7 The Legal Requirements for—and Limits to—the Donor's and the Patient's Consent

Silvia Deuring

7.1 Basic Issues of Informed Consent

7.1.1 "The" Consent in the Context of Generating Brain Organoids

The cells required for the generation of brain organoids can stem from different sources. They can be adult, multipotent stem cells obtained from donor material, which can only differentiate into certain cell types; pluripotent stem cells; stem cells artificially produced from differentiated soma cells, the so-called induced pluripotent stem cells (hiPSCs); and, finally, embryonic stem cells.[1]

If one considers the process of creating brain organoids, it quickly becomes clear that it is hardly possible to speak of "the" consent of the cell donor. In particular when brain organoids are generated from adult stem cells or hiPSCs, a distinction must be drawn between the consent for the collection of the corresponding cells on the one hand and the consent for specific-purpose use after the collection on the other hand. This need to differentiate already results from the fact that different legal interests of the cell donor are affected; moreover, the person collecting the cells and the person using them do not have to be identical.[2] These consents do not always coincide; for instance, the cell collection may originally have been carried

[1] Lancaster et al. (2013), p. 374; Bartfeld and Clevers (2018), p. 91; Taupitz (2020a), p. 805.

[2] On the rights regarding severed bodily substances, see below, Sect. 7.2.2.2. See also Halàsz (2004), p. 216; Central Ethics Committee (2003), pp. 5-6, both also arguing that the removal interferes with bodily integrity, whereas the further use of seperated body substances can violate (only) the right of personality; and Parliamentary Document 16/5374 (2007), p. 72, which also differentiates between removal and further use.

S. Deuring (✉)
Faculty of Law, Ludwig Maximilian University, Munich, Germany
e-mail: silvia.deuring@jura.uni-muenchen.de

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out for completely different purposes, e.g., for diagnostic or therapeutic reasons, with the decision to use the cells for research purposes arising later. This problem does not occur, however, in case of embryonic stem cell use, at least in Germany, where only imported and thus already extracted embryonic stem cells may be used. Incidentally, this study will not touch upon the use of embryonic cells.

In the following, we will proceed as follows: First, we will address general principles of informed consent in German and international law. The concerned person's right to physical integrity as well as of personality will play an important role in this exposition (Sect. 7.1.2). We will subsequently examine the effectiveness of informed consent to the removal of cells specifically for the purpose of generating brain organoids (Sect. 7.2.1). In so doing, we must distinguish between different research objectives and assess how specific the consent must be. This is followed by the question of whether bodily substances that were removed for completely different purposes can also be used without consent for the generation of brain organoids. The answer will depend on the scope of the right of personality regarding separated bodily substances (Sect. 7.2.2). We will then deal with questions of informed consent in autologous and allogeneic transplantation of brain organoids; in the case of allogeneic transplantation, we must differentiate between the donor and the recipient (Sect. 7.3). The study concludes with a brief look at issues of consent in data protection law (Sect. 7.4).

The requirement of informed consent as well as the criteria which the consent must meet differ according to the concerned group of persons. For that reason, the following sections will distinguish between adults, minors who are capable of advanced reflection, and incapacitated persons.

7.1.2 Informed Consent in International and German Law

7.1.2.1 International Standards

At the international level, there are numerous sets of rules predicated on the principle of informed consent, be it in the medical field in general or in the field of scientific research in particular.

For example, the Convention on Human Rights and Biomedicine of the Council of Europe ("Oviedo Convention") from 1997 provides in its Art. 5 that an intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. Although this convention is not binding for Germany,[3] which has not signed nor ratified it, it is binding on a large number of other European states.

[3] In the opinion of the German legislature, it sets too low requirements in some areas and provides too little protection for certain groups of persons. For that reason, some argue that the Convention should be taken into account to the extent it sets higher, not lower, requirements than the German legal system. See, e.g., Breithaupt (2012), p. 243.

The "Oviedo Convention" as well as additional protocols[4] and recommendations[5] to this convention also contain specific regulations on consent to research projects: Pursuant to Art. 16 para. 5 of the Convention, research may only be conducted after informed consent has been given. This requirement is reiterated in Art. 14 of the Additional Protocol to the Convention of Human Rights and Biomedicine Concerning Biomedical Research, and Art. 13 of the Additional Protocol sets out the informed-consent requirements in more detail. This Additional Protocol applies not only to research performed directly on human beings but also to research on body materials taken for the purpose of carrying out that specific research project.[6]

For research on other bodily materials of human origin, i.e., those removed for initial storage and later use in a (still undetermined) research project, or those removed for any other reason other than to carry out the planned research project, the Committee of Ministers of the Council of Europe has drawn up Recommendation CM/Rec(2016)6 on research on biological materials of human origin. Art. 10 and Art. 11 para. 1 of this Recommendation regulate the requirements for informed consent for storage-related collection. Art. 11 para. 2 then deals with consent to storage if the bodily substances were removed for purposes other than storage for research; para. 3, furthermore, addresses the storage of bodily materials that can no longer be identified. Finally, Art. 21 regulates the use of the stored materials for research purposes and establishes the principle, in para. 1, that research on these substances may only be carried out following appropriate consent. Para. 2 deals with exceptions to this principle.[7] In this context, the World Medical Association's (WMA) Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks (2016), which deals with informed consent to the collection, storage, and use of data and biological material from individuals, also deserves mention.

The Declaration of Helsinki of the WMA, as amended by the 64th General Assembly in Fortaleza in 2013, refers specifically to scientific research. It applies to research on humans, including research on identifiable human materials (para. 2 of the preamble) and thus ultimately to the removal and further use of bodily substances, provided they remain identifiable. In particular, para. 26 of the Declaration deals with the scope of informed consent and the obtaining of consent, preferably in writing. In Germany, this declaration must be observed (only) by physicians, pursuant to sec. 15 MBO-Ä (Model Professional Code of Conduct of the German Medical Association) or, to be more precise, the corresponding

[4] Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (2005).

[5] Recommendation Rec(2016)6 of the Committee of Ministers to member states on research on biological materials of human origin.

[6] This can be deduced from Art. 2 no. 2 of the Recommendation CM/Rec(2016)6: "This recommendation does not apply to (...) the use in a specific research project of biological materials of human origin removed for the sole purpose of that project. This is within the scope of the Additional Protocol concerning Biomedical Research (CETS No. 195)."

[7] See Sect. 7.2.2.3.

references in the professional regulations of the federated state medical associations.[8]

The various documents also deal with medical interventions on persons incapable of consent, be they minors or adults. The Oviedo Convention, for example, leaves it to national law to determine when a minor or adult is incapable of giving consent (Art. 6 of the Convention), but provides that in cases of incapacity the consent of the representative must be obtained before any medical intervention (Art. 6 para. 2 and 3 of the Convention). The participation of persons incapable of consenting to research interventions is possible but subject to restrictions (Art. 17 of the Convention): Research on persons incapable of consenting is subsidiary and may only be carried out, furthermore, if the research has the potential to produce real or direct benefits for the health of the person concerned or for other persons of the same age afflicted with the same disease or disorder or having the same condition. Moreover, the research may entail only minimal risk and minimal burden for the individual concerned, and the representative must have given their authorization explicitly and in writing. Furthermore, the person concerned may object to the intervention.

The Declaration of Helsinki also considers permissible, to a limited extent, research interventions on persons incapable of consent; in addition to proxy consent, it requires either an individual benefit, or, like the Oviedo Convention, a benefit for the health of the group represented by the subject, provided the research entails only minimal risks and minimal burdens (para 28). The incapacitated person must be involved in the decision, and his or her objection must be respected (para. 29). Finally, Art. 12 and Art. 21 of Recommendation CM/Rec(2016)6 deal with the removal and storage of bodily substances from persons not able to consent for research purposes. Art. 12 para. 1 and 2 and Art. 21 para. 5 also assume the subsidiarity of such research and require a benefit for the person unable to consent or, failing that, a group benefit. In addition, the removal of the materials may only be accompanied by a minimal risk and a minimal burden.

Moreover, there are specific regulations on the conduct of clinical trials, particularly in the area of medicinal products law. The Regulation (EU) No 536/2014 is particularly relevant in this regard. We will consider these provisions in greater detail below.[9]

7.1.2.2 German Law

Any interference with a person's physical integrity requires informed consent. In German law, this results in particular from the Basic Law ("*Grundgesetz*," GG), which includes a fundamental right to physical integrity (Art. 2 para. 2 sent. 1 GG) and a general right of personality (Art. 2 para. 1 in conjunction with Art. 1 para. 1

[8] Which is why, within the German legal system, the declaration is not only a recommendation. See Kern (2019a), § 4 III.6. para. 36.

[9] See in particular Sect. 7.3.1.3.

GG).[10] Of course, the fact that individuals *must* consent to physical interventions also means that they *may* consent to such measures. Thus, individuals may dispose of their bodies as they see fit.[11] Thus, cell donors may, within the context analyzed in this chapter, consent to the removal of cells not only for therapeutic and diagnostic purposes but also for research purposes, for transplantation purposes, for storage in tissue banks, or for any other kind of processing.[12]

The requirement of informed consent specifically for medical treatments follows from sections 630d and 630e of the Civil Code ("*Bürgerliches Gesetzbuch,*" BGB). The Model Professional Code of Conduct—which is not binding in itself but becomes binding through the adoption of the corresponding clauses in the professional regulations of the federated states' medical associations—also establishes, in its section 8, the requirement of informed consent for medical treatment. Should the person be incapable of consenting, the legal representative or the person authorized for this purpose must be informed and give his or her consent (sec. 630d para. 1 sent. 2, para. 2, sec. 630e para. 4 BGB); failure to do so results in claims for damages under sec. 280 para. 1 BGB and sec. 823 para. 1 BGB.

The Civil Code does not define when a person is capable or incapable of giving consent. According to the explanatory memorandum to the law, patients must be capable of understanding the information so that they may make a self-determined decision and be able to assess the benefits and risks of the specific intervention.[13] Some special laws, however, provide specific definitions: For example, sec. 40b para. 3 sent. 1 of the German Medicinal Products Act (version as of 27 January 2022) defines the capacity of minors to give consent as the ability to grasp the nature, significance and scope of the clinical trial and to act accordingly. The same definition, of course with regard to transplantation, is found in sec. 8 para. 1 sent. 1 no. 5 and sec. 8c para. 2 sent. 1 of the Transplantation Act.

As is already clear from the cited provision of the German Medicinal Products Act, minors are not per se incapable of consent under German law. Instead, their ability to consent depends on their mental maturity.

It is uncontested that parents cannot force a medical intervention against the will of their child if it is capable of giving consent.[14]

It is unclear, however, whether the consent of mature minors is sufficient, or whether their parents must always consent as well.[15] This question arises in equal

[10] Spickhoff (2008), p. 385; Taupitz (2000), p. A12. On the problem of which specific article provides the basis for the right to self-determination, see Müller (2013), p. 175 et seq. Müller argues that the right to consent to physical interventions follows from Art. 2 para. 2 p. 1 GG, and that the right to be informed follows from Art. 2 para. 1 in conjunction with Art. 1 para. 1 GG.

[11] Schroth (2009), p. 722; Halàsz (2004), p. 19.

[12] On possible uses of collected somatic cells, Dettmeyer and Madea (2004), p. 86.

[13] Wagner (2020a), sec. 630d BGB para. 21; for more details, see Taupitz (2012), p. 585; Taupitz (2000), pp. A58 et seq.

[14] Schreiber (2019), p. 223.

[15] On this issue, Katzenmeier (2020), sec. 630d BGB para. 13 et seq; Fink (2005), pp. 78–79; Schreiber (2019), p. 154 et seq.

measure with respect to all personal rights, be it physical integrity or the general right of personality.[16] The starting point is secs. 1626 et seq. BGB. According to these provisions, parents are entitled to parental care for their children; at the same time, however, they must consider the child's increasing ability and need to act independently and responsibly (sec. 1626 para. 2 BGB). In addition, the child has a constitutionally guaranteed right to self-determination. In any event, we can observe a clear tendency: Where there is a risk of grave danger or interventions are irreversible, the requirements for the minor's capacity to consent are either toughened to the point where it can no longer be assumed,[17] or co-consent is deemed necessary.[18]

Some scholars go so far as to argue that both the minor and their legal representative must always give their consent; this, they claim, considers the minor's right to self-determination, by actively involving him or her, and at the same time does not dilute the parents' right of care. Only where risks for the minor are so low that the parents' "interference" is no longer justified should the minor be regarded as autonomous.[19] Yet there is no reason to correct decision of minors if they can exercise their right to self-determination.[20] In principle, therefore, as is also the prevailing doctrine in criminal law,[21] we should allocate an exclusive right to consent, at least in cases in which the minor is not in serious danger. To insist on the principle of co-consent would yield the contradictory outcome that the minor is considered to be, but not treated as, fully capable of consenting.[22] Incidentally, the more a decision implicates the privacy of minors, the more likely it is that their right of personality will override the parents' right of custody, even in the case of irreversible interventions.[23]

For adult persons under custodianship, the custodian must give consent if the person under custodianship is incapable of doing so (secs. 1896 et seq. BGB).[24]

It is also important to note that consent can be revoked at any time informally and without giving reasons (sec. 630d para. 3 BGB). We can also find this provision in specific regulations such as sec. 40b para. 1 of the German Medicinal Products Act (version as of 27 January 2022), Art. 29 para. 2 lit (a) (ii) of the Regulation (EU) No 536/2014.

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[16] Fink (2005), p. 79; on the consent with regard to the right of personality, Schreiber (2019), p. 223 et seq.

[17] Spickhoff (2018a), sec. 107 BGB para. 15; Wagner (2020a), sec. 630d para. 43.

[18] Katzenmeier (2020), sec. 630d BGB para. 14; Lipp (2021c), XIII. D. para. 38; limited to cases of risk of death or considerable damage to health: Taupitz (2000), p. A63 et seq.; on the minor's right of veto, Federal Court of Justice (2007), p. 218. The right to veto differs from co-consent in that the minor does not have to actively exercise his or her right of self-determination. Schreiber (2019), p. 166.

[19] Fink (2005), pp. 79–80; Schreiber (2019), pp. 212, 223–224, likewise argues in favor of a right of co-decision.

[20] Kern (1994), p. 755.

[21] Spickhoff (2018b), sec. 630d para. 8.

[22] Spickhoff (2018a), sec. 107 para. 15; Spickhoff (2008), pp. 389–390; see also Wagner (2020a), sec. 630d para. 43–44.

[23] Thus, in the case of abortion, Higher Regional Court Hamm (2020), p. 1374. Generally, Spickhoff (2018a), sec. 107 para. 15.

[24] Katzenmeier (2020), sec. 630d para. 18 et seq.; Taupitz (2000), pp. A67–A68.

7.2 Generating Brain Organoids for Research

Brain organoids can be generated from cells that have been harvested either for that specific purpose (Sect. 7.2.1) or for another reason, e.g., for therapeutic reasons, with the wish to conduct research with these cells arising at a later point (Sect. 7.2.2). The following sections will address the requirement and scope of informed consent in both situations.

7.2.1 Removal of Body Material Specifically for the Generation of Brain Organoids

Brain organoids can be used for different research purposes. We will therefore differentiate between consent to basic research *in vitro* (Sect. 7.2.1.1), to transplanting brain organoids to animals (Sect. 7.2.1.2) and to drug research as well as personalized medicine (Sect. 7.2.1.3). Finally, we will address the possible scope of the consent (Sect. 7.2.1.4).

7.2.1.1 Removal for the Generation of Brain Organoids for Basic Research In Vitro

7.2.1.1.1 Consent to Research of Adults Capable of Giving Consent

In Germany, only certain fields of research on humans are regulated by specific laws. Where specific regulations do not apply, the legal requirements for human research thus follow from the general provisions of private, criminal, and public law.[25] Sec. 15 para. 3 of the Model Professional Code of Conduct for Physicians, or more precisely the corresponding clauses in the professional regulations of the federated states' medical associations, moreover, establishes the binding force of the Declaration of Helsinki.

The following section addresses basic in vitro research, that is, investigations into the development of certain brain diseases or the development of the human brain in general. It is important to bear in mind, as mentioned in Sect. 7.1.1, that we must distinguish the consent to the physical intervention from the consent to specific further uses of the removed materials.

First of all, the removal of cells to create brain organoids for whatever reason is only possible following informed consent. The concept of voluntary consent is an expression of the right of self-determination and is recognized across the world.[26] The information given before consent has, in the words of the Declaration of Helsinki, to be "adequate" (para. 26): It should enable the subject to weigh the pros and cons of participating in the research project and to make up his or her mind freely. For this reason, the physician must set out the scientific justification of the research project; the planned interventions and the risks involved and how the substances and the concerned person's data will be used, including whether the data

[25] Lipp (2021c), XIII. B. para. 13.

[26] Lipp (2021c), XIII. E. I. para. 50; see above, Sect. 7.1.2.

will be disclosed to third parties. In short, all circumstances that are relevant for the person concerned must be explained to her.[27]

To ensure that the consent remains voluntary, the person concerned can revoke it at any time (see, for example, para. 26 of the Declaration of Helsinki).[28] The physician must also inform the individual about what will happen to the samples, data, and research results should he or she indeed revoke his or her consent.[29] However, the consent cannot be revoked if the substances have been anonymized; the physician must inform the individual of this possibility.[30]

Despite this right to self-determination, it follows from both national and international rules that in vitro brain research is not without limits. The preamble of the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (2005) explicitly states that biomedical research that is contrary to human dignity and human rights should never be carried out, and that the paramount concern is the protection of the human being participating in research. According to its Art. 1, the overall aim of the Convention of Oviedo is to protect the dignity and identity of all human beings with regard to the application of biology and medicine. Para. 9 of the Declaration of Helsinki, moreover, likewise emphasizes the protection of dignity.

In the following, I will lay out the criteria that, according to German law, make inadmissible the consent to a physical intervention or to a research project in general.

First of all, the basis for the removal and further use of body cells is a research contract. Its validity may depend on ethical standards, which are translated into law by sec. 134 (violation of a statutory prohibition) and sec. 138 BGB ("immorality").[31] However, we must distinguish the consent regarding the physical intervention and the further use of the substances from the contract. Thus, consent is possible up to the point of "immorality." It is unclear, however, how to ascertain immorality.

Under criminal law, for instance, there is sec. 228 Criminal Code ("*Strafgesetzbuch,*" StGB), according to which a person cannot consent to immoral bodily harm. A physical intervention is considered immoral—at least according to prevailing doctrine and case law[32]—if it is accompanied by a serious danger to health with the risk of death. The objective of the intervention is, in principle, irrelevant; in other words, an immoral objective does not vitiate the consent to a minor

[27] Lipp (2021c), XIII. E. I. para. 50; see also, National Ethics Council (2004), pp. 16–17, 64–65.

[28] Lipp (2021c), XIII. E. I. para. 51.

[29] National Ethics Council (2004), p. 65; see also Baston-Vogt (1997), p. 274 et seq.

[30] See, e.g., para. 12 of the WMA Declaration of Taipei on Ethical considerations regarding Health Databases and Biobanks (2016); for revocation and its consequences, see National Ethics Council (2004), pp. 69–70.

[31] Kern and Rehborn (2019), sec. 42 para. 79.

[32] For this interpretation, see Stock (2009), p. 155; Suhr (2016), p. 172; Sternberg-Lieben (2019), sec. 228 StGB para. 17–18; Federal Court of Justice (2004), p. 2459.

intervention.[33] However, the objective does play a role when the intervention in question is severe: A severe intervention may be justified following consent if there is a medical reason for it. Consequently, the consent is vitiated if no such reason exists. Yet the immorality of the consent follows from the absence of such reason, not from an "immoral" objective.[34]

In private law, on the other hand, we are left with sec. 138 BGB and sec. 134 BGB, which decree the nullity of immoral contracts and of contracts that violate a statutory prohibition. Because consent is not a contract, however,[35] the question arises as to how we should gauge the immorality of consent, e.g., in the context of sec. 823 BGB, which grants claims for damages for physical interventions carried out without consent. Often scholars will simply re-state that consent must not be immoral; some fail to relate immorality to a specific rule,[36] while others refer to both sec. 228 StGB and sec. 138 BGB.[37] The Federal Court of Justice has also occasionally referred to both provisions;[38] in other instances, it has suggested an analogy to sec. 138 BGB,[39] while in others still it has applied that provision directly.[40]

We will here follow the prevailing approach and apply the principles developed in sec. 228 StGB in private-law contexts as well. This indeed guarantees a uniform standard in matters of the right freely to dispose of one's own body.[41] Furthermore, in light of the right to self-determination, this liberty should only be restricted within narrow limits, namely only when the very objective of protecting the body so demands. The threshold is only reached where the life of the person is at stake, as German law prohibits killing upon request (sec. 216 StGB).[42]

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[33] On the irrelevance, in principle, of ulterior objectives, Sternberg-Lieben (2019), sec. 228 StGB para. 19; Federal Court of Justice (2004), p. 2459; Förster (2020), sec. 823 BGB para. 34; and, as regards the result, Ohly (2002), p. 421.

[34] Hardtung (2017), sec. 228 StGB para. 47; see also Ohly (2002), pp. 421 et seq.

[35] Förster (2020), sec. 823 BGB para. 35; but see Ohly (2002), p. 408.

[36] Spindler (2020), sec. 823 BGB para. 84; Förster (2020), sec. 823 para. 34; Deutsch and Spickhoff (2014), para. 419.

[37] Halàsz (2004), p. 216; Wenzel (2019), chapter 4 para. 158; Prütting and Merrem (2019), sec. 630d BGB para. 11.; diese Uneinheitlichkeit auch feststellend: Ohly (2002), pp. 397–398.

[38] Federal Court of Justice (2017), p. 2686.

[39] Federal Court of Justice (1976), p. 1790.

[40] Federal Court of Justice (1953), p. 701.

[41] Sec. 138 BGB has a much broader scope of application than sec. 228 StGB. Cf. Stock (2009), p. 158. See the rulings of the Federal Court of Justice (1976), p. 1790; Federal Court of Justice (1953), p. 701), which measured the immorality of consent in private law against sec. 138 BGB (applied analogously) and did not focus on a danger to life. Instead, they asked whether the interventions in the body generally violate "what moral conduct is required of the individual within the social community according to the prevailing views of our legal and cultural society" (see Federal Court of Justice (1976), p. 1790, on the case of sterilization). On the application of criminal law restrictions to private law, Ohly (2002), pp. 400 et seq. According to Ohly (2002), we should ask whether the restriction seeks to protect the person consenting, in which case the invalidity of the consent extends to private law (pp. 405–407).

[42] Stock (2009), p. 156, Suhr (2016), p. 172, and Schroth (2009), p. 726, also argue that societal aspects should be left out of the equation when applying sec. 228 StGB, as they would render moot

It follows from this that research subjects may not be exposed to the concrete danger of death or serious bodily harm. Within these limits, medical research on humans is, however, permissible.[43] Accordingly, the removal of cells for the generation of brain organoids is not subject to any reservations, since the removal does not involve any such risks for the cell donor—at least not if the cells are, e.g., blood or skin cells. Whether the person consents for immoral purposes is, as shown above, irrelevant.

Whether the consent to the specific further use of the substances can be considered immoral presents a distinct question. In this context, sec. 228 StGB does not offer any help: first, the use of substances that have already been removed no longer constitutes an encroachment on bodily integrity; second, the provision may not be extended to include other legal interests. As severed bodily substances are covered not by the right of bodily integrity but "only" by the right of personality (and by the right to property),[44] it is questionable whether disposing over those substances can ever be considered immoral: After all, the core of the right of personality consists in the right to define freely what constitutes one's personality, which includes the relationship one desires with one's bodily substances. There is, in particular, no provision in criminal law that sanctions "destroying" another person's right of personality even when that person has granted his or her consent (as is the case, pursuant to sec. 216 StGB, with the right to life).

For that reason, only one other aspect requires consideration: Since the production of brain organoids can at least be considered controversial from an ethical perspective, we must examine whether Art. 1 para. 1 GG, which protects the dignity of the human being, can stand in the way of giving consent to such research. Can Art. 1 para. 1 GG, in other words, restricts the right freely to develop one's own personality and to live accordingly? More, does the consent to the creation of brain organoids from one's own cells even conflict with human dignity?

There is certainly no universal understanding of what human dignity entails. Accordingly, I will briefly attempt to outline a concept of dignity and to apply it to the issue before us.

The German Constitution entrenches the protection of human dignity in its very first provision. The basic premise is that every human being is entitled to recognition of his or her unique value.[45] The special value of human beings follows from their capacity to reason as well as their autonomy. This approach goes back to Immanuel Kant in particular, but can be traced back even further.[46] From a theological perspective (not only that of Christianity[47]), human beings hold a

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the right to self-determination.

[43] Lipp (2021b), VII. E. I. para. 41; Ohly (2002), p. 426.

[44] See Sect. 7.2.2.2.

[45] Dederer (2009), p. 109.

[46] Dederer (2009), p. 107 with reference to John Locke, Giovanni Pico de la Mirandolla and Marcus Aurelius; Lackermair (2017), p. 293. In the field of ethics, the moral status of human beings is often justified with reference to *Kant* or to the autonomy of human beings as well: Chen et al. (2019), p. 466; Karpowicz et al. (2004), p. 334.

[47] Dederer (2009), p. 108.

special position among all creatures (*imago-dei doctrine*), regardless of their respective abilities.[48] From a historical perspective, moreover, Art. 1 GG was a reaction to the Nazi regime; following this period of absolute disregard for the human value of individuals, it seeks to make the respect for the freedom and self-determination of the individual—and indeed of every individual, irrespective of his or her mental or physical characteristics, religion, or other features—the matrix of the state order.[49]

For its part, the Federal Constitutional Court has not explicitly predicated its jurisprudence on specific philosophical or theological ideas. On the basis of the same considerations,[50] however, it has emphasized that dignity is a "value which belongs to man by virtue of his being a person"[51] (although it is best to speak of "human-ness," not of persons[52]). It has also held that Art. 1 GG "is based on the concept of a spiritual and moral being which is designed to determine and develop itself in freedom."[53]

Consequently, we can speak of a violation of dignity when persons are subjected to treatment that calls into question, in a fundamental manner, their right to be respected as a self-determined individual entitled to all humans rights, or when the treatment of human beings bespeaks a wilful disregard for their dignity. The treatment, in other words, must express contempt for the value that an individual has by virtue of his or her personhood.[54] This must be established on a case-by-case basis.[55] To conclude, human dignity implicates the respect for the freedom, autonomy, and uniqueness of each human being as well as respect for the equality of all individuals.[56]

In light of these principles, one could argue that the creation of artificial brains from the cell material of a donor calls into question that person's uniqueness as this creation "duplicates," as it were, his or her brain and thus, ultimately, his or her personality. I do not consider this objection persuasive, however, at least as long as the brain organoids remain as rudimentary as they are today: As things currently stand, there is no evidence that brain organoids have any degree of consciousness or could be able to generate more complex information of any kind.[57] Because of inadequate nutrient, gas, and waste exchange, they are only the size of a few millimeters.[58]

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[48] Dederer (2009), pp. 107–108; Lackermair (2017), p. 290.

[49] Lackermair (2017), pp. 293–294.

[50] Thus also, Dederer (2009), p. 108.

[51] Federal Constitutional Court (1970), p. 26.

[52] Dederer (2009), p. 108; Lackermair (2017), pp. 296–270.

[53] Federal Constitutional Court (1977), p. 227; cf. Dederer (2009), p. 108.

[54] Federal Constitutional Court (1970), p. 26. For criticism of the "wilfulness" personhood criteria, see Lackermair (2017), pp. 269–270.

[55] For more details: Dederer (2009), p. 118 et seq.

[56] Lackermair (2017), p. 297.

[57] Chen et al. (2019), p. 463.

[58] Chen et al. (2019), p. 463.

Furthermore, brain organoids are not even necessarily a miniature version of the entire donor's brain, since they can be limited to region-specific parts.[59] The image of the so-called brain in a vat—that is, "a disembodied organ capable of perception and thought imprisoned in a dehumanizing existence"—is currently far from realistic, given the "lack of sophisticated sensory inputs into developing brain organoids" necessary for "the iterative learning and conditioning that cultivate cognitive processes."[60]

But even once artificial brains become more sophisticated, we should not prematurely assume a violation of the donor's dignity. The following points deserve to be considered:

Since the direct effect on the cell donor is ultimately limited to the removal of the cells, it already seems questionable whether the manner in which the body substances are used can call into question the intrinsic value of the donor.[61]

As brain organoids, in principle, share the individual's nuclear genetic set, they may come close to a cloned version of the donor's brain.[62] Even "real" cloning, however, does not automatically violate the dignity of the copied original—at least not simply because the original now shares his or her genetic setup with another living being (and thus also with a brain of the same genetic origin): the case of identical twins demonstrates that the same genome does not entail the same identity and personality.[63] Thus, one's identity and personality flow above all from one's environment and one's own history, and not just from one's genetic material, whose effects are also considerably influenced by external factors.[64] What is true for cloning probably applies *a fortiori* for brain organoids. If only the brain is "reproduced"—be it a fully functional human brain—far more characteristics that determine the identity and individuality of a human being are lacking, such as his or her appearance, behavioral patterns, etc. The identity of the new brain is new, not an imitation of that of the donor. Arguing otherwise overestimates the importance of the origin of the brain cells for the formation of a personality.[65] More, the mere uncertainty of the research outcome—how far developed the brain organoid may be—does not in itself render a given consent

[59] Qian et al. (2016), pp. 1238 et seq.; Qian et al. (2018), pp. 565 et seq.

[60] Chen et al. (2019), p. 465. See also Farahany et al. (2018), p. 430, who note that it is unclear whether brain organoids will attain consciousness in the future, and Lavazza and Massimini (2018), p. 608, who compare the challenge of detecting brain activity in cerebral organoids with the efforts to assess consciousness in brain-injured non-communicating patients. Incidentally, researchers have already managed to produce neural activity on a region where cells of the retina had formed together with cells of the brain. See Farahany et al. (2018), p. 430; Quadrato et al. (2017), pp. 48–53.

[61] Thus, in the context of human–animal hybrids, Lackermair (2017), p. 299.

[62] Cf. Lavazza and Pizzetti (2020), p. 11, who emphasize that brain organoids are not human beings who are genetically identical to the cloned "original."

[63] Lackermair (2017), p. 301.

[64] Kersten (2004), p. 491; Lackermair (2017), p. 301.

[65] Lackermair (2017), p. 299.

invalid, provided it is ensured that the person giving consent is aware of the uncertainty.[66]

The question, finally, is whether the cultivation of artificial brains constitutes a form of arbitrary manipulation of human beings in general.[67] However, we should be wary of arguments of such general nature. Humans are arbitrarily manipulable in many respects, especially in medical ones: both medical treatments and research measures influence the human body in a more or less artifical way.[68] Furthermore, it is also questionable to assume a dignity of humanity as a whole that can prevail over the rights of individuals.[69] Were we to consider the research measures described here contrary to a "dignity of humanity," we would simply give in to a more or less vague feeling of unease. In so doing, we would disregard, in a paternalistic manner, the will of the donor—who, in the end, consents to an ultimately harmless intervention (such as blood sampling) in order to further important research purposes (e.g.,[70] studying human brain development or modeling central nervous system disorders such as microcephaly,[71] autism spectrum disorders,[72] and Zika virus infections[73]).

Generally speaking, then, it is doubtful whether human dignity, which is supposed to ensure autonomy, can be used to frustrate the will of donors who have autonomously determined what their cells are to be used for. If there is a violation of dignity at all, then only of the "personality" that is "trapped" in the organoid; the only reason the corresponding research would have to cease would be to protect this personality, as opposed to the voluntary donor.[74]

7.2.1.1.2 Consent to Research Involving Persons Incapable of Giving Consent

I will now address questions of consent to the removal of cells from persons incapable of giving consent. Again, consent bears upon two distinct rights: the right to physical integrity, which is implicated by the removal, and the general right of personality, which bears upon the further uses of the collected material. The problem

[66] As regards human cloning Frankenberg (2000), p. 330; as regards human–animal hybrids: Lackermair (2017), p. 288.

[67] See Lackermair (2017), p. 301, who asks that question with regard to hybrids and chimeras.

[68] Lackermair (2017), pp. 301–302.

[69] For arguments in favor, see German Ethics Council (2011), pp. 61–62. For objections, see Lackermair (2017), p. 350 et seq.

[70] Listed by Daviaud et al. (2018), p. 2.

[71] Lancaster et al. (2013), p. 373 et seq.; Li et al. (2017), p. 823 et seq.

[72] Forsberg et al. (2018), p. 1 et seq.

[73] Qian et al. (2016), p. 1238 et seq.; Watanabe et al. (2017), p. 517 et seq.

[74] Kersten (2004), p. 509 et seq.; Buchanan et al. (2012), p. 199; Dreier (2013), Art. 1 sec. 1 para. 109; Lackermair (2017), p. 302 et seq.; Spranger (2001), p. 242; and Schroth (2009), p. 722, all reject the idea of human dignity as a constraint on that person's own rights. For a more cautious approach, see Ohly (2002), p. 414. On Ohly's view, whether one has the right to dispose of one's own rights depends on whether this disposition would cause irrevocable loss of liberty, personal self-determination, or the essential factual prerequisites of a life lived autonomously. There is no such risk in our case, however.

here is that the provisions on the legal representation of minors obligate the parents to consider "the best interest" of the child (sec. 1627 BGB). As regards incapacitated adults, moreover, the law provides that the custodian must attend to the affairs of the person under custodianship in a manner that is conducive to his "welfare" (sec. 1901 para. 2 sent. 1 BGB); to do so, the custodian must consider the wishes of that person (sec. 1901 para. 2 sent. 1 and para. 3 BGB).

For that reason, many scholars doubt that research on persons incapable of giving consent is admissible. The research, they argue, is not in the concerned persons' best interest. Instead, it instrumentalizes them in violation of Art. 1 GG, at least if the research is not expected to be of direct benefit to them (as would be the case with therapeutic research). The inhumane experiments conducted during the Nazi regime suggest proceeding cautiously.[75]

Certainly, historical experience teaches us that the problem of research on persons incapable of giving consent should be handled with sensitivity, and that research with persons incapable of giving consent should be subject to strict conditions. It would go too far, however, to ban it altogether whenever it does not promise any benefit to the person concerned: If researching certain diseases or conditions necessarily involves persons incapable of giving consent and the results of these projects could allow to cure or at least alleviate the suffering of people with the same condition, research on this group of persons should be possible, provided it necessitates only minor physical interventions.[76] To ban research on persons incapable of consent altogether would neglect the right to life and health of other individuals affected by the same diseases and conditions.[77]

Of course, the end cannot justify the means, but we should refrain from labeling a minor intervention carried out for important reasons a violation of dignity. Whether there is a violation of dignity always depends on the circumstances, which means we must consider the intensity and the effects of the intervention as well as its objective.[78] Specific legislation, moreover, already permits some research for the benefit of others. According to the Medicinal Products Act, clinical trials on minors for the benefit of other minors are possible if the research is absolutely necessary, relates to a clinical condition from which the minor suffers, and is only associated with a minimal risk and a minimal burden (sec. 40b para. 4 sent. 1 lit. (a) of the Act in its version as of 27 January 2022). Thus, if we do not wish to consider this Act unconstitutional, we should not deem group-beneficial research implicating persons incapable of giving consent an automatic violation of their dignity.

Admittedly, the Medicinal Products Act deliberately does not allow the research for the benefit of others on *adults* who are incapable of giving consent (sec. 40b para. 4 sent. 3 of the Act in its version as of 27 January 2022). Yet we should not draw any conclusions from this omission; as a specific law, the Medicinal Products

[75] Spranger (2001), pp. 242–243 (see p. 242 for the permissibility of therapeutic research); see also Taupitz (2012), pp. 585–586, and the references cited therein.

[76] Taupitz (2012), p. 586. On the permissibility of research on minors that does not benefit them directly but involves only minor physical interventions, Lipp (2021c), XIII E. I. para. 107.

[77] Taupitz (2012), p. 586.

[78] Taupitz (2012), p. 586.

Act has no effect on research in other areas. Since the welfare of the person under custodianship also includes taking into account his or her preferences, and since these preferences are determinative if higher-ranking legal interests do not stand in the way, participation in research projects by persons under custodianship must be permissible, therefore, if the person concerned wishes to participate and if the research measure entails few, if any, risks.[79] However, even absent such a wish, I believe the well-being of the person is not endangered if he or she does not object,[80] the research involves only minor risks and burdens, and his or her legal representative consents.

It bears emphasizing that these findings are in line with international standards, which do not ban research on persons incapable of giving consent (see Art. 17 of the Oviedo Convention, paras. 28–30 of the Declaration of Helsinki, Art. 12 and 21 para. 5 of Recommendation CM/Rec(2016)6).[81]

From this we can draw the following conclusions for the collection of cells for the generation of brain organoids for research purposes: To begin with, the collection on persons incapable of consent is only permissible if it is associated with minimal risks and burdens, which is likely to be the case with a blood sample, or at least if blood has to be taken anyway.[82] In addition, however, the research objective must require involving persons incapable of giving consent, for instance, because it aims to investigate a disease or condition present in the individual concerned. So this prerequisite will, for example, not be met if the genetic disease to be investigated can simply be "programmed," through genetic modifications, into the cells taken from a person capable of giving consent. For that reason, genetic engineering of this sort should have precedence.

Of course, we must also consider whether the *further use* of bodily substances threatens the well-being of the person incapable of giving consent, thereby preempting his or her representative's consent to such projects. But I do not think that such use impairs the person's right to informational self-determination or of personality in general. Regarding the right to informational self-determination, the data protection regulations already provide sufficient protection against the illegal or improper use (including re-use) of the data.[83] Anonymization, insofar as it is compatible with the research objective, may serve to increase this protection.

Nor do I see a violation of the "right not to know" about one's own genetic makeup, a right that partakes in the protection of informational self-determination.

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[79] On the relevance of the incapacitated person's wish to participate in the research, Lipp (2021c), XIII. E. I. para. 104. But see Spranger (2001), p. 243, who, to protect the person under custodianship from self-harm, argues that his or her wish is irrelevant if it involves any form of research.

[80] For the right to object, see below.

[81] See Sect. 7.1.2.1.

[82] On this controversial point, cf. Spranger (2001), p. 243.

[83] As regards minors, Schreiber (2019), p. 278 et seq, in particular p. 284-285. See Sect. 7.4, on the data protection requirements, pursuant to which the further use of data without the data subject's consent is only permissible if there is an appropriate legal basis and particular protective requirements are met; on the view I advocate, the further use of genetic data is unlawful if the data subject does not consent. Violations may incur onerous financial sanctions; see sect. 41 of the Federal Data Protection Law and Art. 83 para. 5 lit. (a) Reg. (EU) No 2016/679.

In principle, unsolicited feedback on suspicious findings following the genetic analysis of the samples might affect this right. But there is no consensus as to when this right is violated. Thus, it is disputed whether the violation of the "right not to know" requires the explicit prior statement, by the person concerned or his or her representative, that they "do not wish to know."[84] It is also doubtful whether the right is infringed if the information in question—as will often be the case—is given to the legal representative and not to the person to whom it refers.[85] (Although it remains possible, of course, that the person concerned will gain knowledge of the information at a later point, thereby imperiling his or her psychological integrity.)

Moreover, violations of the "right not to know" are somewhat hypothetical because the researchers will anticipate the issue of transmitting random findings and will include them in the consent procedure. If the representative agrees to the feedback, the person incapable of giving consent will then fall within the protection of the Gene Diagnostics Act ("*Gendiagnostikgesetz,*" GenDG)[86]: As this Act provides that genetic examinations of persons incapable of giving consent may only be carried out for diseases that can be treated or prevented, sec. 14 para. 1 GenDG, it follows that only such findings may be communicated.[87]

Finally, a non-consensual further use of the body substance itself for purposes other than those originally planned does not pose any significant danger to incapacitated persons either—concrete to their general right of personality—because further use without consent is only permissible under extremely narrow conditions.[88]

Since research on incapacitated persons is not per se unlawful, then, a few remarks concerning the consent procedure are in order: It is important to note that the researchers must inform not only the legal representatives prior to consent but also the research participants themselves, should the participants have the requisite mental capacity. The persons concerned have information rights as well.[89] Their veto, moreover, must also be taken into account. This applies not only to adults[90] but also to minors, whose wish not to participate in the research measure should be determinative if it is sufficiently clear, serious, and continuous—at least if the research will not produce any direct benefit for the minor.[91] If the minor would not benefit from the research at all, there is no justification, not even pursuant to the right of parental care, to "break" this will.[92]

[84] Taupitz (1998), p. 597 et seq.

[85] See Federal Court of Justice (2014), p. 2192, which in this case denied a violation.

[86] On the applicability of the GenDG—whose sec. 2 para. 2 no. 1 states the Act does not apply to "research"—Schreiber (2019), p. 94.

[87] Schreiber (2019), p. 286.

[88] See Sect. 7.2.2.3.

[89] See Schreiber (2019), p. 293, and the references cited therein; Taupitz (2000), p. A79.

[90] For adults, cf. Lipp (2021c), XIII. E. I. para. 104; for the general context, National Ethics Council (2004), p. 21; Taupitz (2000), p. A75 et seq.

[91] Schreiber (2019), p. 154; Spickhoff (2018b), sec. 630d para. 7; Taupitz (2000), p. A75 et seq.

[92] Schreiber (2019), p. 154.

The Oviedo Convention, for its part, also assumes in Art. 17 para. 1 v that research on persons incapable of consent is only possible if the person concerned does not object. Para. 29 of the Declaration of Helsinki provides, "[w]hen a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected." Specific legislation, finally, likewise provides for the consideration of the opposing will of research participants who are incapable of giving consent.[93] Besides, these groups of persons must also be expressly included in the information procedures when participating in clinical trials of medicinal products.[94]

7.2.1.1.3 Consent to Research Involving Minors Capable of Giving Consent

If minors are capable of giving consent, we must ask ourselves whether they alone can consent to research interventions, or whether the consent of their legal representatives is always necessary as well. Following our findings in Sect. 7.1.2.2, minors with the appropriate mental capacity are authorized to make decisions on their own, unless high risiks—e.g., to the minor's life—make parental involvement appear justified. Specific legislation, such as the rules of the Medicinal Products Act related to clinical trials, which has already been mentioned many times, provides, however, that both minors and their legal representatives must consent (sec. 40b para. 3 sent. 1of the Medicinal Products Act in its version as of 27 January 2022). Some scholars extend this principle to all research interventions; in all matters of research, then, the minor's right to decide would be limited to a right of *co*-decision.[95] I do not find this conclusion persuasive, however. Even in the case of research interventions, the minor's right to exclusive consent should depend on the concrete potential risks the research bears for him or her.

Let us take the example of a blood sample. While the physical intervention itself poses little risk, thereby implying that the consent of minors may suffice, the concrete further use may still imperil the right of personality of minors as well as their property rights concerning the cells collected from their body.[96] As we will see in the following, these property rights make it impossible for minors to give consent without their legal representatives.

Mature minor can consent to interferences with their general right of personality. Crucially, the ethical issues surrounding a research project do nothing to change that: If minors are capable of understanding the significance and scope of the research, including the uncertainty of the research result as well as its ethical significance, then they must have the right to make an autonomous decision. We can draw this conclusion from the idea of the religious maturity of minors, which sec. 5 of the

[93] Such as in Art. 31 para. 1 lit. (c) and Art. 32 para. 1 lit. (c) of the Reg. (EU) No 536/2014.

[94] See Art. 31 para. 1 lit. (b), para. 3 and Art. 32 para. 1 lit. (b), para. 2 of the Reg. (EU) No 536/2014.

[95] Lipp (2021c), XIII. E. I. para. 108.

[96] See Sect. 7.2.2.2.

Act on the Religious Education of Children sets at the age of 14. From this age, the parents' influence in matters of religion, and therefore also in ethical questions, is less legitimate.[97] For that reason, the collection and use and re-use of genetic—and therefore particularly sensitive—data in the context of the generation and examination of brain organoids does not justify depriving minors of their sole decision-making authority, since there is no serious danger to their right to informational self-determination.[98]

What we should not underestimate, conversely, are the consequences of an unwanted feedback regarding genetic aberrations. The physical and psychological integrity of minors will suffer if they fail to come to terms with this information. Moreover, prior discussions between the researcher and the minor regarding possible feedback information will force the minor to decide in advance whether he or she wishes to exercise his or her right not to know. This, too, may prove challenging. For these reasons, we should not prematurely affirm a minor's capacity to give consent.

In the end, however, what frustrates the minor's exclusive right to consent are the property rights implicated by the research we are concerned with here:[99] Research measures impair the minor's property rights if they destroy or process the collected cells,[100] thereby granting the researcher original ownership of the newly created thing (sec. 950 of the Civil Code); this will likely be the case with brain organoids.[101]

This raises the problem that only persons with the capacity to contract, so individuals of age (over 18), may consent to the infringement of their property rights: Secs. 104 et seq. of the Civil Code, which require the parents' involvement for legally disadvantageous transactions, would be undermined if minors could consent to property-altering research without involving their parents. Since the loss of property by means of processing is legally disadvantageous, the consent of the legal representative is necessary,[102] therefore, also for generating brain organoids from cells; as is always the case, the economic value of the bodily substance is irrelevant for the question of whether a legal transaction is legally advantageous or not.

It follows from this that minors are prevented from consenting to research on separated body substances without the consent of their parents, at least if we assume that minors have property rights to substances separated from their body.

7.2.1.2 Removal of Cells for the Generation of Brain Organoids Transferred to Animals

The following section addresses an individual's consent to the transplantation of brain organoids derived from his or her own body cells to animals. The transfer of human brain organoids to animals is not pure science fiction: Research groups have

[97] Fink (2005), p. 80.

[98] As just discussed in the case of research on incapacitated persons.

[99] See Sect. 7.2.2.2, on rights over severed bodily substances.

[100] For the legal consequences of altering a thing by processing it, see secs. 947 BGB et seq.

[101] Cf. Faltus (2021), p. 131.

[102] See generally Klumpp (2017), preliminary remarks to §§ 104 ff., para. 100, and the references cited therein; Fink (2005), p. 77; c.f. Schreiber (2019), p. 319 et seq.

already carried out transplants into rodents. While brain organoids cultivated purely in vitro have a limited lifespan and developmental capacity, as they lack a supply of oxygen and nutrients (vascularization), an appropriate environment in vivo can overcome these limitations.[103] As the experimental transplantations provided the positive finding "that human brain organoids can integrate and form functional circuits in mouse brains," it seems possible that organoids may "provide an alternative to pure populations of a particular cell type, espescially for the treatment of complex brain disorders or injuries,"[104] as "conventional cell-based transplant methods face the hurdles of poor graft survival and inadequate neural differentiation."[105]

As regards the consent requirement for the removal and use of the cells, the principles established above remain applicable[106]: Since it interferes with the concerned person's physical integrity, the removal of cells requires consent; this consent extends to the agreed further use, if only implicitly. As the removal itself cannot be considered immoral within the meaning of sec. 228 StGB, the consent is valid. Again, however, we should take a brief look at the requirements that flow from Art. 1 para. 1 GG. After all, experiments that transplant brain organoids into animals raise the question of where the boundary between humans and animals runs, and to what extent we may cross this boundary.[107]

To begin with, the transplantation of cells to an animal does not entail the sort of "animalization" of the donor that could be incompatible with his dignity[108]—provided one considers "animalization" violative of human dignity in the first place. As we saw above, the simple use of a human being's cells does not call into question his or her quality as a human being.[109] This assessment does not change just because a transplantation creates the so-called neurochimeras. The transplantation does not represent a disregard for the uniqueness of that human being. Thus, the kind of transplantions that merely insert organoids into the brain of a host—e.g., a mouse—almost certainly does not lead to the formation of a complete human personality. In experiments in which mouse embryos were injected with human stem cells, for example, some of these stem cells (0.1%) developed into neuronal cells but did not have any effect on the cognitive abilities of the mice.[110]

Admittedly, the transplantation of organoids differs from that of simple cells: the transfer of brain organoids, and thus of small brain parts, is in principle far more likely to influence the cognitive abilities of the recipient than the transfer of single

[103] Mansour et al. (2018), p. 432 et seq.; Daviaud et al. (2018), p. 1 et seq.

[104] Mansour et al. (2018), p. 440; Daviaud et al. (2018), pp. 2 and 3, also report positive findings.

[105] Daviaud et al. (2018), pp. 1 and 2.

[106] The German Transplantation Act does not apply to the transfer of human tissue or organs to animals, which means that no specific requirements for the informed consent of the cell donor arise from more specific legislation.

[107] See also Farahany et al. (2018), p. 431.

[108] Generally on the creation of chimeras, Lackermair (2017), p. 299.

[109] Lackermair (2017), p. 299.

[110] Muotri et al. (2005), p. 18644 et seq.; Lackermair (2017), p. 68 et seq., 299–300, refers to this experiment to argue against "humanizing" animals through human neuronal cells.

cells, especially because the organoids can generate region-specific neuronal organoids.[111] At the same time, however, the effect is also likely to be limited to a "single discrete function" (if at all) because of the small size of the organoid compared with the host's brain: The achievable effect depends on several variables, including "the percentage of the animal brain that is of human origin, the specific site of brain integration, and host factors such as species and age."[112] Furthermore, current studies suggest that brain organoid transplantations, by causing a surgical cavity, "are more likely to worsen brain function than to improve it."[113] Accordingly, cerebral enhancement is a purely theoretical issue at the moment.[114]

But even if the animal containing a human brain organoid would show rudimentary human behavior (such as the chickens that were transplanted with parts of quail brains in the embryonic stage and then made typical quail sounds[115]), it is doubtful whether this outcome would truly imitate, let alone duplicate, the human personality. A individual's personality is much more complex than generalizable and, above all, rudimentary human behavior. Even if the entire brain of, say, a mouse consisted purely of human cells, moreover, a complete humanization of animals is considered (rather) improbable.[116]

This may be different as regards primates.[117] Even then, however, I submit one should not speak of a disregard for the uniqueness of the donor: As mentioned above, the assumption of such a direct causal connection between the formation of personality and the genetic content of neuronal cells overestimates the influence of the genome.[118] Taking into consideration that personality also, or rather primarily, develops through one's own history and environment, one can at best speak of the emergence of a *new* personality.[119]

Moreover, we should bear in mind once again that the experiments at issue here require the donors' consent, and that it is hardly justifiable to deny them the right to consent on the ground that it would imperil their dignity. If anything requires protection under the right to human dignity, it is the being that results from the research, as the latter may yield a being whose status as human or animal is unclear. We will need to clarify, therefore, where to draw the line between acceptable and

[111] On the possibility of generating not only whole-brain organoids but also region-specific brain organoids, Chen et al. (2019), pp. 463–464, and Daviaud et al. (2018), p. 17 (and the references cited therein). Karpowicz et al. (2004), p. 334, presume there might be a transfer of functional behavior when entire brain regions are transplanted between closely related, functionally and morphologically similar beings, such as chimpanzees and humans.

[112] Chen et al. (2019), pp. 465, 467.

[113] Chen et al. (2019), p. 466.

[114] Chen et al. (2019), p. 467.

[115] Balaban et al. (1988), p. 1339 et seq.

[116] Greely et al. (2007), p. 35; Chen et al. (2019), p. 468; cf. Lackermair (2017), p. 70.

[117] Chen et al. (2019), p. 469, do not answer that question.

[118] Lackermair (2017), p. 299.

[119] Lackermair (2017), p. 300.

non-acceptable forms of cerebral enhancement of animals. This, however, is a question for another day.[120]

In conclusion, then, it is not per se impossible to consent to research involving the transplantation of human brain organoids into animals, especially given the current state of research and the exclusive use of rodents. As regards persons incapable of giving consent and minors capable of giving consent, finally, the principles set out under Sects. 7.2.1.2 and 7.2.1.3 apply here as well.

7.2.1.3 Removal for the Generation of Brain Organoids in the Field of Drug Research and Personalized Medicine

Brain organoids can also be used for testing drugs. In the field of toxicological screening, for instance, they can be used to assess the toxicity of substances. To do so, tissue samples are taken from defined patient groups and propagated.[121] Furthermore, patient-specific organoids can also be used in the field of personalized medicine, where they help find the ideal treatment for a specific patient. Examples include rare diseases for which there are no clinical trials, given the high cost and low benefit, such as rare gene mutations leading to cystic fibrosis.[122] Diseases of the brain may profit from the use of organoids as well.

The question we will now address is whether specific regulations establish special requirements for the consent and information of the cell donor in this context.

With regard to toxicological screenings, first of all, we need to inquire whether the corresponding tests constitute clinical studies.

The version of the German Medicinal Products Act ("*Arzneimittelgesetz,*" AMG) prior to 27 January 2022, which was based on Directive 2001/20/EC (now replaced by Reg. (EU) No 536/2014), provided in sec. 40 para. 1 sent. 3 no. 3 AMG (now replaced by Art. 29 Reg. (EU) No 536/2014 and the amended version of the Medicinal Products Act in its version as of 27 January 2022) that a clinical trial in humans may only be conducted "if and as long as the person concerned (a) has come of age and is capable of recognizing the nature, significance and scope of the clinical trial and of acting accordingly, (b) has been informed in accordance with paragraph 2 sentence 1 and has given his or her written consent [...] and (c) has been informed in accordance with paragraph 2a sentences 1 and 2 and has given his or her written or electronic consent; the consent must also expressly refer to the processing of health data." Special provisions applied to minors and to adults who are incapable of giving consent (sec. 41 para. 3 AMG[123] (now replaced by Art. 31 Reg. (EU) No 536/2014 and the amended version of the Medicinal Products Act in its version as of 27 January 2022) and sec. 40 para. 4 AMG[124] (now replaced by Art. 32

[120] See Chen et al. (2019), p. 469. Farahany et al. (2018), p. 431, suggest a case-by-case evaluation. For Greely et al. (2007), p. 38, a mouse with human language capacities and self-consciousness would at least be "troubling."

[121] Bartfeld and Clevers (2018), p. 93.

[122] Bartfeld and Clevers (2018), p. 93.

[123] Based on Art. 5 Directive 2001/20/EU.

[124] Based on Art. 4 Directive 2001/20/EU.

Reg. (EU) No 536/2014 and the amended version of the Medicinal Prodcuts Act in its version as of 27 January 2022)).

Sec. 4 para. 23 sent. 1 AMG in its version prior to 27 January 2022 defined a clinical trial. To do so, it drew on Directive 2001/20/EC,[125] whose Art. 2 defined clinical trials as "any investigation *in human subjects* intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy." Since the substances we are concerned with are not tested "in human subjects," but only on organoids produced from human cells, I argue that the procedure could not qualify as a clinical trial within the meaning of that provision.

Now, Art. 2 para. 2 of Reg. (EU) No 536/2014 differentiates between a "clinical study" and a "clinical trial." Both, however, relate to investigations "in *relation to humans* (...)."[126] I see two arguments why this revised definition does also not cover the substances relevant here. First, the revision likely did not seek to modify the meaning or scope of the Regulation; the German version, for instance, still uses the words "in humans." Second, the term "in relation to humans" continues to suggest a close relationship to the human body, which means that the use of medicines on substances that have been separated from the body no longer constitutes use "in relation to humans."[127]

I submit that a purposive interpretation yields the same answer. The Regulation seeks to ensure the safety of the test persons,[128] which is not affected if the medicinal product does not enter the body itself. Para. 11 of the recitals states that the risk to subject safety in a clinical trial mainly stems from two sources, the investigational medicinal product and the intervention, but it does not explicate what it means by "*the* intervention"; I contend that it refers to the investigational measures that are carried out on test persons within the framework of a clinical trial to test the effect of the medicinal product; these measures do not apply, of course, when substances are tested on brain organoids only.

Another argument against the classification of drug tests on separated body materials as clinical trials is that some articles—e.g., in Reg. (EU) No 536/2014—are premised on a drug application directly in the human body.[129] Finally, the

[125] Wachenhausen (2016a), sec. 4 AMG para. 184.

[126] The French version of the Directive referred to "chez l'homme," while the Regulation refers to "en rapport avec l'homme."

[127] There does not seem to be any scholarship as yet regarding the changed wording. Neither this term nor the term "in humans" used in the Directive appear anywhere else in the Regulation itself, nor is there any reference to this amendment.

[128] Lipp (2021c), XIII.E.IV.1. para. 71; Wachenhausen (2016b), sec. 40 AMG para. 7.

[129] See, e.g., Art. 31 and 32 (clinical trials on incapacitated subjects and minors), as such a trial can only be carried out if either the subject has a *direct benefit* or there is at least a benefit for the population represented by the subject, provided it imposes only a minimal burden on the subject *in comparison with the standard treatment*. However, neither can the procedure examined here yield a direct benefit nor can the prerequisite be fulfilled that only a minimal burden may exist in com-

conception of the pharmaceutical regulations as a whole suggests that toxicology studies and clinical trials are distinct operations. Thus, sec. 22 AMG requires the submission of documents from both the clinical trial (sec. 22 para. 2 no. 3) and the toxicological studies (sec. 22 para. 2 no. 2) for the authorization of medicinal products. In fact, toxicological tests have always been carried out, as the so-called preclinical studies, on animals or in vitro.[130]

The targeted testing of efficacy for a specific patient in the context of personalized medicine is not a clinical trial either, which means that secs. 40 et seq. AMG as well as Reg. (EU) 536/2014 do not apply. For one, the researchers do not use the medicinal product "in humans." Second, it is already doubtful whether such tests constitute an experiment within the meaning of medicinal products law. It is possible to combine research and therapeutical purposes, thereby conducting a so-called therapeutic experiment. However, an intervention cannot be considered research if it is aimed only at curing an individual person, regardless of whether the measure yields, as a side effect, new insights.[131] Individual healing attempts are therefore not subject to the regulations on clinical trials.[132] It can be difficult to distinguish individual healing attempts from research, of course. A multitude of individual healing attempts does not necessarily constitute research, the threshold is indeed crossed once the new method involves a pilot study or a planned and organized series of healing attempts.[133]

Thus, there are no specific statutory requirements for informed consent in the field of drug research on brain organoids and personalized medicine. Again, then, minors and persons who are incapable of giving consent are subject to the general principles (Sects. 7.2.1.1.2 and 7.2.1.1.3).

7.2.1.4 The Scope of Consent

Yet another question is how specific the person's consent must be. It is unclear, for instance, whether one can consent ex ante to research projects that, at the time of consent, are still unknown.

On the one hand, blanket consents are considered problematic because they lack the specificity that inheres in the concept of informed consent and is based on Art. 2 para. 1 in conjunction with Art. 1 para. 1 GG.[134] Instances of "broad"

parison with the standard treatment. The latter means that no further burdensome interventions may be carried out compared to the standard therapy, such as the collection of samples to test the drug's mode of operation. See Schreiber (2019), p. 248.

[130] Winnands (2016), sec. 22 para. 54; Rehmann (2020), sec. 22 para. 20; Franken (2020), sec. 12 A. para 2 and A.IV. para. 9.

[131] A so-called individual healing attempt. See Lipp (2021c), XIII.E.III. paras. 59 et seq.; Kern (2019b), § 131 I.3. para. 20.

[132] Kern (2019b), § 131 I.3. para. 20; Bender (2005), p. 512.

[133] Lipp (2021c), XIII.E.III. para. 59–61. On the healing attempt as a therapeutic study, if the results are evaluated systematically, Schreiber (2019), p. 8. Bender (2005), p. 515, considers a healing attempt a therapeutic study and therefore research if it comprises at least 10 persons, as this number suggests a certain degree of standardization.

[134] Halàsz (2004), p. 231.

consent—which may refer to a specific research objective or "medical research" in general—are viewed more favorably, on the other hand.[135]

I concur with this approach. It would go too far to void any consent that does not relate to specific research projects, for the right to self-determination must also include the right to accept uncertainty.[136] We can still speak of "informed consent" if the persons concerned are informed about the scope of their consent and know, therefore, what they are getting into.[137] In addition, the persons concerned can always exclude certain areas of research or revoke their consent.[138]

Some scholars suggest that informed consent extends only to research projects that the donor of the body materials can expect and that do not violate legal prohibitions.[139] The question is, however, whether anything is gained by this restriction. After all, research that violates legal prohibitions is always inadmissible. And it is hard to define what research the donor of the substance can expect without accepting precisely the sort of uncertainty the scholars tried to avoid.

Nor does Art. 10 sec. 1 of Recommendation CM/Rec(2016)6 prohibit broad consent. It merely states that "the person concerned should be provided with comprehensible information that *is as precise as possible* with regard to the nature of any envisaged research use and the possible choices that he or she could exercise (...)." As precise as possible includes information that can still be vague because the research project itself is still unknown.

Furthermore, para. 12 of the WMA Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks (2016) likewise permits a "multiple and indefinite use" of body materials donated for research; this, then, encompasses the possibility of broad consent.[140] The Declaration, incidentally, specifies the points about which the researcher must inform the patient. They include in particular "the risks and burdens associated with collection, storage and use of data and material;" "the nature of the data or material to be collected; the procedures for return of results including incidental findings;" "and when applicable, commercial use and benefit sharing, intellectual property issues and the transfer of data or material to other institutions or third countries."

It follows that researchers may generate brain organoids from donated body material, provided the person concerned donated the material for research *in general*. However, donors should be made aware that their substances could become the object of ethically controversial research. For that reason, the information given before consent should comprise some examples, thereby allowing the donors to get a general idea and, if necessary, to restrict the scope of their consent.

[135] See Schreiber (2019), pp. 294–295; Central Ethics Committee (2003), p. 9, which allows for consent that covers "all possible studies"; National Ethics Council (2004), pp. 14, 58–59.

[136] Taupitz and Schreiber (2016), p. 307.

[137] Schreiber (2019), pp. 294–295; Taupitz and Schreiber (2016), p. 307.

[138] Taupitz and Schreiber (2016), p. 307; Schreiber (2019), p. 295.

[139] Halàsz (2004), p. 232.

[140] Schreiber (2019), p. 295, refers to this Declaration in the context of broad consent.

The consent given by representatives in the case of persons incapable of giving consent is limited by default, as research on these groups of persons is per se subsidiary. Moreover, if the research does not bring any benefit to the individual, it must at least produce benefits for members of the same group of persons, as is also explicitly established in Art. 12 para. 1 and Art. 21 para. 5 Recommendation CM/Rec(2016)6 for the collection and use of separated body substances. This restriction, consequently, limits the scope of any instance of "broad" consent. Again, however, the information must only be *as precise as possible* (Art. 12 para. 2 lit. b) ii)). There is some leeway, then, for "broad" consent after all. Particularly in the case of research on brain organoids, however, it remains doubtful whether it is even necessary to use body material from persons incapable of giving consent, since the researchers may be able to artificially produce the relevant diseases if they genetically modify other donated cells.

7.2.1.5 Interim Conclusion

Adults capable of giving consent can consent to the removal of bodily substances for the generation of brain organoids for research purposes. "Immorality" is the only restriction on their right to consent to interventions in their physical integrity; the threshold of immorality is only crossed if the removal procedure threatens the concerned person's life. The right to consent to the use of the substances thus extracted is not subject to this restriction, however, as this would violate the donor's right of personality.

If the substances are to be taken from persons incapable of giving consent, the legal representative must consent to this procedure as well as to the further use of the substances. However, research on persons incapable of giving consent is always subsidiary. It is doubtful, therefore, given the possibility of modifying genes through genetic engineering, whether cells need to be taken from incapacitated persons at all.

If minors are capable of giving consent, they can, generally speaking, decide for themselves whether to participate in research projects. Research projects involving brain organoids constitute an exception, however, as such research impairs the property rights the minor has over the separated substances; to this impairment they cannot consent. Here, then, the consent of both the parents and the child is necessary.

In all cases, the participants, even if they are incapacitated, must be informed of all important aspects of the research project.

7.2.2 Removal of Body Cells for Other Purposes

7.2.2.1 Introduction

If the objective of generating brain organoids from the harvested materials did not yet exist when the harvesting took place, the consent initially granted only justifies the removal of the material and its use within the scope of the purpose of removal.[141]

[141] Lippert (2001), p. 407.

Additional consent may be required for other uses, including the production of brain organoids. We will take a closer look at this requirement in the following.

7.2.2.2 The Right Over Severed Bodily Substances Under German Law

Whether the further use of severed bodily substances requires consent depends on the rights the person concerned continues to hold over severed substances.

First of all, the living human body is not subject to property rights: The body is not a thing.[142] The right to dispose of one's own body follows from the right of personality (Art. 1 para. 1 GG, Art. 1 para. 1 in conjunction with Art. 2 para. 1 GG and Art. 2 para. 1 GG)[143] and the right to physical integrity (Art. 2 para. 2 GG). Most scholars argue that the general right of personality continues to apply to the bodily parts and substances separated from the body.[144] There are, however, good arguments in favor of the substances simultaneously becoming things, thereby falling within the domain of property rights. This means that the donor of the substances can dispose of them in a legal transaction. Thus, he can transfer ownership of the substances to research centers[145] while simultaneously retaining the right of personality regarding said substances.[146] The new owner must take into account the right of personality when exercising his ownership rights: According to sec. 903 sent. 1 BGB, owners can use an object at their discretion, provided there are no conflicting rights of third parties—such as, of course, the right of personality.[147]

In its so-called "sperm decision," the Federal Court of Justice took a somewhat different path. It held that substances which are removed from the body in order to be transferred back at a later point remain part of the body during separation, as they continue to form a "functional unit" with it. Consequently, the destruction of the substances without or against the will of the person from whom they originate constitutes an infringement of physical integrity under sec. 823 para. 1 BGB.[148] However, this decision remains contested (and rightly so). First, the court's

[142] On this now outdated opinion, see Halàsz (2004), p. 15 et seq.

[143] Halàsz (2004), p. 19. According to the so-called superposition thesis, the living body is also a thing, but the property over it is subsumed by the right of personality until a part of the body is separated. See Schünemann (1985), p. 86 et seq.

[144] At least if they contain genetic material, Taupitz (1991), p. 210.

[145] However, it is unclear how separated substances become a thing. For the different approaches, see Halàsz (2004), p. 31 et seq.; Lippert (2001), p. 407.

[146] The opinions on how the right of personality continues to cover the substances after their removal differ. Taupitz (1991), p. 209 et seq., proposes two different solutions: either the right of personality continues to exist, by analogy to sec. 953 BGB, *in the substance* or the use of the substance affects *the donor's* right of personality; Halàsz (2004), p. 36 et seq., emphasizes the connection that remains between the substance and the donor.

[147] On this approach, which combines both rights, Schröder and Taupitz (1991), p. 40 et seq.; Taupitz (1991), p. 209 et seq.; Halàsz (2004), p. 26 et seq.; Lippert (2001), p. 407; Baston-Vogt (1997), p. 285 et seq. On the approach that emphasizes the right of personality, Schröder and Taupitz (1991), p. 38 et seq.; Halàsz (2004), p. 20 et seq. On the approach that emphasizes property rights, Schröder and Taupitz (1991), p. 35 et seq.; Halàsz (2004), p. 22 et seq.

[148] Federal Court of Justice (1994), pp. 127–128.

interpretation goes far beyond the (narrow) wording of sec. 823 para. 1 BGB.[149] Second, the right of personality also protected by sec. 823 para. 1 BGB renders such an extensive reading unnecessary.[150]

Accordingly, every use of bodily substances must be examined for compliance with the former substance bearer's right of personality.[151] Both under private law, i.e., sec. 823 para. 1 BGB, and in the context of constitutional law, a violation of the right of personality is determined by balancing, in a comprehensive manner, the interests concerned.[152] These interests include the researcher's fundamental right to free research under Art. 5 para. 3 GG. In doing so, one should keep in mind that every research activity which involves human material without consent encroaches on the rights of another person. It is doubtful, therefore, whether the right to free research even extends to actions that constitute such an encroachment.[153] Why should a balancing of interests be necessary at all? Would it not make more sense to say that research may not occur absent consent? After all, if research is carried out on a living human being, there is no question that research interests can never justify infringements to the right to self-determination regarding one's body; why this should suddenly be the case once some substances have been separated from the body is certainly a good question.[154]

One possible explanation is that the downgrading of the body part to a thing and the separation from the body weakens the right of personality by changing the relationship with the different kind of substances.[155] But even then we must keep in mind that a weighing of interests only becomes necessary because the holder of the right of personality witnesses an "invasion" of his or her sphere of interests. More, the right to free research is certainly not more valuable, a priori, than the right of personality.[156]

The following observations will disregard property rights regarding bodily substances. Instead, we will assume that patients, by leaving the substances with the physician, either transferred their ownership to said physician (sec. 929 BGB), if need be implicitly, or that they abandoned it (sec. 959 BGB).[157]

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[149] Laufs and Reiling (1994), p. 775.

[150] See Laufs and Reiling (1994), p. 775, who fail to appreciate, however, that this aspect of the right of personality is not about "family planning" as an activity but about the bond that connects the person concerned with his or her body part even though it is separated from him or her.

[151] Taupitz (1991), p. 210.

[152] Schröder and Taupitz (1991), pp. 44, 54; Taupitz (1991), p. 210-211; Taupitz and Schreiber (2016), p. 305; Fink (2005), p. 56.

[153] See, e.g., Halàsz (2004), p. 195, who argues that the self-determination of the rights holder and the physician's right to free research must limit each other. Why should that be so?

[154] See also von Freier (2005), pp. 325–326.

[155] Baston-Vogt (1997), p. 289 et seq.

[156] Schröder and Taupitz (1991), p. 67.

[157] On dereliction and the transfer of ownership, Halàsz (2004), pp. 258–259; Breithaupt (2012), p. 215 et seq.; Schreiber (2019), pp. 320–321.

7.2.2.3 Is Further Use for the Generation of Brain Organoids Compatible With the Donor's Right of Personality?

7.2.2.3.1 Introduction

We should now ask whether every further use of bodily substances without explicit consent infringes the concerned person's right of personality. Were this to be the case, every further use would, in principle, have to be covered by informed consent.[158]

It has to be emphasized that German law does not prejudge the outcome of the weighing process. Sec. 8b of the Transplantation Act, which deals with the donation of organs and tissue removed for other purposes than for transplantation, constitutes an exception, as it explicitly requires consent if the physician decides, at a later point, to transplant the removed material. From this exception in this specific area we cannot draw the overall conclusion, however, that the law mandates informed consent with regard to every conceivable application of body substances.

Finally, it has to be clarified that leaving substances with the physician who analyzed them for therapeutical reasons does not imply consent to other uses than destruction, which is the only further use the patient presumably expects.[159] We should bear in mind that other areas of the law likewise distinguish between destruction and other types of use and that a consent to destroying a substance is distinct from the consent to other uses.[160]

7.2.2.3.2 The Use of Identifiable and Anonymized Material

Most scholars argue that the use of identifiable material absent consent violates the concerned person's right of personality. I agree with this position,[161] in particular if the research is accompanied by genetic analysis, especially of coding regions.[162] In this case, the right of personality—in its manifestation as the right to informational self-determination—is particularly affected, as this type of research may even explore the core of what the right of personality seeks to protect. No interference with this core is permissible without consent.[163] Since even partial genome analysis

[158] Thus Lippert (2001), p. 407, according to whom a separate informed consent is required "in normal cases," but who later limits this statement to research projects in which genetic dispositions are examined (p. 409). See also Dettmeyer and Madea (2004), pp. 85–86. I set to the side other ways—other than giving consent—to allow the use of separated body substances. On this matter, Fink (2005), p. 154 et seq.; Halàsz (2004), p. 233 et seq.

[159] For persuasive arguments against assuming implied consent, Schröder and Taupitz (1991), p. 62; Taupitz (1991), pp. 218–219; Breithaupt (2012), pp. 254–255; von Freier (2005), p. 326.

[160] Thus, e.g., in copyright law, or when a person uses a thing that its owner threw away in the expectation that it would be destroyed. See Taupitz (1991), p. 219.

[161] Based on the principle that research always requires prior consent. See Art. 21 para. 1, para. 2 lit. (a) Recommendation CM/Rec(2016)6, and Art. 22 Oviedo Convention.

[162] Contrary to non-coding material, coding material, which codes for the synthesis of certain proteins, allows drawing conclusions about personal characteristics. See Halàsz (2004), pp. 201–202.

[163] See Halàsz (2004), p. 202, who assigns this data to the core area protected by the right of personality. For a less extensive view, see Fink (2005), p. 66. Generally on research with genetic data, Schröder and Taupitz (1991), p. 64. Schreiber (2019), p. 124 et seq., suggests differentiating, especially with regard to the purpose of the data collection.

can collect personal data, the patient should have the right to decide on the use and disclosure of the data.

Genome analysis poses further risks for the patient, namely when the physician or researcher confronts the dilemma, absent prior clarification, of whether to disclose abnormalities that have an impact on the patient's health. It is possible that the patient does not want to be burdened with such information.[164]

Nevertheless, there are cases in which the researcher should have the right to use identifiable substances without the concerned person's consent. The Declaration of Helsinki (para. 32) and the Recommendation CM/Rec(2016)6 (Art. 21 para. 2 lit. b)), for instance, posit such a right when obtaining consent involves unreasonable effort and when there are clearly overriding research interests.[165] It is essential, however, to bear in mind that both criteria have to be met. Researcher will have to accept administrative efforts and the corresponding lack of time, therefore, provided they do not jeopardize their research objective.[166] Nor should in fact the impossibility to obtain consent—e.g., because there is no way to reach the person concerned—be sufficient in my opinion. Otherwise, the right to self-determination would effectively be negated. The violation of the right of personality does not depend on the possibility to obtain consent but on how incisive the research activity is and which interest the researcher can assert.[167]

The Central Ethics Committee of the German Medical Association and numerous scholars have proposed considering the following criteria in addition to those mentioned in Art. 21 para. 2 lit. b) CM/Rec(2016)6[168]—i.e., a significant research objective and the unreasonableness or impossibility of obtaining consent: the emotional and symbolic significance of the body substance used; a possible further benefit of the substance for the donor; the question of whether the research involves use of the substances that is ethically and legally controversial; the question of whether the substance will be transferred to another human being or whether another use is planned that interferes in a particularly intense way with interests of the donor, such as the collection of personal data, in particular genetic data, or a duplication of the substance due to its special properties; as well as, finally, the possibility of conducting the research on other available substances for which consent has been obtained.[169]

After having dealt with the use of identifiable substances without consent, we should also ask how the anonymization of bodily substances affects the concerned

[164] Schröder and Taupitz (1991), p. 64.

[165] Halàsz (2004), p. 197–199; Schreiber (2019), p. 309; National Ethics Council (2004), pp. 13, 57–58

[166] See Halàsz (2004), p. 196.

[167] See also von Freier (2005), p. 326.

[168] "(...) evidence is provided that reasonable efforts have been made to contact the person concerned (i.); the research addresses an important scientific interest and is in accordance with the principle of proportionality (ii); the aims of the research could not reasonably be achieved using biological materials for which consent or authorisation can be obtained (iii); and there is no evidence that the person concerned has expressly opposed such research use (iv)."

[169] Central Ethics Committee (2003), p. 6; Taupitz (2020a), p. 808; Schröder and Taupitz (1991), pp. 82–83; Schreiber (2019), pp. 309–310.

person's right of personality. Anonymization might facilitate the use of the substances without the donor's consent, as the donor's interest in consenting may be less forthright. Some argue indeed that there are no restrictions in law on research conducted on anonymized substances;[170] others make the more modest claim that the requirements for waiving the consent requirement are more lenient than in the case of identifiable materials.[171] Their background assumption is that the only purpose of extending the right of personality to the further use of bodily subtances is to prevent their individualization, and that anonymization preempts this risk.[172]

This assumption, however, is not entirely correct. Since every cell of a body contains the same genetic code, a complete anonymization may be impossible if corresponding comparison material is available; future medical and electronic developments may exacerbate this problem.[173] It is doubtful, for that reason, whether the current de facto anonymization sufficiently takes into account the donor's privacy interests, especially if the research includes the genetic examination of coding material, thereby allowing the scientist to research the personality traits of identified (or at least identifiable) persons.[174]

The prevailing opinion is also wrong to suggest, moreover, that right of personality over severed bodily materials merely protects the persons concerned against the identification or unauthorized dissemination of their data. I believe the bond that connects the former substance bearers with their now separated substance goes beyond that. As regards the living body, the right of personality transcends a mere right to "data privacy." They also encompass the right to determine who may perform what actions on the body. I do not see any reason why this should change after the separation of materials from the body. Instead, it makes more sense to argue that the right to physical self-determination continues to be effective.[175]

Consequently, any use of bodily substances, identifiable or not, for research purposes requires, in priniciple, the consent of the person concerned.[176] The protection against the identification and attribution of certain characteristics and the right to

[170] This is also the case in Art. 21 para. 4 Recommendation CM/Rec(2016)6. See Breithaupt (2012), pp. 209, 262; Dettmeyer and Madea (2004), pp. 92–93; National Ethics Council (2004), pp. 12–13, 52, 56–57. Halàsz (2004), p. 203, for whom the right of personaltiy protects only "genetically relevant" substances (pp. 56–57), argues that this holds true at least for non-coding bodily materials. Nitz and Dierks (2002), pp. 402-403, also seem to argue that consent is not "normally" required for research on anonymized material. See also Taupitz and Schreiber (2016), p. 306, who argue, however, that the waivability of consent also depends on the type of use. von Freier (2005), p. 323, finally, refers to the statement of the National Ethics Council (2004).

[171] See, e.g., Central Ethics Committee (2003), p. 6, which emphasizes the criterion of anonymization. See also Taupitz (2020a), p. 808; Schreiber (2019), pp. 307–308 and 311.

[172] Cf. von Freier (2005), p. 323

[173] Halàsz (2004), p. 200; Fink (2005), p. 62.

[174] Halàsz (2004), p. 203.

[175] von Freier (2005), p. 324 et seq.; also Halàsz (2004), p. 87 et seq.; Fink (2005), p. 56.

[176] Thus also Freund and Weiss (2004), p. 317; Schreiber (2019), pp. 310 et seq.; von Freier (2005), p. 327; Fink (2005), p. 75, also does not consider consent per se indispensable. Taupitz (2020a), p. 808, focuses on the degree of anonymization but also emphasizes additional aspects.

determine the use of one's own bodily substances are two equally valid rights. Each requires examining whether research without consent violates its precepts. Anonymization can at best overcome the lack of consent as regards the right not to be identified; it does nothing to prevent a violation of the right to decide for oneself how one's bodily substances should be used. Thus, research without consent is only permissible if, on the basis of the criteria established for identifiable materials, the researcher's right to free research proves more important than the donor's right of personality. The exact use of the substances will prove especially important in the weighing process. Ethically or legally controversial uses will tilt the balance in favor of the right of personality.[177]

But does the passage of time or geographic separation maybe weaken—or void—the right of personality?[178] Scholars who support this proposition argue that an individual's legitimate interest in his or her bodily substances—identifiable or not—wanes over time.[179] Yet the question of interest (or disinterest) should not be our point of departure, since the substance carrier is simply unaware of the researchers' intention to use the substances for research purposes.[180]

What if persons incapable of giving consent are concerned? Research on substances already removed for other purposes is of course permissible if the legal representative has consented to that use. Nevertheless, the researchers should prioritize bodily materials removed from individuals who can give consent. This rule, which we can also find in Art. 21 para. 5 (read together with para 2) of Recommendation CM/Rec(2016)6, reflects the principle that only as a last resort should persons incapable of giving consent be exposed to the risks of research interventions. This holds even though research on donated materials poses few risks to the patient—namely, identifiability, even in the case of (de facto) anonymization, data use in violation of data protection regulations, and unwanted feedback regarding genetic aberrations. In my opinion, however (subsidiary) research on these substances should be permissible even without the consent of the legal representative if it meets the criteria that apply to persons capable of giving consent. After all, the criteria limit the options for research and the risks for the concerned individual are negligible.[181]

7.2.2.3.3 The Case of Generating Brain Organoids Without Consent

To conclude, I submit that the use of separated bodily substances to generate brain organoids requires consent, regardless of whether the substances are anonymized or not.

Although brain organoids are not yet very developed, the very principle of generating artificial brain organoids is likely to be ethically controversial, especially since it is not clear at what point scientists will be capable of generating a more developed

[177] Explicitly Fink (2005), p. 75.

[178] For this stance, see Breithaupt (2012), pp. 208–209, and Nitz and Dierks (2002), p. 402.

[179] Baston-Vogt (1997), pp. 291–292.

[180] See also von Freier (2005), p. 326.

[181] For minors, see also Schreiber (2019), p. 312.

brain. Moreover, the question of which status to attribute to the organoids remains unresolved not only from an ethical but also from a legal perspective.[182] Furthermore, although the original material (which may consist of individual cells) may not hold any particular symbolic value, the manufactured product does. For these reasons, we should not assume that everyone will remain indifferent to such research.

The further the development of these organoids progresses, the closer one comes to the problem of cloning. Crucially, the absence of consent in cases of cloning raises the specter of a violation of human dignity: Cloning without consent disregards the genetic uniqueness of the donor by demonstrating to a person that he or she can be duplicated.[183] Of course, the generation of brain organoids does not constitute cloning in the strict sense of term: The brain (organoid) alone does not constitute an entire human being.[184] Still, the concerns that attach to unconsented cloning also apply if researchers generate a large number of (functional?) brains from the cells of one person.

In addition, research on and with brain organoids may also involve genetic analyses. That is the case, for example, of measures to test whether medicines are effective or whether genetic corrections are feasible. If the substances used are identifiable, the lawfulness of the research also clearly turns on the patient's right to informational self-determination.

Research involving brain organoids is particularly controversial from an ethical and legal perspective, of course, when the organoids are transferred to animals.[185] But the unsolicited transfer to other humans also fundamentally affects personality interests,[186] especially if brain areas are affected. It is up to the patient alone to decide whether and in which person his bodily substances should continue to exist.[187] Therefore, a transplantation of brain organoids (or parts thereof) requires consent as well. This requirement, incidentally, already follows from the Transplantation Act (sec. 8b).

Using the donated body materials or the brain organoids produced from them for economic purposes raises questions as well. Since they are things, body substances can (subject to the prohibition of tissue trade according to sec. 17 of the Transplantation Act[188]) be disposed of in legal transactions.[189]

If we stipulate a "right to exploit, for economic gain, one's right of personality," the rights holder may want to transfer the removed substances only in return for

[182] See Lavazza and Pizzetti (2020), p. 13 et seq.; Farahany et al. (2018), p. 432.

[183] Dreier (2013), Art. 1 sec. 1 para. 109.

[184] Lavazza and Pizzetti (2020), p. 11.

[185] See, e.g., the contributions of Greely et al. (2007); Karpowicz et al. (2004) ; Lackermair (2017) ; German Ethics Council (2011).

[186] Schröder and Taupitz (1991), pp. 69–70; Taupitz (1991), p. 210; Taupitz (2020a), p. 808; but see, Fink (2005), p. 70 et seq.

[187] Schröder and Taupitz (1991), p. 66.

[188] See Taupitz (2020a), p. 809; Wernscheid (2012), p. 229.

[189] See Taupitz (1991), p. 217, and Fink (2005), p. 74 and the references cited therein. But see Halàsz (2004), pp. 203–204.

payment if there is a market for corresponding body substances.[190] That means the researcher requires the donor's consent if he or she wishes to conduct such a transaction. Should a right to monetize one's right of personality not exist, the obligation to obtain the patient's consent nevertheless follows from the contract between physician and patient.[191] The purchaser of the body material must, by the way, abide by the same restrictions on the use of the substances as the physician removing the substances.[192] Thus, the purchaser may also not generate brain organoids from the body material without the donor's consent.

Moreover, physicians must also obtain the donor's consent if they first generate brain organoids from the body material and then proceeds to sell them: While donors cease to be the owners of their cells once they have been processed (either because they transferred them to the physician or the researcher[193] or because their ownership ends pursuant to sec. 950 BGB), their personality rights are not affected.[194] The sale of the organoids thus encroaches on the right to monetize one's right of personality (and constitutes a breach of contract), especially if—due to the rarity of their properties—the cells can be used for the creation of expensive, and therefore lucrative, medicinal products.[195]

Whether the researcher may transfer removed cells for free largely depends on the use which the acquirer has in mind.[196] In our case, consequently, neither the first nor the subsequent user may generate brain organoids without the donor's consent.

7.2.2.3.4 What About "Presumed Consent"?

Let us now turn to the question of "presumed consent." Some scholars argue that the use of bodily substances for research is lawful if we can presume the concerned person's consent. If presumed consent can justify a physical intervention (under sec. 630d para. 1 sent. 4 BGB), the argument goes, it must do the same, a fortiori, for the use of bodily materials—which, after all, do not pose any risk to the patient's body or health.[197]

The recourse to presumed consent is in most cases less helpful than may appear at first glance, however: Where there are no indications of the patient's will whatsoever, the range of presumed consent can only be assessed by considering objective

[190] Thus Halàsz (2004), pp. 123–124.

[191] Schröder and Taupitz (1991), pp. 71–72.

[192] Schröder and Taupitz (1991), p. 77.

[193] On the abandonment of property and the implied transfer of ownership, Halàsz 2004, pp. 258–259; Breithaupt (2012), p. 215 et seq.

[194] Halàsz (2004), p. 39, pp. 65–68.

[195] Taupitz (1991), p. 218, argues that a violation of the right of personality becomes likely if the remuneration is especially high, and that there may only be a breach of contract between the doctor and his or her patient in other cases. See also Schröder and Taupitz (1991), pp. 78–79. But see Halàsz (2004), pp. 260–261, according to whom the donor transferred the right to economic exploitation of the materials to the physician or researcher, at least in cases in which he or she transfers his or her ownership to the latter.

[196] For greater detail, see Schröder and Taupitz (1991), p. 77 et seq.

[197] Taupitz and Schreiber (2016), p. 306.

considerations,[198] the same considerations we applied to determine whether the right of personality is violated. So, unless there are clear indications of the patient's will, we cannot simply presume he or she would have consented if at the same time, we would presume a violation of the right of personality by weighing all the interests at stake.[199] Consequently, the generation of brain organoids cannot rely on the concerned individual's presumed consent if there is no indication of that individual's preferences.

Moreover, sec. 630d para. 1 sent. 4 BGB seeks to protect the patients' own interests: In an emergency, they should be able to receive the medical treatment that is in their best interests even though they are incapable of expressing their consent. In the case at hand, however, the presumption of consent aims to protect the interests of others, that is, of the researcher. It is unclear whether presumed consent applies in these cases.[200] If it does, one should employ it with due care, and only if the will of the person concerned is known.[201] Furthermore, to avoid attempts at circumventing the right to self-determination, research cannot be based on presumed consent if the persons concerned could have been asked for their consent in good time.[202]

7.3 The Generation of Brain Organoids for Autologous or Allogeneic Transplantation Purposes

7.3.1 Autologous Transplantation

7.3.1.1 The Scope of the German Transplantation Act

Before we spell out the informed-consent requirement under the German Transplantation Act ("*Transplantationsgesetz*," TPG), we must first inquire whether the Act covers the removal of cells for the purpose of transferring (parts of) brain organoids that were grown from these cells either to the cell donor or to third parties.

According to sec. 1 para. 2 sent. 1 TPG, the Transplantation Act applies to the donation and removal of human organs and tissues for the purpose of transfer as well as to the transfer of the organs or tissues, including preparatory measures. Sec. 1a no. 4 defines tissues as "all components of the human body consisting of cells which are not organs according to no. 1, including individual human cells."[203] Sec. 1a no. 6 defines "removal" as the extraction of organs and tissue. Finally, sec. 1a no. 7 TPG defines "transfer" as "the use of organs and tissues in or on a human recipient as well as the application in humans outside the body."

[198] Wagner (2020b), sec. 630d para. 53.

[199] von Freier (2005), p. 327.

[200] See Freund and Weiss (2004), p. 317 and the references cited therein.

[201] Freund and Weiss (2004), p. 317.

[202] Freund and Weiss (2004), p. 317; Wagner (2020b), sec. 630d para. 52.

[203] The Tissue Directive 2004/23/EC likewise applies to cells. See Art. 2 para. 1, according to which the Directive applies to tissues and cells, and Art. 3 lit. a and b, which defines tissues and cells, respectively. The German legislature then decided, for the sake of simplicity, to use the term "tissue" for both cells and tissues. See Parliamentary Document 16/3146 (2006), p. 24.

It follows from these provisions that the removal of cells generally falls within the scope of the Transplantation Act, since human cells, including one single cell, constitute tissue within the meaning of sec. 1a no. 4 TPG. Furthermore, the separation of these cells from the human body constitutes a removal within the meaning of sec. 1a no. 6 TPG. Sec. 1 para. 2 sent. 1 TPG should then be read to include the removal of tissues and cells that will be transferred not in their original but in a processed state. After all, the wording of the provision is not limited to unmodified and unprocessed uses of the separated tissue on humans.[204] The explanatory memorandum of the *Bundestag* explicitly confirms this reading.[205]

The removal of cells and tissue to produce brain organoids thus falls within the scope of the Transplantation Act. But does the Act also apply to the transfer of the brain organoids themselves? There is no consensus on this matter. Some scholars argue that while the Transplantation Act covers the removal of cells from which artificial organs (and organoids) are generated, it should not apply to the transfer of those organs (or organoids)[206] because sec. 1 para. 2 sent. 1 TPG mentions the transfer of "the" organs and "the" tissues, not "of" organs and "of" tissues; in other words, they believe the Act only covers the transfer of such organs that have already been removed from the body *as organs*.[207]

I believe, however, that the structure of the statute does not allow applying it only to the removal of organs or tissues, but not to their transfer. The law, I submit, links both aspects of a transplantation so closely to one another it is either fully applicable or not applicable at all.

Thus, the permissibility of removal depends on specific requirements for the planned transfer.[208] According to provisions such as sec. 8 para. 1 no. 2 TPG, for instance, the removal of organs and tissues is only permissible if "the transfer of *the* organ or tissue to the intended recipient is suitable, according to medical assessment, to preserve the life of this person or to cure a serious illness in her, to prevent its aggravation or to alleviate its symptoms." If we stipulate that sec. 8 is applicable to the removal of cells intended to be transformed into organoids, we must also argue that the transfer of the organoid itself must constitute the transfer "of *the* organ" (or tissue) as mentioned in this section. For if (brain) organoids cannot be considered "*the* organ or *the* tissue" within the meaning of sec. 8 para. 2 no. 2 TPG, the removal of the cells is either unlawful—because it does not meet the requirements of sec. 8 (*the* removed cells will not be transferred)—or it falls outside the scope of the Transplantation Act, because this Act would apply only to removals with the aim of transferring *the* removed substances. In that case, the specific informed-consent requirements would not apply.

[204] Wernscheid (2012), p. 112; Taupitz (2020a), p. 809; Faltus (2021), p. 131.

[205] Parliamentary Document 16/3146 (2006), p. 21; Wernscheid (2012), p. 112; Taupitz (2020a), p. 809.

[206] Gerke (2020), pp. 291, 295; Taupitz (2020a), pp. 809, 811.

[207] Thus, explicitly, Gerke (2020), p. 295.

[208] König (2005), sec. 1 TPG para. 17; Rixen (2013), sec. 1 TPG para. 3 and footnote 8.

Furthermore, we should bear in mind the wording of sec. 1 para. 2 sent. 1, according to which the Transplantation Act applies to the "removal for the purpose of transfer" as well as to the "transfer of the organs and tissues." It stands to reason that the latter refers to the transfer which was intended at the time of the removal. In other words, we should read the provision as a chronological description of the transplantation process: The physician removes an organ or tissue for a specific transfer and then proceeds to transfer "it" as intended. This means that if the Act were not to cover the transfer of brain organoids, it would not cover the removal for the purpose of this kind of transfer either.

More, it seems contradictory to allow all processing-related intentions during the removal in order to apply the Transplantation Act's relevant provisions but to narrow the statute's scope, because of the processing, when it comes to the transfer itself. Once it has been processed, furthermore, no substance can be considered, strictly speaking, "the" organ or "the" tissue it was at the time of removal, and yet nobody suggests that the Transplantation Act does not apply to the transfer of processed tissue or organs;[209] some authors, for instance, even speak of the transfer of "the tissue" when the tissue in question was artificially produced from human cells.[210] Why, then, should the degree of processing be limited and the threshold exceeded (more or less arbitrarily) once tissue becomes an organ? To the contrary, it is possible to read the wording of sec. 1 para. 2 sent. 2 TPG as "transfer of either the organs and tissues directly obtained, or the organs and tissues produced from the tissue or organs removed, as intended at the moment of removal."

The purpose of the Transplantation Act, which aims to treat the transfer of all human organs and tissues equally, regardless of their origin, points in the same direction. For this reason, artificial organs are also recognized as "parts of the human body" within the meaning of sec. 1a no. 1 TPG, and thus as "organs" within the meaning of the Act, if they were created from human materials.[211] This interpretation is supported by the fact that the Transplantation Act is intended to counteract the dangers arising from the unregulated procurement, processing, storage, and distribution of cells and tissues, such as contamination or the transmission of diseases. These risks also exist in the case of artificially produced tissues (and organs).[212]

Sec. 1a no. 1 TPG, furthermore, does not indicate the Act does not apply to the transfer of brain organoids.[213] According to this provision, the term organs includes "tissues of an organ that can be used for the same purpose as the whole organ in the human body while maintaining the requirements of structure and blood vessel supply, with the exception of such tissues that are intended for the production of advanced therapy medicinal products within the meaning of sec. 4 para. 9 AMG." In other words, tissue that will normally count as an organ loses this organ property if the researcher aims to process it into an ATMP (advanced therapy medicinal

[209] See also Faltus (2021), p. 131.

[210] Gerke (2020), p. 295

[211] Taupitz (2020a), p. 811.

[212] Gerke (2020), p. 291; Taupitz (2020a), p. 811.

[213] But see Taupitz (2020a), p. 811.

product). This tissue does not lose its organ status once it becomes an ATMP. Rather, it is not removed as an organ in the first place, but "only" as tissue within the meaning of sec. 1a no. 4 TPG.[214] However, of course, the Transplantation Act also applies to the transfer of tissue.

The purpose of sec. 1a no. 1 TPG is to make sure this kind of tissue and the substance resulting from its processing fall under the regulations on medicinal products. Thus, the provision exists in its current form because Reg. (EC) 1394/2007 mandated a narrower definition of organs. According to sec. 2 para. 3 no. 8 AMG, organs within the meaning of sec. 1a no. 1 TPG are not medicinal products,[215] but Reg. (EC) 1394/2007 provided for the medicinal product status of certain substances that did fall under the organ definition of the Transplantation Act, such as cells and tissue from organs. Consequently, single cells were completely excluded from the organ definition in 2009, while tissues were excluded to the extent they are intended for the manufacture of ATMPs.[216] In 2012, the definition of organs was further restricted: now, tissue from an organ only constitutes an organ if the requirements for structure and blood vessel supply mirror that of the whole organ—as is the case, for instance, with split liver donations.[217]

It follows that this provision does not directly cover the case examined here. It is already doubtful whether the production of brain organoids even requires tissue—as opposed to single cells—within the meaning of sec. 1a no. 1 TPG. If the researchers only remove single cells, the tissue they remove never constituted an organ in the first place; in other words, it does not qualify as the object which sec. 1a no. 1 TPG sought to cover.

It is more likely, instead, that the legislature did not have the removal of cells to produce brain organoids in mind at all: Today, after all, we can create something like an organ from a substance that initially did not constitute an organ but may do so after being processed, and at the same time qualifies as an ATMP.[218] The question, then, is which property should prevail. Given sec. 1a no. 1 TPG, it makes more sense to prioritize the ATMP property. This entails that sec. 13 of the Medicinal Products Act, which requires a manufacturing authorization, becomes applicable to the production of brain organoids. This permits reviewing whether the production

[214] Pühler et al. (2010), p. 25.

[215] In this context, sec. 17 para. 1 p. 2 no. 2 TPG is very misleading: It refers to medicinal products that are "manufactured from or using organs," which seems to suggest that organs within the meaning of the Transplantation Act can constitute medicinal products in some form after all. To avoid contradicting sec. 2 para. 3 no. 8 of the Medicinal Products Act, sec. 17 para. 2 no. 2 TPG must be read to cover only medicinal products that stem from processed organs which themselves are no longer organs within the meaning of the Transplantation Act—because they no longer form a "functional unit"—and which are also no longer tissues as parts of organs within the meaning of sec. 1a no. 1 TPG.

[216] Parlamentary Document 16/12256 (2009), p. 58 and p. 26; Document of the Federal Council 171/09 (2009), p. 50; Parlamentary Document 16/13428 (2009), pp. 46–47 and p. 75; Federal Law Gazette (2009), p. 2009.

[217] Parliamentary Document 17/7376 (2011), p. 17.

[218] For the medicinal properties of brain organoids, see below, Sect. 7.3.1.3.1.

complies with the requisite technical standards.[219] Furthermore, pharmaceutical regulations on preclinical and clinical testing can be used as a prerequisite for a marketing authorization.[220]

This, it bears emphasizing, would not be the first time that sec. 1a no. 1 TPG would be applied to cases beyond its wording. Thus, the provision also comes into play when a whole organ is removed for the purpose of creating an ATMP, even though the provision states that *tissue from organs* destined to become an ATMP loses its organ property; in this case, then, the whole organ loses its organ property and becomes tissue, as which it is then removed.[221]

To make a long story short, the Transplantation Act applies to the removal of cells to produce brain organoids as well as to their transfer. The reason for that is that organoids constitute tissue within the meaning of the Transplantation Act.[222] They do not count as organs, since they acquire the properties of an ATMP through processing and the Transplantation Act states that tissue ceases to be an organ in case of doubt; but the Act likewise applies to the transfer of tissue.

The removal thus gives rise to specific informed-consent requirements under the Transplantation Act, in particular under secs. 8 et seq. TPG. The Transplantation Act does not regulate the admissibility of transfer of tissue.[223] By subjecting the removal of tissue from living donors to certain conditions, in particular recipient-related criteria (sec. 8 para. 1 no. 2), it does, however, at least indirectly, restrict the possibilities of transfer.

In interpreting both the general regime that governs curative treatments or attempts[224] and the Medicinal Products Act,[225] we must always bear these provisions of the Transplantation Act in mind. In particular, secs. 40 et seq. of the Medicinal Products Act, which regulate the prerequisites of clinical trials, do not constitute a lex specialis compared to the donor regulations of the Transplantation Act; accordingly, the provisions of the Medicinal Products Act cannot loosen the restrictions on permissible donation. First, the reason why secs. 40 et seq. of the Medicinal Products Act are not a lex specialis is that they seek to protect the drug recipient, whereas the secs. 8 et seq. TPG serve to protect the donor. However, the two are not necessarily identical. Second, had the legislator wished to allow autologous transplantations for experimental purposes such as in clinical trials, he could have done so expressly in sec. 8c TPG—a provision that was adopted in 2007[226], i.e., long after the adoption of the provisions on clinical trials.

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[219] Faltus (2021), p. 131.

[220] Faltus (2021), p. 131.

[221] Thus for the removal of pancreata Pühler et al. (2010), p. 25.

[222] Gerke does not address tissue property and concludes that the transfer of artificial organs does not fall under the Transplantation Act: Gerke (2020), p. 295.

[223] König (2005), sec. 1 TPG para. 17; Rixen (2013), sec. 1 TPG para. 3, also fn 8.

[224] König (2005), sec. 1 TPG para. 17.

[225] See Sects. 7.3.1.3.2 and 7.3.1.3.3, for autologous transplantation, and Sect. 7.3.2.3 for allogeneic transplantation.

[226] Federal Law Gazette (2007), p. 1580.

It bears emphasizing that the Transplantation Act applies irrespective of whether a donation or an autologous transplantation of the brain organoid is planned. According to sec. 1 para. 3 TPG, the Act does not apply to tissues that are removed from a person during the same surgical procedure in order to be transferred back to that person without changing their substantial condition (no. 1). This exception is irrelevant for our purposes, however, because the production of brain organoids requires a change in the substance of cells.[227]

Finally, according to sec. 1 para. 3 no. 2 TPG, the Act does not apply to the removal of blood, which means that the Act does not cover the collection of nuclei-containing blood cells for further donation purposes.[228]

7.3.1.2 Requirements for Informed Consent

Section 8c TPG deals with the informed constent for autogologous transplantations and reflects the general principles that all curative interventions must be medically indicated and require informed consent[229]: It provides that the removal for the purpose of retransfer—i.e., for an autologous transplantation—is only permissible if the person is capable of giving consent, has been informed in accordance with sec. 8 para. 2 sent. 1 and 2 TPG, and has consented to the removal and retransfer (sec. 8c para. 1 no. 1 lit. a) and lit. b)).

The information must cover the purpose of the measure, the prospects of success, possible consequences, and any circumstances that the person concerned evidently considers important; that is also the novelty of the procedure. The same, incidentally, follows from the general principles for new curative methods as well as, generally speaking, from sec. 630e para. 1 sent. 2 BGB.[230] The content of the information and the donor's declaration of consent must also be included in a transcript signed by the persons providing the information as well as the donor (sec. 8 para. 2 sent. 4, 8c para. 4 TPG). Consent may be revoked in writing, electronically or verbally (sec. 8 para. 2 sent. 6, 8c para. 5 TPG).

Crucially, sec. 8c para. 1 no. 2 TPG provides that the removal and retransplantation of the organ or tissue must take place within the context of a *medical treatment* and be necessary—according to scientific consensus—for that treatment. Thus, an autologous transplantation may be used for a curative treatment, and probably also for a curative attempt.[231] It may not be used, conversely, for non-indicated medical interventions,[232] including interventions for research purposes. Researchers must

[227] Thus generally for hiPS cell therapies, Gerke (2020), p. 296. For the requirements under sec. 1 para. 3 no. 1 TPG, see Rixen (2013), sec. 1 TPG para. 10.

[228] Gerke (2020), p. 298. See Sect. 7.3.3.

[229] Schmidt-Recla (2013), sec. 8c TPG para. 3.

[230] On the duty to inform about the prospects of success of an organ transplantation, see Müller (2013), p. 167, and below, Sect. 7.3.2.3.

[231] König (2005), sec. 1 TPG para. 17, mentions the possibility of a curative attempt in the context of transplantations (albeit before sec. 8c was adopted).

[232] Schmidt-Recla (2013), sec. 8c TPG para. 6.

bear this in mind when they plan an experiment that falls under the provisions of pharmaceutical law on clinical trials.[233]

In the case of incapacitated persons, a removal for the purpose of retransfer is lawful under sec. 8c para. 2 BGB once the representative has given his or her informed consent, provided the measure does not threaten the welfare of the incapacitated person.[234] To account for the donor's best interests, the representative must give his or her consent if the tissue removal for the purpose of retransfer constitutes a medically indicated and standard treatment. This holds for minors[235] as well as for adults under custodianship. The custodian, moreover, must comply with the wishes of the incapacitated adult; in other words, the wishes specify what counts as the incapacitated person's welfare, provided the wishes do not jeopardize the person's higher-ranking legal interests and do not significantly worsen her overall situation (sec. 1901 para. 3 sent. 1 BGB).[236] In case of doubt, however, the representative must respect the incapacitated adult's self-determination.[237] If the person under custodianship refuses to undergo curative treatment, a coercive treatment is only permissible under the conditions of sec. 1906a BGB.

Curative attempts, that is, treatments that have not yet become the medicial standard, are also not automatically incompatible with the best interests of the minor or incapacitated adult.[238] Therefore, deciding whether they are permissible requires a risk-benefit assessment.

7.3.1.3 Can a Retransfer Constitute a Clinical Trial?

7.3.1.3.1 The Medicinal Properties of Brain Organoids

The provisions on clinical trials that subject informed consent to specific requirements are only applicable to the autologous transplantation of brain organoids if the latter qualify as medicinal products. In the following, I will explain why I believe that to be the case.

According to sec. 2 para. 1 AMG, medicinal products are "any substance or combination of substances 1. intended for use in or on the human or animal body and presented as having properties for treating or alleviating or preventing disease in human beings or animals or 2. which may be used in or on the human or animal body or administered to a human or an animal either with a view a) to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or b) to making a medical diagnosis." This definition corresponds (apart from the reference to animals) to that in Art. 1 no. 2 Directive 2001/83/EC, as amended by Art. 1 of the Directive 2004/27/EC.

[233] See Sects. 7.3.1.3.2 and 7.3.1.3.3, for autologous transplantations.

[234] For incapacitated minors, see sec. 1627 BGB. For incapacitated adults under custodianship, see sec. 1901 para. 2 and 3 BGB.

[235] Schmidt-Recla (2013), sec. 8c TPG para. 12.

[236] Schneider (2020), sec. 1901 BGB para. 11.

[237] Schneider (2020), sec. 1901 BGB para. 15.

[238] Lipp (2021c), XIII.D. para. 36, 38; Deutsch and Spickhoff (2014), para. 1138-139, 1334.

First of all, organoids that are transplanted for therapeutic reasons are medicinal products, as they are intended to cure human diseases and can be used in or administered to human beings in order to restore, correct or modify physiological functions by exerting a pharmacological, immunological, or metabolic action (Art. 1 no. 2 lit. (a) and lit. (b) of Directive 2001/83/EC as well as sec. 2 para. 1 no. 1 and 2 AMG).[239] The materials generated from hiPS cells are also "substances" as defined in Art. 2 para. 1 no. 3 of Directive 2001/83/EC (and sec. 2 para. 1, 3 no. 3 AMG), that is, any matter, irrespective of its origin (which may be human).

There is also the category of the so-called advanced therapy medicinal products (ATMP), which, according to Art. 4 para. 9 AMG, include gene therapy medicinal products, somatic cell therapy medicinal products, or tissue engineered products in accordance with Art. 2 para. 1 lit. (a) of the 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. Art. 2 para. 1 lit. (a) of the Reg. (EC) No 1394/2007 defines ATMP as "any of the following medicinal products for human use: a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, a tissue engineered product as defined in lit. (b)."

HiPS-cell-based therapeutics such as organoids are ATMPs within the meaning of sec. 4 para. 9 AMG or Art. 2 para. 1 lit. (a) Reg. (EC) No 1394/2007.[240]

Because of the processing steps that they undergo, extracted cells constitute the so-called tissue engineered products as defined in Art. 2 para. 1 lit. (b) Reg. (EC) 1394/2007 which reads as follows: "[t]issue engineered product means a product that contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. A tissue engineered product may contain cells or tissues ofhuman or animal origin, or both." According to Art. 2 para. 1 lit. (c), "cells or tissues shall be considered 'engineered' if they have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved (the manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations) or the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor."

The cells from which the brain organoids are generated must first be reprogrammed into hiPS cells and are then differentiated into brain cells. This process constitutes "engineering" within the meaning of the regulation because it achieves biological characteristics, physiological functions, or structural properties that are relevant for the intended regeneration, repair, or replacement.[241] Finally, brain

[239] Gerke (2020), p. 254; Taupitz (2020a), p. 811.

[240] For greater detail, see Gerke (2020), pp. 254 et seq.; Taupitz (2020a), pp. 811–812.

[241] For hiPS cell-based therapeutics in general, see Gerke (2020), pp. 254–255. For organoids, see Taupitz (2020a), pp. 811–812.

organoids also have the purpose—at least in the context of transplantations—of being used in or administered to human beings with a view to regenerating, repairing, or replacing a human tissue.

A question we do not have to answer is whether brain organoids also fall under the definition of a somatic cell therapy medicinal product (Para. 2.2 of Part IV Annex I Dir. 2001/83/EC), since Art. 2 para. 4 Reg. (EC) No 1394/2007 provides that somatic cell therapy medicinal products which also constitute tissue engineered products shall only be considered the latter.

Furthermore, genetic changes to the cells or the brain organoid may cause the latter to become a gene therapy medicinal product. An ATMP which is both a gene therapy medicinal product and a tissue engineered product shall be considered a gene therapy medicinal product (Art. 2 sec. 5 Reg. (EC) No 1394/2007). The definition of gene therapy medicinal products is layed down in Part IV of annex I of the Dir. 2001/83/EC, as amended by the Dir. 2009/120/EC: "Gene therapy medicinal product means a biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence; (b) its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence."

It is hard to assess in the abstract whether a brain organoid with genetically modified genetic information constitutes a gene-therapeutical medicinal product. Whether it contains a recombinant nucleic acid—so that its therapeutic, prophylactic, or diagnostic effect relates directly to that recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence—depends on the method used.[242]

7.3.1.3.2 The Admissibility of Clinical Trials Under the German Medicinal Products Act in its Version Prior to 27 January 2022

Since brain organoids are medicinal products, secs. 40 et seq. AMG apply if these organoids or parts thereof are transferred back to the donor in the context of clinical trials. To decide whether the autologous transfer of brain organoids designed as a clinical trial is permissible, we must also bear in mind the requirements of the Transplantation Act. This yields the following observations.

An autologous transplantation cannot be carried out as a clinical trial on *healthy adults capable of giving consent*. Although clinical trials on these persons are permissible in principle (sec. 40 para. 1 sent. 3 AMG), the Transplantation Act requires that the removal and transfer of autologous tissue must take place in the context of *medical treatment* (sec. 8c para. 1 no. 2 TPG). This means that all non-indicated

[242] It is doubtful, for instance, whether the CRISPR/Cas method, which can change the genetic information of a cell through self-repair mechanisms, creates a gene-therapeutical medicinal product. For an analysis under the German Gene Technology Act, see Deuring (2020), pp. 379 et seq.

medical interventions are excluded,[243] including pure research interventions that fall under the Medicinal Products Act. The same applies to healthy minors.

However, this also means that *adults suffering from a disease who are capable of giving consent can* participate in corresponding clinical trials (sec. 41 para. 1 AMG), provided the use of the medicinal product is indicated, according to scientific consensus, in order to save the life of these persons, restore their health, or alleviate their suffering.

In principle, it is also permissible to conduct clinical trials without direct benefit for the participant if they are at least associated with a direct benefit for the group of patients suffering from the same disease as this person. Due to sec. 8c para. 1 no. 2 TPG, a group benefit is not sufficient, however, since it means the transplantation no longer takes place in the context of a medical treatment and is not necessary for "*the* treatment." It is doubtful, moreover, whether a transplantation without medical necessity would be medically justifiable and therefore admissible as an admissible clinical trial in the first place.

If, however, the clinical trial on adults suffering from a disease and capable of giving consent is permissible in the case of self-benefit, they themselves consent to their participation in writing (sec. 40 para. 1 sent. 3 no. 3 lit. (b) AMG), provided they have been informed according to sec. 40 para. 2 AMG. According to that provision, the persons concerned must be informed about the nature, significance, risks, and implications of the clinical trial as well as about their right to terminate their participation at any time; moreover, they must also receive the information in written form. According to sec. 40 para. 2a sent. 1 AMG, finally, the individuals must be informed about the purpose and scope of the processing of their personal data, in particular their health data.

Sec. 41 para. 2 AMG and sec. 41 para. 3 AMG provide that minors and incapacitated adults who suffer from a disease may participate in corresponding studies. If the conditions stated therein are met, we can assume that the treatments are not contrary to the best interests of these individuals (sec. 1627, 1901 para. 2 and 3 BGB).

This means that *minors who suffer from a disease* may participate if the use of the medicinal product is indicated, according to scientific consensus, in order to save the life of these minors, restore their health, or alleviate their suffering (sec. 41 para. 2 sent. 1 no. 1 AMG). Alternatively, there must be a direct benefit for the group of patients suffering from the same disease (no. 2 lit. (a)), and the research may cause only a minimal risk and burden for the person concerned (no. 2 lit. (d)). At this point, we must recall the requirements of sec. 8c para. 1 no. 2 TPG, however, according to which a group benefit does not suffice.

If the trial is admissible, the researcher must ask the legal representatives for their consent (sec. 40 para. 4 no. 3 sent. 1 AMG) after informing them in accordance with para. 2. The trial must honor the presumed will of the minors to the extent it can be identified (para. 4 no. 3 sent. 2). The minors must also be informed about the trial, the risks, and the benefits if they have the requisite age and mental maturity. If the minors declare that they do not wish to participate in the clinical trial, or express

[243] Schmidt-Recla (2013), sec. 8c TPG para. 6.

their dislike in some other manner, this will must be taken into account (sent. 3). If the minors are capable of understanding the nature, significance, and implications of the clinical trial and of acting accordingly, and is thus capable of giving consent, their consent is also required (sent. 4).

For *adults who are incapable of giving consent and suffer from a disease*, by and large the same principles apply. According to sec. 41 para. 3 no. 1 AMG, the use of the medicinal product to be tested must be indicated, according to scientific consensus, in order to save the life of the persons concerned, restore their health or alleviate their suffering; in addition, such research must relate directly to a life-threatening or highly debilitating clinical condition in which the persons concerned find themselves, and the clinical trial must be associated with the least possible burden and other foreseeable risks for these persons; both the degree of burden and risk must be specifically defined in the trial protocol and constantly reviewed by the investigator. The clinical trial may only be conducted if there is a reasonable expectation that the benefits of using the investigational medicinal product for the persons concerned outweigh the risks or that there are no risks. Consent is given by the legal representatives after they have been informed in accordance with sec. 40 para. 2. Sec. 40 para. 4 no. 3 sent. 2, 3, and 5 apply accordingly. Under German law, then, only direct self-benefit justifies research on persons incapable of giving consent; a mere group benefit does not.

7.3.1.3.3 The Admissibility of Clinical Trials Under Regulation (EU) 536/2014 and the German Medicinal Products Act in its Amended Version as of 27 January 2022

Now, Reg. (EU) No 536/2014 governs questions of consent to clinical trials. Its Art. 28 para. 1 lit. (b), for example, stipulates that subjects or—if a subject is unable to give informed consent—his or her legal representative must be informed in accordance with Art. 29 paras. 2–6. Art. 28 para. 1 lit. (c) states that the subject or, if a subject is unable to give informed consent, his or her legal representative shall give informed consent in accordance with Art. 29 para. 1, 7, and 8.

As regards the admissibility of clinical trials, the Regulation distinguishes between capacitated adults, incapacitated subjects (Art. 31), and minors (Art. 32).

If the criteria of sec. 8c TPG are met, *adults who can give consent* may participate in clinical trials with brain organoids. The Regulation, in other words, changes nothing in this respect.

The law on incapacitated subjects remains largely the same as well. According to Art. 31 and Art. 32 of the Regulation, clinical trials on *incapacitated subjects and minors* are only permitted under certain conditions, as researchers should prioritize trials on subjects who are capable of giving consent (Art. 31 para. 1 lit. (e); Art. 32 para. 1 lit. (f)). Thus, the clinical trial must relate directly to a medical condition from which the subject suffers (Art. 31 para. 1 lit. (f), Art. 32 para. 1 lit. (f)) and must either produce a direct benefit for the subject itself or at least for the population represented by the subject. In the latter case, the clinical trial must pose only minimal risk to, and will impose minimal burden on, the subject concerned in

comparison with the standard treatment of the subject's condition (Art. 31 para. 1 lit. (g); Art. 32 para. 1 lit. (g)).

Art. 31 para. 2 points out that more stringent rules prohibiting the conduct of clinical trials on incapacitated subjects remain permissible. German law has made use of this authorization, excluding group-beneficial research on incapacitated adults. The new version of sec. 40b para. 4 sent. 3 AMG, in principle, renders impermissible research projects without direct personal benefit. Thus, the representative is not able to consent to such research projects. Such projects are only permissible insofar as the persons concerned, as persons of legal age who are capable of giving consent have stipulated in writing, upon receiving medical information, that they consent to certain group-beneficial clinical trials in the event that they will be incapable of giving consent. Again, of course, we must bear in mind the conflict with sec. 8c para. 1 no. 2 TPG, pursuant to which clinical trials consisting in the transfer of brain organoids may only take place if there is an intrinsic benefit as defined in this regulation.

Furthermore, both incapacitated subjects and minors must themselves receive the information to which Art. 29 para. 2 refers, and they must do so in a manner that reflects their capacity to understand it (Art. 31 sec. 1 lit. (b); Art. 32 sec. 1 lit. (b)). If they can form an opinion and assess the information they have received, their wish not to take part or to withdraw must be respected (Art. 31 sec. 1 lit. (c); Art. 32 sec. 1 lit. (c)). The new version of sec. 40b para. 3 sent. 2 and para. 4 sent. 2 AMG goes even further, however, providing that the researcher must respect any form of dismissive attitude. All in all, Art. 31 para. 3 and Art. 32 para. 2 stress that the subjects shall take part in the informed consent procedure as much as possible. The new version of sec. 40b para. 3 sent. 1 AMG, incidentally, continues to provide for the co-consensual solution in cases where minors can give consent. Art. 29 para. 8 of the Regulation expressly allows the Member States to retain the co-consensual solution.

7.3.2 Allogeneic Transplantation

7.3.2.1 The Donor's Consent to the Collection of Cells and the Transfer of the Organoid

The removal of cells for the purpose of donation interferes with the physical integrity of the donor and therefore requires his or her consent.[244] This consent is regulated in sec. 8 TPG. Since the collection is always carried out for a specific purpose, the donor simultaneously declares his or her consent to the specific further use, i.e., to the transplantation envisaged at the time of the collection. Although the Transplantation Act only mentions the "consent to removal" and does not touch upon the consent to further uses,[245] the latter remains necessary. But, as just seen,

[244] Ulsenheimer (2019), chapter 24 § 152 IV.2. para. 31; Lipp (2021a), VI.A.I.6.a) para. 30.

[245] In contrast to the Transplantation Act, sec. 6 para. 1 sent. 3 TFG does provide for separate consent.

donors may imply they consent when they consent to the removal *for the purpose of donation*.

The removal of tissue or organs for the purpose of donation is only permissible if the person is of age and capable of giving consent, has been informed in accordance with sec. 8 para. 2 sent. 1 and 2 TPG[246] and has consented to the removal (sec. 8 para. 1 sent. 1 no. 1 lit. (a) and (b) TPG). In addition, the person must be suitable as a donor and may not be endangered beyond the risk of the operation or seriously impaired beyond the immediate consequences of the collection (lit. (c)). According to no. 2, the transfer of the organ or tissue to the intended recipient must be suitable, according to medical assessment, to preserve the life of this person or to cure a serious illness from which he or she suffers, to prevent its aggravation or to alleviate its symptoms.

Furthermore, compared to autologous transplants, the information about allogeneic transplants has to fulfill an additional criterion: It must be provided in the presence of another physician (sec. 8 para. 2 sent. 3).

We can also find many of these elements—particularly the requirements of informed consent and that the donation must have a therapeutic purpose—in the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin. Art. 14 sec. 1 states that the removal of organs or tissue may not be carried out on persons incapable of consent. Exceptionally, regenerative tissue can be removed, especially if the recipient is a sibling of the donor and the donation has the potential to save the recipient's life.[247] German law, which is much more restrictive in this respect, does not even permit the donation of single cells by persons incapable of giving consent; the only exceptions are the donation of blood cells within the scope of the Transfusion Act and, pursuant to sec. 8a TPG, of bone marrow.

7.3.2.2 Donor Consent to Transfer of Organoids Under the Special Conditions of Sec. 8b TPG

If organs or tissues have been removed from a living person as part of a medical treatment of that person, their transfer is only permissible pursuant to sec. 8b para. 1 sent. 1 TPG if the person has the capacity to consent, has been informed in accordance with sec. 8 para. 2 sent. 1 and 2 TPG, and has consented to the transfer.

7.3.2.3 The Consent of the Recipient to the Transfer of the Organoids

The Transplantation Act does not contain regulations on the information and consent of the recipient. We can find the relevant law, therefore, in secs. 630d, 630e BGB. According to sec. 630d para. 2 BGB, effective consent requires that the patient or the person entitled to consent[248] has been informed in accordance with

[246] On the scope of the information, see Sect. 7.3.1.2.

[247] See Art. 14 sec. 2, also with regard to further conditions.

[248] That is, the legal representative of minors, sec. 1626 et seq. BGB, the custodian of incapacitated adults, sec. 1896 et seq. BGB, or the authorized representative, sec. 1901c BGB.

sec. 630e para. 1 to 4. According to sec. 630e para. 1 sent. 1 BGB, the physician is obliged to inform the patient of all circumstances essential to his or her consent. According to para. 2, this includes, above all, the nature, extent, implementation, expected consequences and risks of the measure as well as its necessity, urgency, suitability, and prospects of success regarding the diagnosis or therapy. In the context of allogeneic transplantations of brain organoids or parts thereof, this includes information about the artificiality of the transplanted cells. Both this and the novelty of the procedure increase the requirements which the information must fulfill. Thus, the recipient must be comprehensively informed about the uncertainties of the treatment as well as the unknown chances and risks.[249] The right of personality of minors and incapacitated persons requires, moreover, that they too be provided with the essential information, not only their legal representative.

If the transplantation is carried out as a clinical trial, the provisions of medicinal products law apply, namely, secs. 40 et seq. AMG and Reg. (EU) No 536/2014. Moreover, we must bear in mind what we established, in Sects. 7.3.1.3.2 and 7.3.1.3.3, on the interaction between the Medicinal Products Act and the Transplantation Act: Since sec. 8 para. 1 sent. 1 no. 2 TPG only permits the collection of organs and tissues if the recipient exhibits certain characteristics, a donation for clinical trials is only lawful if the trial excludes participants who do not fulfill these criteria. This means that only persons who suffer from a severe disease can participate in the trials, provided the transplantation promises a benefit described in more detail in sec. 8 para. 1 no. 2 TPG (read together with the provisions of pharmaceutical law, which likewise specify the benefit that must be achieved if the trial involves persons suffering from a disease).

There are less problems, conversely, when the physician transfers brain organoids, within the context of a clinical trial, that were produced from tissue removed for purposes other than donation, sec. 8b TPG. In this case, the recipient must only fulfill the requirements that arise under medicinal products law; sec. 8b TPG does not add any conditions.[250] As already mentioned, it remains doubtful, however, whether a transplantation that does not respond to a medical necessity can be justified. On that view, we may have to rule out research that exclusively benefits others anyway.

7.3.3 The Collection of Nuclei-Containing Blood Cells

If brain organoids are produced using blood cells that contain nuclei, the procedure to collect the blood cells is covered by the Transfusion Act ("*Transfusionsgesetz,*" TFG). According to sec. 28 TFG, the Transfusion Act "does not apply to the collection of a minor amount of blood for diagnostic purposes, to homeopathic autologous

[249] Müller (2013), p. 166. Generally on the scope of the obligation to provide information in the case of novel medical methods, Lipp (2021c), XIII.D. para. 32; Deutsch and Spickhoff (2014), para. 1333.

[250] See Sects. 7.3.1.3.2 and 7.3.1.3.3, for the admissibility of clinical trials.

blood products [or to] autologous blood for the production of tissue engineered products"; this exception, however, covers collections with the purpose of propagation or the processing of other autologous body cells, not the collection of blood cells to produce hiPS cells.[251]

Sec. 6 TFG contains special requirements for informed consent to the collection of a "blood donation." They are relevant for our purposes if the collection of blood cells with the aim of cultivating brain organoids constitutes a "donation" within the meaning of sec. 2 no. 1 TFG. According to this provision, a "donation is the quantity of blood or blood components removed from humans which is an active substance or medicinal product or is intended for the production of active substances or medicinal products and other products for use in humans." The term "donation," then, does not describe the act of transferring a blood sample to another person. Rather, it refers to the collected blood itself, to the result of the blood extraction.

The collection of blood cells with the aim of cultivating brain organoids meets the conditions of this definition since brain organoids are medicinal products and are intended for use in humans. True, both the hiPS cells produced from the collected blood cells and the brain organoids that result from the hiPS cells are themselves no longer subject to the Transfusion Act: they are tissue within the meaning of sec. 1a no. 4 TPG, not blood or blood components.[252] The Transfusion Act remains applicable to the removal of the cells, however, because sec. 2 no. 1 extends the Act's coverage to any blood donation that will be used for medicinal products and other products in general. It is irrelevant whether the product for which the blood cells were removed falls under the Transfusion Act itself (e.g., because it is a blood product). Finally, the Transfusion Act provisions on the collection of blood cells apply regardless of whether the blood cells—or the products derived from them—are intended for an allogeneic or autologous use. After all, sec. 2 no. 1 TFG only mention the "use on humans."

Sec. 6 TFG is thus applicable to the collection of blood cells in order to produce brain organoids that will then be used for autologous or allogeneic transplantations. It provides that the persons concerned must be competently informed about the nature, significance and performance of the removal and the associated examinations. They must also declare that the donation may, in fact, be used. The consent must be confirmed in writing.

While sec. 8 para. 1 no. 2 TPG specifies who may receive allogeneic transplants, sec. 6 TFG does not contain comparable restrictions on the group of people eligible to receive blood donations. Since the Transfusion Act regulates the removal, but not the transfer itself, and the Transplantation Act, despite the tissue properties of brain organoids, does not directly regulate the transfer of tissue, no law limits the eligibility of recipients of brain organoids generated from blood cells. Unlike in the case of organoids produced from other cells, then, secs. 40 et seq. AMG are, in principle,

[251] Faltus (2016), p. 643; Gerke (2020), p. 298 ; Tag (2017), sec. 28 TFG para. 1.

[252] Thus for hiPS cells Gerke (2020), p. 299. For a definition of blood and blood components, see Gerke (2020), p. 297.

fully applicable. The legislature's decision only to regulate the requirements for recipients of cell collections that fall under the Transplantation Act suggests we should not transfer these requirements to the recipients of organoids produced from blood cells. Evidently, the purpose of sec. 8 para. 1 no. 2 TPG was to restrict the removal of certain substances, not to restrict the transfer itself.[253] Whether it is legitimate, from a medical perspective, to include healthy individuals, or whether the Medicinal Products Act precludes their participation, is a different question, of course.

The Transfusion Act does not contain any explicit provisions on the collection of blood from minors or incapacitated adults. There is no reason, however, why the representative or custodian should not be able to consent, according to the principles that generally apply to curative treatments and new curative methods, to the collection of blood cells to produce brain organoids for the purpose of retransplantation.[254] Extracting blood for the purpose of transplanting the resulting organoid to another person, however, may not be in the "best interests" of the person concerned, or conducive to his or her "welfare" (sec. 1627, 1901 para. 2 and 3 BGB), since he or she does not stand to benefit personally.[255] However, each case will have to be assessed individually. Thus, the terms "welfare" or "best interest" can also be understood more broadly (e.g., to enable the healing of a parent if the intervention is negligible). The welfare of persons under custodianship, moreover, partly depends on their personal wishes anyway (sec. 1901 para. 2 and 3 BGB).

7.3.4 Interim Conclusion

The Transplantation Act covers the collection of cells other than nuclei-containing blood cells for the autologous and allogeneic transplantation of brain organoids. Consequently, the informed-consent requirements prior to collection result from secs. 8 et seq. TPG. The transplantation act does not specifically regulate the admissibility of the transfer of organoids, which constitute tissue within the meaning of the act. However, the requisite requirements follow implicitly from the regulations on tissue removal.

Sec. 8c TPG applies to autologous transplants. This means, first of all, that the person concerned or, if he or she is incapable of doing so, his or her legal representative must consent to the procedure. It also follows that autologous transplantation may only take place in the context of medical treatment. That notably excludes experimental transplantations that "only" aim to benefit the population represented by the person concerned. This is particularly important in the context of clinical trials.

According to sec. 8 TPG, allogeneic transplants are only permissible if the donor is of age *and* capable of giving consent. In addition, the transplant must be suitable for

[253] See also Rixen (2013), sec. 1 para. 3 footnote 8.

[254] Thus for autologous blood transfer Tag (2017), sec. 6 TFG para. 10.

[255] Tag (2017), sec. 6 TGG para. 6.

preserving the life of this person or for curing a serious illness, for preventing its aggravation or alleviating its symptoms. This limits the effect of the provisions regarding clinical trials, as such trials are, because of the Transplantation Act, only permissible if the person concerned will benefit personally. The restriction does not apply, however, if the physician uses body materials that were removed for other purposes (sec. 8b TPG); in that case, the admissibility of clinical trials solely depends on the requirements established in the Medicinal Products Act (and Reg. (EU) 536/2014).

In the case of the collection of nuclei-containing blood cells for the autologous or allogeneic transfer of brain organoids generated from them, the informed-consent requirements follow from sec. 6 TFG. Unlike the Transplantation Act, the Transfusion Act does not impose any restrictions on who may receive the transfer.

7.4 Questions of Data Protection

Research with brain organoids generates data, specifically genetic data, at least if the procedure or the planned investigations involve the analysis of the genome. This brings the regulations of data protection law into play.

To begin with, most scholars do not consider the separated body substance itself—i.e., the removed cells and the organoid created from them—data: According to Art. 4 no. 1 of the Regulation (EU) No 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, "'personal data' means any information relating to an identified or identifiable natural person ('data subject') (...)."[256] According to Art. 4 no. 13, "genetic data" means "personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question."

Body substances, in other words, constitute the "biological sample" mentioned in Art. 4 no. 13, but not the data itself.[257] Classifying bodily substances as data would have the unacceptable consequence, moreover, that the removal of bodily material, which would then be considered data collection, would at times be possible without the consent of the person concerned.[258]

The analysis of substances, at least of identifiable and not (de facto) anonymized ones,[259] falls within the scope of Reg. (EU) No 2016/679, however, as it can

[256] See recital 26 for the criteria that determine whether a person is "identifiable." It remains disputed whether a pseudonymization (Art. 4 no. 5 Reg. (EU) No 2016/769) qualifies, at least from the perspective of the data processing agents, as anonymization. See Spindler and Dalby (2019a), Art. 4 Reg. (EU) No 2016/769 paras. 14 et seq.; Taupitz (2020b), pp. 606 et seq.

[257] See Schreiber (2019), p. 105, and the references cited therein. Breyer (2004), p. 660, Breithaupt (2012), p. 240, and Fink (2005), p. 60, also reject classifying body substances as data.

[258] von Freier (2005), p. 324; Schreiber (2019), p. 105.

[259] Schreiber (2019), pp. 130–131; for greater detail on the meaning of anonymization and de facto anonymization, especially in the context of genetic data, see Taupitz (2020b), p. 605 et seq.

generate genetic data.[260] It constitutes a collection of data within the meaning of Art. 4 no. 2, which defines "processing of data." Genetic data are particularly protected, as they constitute, according to Art. 9, a special category of data. For that reason, they may only be processed if the following specific requirements are met.

According to Art. 9 para. 2 lit. a), data such as genetic data may be processed "if the data subject has given explicit consent to the processing of those personal data for one or more specified purposes (...)." Consent is defined in Art. 4 no. 11 as "any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her." It is important to note that consent must be explicit; implied consent is not sufficient.[261] Written consent, however, is not required.[262] The information requirements, moreover, follow from Arts. 13 et seq. The requisite information includes the purpose of and responsibility for the processing, contact details, the intended data transfer—in particular to countries outside the EU—as well the rights of the data subjects. The latter must include, among other things, the right to withdraw consent and the right to information.[263]

However, Art. 9 para. 2 lit. (j) also permits the processing of particularly sensitive data without consent if "processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1) based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject." According to Art. 89 para. 1, the provisions at national or EU level that implement Art. 9 para. 2 lit. (j) must provide "appropriate safeguards for the rights and freedoms of the data subject." The German legislature, for its part, has implemented Art. 9 para. 2 lit. (j) in the new Federal Data Protection Act ("*Bundesdatenschutzgesetz,*" BDSG).[264] Art. 27 para. 1 sent. 1 BDSG provides that the processing of sensitive data is also permissible absent consent for *scientific or historical research purposes or for statistical purposes, if* this is necessary to achieve the stated purposes and the interests of the responsible person in the processing significantly outweigh the interest of the data subject who my refuse any processing of his or her data.[265] Some argue that we should read Art. 27 narrowly

[260] Art. 4 no. 1; Schreiber (2019), p. 106; Fink (2005), p. 61.

[261] Schreiber (2019), p. 109; Albers and Veit (2020), Art. 9 Regulation (EU) No 2016/679 para. 50-51.

[262] Schreiber (2019), p. 109.

[263] Schaar (2017), p. 215.

[264] The BDSG applies to public bodies of the federal level as well as to private persons. The data protection laws of the *Länder* will not be dealt with separately in this chapter.

[265] Spindler and Dalby (2019b), Art. 9 Regulation (EU) No 2016/679 para. 25; Schreiber (2019), p. 116. For greater detail regarding the balancing of interests, especially the possibility of obtaining consent, see Taupitz (2020b), p. 621 et seq. For criticism, see Fleischer (2018), p. 302.

and demand that the research in question cannot be carried out in any other way than by processing the data in question.[266]

In any event, data processing is only permissible pursuant to Art. 27 para. 1 sent. 1 BDSG if the responsible person takes appropriate and specific measures to protect the interests of the data subject in accordance with Art. 22 para. 2 sent. 2 BDSG, which provides a ten-point example catalogue of protective measures.[267] This provision aims to fulfill the requirements for protective measures to safeguard the rights of the data subjects as provided in Art. 9 para. 2 lit. (j) and Art. 89 of the EU-Regulation.[268]

In the context of data collection on the basis of such "research clauses" as Art. 27 BDSG, children, who enjoy special protection under the General Data Protection Regulation, must be paid particular attention to. Thus, it follows from Art. 6 para. 1 lit. (f), at least for "normal" data, that processing data of children without the consent of their parents is only permissible following a particularly careful consideration of their interests.[269]

It remains to be seen, however, whether "research clauses" such as sec. 27 para. 1 sent. 1 BDSG should even apply to genetic data. Most scholars consider the latter part of the core of fundamental personality rights. For that reason, they argue that the processing of (certain) genetic data should not be permissible absent explicit consent.[270] At least according to the German Federal Constitutional Court, however, the analysis of *non-coding* gene segments does not implicate the core of the right of personality: examining non-coding areas, the Court argued, does not allow any conclusions about personality-relevant characteristics such as hereditary dispositions, character traits or diseases of the person concerned. It does not, in other words, permit the creation of a personality profile.[271]

The Court did not explicitly comment on examinations of coding areas. We can infer from the decision, however, that the creation of a personality profile through genetic examinations does indeed affect the core of the right of

[266] Schreiber (2019), p. 116; Fleischer (2018), p. 302.

[267] Schreiber (2019), p. 117.

[268] Schreiber (2019), p. 117.

[269] Schreiber (2019), pp. 119–120.

[270] See, e.g., Goerdeler and Laubach (2002), p. 117; Keller (1989), p. 2292. Fink (2005), p. 66, argues that the core of the right of personality is not affected if the research merely aims to uncover the (not yet established) connection between genetic predispositions and the development of a disease (i.e., a personality-related characteristic). Taupitz (2020b), p. 613 et seq., argues that the "research clauses" apply to genetic data, as neither Art. 9 nor sec. 27 differentiate between genetic data and other sensitive data. Yet, Art. 9 para. 4 allows the member states to introduce further conditions, including limitations, with regard to the processing of genetic data. This allows narrowing the scope of sec. 27, if the consideration of fundamental rights requires it, without coming into conflict with EU law. See Schreiber (2019), p. 122.

[271] Federal Constitutional Court (2000), p. 32.

personality.[272] I suggest we go further and consider, in principle, any examination that yields information on personal characteristics an intrusion on the core of the right of personality, regardless of whether it suffices to establish an entire profile of the person concerned. After all, it makes little sense to exclude a characteristic that the person concerned considers particularly sensitive and intimate—an assessment that, incidentally, cannot be reviewed against an objective standard. Furthermore, a single point of data can be particularly sensitive as well: If it falls into the wrong hands (e.g., insurance companies, employers, etc.), the person concerned may run the risk of considerable disadvantages. Alternatively, we should regard at least some genetic data as part of the core of the fundamental right of personality, viz., data that, if it falls into the wrong hands (e.g., employers, insurance companies, etc.), may create considerable disadvantages for the person concerned.[273]

It follows, then, that research involving the examination of coding gene segments cannot in principle be based on "research clauses" but requires the consent of the person concerned or their representative. This finding adds to our previous ones: We have already established that the generation of brain organoids from substances that have been separated for other purposes requires the consent of the donor. Now we know this applies even more if the research conducted with the organoids involves the investigation of coding gene segments.

If the genetic data was collected upon the donor's consent, however, the question arises whether the data may subsequently be processed for purposes other than those for which they were originally collected. Data protection law provides for such further use within narrow limits. In principle, Art. 5 para. 1 lit. (b) Reg. (EU) No 2016/679 makes clear, data may only be used and thus further processed for the purpose for which they were collected. This applies not only to the first user but also to subsequent users.[274] Further processing for other purposes is only permissible if the new purpose is compatible with the original one. This compatibility test requires an evaluative judgment,[275] although further processing for other research purposes should always, in accordance with Art. 5 para. 1 lit. (b), be considered compatible,

[272] Fink (2005), p. 66. But see Schreiber (2019), p. 123 et seq., who argues the purpose of the use should also be relevant. The objection to this argument, however, is that it eviscerates the notion of a fundamental right's core protection. In particular, it does not follow from the Federal Constitutional Court's "Diary Decision" that the purpose of use alters the personal and intimate nature of the data concerned. Rather, the Court argued (in a questionable manner) that the diary entries could be used for criminal investigations because they "inherently affect"—by providing information about the cause and background of the criminal offense—"the sphere of others or the interests of the community" (Federal Constitutional Court 1989, p. 379). Crucially, the information embodied in one's genes does not "inherently affect" the interests of others or the community.

[273] See Taupitz (2020b), p. 609.

[274] Schreiber (2019), p. 280; Taupitz (2020b), p. 619.

[275] Schreiber (2019), p. 281.

provided the requirements of Art. 89 para. 1 Regulation (EU) No 2016/679 are met.[276]

In the case of further use for purposes other than research, the compatibility test shall be based on Art. 6 para. 4 Regulation (EU) No 2016/679, which contains a non-exhaustive list of criteria.[277]

Moreover, contrary to recital 50—which is considered a drafting error—a separate legal basis is required for each further use.[278] As a result, further processing of particularly sensitive personal data must fulfill one of the conditions of Art. 9 para. 2 Regulation (EU) No 2016/679.[279] Art. 27 para. 1 sent. 1 BDSG, which complements the opening clause of Art. 9 para. 2 lit. (j) Regulation (EU) No 2016/679, can (again) be used as a legal basis in this regard.[280] As we have seen above, however, the research clause does not apply to genetic data, at least not to data that results from coding areas; further use of such data without the consent of the data subject is therefore impermissible.

This means that genetic data collected in the context of (consensual) research with and on brain organoids cannot be reused for other research purposes without explicit consent. It also means that the non-consensual disclosure of such data to third parties—which, if the third parties want to carry out research projects with the data, is covered, in principle, by Art. 9 para. 2 lit. (j) Regulation (EU) No 2016/679 in conjunction with Art. 27 BDSG[281]—is unlawful, as Art. 27 BDSG does not apply to genetic data. If the person disclosing the data is a physician, it should also be noted that he or she is bound to medical confidentiality under sec. 203 of the Criminal Code.[282]

Moreover, data protection law also provides for the possibility of "broad consent." As a result, the data subject's consent may refer to the processing of data not only in a specific research project but more generally in different research areas. Consider, for instance, recital 33: "It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research."[283]

[276] Schreiber (2019), p. 281.

[277] Schreiber (2019), p. 281.

[278] Schantz (2016), p. 1844. See also Schantz (2020), Art. 5 Regulation (EU) No 2016/679 para. 22; Spindler and Dalby (2019b), Art. 9 Regulation (EU) No 2016/679 para. 23; Schreiber (2019), pp. 282–283; Fleischer (2018), p. 294 et seq. For a contrasting opinion, see Schlösser-Rost (2020), sec. 27 BDSG para. 13.

[279] Weichert (2017), p. 540; Schreiber (2019), p. 283.

[280] Fleischer (2018), p. 301; Greve (2020), sec. 27 BDSG para. 15.

[281] Albers and Veit (2020), Art. 9 Regulation (EU) No 2016/679 para. 88; also in favor of disclosure being a form of processing, Taupitz (2020b), p. 618 et seq.

[282] On this provision, Fleischer (2018), pp. 308–309.

[283] Schreiber (2019), p. 111; Fleischer (2018), p. 296.

7.5 Conclusion

Because they have a right to self-determination, adults capable of giving consent can consent to research on and with brain organoids generated from cells taken from their bodies. For persons incapable of consent, the right to consent lies with their legal representative: This group of individuals, I have argued, is not generally barred from participating in research project, provided the project in question does not conflict with their best interests and welfare. That is all the more true if the research project involves only minor physical interventions. The only thing that may exclude this group from research projects involving brain organoids is the possibility to conduct the research just as effectively with cells—and, therefore, brain organoids—that originate from persons who *can* give consent. Minors who are capable of giving consent may not consent to research projects on their own, since the projects affect the right to property that persons hold with regard to their separated bodily substances.

The information provided to the person concerned or his or her legal representative must touch upon all relevant circumstances, such as the planned intervention, the associated risks, and the intended use of both the substances and the data, including a possibly intended disclosure to third parties. The person concerned must also be informed of his or her right of revocation as well as of what will happen to the substances, the data, and the research results should he or she exercise that right.

In my opinion, it is impermissible to use, without the concerned person's consent, substances that were separated for other ends in order to generate brain organoids for research purposes. First, this results from the fact that such research may be considered controversial from an ethical perspective; moreover, the patient's right to informational self-determination is violated if the substances are not anonymized. Second, the research may involve the collection of genetic data, which, according to data protection regulations, requires consent—at least in the case of identifiable materials. (Admittedly, this point is disputed.) Nor is the non-consensual disclosure of genetic data relating to indetifiable subjects to third parties lawful, even if the third parties merely wish to use the data for their research.

Both in terms of data protection law and in general, however, the so-called broad consent is permissible. The person concerned, therefore, may consent to the removal and disposal of bodily substances for research in general. In principle, this also applies to individuals who cannot give consent. The information provided should, however, indicate that the individual has the right to exclude those types of research of which he or she does not approve.

If brain organoids are to be (re)transplanted, the Transplantation Act and the Transfusion Act become relevant, depending on the cell type to be removed from a person's body. Moreover, the Transplantation Act and the regulations on medicinal products (the German Medicinal Products Act and Reg. (EU) 536/2914) must be read together and complement each other whenever brain organoids are to be transferred in the context of clinical trials. This means that transplantations—be they autologous or allogeneic—may only be carried out in the context of clinical trials if the person concerned can expect a direct benefit. A benefit for the population he or she represents is not sufficient. The same result, incidentally,

may already follow from a risk–benefit assessment of the transplantation. It is doubtful whether a transplantation for research purposes is lawful absent medical necessity.

The informed-consent requirements regarding the donor follow from the Transplantation Act and the Transfusion Act; regarding the recipient, they follow from the Medicinal Products Act (Reg. (EU) 536/2014) if the transplantion occurs within the context of a clinical trial. If the transplantation does not occur during a clinical trial, informed consent regarding the recipient is subject to the general principles established in sec. 630d and 630e of the Civil Code.

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