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The Regulation of Human Germline Genome Modification in Europe

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I INTRODUCTION

One of the distinctive traits of Europe is the scope and breath of international cooperation and integration projects that states of the 'Old Continent' have developed since the end of the Second World War. Devastated by two consecutive continent-wide wars during the first half of the twentieth century – conflicts that eventually spread out to engulf the whole globe – during the second half of the century European nations embarked on an ambitious project of integration and transfer of sovereignty to shared supranational institutions to avoid future wars. The two main pillars of this 'European Project' are the European Union (EU) and the Council of Europe (CoE). The CoE was founded in 1949 by 10 western European states to uphold human rights, democracy and the rule of law in Europe. Over the next 70 years, it expanded to include, nowadays, 47 states. In 1951, six of those core European states (France, Germany, Italy, Belgium, the Netherlands and Luxembourg) started a limited attempt to integrate the market of the resources over which Germany and France had fought repeatedly since industrialization: coal and steel. Later, it expanded to pooling the resource of the future – atomic energy – and, eventually, to establish a customs union and integrate markets in general to ensure free circulation of persons, goods, services and capital. Eventually, the three European Communities became one, and then, in the 1990s, the European Community morphed into the present European Union: a quasi-federal project that has been given by its member states considerable powers to regulate all aspects of their economic and social life, and that is increasingly acting as one vis-à-vis the rest of the world.[1]

[1] Euratom remains an entity distinct from the European Union, but it is governed by the same EU institutions.

Although the CoE and the European Union are separate and distinct organizations, with somewhat different goals, they have much in common and overlap. Besides having a remarkably similar flag (12 yellow stars on a background of just a different shade of blue), all 28 members of the European Union are members of the CoE. Indeed, in the past, membership to the latter has been considered a prerequisite for accession to the former. Their authority and legal instruments (e.g. treaties, directives, regulations) affect the way in which members operate within the national boundaries, between them and with the rest of the world.

Historically, European nations have played a key role in humanity's scientific and technological progress, and this carries on into the twenty-first century. In aggregate, they continue influencing the direction and speed of scientific progress worldwide, directly and indirectly. In 2016, the gross domestic expenditure on research and development of the combined 28 EU members stood at 303 billion euros.[2] While that was just two-thirds of the same expenditure of the United States, it was almost 50% higher than China's, more than double the expenditure of Japan and more than five times higher than South Korea.[3] European states, through the European Union, influence the direction of research globally, because research done by European research institutions often involves non-European researchers as co-investigators. The European Union has international agreements for scientific and technological cooperation with 20 countries. These create a framework for joint projects, sharing of facilities, staff exchanges or the organization of specific events. Also, EU research funding is accessible to non-EU scientists. For instance, 13 non-EU states (including Norway, Israel and Switzerland) have 'Associated Country' status and contribute to the budgets of 'Framework Programmes for Research and Technological Development' proportionally to their GDP.[4] Their scientists have access to funding through EU Framework Programmes.

[2] Gross domestic expenditure on R&D (GERD) includes expenditure on research and development by business enterprises, higher education institutions, as well as government and private non-profit organizations. Eurostat Statistics Explained, 'R & D Expenditure' (March 2018) https://ec.europa.eu/eurostat/statistics-explained/index.php/R_%26_D_expenditure accessed 24 September 2018. However, measured by proportion of the gross domestic product (Research and Development Intensity), the 28 EU members combined rank was well below the corresponding ratios recorded in Japan (3.29 per cent, 2015 data) and the United States (2.79 per cent, 2015 data), as has been the case for a lengthy period of time. In 2015, R&D intensity in China surpassed that of the EU-28, with Chinese R&D expenditure equivalent to 2.07 per cent of GDP. Ibid.

[3] Ibid.

[4] The EU 'Framework Programmes for Research and Technological Development' are funding programmes created by the European Union/European Commission to support and foster research in the European Research Area. The specific objectives and actions vary between

Finally, as we will see, so far Europe is the only region of the globe to have regulatory frameworks for biomedical research. This consideration alone justifies a discussion of Europe separate and distinct from the one that we will have in the following chapters of the national regulatory framework of some selected EU and CoE members. Thus, in this chapter we discuss first the CoE. After a brief introduction of its history, goals and structure, we will discuss the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (better known as the 'Oviedo Convention'), the first, and to date still the only, multilateral treaty entirely devoted to biomedicine and its human rights aspects. Then, we will turn to the European Union. Again, after a brief introduction, we will discuss the specific EU legislation that affects research on human embryos, germline cells and their genetic modification. We will follow it 'from the bench to bedside', highlighting contradictions, gaps and issues. Our conclusions, drafted in a historical time of uncertainty over the 'European Project', suggest a way forward.

II THE COUNCIL OF EUROPE

1 *Introduction*

The Council of Europe (in French, *Conseil de l'Europe*) is the continent's oldest political organization.[5] It was founded in 1949, in the aftermath of the Second World War, by 10 western European states, to uphold human rights, democracy and the rule of law in the continent.[6] It was headquartered in Strasbourg, Alsace, a European region that had been bitterly fought over by France and Germany at least since 1870. Over the next 70 years, the CoE expanded its membership to include, nowadays, nearly all European states: 47 states, from Iceland and Portugal to the west, to Russia and Turkey to the east. Twenty-eight of these are also members of the European Union. Moreover, a number of non-European states (i.e. Australia, Canada, Japan, Mexico and

periods. So far, there have been eight 'Framework Programmes' (abbreviated FP1 to FP8). The Focus of FP8, also known as Horizon 2020, is innovation. See, in general, European Commission, 'Research and Innovation' https://ec.europa.eu/info/research-and-innovation_en accessed 24 September 2018. On Horizon 2020, see below, Section III.2.d.iii.

5 On the Council of Europe, see, in general, S Schmahl and M Breuer (eds.), *The Council of Europe: Its Law and Policies* (Oxford University Press 2017).

6 Belgium, Denmark, France, Ireland, Italy, Luxembourg, the Netherlands, Norway, Sweden and the United Kingdom.

the United States) and other entities (e.g. the Holy See and the European Union) participate in its works as 'Observers'.

The CoE's statutory bodies are: (i) the Council of Ministers, the decision-making body comprising the foreign ministers of all member states or their permanent diplomatic representatives in Strasbourg; (ii) the Parliamentary Assembly, composed of 324 national politicians representing the parliaments of the CoE's 47 member states; and (iii) the Secretariat. Given the topic of this volume, another CoE body worth of mention is the Committee on Bioethics (DH-BIO). It was created in 2012, following a reorganization of intergovernmental bodies at the CoE.[7] This Committee meets twice a year, consisting of delegations of the 47 member states with expertise in the various aspects of bioethics. It reports to the Council of Ministers and it is assisted by a permanent secretariat, the Bioethics Unit, acting under the Directorate General Human Rights and Rule of Law of the Council of Europe.

Unlike the European Union, the Council of Europe does not have the power to create norms that are binding for its members. What it does, instead, is provide a forum for the discussion and adoption of treaties in the fields of its competence (i.e. human rights, democracy and rule of law) that members are subsequently encouraged to ratify.[8] The most famous of such treaties is certainly the European Convention on Human Rights and Fundamental Freedoms (ECHR).[9] The ECHR was adopted in 1950 and is the linchpin of the European human rights regime. Over the years, it has been modified and upgraded by a series of protocols (16 to date), which have expanded the list of rights and modified the oversight mechanisms.[10] Besides the Statute of the Council of Europe, which is the organization's constitutive treaty, the ECHR is the only other treaty that all Council members must ratify, and its protocols enter into force only after they have been ratified by all members. We will discuss it in more detail further below.[11]

The ECHR, both in its original form and after revisions brought about by the protocols, focuses mostly on civil and political freedoms. Many economic, social and cultural rights are not included in it but are rather protected under

[7] The DH-BIO has taken over the responsibilities of the Steering Committee on Bioethics (CDBI) for the tasks assigned by the Oviedo Convention, as well as for the intergovernmental work on the protection of human rights in the field of biomedicine.

[8] Also states with Observer Status, as well as the European Union, can become parties to certain CoE treaties, if they wish to do so.

[9] [European] Convention for the Protection of Human Rights and Fundamental Freedoms, ETS No 5 (European Convention on Human Rights, as amended) (ECHR).

[10] Protocols to the ECHR enter into force only when they have been ratified by all CoE member states.

[11] See, in this chapter, Section II.4.

a second CoE treaty called the European Social Charter.[12] For the purposes of this volume, it is worth mentioning that the 'right to science' is not mentioned either in the ECHR or in the European Social Charter, despite the fact that at the time of their drafting other international human rights instruments had already declared it. The 'right to health' is only mentioned in the European Social Charter, not in the ECHR, despite subsequent protocols to the ECHR adding other social and cultural rights to it, such as the right to education.

The ECHR was the first major treaty adopted under the aegis of the CoE. Since then, more than 200 treaties and protocols have been adopted. Among those, one in particular is relevant for the question of the regulation of human germline genome editing: the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, adopted by the Council of Ministers of the CoE on 4 April 1997 in Oviedo, Spain.[13]

2 *The Oviedo Convention*

a Background and Overview

The 'Oviedo Convention' is the first, and to date still the only, multilateral treaty entirely devoted to biomedicine and its human rights aspects, not just in the CoE but in the world.[14] Although the CoE had actually been involved in addressing bioethical issues since the 1980s, the drafting of the Oviedo Convention started in 1992 and lasted through 1996, an aeon ago as far as research on genetics is concerned, before many of the discoveries that have revolutionized biomedicine and genetics during the past 20 years were made.

In 1985, the Committee of Ministers created the Ad Hoc Committee of Experts on Bioethics (CAHBI), working under its direct authority, and

[12] European Social Charter (revised), ETS No 163.

[13] Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (opened for signatures on 4 April 1997, entered into force 12 January 1999) ETS No 164 (Oviedo Convention).

[14] On the Oviedo Convention, see, in general: R Uerpmann-Wittzack, 'Convention on Human Rights and Biomedicine' in Stefanie Schmahl and Marten Breuer (eds.), *The Council of Europe: Its Law and Policies* (Oxford University Press 2017) 572–588; H Gros Espiell, J Michaud and G Teboul (eds.), *Convention sur les droits de l'homme et la biomédecine: analyses et commentaires* (Paris: Economica 2010); Council of Europe, *Biomedicine and Human Rights: the Oviedo Convention and its Additional Protocols* (Council of Europe 2009); R Andorno, 'First Steps in the Development of an International Biolaw' in C Gastmans and others (eds.), *New Pathways for European Bioethics* (Intersentia 2007) 121–138.

entrusted it with the intergovernmental activities of the CoE in the field of bioethics. In 1992, the CAHBI became the Steering Committee on Bioethics (CDBI). The CDBI set up a Working Party responsible for drafting a 'Convention on Biomedicine'.[15] In 1994, the CDBI adopted a first draft, which was released by the Council of Ministers for public consultation. The draft received considerable criticism and was consequently thoroughly revised. In 1996, the CDBI submitted a final draft to the Council of Ministers, which adopted it and opened it for signature.

The Oviedo Convention was conceived from the very beginning as a 'framework treaty', a binding international legal instrument but one that contains only broad, general principles, which are intended to be developed subsequently, internationally by additional protocols on specific issues and nationally by specific legislation. It was also one that CoE member states were free to decide to ratify or ignore. To fill the framework with specific content, to date, the CoE has adopted and opened for signature and ratification four additional protocols: on the Prohibition of Cloning of Human Beings (1998);[16] on Transplantation (2002);[17] on Biomedical Research (2004);[18] and on Genetic Testing for Health Purposes (2008).[19] We will revert to these later.

Article 1 of the Oviedo Convention leaves it to each ratifying state to 'take in its internal laws the necessary measures to give effect to the provisions' of the Convention. Some provisions are regarded as self-executing, such as those related to some individual rights – for example, the 'right to information', the requirement of 'informed consent' and the prohibition of non-discrimination.[20] Also some prohibitory norms established by the Convention, such as the prohibition of creation of embryos for research, might have direct application

[15] The Working Party was originally chaired by Dr Michael Abrams (UK) and, after his untimely death, by Mr Salvatore Puglisi (Italy). Explanatory Report, para. 5.

[16] Additional Protocol on the Prohibition of Cloning Human Beings (adopted by the Committee of Ministers on 6 November 1997, entered into force on 1 March 2001) ETS No 164. To date, it has been ratified by 24 states.

[17] Additional Protocol concerning Transplantation of Organs and Tissues of Human Origin (adopted by the Committee of Ministers on 8 November 2001, entered into force on 1 May 2006) ETS No 186. To date, it has been ratified by 15 states.

[18] Additional Protocol on Biomedical Research (adopted by the Committee of Ministers on 30 June 2004, entered into force on 1 September 2007) ETS No 195. To date, it has been ratified by 12 states.

[19] Additional Protocol concerning Genetic Testing for Health Purposes (adopted by the Committee of Ministers on 7 May 2008, opened for signature on 27 November 2008, entered into force on 1 July 2018) ETS No 203. To date, it has been ratified by five states.

[20] Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Explanatory Report), para. 20. Available at: https://rm.coe.int/168000cde5 accessed on 8 December 2018.

in some member states, depending on their constitutional and legal system. However, it is for each state to adopt the necessary domestic legal instruments to give effect to the Convention and establish sanctions for its violation,[21] and it is for national courts to enforce the rights.[22]

In other words, the Oviedo Convention just established minimum common standards. States that ratify it cannot adopt a lower level of protection of human rights in the biomedical field when they decide to legislate on bioethics.[23] And those who do not agree with these standards, for whatever reason, are free not to ratify it. Of course, when the Convention was negotiated and drafted, a concerted effort was made to find as wide as possible common ground between European states, if not all, at least the major ones, even if many fundamentally disagreed on how to approach the most ethically divisive issues relating to biomedicine. The difficulty of reaching agreement explains why the Convention lacks any definition of terms, and why many of its provisions are very general.

b The Rights and Duties Contained in the Oviedo Convention

The Oviedo Convention consists of a preamble and 28 articles, organized into 14 chapters. The general norms are contained in Chapter I (Articles 1 to 4): Purpose; Primacy of Human Being; Equitable Access to Healthcare; Professional Standards. Chapters II to VII set up substantive provisions relating to specific bioethical issues, such as: consent; right to information and right not to be informed; protection of persons undergoing research; principles regulating organs and tissue removal; prohibition of financial gain; as well as two issues particularly relevant for the present discussion: interventions on the human genome (Article 13) and research on embryos in vitro (Article 18). Finally, Chapters VIII to XIV include the procedural norms, treaty organs and final clauses.

[21] Oviedo Convention, art. 25.

[22] Ibid., art. 23.

[23] Restrictions are allowed only if 'prescribed by law and are necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health and for the protection of rights and freedoms of others' (Oviedo Convention, art. 26.1). No restriction can be put on the rights contained in art. 11 (non-discrimination), 13 (intervention on human genome), art. 14 (prohibition of sex selection), art. 16 (rights of persons undergoing research), art. 17 (protection of persons not able to consent); arts. 19 and 20 (removal of organs and tissue from living donors for transplantation purposes), and art. 21 (prohibition of financial gain). However, art. 18 (prohibition of creation of embryos for research) is not one of the non-derogable rights.

The notion of 'human dignity' is clearly the bedrock of the Oviedo Convention. It is enshrined in its full title: 'Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine'. The Preamble refers three times to this concept: the first, when it recognizes 'the importance of ensuring the dignity of the human being'; the second, when it recalls that 'the misuse of biology and medicine may lead to acts endangering human dignity'; the third, when it expresses the resolution of taking the necessary measures 'to safeguard human dignity and the fundamental rights and freedoms of the individual with regard to the application of biology and medicine'. Finally, according to Article 1, the Convention aims to 'protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine'.

The fact that Article 1 mentions both 'everyone' and 'human beings' is not due to poor drafting. Again, it was a deliberate choice to bypass disagreement between member states on the legal status of the human embryo and whether and at what stage of development legal personality is attached.[24] According to the Explanatory Report of the Oviedo Convention, 'it was a generally accepted principle that human dignity and the identity of the human being had to be respected as soon as life began' but without clarifying when that occurs.[25] Thus, the drafters deliberately used simultaneously two different expressions – 'everyone' (in French *toute personne*) and 'human being' (in French *être humain*) – to refer to the subject of the protection granted by the Convention, without defining either concept nor specifying whether they are synonymous.

As a direct corollary of the idea of human dignity, Article 2 assigns the highest priority to the interests and welfare of the 'human being', whose respect 'shall prevail over the sole interest of society or science'. As the Explanatory Report of the Convention says, '[p]riority is given to the [interests of the human being], which must in principle take precedence over [the interests of science or society] in the event of a conflict between them. One of the important fields of application of this principle concerns [scientific] research'.[26] Also, '[t]he whole Convention, the aim of which is to protect

[24] Steering Committee on Bioethics (CDBI), *Preparatory Work on the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine* (ETS No 164, CDBI/INF (2000) 1, Council of Europe, 2000) 10–13.

[25] Explanatory Report (n 20), paras. 18–19; Steering Committee on Bioethics (CDBI), *Preparatory Work* (n 24), 10–13.

[26] Explanatory Report (n 20) para. 21.

human rights and dignity, is inspired by the principle of the primacy of the human being, and all its articles must be interpreted in this light'.[27] Similar provisions are also found in the Declaration of Helsinki on Biomedical Research[28] and in the UNESCO Universal Declaration on the Human Genome and Human Rights.[29]

Be that as it may, the practical consequences of giving priority to the interests and welfare of the human being over the interests of society or science are unclear. First of all, it builds a straw man out of the interests of society and science. It suggests that the interests of science and the interests of human beings are in opposition with one another and that there is a need to protect humans against scientific research and its applications. Granted, there have been egregious cases where humans have been forced or manipulated to participate in experiments against their will or without having been informed about the risks involved. The prohibition against such conducts by the scientific community is firmly established in international human rights law. For instance, the International Covenant on Civil and Political Rights (ICCPR) establishes that subjecting persons without his or her free consent to medical or scientific experimentation is prohibited.[30] In international bioethics law, this prohibition translates into a fundamental right of everyone to free and informed consent, and specifically to the right to be able to freely give or refuse any intervention involving their person regardless of purpose, including research, and special protection to those persons who are unable to give free and informed consent, from being used as means to achieve scientific progress.[31] However, rare and egregious cases of transgressions of these limits by scientists notwithstanding should not detract us from the fact that the general objective of biomedical research is to develop knowledge for the diagnosis, treatment and prevention of disease and to improve human health. This is, after all, the purpose of all medical activity and research, and the work of scientists, over the centuries, has improved and continues improving the

[27] Ibid., para. 22.a.

[28] World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Subjects* (as amended through 2013); World Medical Association, *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects* (as amended through 2013).

[29] UNESCO Universal Declaration on the Human Genome and Human Rights (adopted by UNGA Res 152) A/RES/53/152.

[30] International Covenant on Civil and Political Rights (ICCPR) (adopted 19 December 1966, *entered into force* 23 March 1976) 999 U.N.T.S. 171, art. 7.

[31] Oviedo Convention, art. 5. See also Explanatory Report (n 20), paras. 34–40, and *VC v Slovakia*, App No 18968/07, European Court of Human Rights (Judgment of 8 November 2011).

human condition by all metrics. If that is taken into consideration, the interests of science and the interests of human beings may not only be compatible but actually reinforce each other. The latter is the rationale for the former. This understanding of the relationship between scientific progress and human interests is central in international human rights law. Both the Universal Declaration of Human Rights and the International Covenant on Economic, Social and Cultural Rights (ICESCR) uphold the right to science and the rights of science as international human rights that are compatible with other rights, including civil, political, economic and social rights, recognized in international law.[32]

Of course, the 'right to science' and the 'rights of science' are not absolute human rights.[33] They can be limited but only in so far as their limitations may be compatible with the nature of these rights and solely for the purpose of promoting the general welfare in a democratic society.[34] However, precisely because of their status as *human* rights, the protection of the right to science and the rights of science cannot be automatically subordinated to the protection of other rights. Nevertheless, the Oviedo Convention seems to consider these rights as secondary to all other rights. The fact that the Oviedo Convention itself, in the Preamble, says that the drafters bore in mind the Covenant on Economic, Social and Cultural Rights and the Universal Declaration adds to the perplexity.

For the purposes of this volume, Chapter IV and Chapter V are the most salient ones. Chapter IV (Articles 11–14) is entitled 'Human Genome'. The Explanatory Report of the Oviedo Convention shows that the drafters had a particular understanding of genetic testing and gene therapy, one that reflects the state of knowledge of the time, but one that is becoming outdated: '[g]enetic testing consists of medical examinations aimed at detecting or ruling out the presence of hereditary illnesses or predisposition to such illnesses in a person by directly or indirectly analysing their genetic heritage (chromosomes, genes)'.[35] As also stated in the same report:

> The aim of gene therapy is to correct changes to the human genetic heritage which may result in hereditary diseases. The difference between gene therapy and the analysis of the genome lies in the fact that the latter does not modify

[32] International Covenant on Economic, Social and Cultural Rights (ICESCR) (adopted 16 December 1966, entered into force 3 January 1976) 993 UNTS 3, art. 15.1.b; Universal Declaration of Human Rights (adopted 10 December 1948 UNGA Res 217 A(III) (UDHR), art. 27.

[33] On the 'right to science' and the 'rights of science', see, in this book, Chapter 2.

[34] See, in this book, Chapter 2 and Chapter 22.

[35] Explanatory Report (n 20) para. 72.

> the genetic heritage but simply studies its structure and its relationship with the symptoms of the illness. In theory, there are two distinct forms of gene therapy. Somatic gene therapy aims to correct the genetic defects in the somatic cells and to produce an effect restricted to the person treated. Were it possible to undertake gene therapy on germ cells, the disease of the person who has provided the cells would not be cured, as the correction would be carried out on the cells whose sole function is to transmit genetic information to future generations.[36]

Article 11 contains a generic and uncontroversial prohibition of unfair discrimination on grounds of 'genetic heritage'. Article 12 restricts 'predictive genetic test', that is to say '[t]ests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease', to 'health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling'. While it did not rule out preimplantation genetic diagnostics (PGD) per se, it did not specify that it could be used in the context of artificial reproductive technology. The ambiguity made it so that, in the following years, some states outlawed PGD (e.g. Italy and Germany), while others allowed it.[37] Also, developments in genetic engineering have rapidly put in question the wisdom of this provision and whether it does actually protect fundamental human rights, at least as long as it is worded as it is. For instance, in recent years, a whole new industry has emerged that offers genetic test kits that allow finding out information about an individual ancestry. This testing does not have medical purposes (or medical purposes might be incidental), can be obtained without genetic counselling and has become very popular. This development generated the adoption in 2008 of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes that we will discuss below.[38]

Article 13, entitled 'Interventions on the Human Genome', provides: 'An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.' Again, the Explanatory Report sheds some light on the purpose of this norm.

[36] Ibid., para. 73.

[37] On Germany's and Italy's bans of PDG, see, in general, B Bock Von Wülfingen, 'Contested Change: How Germany Came to Allow PGD' (2016) 3 *Reproductive Biomedicine & Society Online* 60, 60–67; A Boggio and G Corbellini, 'Regulating Assisted Reproduction in Italy: A 5-year Assessment' (2009) 12.2 *Human Fertility* 81–88.

[38] See, in this chapter, Section II.3.

> The progress of science, in particular in knowledge of the human genome and its application, has raised very positive perspectives, but also questions and even great fears. Whilst developments in this field may lead to great benefit for humanity, misuse of these developments may endanger not only the individual but the species itself. The ultimate fear is of intentional modification of the human genome so as to produce individuals or entire groups endowed with particular characteristics and required qualities.[39]

To address these still-speculative fears, the drafters clarified that Article 13 establishes that 'any intervention which aims to modify the human genome must be carried out for preventive, diagnostic or therapeutic purposes'. Moreover, 'interventions aimed at modifying genetic characteristics not related to a disease or to an ailment are prohibited'.[40] They left the door open to somatic cell gene therapy, at that time at the research stage, but only as long as done in compliance with Chapter V (Articles 15 through 18).[41] This includes not only the uncontroversial requirements of protection of persons undergoing research but also the prohibition of the creation of embryos solely for research, which later on in history created numerous problems to stem cell research. What is categorically prohibited are

> [i]nterventions seeking to introduce any modification in the genome of any descendants ... [I]n particular genetic modifications of spermatozoa or ova for fertilization are not allowed. Medical research aiming to introduce genetic modifications in spermatozoa or ova which are not for procreation is only permissible if carried out *in vitro* with the approval of the appropriate ethical or regulatory body.[42]

Clearly, the drafters approached the 'human genome' as a single public good, one that needs special protection.[43] They did not pause to consider that within the 'human genome' there are considerable variations, both between populations and down to the individual level. They also did not pause to consider, or decided to avoid, the intricate question of what is 'normal' human

[39] Explanatory Report (n 20) para. 89.
[40] Ibid., para. 90.
[41] Idem. They excluded from the norm unwanted side effects on the germ cell line, too. Oviedo Convention, Explanatory Report (n 20) para. 92.
[42] Ibid., para. 91.
[43] This is the approach followed also by the UNESCO Universal Declaration on the Human Genome and Human Rights, which declares in Article 1: 'The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity.' See, in general, J Buttigieg, *The Human Genome as Common Heritage of Mankind* (Ibidem Verlag 2018).

genome and what a genetic defect is, and what implications that distinction has, and the ethics of prohibiting interventions that limit the capacity to treat inheritable genetic diseases. Perhaps they did not intend to protect the human genome per se, but rather the embryo, and, to enhance its protection, added this befuddling provision.

The legislative history of Article 13 reveals that the drafters struggled mightily finding the right balance between protection of the human genome and not blocking science. During an early meeting, in 1992, several experts who had been summoned to provide the Working Party with scientific advice were reportedly in favour of prohibiting interventions on the germ cell line. They felt it necessary, given the then state of scientific knowledge, to prohibit such interventions considering the unpredictability of their side effects and effects on subsequent generations.[44] However,

> other participants felt that the option should nevertheless be left open and that it might be possible to authorize germ cell therapy, although the intervention would need to carry a certain number of guarantees which were not available at the present stage of scientific knowledge. If on the other hand such therapy proved its worth and reliability, these experts might be able to accept it under certain conditions.[45]

Alternative language was proposed. The Working Party eventually chose to keep the language prohibiting germ cell therapy but 'agreed unanimously to specify that the provision would need to be reviewed within a certain time (e.g. five years after the entry into force of the Convention) having regard to the current progress in knowledge'.[46] Regrettably, the provision requesting revision of Article 13 after five years never made it to the final text. What made it was instead a general and optional process to amend the Convention, through a public debate.[47]

The Steering Committee on Bioethics debated at length also whether research on germ cell lines was to be allowed.[48] Alternative language considered included: 'Any intervention with the aim of modifying the genetic characteristics in the germ cell line is prohibited' and '[a]ny intervention with the aim of modifying genetic characteristics transmissible to descendants of persons is prohibited'.[49] However, the final text more convolutely provides:

[44] CDBI, Preparatory Work (n 24) CORED 14–16/12/92, 63.
[45] Ibid.
[46] Ibid.
[47] Oviedo Convention, art. 28 and 32.
[48] See, e.g., CDBI, Preparatory Work (n 24) CDBI 20–22/11/95, 66.
[49] Ibid.

'An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants'.[50]

As Iñigo de Miguel Beriain and Carlos Casabona note in this volume, the Oviedo Convention does not specify what 'human genome' or 'descendant' are nor clarifies what 'aimed at' in Article 13 means.[51] Acutely, they pointed out that the human genome changes only when a new gene is added to the already vast and diverse pool of the human genome. However, human germline editing is limited to replacing a pathologic gene with its healthy expression. In such a limited intervention, one that nowadays is technically possible thanks to the advent of the CRISPR family of technologies, nothing 'new' is added to the human genome pool. If gene editing is done to prevent or correct genetic mutations – themselves a threat to the integrity and future of human identity – and no new genetic material is introduced, then it is difficult to see how germline genetic editing could be regarded as an assault on human dignity, one that the drafters of the Oviedo Convention intended to prohibit.[52]

Also, because the Convention does not define the term 'descendant', it is not clear whether a mere embryo, as opposed to a fetus or even a newborn, might be considered a 'descendant' and whose genetic manipulation might be prohibited. That hinges on the legal definition and consequent status of the embryo, a question that the drafters of the Oviedo Convention deliberately left unaddressed to avoid interjecting themselves in a cultural and scientific contentious debate dividing European nations.

Chapter V (Articles 15–18) is entitled 'Scientific Research'. Article 15 contains a general statement whereby: 'Scientific research in the field of biology and medicine shall be carried out freely'. It also adds 'subject to the provisions of the Convention' and other unspecified 'legal provisions ensuring the protection of the human being'.[53] Articles 16 and 17 regard the protection of persons subject to research. Article 18, entitled 'Research on Embryos *In Vitro*', is another article of the Oviedo Convention that is key for the purposes of this volume. It recites: '(1) Where the law allows research on embryos *in vitro*, it

[50] Oviedo Convention, art. 13.

[51] See, in this book, Chapter 13.

[52] I De Miguel Beriain, 'Should Human Germline Editing Be Allowed? Some Suggestions on the Basis of the Existing Regulatory Framework' (2018) *Bioethics* https://doi.org/10.1111/bioe.12492 accessed 12 October 2018; A Nordberg and others, 'Cutting Edges and Weaving Threads in the Gene Editing (Я)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns' (2018) *Journal of Law and the Biosciences* 1–49, 26.

[53] The Explanatory Report and the Preparatory Work fail to shed any light on what these 'other legislative instruments' are.

shall ensure adequate protection of the embryo. (2) The creation of human embryos for research purposes is prohibited.'

As in the case of much of the rest of the Convention, the drafters tried to strike a delicate balance between opposing views about the status of human embryos. It leaves to member states to legally define the 'embryo' and to decide whether to allow or ban research on embryos that are in excess after in vitro fertilization (IVF) and in lab. All it demands is that when states allow research on embryos in vitro, they give embryos 'adequate protection'. Likewise, the Convention does not explain what 'adequate protection' means and how that is compatible with their use as research material. At the same time, it draws the line at the creation of embryos ad hoc for research purposes, a provision that in some states was invoked to block altogether scientific research involving human embryos and in others to create considerable difficulty.

While most of the Convention avoided drastic legal innovations and tended to simply repeat what was already stated at that time in many national legislations, Article 18.2 was the only new innovative norm and, unsurprisingly, was hotly debated during the drafting.[54] The Working Party could not decide on whether the article should be included. To avoid stalling the drafting of the whole Convention, it passed the hot potato to the Steering Committee on Bioethics.[55] At the Committee, several delegations proposed to leave the matter to a separate protocol, but the idea was eventually abandoned when it became clear that such a protocol would have little chance of success.[56] After a discussion, the Committee voted 11 to 6 (2 abstentions) to include Article 18.2 in the Convention.[57] Discussions continued for four more years on how to word it, with several votes, many of them very close.[58]

Despite all, the final wording of the Convention ended up being unacceptable to many states, but for opposite reasons. Germany, because of its history and domestic politics that give southern regions, mostly catholic, a strong voice, tends to have very strong ethical and legal oppositions to any research involving human embryos.[59] During the drafting, the German representatives argued that the Oviedo Convention was too liberal, in particular on embryo experimentation, and, thus, incompatible with the Embryo Protection Act it

[54] V Lúcia Raposo, 'The Convention of Human Rights and Biomedicine Revisited: Critical Assessment' (2016) 20:8 *International Journal of Human Rights* 1277–1294, 1279; R Ashcroft, 'Could Human Rights Supersede Bioethics?' (2010) 10:4 *Human Rights Law Review* 639–660, 657.

[55] CDBI, Preparatory Work (n 24) CORED 9-12/11/92, 81.

[56] Ibid., BDBI 24-27/11/92, 81.

[57] Ibid.

[58] Ibid., 82–88.

[59] On Germany, see in this book, Chapter 8.

had adopted in 1990.[60] To this date, it has not ratified the Oviedo Convention and it is unlikely to do so. Italy, Ireland, Poland and Austria, countries where the Catholic Church has considerable influence, voiced similar concerns and are still on the fence regarding ratification.[61] On the other hand, the United Kingdom,[62] but also Belgium[63] and Netherlands,[64] which allow some of the conduct prohibited by the Oviedo Convention, could not accept the prohibition of creating embryos for research purposes. None of them has, so far, ratified the Oviedo Convention, nor do they seem likely to do so, as long as the text remains what it is.

Both sides overplayed their position at the negotiating table during the drafting of the Convention, resulting in an outcome that satisfies few. The Oviedo Convention to date has been ratified by just 29 out of 47 CoE members. Of the states surveyed in this book, only Spain, France and Switzerland have done so. The odd result is that many of the states who played a key role in the drafting of the Convention (e.g. the United Kingdom, Germany and Italy) are not party to it, and therefore not bound by it, while those who had little say in its making are the ones bound by it.[65]

As long as Articles 13 and 18 are worded as they are, it is unlikely the number of ratifications will grow. The Convention provides for an amendment procedure. Any party to the Convention, the Committee on Bioethics and the Committee of Ministers can propose amendments. The Committee on Bioethics is to discuss the amendment, vote by two-thirds majority on it and then forward it to the Committee of Ministers for approval.[66] This process must also take into account Article 28 of the Convention, which calls for an 'appropriate public discussion in the light, in particular, of relevant medical, social, economic, ethical and legal implications'.

[60] Embryonenschutzgesetz vom 13. Dezember 1990 (BGBl. I S. 2746), das zuletzt durch Artikel 1 des Gesetzes vom 21. November 2011 (BGBl. I S. 2228) geändert worden ist [Act for the Protection of Embryos (The Embryo Protection Act), Federal Law Gazette I 2746 (December 13, 1990), Article 1 amended in Federal Law Gazette I 2228 (November 21, 2011). The human embryo is also protected under the German Constitution (*Grundgesetz*). The Constitution states that 'human dignity is inviolable' and that 'everyone has the right to life and inviolability of his person' (art. 1.1). Nonetheless, it also states that freedom to pursue science and research is protected (art. 5.3). Basic Law for the Federal Republic of Germany, as last amended 23 December 2014.

[61] On Italy, see, in this book, Chapter 12.

[62] On the UK, see, in this book, Chapter 7.

[63] On Belgium, see, in this book, Chapter 9.

[64] On the Netherlands, see, in this book, Chapter 11.

[65] V Bellver Capella, 'Los Diez Primeros Años del Convenio Europeo sobre Derechos Humanos y Biomedicina: Reflexiones y Valoración' (2008) XIX: 3 Cuadernos de Bioética, 401–421, 405.

[66] Oviedo Convention, art. 32.6.

In 2015, the Committee on Social Affairs, Health and Sustainable Development of the Parliamentary Assembly of the CoE noted that while Article 13 prohibits interventions on the human genome that are not for preventive, diagnostic or therapeutic purposes and are inheritable, 'this Convention has not yet been ratified by all Council of Europe member States and even those that may have interpret the limits of this prohibition differently'.[67] Thus, the Committee asked the Parliamentary Assembly 'to study the health, ethical, and human rights risks and challenges related to the [gene-editing] techniques' use and regulation with a view to making the appropriate recommendations to the Committee of Ministers on possible action to be taken to provide a common framework for the use of these technologies'.[68]

In November 2017, the same Committee issued a report, entitled 'The Use of New Genetic Technologies in Human Beings', recommending the Parliamentary Assembly to recommend the Council of Ministers to adopt a five-step plan that includes: (i) urging member States which have not yet ratified the Oviedo Convention to do so without further delay, or, as a minimum, to put in place a national ban on establishing a pregnancy with germline cells or human embryos having undergone intentional genome editing; (ii) fostering a broad and informed public debate; (iii) instructing the Council of Europe Committee on Bioethics (DH-BIO) to assess the attendant ethical and legal challenges; (iv) developing a common regulatory and legal framework; and (v) recommending that member States, on the basis of the other steps, develop a clear national position on the practical use of new genetic technologies, setting the limits and promoting good practices.[69] The Parliamentary Assembly adopted the recommendation as its own almost verbatim shortly thereafter and passed it on to the Council of Ministers.[70]

Yet, it is hard to see how this could remove the blocks that have prevented the Convention from gathering, if not ratification by all CoE members, at least support from the major states. It is obvious that ratification of the Oviedo Convention must be the last step in the plan, not the first, and must be reached only after the Convention has been amended. One possible way out of the

[67] Parliamentary Assembly, Committee on Social Affairs, Health and Sustainable Development, 30 November 2015, Doc 13927.

[68] Ibid.

[69] Parliamentary Assembly, Committee on Social Affairs, Health and Sustainable Development, 24 May 2017, Doc 14328.

[70] Parliamentary Assembly, Recommendation 2115 (2017) (The use of new genetic technologies in human beings).

impasse would be to delete from the Convention at least Articles 13 and 18. These two articles could become the object of much more detailed regulation in a separate protocol or two, as other controversial biomedical issues such as end-of-life decisions. This way states that want to give embryos and germline cells high level of protection could go ahead and ratify them, while states that are happy with the status quo could finally ratify the framework Convention. This would ensure that the citizens of this second group of states enjoy, as a matter of international law, the rights that all other articles of the Oviedo Convention describe. This would be a step forward towards the adoption of a truly single bioethics law in Europe.[71] However, for political reasons, it is unlikely this pragmatic solution will be adopted. 'Prohibitionist' states are more concerned about preventing conduct in the territory of other fellow European states than about the Convention preventing them from adopting higher standards of protection of the human embryo for activities taking place within their jurisdiction.

At the time of writing this book, the Committee on Bioethics has yet to present a detailed analysis that could provide some further insights. In 2015, it issued a general statement concerning the call for an in-depth analysis of the potential risks of genome editing and for international and regional debate on its implications for human beings. It recognized the potential of new genome-editing technologies, such as CRISPR-Cas9, for research to understand the causes of diseases and for future treatment as well as to improve health. However, it also expressed concern about the application of genome-editing technologies to human gametes or embryos in the light of the many ethical, social and safety issues, particularly from any modification of the human genome, which could be passed on to future generations. It then held that the ethical and legal challenges raised by these emerging genome-editing technologies are better addressed in the light of the principles laid down in the Oviedo Convention.[72] Recently, in December 2018, following the second International Summit on Human Genome Editing and the announcement of the birth of two babies in China following germline genome modification, the Committee reiterated its 2015 statement, stressing that 'ethics and human rights must guide any use of genome editing technologies' and that the Oviedo Convention provides a unique reference framework to that end.[73]

[71] R Andorno, *Principles of International Biolaw: Seeking Common Ground at the Intersection of Bioethics and Human Rights* (Brussels: Bruylant 2013).

[72] Committee on Bioethics, *Statement on Genome Editing Technologies* (Council of Europe, Strasbourg, 2015), Doc. DH-BIO/INF (2015) 13 FINAL.

[73] Newsroom, 'Statement by the Council of Europe Committee on Bioethics: "Ethics and Human Rights Must Guide Any Use of Genome Editing Technologies in Human Beings"' (Council of Europe, Strasbourg, 30 November 2018) www.coe.int/en/web/portal/-/ethics-and-

Alas, keep referring to the Oviedo Convention as the gold standard is not going to do much to improve it.

3 *The Additional Protocols to the Oviedo Convention*

As it was mentioned, to fill the framework with specific content, to date, the CoE has adopted and opened for signature and ratification four additional protocols: on the Prohibition of Cloning of Human Beings (1998);[74] on Transplantation (2002);[75] on Biomedical Research (2004);[76] and on Genetic Testing for Medical Purposes (2008).[77]

The Additional Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings was adopted in 1998 and entered into force in 2001. So far, it has been ratified by 24 states.[78] It is the first and only binding international legal instrument on this issue. It prohibits 'any intervention seeking to create a human being genetically identical to another human being alive or dead'.[79] While it does not define 'human being', by 'human being genetically identical' it means the creation of a 'human being sharing with another the same nuclear gene set'.[80] Thus, it does not apply to the cloning of cells and tissue for research and therapeutic purposes. No exemption from this prohibition (e.g. for reasons of public safety, prevention of crime, protection of public health or the protection of the rights and freedoms of others) is admissible.

The Additional Protocol on Transplantation was adopted in 2001 and entered into force in 2006. So far, it has been ratified by 15 states. It contains general principles and specific provisions regarding the transplantation of organs and tissues of human origin for therapeutic purposes. Among the general principles there are equitable access to transplantation services for patients; transparent rules for organ allocation; health and safety standards; the prohibition of financial gain by donors; and the need for donors, recipients,

human-rights-must-guide-any-use-of-genome-editing-technologies-in-human-beings-, accessed 21 December 2018.

74 (n 16).

75 (n 17).

76 (n 18).

77 (n 19).

78 Ratification of the Oviedo Convention is a prerequisite for ratification of its protocols. Thus, those states that have not ratified the Oviedo Convention have not ratified its additional protocols either.

79 Additional Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings, art. 1.1.

80 Ibid., art. 1.2.

health professionals and the public to be properly informed. The specific provisions cover the removal of organs from living and deceased persons; the use made of the organs and tissues removed; confidentiality; sanctions and compensation.

The Additional Protocol on Biomedical Research was adopted in 2004 and entered into force in 2007. To date, it has been ratified by 12 states. It builds on the principles embodied in the Oviedo Convention, to protect human rights and dignity in the specific field of biomedical research. Its purpose is to define and safeguard fundamental rights in biomedical research, in particular of those participating in research. The Protocol covers the full range of biomedical research activities involving interventions on human beings. It restates the fundamental principles guiding research involving human beings, such as the free, informed, express, specific, and documented consent of the person(s) participating. It addresses issues such as risks and benefits of research, consent, protection of persons not able to consent to research, scientific quality, independent examination of research by an ethics committee, confidentiality and the right to information, undue influence, safety and duty of care.

Finally, the Protocol on Genetic Testing for Health Purposes was adopted in 2008 and entered into force on 1 July 2018. So far, it has been ratified by five states, which is the threshold for entry into force. This protocol sets down principles relating inter alia to the quality of genetic services, prior information and consent and genetic counselling. It lays down general rules on the conduct of genetic tests, and, for the first time at the international level, deals with genetic tests directly accessible to the public. It specifies the conditions in which tests may be carried out on persons not able to consent. Also covered are the protection of private life and the right to information collected through genetic testing.

4 *The European Convention on Human Rights*

As it was said, the European Convention on Human Rights and Fundamental Freedoms (European Convention) is the linchpin of the European human rights regime.[81] Neither the European Convention nor its protocols, which extended the list of rights, mention the 'right to health', the 'right to science' or the 'rights of science'. The Convention, both in its original form and after revisions brought about by the protocols, focuses mostly on civil and political freedoms. However, it contains some articles that over the years have been used by advocates and patients to address issues raised by biotechnology,

[81] See, in this chapter, Section II.1.

artificial reproductive technology and the question of the legal status of the human embryo. These include Article 2 (Right to Life),[82] Article 8 (Right to Respect for Private and Family Life)[83] and Article 14 (Prohibition of Discrimination).[84] As in the case of every human rights treaty, the rights contained in these articles are formulated very broadly, leaving much room for interpretation. However, interpretation and reading between the lines of the Convention cannot go as far as inventing rights that states did not intend to recognize.

The European Court of Human Rights is the international court with jurisdiction over alleged violations of the human rights contained in the Convention of natural and legal persons committed by any of the 47 members of the CoE within their jurisdiction. Composed of 47 judges – one for each CoE member state, and divided into four chambers and a Grand Chamber – it issues binding decisions that can be enforced by national courts.[85] By all metrics, it is the most important and effective of all international human rights adjudicative bodies.[86] While a full discussion of the Court is certainly beyond the scope of this book, we should mention here a few cases that are relevant for biomedicine and artificial reproductive technology.

In 2012, in *Costa and Pavan* v. *Italy*, the Court found the prohibition of PGD contained in the version of Law 40/2004 then in force in Italy to be a violation of Article 8 of the European Convention on Human Rights because the applicants' desire to resort to artificial reproductive technology and

[82] European Convention on Human Rights, Article 2: '1. Everyone's right to life shall be protected by law. No one shall be deprived of his life intentionally save in the execution of a sentence of a court following his conviction of a crime for which this penalty is provided by law. 2. Deprivation of life shall not be regarded as inflicted in contravention of this Article when it results from the use of force which is no more than absolutely necessary: (a) in defense of any person from unlawful violence; (b) in order to effect a lawful arrest or to prevent the escape of a person lawfully detained; (c) in action lawfully taken for the purpose of quelling a riot or insurrection.'

[83] Ibid., art. 8: '1. Everyone has the right to respect for his private and family life, his home and his correspondence. 2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.'

[84] Ibid., art. 14: 'The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, color, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status.'

[85] See, in general, E Lambert Abdelgawad, *The Execution of Judgments of the European Court of Human Rights* (2nd ed., 2008).

[86] On the European Court of Human Rights, see, in general: D John Harris and others, *Law of the European Convention on Human Rights* (4th ed., 2014).

embryo screening to have a child not affected by a genetic disorder of which they were healthy carriers was an expression of their private and family life.[87]

A second case, again against Italy, was decided in 2015. *Parrillo* v. *Italy* was about a couple whose IVF surplus embryos had been cryopreserved. After the death of her partner, Ms Parrillo decided to donate the embryos to scientific research. However, Law 40/2004 prohibits the use of human embryos for anything other than reproduction.[88] Ms Parrillo alleged that the prohibition violated her right to respect for private life (Article 8),[89] as well as of her right to private property (Article 1 of Protocol No. 1),[90] and freedom of expression (Article 10). Noting that the embryos contain the genetic material of the applicant and thus represent a constituent part of her identity, the Court's Grand Chamber concluded that Ms Parrillo's ability to exercise a choice regarding the fate of the embryos concerned an intimate aspect of her personal life and was related to her right to self-determination.[91] Therefore, the prohibition to donate embryos to scientific research interfered with Ms Parrillo's right to private life.[92]

However, the right to a private life is not an absolute right. It can be limited. Thus, the Court next considered whether this interference was 'in accordance with the law' as required by Article 8.2 of the Convention, which recites: 'There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others'.[93] While the Court recognized that the aim pursued by

[87] *Costa and Pavan* v. *Italy*, Application No 54270/10, European Court of Human Rights (Judgment of 28 August 2012) para. 57.

[88] Law No 40 of 19 February 2004 'Rules on Medically Assisted Procreation' (In Italian, *Norme in materia di procreazione medicalmente assistita*) art. 13. For a rough translation in English, see European Institute of Bioethics, 'Rules on Medically Assisted Procreation' (Italian Parliament, 2004) www.ieb-eib.org/en/pdf/loi-pma-italie-english.pdf accessed 27 February 2017.

[89] European Convention on Human Rights, art. 8.

[90] Article 1.1 of Protocol No 1 (Protection of Property) to the European Convention on Human Rights states: 'Every natural or legal person is entitled to the peaceful enjoyment of his possessions. No one shall be deprived of his possessions except in the public interest and subject to the conditions provided for by law and by the general principles of international law.' Protocol to the Convention for the Protection of Human Rights and Fundamental Freedoms (18 May 1954) ETS No 9, art. 1.1.

[91] *Parrillo* v. *Italy*, Application No 46470/11, European Court of Human Rights (Grand Chamber Judgment of 27 August 2015), paras. 158–159.

[92] Ibid., para. 161.

[93] Ibid.

Italy (the protection of the embryo's potential for life) could be justified by the aim of 'protecting morals and the rights and freedoms of others', it also stressed that this did not imply any assessment by the Court as to whether the word 'others' extended to human embryos.[94] Eventually, the Court decided that, given the lack of a European consensus on the matter, Italy was to be given a wide margin of appreciation,[95] and did not find a violation of Article 8.2 of the European Convention.[96] As to the claims that Article 1 of Protocol No. 1 and Article 10 had been violated, the Grand Chamber found them inadmissible because an embryo cannot be considered property in the economic and pecuniary sense of that article,[97] and the right to freedom of expression in this case was not vested in the applicant directly, but rather in researchers and scientists.[98]

Three more relevant cases are *Evans* v. *United Kingdom*, *Dickson* v. *United Kingdom* and *S.H. and Others* v. *Austria*. They all concern various aspects of artificial reproductive technology. In *Evans*, the Court found that the UK laws allowing withdrawal of consent to use cryopreserved embryos by one of the partners had not violated the Convention.[99] *Dickson* was about a couple who could not resort to IVF because the husband was in detention serving a 15-year sentence for murder, and the Court ruled in their favour.[100] Artificial insemination was the applicants' only realistic hope to conceive a child. The Grand Chamber observed that, while the inability to beget a child might be a consequence of imprisonment, it was not an inevitable one, since giving access to artificial insemination facilities would not have involved any security issues or imposed any significant administrative or financial demands on the state. Accordingly, the Court held that there had been a violation of Article 8 of the Convention, as a fair balance had not been struck between the competing public and private interests.[101]

S.H. and Others v. *Austria* was brought by two couples who challenged Austria's ban of heterologous artificial insemination, claiming violations of

[94] Ibid., para. 167.
[95] Ibid., paras. 174–176.
[96] Ibid., para.197.
[97] Ibid., para. 215.
[98] *Parrillo* v. *Italy*, Application No 46470/11, European Court of Human Rights (Decision on Admissibility of 28 May 2003).
[99] *Evans* v. *United Kingdom*, Application No 6339/05, European Court of Human Rights (Grand Chamber Judgment of 10 April 2007).
[100] *Dickson* v. *United Kingdom*, Application No 44362/04, European Court of Human Rights (Judgment of 4 December 2007).
[101] Ibid., para. 82.

Article 8 and Article 14.[102] The Court found a violation of Article 14 of the Convention in conjunction with Article 8. However, on appeal, in 2010, the Court's Grand Chamber concluded that there had been no violation of Article 8 per se because the Austrian legislature did not exceed the margin of appreciation afforded to it at the relevant time, either in respect of the prohibition of egg donation for the purposes of artificial procreation or in respect of the prohibition of sperm donation for IVF.[103] In fact, although there was a clear trend across Europe in favour of allowing gamete donation for IVF, there was not yet a consensus on the matter nor settled legal principles.[104]

All in all, when confronted with matters raising bioethical contentious or difficult questions, the European Court of Human Rights has shown significant willingness to defer to states and to allow them sometimes a wide margin of appreciation, as long as the laws or actions in question do not appear to be discriminatory or arbitrary and strike a fair balance between the competing interests and values at play.

5 *Other CoE-Relevant Treaties*

Finally, to conclude the overview of CoE's legal instruments relevant for a discussion of human genome germline modification one must mention the Council's data protection framework, in particular the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data[105] and the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.[106]

As the name of the former suggests, the first is a treaty aiming to protect the right to privacy of individuals, taking account of the increasing flow across frontiers of personal data undergoing automatic processing. When it was adopted, in 1981, it was the first treaty in the world of its kind. In addition to providing guarantees in relation to the collection and processing of personal data, it outlaws the processing of 'sensitive' data on a person's race, politics, health, religion, sexual life, criminal record, etc., in the absence of proper legal safeguards. The Convention also enshrines the individual's right to know

[102] *SH and others* v. *Austria*, Application No 57813/00, European Court of Human Rights (Judgment of 1 April 2010).
[103] Ibid., para. 115.
[104] Ibid., para. 96.
[105] Convention for the Protection of Individuals with Regard to Automatic Processing of Personal Data, CETS 108.
[106] European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, CETS 123.

that information is stored on him or her and, if necessary, to have it corrected. The Convention also imposes some restrictions on transborder flows of personal data to states where legal regulation does not provide equivalent protection. The data protection Convention was updated and improved in Amendments approved by the Committee of Ministers, in Strasbourg, on 15 June 1999, to take into account the advent of the Internet and the expansion of data processing capacities.[107] The principles of transparency, proportionality, accountability, data minimization, privacy by design, etc., are now acknowledged as key elements of the protection mechanism and have been integrated in the modernized instrument.[108] All members of the Council of Europe have ratified the treaty, as well as six non-members (Mauritius, Senegal, Tunisia, Uruguay, Cabo Verde and Mexico).[109]

The European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes was adopted by the CoE in 1986 primarily to reduce both the number of experiments and the number of animals used for research.[110] To this end, it contains a number of principles that guide the national policies of those states that have ratified it, such as refraining from experimenting on animals except where there is no alternative; seeking alternative methods; selecting animals to experiment on the basis of clearly established quantitative criteria and well caring for and sparing avoidable suffering whenever possible.

III THE EUROPEAN UNION

1 *Introduction*

The European Union was established in 1992 by the Treaty of Maastricht to 'continue the process of creating an ever-closer union among the peoples of Europe',[111] a process that had started in the aftermath of the Second World

[107] 'Amendments approved by the Committee of Ministers, in Strasbourg, on 15 June 1999, ETS No 108' (Council of Europe, 1999) https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=0900001680078c2b8 accessed 10 December 2018.

[108] See CoE, 'The Modernised Convention 108: Novelties in a Nutshell' https://rm.coe.int/16808accf8 accessed 5 November 2018.

[109] See CoE, 'Chart of Signatures and Ratifications of Treaty 108' (2018) www.coe.int/en/web/conventions/full-list/-/conventions/treaty/108/signatures?p_auth=maZNKP38 accessed 5 November 2018.

[110] To date, it has been ratified only by 22 CoE members, including the European Union. See CoE, 'Chart of Signatures and Ratifications of Treaty 123' (2018) www.coe.int/en/web/conventions/full-list/-/conventions/treaty/123/signatures?p_auth=7Jfxuyy8 accessed 5 November 2018.

[111] Preamble of the Treaty on European Union (signed in Maastricht on 7 February 1992) OJ C 191, 1–112.

War with the creation of the three European Communities: the European Coal and Steel Community,[112] the European Economic Community (EEC)[113] and the European Atomic Energy Community.[114] Over the next four decades, this limited project of regional economic integration broadened and deepened to include political issues, such as foreign and security policy, justice and home affairs, social policy, consumer protection, industry, environment, public health and safety, and many others.

Membership expanded, too. Starting with the founding six states (Belgium, France, West Germany, Italy, Luxembourg and the Netherlands), the Communities expanded first, in 1973, to the north-east (the United Kingdom, Ireland and Denmark), then, in the 1980s, to the south (Portugal, Spain, and Greece), then, in the 1990s to the north and east (Sweden, Finland, Austria and East Germany, as a result of German reunification), and finally in the 2000s to the east and south, when 11 states from Central and Eastern Europe and the Balkans, as well as Cyprus and Malta, became part of the Union.[115] Nowadays, the European Union is composed of 28 member states. While in the near future the UK might leave it due to the outcome of the 'Brexit referendum',[116] others, particularly in the Balkans, might join.[117]

The expansion and deepening of the European integration process happened in stages, each marked by a new treaty. At the beginning of the 2000s, its members looked ready to leap forward towards the creation of a European federal state. Negotiations to modify EU institutions began in 2001, resulting in the adoption of a European Constitution, which would have repealed the existing European

[112] ESCS Treaty or Paris Treaty: Treaty Establishing the European Coal and Steel Community (entered into force 18 April 1951, no longer in force and end of validity 23 July 2002) 261 UNTS 140.

[113] EEC Treaty or Treaty of Rome: Treaty Establishing the European Economic Community (entered into force 25 March 1957) 298 UNTS 3, 4 Eur. Y.B. 412

[114] EAEC Treaty or EURATOM Treaty: Treaty Establishing the European Atomic Energy Community (entered into force 25 March 1957) 298 UNTS 259.

[115] Bulgaria (2007), Croatia (2013), Czech Republic (2004), Cyprus (2004), Estonia (2004), Hungary (2004), Latvia (2004), Lithuania (2004), Malta (2004), Poland (2004), Romania (2007), Slovakia (2004) and Slovenia (2004).

[116] However, at the time of this writing it is not yet clear whether the UK will actually exit. On 10 December 2018 the Court of Justice of the European Union ruled that the UK could unilaterally suspend the exit process, if it wishes to do so. See Case C-621/18, Request for a preliminary ruling under Article 267 TFEU from the Court of Session, Inner House, First Division (Scotland, United Kingdom), made by decision of 3 October 2018, received at the Court on the same day, in the proceedings, Judgment of the European Court of Justice, 10 December 2018.

[117] As of 2018, there are five candidates for future EU membership: Turkey, Macedonia, Montenegro, Albania and Serbia. Other potential candidates for future EU membership are Kosovo and Bosnia Herzegovina.

treaties. However, when it was put to the vote of the citizens of each member state, it was rejected after the electors in France and the Netherlands voted against it. After a period of reflection, member states agreed to amend instead the existing treaties, salvaging a number of the reforms that had been envisaged in the botched constitution. The result was the so-called Reform Treaty, adopted in Lisbon in 2007 and entered into force in 2009.[118]

The most important changes brought about by the Treaty of Lisbon are the abandonment of unanimity for qualified majority to take decisions in the major policy areas; a more powerful European Parliament; the conferral of legal personality to the European Union, distinct and separate from that of its member states; the creation of a President of the European Council and a High Representative of the Union for Foreign Affairs and Security Policy; and the adoption of the Union's 'Bill of Rights', called the Charter of Fundamental Rights of the European Union (EU Charter).

As to governance, the European Union's main institutions are the Council of the European Union, the European Parliament, the European Commission and the Court of Justice of the European Union. The Council is composed of the 28 member states, represented by their ministers, who meet to discuss, amend, adopt laws, and coordinate policies.[119] The European Parliament is directly elected by the EU citizens every five years and is composed of 751 members.[120] It shares legislative and budgetary powers with the Council and has certain exclusive scrutiny and appointments powers. The European Commission is the European Union's executive arm.[121] It initiates the law-making process by proposing new EU legislation and is responsible for enforcing EU law and policies. Finally, the Court of Justice of the European Union (CJEU, or Court of Justice) ensures that the Union's laws are interpreted and applied the same in all member states.[122] It also settles disputes between national governments and EU institutions and can in some circumstances adjudicate claims brought by legal or natural persons against EU

[118] Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community (signed at Lisbon, 13 December 2007) OJ C 306, 1–271.

[119] The Council of the European Union is not to be confused with the European Council, which are quarterly summits where EU leaders meet to set the broad direction of EU policy-making. 'The Council of the European Union' www.consilium.europa.eu/en/council-eu/ accessed 9 October 2018; 'The European Council' www.consilium.europa.eu/en/european-council/ accessed 9 October 2018.

[120] 'The European Parliament' www.europarl.europa.eu/portal/en accessed 9 October 2018.

[121] 'The European Commission' https://ec.europa.eu/commission/index_en accessed 9 October 2018.

[122] 'The Court of Justice of the European Union' https://curia.europa.eu/jcms/jcms/j_6/en/ accessed 9 October 2018.

institutions. To ensure harmony in the interpretation of EU law, national courts can refer cases to the Court of Justice for preliminary rulings that are binding both for the court that requested it and also for all member states.

2 *The Regulatory Environment*

a EU Primary Law

Although the European Union failed to give itself a federal constitution, the triad made of the EU Charter on Fundamental Rights[123] and the two constitutive treaties – the Treaty of the European Union (TEU, originally the Treaty of Maastricht)[124] and the Treaty of the Functioning of the European Union (TFEU, originally the Treaty of Rome, which created the European Economic Community)[125] – is the Union's 'primary law'. They are the de facto 'constitution of the European Union', in the sense that all EU law-making activities must find their legality in them and must be compatible with them.[126]

The TEU and TFEU set out the goals of the Union and the principles on which it is based, as well as its organs, powers, composition and competences. The EU Charter of Fundamental Rights contains a list of fundamental rights everyone within the jurisdiction of the European Union enjoys. When first proclaimed in 2001, the EU Charter was not legally binding for the member states. However, following the Lisbon Treaty, the Charter was attached to, and given the same legal value as, the constitutive treaties.[127] However, unlike the European Convention of Human Rights, those who must ensure respect for the rights included in the EU Charter are not primarily states but the

[123] Consolidated Version of the Treaty of the European Union, with the amendments introduced by the Treaty of Lisbon (signed on 13 December 2007 and entered into force on 7 December 2009) OJ C 326, 13–390.

[124] Charter of Fundamental Rights of the European Union (proclaimed by the European Parliament on 7 December 2000 and entered into force in adapted wording with the date of the entry into force of the Lisbon Treaty on 7 December 2009) OJ C 326, 26 October 2012 (TEU) 391–407.

[125] Consolidated version of the Treaty on the Functioning of the European Union, with the amendments introduced by the Treaty of Lisbon (signed on 13 December 2007 and entered into force on 7 December 2009) OJ C 326 (TFEU) 47–390.

[126] Since the entry into force of the Lisbon Treaty in 2009, the EU Charter has the same legal value of the two constitutive treaties and must also be respected by the Union as a matter of primary or 'constitutional' law. TEU, art. 6.1.

[127] Ibid. See, also, N Foster, *Foster's EU Law* (6th ed., Oxford, Oxford University Press 2017) 106–107.

European Union itself.[128] Under the Charter, the European Union must act and legislate consistently with the Charter and courts will strike down legislation adopted by the European Union's institutions that contravenes it. Member states must comply with it only in so far as they are implementing EU law.[129]

The EU Charter was drafted in the early 2000s. Because of its novelty, to date it is the only enunciation of human rights of a general nature to consider how the rapid scientific developments in biology and medicine may affect fundamental human rights. The most important right is included in Title I related to dignity rights and incorporates some of the basic rights and principles included in the Oviedo Convention.[130] Notably, Article 3 of the Charter, entitled 'Right to the Integrity of the Person', establishes that in the fields of biology and medicine the 'free and informed consent of the person concerned' must be respected.[131] The same article also sets forth three prohibitions: the prohibition of 'eugenic practices, in particular those aiming at the selection of persons',[132] of 'making the human body and its parts as such a source of financial gain'[133] and of 'reproductive cloning of human

[128] EU Charter on Fundamental Rights, art. 51.1: 'The provisions of this Charter are addressed to the institutions, bodies, offices and agencies of the Union with due regard for the principle of subsidiarity and to the Member States only when they are implementing Union law. They shall therefore respect the rights, observe the principles and promote the application thereof in accordance with their respective powers and respecting the limits of the powers of the Union as conferred on it in the Treaties.' Charter of the Fundamental Rights of the European Union [2000] OJ C 364/1.

[129] A Ward, 'Article 51 – Field of Application' in S Peers and others (eds.), *The EU Charter of Fundamental Rights: A Commentary* (Oxford, Beck/Hart Publishers 2014) 1456–1497.

[130] The provisions of the Oviedo Convention of special importance are Article 5 of the Oviedo Convention related to free and informed consent and Article 21 prohibiting using the human body for financial gain as well as Additional Protocol to this Convention related to the prohibition against human cloning. See S Michalowski, Article 3 in S Peers and others (eds.), *EU Charter of Fundamental Rights: A Commentary* (Oxford, Beck/Hart Publishers 2014) 39–102, 44.

[131] Ibid., art. 3.2.a. That this right includes the right of donors has been confirmed in a Court of Justice judgment of 9 October 2001 in Case C-377/98 *Netherlands* v. *European Parliament and Council* [2001] ECR-I 7079, at grounds 70, 78 to 80. To some extent, this right finds a basis in Article 7 of the International Covenant of Civil and Political Rights (n 30) according to which 'no one shall be subject without his free consent to medical or scientific experimentation'. Insofar as it applies to reproductive health, Article 3 finds some support in Article 16 of the UN Convention on the Elimination of Discrimination against Women, which establishes the rights of women to 'decide freely and responsibly on the number and spacing of their children and to have access to the education, information and means to enable them to exercise these rights'. Convention on the Elimination of All Forms of Discrimination Against Women (adopted on 18 December 1979) 1249 UNTS 13.

[132] EU Charter on Fundamental Rights, art. 3.2.b.

[133] Ibid., art. 3.2.c.

beings'.[134] The EU Charter does not define 'eugenic practices'. However, the Explanations of the Charter indicate that the drafters intended to prohibit those practices that constitute a crime under the Rome Statute of the International Criminal Court,[135] such as the organization and implementation of selection programmes for sterilization, forced pregnancy and compulsory ethnic marriage, among others.[136] The prohibition of human cloning is limited, too, since it only concerns reproductive cloning of human beings, but no other forms of cloning.[137]

Whether Article 3 of the EU Charter prohibits human germline genome modification is unclear.[138] For a start, the EU Charter does not mention it. Although Article 1 of the Charter declares 'human dignity is inviolable . . . [i]t must be respected and protected', in the absence of a definition of 'dignity' in the Charter or its Explanations, it is not evident that human genetic engineering would per se amount to a violation of the obligation to respect human dignity. Also, although Article 3.1 declares '[e]veryone has the right to respect for his or her physical and mental integrity', it is not evident how human germline genome modification might violate someone's physical and mental integrity either. Moreover, it is unclear whether the right to the physical integrity of persons extends also to future generations and under what conditions. At the same time, there are other articles in the Charter that protect the right to conduct scientific research, such as Article 13, according to which 'the arts and scientific research shall be free of constraint' and that 'academic freedom shall be respected'. Although the Explanations stress that freedom of scientific research is not absolute and that its exercise must be compatible with the obligation to respect and protect human dignity and may be subject to the limitations authorized by Article 10 of the ECHR (freedom of expression), so far neither the legislative bodies of the European Union nor the judicial ones have clarified where the balance should be struck.[139]

[134] Ibid., art. 3.2.d.

[135] Rome Statute of the International Criminal Court (entered into force 1 July 2002) 2187 UNTS 90.

[136] Explanations Relating to the Charter of Fundamental Rights (2007) OJ C 303/2, 17–35 (Explanations) 18.

[137] Ibid., 18. According to the Explanations, the prohibition against the reproductive cloning of human beings 'neither authorises nor prohibits other forms of cloning. Thus it does not in any way prevent the legislature from prohibiting other forms of cloning,' in line with the Oviedo Convention.

[138] For example, it is not mentioned in the analysis of Article 3 of the EU Charter of Fundamental Rights by Sabine Michalowski, 'Article 3' in S Peers and others (eds.), *EU Charter of Fundamental Rights: A Commentary* (Oxford, Beck/Hart Publishers 2014) 39–102.

[139] Ibid., 17 and 22.

Finally, it should be noted that the EU Charter recognizes the 'right to health', which is included in Title IV related to solidarity rights. According to Article 35: 'Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all the Union's policies and activities.' The formulation of this article has been inspired by international human rights treaties, including Article 3 of the Oviedo Convention, according to which 'Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate equality' as well as the European Social Charter.[140] According to the explanatory notes of the EU Charter, Article 35 is based on Articles 11 and 13 of the European Social Charter.[141] The objectives are to improve public health, prevent physical and mental illness and diseases, and obviate sources of danger to physical and mental health. The EU involvement on matters of public health covers 'the fight against major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education, and monitoring, early warning of and combating serious cross-border threats to health'.[142] However, the fact that, according to EU law, Article 35 establishes 'principles' instead of 'rights' means that more detailed legislation must be adopted for any health-related rights to be judicially enforceable in the courts.[143] Whether European Union and national law blocking research on human germline modification, research that could lead to eliminating entirely many hereditary genetic diseases, could be seen as contrary to the objective of attaining a 'high level of human health protection' remains to be seen.

[140] Articles 11 and 13 of the European Social Charter. See C A Young, 'Fundamental Rights and EU Health Law and Policy' in T K Hervey, C A Young, and L E Bishop, *Research Handbook on EU Health Law and Policy* (Cheltenham, UK, Edward Elgar Publishing 2017) 82–108, 90–91.

[141] Explanations relating to the Charter of Fundamental Rights of the European Union, 27.

[142] TFEU, art. 168.1.

[143] On the distinction between 'rights' and 'principles', see Explanations relating to the Charter of Fundamental Rights of the European Union, 35, which clarifies Article 52.5 of this charter; K Leanerts, 'Exploring the Limits of the EU Charter of Fundamental Rights' (2012) 8 *European Constitutional Law Review* 375, 400, and the analysis of the Advocate General Cruz Villalón in his Opinion *AMS* v. *CGT* ECLI:EU:C:491, [2013] paras. 43–80.

b International Law and the European Union

According to the Treaty of Lisbon the European Union has legal personality distinct and separate from that of its member states.[144] The fact that the Union has legal personality means it has international obligations of its own.[145] The European Union is a member of international organizations alongside some or all of its members (e.g. the World Trade Organization (WTO)) and has the power to conclude treaties where it has competence to act, either explicitly or implicitly.[146] International agreements entered into by the European Union are regarded as an integral part of the EU legal order and may under certain circumstances be directly effective (self-executing). However, to date, much of the case law of the Court of Justice in this field concerns the legal effects of WTO agreements,[147] and does not centre on international human rights instruments. Moreover, although the European Union is party to several treaties, including the CoE's Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes,[148] it has not yet ratified the European Convention on Human Rights, even though it is required to do so by its own constitutive treaties.[149] Neither has it ratified the European Convention on Human Rights and Biomedicine (Oviedo Convention).[150] Also, the European Union is not party to the ICESCR, which is a treaty only open for signature to states.[151]

That the European Union is not a party to these human rights treaties does not affect the human rights obligations by its member states, which are, all of them, parties to the Covenant and the European Convention on Human Rights.[152] However, the fact that all EU states must respect the rights and

[144] TEU, art. 47. See, however, pre-Lisbon case law of the Court of Justice according to which the European Community was granted international legal personality, e.g. Case 22/70 *Commission* v. *Council* (AETR/ERTA) (1971) ECR 263.

[145] TFEU, art. 216.2.

[146] TFEU art. 216.1; TEU art. 37.

[147] P Craig and G de Búrca, *EU Law: Text, Cases and Materials* (6th ed., Oxford, Oxford University Press 2015) 362.

[148] European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, 18 March 1986, ETS No 123. The EU ratified it on 30 April 1998. It entered into force for the EU on 1 November 1998.

[149] TEU, art. 6.2.

[150] Nine out of 28 EU states have not ratified the Oviedo Convention, among them, the United Kingdom.

[151] ICESCR, art. 26.1. The EU has not ratified any international human rights treaties with the exception of the Convention on the Rights of Persons with Disabilities (2006), which it ratified on 23 December 2010. Convention on the Rights of Persons with Disabilities (entered into force 13 December 2006) 2515 UNTS 3.

[152] TEU, art. 6.2.

freedoms established in these legal instruments by virtue of their own ratification is not sufficient to make them binding on the European Union itself, even though the European Union still needs to take account of them 'through interpretation in the light of the Member States' obligations due to the principle of sincere cooperation'.[153] Thus, even if the Union itself is not formally bound to give effect to, for example, the right to science or the right to health as laid down in the Covenant, its institutions must consider these rights, to the extent that they are regarded as general principles of the Union's law and 'result from the constitutional traditions common to the Member States'.[154]

In sum, there are three formal sources of EU human rights law: the EU Charter, the European Convention on Human Rights and the general principles of EU law. Out of these, the EU Charter is the most important one, as also manifested in the case law of the Court of Justice. The general principles are a body of legal principles, including human rights, which were articulated and developed by the Court of Justice before the EU Charter was drafted. General principles are a more ambiguous source said to derive from national constitutional traditions, from the ECHR, and from other international treaties signed by the member states.[155] Even if the definition of general principles included in Article 6.3 of the TEU makes no explicit reference to other international human rights instruments besides the ECHR as a source of EU human rights law, the Court of Justice occasionally cites such instruments,[156] including the Covenant on Economic, Social and Cultural Rights,[157] even if the European Union is not itself party to these instruments. However, importantly, it has rejected reliance on the Oviedo Convention since the European Union has not signed it and since, as the Court of Justice pronounced in 2010, 'of the Member States, only a small majority of them have actually ratified the Convention'.[158]

[153] TEU, art. 4.3. See also K S Ziegler, 'The Relationship between EU Law and International Law' in D Patterson and A Södersten (eds.), *A Companion to European Union Law and International Law* (Malden, John Wiley & Sons 2016) 42–61.

[154] TEU, art. 6.3.

[155] Craig and de Búrca, *EU Law* (n 147) 380.

[156] Ibid., 385. For example, the Court of Justice has cited the UN Convention on the Rights of the Child in Case C-540/03 *European Parliament* v. *Council* (2006) ECR I-5769, (57) and the UN Convention on the Rights of Persons with Disabilities (which the EU ratified in 2010) in Case C-354/13 *FOA* v. *Kommunernes Landsforening (Kaltoft)* EU:C:C:2014:2463 (53).

[157] See, e.g., Case C-5/12, *Marc Betriu Montull* v. *Instituto Nacional de la Seguridad Social* ECLI:EU:C:2013:571 and Case C-73/08 *Nicolas Bressol and Others and Céline Chaverot and Others v Gouvernement de la Communauté française* ECLI:EU:C:2010:181.

[158] See judgment of the Court of Justice on 3 June 2010 in Case C-237/09 *État belge* v. *Nathalie De Fruytier* ECLI:EU:C:2010:316.

Moreover, it is unclear whether the sources of EU human rights law include customary international law,[159] including the Universal Declaration of Human Rights, which proclaims the right of everyone to share in scientific advancements and its benefits,[160] Even if the Court of Justice sometimes cites the Universal Declaration of Human Rights in its judgments, it is when the Declaration refers to so-called general principles of EU law, such as the principle of non-discrimination, in preliminary rulings.[161] Beyond this, the case law of the Court of Justice reveals reluctance to discuss international human rights law as a matter of customary international law, and instead prefers to read them in the EU Charter and the European Convention on Human Rights.[162] Indeed, even if many provisions of the EU Charter 'are themselves based on international human rights instruments, as the explanatory notes to the Charter indicate, those international instruments and the courts or bodies established to interpret them have not yet – apart from the European Convention on Human Rights and Court of Human Rights – been treated as influential or persuasive authority in the interpretation by the ECJ of Charter provisions'.[163]

Against this background, it is unlikely the 'right to science' and the 'rights of science' contained in the Covenant on Economic, Social and Cultural Rights and the Universal Declaration of Human Rights could be successfully invoked before the Court of Justice and other EU institutions. The Court of Justice's emphasis on the autonomy of the EU legal order in relation to international law in its recent case law, particularly when rejecting the draft Agreement on Accession of the European Union to the ECHR, indicates a reluctance to rely on and subordinate itself to international human rights instruments and mechanisms.[164] Moreover, should the right to science one day be included in the EU Charter, it will probably find its place alongside the right to health and other solidarity rights that require the adoption of specific legislation by

[159] S Besson, 'General Principles and Customary Law in the EU Legal Order', in S Vogenauer and S Weatherill (eds.), *General Principles of Law. European and Comparative Perspectives* (Hart Publishing 2017) 105–129.

[160] UDHR, art. 27.1.

[161] See, e.g., C-144/04 *Mangold* ECLI:EU:C:2005:709 and C-411/05 *Palacios de la Villa* ECLI:EU:C:2007:604. But note that in Case C-135/08 *Rottmann* ECLI:EU:C:2010:104, the Court of Justice of the European Union cites Article 15 of the Universal Declaration of Human Rights (related to the right to nationality).

[162] Cases C-402 and 415/05 *P Kadi & Al Barakaat International Foundation* v. *Council and Commission (Kadi I)* (2008) ECR I-6351, (308); and Case 584/10 P *Commission* v. *Kadi (Kadi II)* EU:C:2013:518.

[163] Craig and de Búrca, *EU Law* (n 147) 387.

[164] Opinion 2/13 on EU Accession to the ECHR EU:C:2014:2454 (192).

member states or the European Union itself before the right can be judicially enforced before courts.[165]

c Relevant Regulations and Directives

The key legal instruments of the European Union are 'regulations' and 'directives'. A 'regulation' is specific legislation that, once it has entered into force, is self-executing and is immediately and directly applicable across the Union.[166] EU member states are not obliged to transform EU regulations into national regulations except for when required by the regulation itself or required to ensure its effectiveness.[167] Conversely, a 'directive' just sets out goals that all EU states must achieve, leaving it up to each of these states to devise and adopt their own laws on how to reach them.[168]

In the case of 'directives' EU states are given some discretion and time to define the measures needed to give effect to them, while they have no such leeway when it comes to 'regulations'.[169] EU directives are not directly applicable in the sense of being automatic and general in application, and affording rights without further implementation. However, there are directives that give rise to directly enforceable rights in specific circumstances, such as when a directive has not been implemented at all or has been implemented incorrectly.[170]

In either case, EU member states have the primary responsibility to enforce EU regulations and directives within their jurisdictions. The national courts of EU member states have an important function in enforcing EU law. Regulations have 'direct effect' in the sense of being enforceable in national courts provided the provisions are clear and precise, as well as unconditional,

[165] For the distinction between 'rights' and 'principles', see EU Charter, art. 52.5. Several *rights* recognized in the ICESCR are understood as *principles* in EU law. In practice, this means that these rights will be justiciable only following implementing acts of the European Union or the member states and only in relation to interpretation or rulings on the legality of such acts. See Craig and de Búrca, *EU Law* (n 147) 398–399.

[166] TFEU, art. 288: 'A regulation shall have general application. It shall be binding in its entirety and directly applicable in all member states.'

[167] Case 39/72 *Commission* v. *Italy* ECLI:EU:C:1973:13; and Case 128/78 *Commission* v. *United Kingdom* ECLI:EU:C:1979:32.

[168] Other legal acts of the EU include 'decisions' that are binding on those to whom it is addressed and is directly applicable. By contrast, neither 'recommendations' nor 'opinions', while defined as legal acts, have any legal consequences since they are not binding.

[169] TFEU, art. 288: 'A directive shall be binding as to the results to be achieved, upon each member state to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

[170] N Foster, *Foster on EU Law* (6th ed., Oxford, Oxford University Press 2017) 120–121.

and do not require implementing measures by the member states or the European Union itself that give them discretion.[171] Such regulations have 'vertical direct effect', meaning individuals can invoke the rights recognized in them against EU member states, and 'horizontal direct effect', meaning individuals can invoke them against other individuals. Also directives can give rise to direct effect provided their provisions meet the mentioned criteria concerning clarity, precision, etc.[172] and the time limit for implementing the directive has expired.[173] However, unlike regulations, directives only have vertical, not horizontal, effect.[174]

EU law-making procedures are notoriously complex even if the Lisbon Treaty rationalized them, at least to some extent. There are now essentially three ways in which laws are made in the European Union of which the most important one is the 'ordinary legislative procedure', the normal method for making EU legislation.[175] The legislative process is initiated by a Commission proposal.[176] Under the 'ordinary legislative procedure', EU legislation, such as a regulation or a directive, is adopted jointly by the Parliament and the Council.[177]

Whether and to what degree the European Union can legislate on a given issue or process varies and depends on its competences in specific fields. The EU law-making competences in different areas are not necessarily exclusive but often shared with EU states (e.g. in the case of internal market, research,

[171] Case 26/62 *Van Gend Loos* ECLI:EU:C:1963:1

[172] Case 9/70 *Grad* ECLI:EU:C:1970:78; and Case 41/74 *Van Dyjn* v. *Home Office*, ECLI:EU:C:1974:133.

[173] Case 148/78 *Public Ministero* v. *Ratti* ECLI:EU:C:1979:110. Also see Case C-144/04 *Mangold* ECLI:EU:C:2005:709, according to which the time limit is not applicable if unimportant.

[174] Case 152/84 *Marshall* v. *Southhampton Area Health Authority* ECLI:EU:C:1986:84.

[175] The 'ordinary legislative procedure' is detailed in art. 294 of the TFEU. The other two law-making procedures are the 'special legislative procedure' (TFEU, art. 289.2–4) and the 'consent procedure'. The consent procedure means that the European Parliament's consent is required by the Council concerning membership applications to the European Union, the Union's membership of international agreements and organizations, and association agreements with third countries (TEU, arts. 49 and 50; TFEU, arts: 218 and 217). For EU law-making procedures, see Foster, *Foster on EU Law* (n 170) 132–136.

[176] But note TFEU, art. 289.4: 'In the specific cases provided for by the Treaties, legislative acts may be adopted on the initiative of a group of Member States or of the European Parliament, on a recommendation from the European Central Bank or at the request of the Court of Justice or the European Investment Bank.'

[177] TFEU, art. 289.1: 'The ordinary legislative procedure shall consist in the joint adoption by the European Parliament and the Council of a regulation, directive or decision on a proposal from the Commission. This procedure is defined in Article 294.' As defined in Article 294 of the TFEU, the co-decision procedure is central to the Community's law-making procedures. It is based on the principle of parity and means that neither institution (European Parliament or Council) may adopt legislation without the other's assent.

and common safety concerns in public health matters),[178] or supplementary to state competences (e.g. in the case of public health).[179] This complex arrangement reflects the centrality of shared competence areas within the European Union and the question when it may act in these areas. The general thrust is that EU action should be taken as openly and as closely as possible to the citizens, and must respect the 'subsidiarity principle', which states that the Union acts 'only if and insofar as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at the central level or at regional or local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at the Union level'.[180] Also relevant is the proportionality principle, according to which the European Union shall act only when deemed necessary.[181] However, the practical significance of these principles remains unclear. This renders the areas falling under 'shared competences' especially complex.

Most EU legislation related to human germline genome modification is the result of EU exercise of 'shared competence' in the area of the 'internal market'.[182] Here the European Union is granted subsidiary law-making power to provide for measures to complete the internal market and for the harmonization of laws affecting the establishment and functioning of the internal market.[183] More specifically, the Union 'shall adopt measures with the aim of establishing or ensuring the functioning of the internal market . . . [which] shall comprise an area without internal frontiers in which the free movement of good, persons, services and capital is ensured'.[184] To achieve this objective, '[t]he European Parliament and the Council shall, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States'.[185] The Commission, when making proposals on measures concerning 'health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. Within their respective powers, the European Parliament and the Council will also seek to achieve this objective.'[186]

[178] TFEU, art. 4.2.
[179] Ibid., art. 6.
[180] Ibid., art. 5.
[181] Ibid., art. 5.2.
[182] Ibid., art. 4.2.a.
[183] Ibid., arts. 114 and 115.
[184] Ibid., art. 26.
[185] Ibid., art. 114.1.
[186] Ibid., art. 114.3.

Other relevant EU legislation has been adopted on the basis of 'common safety concerns in public health matters'.[187] Article 168.4 of the TFEU gives the European Parliament and the Council a specific mandate to adopt: (a) 'measures setting high standards of quality and safety of organs and substances of human origin'; (b) 'measures in the veterinary and phyto-sanitary fields which have as their direct objective the protection of public health'; and (c) 'measures setting high standards of quality and safety for medicinal products and devices for medical use'.

The EU efforts to achieve the established objectives related to the internal market as well as health and safety concerns have generated several directives and regulations that are relevant for the topic in this book. The question of human germline genome modification arose for the first time in the context of the consideration of legislation to harmonize the protection of biotechnological inventions across the Union to facilitate investment in biotechnology. The action was justified by the Union's shared competence in the field of internal market, specifically to harmonize national laws in the field of intellectual property.[188] It resulted in the adoption in 1998 of Directive 98/44/EC on the Legal Protection of Biotechnological Inventions (Biotech Directive).[189] Although ethical and human rights considerations had not put the question on the EU agenda, they played a major role in the deliberations, delaying the adoption of the Directive for almost ten years. In the end, the Biotech Directive incorporated a well-established rule found in patent law of all developed countries and in international treaties, according to which inventions are not patentable if they are contrary to public order or morality. The Biotech Directive considers processes for cloning of human beings, processes for modifying the germline genetic identity of human beings and uses of human embryos for industrial or commercial purposes not patentable.[190]

[187] TEU, art. 4.

[188] Case 377/98 *Netherlands* v. *Parliament* and *Council* ECLI:EU:C:2001:523. This case was an unsuccessful application for annulment of the Biotech Directive on the ground that it had been incorrectly adopted on the basis of Article 100a of the EC Treaty (art. 95 following the entry into force of the Amsterdam Treaty and art. 114 of the TFEU).

[189] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213, 13–21. This directive was adopted on the basis of Article 100a of the EC Treaty (Article 95 following the entry into force of the Treaty of Amsterdam and Article 114 following the entry into force of the Lisbon Treaty).

[190] See Article 6 of the Biotech Directive. The same exceptions are included in the Implementation Regulations of the European Patent Convention of 1977 as revised in 2000. According to Rule 28 concerning the implementation of article 53(a) of this Convention: 'European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following: (a) processes for cloning human beings; (b)

Following the adoption of the Biotech Directive, the European Union has adopted several other directives and regulations that are relevant for human germline modifications, including:

(i) Directive 2001/20/EC on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use ('Clinical Trials Directive');[191]

(ii) Regulation 536/2014 of the European Parliament and of the Council of 16 April 2004 on Clinical Trials on Medicinal Products for Human Use, repealing Directive 2001/20/EC ('Clinical Trials Regulation');[192]

(iii) Directive 2004/23 of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells ('Human Tissues and Cells Directive');[193]

(iv) Regulation 1394/2007 of the European Parliament and the Council of 13 November 2007 on Advanced Therapy Medicinal Products, amending Directive 2001/83/EC and Regulation (EC) No 726/2004 ('Advanced Therapy Regulation');[194] and

processes for modifying the germ line genetic identity of human beings; and (c) uses of human embryos for industrial or commercial purposes.'

[191] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 34–44.

[192] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance, OJ L 158, 27.5.2014, 1–76.

[193] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 48–58. See also Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

[194] 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 (Text with EEA relevance), OJ L 324, 121–137.

(v) Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes ('Animal Protection Directive').[195]

Among them, the most important ones are the first two: the 2001 Clinical Trials Directive and the 2014 Clinical Trials Regulation, which will replace the former in 2019. The aim of the Clinical Trials Directive is to harmonize laws related to clinical trials of medicinal products across the European Union. Although it permits clinical trials involving medical products for 'gene therapy, somatic cell therapy, including xenogenic cell therapy and all medicinal products containing genetically modified organisms', it imposes a ban on gene therapy trials 'which can result in modifications to the subject's germ line genetic identity'.[196] The Clinical Trials Regulation was adopted to make it easier to conduct multicentre clinical trials involving several EU states and to improve transparency of information so as to avoid unnecessary duplication of trials.[197] It reaffirms the ban of gene therapy trials which can result in modifications to the subject's germline genetic identity.[198] Additionally, it requires EU states to specify penalties applicable to infringements of its rules and to 'take all measures necessary to ensure that they are implemented'.[199]

Finally, the European Union shares competences with member states in the field of research.[200] According to primary EU law, 'in the areas of research, technological development and space, the Union shall have competence to carry out activities, in particular to define and implement programs; however, the exercise of that competence shall not result in member states being prevented from exercising theirs'.[201] In this regard, the European Parliament and the Council, acting in conformity with the ordinary legislative procedure after consulting the Economic and Social Committee, shall adopt multi-annual 'Framework Programmes' setting out the objectives to be achieved in the fields of research and technological development, including the amount of the EU budget allocated to Union financial participation in these

[195] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes Text with EEA relevance, OJ L 276, 33–79.
[196] Clinical Trials Directive, art. 9.6.
[197] This will be achieved through the creation of a single EU clinical trial portal and database by the European Medicines Agency that will also manage it.
[198] Clinical Trials Regulation, art. 90.
[199] Ibid., art. 94.
[200] TEU, art. 4.
[201] TFEU, art. 4.3.

programmes.[202] These are the so-called Framework Programmes for Research and Technological Development created by the Union to support and foster research in what has been coined the 'European Research Area'.[203] The specific objectives and actions of these programmes vary between funding periods. So far, there have been eight 'Framework Programmes' (FP). The focus of FP8, also known as Horizon 2020, is innovation, delivering economic growth faster and delivering solutions to end users.[204] The budget of FP8 (2014–2020) is about 77 billion euros. The Commission has proposed to increase it to 97.6 billion euros for the follow-up programme (FP9 – Horizon Europe) that will run from 2021 to 2027.

Horizon 2020 was established by EU Regulation 1291/2013.[205] It is the result of the EU exercise of its competences in the field of research to achieve the objective of ensuring that the conditions for the competitiveness of the Union's industry exists through the adoption of specific measures, excluding the harmonization of national laws.[206] Article 19 of this regulation specifies the fields of research not eligible for funding. Among them there is 'research activity intended to modify the genetic heritage of human beings which could make such changes heritable', while exempting 'research relating to

[202] TFEU, art. 182.1.

[203] TFEU, art. 179.1. In line with this article: 'The Union shall have the objective of strengthening its scientific and technological bases by achieving a European research area in which researchers, scientific knowledge and technology circulate freely, and encouraging it to become more competitive, including in its industry, while promoting all the research activities deemed necessary by virtue of other Chapters of the Treaties.'

[204] In the first three years of Horizon 2020's implementation, the main beneficiaries of the programme have been higher education and research organizations, which together received 64.9% of the funding, the private sector receiving 27.7% and public authorities and other types of organizations 7.3%. European Commission, 'Key Findings from the Horizon 2020 Interim Evaluation' (European Commission, 2017) 4 https://ec.europa.eu/research/evaluations/pdf/brochure_interim_evaluation_horizon_2020_key_findings.pdf accessed 12 October 2018.

[205] Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 – the Framework Programme for Research and Innovation (2014–2020) and repealing Decision No 1982/2006/EC Text with EEA relevance, OJ L 347 (Horizon 2020 Regulation) 104–173. This regulation was adopted on the basis of Articles 173.3 and 182.1 of the TFEU. The first article refers to policies and activities to achieve the Union's commitments. Its adoption was motivated by the Union's commitment to foster 'better exploitation of the industrial potential of policies of innovation, research and technological development'. The latter article states that the European Parliament and the Council, acting in accordance with the ordinary legislative procedure after consulting the Economic and Social Committee, shall adopt a 'multiannual framework programme, setting out all the activities of the Union'. The framework shall establish the scientific and technological objectives to be achieved in the field of research and technological development.

[206] TFEU, art. 173.3.

cancer treatment of the gonads', which can be financed. Also excluded from EU funding is 'research activity aiming at human cloning for reproductive purposes' and 'research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer'. Finally, while research on human stem cells may be financed, depending both on the contents of the scientific proposal and on the legal framework of the member states involved, 'no funding shall be granted for research activities that are prohibited in all the Member States'. Furthermore, 'no activity shall be funded in a member state where such activity is forbidden'.[207]

Overall, although the European Union is famous – or infamous, its detractors would say – for regulating issues down to the smallest detail, when it comes to biotechnology, its directives and regulations are surprisingly vague. For instance, the Human Tissues and Cells Directive does not define 'gametes', 'eggs', 'sperm', 'adult stem cells' and 'embryonic stem cells', although they are its main object. It does not univocally define an 'embryo' either.[208] Although 'human embryos' are mentioned several times in the Biotech Directive and the Horizon 2020 Regulation, neither defines them.[209] EU law does not specify what 'activities which can result in modifications of germ line genetic identity'[210] or what activities 'intended to modify the genetic heritage of human beings which could make such changes heritable'[211] are. It does not clarify when a genetic modification becomes inheritable. Also, albeit EU law bans general research involving human germline genome modification, the ban is not formulated identically in various pieces of legislation. For instance, whereas the Biotech Directive concerns

[207] Horizon 2020 Regulation, art. 19.4.

[208] In 2016, the EU Expert Group on the Development and Implications of Patent Law in the field of Biotechnology and Genetic Engineering discussed the meaning of human embryo. In its report, it posed the question whether a further clarification of human embryo is needed as new technologies become available, like the artificial creation of human germ cells that could lead to the artificial creation of human embryos as entities. It concluded that if these entities are inherently capable of developing into a human being, they, too, must be considered human embryos. Therefore, for the purpose of the Biotech Directive, an embryo produced by means of artificial germ cells should be treated in the same way as natural embryo produced by the fusion of an oocyte and a sperm cell and that no further clarification is needed. Final Report of the Expert Group on the Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering (E02973), 17 May 2016, 145.

[209] See Article 6.2.c of the Biotech Directive concerning the unpatentability of uses of human embryos for industrial or commercial purposes, and Article 19 of the Horizon 2020 Regulation concerning the non-eligibility for EU funding of research activity limited to create human embryos solely for the purpose of research or for the purpose of stem cell procurement.

[210] Clinical Trials Regulation, art. 90.

[211] Horizon 2020 Regulation, art. 19.

modifications of 'the genetic heritage of human beings',[212] the Clinical Trials Directive/Regulation refers to modifications to 'the subject's germ line identity'.[213] The language changes somewhat again in the Horizon 2020 Regulation, which talks about modifications of 'the genetic heritage of human beings which could make such changes heritable'.[214]

The vagueness of EU legislation in this area may be explained in the light of the subsidiarity principle that governs and limits EU efforts to harmonize national laws in this area. In areas where the EU has shared competence, intervention by the Union is permissible only when the objectives of an action cannot be sufficiently achieved by the member states, but can better be achieved at the Union level, 'by reason of the scale and effects of the proposed action'.[215] At the same time, as will be discussed in the next section, the case law of the CJEU seems to reveal the importance of providing an EU definition of 'embryos'.

All in all, the lack of clarity is perplexing if one considers that the European Union prides itself on its transparent legislative process, one where the public has ample opportunities to weigh in. If these vague provisions confuse experts, it is hard to see how the wider public could be able to debate their merits.[216] Also, the vagueness of EU legislation on the matter is even more striking if one compares it with the very detailed and sophisticated EU legal regime in place for genetically modified plants and animals (genetically modified organisms – GMO).[217]

d Decisions of the Court of Justice of the European Union

The Court of Justice of the European Union is the principal judicial organ of the European Union and its mission is to ensure that the law is observed in the interpretation and application of the treaties of the European Union and secondary legislation.[218] To this end, it reviews the legality of actions taken by

[212] Clinical Trials Directive, art. 9.6.
[213] Ibid., art. 90.
[214] Horizon 2020 Regulation, art. 19.
[215] TEU, art. 5.c.
[216] See, e.g., EU Expert Group on Ethics, Science and Technology, Statement on Gene Editing (2016).
[217] On the regulation of GMOs in the EU, see M Weimer, *Risk Regulation in the Internal Market: Lessons from Agricultural Biotechnology* (Oxford University Press 2019).
[218] On the CJEU, see, in general, T Horsley, *The Court of Justice of the European Union as an Institutional Actor: Judicial Lawmaking and its Limits* (Cambridge University Press 2018), and SK Schmidt, *The European Court of Justice and the Policy Process: The Shadow of Case Law* (Oxford University Press 2018).

the EU's institutions, enforces compliance by member states with their obligations, in co-operation with the national judiciary of the member states, and interprets EU law. The CJEU also resolves legal disputes between national governments and EU institutions, and may take action against EU institutions on behalf of individuals, companies or organizations whose rights have been infringed.

The CJEU consists of two main courts: the 'Court of Justice' and the 'General Court'. The Court of Justice, formerly known as the European Court of Justice (ECJ), is the supreme court of the European Union. It consists of one judge from each EU member country, as well as 11 Advocates General. Each Advocate General is a non-voting member of the Court who delivers an impartial opinion to the other judges on the legal issues raised in the case. It rules on applications from national courts for 'preliminary rulings', and certain actions for annulment and appeal. The General Court, composed of 47 judges (to be increased to 56 in 2019), hears applications for annulment from individuals, companies and, less commonly, national governments, focusing on competition law, state aid, trade, agriculture and trademarks.

Over the years, the CJEU has decided a few cases that touch upon issues relevant for a discussion of human genome modification. The most relevant ones are *Brüstle* v. *Greenpeace* and *International Stem Cell Corporation* v. *Comptroller General of Patents, Designs and Trade Marks*. In 2012, in *Brüstle* v. *Greenpeace*, the CJEU was called to define the term 'human embryo' for the purpose of the interpretation and application of the Biotech Directive.[219] The case stemmed from a dispute between Greenpeace and Dr Oliver Brüstle, a German scientist known for his research on stem cells. Greenpeace sought the annulment of a German patent for a biotechnological invention made by Dr Brüstle concerning neural precursor cells (i.e. immature body cells capable of forming mature cells in the nervous system, such as neurons) and, specifically, the processes for their production from embryonic stem cells and their use for therapeutic purposes. According to Greenpeace, the patent violated the ban on using human embryos for industrial or commercial purposes contained in the Biotech Directive. The German Federal Court of Justice (*Bundesgerichthof*), before which the case was pending, raised with the CJEU the issue of what the Biotech Directive means by 'human embryo' and by 'use for industrial or commercial purposes', especially where the embryo is used for the purposes of scientific research.

[219] Case C-34/10. *Oliver Brüstle* v. *Greenpeace eV*. (Reference for a preliminary ruling from the Bundesgerichtshof), Judgment of the Court of Justice (Grand Chamber) of 18 October 2011. E.C.R. 2011 I-09821.

The CJEU started by emphasizing that the letter of Article 6.2 of the Biotech Directive and its object and aim lead to the observation that the concept of 'human embryo' 'constitutes an autonomous concept of Union law which must be interpreted in a uniform manner throughout its territory'.[220] In fact, the lack of a uniform definition would induce the authors of certain biotechnological inventions to seek registration in the jurisdiction with the least restrictive definition of an embryo, which would adversely affect the smooth functioning of the internal market. Then it pointed out that the Biotech Directive seeks to promote investment in the field of biotechnology, while specifying that the use of biological material originating from humans must be consistent with regard for fundamental rights and, in particular, the dignity of the person.[221] In this light, it proceeded to define the 'human embryo' as 'any human ovum . . ., as soon as fertilised, . . . since . . . fertilisation is such as to commence the process of development of a human being'.[222] Moreover, the same applies to a non-fertilized human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilized human ovum whose division and further development have been stimulated by parthenogenesis, because, even if those organisms have not, strictly speaking, been the object of fertilization, due to the effect of the technique used to obtain them, they are 'capable of commencing the process of development into a human being just as an embryo created by fertilization can do so'.[223]

Ultimately, the CJEU left to national courts to determine whether the specific patent application that gave rise to the case could be granted in light of the principles laid out by the Court.[224] In addition, the Court ruled that the exclusion of patentability 'concerning the use of human embryo for industrial or commercial purposes [in the Biotech] Directive also covers use for purposes of scientific research'.[225] However, use of human embryos that is both for therapeutic or diagnostic purposes and useful is patentable.[226] Lastly, the Court specified that the Biotech Directive excludes the patentability of inventions whose production necessitates the prior destruction of human embryos or their use as a base material.[227]

[220] Ibid., para. 26.
[221] Ibid., para. 32.
[222] Ibid., para. 35.
[223] Ibid., para. 37.
[224] Ibid., para. 38.
[225] Ibid., para. 46.
[226] Ibid.
[227] Ibid., para. 52.

International Stem Cell Corporation v. *Comptroller General of Patents, Designs and Trade Marks* offered the Court a chance to partially backtrack the *Brüstle* decision, which many saw as a threat to stem cell research in Europe.[228] This case was about a lawsuit brought against the UK Patent Office by International Stem Cell Corporation, a California-based 'publicly traded clinical stage biotechnology company',[229] for refusing to register two national patent applications related to the use of chemical or electrical techniques to activate unfertilized human eggs. The legal issue stemmed from the fact that this process, called 'parthenogenetic activation', stimulates ova in a way which is similar, at least initially, to the process by which an embryo forms from a fertilized egg.

Implementing the Biotech Directive, and citing the CJEU decision in *Brüstle*, the UK Patent Office declined registration of the patents on the ground that they violated UK law, and specifically the rule on non-patentability of the commercial and industrial exploitation of human embryos. The Chancery Division (Patents Court) of the High Court of Justice England and Wales referred the matter to the CJEU, requesting it to clarify whether 'unfertilised human ova whose division and further development have been stimulated by parthenogenesis, and which, in contrast to fertilised ova, contain only pluripotent cells and are incapable of developing into human beings' are covered by the Biotech Directive's ban of patentability.[230]

The Court noted that the written observations filed before it in *Brüstle* indicated that parthenotes (activated ova) did have the capacity to develop into a human being.[231] However, in the present case, the parties agreed that, according to current scientific knowledge, parthenotes are not capable of commencing the process of development that leads to a human being.[232] Because of these considerations, the CJEU concluded that parthenotes would not, in and of themselves, constitute human embryos, provided that they are not inherently capable of developing into human beings. It also introduced a caveat when it held that the ruling did not concern parthenotes

[228] Case-364/13, *International Stem Cell Corporation* v. *Comptroller General of Patents, Designs and Trade Marks*. Request for a preliminary ruling under Article 267 TFEU from the High Court of Justice (England & Wales), Chancery Division (Patents Court) (United Kingdom), made by decision of 17 April 2013, received at the Court on 28 June 2013. Judgment of the Court of Justice on 18 December 2014, para. 38.

[229] See International Stemcell Corporation, 'Cells for Research and Therapy' http://internationalstemcell.com/ accessed 12 October 2018.

[230] Case-364/13, para. 20.

[231] Ibid., para. 32.

[232] Ibid., para. 33.

subjected to additional genetic manipulation.[233] The CJEU said that the question of whether a parthenote is inherently capable of developing into a human being was one which the referring court should determine 'in light of current scientific knowledge'.[234]

This decision altered once more the European patenting regime for human embryonic stem cell (hESC) applications, by stating that moral restrictions against hESC patents are only applicable to such cells derived from embryos that had the potential to develop into a human being. Consequently, human parthenogenic stem cells (hpSCs)-based inventions became patentable in Europe.

Overall, the *International Stem Cell Corporation* revealed a Court that struggles with basic science and that is ready to backtrack previous decisions if it is presented new, undisputed, scientific evidence. The decision was welcomed as a step forward towards striking a balance between protecting human dignity and integrity while granting patent incentives for biomedical research, although some took exception with it because the ruling leaves considerable discretion to national courts. Furthermore, the ruling is limited to very specific human embryonic stem cells and does not clarify if it extends to other non-totipotent human embryonic stem cells, such as stem cells created through somatic cell nuclear transfer.[235]

d Oversight and Supervisory Bodies

Besides the CJEU, several EU bodies, committees and agencies monitor and supervise the Union's legal regime regulating research on human embryos. Even if the main responsibility for enforcement rests with the individual member states, the European Commission, including its Expert Group on Ethics in Science and Technology, has important functions with respect to monitoring, supervision and advice, as does the European Research Council, which is responsible for EU funding, and the Court of Justice of the European Union, as we just saw.

i The European Commission

EU states are responsible for giving effect to the laws, regulations and administrative provisions necessary to comply with the Biotech Directive, and for

[233] Ibid., para. 35.
[234] Ibid., para. 36.
[235] A Nordberg and T Minssen, 'A "Ray of Hope" for European Stem Cell Patents or "Out of the Smog into the Fog"? An Analysis of Recent European Case Law and How it Compares to the US' (2016) 47:2 *International Review of Intellectual Property and Competition Law* 138, 138–177.

informing the Commission about the actions taken.[236] The Commission, for its part, has several reporting obligations to the European Parliament and the Council related to implementation. For a start, every five years, it must report any problems encountered in the relationship between the Biotech Directive and international human rights treaties ratified by the EU states.[237] Moreover, within two years of entry into force of this directive, it must issue a report assessing the implications for basic genetic research of failure to publish, or late publication of, papers on subjects which could be patentable.[238] Also, it must report annually to the same institutions on the development and implications of patent law in the field of biotechnology and genetic engineering.[239] In 2012, the Commission set up an Expert Group to prepare the annual reports.[240] However, this group does not address any ethical issues. These are the remit of the European Group on Ethics in Science and New Technologies, which we will discuss later.

EU states are also responsible for the enforcement of the Clinical Trials Regulation once it enters into force in 2019 by adopting the administrative provisions and penalties necessary to comply with it. Moreover, each EU state must set up an Ethics Committee consisting of healthcare professionals and non-medical members responsible for protecting the rights, safety and well-being of human subjects involved in trials.[241] The Ethics Committees issue opinions on the ethical aspects of clinical trials before they begin, at the request of the competent authority of the member state. A clinical trial cannot go ahead unless the national Ethics Committee has approved it. Written (as opposed to tacit) authorization is a must for clinical trials of medicinal products for gene therapy, somatic cell therapy, including xenogenic cell therapy, and the like.[242]

The Clinical Trials Regulation seeks to improve existing administrative procedures by establishing a streamlined application procedure for patent authorization via the creation of a single entry point – an EU portal and database – for all clinical trials conducted in the European Union. When the Regulation enters into force in 2019, registration via the portal will be a requisite for the assessment of any application, although, again, the final

[236] Biotech Directive, art. 15.
[237] Ibid., art. 16.a.
[238] Ibid., art. 16.b.
[239] Ibid., art. 16.c.
[240] Commission Decision of 7.11.2012 on setting up a Commission Expert Group on Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering (C(2012) 7686 final).
[241] Clinical Trials Directive, art. 6.
[242] Ibid., art. 9.2.

authorization and oversight of clinical trials will remain the responsibility of member states. The European Commission will supervise this process through the collection and distribution of national reports on trial results. It will also grant market authorizations of new medicinal products following a scientific evaluation made by the European Medicines Agency (EMA), which will manage the EU single portal and database. It should also be mentioned that the EMA and the Commission produce guidelines to harmonize practice. For instance, in 2006, EMA issued a guideline on inadvertent germline transmissions, recommending the conduct of non-clinical studies to prevent involuntary transgressions of the ban on human germline modifications.[243]

II THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES

In 1991, the Commission set up an expert group called the European Group on Ethics in Science and New Technologies (EGE). The EGE is an independent body of the President of the Commission that gives advice on all aspects of Commission legislation and policies where ethical, societal and fundamental rights dimensions intersect with the development of science and new technologies.[244] It is composed of 15 members – independent experts from diverse academic fields – who are appointed by and report to the Commission President, although it provides advice to the Commission College as a whole.

The EGE has a Secretariat, supported by the Commission, whose mandate is to integrate ethics at the international and inter-institutional levels, including within the Commission itself. The Secretariat also constitutes a platform for the Commission's International Dialogue on Bioethics, a forum that brings together the national ethics councils of 97 states (the 28 EU states, plus the states of the G20 forum and others). Additionally, the Secretariat represents the European Union in liaising with international organizations relevant for the ethical implications of science and new technologies (e.g. the UN and its agencies, the OECD and the Council of Europe). Moreover, it chairs and convenes the inter-service group on Ethics and EU policies, which

[243] European Medicines Agency, Guideline on Non-Clinical Testing for Inadvertent Germline Transmission of Gene Transfer Vectors, 16 November 2006, Doc. Ref. EMEA/273974/2005.

[244] See European Commission, 'The European Group on Ethics in Science and New Technologies (EGE) http://ec.europa.eu/research/ege/index.cfm accessed 12 October 2018. For the EGE mandate, see Commission Decision SEC (97) 2404 of 16 December 1997; Amendment to the Remit: Commission Decision C(2001) 691 of 26 March 2001; Renewal of the Remit: Commission Decision 2005/383/EC of 11 May 2005; Renewal of Mandate: Commission Decision 2010/1/EU of 23 December 2009; Renewal of the Mandate: Commission Decision (EU) 2016/835 of 25 May 2016.

coordinates Commission activities in the field of bioethics and ethics of science and new technologies of growing importance for the European Union.

So far, the EGE has published 29 opinions and 3 statements on a range of critical issues, including on animal welfare, genetically modified organisms, biodiversity, nanotechnology, and stem cell research.[245] Of these, some have particular relevance for the purpose of this book, such as the two opinions produced during the process of drafting the Biotech Directive,[246] and its comment on the use of human embryos in EU-funded research.[247] More recently, it issued two statements, one on research integrity and another one on gene editing.[248] Some of these opinions/statements address the ethical defensibility of human germline engineering.

The Commission's drafting of what came to be the Biotech Directive prompted the EGE to issue two opinions. In the first, which it drafted on its own initiative, it promoted an open-minded view on the idea of patenting inventions related to gene editing but also held that certain types of genetic manipulations should be prohibited and that this should be 'mainly a matter to be dealt with under the competent branches of public law dealing with the use and commercialization of research results in respect to public safety, health, environment and animal welfare'.[249] While acknowledging 'the need to reaffirm the ban on genetic engineering for non-therapeutic purposes, contrary to the dignity of man', the EGE also felt that the Biotech Directive was 'not the right place to deal with the very complex issue of the legitimacy of germinal therapy'.[250] Instead, these concerns should be considered mainly in its recitals.

The following year, the EGE issued a second opinion on a new draft of the Biotech Directive. This opinion endorses the patentability of somatic gene therapy for its potential to cure serious diseases and because the use of new therapeutic products in this field could be of great interest for the development of EU biotechnological industry.[251] It then noted that 'because of the

[245] European Commission, 'EGE Reports, Opinions, and Statements' https://ec.europa.eu/research/ege/index.cfm?pg=reports accessed 11 October 2018.

[246] EGE Opinion No 3 on Ethical Questions Arising From the Commission Proposal for a Council Directive for Legal Protection of Biotechnological Inventions (1993); and EGE Opinion No 4 on Ethical Implications of Gene Therapy (1994).

[247] EGE Opinion No 12 on Ethical Aspects of Research Involving the Use of Human Embryo in the Context of the 5th Framework Program (1998).

[248] Statement on the Formulation of a Code of Conduct for Research Integrity for Projects Funded by the European Commission (2015); and Statement on Gene Editing (2016).

[249] EGE Opinion No 3, para. 2.2.3.

[250] Ibid., para. 2.2.3.

[251] EGE Opinion No 4, para. 1.6.

important controversial and unprecedented questions raised by germ line therapy, and considering the actual state of the art, germ line gene therapy on humans is not at the present time ethically acceptable'.[252]

Thereafter, it took more than 20 years for EGE to return to this question, and when it did it was because of the rapid development in gene technologies, such as CRISPR-Cas9, which had moved human germline genome modification 'out of the realm of the theoretical', meaning that clinical applications are becoming feasible.[253] This development led the group to issue a statement on gene editing to promote a new debate on how to respond to the challenges posed to the international regulatory environment. The statement stresses that a pressing question is whether germline editing technology research should be suspended, which requires careful consideration given the profound potential consequences of this research for humanity.[254] It also points to the challenge posed by human germline engineering when it blurs the lines between basic and translational research, on the one hand, as well as between therapeutic and enhancement goals in clinical applications, on the other.[255] In response to disagreement among the members of the group whether continued research should be allowed, the EGE called for a debate on the acceptability and desirability of gene editing. This debate should go beyond expert committees and engage civil society and touch upon safety issues and potential health risks or benefits of gene editing technologies as well as human dignity, justice, equity, proportionality and autonomy.[256] So far, this proposal has not generated any EU-sponsored initiatives to promote such a debate.

III THE EUROPEAN RESEARCH COUNCIL

The European Research Council (ERC), which was set up by the European Commission in 2007, is responsible for managing the Horizon 2020 programme. To ensure respect for EU-imposed ethical rules and restrictions, including those under international law,[257] the ERC has set up an Ethical Appraisal Procedure to

[252] Ibid., para. 2.7.
[253] EGE Statement on Gene Editing (2016) 1.
[254] Ibid., p. 2.
[255] Ibid.
[256] Ibid.
[257] Horizon 2020 Regulation, art. 19: 'All the research and innovation activities carried out under Horizon 2020 must respect ethical principles and relevant national, EU and international legislation, including the EU Charter and the ECHR and its Additional Protocols'. Furthermore, 'particular attention shall be paid to the principle of proportionality, the right to privacy, the right to the protection of personal data, the right to the physical and mental integrity of a person, the right to non-discrimination and the need to ensure high levels of human health protection.'

review applications for ERC grants.[258] Under this procedure independent experts and/or qualified staff examine the ethical aspects of all proposals considered for funding through the Horizon 2020 programme.[259] It starts with an 'ethics screening' followed by an 'ethics assessment', if appropriate.[260] The review can lead to the inclusion of ethics requirements in the grant agreement. The ERC policy is that Horizon grant applicants and holders have the primary responsibility for the detection of scientific misconduct and for the investigation and adjudication of any breaches of research integrity. However, the ERC attends to all concerns about potential scientific misconduct or suspected breaches of research integrity that may arise during the execution of an ERC project. In case of substantial breach of ethical principles, research integrity or relevant legislation, an 'ethics audit' can be carried out, leading to an amendment of the agreement and, in severe cases, to a grant reduction or to its termination in line with the agreement rules.[261]

3 *The Regulation from Bench to Bedside of Human Germline Genome Modification in the European Union*

Let us now summarize how EU legislation regulates the so-called translational pipeline, the process of the creation of new medicines, from the bench to bedside, in the case of human germline genome modification.

It must be kept in mind that, since the EU competences over scientific research and its applications are still limited, the EU legal framework is necessarily incomplete. A full account of the substantive provisions that must be respected in any given EU state must take into consideration the national laws of that state. The following analysis centres on EU legislation alone. The national legal frameworks of some selected EU members will follow in the subsequent chapters.

a Basic Research

Although the European Union does not fund research involving the use of techniques that can lead to alterations of the germline identity of human subjects, it does not seem to rule out funding research projects that involve

[258] The legal basis for the ethics review is Horizon 2020 Regulation, art. 14.
[259] ERC Rules for Submission and Evaluation. Commission Decision C(2017)4750, Version 3.0, 14 July 2017.
[260] Ibid., ERC Rules for Submission and Evaluation, Annex A.
[261] Multi-Beneficiary General Model Grant Agreement (H2020 General MGA – Multi) Version 5.0 18 October 2017, art. 43 (reduction) and art. 48.1 (suspension).

using genome-modifying technologies on gametes, embryos or embryonic stem cells, as long as this use is consistent with the law of the member state in which the research is carried out.[262]

The European Union has taken a permissive approach to research on adult and embryonic human stem cells. Since 2002, it has funded research on human embryonic stem cells provided this research is carried out in compliance with the European ethical and legal framework for research on stem cells and the laws of the state in which they are doing their research. However, EU funds may not be used for derivation of new stem cell lines, or for research that destroys the embryos (blastocysts), including for the procurement of stem cells.

The procurement of gametes or embryos for research purposes is regulated at the national level. The Human Tissues and Cells Directive, which sets standards of quality and safety for the donation of human tissues and cells, does not extend to in vitro research.[263] Be that as it may, it is understood that Article 3 of the EU Charter, on the right to the integrity of the person, requires the 'free and informed consent of the person concerned' in the fields of biology and medicine. According to the CJEU case law, this right encompasses respect for the rights of donors.[264]

Finally, even where national laws permit creating human embryos only for research purposes, the European Union does not finance this research. As was said, according to Article 19.3(c) of the Horizon 2020 Regulation, the European Union does not fund 'research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer'.[265] Also, the use of EU funds for the derivation of new stem cells, or for research that destroys embryos, including for the procurement of stem cells. Even so, the EU approach was challenged by a pro-life group, One of Us (*Uno di Noi*). In 2012, the group had

[262] Horizon 2020 Regulation, art. 19.4 states: 'Research on human stem cells, both adult and embryonic, may be financed, depending both on the contents of the scientific proposal and the legal framework of the Member States involved. No funding shall be granted for research activities that are prohibited in all the Member States. No activity shall be funded in a Member State where such activity is forbidden.'

[263] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Settings Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells, Recital 11.

[264] This understanding has been confirmed in a Court of Justice judgment of 9 October 2001, in Case C-377/98 *Netherlands* v. *European Parliament and Council* [2001] ECR-I 7079, at grounds 70, 78 to 80.

[265] Commission Communication COM (2014) 355 final, of 28 May 2014, on the European Citizens' Initiative 'Uno di Noi', 7. Available at: https://ec.europa.eu/transparency/regdoc/rep/1/2014/EN/1-2014-355-EN-F1-1.Pdf accessed on 21 December 2018.

brought a petition to the Commission demanding the ban of stem cell research because it causes the destruction of human embryos.[266] In 2014, the Commission replied that it would not take any action in response to the petition, prompting the group to take legal action for annulment of the communication before the General Court.[267] The General Court dismissed the action. Specifically, it held that the claimants could not rely on the *Brüstle* judgment since it was limited to the question of whether a biotechnological invention involving the use of embryos is patentable and does not extend to the question of whether scientific research involving the use (and destruction) of human embryos may be financed by EU funds.[268] Moreover, according to the Court, the Commission's ethical approach to stem cell research cannot be said to involve a manifest error of assessment as required for actions of annulment. In this regard, it highlighted that the Commission had taken 'into account the right to life and human dignity of human embryos, but, at the same time, [considered] the needs of [human embryonic stem cell] research, which may result in treatments for currently-incurable or life-threatening diseases, such as Parkinson's, diabetes, stroke, heart disease and blindness'.[269]

b Preclinical research

Animal welfare is an important value of the Union. This is manifested by the fact that it has had legislation to protect animals used for scientific purposes in place since 1986. The European Union is also a party to the Council of Europe's Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, which it ratified in 1998.[270]

The most relevant piece of EU legislation in this field is Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes (Animal Protection Directive), in force since 1 January 2013.[271] This directive applies to any 'use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which

[266] Ibid.

[267] Case T-561-144 *One of Us and Others* v. *Commission* ECLI:EU:T:2018:210 (Judgment of the General Court of the European Union on April 23, 2018).

[268] Ibid., paras. 174–175.

[269] Ibid., para. 176.

[270] European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, 18 March 1986, ETS No 123.

[271] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes, OJ L 276, 20.10.2010, 33–79.

may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice'.[272] The protection revolves around the principle of reduction, replacement and refinement (referred to as the 'Three Rs principle'). In short, it requires that EU states ensure that (1) wherever possible, a scientific method or testing strategy that does not involve the use of live animals is used; (2) the number of animals used in projects is reduced to a minimum without compromising the project's objective; and (3) the refinement of breeding, accommodation and care, and of methods used in procedures, eliminates or reduces to the minimum any possible pain, suffering, distress or lasting harm to the animals.[273]

In line with the directive, procedures on animals may only be carried out for the purposes of basic, translational or applied research if it aims to avoid, prevent, diagnose or treat disease, ill-health or other abnormality or their effects in human beings, animals or plants.[274] As a general rule, endangered species and non-human primates must not be used, unless the purpose of the procedure meets this stated aim, and if there is a scientific justification to the effect that the purpose of the procedure cannot be met by the use of other species or animals.[275] EU member states must set up a national committee for the protection of animals used for scientific purposes, which will advise the competent authorities and animal-welfare bodies on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practices.[276]

The Animal Protection Directive covers any course of action intended or likely to result in the creation and maintenance of genetically modified animals.[277] Besides concerns about the health and welfare of these genetically modified animals, the European Union is concerned about possible adverse effects of introducing such animals into the food chain and the human diet. A basic question at the moment is whether food derived from these animals may be placed on the EU market, which is currently not the case. To anticipate these developments, the EU Food Safety Authority has issued guidelines on how to assess the risks should applications for food and feed

[272] Ibid., art. 3.1.
[273] Ibid., art. 4.
[274] Ibid., arts. 5.a and b.i.
[275] Ibid., art. 7 (endangered species) and art. 8 (non-human primates).
[276] Ibid., art. 49.
[277] Ibid., art. 3.1.

derived from these animals be submitted for market authorization in the European Union.[278]

Since the directive only contains minimum standards, EU states may opt for a more extensive protection of animals as long as they are compatible with the TFEU.[279] Also, because the Animal Protection Directive is just a directive, it is not self-executing but must be transposed into national law. In practice, this means that EU researchers must consult relevant national law of the member state in which they are located to find out what the exact rules are.

c Clinical Research/Applications

Clinical research involves a living person whose germline tissue is modified in vivo or who receives germline tissue that was modified ex vivo (by transferring a modified embryo in the uterus of a research participant) to test the safety and efficacy of germline engineering. Should this procedure be permitted at some point in the future, EU legislation concerning safety standards for the process of implanting tissues or cells into a human body will become applicable.[280] The Human Tissues and Cells Directive covers the entire chain of activities: from donation to procurement, testing, processing, preservation, storage and distribution to the site of medical use or to the site where manufactured products are made from human tissues and cells.[281] The concept of 'cells' is defined as 'individual human cells or a collection of human cells when not bound by any form of connective tissue';[282] and 'tissue' means 'all constituent parts of the human body formed by cells', which include fetal tissue, reproductive cells (semen, sperm, and ova) as well as stem cells.[283] The term 'donor' includes 'every human source, whether living or deceased, of human cells or tissues' and 'donation' means 'donating human tissues or cells intended for human applications'.[284] Finally, 'human application'

[278] See Guidance on the Risk Assessment of Food and Feed from Genetically Modified Animals and on Animal Health and Welfare Aspects (2012) 10:1 EFSA Journal 2501; and Guidance on the Environmental Risk Assessment of Genetically Modified Animals (2013) 11:5 EFSA Journal 3200.

[279] Animal Protection Directive, art. 2.

[280] Human Tissues and Cells Directive, recital 2.

[281] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Settings Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells.

[282] Ibid., art. 3.a.

[283] Ibid., art. 3.b.

[284] Ibid., art. 3.c and d.

means 'the use of tissues or cells on or in a human recipient and extracorporal applications'.[285]

The Human Tissues and Cells Directive contains minimum standards, in the sense that it does not prevent a member state from imposing more stringent measures. For example, member states may well prohibit donations of human tissues and cells to be implanted in a human body.[286] For those states that do not prohibit it, they must designate the competent authority or authorities responsible for implementing the requirements included in the directive, which will supervise compliance, including through inspections and control measures.[287] The directive also imposes obligations on member states regarding the import/export of human tissues and cells, and to set up a system of notification and investigation of adverse reactions.

We have already mentioned EU legislation relating to clinical trials for medicinal products. The Clinical Trials Regulation (replacing the Clinical Trials Directive) ensures that the rights, safety and well-being of human subjects are protected. The current ban on gene therapy trials that can result in modifications to the subject's germline rules out the possibility of testing genetic modification technologies, such as CRISPR-Cas9, on embryos and gametes that are then implanted in a woman to initiate a pregnancy.[288] If this ban is lifted in the future, human germline engineering would likely be regarded as an 'advanced therapy medicinal product' in line with the Advanced Therapy Medicinal Product Regulation.[289] According to this regulation, gene therapy, somatic cell therapy and tissue engineering products qualify as medicinal products whose safety and quality must be tested in clinical trials. In this context, it sets out a definition of 'engineered' cell or tissue. For this, at least one of the following conditions must be fulfilled: (a) the cell or tissue must 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; or (b) the cell or tissue is not intended to be used for the same essential function or functions in the recipient as in the donor.[290] The Regulation also provides

[285] Ibid., art. 3.l.
[286] Ibid., art. 4.2.
[287] Ibid., arts. 6 and 7.
[288] Clinical Trials Regulation, art. 90.
[289] Regulation 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products, amending Directive 2001/83/EC and Regulation 726/2004, OJ L 324, 10.12.2007, pp. 121–137 ('Advanced Therapy Medicinal Products Regulation'), arts. 1.a and 4.
[290] Ibid., art. 2.c.

a clarification of the term 'manipulation', which means, among other things, cutting, grinding, shaping, cryopreservation and vitrification.[291]

The general principle is that a clinical trial can be conducted only if the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests, and if it is designed to generate reliable and robust data.[292] Therefore, a clinical trial must be subjected to scientific and ethical review for authorization.[293] It can only be done if 'the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored'. Also, the subjects must give their informed consent in writing, and if not able to give informed consent, then their legal representatives.[294] Moreover, a clinical trial must have been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, a condition that must be constantly monitored. Specific attention is paid to vulnerable populations, including minors, incapacitated, and breastfeeding or pregnant women.[295] Finally, the sponsors of a clinical trial and the investigator must ensure respect for the protocol and the principles of good clinical practice.[296]

IV CONCLUSIONS

All in all, the current EU/CoE regulatory framework for genome editing of human germline cells is still rather patchy and lacks coherence, hardly facilitating the work of scientists who seek to develop inroads in cures for inheritable genetic diseases. The EU regulatory environment is quite complex, but also limited in scope and probably inadequate to advance scientific progress on germline genome editing. The Biotech Directive does not provide a comprehensive framework regulating biotechnological research. It addresses only the question of the patentability of biotechnological inventions. The Clinical Trials Directive, to be replaced in 2019 by the Clinical Trials Regulation, does not unambiguously rule out research involving genetic modification of human germline cells. It is even unclear whether clinical research on somatic cell therapy can be carried out as long as there is a chance it could cause unintentional modification of the germline genome.

[291] Ibid., Annex I.
[292] Ibid., art. 3.
[293] Ibid., art. 6.
[294] Ibid., art. 28.
[295] Ibid., arts. 31, 32 and 33.
[296] Ibid., art. 47.

Some could argue that EU primary law, and specifically the Charter of Fundamental Rights of the European Union, does provide a framework for informing a discussion on European governance of human germline genome modification. After all, it proclaims that human dignity is inviolable, and that it must be respected and protected.[297] It also states that 'everyone has the right to respect for his or her physical and mental integrity'.[298] However, these very generic provisions create more questions than answers. For instance, the Charter does not specify who 'everyone', the beneficiary of the rights, is: does it include human life before birth? Does it include future generations? Also, it is far from evident that germline therapy inherently violates human dignity. Indeed, if it does provide a cure for genetic diseases that condemn scores to a short and painful life, it could be argued that not only does it ensure respect for this right, but also helps protecting it. Indeed, let us not forget that in the European Union 'everyone has the right of access to preventive health care and the right to benefit from medical treatment and that a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities'.[299]

Of the 28 members of the European Union, 11 have not ratified the Oviedo Convention and are unlikely to do so as long as it remains worded as it is now. This group comprises states like Germany, Austria, Italy, Ireland and Poland who think the Convention does not include sufficient guarantees for the human embryo, and states like the United Kingdom, Belgium, the Netherlands and Sweden, and, outside the European Union, Russia, who believe the Convention excessively restricts research. Seemingly, what prevents the adoption of a comprehensive, clear and consistent 'European' regulatory framework is a fundamental difference of views within the European Union and the CoE on some fundamental issues. As it stands, the 'European' regulatory framework neither blocks research nor facilitates it.

For those states that would like to prevent research on human germline genome modification, the Oviedo Convention is not enough. First, the Convention's prohibitory provisions are vaguely worded and open to interpretation. Moreover, states can attach reservations to their instrument of ratification of the Convention.[300] Second, the Convention leaves it to each

[297] Charter of Fundamental Rights, art. 1.

[298] Ibid., art. 3.1.

[299] Ibid., art. 35.

[300] 'Exceptionally and under the protective conditions prescribed by law, the removal of regenerative tissue from a person who does not have the capacity to consent may be authorized provided the following conditions are met … .ii the recipient is a brother or sister of the donor.' Oviedo Convention, Article 20.2.ii. Croatia, for instance, ratified with

state to adopt the necessary domestic legal instruments to give it effect and establish sanctions for its violations.[301] Third, it is up to national courts to enforce it domestically.[302] Finally, the European Court of Human Rights does not have jurisdiction over the Oviedo Convention. Its jurisdiction is limited to the European Convention on Human Rights only. All it can do is issue advisory opinions at the request of one the parties or the Committee on Bioethics. So far, it has received none.[303] Violations of the Oviedo Convention are instead addressed politically within the Council of Ministers.

Although the Convention allows states to adopt more stringent standards of protection if they wish to do so, it is not prohibitory enough to earn the ratification of those who elevate the human embryo to the status of human being. However, it is too restrictive, especially in Articles 13 and 18, to keep out those states who believe research should not be unduly hampered.

As to the European Union, it does not prevent research on human germline genome modification per se, but it makes it difficult to fund it. The funds in the current Framework Programme (FP8, also known as Horizon 2020) cannot be tapped for research intending 'to modify the genetic heritage of human beings which could make such changes heritable',[304] and 'research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer'.[305] However, although researchers cannot tap EU Framework Programme Funds, they can still be funded nationally or privately.

The Biotech Directive discourages private investment in research because it excludes the patentability of processes that modify the germline genetic identity of human beings and the use of human embryos for industrial or commercial purposes. It remains to be seen what will happen to the prohibition of patentability the day researchers somewhere else in the world develop

a reservation to Article 20.2.ii, which allows the removal of regenerative tissue from a person who is not able to consent when no compatible donor with the ability to consent is available, and the recipient is a brother or sister of the donor. Croatia entered a reservation because this provision is not compatible with its law on the Removal and Transplantation of Human Body Parts, which allows the transplantation of regenerative tissue from a minor also for the benefit of his/her parents. Narodne Novine, Official Gazette of the Republic of Croatia, No 53/91.

301 Oviedo Convention, art. 25.

302 Ibid., art. 23.

303 However, the European Court of Human Rights has relied on the text of the Oviedo Convention when adjudicating on violations of the European Court of Human Rights. See, in general, F Seatzu, 'The Experience of the European Court of Human Rights with the European Convention on Human Rights and Biomedicine' (2015) 31:81 *Utrecht Journal of International and European Law* 5, 5–16.

304 Horizon 2020 Regulation, art. 19.2.b.

305 Ibid., art. 19.2.c.

therapies that modify human germline genome. If foreign pharmaceutical companies are not able to secure patents in Europe, they will simply not commercialize their therapies in the European Union, probably causing the EU public to put pressure on the EU Commission to reconsider the ban. However, for the time being the Biotech Directive stands.

Then, there is the obstacle of the Clinical Trials Regulation. The Regulation, which will come into force in 2019, is about the 'implementation of good clinical practices in the conduct of clinical trials *on medicinal products* for human use'.[306] It bans gene therapy trials 'which can result in modifications to the subject's germ line genetic identity'.[307] Although some argued that because in human germline genome modification no medicinal product is created, and it is rather a process or technique, and, therefore, the Clinical Trials Regulation should not apply,[308] the language of the Regulation and Directive is clear enough to block research moving toward clinical trials.

Future litigation before the Court of Justice of the European Union or intervention by the EU Commission might clarify more the framework, but it is anyone's guess in what direction. Given the cleavage between EU member states on the broader principles, the EU Commission is unlikely to intervene further and risk picking a fight with major member states over a matter that the overwhelming majority of the public does not understand. One should not count on the CJEU either, as, on genetic engineering, it has shown little capacity to assess scientific arguments, and a marked inclination to follow the *vox populi* and above all a strict interpretation of the so-called precautionary principle.[309]

[306] Regulation 536/2014 of the European Parliament and of the Council of 16 April 2004 on Clinical Trials on Medicinal Products for Human Use. [Italics of the authors].

[307] Clinical Trials Directive, art. 9.6, last line.

[308] I De Miguel Beriain, 'Legal Issues Regarding Gene Editing at the Beginning of Life: an EU Perspective' (2018) 12 *Regenerative Medicine* 671. Directive 2001/20/EC, on the other hand, refers to 'clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogeneic cell therapy and all medicinal products containing genetically modified organisms'. Nevertheless, gene editing in embryos does not create a product and still less a 'medicinal product', because it does not create any 'substance' (something separate from the human being in question that is used by or administered to such a human being with a view to restoring, correcting or modifying physiological functions) (citing JL Davies, *The Regulation of Gene Editing in the UK* (2016). On the contrary, it involves the application of a process or technique. Therefore, it is unclear if and how the directive or the regulation that will repeal it will apply to embryonic gene editing, because it may be that some of those modifications will not be considered clinical trials as such (citing J Kipling, *The European Landscape for Human Genome Editing: A Review of the Current State of the Regulations and Ongoing Debates in the EU* (2016)).

[309] On 25 July 2018, the CJEU ruled on the case *Confédération Paysanne and Others* v. *Premier Ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt*, C-528/16. Although the case did not regard human cells, it did discuss CRISPR-Cas9 and its effects of the genome of

Europe, both in its EU and CoE meaning, prides itself on its transparent legislative process, one where the public has ample opportunities to weigh in. Recently, both the Parliamentary Assembly of the Council of Europe and the EU European Group on Ethics in Science and New Technologies called for a 'broad and informed public debate',[310] one that goes 'beyond expert committees and engage civil society and touch upon safety issues and potential health risks or benefits of gene editing technologies as well as human dignity, justice, equity, proportionality and autonomy'.[311] So far, these debates have not started. However, if the current regulatory frameworks befuddle legal, scientific and ethical experts, it is hard to see how the wider European public could be able to debate their merits without falling back on entrenched cultural divides that have little to do with science. Given the current political climate in Europe, characterized by rising populism and general distrust for experts of any kind, it might be better to let this dog sleep.

plants in the particular case. Specifically, the case raised the question of whether organisms obtained by mutagenesis, including gene editing techniques such as CRISPR, are subject to the same regulations for genetically modified organisms as transgenic organisms.

The European Union has one of the most stringent regulatory framework for Genetically Modified Organisms, Directive 2001/18/EC on Genetically Modified Organisms (GMO Directive) (OJ 2001 L 106, 1) being the most important instrument. Overall, the European Union relies on a strict interpretation of the 'precautionary principle' to determine what GMOs can be cultivated in Europe. It demands a pre-market authorization for any 'new food' (GMOs and irradiated food) to enter the market and a post-market environmental monitoring, carried out by both the European Food Safety Authority and the member states. Currently, the European Union allows the cultivation of only 62 GMO varieties of six plants (cotton, maize, oilseed rape, soybean, sugar beet and swede rape). It does not allow the cultivation of many GMOs that are commonly cultivated and consumed around the world, which caused other states where these GMOs are cultivated to accuse the European Union of protectionism and challenging, successfully, the restrictive practices before the World Trade Organization.

In the *Confédération Paysanne* case, the Court, ignoring the opinion of its own Advocate General, and to the surprise of many scientists, took the view that organisms obtained by mutagenesis are GMOs within the meaning of the GMO Directive. It did not consider the scientific evidence and instead relied on a narrow interpretation of the 'precautionary principle'. The Court considered that the risks linked to the use of new mutagenesis techniques might prove to be similar to those that result from the production and release of a GMO through transgenesis, since the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into the organism (transgenesis), and those new techniques make it possible to produce genetically modified varieties at a rate greater than those resulting from the application of conventional methods. Thus, the Court concluded that, considering these potential risks, excluding organisms obtained by new mutagenesis techniques from the scope of the GMO Directive would compromise the objective pursued by the directive, and would fail to respect the precautionary principle which the directive seeks to implement.

[310] EGE Statement on Gene Editing (2016), 2.

[311] Ibid.