The Global Person: Pig-Human Embryos, Personhood, and Precision Medicine

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ABSTRACT

Chimeras, in the form of pig-human embryos engineered by CRISPR-Cas9 and other biotechnologies, have been created as potential sources of organs for transplantation. Against that background, and in an era of "precision medicine," this Article examines the concept of the global genetically modified person and asks whether humanness and personhood are being eroded, or finding new boundaries in intellectual property and constitutional law.

INTRODUCTION

The late twentieth and early twenty-first centuries have heralded the age of the global person—the genetically engineered human being.[1]

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1. For recent developments, see Hong Ma et al., *Correction of a Pathogenic Gene Mutation in Human Embryos,* 548 NATURE 413, 413 (2017); *see also* Marcia Frellick, *Research Unveiled in First Human Embryo Gene Editing in US*, MEDSCAPE (Aug. 2, 2017), http://www.medscape.com/viewarticle/883503; *Review of Mitalipov Paper CRISPR'ing Human Embryos: Transformative Work on the Edge,* THE NICHE: KNOEPFLER LAB STEM CELL BLOG (Aug. 2, 2017), https://ipscell.com/2017/08/review-mitalipov-paper-crispring-human-embryos-transformative-work-edge/; Xiangjin Kang et al., *Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing*, 33 J. ASSISTED REPROD. & GENETICS 581, 581 (2016); Puping Liang et al., *CRISPR/Cas9-mediated Gene Editing in Human Tripronuclear Zygotes*, 6 PROTEIN & CELL 363, 363 (2015); Ewen Callaway, *Second Chinese Team Reports Gene Editing in Human Embryos*, NATURE (Apr. 8, 2016), https://www.nature.com/news/second-chinese-team-reports-gene-editing-in-human-embryos-1.19718.

The global search not only for cures for illness and disease,[2] but also for perceived enhancement, has led to a rush to eliminate, modify, and patent certain genetic defects. In this version of globalization alchemy, the human genome is mined globally for genetic nuggets to be shaped; redesigned; and, in some cases, monopolized. In a recent iteration of these trends, scientists have created pig-human embryos[3] containing elements of both species. These embryos are designed as sources of organs that will be recognized, or at least not rejected, by the human immune system. The National Institutes of Health (NIH) contemporaneously proposed an end to its ban on funding for research that involves transplanting human stem cells into nonhuman animal embryos.[4]

The advent of such chimeras, or genetic combinations, is complimented by the development of new gene editing technologies, including CRISPR-Cas9, a gene editing tool that brings about what are hoped to be precisely targeted changes to the genome of living cells.[5] CRISPR-Cas13[6] and zinc finger nuclease therapy are beginning to jostle with CRISPR-Cas9 for human gene editing primacy, with the zinc finger therapy enabling changes to DNA in the human body.[7] Yet such changes, when applied to reproductive cells, will alter the human gene pool in ways that are difficult to predict.[8] These changes come at a time when individuals are attempting to do their own gene editing.[9] Legal

2. Michael Nedelman, *FDA Announces First US Gene Therapy Approval for Cancer Treatment*, CNN (Aug. 30, 2017, 5:07 PM), http://edition.cnn.com/2017/08/30/health/fda-first-gene-therapy-leukemia/index.html.

3. Jun Wu et al., *Interspecies Chimerism with Mammalian Pluripotent Stem Cells*, 168 CELL 473, 474 (2017); Sara Reardon, *Hybrid Zoo: Introducing Pig-Human Embryos and a Rat-Mouse*, NATURE (Jan. 26, 2017), https://www.nature.com/news/hybrid-pig-human-embryos-and-a-rat-mouse-1.21378.

4. Lenny Bernstein, *NIH May Allow Funding for Human-Animal Stem Cell Research*, THE WASH. POST (Aug. 5, 2016), https://www.washingtonpost.com/news/to-your-health/wp/2016/08/05/nih-may-allow-funding-for-human-animal-stem-cell-research/?utm_term=.bd54df01a1b4.

5. Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 819 (2003).

6. David B.T. Cox et al., *RNA Editing with CRISPR-Cas13*, 358 *SCIENCE 1019, 1019 (2017).*

7. Human gene editing had previously taken place by removing cells from the human body, editing them, and returning the edited cells to the body. James Gallagher, *First Gene-Editing in Human Body Attempt*, BBC NEWS (Nov. 16, 2017), http://www.bbc.co.uk/news/health-42009929.

8. The difficulty of predicting outcomes occurs in part because of pleiotropy, which refers to one gene influencing numerous seemingly unrelated expressed (or phenotypic) traits or characteristics.

9. *See* Alex Pearlman, *Biohackers Are Using CRISPR on Their DNA and We Can't Stop It*, NEW SCIENTIST (Nov. 15, 2017), https://www.newscientist.com/article/mg23631

questions abound, not least whether the combination of human genes with nonhuman animal genes in organ-rich chimeras will render more tenuous our understanding of what it is to be human. Will humanness be redefined? Will it become increasingly difficult to decide which beings qualify for the traditional legal protections of personhood?

I. A BRIEF HISTORY

A. Chimeras

Homer described a cross-species chimera: a fire-breathing hybrid "of immortal make, not human, lion-fronted and snake behind, a goat in the middle."[10] The sighting of a chimera was thought to be an omen for disaster. But it was probably the mythical centaurs of ancient Greece that first sported a human head.[11] Most centaurs were portrayed as dangerously aggressive, yet, the centaur Chiron, the tutor of Asklepios, the god of medicine, was recognized for his medical skills and wisdom.[12] Marvel, as one might, at these mythical cross-species creatures and the vivid imaginations of their authors, modern chimeras embody not only the promise of cures but also very real problems for present-day lawyers and for science and society in the twenty-first century.

A chimera, in genetic parlance, is an organism or tissue that contains at least two different sets of DNA.[13] Pig-human embryos are chimeras: combinations of human and nonhuman animals, in embryonic form. Such chimeras were announced in 2017, by Jun Wu; Juan Carlos Izpisua Belmonte; and their colleagues at the Salk Institute in La Jolla, California.[14] The chimeras were created by injecting different types of induced pluripotent human stem cells directly into more than 1,400 pig embryos. The resultant embryos developed post implantation in a pig

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520-100-biohackers-are-using-crispr-on-their-dna-and-we-cant-stop-it/ (last updated Nov. 16, 2017); *see also DIY Bacterial Genome Engineering CRISPR Kit*, AMAZON.COM, https://www.amazon.com/DIY-Bacterial-Genome-Engineering-CRISPR/dp/B071ZXW1TW (last visited Mar. 1, 2018).

10. HOMER, ILIAD ch. 6, 179–82 (William F. Wyatt ed., A. T. Murray trans., Harvard Univ. Press 2d ed. 1924).

11. The satyrs of Greek mythology, and their Roman counterparts, the fauns, had human-like heads, but with horns. The minotaurs were essentially bulls, only their lower half human. *See* WILLIAM SMITH, 1 DICTIONARY OF GREEK AND ROMAN BIOGRAPHY AND MYTHOLOGY 666 (William Smith ed., 1849).

12. *Asklepios*, THEOI.COM, http://www.theoi.com/Ouranios/Asklepios.html (last visited Mar. 1, 2018).

13. *Chimeric,* MERRIAM WEBSTER MEDICAL DICTIONARY, http://www.merriam-webster.com/medical/chimeric (last visited May 4, 2018).

14. Wu et al., *supra* note 3, at 474.

host, a sow surrogate mother. Scientists then noted where the human cells took hold in the developing embryos over periods of twenty-eight days, at which point the embryos were destroyed. The different kinds of human cells that were used were: so-called "naïve" cells that resemble cells from an earlier developmental origin with unrestricted developmental potential; "primed" cells that have developed further, but remain pluripotent;[15] and "intermediate" cells that are somewhere in between the other two types of cells in terms of their developmental stage. All the human cells were modified to produce a green fluorescent protein so that they could be identified within the newly created chimeras.[16] The authors noted that the intermediate type of human stem cell "contributed" most to the pig-human chimeras.[17] The team created 186 later-stage chimeric embryos that survived up to twenty-eight days in utero until destroyed, with an estimated about one in one hundred thousand human cells in each embryo.[18] The aim of the Salk team is greatly to increase the proportion of human to pig cells with the aim of using these chimeras as sources of organs that will not be rejected when transplanted into human beings. The greater the proportion of human cells in the chimeras, the lesser the chance that the human immune system will reject the organs taken from the pig-human chimeras. These are the first documented human-nonhuman chimeras to have survived and grown inside a nonhuman animal. Other teams are working on alternative solutions to the shortage of organs for transplant; experimenting, for example, with 3-D printing of organs produced from stem cells.[19] The use of nonhuman animal organs as protein scaffolds[20] is also showing promise.

B. Precision Medicine, CRISPR-Cas9, and a New Source of Organs

President Obama launched the Precision Medicine Initiative in

15. Pluripotent cells are immature cells or stem cells capable of giving rise to several different cell types. *What is the Difference Between Totipotent, Pluripotent, and Multipotent?*, N.Y. ST. STEM CELL SCI., https://stemcell.ny.gov/faqs/what-difference-between-totipotent-pluripotent-and-multipotent (last visited Mar. 1, 2018).

16. Reardon, *supra* note 3.

17. *Id.*

18. Wu et al., *supra* note 3, at 480.

19. *See* Jeong Hun Park et al., *Current Advances in Three-Dimensional Tissue/Organ Printing*, 13 TISSUE ENGINEERING & REGENERATIVE MED. 612, 612 (2016); *see also* Dina Radenkovic et al., *Personalized Development of Human Organs Using 3D Printing Technology*, 87 MED. HYPOTHESES 30, 31 (2016).

20. Clare Wilson, *Donor Organs Created by Dissolving and Rebuilding Pig Livers*, NEW SCIENTIST (Oct. 30, 2017), https://www.newscientist.com/article/2151910-donor-organs-created-by-dissolving-and-rebuilding-pig-livers/.

2015.[21] It was intended to go beyond the initial sequencing of the human genome, with researchers collecting comparative data on numerous individual genomes and better identifying the polymorphisms or defects that lead to illness. The principal aim of the initiative was to find cures or treatments for the illnesses identified as having genetic links and, ultimately, to customize care and treatments so that they may be tailored to individual patients or groups of patients. If successful, precision medicine could, amongst other benefits, greatly reduce not only the cost of such treatments but also the well-meaning yet unnecessary suffering inflicted on patients who, because of their genetic makeup, are unlikely actually to be helped by the existing treatments. Positive results of this kind are already being achieved in the field of clinical oncology, in which genetic tests can identify patients who are not likely to benefit from existing chemotherapies used to treat breast, prostate, and colon cancers.[22]

Increasing knowledge about the role of genes that cause illness and undesired characteristics comes at a time when the patented technology known as CRISPR-Cas9 facilitates much more precise and targeted (if by no means entirely predictable) modification of the human genome than previous genetic engineering techniques. Unintended consequences are still a feature of the technology because the genes that are edited frequently code for more than one characteristic and not all the interactions are known.

CRISPR-Cas9 technology uses two key molecules that introduce a change or mutation into the DNA: first, an enzyme called Cas9 acts as a molecular scissors by cutting the two strands of DNA at a specific location in the genome so that pieces of DNA can then be added or removed and, secondly, a piece of RNA called guide RNA or gRNA. This consists of a small piece of pre-designed RNA sequence (about twenty bases long) located within a longer RNA scaffold. The scaffold part binds to DNA and the pre-designed sequence guides the Cas9 enzyme to the right part of the genome so that it cuts at the intended point in the genome. In theory, the guide RNA will bind only to the target sequence and not to other regions of the DNA. Once the Cas9 enzyme makes a cut across both strands of the DNA, the cell recognizes that its DNA is

21. The initiative was announced by President Obama during the 2015 State of the Union Address. Barack Obama, President of the United States, State of the Union Address (Jan. 20, 2015).

22. *See Oncotype DX Personalizes Treatment Options and Improves Outcomes*, GENOMIC HEALTH, http://www.genomichealth.com/en-US/oncotype_iq_products/oncotype_dx.aspx (last visited Mar. 1, 2018); *see also* Joseph A. Sparano et al., *Prospective Validation of a 21-Gene Expression Assay in Breast Cancer*, 373 NEW ENG. J. MED. 2005, 2007 (2015).

damaged and tries to repair it. The technology can be used to introduce changes to one or more genes in a cell.[23]

CRISPR-Cas9 technology was used to assist in the creation of the chimeras. For example, Jun Wu, of Juan Carlos Izpisua Belmonte's team at the Salk Institute, used CRISPR technology to create mouse embryos without the genes that cause organs to form.[24] The scientists then injected rat stem cells into the mouse embryos and implanted the embryos into a mouse's uterus. Because the rat cells still contained genes for organ formation, the resulting chimeras had organs that were composed largely of rat cells. The animals lived for up to two years, the normal lifespan of a mouse.[25] Rat cells also grew to form a gall bladder in a mouse, even though rats stopped developing this organ over the 18 million years since rats and mice separated evolutionarily. Jun Wu explained that this suggests that the reason a rat does not generate a gall bladder is not because it cannot, but because the potential has been hidden by a rat-specific developmental program.[26]

CRISPR-Cas9 has also been used to reduce the immunogenicity of pigs by removing specific antigens. For instance, a team at Harvard led by George Church has published a paper on using CRISPR-Cas9 to remove endogenous retroviral genes in pigs for the purpose of reducing immune reactions in pig-human chimeras.[27] This was no small modification. One application of CRISPR-Cas9 operated to alter at least sixty-two porcine retroviral genes in each pig. But these are not the only antigenic proteins in pigs and it has been suggested that the chances of successfully reducing immune system reactions will be improved by

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23. Alex Reis et al., *CRISPR/Cas9 and Targeted Genome Editing: A New Era in Molecular Biology*, NEW ENG. BIOLABS (2014), https://www.neb.com/tools-and-resources/feature-articles/crispr-cas9-and-targeted-genome-editing-a-new-era-in-molecular-biology; *What is CRISPR-Cas9?*, YOURGENOME.ORG, https://www.yourgenome.org/facts/what-is-crispr-cas9 (last updated Dec. 19, 2016). CRISPR-Cas9 technology is already being refined. Nicole M. Gaudelli et al., *Programmable Base Editing of A•T to G•C in Genomic DNA Without DNA Cleavage,* 551 NATURE 464, 464 (2017); Cox et al., *supra* note 6, at 1024.

24. A Japanese team had created a rat/mouse chimera in 2010. That chimera was a mouse with pancreatic tissue formed from rat cells. Toshihiro Kobayashi et al., *Generation of Rat Pancreas in Mouse by Interspecific Blastocyst Injection of Pluripotent Stem Cells*, 142 CELL 787, 788 (2010).

25. Wu et al., *supra* note 3, at 481; Reardon, *supra* note 3.

26. Wu et al., *supra* note 3, at 475.

27. *See* Luhan Yang et al., *Genome-Wide Inactivation of Porcine Endogenous Retroviruses (PERVs)*, 350 SCIENCE 1101, 1101, 1103 (2015); *see also* Dong Niu et al., *Inactivation of Porcine Endogenous Retrovirus in Pigs Using CRISPR-Cas9*, 357 SCIENCE 1303, 1303 (2017); Karen Weintraub, *Gene-Editing Success Brings Pig-to-Human Transplants Closer to Reality*, SCI. AM. (Aug. 10, 2017), https://www.scientificamerican.com/article/gene-editing-success-brings-pig-to-human-transplants-closer-to-reality/.

combining the pig-human chimera work with CRISPR gene editing designed to reduce antigenicity—the ability to cause the production of antibodies.[28] This work clearly has important implications for reducing the likelihood of the rejection of organs removed from pig-human chimeras and transplanted into humans.

C. Global Sub-Species and Cross-Species Studies

Work in this field is being conducted across the globe with teams from the United States, Japan, and China leading the way. But it was not until 2001 that scientists from the United States, the United Kingdom, Japan, France, Germany, and China, who had been working collaboratively on what they called the Human Genome Project, published the first analysis of the human genome sequence,[29] making this a truly global enterprise. The following years brought further understanding of the human genome and its polymorphisms and, in 2014, scientists comparing human, fly, and worm genomes noted that these species have extensively shared genetics. The findings offered cross-species insights into embryonic development and gene regulation.[30] Creations such as pig-human embryos were already further from the realms of myth.

Also in 2014, an international team, including researchers from the National Institutes of Health (NIH), completed the first comprehensive characterization of genomic diversity across sub-Saharan Africa.[31] The study provided insights into medical conditions of people of sub-Saharan African ancestry. In 2015, an international team of scientists from the 1000 Genomes Project Consortium created the world's largest catalogue of genomic differences among humans,[32] providing researchers with indications of why some people are susceptible to various diseases. That same year, transgenic zebrafish were developed as a live animal model of mutagenesis, promising cancer researchers new methods of

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28. *Perspectives on Pig Human Chimera Paper*, THE NICHE: KNOEPFLER LAB STEM CELL BLOG (Jan. 26, 2017), https://ipscell.com/2017/01/perspective-on-pig-human-chimera-paper/.

29. *Eric S. Lander et al., Initial Sequencing and Analysis of the Human Genome, 409 NATURE 860, 860 (2001).*

30. *See* Alan P. Boyle et al., *Comparative Analysis of Regulatory Information and Circuits Across Distant Species*, 512 NATURE 453, 453 (2014).

31. *See* Deepti Gurdasani et al., *The African Genome Variation Project Shapes Medical Genetics in Africa*, 517 NATURE 327, 327–32 (2015).

32. *About IGSR and the 1000 Genomes Project*, THE INT'L GENOME SAMPLE RESOURCE, http://www.internationalgenome.org/about (last visited Mar. 1, 2018).

developing pharmaceuticals.[33]

Research funded by the National Human Genome Research Institute (NHGRI), part of NIH, provided new insights into the effects and roles of genetic variation and parental influence on gene activity in mice and humans.[34] NIH researchers also discovered that the genomic switches of a blood cell are crucial to regulating the human immune system.[35] Their findings were an important step in the development of personalized medicine for those with autoimmune disorders. The following year, NHGRI researchers began to collaborate with physicians and medical geneticists around the world to create the Atlas of Human Malformation Syndromes in Diverse Populations, and NHGRI funded a study of the impact of genomics in American Indian and Alaskan native communities.[36]

By 2016, an international team of more than 300 scientists had conducted an extensive investigation of the underlying genetic architecture of type 2 diabetes.[37] Their findings suggested that most of the genetic risk for type 2 diabetes can be attributed to common shared genomic variants. In the final paragraph of their published paper, the team concluded that "Genome sequencing in much larger numbers of individuals than included in the current study are [*sic*] needed and will no doubt provide foundational information to guide such experimentation and connect the results to human population variation, physiology, and disease."[38] Connections with racial variation are being sought. As one might imagine, these global analyses depend heavily on information technology, not least for storage and analysis of data.

D. The Information Technology Effect

The Precision Medicine Initiative announced in 2015 was designed to collect and compare data on large numbers of individual genomes.[39]

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33. *See* Gaurav K. Varshney et al., *High-Throughput Gene Targeting and Phenotyping in Zebrafish Using CRISPR/Cas9*, 25 GENOME RES. 1030, 1030 (2015).

34. *See generally* James J. Crowley et al., *Analyses of Allele-Specific Gene Expression in Highly Divergent Mouse Crosses Identifies Pervasive Allelic Imbalance*, 47 NATURE GENETICS 353 (2015).

35. *See* Golnaz Vahedi et al., *Super-Enhancers Delineate Disease-Associated Regulatory Nodes in T Cells*, 520 NATURE 558 (2015).

36. *National Human Genome Research Institute (NHGRI)*, NAT'L INSTITUTES OF HEALTH, https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-human-genome - research-institute-nhgri (last updated Mar. 1, 2018).

37. *Id.*

38. Christian Fuchsberger et al., *The Genetic Architecture of Type 2 Diabetes*, 536 NATURE 41, 49 (2017).

39. Obama, *supra* note 21.

The main purpose of the initiative was to find cures or treatments for genetic illnesses. But the enterprise was inherently global, with international genome database networks increasingly deployed for the purposes of large-scale comparison. Several collaborations over international databases are currently underway. Note, for example, the International Nucleotide Sequence Database Collaboration,[40] which is a joint effort to collect and disseminate computerized databases of DNA and RNA sequences. It includes information from the DNA Databank of Japan; GenBank in the United States; and the European Nucleotide Archive, the latter based in the United Kingdom. New and updated data on genetic nucleotide sequences contributed by research teams to each of the three databases are synchronized by staff at each of the collaborating organizations.[41]

An International HapMap Consortium[42] is at work on the International HapMap project, the aim of which is to determine the common patterns of DNA sequence variation in the human genome and to put this information into the public domain.[43] This international consortium is developing a map of these patterns across the genome by determining the genotypes of one million or more sequence variants, their frequencies, and the degree of association between them, using DNA samples from populations with ancestry from parts of Asia, Africa, and Europe. It was hoped that the HapMap would allow the discovery of sequence variants that affect common diseases and would facilitate development of diagnostic tools and therapeutic interventions. The Human Genome Project[44] is related to the entire human genome, including approximately 99.9 percent of the human genome that all human beings are thought to have in common, whereas the HapMap would characterize the common patterns within the 0.1 percent of the genome in which we differ from each other.

In the United States, a move to digitize patients' genetic records is

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40. INT'L NUCLEOTIDE SEQUENCE DATABASE COLLABORATION, http://www.insdc.org/ (last visited Mar. 1, 2018).

41. Ilene Karsch-Mizrachi et al, *The International Nucleotide Sequence Database Collaboration*, 40 NUCLEIC ACIDS RES. D33, D33–D36 (2012).

42. Richard A. Gibbs et al., *The International HapMap Project*, 426 NATURE 789, 789 (2003).

43. The HapMap (short for "haplotype map") is a catalog of common genetic variants known as single nucleotide polymorphisms or SNPs. Each SNP represents a difference in a single DNA building block, called a nucleotide. These variations occur normally throughout a person's DNA. When several SNPs cluster together on a chromosome, they are inherited as a block known as a haplotype. The HapMap describes haplotypes, including their locations in the genome and how common they are in different populations throughout the world. *What is the International HapMap Project?*, GENETICS HOME REFERENCE (Feb. 27, 2018), https://ghr.nlm.nih.gov/primer/genomicresearch/hapmap.

44. Gibbs et al., *supra* note 42, at 793.

also much in evidence in various institutional choices. In 2015, the Undiagnosed Diseases Network (UDN) opened the UDN Gateway, an online patient application, to streamline the patient application process across its individual clinical sites. The same year, the Electronic Medical Records and Genomics Network (eMERGE) began its Phase III with nine new investigator sites, two central sequencing and genotyping facilities, and a coordinating center.[45] In 2016, NHGRI funded researchers at its Centers of Excellence in Ethical, Legal and Social Implications Research program to examine the use of genomic information in the prevention and treatment of infectious diseases; genomic information privacy; and communication about prenatal and newborn genomic testing results.[46]

That year, NHGRI also launched the Centers for Common Disease Genomics, which uses genome sequencing to explore the genomic aspects of common maladies such as heart disease, diabetes, stroke, and autism. Concurrently, NHGRI awarded approximately 11.1 million dollars to support research aimed at identifying differences—called genetic variants—in the less-studied regions of the genome that are responsible for regulating gene activity.[47] The Genomic Healthcare Branch of the NIH convened a meeting with fourteen family health history tool developers and vendors to assess their approaches to addressing gaps in current electronic health records.[48]

Others have addressed concerns about the privacy of genetic data and the potentially adverse uses of this information,[49] but it is important to record here recent threats to the anonymity of stored genetic data. The Genetic Information Nondiscrimination Act of 2008[50] and the Americans with Disabilities Act of 1990[51] are amongst the laws that guard the privacy of genetic information and protect it from adverse uses by employers and insurers. But a recent, little noted, bill, associated with proposed revisions of the Patient Protection and

45. *National Human Genome Research Institute (NHGRI), supra* note 36.

46. *Id.*

47. *Id.*

48. *Id.*

49. See, for example, Janet A. Kobrin, Comment, *Medical Privacy Issue: Confidentiality of Genetic Information*, 30 UCLA L. REV. 1283 (1983) (discussing how the law and courts have not kept pace with the widespread and increasing public use of genetic counseling services); George J. Annas, *Privacy Rules for DNA Databanks: Protecting Coded 'Future Diaries'*, 270 JAMA 2346, 2346 (1993) ("Current rules for protecting the privacy of medical information cannot protect either genetic information or identifiable DNA samples stored in databanks.").

50. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (2008) (codified as amended in scattered sections of 29 U.S.C. and 42 U.S.C.).

51. 42 U.S.C. § 12101 (1990) (amended 2009).

Affordable Care Act,[52] whilst purporting to support the Affordable Care Act's incentivization of wellness, could have removed privacy protections from those seeking to enjoy the benefit of the wellness incentives. The Preserving Employee Wellness Programs Bill of 2017 is worth quoting in full and would have exempted

> workplace wellness programs from: (1) limitations under the Americans with Disabilities Act of 1990 on medical examinations and inquiries of employees, (2) the prohibition on collecting genetic information in connection with issuing health insurance, and (3) limitations under the Genetic Information Nondiscrimination Act of 2008 on collecting the genetic information of employees or family members of employees. This exemption applies to workplace wellness programs that comply with limits on rewards for employees participating in the program. Workplace wellness programs may provide for more favorable treatment of individuals with adverse health factors, such as a disability. Collection of information about a disease or disorder of a family member as part of a workplace wellness program is not an unlawful acquisition of genetic information about another family member.[53]

If passed into law, this bill would, under the shading umbrella of other proposed changes to healthcare law, have undermined the genetic privacy protections established in the Genetic Information Nondiscrimination Act and the Americans with Disabilities Act. And that at a time when our expanded understanding of genetics makes it increasingly easy to identify supposedly anonymous individuals from databases containing their genetic information.

E. Ethical Concerns

This article includes consideration of human gene-editing and the creation of pig-human embryos as sources of organs and spare parts. Those with a sense of history, as well as of science and law, will appreciate that the medical and legal histories of the science of genetics have not been uniformly glorious. Sir Francis Galton, a half-cousin of

52. Pub. L. No. 111-148, 124 Stat. 119 (2010).
53. H.R. 1313, 115th Cong. (2017).

Charles Darwin, invented the term eugenics in 1883[54] to describe a set of ideas discussed at least since Plato recommended selective breeding to create a "guardian" class.[55]

Galton's form of eugenics through controlled breeding was popular amongst still celebrated English and Irish figures, including George Bernard Shaw, Bertrand Russell, Sidney and Beatrice Webb, and John Maynard Keynes; it was also enthusiastically espoused by Hitler in *Mein Kampf*,[56] along with sterilization legislation already implemented at that time in numerous U.S. states. The legislation, which was copied by Nazi Germany,[57] legalized enforced sterilization of various persons deemed to be defective—a position upheld as constitutional in the United States by Justice Oliver Wendell Holmes, writing the decision of the U.S. Supreme Court in *Buck v. Bell* in 1927.[58] The practice of forced sterilization continued in certain instances in the United States until the 1980s, and attenuated forms of it arguably still exist within the criminal justice system of today.[59]

Against that background, it is significant that those working in the field of genetic engineering have been the first to identify ethical questions about their own experiments. Dr. Jun Wu, in announcing the pig-human embryos, raised issues about the percentage of human to nonhuman cells in the chimeras.[60] The following was written by Professor Paul Knoepfler, shortly before the pig-human embryos were announced by the team at Salk, and other chimeras were announced by some of Knoepfler's own colleagues at UC Davis:

> As a stem cell and developmental biologist, I find the

54. *See* FRANCIS GALTON, INQUIRIES INTO HUMAN FACULTY AND ITS DEVELOPMENT (JM Dent & Sons 2d ed. 1907) (1883) (describing how eugenics refers to the science of improving stock including human races or strains of blood); *Eugenics*, STAN. ENCYCLOPEDIA OF PHIL. (July 2, 2014), https://plato.stanford.edu/entries/eugenics/.

55. See Book 1 of Plato's Socratic dialogue in PLATO, *The Republic of Plato*, *in* 2 THE WORKS OF PLATO: A NEW AND LITERAL VERSION, CHIEFLY FROM THE TEXT OF STALLBAUM 1 (Henry Davis trans., London, George Bell & Sons 1879) (describing how the different classes in Athenian society were determined by eugenics).

56. ADOLF HITLER, MEIN KAMPF (Stackpole Sons trans., 1939) (1925).

57. STEFAN KÜHL, THE NAZI CONNECTION: EUGENICS, AMERICAN RACISM, AND GERMAN NATIONAL SOCIALISM 86 (2002).

58. *See* 274 U.S. 200 (1927).

59. *See* Sam P.K. Collins, *Tennessee Prosecutor Insisted Woman Undergo Sterilization as Part of Plea Deal*, THINKPROGRESS (Mar. 30, 2015, 4:41 PM), https://thinkprogress.org/tennessee-prosecutor-insisted-woman-undergo-sterilization-as-part-of-plea-deal-a1ad95a5e045/; *see also 4 Cases of Sterilization as Part of Plea Deal*, USA TODAY (Mar. 28, 2015, 2:42 PM), https://www.usatoday.com/story/news/nation/2015/03/28/cases-where-sterilization-was-part-of-plea-negotiations/70593962/.

60. *See* Wu et al., *supra* note 3, at 479–80.

prospect of chimera research exciting, and generally support this work, as long as it is conducted under appropriate oversight and training. But there are tough bioethical questions here, too.

For instance, how long should human chimeras be permitted to develop in a research laboratory? There is no universal, concrete answer, but this question must be discussed and clear guidelines established depending on the number of human cells used.

How do we handle human cells being present in a developing chimeric brain? How many human cells would be too many, risking creating a brain that has substantial human attributes? There is a Catch-22 situation here. The closer you get to the valuable range for neuroscience research (at least a few percent human neurons, for instance, in the chimeric brain), the thornier the ethics get.

To illustrate the complexity, we can look at the example of a recent study[61] in which scientists created chimeric mice with a type of human brain cell called glia; these cells were present in a high abundance in the mouse brains. While glia are not believed to directly contribute to human thought, as neurons do, these chimeric mice were much smarter than normal mice. For instance, the chimeras were about twice as good at navigating mazes as regular mice and exhibited other signs of exceptional memory. This intriguing finding also points to the complexities of possible human chimera outcomes. There's no clear dividing line on the question of "overly" human chimeric brains because we lack an understanding of at what point "humanization" of an animal brain could lead to more human-like thought or consciousness. We don't even know when this happens in the normal developing human brain.

What if a research team, only after studying a chimeric

61. *See* Chen Chen et al., *Humanized Neuronal Chimeric Mouse Brain Generated by Neonatally Engrafted Human iPSC-derived Primitive Neural Progenitor Cells*, JCI INSIGHT, Nov. 17, 2016, at 1.

> brain, realized that despite careful planning they had created a chimera that had an unexpectedly high number—say, 50 percent—of human neurons? Is it then retroactively unethical to have made and used that chimera in research? Did that chimera potentially fall into some uncomfortable gray zone between an animal and human research subject? What if researchers developed an organ transplant chimera that was all pig except for one human kidney, but it also accidentally had human sperm or eggs? Is that ethically okay, as long as it isn't allowed to breed?
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> . . .
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> Other tough questions are popping up as well in related areas of cutting-edge research using human pluripotent stem cells. For example, researchers are now able to grow miniature versions of human brains and other organs from pluripotent stem cells in a dish in the lab. This powerful research on so-called human "organoids" has tremendous potential for biological research and organ transplants. But along with that potential come profoundly challenging questions. What if human mini-brains in a dish could "think" or be conscious at a certain level? Some scientists believe that could never happen. I am not so sure that "never" is a safe response. These are not just philosophical musings. While my own laboratory does not do chimera research, right now there are human mini-brains in development.[62]

In a more recent article, written after the announcement of the pig-human embryos, Professor Knoepfler stated:

> Even with complementation (where for example a pig chimera would ideally only have human cells contributing to one organ such as a kidney or pancreas) one of the ethical dilemmas is that the chimeras would have to be taken to term in order to get a usable human pancreas. It is unclear if taking a human-animal

62. Paul Knoepfler, *Human Chimera Research's Huge (and Thorny) Potential*, WIRED (Sept. 19, 2016, 7:00 AM), https://www.wired.com/2016/09/human-chimera-researchs-huge-thorny-potential/.

> chimera to term could be ethically permissible. In [the] paper,[63] the team isolated the human-pig chimeras for analysis very early in development. Other ethical challenges include avoiding excessive (however one defines that) human cell contribution to chimeric brains and any human contribution to germ [or reproductive] cells. Potential safeguards for the latter include never letting the animals be bred or always including a genetic change making them sterile or both. Overall, this is exciting research in an ethically challenging arena. The real hope here long term for a new source of organs for transplants is extremely important given the massive need amongst patients, many of whom die on the waiting list. This development also makes starting to tackle the bioethical issues now rather than later a wise choice.[64]

These are clearly extremely important questions for lawyers, scientists, ethicists, and society in general; yet, thus far, lawyers and lawmakers have tended to engage with genetic engineering mainly in the relatively narrow arena of patent law.

II. THE GENE RUSH: PATENT CLAIMS AND A CHRONICLE OF PERCENTAGES FORETOLD

In 1997, the cell biologist Stuart Newman foreshadowed 2017's pig-human embryos when he applied to the U.S. Patent and Trademark Office (USPTO) for a patent on proposed "chimeric embryos and animals containing human cells."[65] The embryos were created for the purpose of providing organs for transplant into humans, which is also the main purpose of the pig-human embryo work. The patent application was ultimately rejected in 2005.[66] The USPTO offered some remarks in an early press release, stating that a human-nonhuman chimera may be ineligible for patent protection because of a failure to meet the moral

63. *See* Wu et al., *supra* note 3, at 484.

64. *Perspectives on Pig Human Chimera Paper*, *supra* note 28.

65. Chimeric Embryos and Animals Containing Human Cells, U.S. Patent Application No. 08/993,564 (filed Dec. 18, 1997) (status abandoned for failure to respond to office action).

66. *See* Rick Weiss, *U.S. Denies Patent for a Too-Human Hybrid*, WASH. POST, Feb. 13, 2005, at A03.

utility requirement under § 101,[67] and in a later decision letter to Newman, rejecting the application because human beings are not patentable subject matter.[68] Yet this left considerable doubt as to how it might be determined whether the subject of such a patent application was too human to qualify for a patent, as the USPTO had decided in this instance.

As far back as 1987, after the decisions in *Diamond v. Chakrabarty*[69] and *Ex Parte Allen*,[70] the USPTO announced with express, but unspecific, reference to the Constitution,[71] a policy that human beings would not be considered patentable subject matter.[72] The policy was later included in Section 2105 of the Manual of Patent Examining Procedure, which states that if "the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to non-statutory subject matter."[73]

Yet it was not until 2011 that Congress passed Section 33(a) of the America Invents Act,[74] which provides that: "Notwithstanding any other

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67. *See* Press Release, U.S. Patent & Trademark Office, Facts on Patenting Life Forms Having a Relationship to Humans (Apr. 1, 1998), https://www.uspto.gov/about-us/news-updates/facts-patenting-life-forms-having-relationship-humans.

68. *See Patent Application is Disallowed as 'Embracing' Human Being*, 58 Pat. Trademark & Copyright J. (BNA) No. 1430, at 203 (June 17, 1999); *see also* Yvonne Cripps, *The Art and Science of Genetic Modification: Re-Engineering Patent Law and Constitutional Orthodoxies*, 11 IND. J. GLOBAL LEGAL STUD. 1, 21 (2004); Weiss, *supra* note 66.

69. In *Chakrabarty*, the Supreme Court held that a genetically engineered *pseudomonas* bacterium, modified to consume crude oil, was patentable because the inventor had "produced a new bacterium with markedly different characteristics from any found in nature, and one having the potential for significant utility. His discovery is not nature's handiwork, but his own . . . ." 447 U.S. 303, 310 (1980); *see also* Cripps, *supra* note 68, at 8.

70. *See Ex parte* Allen, 2 U.S.P.Q.2d (BNA) 1425, 1426 (B.P.A.I. Apr. 3, 1987) (involving a patent on polyploid oysters).

71. For further analysis of constitutional aspects, see my discussion of humanness, personhood, and dignity, *infra* page 721.

72. Donald J. Quigg, *Animals–Patentability*, 1077 OFF. GAZ. PAT. & TRADEMARK OFFICE 24 (1987). This policy statement was unsuccessfully challenged in Animal Legal Def. Fund v. Quigg, 932 F.2d 920 (1991), in which it was held that judicial review is rare in such cases because third party plaintiffs, under the Administrative Procedures Act, lack standing to challenge the Patent and Trademark Office's interpretation of existing law.

73. U.S. PATENT & TRADEMARK OFFICE, U.S. DEP'T OF COMMERCE, MPEP § 2105 (8th ed. Rev. 9, Aug. 2012).

74. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 340 (2011) (codified as amended in scattered sections of 35 U.S.C.). Research by Gleicher and Tang which "involved the mixing of embryonic cells of different genders," see Norbert Gleicher & Ya Xu Tang, Blastomere Transplantation in Human Embryos May Be a Treatment for

provision of law, no patent may issue on a claim directed to or encompassing a human organism."[75] Picture and pity those in the USPTO, who, having awaited legislative guidance for decades, were still left without an accompanying statutory definition or guidance on what constitutes a "human organism" for the purposes of the legislation. The words "directed to or encompassing" are bound to lead to trouble in their own right, but trouble perhaps of a more manageable kind than the still undefined "human organism." Will the presence of more than 50 percent human genes, or some other arbitrary percentage, become a criterion or even the determinant for denial of patents on human-nonhuman animal chimeras?

In general, and especially after the *Roslin* case,[76] it might be thought that human organisms are not novel for the purposes of patent law under 35 U.S.C. § 102. But the *Roslin* case involved the defeat of a patent on a *cloned* creature ("Dolly," the sheep clone), not a deliberately genetically engineered chimera. A human or nonhuman animal modified to be a chimera could be regarded as highly novel and a product of man rather than nature for the purposes of patent law. Even the decision in *Roslin* might be questioned on the ground that no mammal, such as Dolly, had ever been invented by somatic cell nuclear transfer (as opposed to embryo splitting).[77] That nuclear transfer into a donor egg cell left Dolly with mitochondrial DNA from the egg cell donor, in addition to the DNA from the somatic cell donor. It is also important to note that even clones are not epi-genetically[78] identical to

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Single Gene Diseases, 81 FERTILITY & STERILITY 977, 980–81 (2004), spurred Congress to introduce the Weldon Amendment, first proposed as a rider to the Commerce-Justice-State Appropriations bill for fiscal year 2004, see H.R. 2799, 108th Cong. § 801 (2003), and passed as part of the Consolidated Appropriations Act of 2004. It stated that "[n]one of the funds appropriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism." H.R. 2799, *supra*. Congress reenacted the amendment each year until it was implemented as section 33(a) of the America Invents Act. See Ava Caffarini, Directed to or Encompassing a Human Organism: How Section 33 of the America Invents Act May Threaten the Future of Biotechnology, 12 J. MARSHALL REV. INTELL. PROP. L. 768, 776–77 (2013); see also Yaniv Heled, On Patenting Human Organisms or How the Abortion Wars Feed into the Ownership Fallacy, 36 CARDOZO L. REV. 241 (2014) (discussing the effects of section 33 of the America Invents Act).

75. H.R. 2799, *supra* note 74.

76. *See In Re* Roslin Inst. (Edinburgh), 750 F.3d 1333 (Fed. Cir. 2014) (cloned mammals are not patentable subject matter). See also Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013), in which the Supreme Court ruled that merely isolated human DNA is an unpatentable product of nature.

77. Cripps, *supra* note 68, at 9–10.

78. The word "epigenetic" translates from the Greek word "epi" to mean upon the genetic sequence. The term has come to refer to any process, including environmental influence, that alters gene activity or expression (the phenotype) (for example, by

the creatures from which they are cloned. So, even Dolly, though a clone, was arguably novel and markedly different from other sheep. But how marked must the marked in "markedly different" be? The court in *Roslin* decided this issue, in part, on the more narrowly technical point that such differences from other sheep as are identified here were not expressly stated in the claims in the Roslin Institute's patent application. As indicated above, however, a deliberately genetically modified creature, especially a chimera, is less likely than a clone to be barred from patentability by being viewed as a product of nature, as opposed to a product of man.

To be patented, an invention must, in broad terms, be novel, nonobvious, and useful. This latter requirement is known in patent law as utility. In *Lowell v. Lewis*, Justice Story identified a further requirement of what has come to be known as moral utility. He stated:

> All that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society. The word 'useful,' therefore, is incorporated into the [patent] act in contradistinction to mischievous or immoral. For instance, a new invention to poison people, or to promote debauchery, or to facilitate private assassination, is not a patentable invention.[79]

Using this moral utility doctrine, which is not enshrined in statute as it is in Europe, the U.S. courts invalidated patents on inventions, such as gaming machines, well into the twentieth century.[80] In the *Juicy Whip* case,[81] the Court of Appeals for the Federal Circuit cast doubt on the doctrine and it began to fall into disuse, though it found its way into the twenty-first century in *Geneva Pharmaceuticals, Inc. v. Glaxosmithkline PLC.*, in which the court noted that a "patent possesses utility 'if it will operate to perform the functions and secure the results intended, and its use is not contrary to law, *moral* principles, or public

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switching genes on and off) without changing the underlying DNA sequence (the genotype), and leads to modifications that can be transmitted to daughter cells (although experiments show that some epigenetic changes can be reversed). *See* Bob Weinhold, *Epigenetics: The Science* of Change, ENVTL. HEALTH PERSP., Mar. 2006, at A160, A163.

79. Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817).

80. Benjamin D. Enerson, Note, *Protecting Society from Patently Offensive Inventions: The Risk of Reviving the Moral Utility Doctrine*, 89 CORNELL L. REV. 685, 686–88 (2004); Robert P. Merges, *Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies*, 47 MD. L. REV. 1051, 1063 (1988).

81. Juicy Whip, Inc. v. Orange Bang, Inc., 185 F.3d 1364, 1366–68 (Fed. Cir. 1999).

policy.'"[82] And it is, of course, also open to the Supreme Court to revitalize and deploy the moral utility doctrine.

For all the infelicities of the moral utility doctrine, which turns patent examiners and appellate bodies into understandably reluctant arbiters of morality with little or no legislative guidance, a patent on a significantly human chimera may provide the impetus for the Supreme Court to revive the doctrine in the absence of a legislative definition of a "human organism" for the purposes of section 33(a) of the America Invents Act.

Because patents are territorial in the sense that they only protect the inventor in the country, block, or jurisdiction in which a patent is granted, American and other inventors may well wish to patent their inventions in other jurisdictions, including Europe, under, *inter alia*, the European Patent Convention (EPC). Article 53(a) of the EPC expressly prohibits the granting of patents which would be "contrary to *ordre public* or morality."[83] The same prohibition appears in Article 6 of the European Directive on the Legal Protection of Biological Inventions,[84] which states that, in the context of European patent law:

> 1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.
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> 2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
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> (a) processes for cloning human beings;

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82. Geneva Pharms., Inc. v. Glaxosmithkline PLC, 213 F. Supp. 2d 597, 610 (E.D. Va. 2002) (citing Callison v. Dean Novelty Co., 70 F.2d 55, 58 (10th Cir. 1934)) (emphasis added).

83. Convention on the Grant of European Patents, art. 53(a), Oct. 5, 1973, 1065 U.N.T.S. 255 [hereinafter Patent Convention]. Note also that, under Article 27(2) of the TRIPS agreement, "Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect '*ordre public*' or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law." The Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1C, art. 27(2), Apr. 15, 1994, 1869 U.N.T.S 299.

84. Council Directive 98/44, art. 6, 1998 O.J. (L 213) 13, 18–19 (EC), http://data.europa.eu/eli/dir/1998/44/oj [hereinafter Biotech Directive].

> (b) processes for modifying the germ line genetic identity of human beings;
>
> (c) uses of human embryos for industrial or commercial purposes;
>
> (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.[85]

Philip Grubb has addressed the distinction between *ordre public* and morality, stating that adultery in private may be considered immoral, but, if performed in the public street, might be viewed as contrary to *ordre public*.[86] He also argues that a breach of *ordre public* means more than what English law would regard as a disturbance of the peace; suggesting that, under German law, it would mean a violation of a basic constitutional right, such as the right to life, personal freedom, human dignity, and freedom from bodily harm.[87] His analysis also serves to illustrate the problem of different standards of morality in different jurisdictions. Article 6 (2) of the European Directive is focused on processes and uses, rather than the products of processes, and thus none of the unpatentable inventions listed in Article 6 (2) appears squarely to cover the pig-human embryos, which is not of course to say that they may not be regarded as immoral in terms of Article 6 (1). In practice, however, although the morality of an invention

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85. *Id.* Note also that the EPO has revised European patent regulations to exclude from patentability plants and animals resulting from essentially biological breeding practices. The EU Directive had contained a much debated ambiguity, which excluded biological breeding processes themselves from patentability, but did not clearly prevent the patenting of the plants and animals resulting from those processes. The European Commission released a notice in November 2016 asserting that it was the European Parliament's intention that not only such breeding processes, but also their resulting offspring, are unpatentable. *See* Commission Notice on Certain Articles of Directive 98/44, 2016 O.J. (C 411) 3. The EPO has now amended the regulations and the new rules took effect on 1 July 2017. Patent Convention, *supra* note 83, at 419–20 (as amended by Decision of the Admin. Council of 29 June 2017 amending Rules 27 and 28 of the Implementing Regulations to the European Patent Convention Decision (CA/D 6/17), A56 (June 29, 2017)); *see also* Steven J. Zweig, *Selected Developments in Biotechnology Law and the Biotechnology Industry*, 36 BIOTECHNOLOGY L. REP. 147, 147 (2017).

86. *See* PHILIP W. GRUBB ET AL., PATENTS FOR CHEMICALS, PHARMACEUTICALS, AND BIOTECHNOLOGY: FUNDAMENTALS OF GLOBAL LAW, PRACTICE, AND STRATEGY 343 (6th ed. 2016).

87. *Id.*

is to be taken into account in European patent law, patent examiners and appellate bodies have been very reluctant to decide that any particular invention is immoral or contrary to public order, either under Article 53(a) of the EPC[88] or Article 6 of the European Directive, though abhorrence or unacceptability to members of the public have sometimes been referred to as the determining factors or tests.[89] Are the pig-human embryos, especially if brought to term, abhorrent or unacceptable?

III. HUMANNESS, PERSONHOOD, AND DIGNITY

The following definition of the words "person" and "human being" appears in 1 U.S.C. § 8(a): "In determining the meaning of any Act of Congress, or of any ruling, regulation, or interpretation of the various administrative bureaus and agencies of the United States, the words 'person', 'human being', 'child', and 'individual', shall include every infant member of the species *homo sapiens* who is born alive at any stage of development."[90] While the words "at any stage of development" are interesting in this context, (not least in terms of the stem cells at various stages of development that are used to create chimeras),[91] the definition casts little light on chimeras involving human genes—such creatures having been quietly moored in the realms of myth at the time the section was drafted. The reference to the species *homo sapiens* might at first sight be thought to be helpful in our inquiry. But, as *homo sapiens* is the only extant human species, we are drawn back to the question of how we decide whether or when a chimera substantially involving human genes, mixed with nonhuman animal genes, would qualify—or fail to qualify—as a member of that species. We are, after all, in scientific terms, the human animal: members of the animal kingdom.

The Thirteenth Amendment to the U.S. Constitution arguably

88. See the patent granted on the "Harvard mouse." European Patent No. EP0169672 (application published Jan. 29, 1986); *Decisions of the Examining and Opposition Divisions*, OFFICIAL J. EUROPEAN PAT. OFF., Oct. 1992, at 556, 588. Though contrast with that the decision taken by the European Patent Office on the same day on the Upjohn mouse. *Bioethics and Patent Law: The Case of the Oncomouse*, WIPO MAGAZINE (June 2006), http://www.wipo.int/wipo_magazine/en/2006/03/article_0006.html. See also the decision of the Canadian Supreme Court in Harvard Coll. v. Canada (Comm'r of Patents), [2002] 4 S.C.R. 45 (Can.).

89. See, for example, R. v. Leland Stanford/Modified Animal, 2002 Eur. Pat. Off. Rep. 2, 16, 23 (Opposition Div.) (applying the public abhorrence test).

90. 1 U.S.C. § 8(a) (2018). Fetuses are not constitutional persons under the Fourteenth Amendment. Roe v. Wade, 410 U.S. 113 (1973).

91. *See* 1 U.S.C. § 8(a) (2018).

prohibits patents on human beings,[92] and, interestingly, unlike, for example, the Fifth and Fourteenth Amendments, confers protections on a "party" rather than a person.[93] It binds private citizens, unlike other constitutional provisions which apply only to state actors. The Fourteenth Amendment to the Constitution confers privacy rights and personhood on persons, as defined in constitutional law.[94]

I have written elsewhere about the possible application of the Thirteenth and Fourteenth Amendments to the protection of human clones.[95] At least in the case of a clone of a non-genetically-modified human being, there should be little doubt that the clone is human and thus entitled to the protections of the Constitution. But how much *nonhuman* DNA must be incorporated in a chimera before it loses constitutional protections? *Or*, the obverse, how much *human* DNA must be embodied in a nonhuman animal before it gains those protections? There will be dispute about how we define human DNA.

How do we decide which entities are persons? We know that corporations and certain other collective entities qualify.[96] The distinction between human and other persons for constitutional purposes is sometimes discussed in terms of a distinction between so-called natural persons and legal or juridical persons.[97] But it is unlikely that creatures such as pig-human chimeras would not be regarded as persons solely on the grounds that they are not truly natural, as opposed to man-made or modified by man. "Natural" in this jurisprudential usage seems to refer more to the biological or animate, as opposed to the inanimate in the case of a corporation, though it can be argued that a corporation is simply an aggregation or collective of individual living persons (*universitas personarum*) and gains its status as a person in that way.[98]

Section 1, Article 2, of the Constitution sets forth the eligibility requirements for serving as President of the United States as follows: "No Person except a natural born Citizen, or a Citizen of the United States, at the time of the Adoption of this Constitution, shall be eligible

92. Cripps, *supra* note 68, at 18–20.

93. George Rutherglen, *State Action and the Thirteenth Amendment*, 94 VA. L. REV. 1367 (2008).

94. *See, e.g.,* Roe, 410 U.S. at 113.

95. Cripps, *supra* note 68, at 18–20.

96. Santa Clara Cty. v. S. Pac. R.R., 118 U.S. 394, 396 (1886) (equal protection); Chicago, Milwaukee & St. Paul Ry. Co. v. Minnesota, 134 U.S. 418, 456–457 (1890) (due process).

97. Louisville, Cincinnati & Charleston R.R. v. Letson, 43 U.S. 497, 519–21 (1844).

98. Pembina Consol. Silver Mining & Milling Co. v. Pennsylvania, 125 U.S. 181, 189 (1888).

to the Office of President . . . ."[99] The phrase "natural-born Citizen" is not used in the Fourteenth Amendment, though the latter does extend its protections to "all persons born or naturalized in the United States."[100] Chimeras may be born in relatively conventional ways so the word "born" does not rule out chimeras. But what does "natural" mean in this context? It seems mainly to qualify the word "born" and perhaps distinguish the "natural born" from those who are naturalized.

As we have already seen, there is a distinction between constitutional personhood and humanness. Self-awareness does not seem to be the key to either humanness or constitutional personhood, especially for corporations as persons, though that depends somewhat on how one defines awareness and on whose part it should exist in a corporation. Self-awareness is certainly not necessary for personhood, especially at the individual level. At the species level, it might be observed that members of the species *Homo sapiens* are generally characterized by self-awareness even if individual persons, for example, those on a ventilator, might no longer have self-awareness; though the legal system might deem such individuals not to be live persons if there has been total (including brain stem) brain death.[101] We also still treat anencephalic babies, born with little or no functioning cerebrum, as both human and entitled to the protections of constitutional personhood, though the American Medical Association briefly dissented from that view in the past, in a bid to use severely anencephalic babies as a source for much-needed organs.[102]

Do international instruments provide more answers than domestic law to questions of whether human-nonhuman chimeras qualify for personhood or even designation as human? In the international arena, attempts have been made to protect "dignity," presumably from abhorrent or unacceptable assaults,[103] but, again, the prerequisite for the international treaty protections of dignity is that those whose dignity is being protected are defined as human. The Oviedo 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[104] might be thought to throw some light

99. U.S. CONST. art II, § 1.

100. U.S. CONST. amend. XIV.

101. *See* UNIF. DETERMINATION OF DEATH ACT § 1 (NAT'L CONFERENCE OF COMM'RS ON UNIF. STATE LAWS 1980).

102. *See* BARRY R. FURROW ET AL., HEALTH LAW: CASES, MATERIALS AND PROBLEMS 1271–88, 1509–34 (7th ed. 2013).

103. See Cripps, *supra* note 68, for a discussion of those words in the context of patent law.

104. 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

on this issue, though the United States is not a signatory. The Oviedo Convention contains provisions that relate to concerns about research into the human genome. It addresses genetic testing, the storage of genetic data and modification of the human genome. Genetic testing as a tool for discrimination is prohibited under Article 11, while Article 12 allows genetic testing only to improve health or for scientific research linked to health purposes. Similarly, Article 13 generally prohibits modification of the human genome, unless for health-related purposes. Because the Convention was signed as far back as 1997, one can perhaps forgive drafters and signatories for failing to foresee that a definition of "human" might well be required. Some might argue that a chimera, such as a pig-human, is not a human for the purposes of the protections offered by the Convention, depending on how much nonhuman DNA the chimera contains. There might, for example, not be discrimination against a human if the being discriminated against is deemed not to be sufficiently human. These questions should not be regarded as merely theoretical, as we have noted above in regard to the already expressed concerns of cell biologists working in institutions where embryonic human-nonhuman chimeras have been created.[105] Nor is the Oviedo Convention alone in failing to define human beings or persons for the purposes of the proffered international legal protection. The same problem is, for example, evident in UNESCO's Universal Declaration on the Human Genome and Human Rights;[106] UNESCO's International Declaration on Human Genetic Data;[107] UNESCO's Universal Declaration on Bioethics and Human Rights; [108] and the UN's International Covenant on Economic, Social and Cultural Rights.[109]

CONCLUSION

Socrates's defense of the importance of the examined life[110] can be

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Biomedicine, *opened for signature* Apr. 4, 1997, 2137 U.N.T.S. 171 [hereinafter Convention on Human Rights] (entered into force Jan. 12, 1999).

105. *See* Wu et al., *supra* note 3, at 479–80 as discussed on pages 712–715 of this article.

106. UNESCO Res. 29 C/16, Universal Declaration on the Human Genome and Human Rights (Nov. 11, 1997).

107. UNESCO Res. 32 C/22, International Declaration on Human Genetic Data (Oct. 16, 2003).

108. UNESCO Res. 33 C/36, Universal Declaration on Bioethics and Human Rights (Oct. 19, 2005).

109. International Covenant on Economic, Social and Cultural Rights, Dec. 16, 1966, 993 U.N.T.S. 3.

110. At his trial, see THOMAS C. BRICKHOUSE & NICHOLAS D. SMITH, PLATO'S SOCRATES 201 (1994). And in Book II of his Socratic dialogue, *Republic,* Plato imagines Socrates

seen to have additional layers of significance in this age of gene editing, which ushers in the writing as well as reading of the human genetic code.[111] Our genes interact internally and with our environment[112] in ways that are beyond our current understanding, not least as to the precise consequences of gene editing, and it is important that we do our best to ensure that the phrase "precision medicine" turns out not to be a misnomer. CRISPR-Cas9 may well be a more promising and precise gene editing tool than any we have had before but the ongoing effects of its application are far from clear, both scientifically and in terms of wider societal outcomes. Negative consequences—not least in terms of potentially patenting as a chimera a significantly human organism—and erosion of personhood, must be considered even, or especially, as the forward thrusts of scientific discovery and technological application promise exciting cures. History does indeed seem to repeat itself and elimination of illness and deemed defect has, as we have seen, been a temptation badly mishandled in the past, and not so distant past.[113]

Treatments for rare diseases, which have not tended to attract significant capital, could well be assisted by modification of the human genome, but it is not clear that the benefits of gene-editing will be shared with uncommonly afflicted individuals. Nor are those who suffer from more common illnesses guaranteed affordable medicine, with examples of price-gouging in the pharmaceutical sector,[114] and patient protections in the Affordable Care Act under threat.[115] Yet there are

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suggesting to his young companion, Glaucon, that they look for justice in a city rather than in an individual man. After attributing the origin of society to the individual not being self-sufficient and having many needs which he cannot supply himself, they go on to describe the development of the city. Socrates first describes the "healthy state," but Glaucon asks him to describe "a city of pigs," as he says that he finds little difference between the two. Socrates then goes on to describe the luxurious city, which he calls "a fevered state." This, he feels, requires a "guardian class" to defend and attack on its account. *See* PLATO, *supra* note 55.

111. *See generally* SIDDHARTHA MUKHERJEE, THE GENE: AN INTIMATE HISTORY (2017) (tracing the history and development of the human understand of the gene).

112. *See* Weinhold, *supra* note 78, for a discussion of epigenetics.

113. *See supra* pages 711–712.

114. Note, for example, the 5000% increase in a drug price—the drug still costs 2,500% more than before the arbitrary price rise. Andrew Pollack, *Drug Goes From $13.50 a Tablet to $750, Overnight*, N.Y. TIMES (Sept. 20, 2015), https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html; Heather Long, *Here's What Happened to AIDS Drug that Spiked 5,000%*, CNN MONEY (Aug. 25, 2016, 12:10 PM), http://money.cnn.com/2016/08/25/news/economy/daraprim-aids-drug-high-price/index.html.

115. *See* Act of Dec. 22, 2017, Pub. L. No. 115-97, § 11081, 131 Stat. 2054, 2092; *see also* Exec. Order No. 13,813, 82 Fed. Reg. 48,385 (Oct. 12, 2017).

countervailing influences, as in the *Myriad Genetics* case,[116] which called a halt to the systematic patenting of unmodified human genes. Prior to such patent claims, these might well have been viewed as part of the common heritage of mankind. Orthodox patent law had traditionally not allowed patents on products of nature, which is how merely isolated genes might well be described. It took the Supreme Court of the United States ultimately to rule out such patents[117] and, in a series of cases,[118] to rein in the United States Court of Appeals for the Federal Circuit, which had previously[119] displayed a rather instinctively pro-patent approach across a range of issues,[120] perhaps for a time losing sight of the fact that over-patenting things and creatures that are not, in traditional patent law terms, truly inventive or patentable, can have a chilling effect on innovation.

The advent of embryonic human-nonhuman chimeras, accompanied by the marriage of CRISPR-Cas9 to stem cell technology, threatens to challenge and even redefine what it means to be human. It would be lamentable if, despite the prohibition in Section 33 (a) of the America Invents Act, a modified human being, in the garb of a chimera, were to lurch through the system and be patented. And will such human-nonhuman animal chimeras be regarded as persons for constitutional purposes? Be prepared for gradual, almost casual, abrasion of personhood.

Thomas Larsson, in his book, *The Race to the Top: The Real Story of Globalization*, states that globalization "is the process of world shrinkage, of distances getting shorter, things moving closer. It pertains to the increasing ease with which somebody on one side of the world can interact, to mutual benefit, with somebody on the other side of the world."[121] The word "mutual" in that quote gives pause for doubt in terms of what the author alleges is the "real story" of globalization. I

116. *See* Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 590 (2013) (considering the "delicate balance between creating 'incentives that lead to creation, invention, and discovery' and 'imped[ing] the flow of information that might permit, indeed spur, invention.'").

117. *See id.* Note also that attempts by Myriad Genetics to obtain injunctive relief against a variety of organizations, (post-*Myriad Genetics* in the Supreme Court), have failed, confirming the futility of Justice Thomas's attempt to create a meaningful legal distinction between copy DNA (cDNA) and DNA.

118. *See, e.g.*, Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 87–91 (2012).

119. Compare, more recently, *In Re* Roslin Inst. (Edinburgh), 750 F.3d 1333 (Fed. Cir. 2014).

120. *See* Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303, 1324–33 (Fed. Cir. 2012).

121. TOMAS LARSSON, THE RACE TO THE TOP: THE REAL STORY OF GLOBALIZATION 9 (2001).

suppose it depends on how one defines mutuality.

In the sense of closeness with those in other parts of the world, the ultimate globalization could be said to come with the knowledge and digitization of how similar human genomes are to one another and with the observation that the percentage differences between nonhuman animal genomes and human genomes are surprisingly slight: as, to some extent, are those between plant and human genomes. Yet that perspective, based on an even approximate percentage calculation of genes, is in danger of leaving out the human element—the humanness of us all. Whilst it is important that we do not stifle or unnecessarily impede promising biomedical development, we should proceed cautiously to avoid undermining, incrementally and ironically, the very humanness that we seek to protect in our search for restorative organs and other improvements. Inquire, potentially, of the sources of the organs and spare parts that scientists are working so hard to modify in the human-nonhuman chimeras. You, or the patent office, determine the essential proportions.