considerations related to the discussion in Germany.

2 | BIOMEDICAL OUTLOOK

When, in 2003, for the first time the spontaneous formation of oocyte-like cells from mouse ES cells in vitro was reported, scientific interest increased regarding actively inducing gametogenesis in cultured pluripotent stem cells in order to produce so-called artificial gametes. Since then, rapid progress has been made in systematically identifying critical biological factors and marker molecules for germ cell differentiation. On these grounds Hayashi and coworkers have demonstrated in a series of publications since 2011 the combined in vitro and in vivo differentiation of murine ES cells and iPS cells into functional sperm cells as well as oocytes, which, after fertilization and transfer to a...
Artificial configuration in human artificial gametes. Many scientists expect these results to be transferable to the human species.

The handling of natural human gametes, germ cells, and embryos is regulated by law in Germany on a broadly accepted basis. However, the possibility of generating artificial gametes from human pluripotent stem cells raises novel ethical and legal questions, which are expected to also challenge the current ethical norms and legal provisions. As the generation of artificial gametes from human pluripotent stem cells and their selective genetic modification is acknowledged as being technically possible in the not too distant future, the question arises as to whether it is necessary and if so, how to condense the biological and medical developments as well as philosophical, ethical, and legal issues into an appropriate ethically reflected legal framework.

The imminent relevance of this task is emphasized by the rapid development of new reproductive technologies and their profound social and political impact, which makes normative considerations with long-term validity necessary in advance. This has provided the basis for a memorandum concerning genetic modification of germ cells using CRISPR/Cas9 or other technologies by leading scientists in the field of molecular biology, which has been challenged by a recent publication by Mitalipov, providing proof-of-concept for successful CRISPR/Cas9-based genome engineering in human embryos.

Addressing this complex situation, this article differentiates three potential applications of human artificial gametes in medicinal sciences: First, studies of the in vitro differentiation of human pluripotent stem cells into functional gametes, including fertilization experiments in vitro, but no transfer into a living being, thus providing a tool to study germ cell development in vitro. Second, the generation of germ-line progenitor cells that can be transplanted into patients suffering from impaired gametogenesis to rescue the physiological reproductive biology. Third, the use of artificial human gametes during in vitro fertilization (IVF) approaches.

2.1 | Research involving human artificial gametes

Current research investigates the in vitro differentiation of human iPSCs into functional gametes in order to understand the molecular pathways involved in the generation of germ cells and to get deeper insights into impaired gametogenesis as source of infertility. Thus, fertilization of iPSC-derived artificial gametes and subsequent studies of early human embryo development will probably gain more momentum in upcoming studies and will question the consistency of the germline-cycle paradigm which strictly separates the everlasting cycle of germ cell propagation to the following generations from somatic cell differentiation of the given individual. Considering recent advances in human embryo cultivation techniques, a prolonged investigation period covering even ‘post-implantation’ stages might become feasible in the near future.

2.2 | Artificial germ cell progenitor cells as cellular transplant for the treatment of infertility

Autologous or allogeneic spermatogonial stem cell transplantation is currently discussed as a future therapeutic option to restore spermatogenesis in male patients that have survived prepubertal cancers or patients suffering from azoospermia for other reasons. Similarly, females suffering from ovarian insufficiency may benefit from a cellular transplant that is able to restore the impaired oogenesis. Considering the advances in driving murine pluripotent stem cells into immature gametes that mimic the features of primordial germ cells and that were able to restore fertility after transplantation into murine gonads, one could extrapolate that similar approaches would become feasible with human pluripotent cell-derived primordial germ cells as well. However, little is known about the risk of accidental mutations during the subsequent meiotic cleavage cascade of the transplanted cells in the physiological niches provided by the ovaries or testicles, and thus the overall safety assessment of the resulting gametes needs some special attention.

2.3 | Use of artificial gametes in assisted reproductive technologies

Recent experiments that resulted in live born mice derived from artificial gametes that were generated from murine pluripotent stem cells heated up the debate on the potential use of human pluripotent stem cells during assisted reproduction approaches. From the sheer technical perspective, the meiotic cleavage cascade might be considered the most critical step, which might be very vulnerable for chromosomal aberrations and other genetic alterations. Since both male and female stem cell-derived gametogeneses are studied quite intensively, one could expect that artificial sperm cells might become an alternative cell source for the fertilization of normal oocytes or that artificial oocytes might be fertilized with normal sperm. Even more complex, one may
hypothesize that if both partners are unable to produce natural gametes, an IVF approach could be performed using an artificial oocyte and artificial sperm cells. Finally, one could postulate that by means of genetic engineering, male pluripotent stem cells could also be differentiated into artificial oocytes, or female stem cells might be tweaked into sperm cells. If the generation of such ‘counter-gender’ germ cells becomes a realistic scenario, fertilized embryos might be generated from a single parent or from a same-sex couple.

However, the fundamental question arises as to which legal provisions regarding these three scenarios of action exist in Germany, and which ethical background may be relevant in order to design a legal framework specific to the use of human artificial gametes.

3 | LEGAL ASSESSMENT OF THE SCENARIOS

The applicable legal framework in Germany is essentially set up by statutory law and constitutional law. The Embryo Protection Act (EPA), the Medicinal Products Act (MPA), and the Transplantation Act (TPA) will play a decisive role. The EPA, MPA, and TPA have been adopted by the German Parliament and are, thus, acts of parliament, i.e., they constitute ‘statutory law’ as compared to the higher ranking ‘constitutional law’. Besides, the statutory law provisions of the Genetic Diagnosis Act (GDA) and the Genetic Engineering Act (GEA) will have to be taken into account. Furthermore, the Basic Law (BL), i.e., the German Constitution, must be considered. In this respect, the guarantee of human dignity (Art. 1(1) BL), the right to life and physical integrity (Art. 2(1) BL), and the ‘general right to personality’ (Art. 1(1) in conjunction with Art. 2(1) BL) as well as the right to reproduction will be of importance.

3.1 | Research involving human artificial gametes

As mentioned above, it must be considered that artificial gametes could be used for scientific studies on artificial gametes as well as on the processes of their generation. In addition, artificial gametes could be used for fertilization experiments in vitro.

3.1.1 | Statutory law

Research with unfertilized artificial gametes

Research with unfertilized artificial gametes is arguably in compliance with the EPA. Even if the research includes the genetic modification of the gametes, any such research seems not to be contrary to Sec. 5(1) and Sec. 5(2) EPA.

Sec. 5(1) EPA prohibits the genetic modification of a human ‘germ line cell’. However, unfertilized artificial gametes or their progenitor cells, presumably, do not qualify as ‘germ line cells’ within the meaning of Sec. 5(1) EPA. The term ‘germ line cell’ is defined in Sec. 8(3) EPA. According to Sec. 8(3) EPA, ‘germ line cells’ are all cells that ‘lead from the fertilized egg cell in one cell line to the egg and sperm cells of the resultant human being’. Obviously, artificially created unfertilized oocytes do not form ‘fertilized eggs’ within the meaning of that definition. Furthermore, artificially created germ cells might not be considered to be part of a ‘cell line leading from a fertilized egg to the egg and sperm cells of the resultant human being’, since artificial gametes are derived from iPSC cells, which, in turn, are derived from adult somatic cells. Adult somatic cells, however, are arguably not part of the germ line. Furthermore, according to Sec. 8(3) EPA, germ line cells are also ‘egg cell[s] from capture or penetration of the sperm cell until the ending of fertilization by fusion of the nuclei’. As artificial oocytes are not fertilized, they do not fulfill this part of the definition either.

Sec. 5(2) EPA prohibits the use of ‘a human germ cell with artificially altered genetic information for fertilization’. In this context, the research does not involve fertilization and is not aimed at fertilization. Accordingly, the requirements under Sec. 5(2) EPA are not met. This interpretation of Sec. 5(1), Sec. 5(2), and Sec. 8(3) EPA is in line with classical means of legal interpretation. Any other interpretation would very probably go beyond the wording of the said provisions. The meaning of the wording of criminal law provisions as of Sec. 5

10Embryo Protection Act—EPA: Gesetz zum Schutz von Embryonen (Embryonschutzgesetz—EStG) of 13 December 1990 (Bundesgesetzblatt I 1990, p. 2746). English version: http://www.auswaertiges-amt.de/cae/servlet/contentblob/480804/publicationFile/5162/Embryonenschutzgesetz—EStG.pdf
11Medicinal Products Act—MPA: Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz—AMG) of 12 December 2005 (Bundesgesetzblatt I 2005, p. 3394). English version: https://www.gesetze-im-internet.de/englisch_amg/index.html.
12Transplantation Act—TPA: Gesetz über die Spende, Entnahme und Übertragung von Organen und Geweben (Transplantationsgesetz—TPG) of 4 September 2007 (Bundesgesetzblatt I 2007, p. 2206).
13Genetic Diagnosis Act—GDA: Gesetz über genetische Untersuchungen beim Menschen (Gendiagnostikgesetz—GenDG) of 31 July 2009 (Bundesgesetzblatt I 2009, p. 2529, 3672).
14Genetic Engineering Act—GEA: Gesetz zur Regelung der Gentechnik (Gentechnikgesetz—GenTG) of 16 December 1993 (Bundesgesetzblatt I 1993, p. 2066). English version: http://web.uni-frankfurt.de/si/gentech/GenTGengl10-95c.pdf.
15Basic Law—BL: Grundgesetz für die Bundesrepublik Deutschland (GG) of 23 May 1949 (Bundesgesetzblatt 1949, p. 1). English version: https://www.bundestag.de/blob/284870/ce0d03414872b427fe57f2ee1f022307/g10-95c.pdf.
16Concerning its constitutional basis see infra footnote 53.
In sum, in German Statutory Law it is decisive whether artificial oocytes qualify as ‘egg cells’ within the meaning of the EPA.30

3.1.2 | Constitutional law

Under German constitutional law, the basic right to science and research (Art. 5(3)(1) BL)31 covers research on artificial gametes. Research with artificial gametes as such or on the processes of their generation is covered by the said constitutional freedom. What is more, there seems to be no justification for any interference with this basic right in this context.32 In fact, research with natural gametes is also covered by, and protected under, the basic right to science and research.33 However, the situation is somewhat more intricate if the artificial gametes are fertilized. In this case, several constitutional norms and values come into play, e.g., the ‘general right to personality’ (Art. 2(1) in conjunction with Art. 1(1) BL) of the donor(s) of the somatic cells which the artificial gametes were derived from. In addition, the guarantee of human dignity (Art. 1(1) BL) and the right to life and physical integrity (Art. 2(2)(1) BL) of the embryonic entity resulting from fertilization of the artificial gametes have to be taken into consideration if these constitutional provisions apply at all, though. Whether the embryonic entity is protected under Art. 1(1) and Art. 2(2)(1) BL depends on two conditions: The first condition is that Art. 1(1) and Art. 2(2)(1) BL apply to prenatal human life in general.34 The second condition is that the constitutional status of unborn human life under Art. 1(1) and 2(2)(1) BL is independent of the ‘artificiality’ of the gametes used to create the human embryonic entity. This second issue demands a thorough examination of the question of whether the artificiality of gametes can justify a distinction between embryonic entities of ‘artificial origin’ and embryonic entities of ‘natural origin’ and whether that distinction may imply that ‘artificial’ embryos enjoy an inferior, or even no, constitutional status compared to ‘natural’ embryos.35 Therefore, we must explore whether constitutional law allows for a concept of ‘naturalness’ which

22Sodan, H. (2015). In id. (Ed.), (3rd ed.), Art. 103, para. 19 et seq.; Degenhart, C. (2014). In Sachs, M. (Ed.), (7th ed.), Art. 103, para. 69.

23The EPA is part of German criminal law.

24BVerfGE 71, 108, (115); 73, 206 (234); 75, 329, (341); 92, 1, (12); Degenhart, C. (2014). In Sachs, M. (Ed.), (7th ed.), Art. 103, para. 69.

25Genetic modification of human somatic cells for cellular biology basic research is covered by the GEA as long as no gene therapy on humans is concerned, BT-Drs. 11/5622, 23; Schlüter, J. (2008). Schutzkonzepte für menschliche Keimbahnzellen in der Fortpflanzungsmedizin, p. 196. However, according to the German legislator, genetic engineering operations involving germ line cells shall not be covered by the GEA, BT-Drs. 11/5622, 23.

26Anyone will be punished with up to three years imprisonment or a fine, who . . . 2. attempts to fertilize artificially an egg cell for any purpose other than bringing about a pregnancy of the woman from whom the egg cell originated, […]’.

27Everyone who disposes of, or hands over or acquires, or uses for a purpose not serving its preservation, a human embryo see Dederer, H.-G., Böhm, K., Endrich, T., Enghofer, F., Jung, B., & Laimböck, L. (2014). «Natürlichkeit» als (Zusatz-) Kriterium für die Statusbestimmung des Embryos? In T. Heinemann, H.-G. Dederer, & T. Cantz (Eds.), Entwicklungsbio logische Totipotenz in Ethik und Recht (p. 109 et seqq.), V & R unipress.

28For the legality of fertilizing artificial germ cells according to Sec. 5(1) and (2) EPA see 3.2.1.

29‘Capable of developing’ within the meaning of Sec. 8(1) EPA simply means to be able to proliferate, BT-Drs. 11/5460, 12; Taupitz, J. in: Günther, H.-L., Taupitz, J., & Kaiser, P. (Eds.), 2. ed. 2014, Sec. 8, para. 21.
privileges ‘natural’ embryonic entities or whether, for example, the constitution grants the legislature a certain margin of discretion in regulating ‘artificial’ embryonic entities differently from ‘natural’ embryonic entities. In this respect, ethical approaches regarding ‘naturalness’ have to be taken into account as well. Finally, the constant availability of artificial gametes and embryonic entities derived therefrom may play a decisive role in determining the constitutional status of such embryonic entities.

3.2 | Artificial germ cells or progenitor cells as cellular transplant for the treatment of infertility

From a scientific point of view, artificial gametes may be used primarily for research purposes. Nevertheless, some scientists explicitly emphasize the potential of artificial gametes for reproductive purposes as well. In particular, it might be possible to use progenitor cells of artificial sperm cells for treatment of male infertility. This involves a combined in vitro–in vivo method as described above in more detail.

3.2.1 | Statutory law

EPA

Supposedly, neither artificial gametes nor their progenitor cells are ‘germ line cells’ in accordance with Sec. 8(3) EPA. If so, their generation and use for an in vitro–in vivo therapy is not contrary to Sec. 5(1) EPA. Whether this procedure runs counter to Sec. 5(2) EPA is a more controversial issue. This provision requires a ‘human germ cell with artificially altered genetic information’. Artificial gametes may qualify as ‘germ cells’ within the meaning of Sec. 5(2) EPA. The actual problem is whether the ‘genetic information’, i.e., the DNA, of the artificial gametes is ‘artificially altered’ within the meaning of Sec. 5(2) EPA through the processes of reprogramming and differentiation. Perhaps these processes might affect the epigenetic traits of the cells only. In contrast, the production of iPS cells and their differentiation into germ cells might generate cells which are, with regard to their ‘genetic information’, not absolutely ‘footprint free’. This means that the reprogramming of adult somatic cells into iPS cells might lead to a temporary or permanent genetic modification of the cells. Furthermore, the haploidization of the iPS cells during the induced meiosis on their way to become artificial gametes could be considered an artificial alteration of the genome according to Sec. 5(2) EPA as well. This may apply even more as there are so-called ‘cross overs’ during meiosis, i.e., random exchanges of sections of DNA sequences of the homologous pairs of chromosomes.

If the therapy is deliberately combined with genetic modifications of the artificial gametes or their progenitor cells (using, e.g., the new genome editing techniques like CRISPR-Cas9), Sec. 5(2) EPA may be applicable in any case. However, if genetic alterations brought about by genome editing techniques are similar to natural point mutations, one may argue that the genetic information has not been modified ‘artificially’ within the meaning of Sec. 5(2) EPA.

There is still another intriguing question in this context if the in vivo matured sperm cells fertilize natural oocytes in the course of natural reproduction. The natural oocytes are ‘germ line cells’ according to Sec. 5(1) in conjunction with 8(3) EPA. Thus, the question arises of whether the genome of those oocytes is modified ‘artificially’ (in the course of fertilization) and, therefore, this action is in contradiction to Sec. 5(1) EPA. For the in vivo matured sperm cells are derived from artificial progenitor cells and any fertilization of natural oocytes by these sperm cells could be considered an artificial genetic modification of the oocytes.

MPA

The artificial, still not completely matured, gametes in vitro, or their artificial progenitor cells in vitro, respectively, which may be used for transplantation and subsequent in vivo-maturation, might qualify as ‘advanced therapy medicinal products’ (ATMPs) according to Sec. 4(9) MPA.

36There are many proponents of a privileged role of ‘naturalness’ in (bio-) ethics, who can draw on a corresponding tradition dating back to antiquity, see, e.g., Advena-Regnery, B. (2014). Natürlicher embryo—Geeignetes Wertprädikat für die Bioethik? In T. Heinemann, H.-G. Dedeker, & T. Cantz (Eds.). Entwicklungsbiologische Totipotenz in Ethik und Recht (p. 230 et seqq). V & R unipress; Siep, L. (1996). Die »Natürlichkeit« der Natur und die Zumutbarkeit von Risiken. In Jahrbuch für Christliche Sozialwissenschaften (JCSW), p. 238; Woopen, C. (2004). Stammzellen: Müssen wir neu definieren, was es heißt, ein menschliches Wesen zu sein? In L. Honnefelder & C. Streffer (Eds.). Jahrbuch für Wissenschaft und Ethik, 9, p. 138 et seq.

37Deng, J. M., Satoh, K., Wang, H., Chang, H., Zhang, Z., Stewart, M. D., . . . Behringer, R. R. (2011). Generation of viable male and female mice from two fathers. Biology of Reproduction, 84, pp. 613 et seq. Heindryckx, B., De Sutter, P., Dhont, M., & Van der Elst, J. (2007). Embryo development after successful somatic cell nuclear transfer to in vitro matured human germinal vesicle oocytes. Human Reproduction, 22, 1982 et seqq.; Smajdor, A., & Cutas, D. (2015). Artificial Gametes (p. 4). London: The Nuffield Council on Bioethics. Retrieved from http://nuffieldbioethics.org/wp-content/uploads/Background-paper-2016-Artificial-gametes.pdf.

38Progenitor cells of artificial oocytes may be also used for treatment of female infertility.

39Supra 2.2.

40See 3.1.1.

41Anyone who artificially alters the genetic information of a human germ line cell will be punished with imprisonment up to five years or a fine.

42Likewise anyone will be punished who uses a human germ cell with artificially altered genetic information for fertilization.
2(1)(a) Regulation (EC) 1394/2007. According to this legal definition, ATMPs are gene therapy medicinal products, somatic cell therapy medicinal products, and tissue-engineered products. The still not fully matured artificial gametes, or their artificial progenitor cells, respectively, do not regulate, repair, replace, add, or delete a genetic sequence within the patient’s organism. Thus, they probably do not qualify as gene therapy medicinal products. However, they might form somatic cell therapy medicinal products or tissue-engineered products. In consequence, an artificial gametes-based therapy would have to meet the requirements for ATMPs laid down in the MPA and in Regulation (EC) 1394/2007, including those for manufacture, marketing authorization, and clinical trials of ATMPs. However, Sec. 4(30)(2) MPA explicitly excludes ‘germ cells’ from the term ‘medicinal products’ and ‘tissue preparations’. Accordingly, the applicability of the MPA to artificial gametes-based therapies is somewhat doubtful and needs to be explored carefully.

TPA
The artificial, not fully matured, sperm cells in vitro, or their artificial progenitor cells in vitro, respectively, which are to be transplanted into the testicles of the patient qualify as ‘tissue’ in accordance with Sec. 1a(4) TPA. Therefore, the provisions of the TPA concerning donation, biopsy, and transfer of tissues, including any preparatory measures, have to be respected in the case of an artificial gamete-based therapy (see Sec. 1(2) TPA).

Data protection law
To guarantee the health of the patient, the safety of the transplant has to be demonstrated. This holds true in particular if, and to the extent that, the combined in vitro–in vivo-therapy requires prior authorization by an administrative authority, e.g., the Paul Ehrlich Institute (PEI) in Langen. Therefore, the applicant for authorization might have to submit extensive biological data resulting from a comprehensive screening of the genome and the proteome of the artificial, not fully matured, germ cells in vitro, or their artificial progenitor cells in vitro, respectively, in order to establish the safety of the transplants. Hence, the provisions of the GDA may have to be satisfied.

Of course, a preimplantation genetic diagnosis (PGD) could be another solution to the safety problem. In this case, the germ cells of the patient (having recovered from infertility) would be used for IVF. The resultant embryo could then be subjected to PGD, although PGD is generally prohibited under Sec. 3a(1) EPA. It is only allowed under exceptional circumstances and in accordance with Sec. 3a(2) and (3) EPA. Hence, the revision of Sec. 3a EPA might be necessary.

3.2.2 | Constitutional law
Constitutional concerns relate to potentially conflicting basic rights. For example, on the side of the patient, the right to physical integrity (Art. 2(2)(1) BL), to bio-informational self-determination (Art. 2(3) in conjunction with Art. 1(1) BL) and the right to reproduction, or reproductive self-determination, may be at stake. In addition, on behalf of the resultant child, its human dignity (Art. 1(1) BL), its right to physical integrity (Art. 2(2)(1) BL), and its well-being must be respected. Another issue might be whether the constitution supports, or calls for, a concept of ‘naturalness’ with regard to human reproduction.

3.3 | Use of artificial gametes in assisted reproductive technologies
Artificial gametes could help to give birth to a genetically related child by way of ‘classic’ assisted reproduction such as IVF. In particular, couples whose fertility cannot be recovered by means of the aforementioned combined in vitro–in vivo-method might be able to have genetically related children through IVF using artificial gametes derived in whole or in part from their own somatic cells via iPS cells. Moreover, also completely new scenarios of human reproduction might be possible. In particular same-sex couples could have genetically related children. What is more, any individual might be able to replicate himself or herself, respectively, by reprogramming his or her adult somatic cells via iPS cells into both artificial egg and sperm cells. The result would be a child with just one parent (‘single parent’), i.e., the child would be genetically related to only one person.

49 Advanced therapy medicinal product means any of the following medicinal products for human use: (a) a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, (b) a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, and (c) a tissue engineered product as defined in point (b) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation EC No 726/2004 (OJ L 324, 10.12.2007, p. 121).

50 See Art. 2(1)(a) Regulation (EC) 1394/2007 in conjunction with Part IV of Annex I to Directive 2001/83/EC.

51 Im Sinne dieses Gesetzes […] 4. sind Gewebe alle aus Zellen bestehenden Bestandteile des menschlichen Körpers, die keine Organe nach Nummer 1 sind, einschließlich einzelner menschlicher Zellen’ (within the meaning of this act, […] tissue are all elements of the human body which are made up of cells and which are not organs according to no. 1, including single human cells).

52 Dieses Gesetz gilt für die Spende und die Entnahme von menschlichen Organen oder Geweben zum Zwecke der Übertragung sowie für die Übertragung der Organe oder der Gewebe einschließlich der Vorbereitung dieser Maßnahmen. Es gilt ferner für das Verbot des Handels mit menschlichen Organen oder Geweben. (This law applies to the donation and the removal of human organs or tissues for the purpose of transplantation as well as to the transplantation of the organs and tissue including the preparation of these measures).

53 The constitutional basis for the right to reproduction, or to reproductive self-determination, is an unsettled question. For some authors it is implied in the right to start a ‘family’ according to Art. 6(1) BL (Müller-Terptz, R. (2014), in A. Spickhoff (Ed.), (2nd ed.), Art. 6 GG, para. 1 et seq.), for others in the ‘general right of personality’ (Müller-Gotzmann, C. (2009). Artifielle Reproduktion und gleichgeschlechtliche Elternschaft, p. 282 et seq. with further references), and for some in a combination of the aforementioned rights (Heun, W. (2008). Restriktionen assistierter Reproduktion aus verfassungsrechtlicher Sicht. In G. Bockenheimer-Lucius, P. Thorn, & C. Wendehorst (Eds.), Umwege zum eigenen Kind. Ethische und rechtliche Herausforderungen an die Reproduktionsmedizin 30 Jahre nach Louise Brown, p. 51 et seq.).

54 The child’s well-being has two constitutional bases: on the one side Art. 6 (2) BL and on the other side the ‘general right to personality’. Müller-Terptz, op. cit., note 53, para. 12; Jestaedt, M. (2016), in W. Kahl, C. Waldhoff, & C. Walter (Eds.), Art. 6 Abs. 2 u. 3, para. 33 et seq.
3.3.1 | Statutory law

EPA

In particular, the provisions of the EPA must be observed. Concerning Sec. 5(1) and Sec. 5(2) EPA, see supra 3.2.1. Other provisions of the EPA must be respected as well, however, e.g., the prohibition of oocyte donation (Sec. 1(1)(1) and Sec. 1(1)(2) EPA)^55 and of unauthorized IVF (Sec. 4(1)(1) EPA)^56

A ‘single-parenthood’ as described above might run counter to Sec. 6 EPA prohibiting cloning^57 as well as to Sec. 173 Criminal Code;^58 according to which incest is a punishable offence.^59 Additionally, in case the ‘single parent’ is male, a surrogate motherhood is indispensable. However, surrogate motherhood is contrary to Sec. 1(1)(7) EPA.°° The same reasoning would apply to male homosexual couples. Artificial gametes also enable parenthood of deceased persons (if there is still a living somatic cell available). This might be in violation of Sec. 4(1)(3) EPA or Sec. 1(1)(2) EPA.°°

Data protection laws

To establish the safety of the artificial gametes and, thus, to ensure the safety of the (surrogate) mother’s and the child’s health, comprehensive screening of the artificial gametes will be necessary. Therefore, data protection laws will play a role again.°°

Supra 3.2.1.

TPA—Tissue Regulation

Another important issue is whether Sec. 6 of the Transplantation Act—Tissue Regulation,^64 which lays down the requirements for the use of gametes in the course of a medically assisted fertilization, applies to artificial germ cells as well.

Family law

Sec. 1591 et seq. CC^65 defines who is the mother and the father of a child. The woman who gives birth to the child is, from a legal point of view, the ‘legal mother’ of the child according to Sec. 1591 CC.°° If she is married, paternity will fall to her husband, i.e., he is the ‘legal father’ (Sec. 1592(1) CC).^57

Therefore, in the case of surrogate motherhood, the surrogate mother is, legally speaking, the ‘mother’ in accordance with Sec. 1591 CC, and her husband is, legally speaking, the ‘father’ in accordance with Sec. 1592(1) CC, even if the oocyte donated by another woman was not fertilized with his sperm cells. Both the ‘legal mother’ and the ‘legal father’ are, however, not the ‘genetic’ parents of the child. This issue is, of course, not unique to the use of human artificial gametes for reproductive purposes, because IVF coupled with gamete donation has already opened the doors to surrogate motherhood.

However, the specificities of IVF using artificial human gametes raise new and even more intricate problems and may, a fortiori, call for an amendment to the civil law rules on descent and on adoption in order to bring family law in line with modern reproduction technologies.

For example, the use of artificial gametes for reproduction purposes may result in ‘single parenthood’.°° This person, if a woman or a (woman-to-male) transgender, may also give birth to the child. Accordingly, the resultant child would have only one ‘single parent’ from a genetic point of view, but also, legally, if the woman was not married at the date of birth.

3.3.2 | Constitutional law

The diverse kinds of IVF using artificial gametes pose challenges to constitutional law too. With respect to potential parents, their basic right to reproduction, or to reproductive self-determination, comes into play. If the right to reproduction, or to reproductive self-determination is enshrined in Art. 6(1) BL°°, i.e., the right to

Transplantation Act—Tissue Regulation: Verordnung über die Anforderungen an Qualität und Sicherheit der Entnahme von Geweben und deren Übertragung nach dem Transplantationsgesetz (TPG—Gewebeverordnung—TPG—GewV) of 26 March 2008 (Bundesgesetzblatt I 2008, p. 512). This act is, according to its Sec. 1, generally applicable to all tissues within the meaning of Sec. 1a(4) TPA.

Civil Code (CC): Bürgerliches Gesetzbuch (BGB) of 2 January 2002 (Bundesgesetzblatt I 2002, p. 42, 2909; I 2003, p. 738). English version: https://www.gesetze-im-internet.de/englisch_bgb/

The mother of a child is the woman who gave birth to it.

The father of a child is the man 1. who is married to the mother of the child at the date of the birth.

Marriage and the family shall enjoy the special protection of the state.

°°See supra 3.2.1.
‘family’, the question may arise of whether the constitutional notion of ‘family’ implies the ‘naturalness’ of the reproduction process. IVF using human artificial gametes, however, renders highly artificial ways of human reproduction possible. For example, artificial oocytes may be derived from male iPS cells, and artificial gametes could be produced from same-sex couples or from the same person entailing ‘single parenthood’. In addition, artificial gametes could be used for IVF purposes even after the donor of the somatic cells, which the gametes were derived from via iPS cells, has deceased. In addition, the child’s right to know his or her descent, which is encapsulated in the ‘general right to personality’, has to be taken into account as well. Conversely, the donors of somatic cells, which the artificial gametes were derived from via iPS cells, might claim to have a constitutional right to know their progeny.

The aforementioned rights may be restricted for reasons of the child’s well-being, especially the child’s quest, and development of, his or her personal identity. Accordingly, the question has to be answered of whether IVF using artificial gametes, in particular whether ‘single-parenthood’, parenthood of same-sex couples or descent from deceased persons, endangers or even harms the child’s (psychological and mental) well-being. In addition, the physical integrity of the child as well as that of the mother may call for strict requirements concerning the safety of the artificial gametes used for reproduction purposes.

### 3.4 Property vs. personality rights

All three scenarios raise the question of who has the right to decide on the use of artificial gametes, especially on their generation, modification, and use. Since this right affects the legal assessment of all aforementioned scenarios, it may, and shall, be discussed separately.

In German law, individual rights to decide on the use of objects may be property rights or personality rights. Therefore, the decisive question is whether human cells, in particular adult somatic cells, iPS cells, and artificial gametes are ‘things’ within the meaning of the law, i.e., ‘corporeal objects’ according to Sec. 90 CC. ‘Things’ can be owned by persons who may exercise their ownership rights such as the right to possess, use, and dispose of their property and the right to transfer ownership. If adult somatic cells, iPS cells and artificial gametes are not ‘things’ within the meaning of Sec. 90 CC, it may be the donor who has the right to possess, use, and dispose of his or her cells and all cells derived therefrom. Such a donor’s right may follow from the donor’s ‘general right to personality’ under Art. 2(1) in conjunction with Art. 1(1) BL.

Among German scholars, the classification of detached parts of the human body as ‘things’ within the meaning of Sec. 90 CC and the related law of property, or as special corporeal objects not covered by Sec. 90 CC and the related rules on property, has been highly controversial for decades. The divergent arguments in this discussion must be taken into account and examined for their applicability to artificial gametes. It may be that the best results might be offered by a ‘Solomonic solution’ which would allow property and personality rights to exist in parallel. Such a solution might best accommodate the close relationship of the donor with ‘his’ or ‘her’ cells and practical needs concerning, e.g., the marketability of the cells.

Assuming these cells, in particular adult somatic cells, iPS cells, and artificial gametes, are ‘things’, and therefore subject to property law, peculiar questions of ownership may arise. For example, one question may be whether the donor of adult somatic cells becomes their owner in accordance with Sec. 953 CC at least by the way of an analogous application of this provision. The following question may be whether the scientist or the reproductive physician who reprograms the somatic cells into iPS cells and who differentiates these cells into artificial gametes becomes the owner of the gametes by way of ‘processing’ or ‘transformation’ in accordance with Sec. 950(1) CC.

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70VerfGE 79, 256 (268 et seq.); Dreier, in: id. (ed.), 3. ed. 2013, Art. 2 l. para. 78; Giesen, D. (1989). Genetische Abstammung und Recht, Juristen Zeitung (JZ), p. 367 et seq.
71Supra 2.1–2.3.
72Brohm, W. (1998), Forum: Humanbiotechnik, Eigentum und Menschenwürde, Juristische Schulung, 201; Bernat, E. (1989). Rechtsfragen medizinisch assistierter Zeugung, p. 115 et seq.; Precht, H. (1986). Gentechnologie, Humangenetik und neue Reproduktionstechniken. In H. Däubler-Gmelin (Ed.), Forschungsobjekt Mensch: Zwischen Hilfe und Manipulation, p. 50.
73See, e.g., Velte, G. (2015). Die postmorteale Befruchtung im deutschen und spanischen Recht, p. 216 et seq.; Bilsdorfer, P. (1984). Rechtliche probleme der in-vitro-fertilization und des embryo-transfers. Monatsschrift für Deutsches Recht, 804.
74In favour of such an approach concerning detached parts of the body in general: Freund, G., & Weiss, N. (2004). Zur Zulässigkeit der Verwendung menschlichen Körperr materials für Forschungs- und andere Zwecke. Medizinrecht (MedR), 316. Concerning (natural) gametes in particular: Schroder, M., & Taupitz, J. (1991). Menschliches Blut: verwendbar nach Belieben des Arztes? p. 93 et seq.; Zerr, C. (2004). Abgetrennte Körperteile im Spannungsfeld zwischen Personlichkeitsrecht und Vermögensrecht, p. 186, 222; Roth, C. (2009) Eigentum an Körperteilen, p. 76 et seq.; Halász, C. (2004). Das Recht auf bio-materielle Selbstbestimmung, p. 126 et seq.
75In favour of this opinion with regard to ‘natural’ germ cells: Stresemann, C. (2015). In F. Säcker, R. Rixecker, H. Oetker, & B. Limperg (Eds.), (7th ed., Sec. 90, para. 26 et seq.; Koch, H.-G. (1986). Medizinisch unterstützte Fortpflanzung beim Menschen—Handlungsleitung durch Strafrecht? Medizinrecht, 262.
76Only corporeal objects are things as defined by law.
77In favour of such an approach concerning detached parts of the body in general: Freund, G., & Weiss, N. (2004). Zur Zulässigkeit der Verwendung menschlichen Körperr materials für Forschungs- und andere Zwecke. Medizinrecht (MedR), 316. Concerning (natural) gametes in particular: Schroder, M., & Taupitz, J. (1991). Menschliches Blut: verwendbar nach Belieben des Arztes? p. 93 et seq.; Zerr, C. (2004). Abgetrennte Körperteile im Spannungsfeld zwischen Personlichkeitsrecht und Vermögensrecht, p. 186, 222; Roth, C. (2009) Eigentum an Körperteilen, p. 76 et seq.; Halász, C. (2004). Das Recht auf bio-materielle Selbstbestimmung, p. 126 et seq.
78Products and other components of a thing, even after separation, belong to the owner of the thing, unless sections 954 to 957 lead to a different conclusion’.
79Müller, R. (1997). Die kommerzielle Nutzung menschlicher Körperteilen, p. 50.
80A person who, by processing or transformation of one or more substances, creates a new movable thing acquires the ownership of the new thing, except where the value of the processing or the transformation is substantially less than the value of the substance. Processing also includes writing, drawing, painting, printing, engraving or a similar processing of the surface.”
4 | ETHICAL BACKGROUND

An ethical evaluation of the generation and use of human artificial germ cells may start with the question that asks in which regard natural and artificial germ cells differ from each other. Obviously, it is the artificiality, i.e., the artificial origin and differentiation of human artificial germ cells, as well as the availability, usability, and manipulability, i.e., their use for novel scenarios in research, therapy, and reproduction, which may raise ethical concerns. Those concerns may apply to the artificial germ cells themselves; however, they also apply to human embryos generated by fertilization using artificial germ cells if those totipotent entities can still be considered human embryos. Since a key question for legal provisions will be how to appropriately define the moral and legal status of artificial gametes and embryos generated by using them for fertilization, the following reflections will focus on this issue.

4.1 | Artificiality as a normatively relevant criterion?

Why does concern arise about artificiality in the context of reproduction? The invention of techniques such as pharmacological contraception, IVF techniques (IVF and intracytoplasmic sperm injection [ICSI]), and PGD, has already strengthened the view that human reproduction is not a blind natural process but can be controlled by the decisions and actions of human subjects. Thus, human reproduction is widely understood as being a self-determined act and an issue of personal autonomy. The generation of artificial gametes from somatic cells for the purpose of reproduction could be regarded as supporting this view. However, it also tremendously extends this view as novel scenarios, e.g., treatment of so far incurable infertility or novel forms of human genealogy, will become feasible. These novel possibilities and choices of action can be considered as extending reproductive self-determination since now a variety of personal conditions can be determined, not merely whether and when to have a child.

Acting on the basis of increased knowledge and self-determined interference with natural processes of human reproduction is associated with an increasing responsibility on the part of the interfering subject. The assessment of whether an action is considered ethically responsible within the specific context of artificial gametogenesis requires, besides defining the addressees of responsibility, criteria, arguments, and norms. With regard to the latter, many established legal norms concerning human reproduction in Germany, as laid down in the EPA, appear to be oriented towards preserving the background of natural processes of reproduction in a way that only the minimum interference necessary to artificially support these natural processes has been legalized. The provisions set by the Act were predominantly based on ethical and philosophical considerations such as safety and risk assessment with regard to the well-being of the child as well as categorical arguments such as protection from heteronomy and interfering with the germ line. However, the resulting normative framework was widely consistent with excluding actions other than those supporting the equivalent reproductive processes observed in nature. Apparently, in the context of interfering with human reproduction, responsible action was considered as following the criterion of ‘naturalness’. This was possible as long as the techniques to be applied tried to emulate the natural processes, e.g., IVF.

Not only in law but also in philosophy, arguments of naturalness seem to play an important role in the context of human reproduction. Despite the fact that arguments based on naturalness have been considered notoriously difficult, there are current well-regarded philosophers who point, although in different ways, to the need for nature as a reference in (bio-)ethics.\(^1\) An example for the substantial role of naturalness in the context of human reproduction might be meiotic cell division, since this process results in the stochastic recombination of genes during gametogenesis, therefore providing the natural basis of the genetic unpredictability of each individual human subject. This is widely considered a precondition for the self-understanding of a subject which, by the very nature of the processes taking place during its coming into existence, escaped the possibility of having been planned and designed by other subjects. The ethical debate on, and rejection of, cloning human beings centres, among others, on this argument.

In artificial gametogenesis, the natural process of meiotic cell division and recombination by sexual procreation is retained. However, at the same time, the generation of artificial gametes from pluripotent stem cells is highly artificial and not represented in nature. Since artificial gametes are made from somatic cells, and embryos generated by using artificial gametes may be considered as being made as well, the status of these cells and entities needs to be defined.

4.2 | Person vs. thing. Dignity vs. price

The example of meiotic cell division shows that natural conditions in the context of reproduction may have profound relevance for human self-understanding. Rather than being ‘made’, man considers himself as someone who ‘is becoming’. Yet, even as someone who considers himself as becoming, the conditio humana calls for dealing with the natural conditions and for considering it as a task to form these conditions.\(^2\)

Since antiquity, defining the relationship between condition and task is a substantial effort of philosophy which is currently experiencing new dimensions through a variety of novel technical possibilities, especially in life sciences.

Against this background, a key question for legal consideration is whether artificial gametes and embryonic entities generated by using artificial gametes for fertilization can be categorized as things due to their artificial origin, thereby falling under property rights usually associated with things, or whether they have to be viewed either as being governed by the cell donor’s personality rights or even, as regards embryonic entities, holders of personal rights by themselves. This question is of paramount importance for the ethical context. Moreover, the question itself already shows the great impact the possibility of

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\(^1\) See, e.g., McDowell, J. (2001). Geist und Welt. Frankfurt a.M.; Siep, L. (2004). Konkrete Ethik. Frankfurt a.M.; Quante, M. (2000). Zurück zur verzauberten Natur—ohne konstruktive Philosophie? In: Deutsche Zeitschrift für Philosophie, 48, 953–965; Honnefelder, L. (2011). Welche Natur sollen wir schützen? Über die Natur des Menschen und die ihn umgebende Natur. Berlin.

\(^2\) Cf. Honnefelder, op. cit. note 81.
generating artificial gametes would have on our normative self-understanding. Even if the normative assessment of natural gametes has so far not been fully clarified, the possibility of human artificial gametes raises questions, i.e., whether they should be viewed as things, what relationship exists between the artificial gametes and the embryonic entities generated by using them for fertilization, and whether a person, i.e., a legal subject, emerges and develops from a thing, i.e., a legal object. To find legal answers to these questions appears difficult since German law only defines two classes: legal subjects with personality rights and legal objects subject to property law. Whether a third possibility exists is an issue for discussion.

The legal dichotomy of persons and things is a predominantly distinct one and does not allow an overlapping classification. But the question of whether the dichotomy is only obligatory in a synchronous perspective or also in a causal or genealogical point of view is debatable. A good example of this notoriously difficult problem is the qualification of the different evolutionary phases in human development. From the moment of birth until death, every human being possesses the status of a person according to German law. He or she is always a legal person and bearer of human rights such as the right to life. However, the legal status of human beings before birth and after death is subject to debate in law. Following the predominant opinion, unborn children are protected by basic rights and as such are protected against abortion by criminal law. But this does not mean that unborn children are legally equivalent to born human beings, which is demonstrated by their general lack of legal capacity under statutory law. Likewise, defining the legal status of corpses seems to be difficult. Although post-mortem personality rights exist with regard to corpses, they are not property, i.e. not governed by property law. Thus, it seems that neither the unborn child nor the corpse is defined as a thing by German law, but at the same time they are not legally equivalent to born and living human beings.

The legal dichotomy between person and thing seems to be stretched to its limits regarding ontogenesis, the temporal development of human beings.

Embryos and corpses are not qualified as things in a natural context but rather as person-like entities. As a result, a continuously developing human entity does not go through both phases of being an object and a subject according to law. If one qualified fertilized artificial gametes as legal objects, then the question needs to be addressed of whether a legal person can emerge out of a legal object.

The complementary relationship between person and thing is not only relevant in everyday life but can also be, in a similar but not completely alike way, found in the Kantian distinction between dignity and price. In his Groundwork for the Metaphysics of Morals, Kant writes: 'In the realm of ends everything has either a price or dignity.' And with this the ‘realm of ends’ is, in a similar way to distinction between person and thing, divided dichotomously into that which has a price, and that which is ‘above all price’, and therefore has dignity. Phrased in an analogous way, one could even here see a complementary relationship between legal object and legal subject.

However, the following elaborations shall neither be an exegesis of Kantian moral philosophy nor an interpretation of the German constitution and its 'Objektformel', but an analysis of, in an ethical way, relevant criteria for the described dichotomy, which obviously builds the thematic framework for the normative classification of artificial gametes and the embryonic entities generated by using them for fertilization. The qualification of artificial gametes is of importance, independent of their use in research, therapy, or assisted reproduction. Researchers must know if they are experimenting with possible bearers of human rights and the right to life, or if their object of research is just a cell, a pharmaceutical/drug, tissue, or a possibly patentable invention.

Thus, the determination of status must be the basis for a normative judgement of production and usage of artificial gametes in the three action contexts given above, i.e., research, therapy, and assisted reproduction. The central problem which must be solved for the legal and ethical classification is that of the status of artificial gametes and the embryonic entities which result from using them for fertilization. Since neither the legal nor the ethical status of embryonic entities is unambiguously defined, an easy and clear-cut answer for the status of their artificial ‘equivalents’ can hardly be expected.

For these reasons, appropriate criteria for the qualification of the legal and ethical status are required, which are applicable in the realms of research and therapy as well as in assisted human reproduction. However, criteria which are obligatory for a legal definition often cannot simply be transferred and used for an ethical analysis. Therefore, the following considerations will be based on ethical criteria, which, however, will be as far as possible in accordance with corresponding legal criteria.

The elaborations given above show the difficulty in qualifying or defining a status of a human being, given the continuity of human development, i.e., its extension in time. This leads to the question of why an entity may be defined by different criteria at different time points during its development. For example, it needs to be clarified whether the occurrence of death changes the status of an individual from a legal subject to a legal object, or whether the status of an unborn changes to that of a person by the event of his or her birth. These questions are so far not solved from a legal perspective.

On these grounds, the generation of artificial gametes leads to the additional question of whether an intentional interference into an entity may significantly affect the status of this entity, and if it does whether these circumstances have additional effects on the qualification of the said entity in later stages of its development. Are artificial gametes which were generated from somatic cells to be qualified as equal compared with natural germ cells? This question raises the more explicit question of the relationship between natural—biological processes on the one hand and artificial—intentional action on the other

[83] Kant, I. (2002). Groundworks for the Metaphysics of Morals (edited and translated by Allen W. Wood). New York, p. 52 (Ak 4:434).

[84] Ibid.
hand. Determining this relationship will be relevant particularly for two reasons: First, for determining the status of artificial gametes and the embryonic entities generated by them, and second, for determining a responsible handling of these novel technologies and the products generated using them.

As shown above, the events of birth and death influence the qualification provided by legal determination. With regard to human development throughout time, a dichotomic differentiation between thing and person does not seem possible. However, there is the possibility that the artificiality of an entity may have an influence on their legal determination and ontological classification. After all, we do differentiate between ‘becoming’ and ‘made’, although it is increasingly difficult to make this distinction in the light of the recent development of technical possibilities. Yet, the interesting question remains of whether the relationship between ‘natural’ and ‘artificial’ can be viewed analogously to the difference between ‘person’ and ‘thing’ or between ‘dignity’ and ‘price’ as outlined above. It can be anticipated that these term pairs are not synonymous, since the extensions of the respective terms are not consistent with each other.

The qualifications of an IVF child and a born clone as persons carrying dignity clearly show that the artificiality of their genesis is by no means the only criterion of qualification. Besides from naturalness, other criteria are needed for a thorough classification.

### 4.3 | Concept of naturalness

The reasoning given above shows that the notions of ‘naturalness’ and ‘artificiality’ are not irrelevant for the status of an entity. The artificial generation of gametes raises the question of whether all entities created artificially should be regarded as things, not as persons. In analogy to the explanations given above with regard to the determination of an embryo or a corpse, we ask whether an entity should not only be qualified by birth or death but also on grounds of the artificiality of its generation, and whether its legal nature may be changed, due to this criterion, in a normatively relevant way. The legal analysis as given above asks whether a ‘concept of naturalness’ is required in order to reach a substantial and sound qualification. Yet, how can naturalness or artificiality become relevant in normative terms? How can naturalness be of importance for the dichotomic classification of persons and things?

It is a notable that the vast majority of entities which are classified as persons by law are natural entities. On the contrary, technical or artificial products are never classified as persons. This fact is mirrored by the term ‘natural person’. Also, the quantity of things contains predominantly artificial, not natural entities. Even if the extensions of the terms are not completely consistent, there are similar assignments. Qualification becomes difficult if entities have natural as well as artificial characteristics, e.g., transplants. Naturalness and artificiality appear to be significant for qualification. However, the assignment of children conceived by IVF or even human clones to the term ‘person’ indicates that the artificiality of a person cannot be sufficient to prevent his or her qualification as a person. The controversial debates about these methods of reproductive medicine illustrate that an ever-increasing level of artificiality in this specific context raises problems for normative classifications. How can the relevance be determined more closely?

With regard to the term ‘nature’, several meanings need to be differentiated: In a holistic understanding the term ‘nature’ can be understood as ‘existence per se’ and, thus, comprise the whole universe. Nature can also be understood as the specific part of reality which may be in contrast to various non-natural parts of reality such as technique, culture, the spheres of spiritual or the divine. Moreover, nature may be understood as characteristic of the reality or as the being (nature) of a thing, the latter being reflected, e.g., by the often used linguistic term ‘in the nature of the thing’ or the term ‘nature of the law’ which both indicate an essential characteristic of a given entity. In modern times, the term nature is often used to mean something which is subject to the laws of nature.

Since it is obvious that a concept of naturalness is needed, it is important to define the way nature is understood. For determining the status of artificial gametes, the term ‘nature’ will be used to mean the being of a thing as it was developed by the Greek philosopher Aristotle.

### 4.4 | Nature vs. art/technique

In the ontological tradition, artificial and natural entities are differentiated according to the different ways of their genesis. Aristotle claims a dichotomic classification of natural and artificial entities and thereby relates the term nature of individual things. In the second book of Physics, Aristotle starts with the statement: ‘Of the things that exist, some exist by nature, some from other causes.’ He substantiates this differentiation by claiming that a natural thing has ‘within itself a principle of motion and stationariness’, but the ‘products of art’ contrary to those ‘have no innate impulse to change’. Thus, Aristotle makes a difference between natural and artificial things with regard to the cause of alteration which traditionally is called ‘efficient cause’.

In the next step Aristotle designates this difference as being essential: ‘Nature is a source or cause of being moved or of being at rest in that to which it belongs primarily, in virtue of itself and not in virtue of a concomitant attribute.’ Aristotle thereby identifies self-movement as an essential characteristic of natural entities, which, by this very characteristic, differ from technical or artificial entities made by man. Due to the self-movement of natural entities they are acknowledged as ‘becoming’, not as ‘made’.

Due to constant progress in technology, it is increasingly difficult to maintain the claim of a strict dichotomy of ‘natural things and artificial things’. Yet, there exist many entities which can be, on the basis of their self-movement, allocated without any problems to one of the classes. Inorganic and organic entities are, as a general rule, not a product of human manufacture but carry within themselves the cause for their origin and development. In contrast, the cause of origin of

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86 Aristotle, Physics, pp. 192b8. (Translation under the editorship of W. D. Ross).
87 Ibid.
88 Cf. Ackrill, J. L. (1985) Aristoteles. Berlin/New York, p. 55.
89 Aristotle, op. cit., note 86, pp. 192b22f.
technical entities is always outside themselves. They are the products and results of artificial manufacturing. The Greek word physis and the Latin word nascire carry the meaning of seed, growing, and giving birth in contrast to the meaning of manufacturing and making.

4.5 Expression of the subject vs. characteristics

If the differentiation between natural things and artificial things is transferred to the relationship between person and thing, it becomes clear that naturalness cannot, like person and thing, be understood as a subject. Rather, naturalness is an essential non-accidental characteristic which allows for the differentiation of natural entities from technically manufactured entities. Unlike person and thing which we understand as expressions for subjects and therefore reflect substances, the understanding of nature is that of a characteristic which enables statements on the quality of a subject respective substance.

The ethical analysis of a 'concept of naturalness' reveals that, according to the Aristotelian as well as everyday life understanding of nature, nature cannot be viewed as a subject but as an essential characteristic in the form of the self-movement which allows the classification of natural and artificial entities. As shown in the legal analysis above, such qualification is relevant for everyday life as well as for normative considerations since the question of how to understand nature becomes particularly virulent with regard to novel possibilities of artificial interference.

Indeed, the characteristic of self-movement of a subject respective substance appears to be relevant also for German legislation, as the legal definition of a human embryo in the German EPA refers to the characteristic of self-developing:

For the purpose of this Act, an embryo already means the human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, and further, each totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual under the appropriate conditions for that. (Sec. 8(1) EPA)

In the EPA, the embryo is viewed as a self-developing entity which, although dependent on various external conditions, performs its own development by way of self-movement. However, it has to be kept in mind that the characteristic of self-movement which was shown as being essential in an Aristotelian view does allow a classification of natural and artificial entities but is not likewise essential for the classification of person and thing. This is because the term nature bears an ambiguous meaning and gains its definition by its respective contrary, e.g., culture, artificiality, or freedom.

Although the characteristic of self-movement is sufficient to differentiate between natural and artificial entities, it is obviously not sufficient to differentiate between person and thing. This may be reflected in the so far not entirely clarified definitions of human embryos, human corpses as well as animals. Thus, the essential characteristic of self-movement appears not to be essential in every context. The characteristic of self-movement is not irrelevant for the differentiation between person and thing, yet it is by no means sufficient.

Considering this, it appears to be necessary to work on identifying and analyzing further criteria, which may be suitable to achieve an adequate qualification. These criteria may not provide a clear distinction between person and thing, thereby indicating that for the assessment of artificial gametes a clear distinction may not be possible.

Those criteria may include:

1. Availability: The possibility of generating human gametes in abundance, either from ES or individual iPS cell lines, would facilitate dramatically access to human gametes with the possible consequence of encouraging views on correlating large quantities with reduced value and, thus, applying economically grounded criteria to the evaluation of human gametes and eventually embryos which may result in a silent change of their normative status and that of embryos generated from them. What might be considered a benefit for reproductive medicine and research, i.e., the availability of so-called ‘research embryos’, could lead to an increasing objectification and devaluation of human embryos. Also, the meaning of parenthood and the respective responsibility needs to be evaluated against the background of abundant amounts of embryos being generated from artificial gametes of individuals. In this context the question of ownership of artificial gametes also arises.

2. Usability: The opportunity of generating artificial gametes from iPS cells will make it possible for individuals to have genetically related children, even in the case of sterility or infertility. Given the extensive manipulation of cells necessary to accomplish this task, questions need to be addressed as to whether satisfying the drive of having genetically related children justifies using artificial gametes. In this context, the meaning of human reproduction as well as the medical status of infertility, e.g., disease or dysfunction, needs to be considered. In addition, the techniques open up novel genealogical possibilities which are not represented in nature.

Moreover, human artificial gametes offer the opportunity to be produced from the genetic founder in stages of life naturally not compatible with gametogenesis or from deceased persons, or from human embryos via ES cell lines. Also, the new opportunities prompt the question, for example, of whether it is justified to differentiate gametes bearing the opposite gender compared with that of the pluripotent stem cells they were derived from, i.e., oocytes from male pluripotent stem cells, in order to generate children which are genetically related to both same-sex partners. In addition, it must be considered whether oocytes and sperm cells derived from the same iPS cell line should be used for fertilization with each other, thus forming an embryo by sexual fertilization which originated genetically from the same individual.

3. Manipulability: In vitro artificial gametogenesis depends on expandable pluripotent stem cells and stem cell-derived primordial germ cells which are assumed to be easily genetically modified by novel technologies such as CRISPR-Cas9 or TALEN. For example, on the
basis of these procedures, multiple genetic bi-allelic alterations could be introduced in cells in order to erase several genetic dispositions for genetic diseases, thereby creating an individual’s genetically corrected ‘master’ cell line for gametogenesis. Actively interfering with the genetic traits of all possible descendants of an individual may represent a novel quality of ‘therapy’ as this action could be considered neither an individualized therapy nor a therapy of an individual.

These criteria may provide a frame for identifying and analyzing ethically relevant questions with regard to the generation and use of human artificial gametes. The criteria refer to the differentiation of human artificial gametes and natural gametes, and thus represent viewpoints on the interference with nature.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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