GERMLINE DOPING FOR HEIGHTENED PERFORMANCE IN SPORT

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In recent years, gene editing techniques such as CRISPR-cas9 have begun to enable the genetic makeup of organisms – including humans – to be precisely designed and engineered. Human embryonic gene editing is both nascent and highly contentious, with many within the scientific community cautioning against its use. However, given the long history of new technologies being used to confer a competitive advantage in sport, it is likely only a matter of time before human embryonic germline editing is explored to heighten athletic performance. As the technology develops, there is an urgent need to better-understand the legal landscape around germline doping to ensure the safety and wellbeing of athletes, and the integrity and value of the sports they participate in.

Introduction – Part I

'The most important thing in the [Olympic] Games is not to win, but to take part, just as the most important thing in life is not the triumph but the struggle. The essential thing is not to have conquered, but to have fought well.'
('The Olympic Creed')[1]

'Winning medals must always be the primary goal.'
(US Olympic Committee Overview Commission)[2]

The concept of utilising cutting edge technologies to gain advantage in professional sports, both in domestic and international competition, is as old as sports themselves. As such, athletes have frequently used performance enhancements as tools to better cope with fatigue and pain, or boost physiological performance – despite the potentially lethal nature of approaches such as augmenting the blood.[3] Shifts in social norms in the 20th century, along with

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The authors gratefully acknowledge the Global Sports Institute at Arizona State University and the Carnegie Corporation of New York which generously funded our research in this article.

1 Committee on Energy and Commerce, US House of Representatives, Washington DC, 30 July 1987, 49 (Ollan Cassell, quoting Baron Pierre de Coubertin).

2 Michael Janofsky, 'Steinberg Report Faults U.S. Progress', *New York Times* (20 February 1989) <https://www.nytimes.com/1989/02/20/sports/steinbrenner-report-faults-us-progress.html>.

3 See E Randy Eichner, 'Blood Doping: Infusions, Erythropoietin and Artificial Blood' (2007) 37(4–5) *Sports Medicine* 389, 390.

the deaths of a number of high-profile athletes,[4] acted as a catalyst for greater oversight of professional sport, with many of these traditional 'tools' becoming classified as illegal forms of cheating.[5] Yet such bans have done little to prevent athletes, and the experts they turn to, from employing cutting edge technologies in return for competitive advantages in the form of personal, economic, and political gain.[6] It follows that the bodies responsible for testing athletes, such as the World Anti-Doping Agency ('WADA'), constantly need to respond to novel performance enhancing substances or methods. As a result, they often must 'play catch-up' with scientific and athletic communities;[7] a classic illustration of the obstacles facing those charged with governing emerging technologies.[8]

Amidst the myriad pharmaceutical and hormonal enhancements[9] available to athletes (as well as non-athletes), along with technological advancements to athletic gear and equipment,[10] gene editing has emerged as a new tool with high potential to disrupt and transform athletic competition.[11] Such gene editing tools allow for experts to precisely and selectively insert, eliminate, or modify desired portions of DNA within living cells.[12] Substantial advances in gene editing capabilities began with the development of zinc finger nucleases and Transcription Activator-Like Effector Nuclease ('TALENs') technologies, though high costs and expertise required blunted their utility.[13] Over the past seven years, attention has shifted to more precise techniques such as CRISPR-Cas9 that offer swift, cheap, malleable, and easy-to-use alternatives.[14] CRISPR arose from the discovery of an immunity mechanism in bacteria where enzymes leveraged 'clustered regularly interspaced short palindromic repeat' ('CRISPR')

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4 The deaths of 20 or more cyclists around the turn of the millennium may have resulted from 'blood doping'. See Haroon Siddique, 'Blood Doping: What Is It and Has Anyone Died As a Result?', *The Guardian* (2 August 2015) <https://www.theguardian.com/sport/2015/aug/02/blood-doping-what-is-it-and-has-anyone-died-as-a-result-of-it>.

5 Though debate exists over why and how doping or other technological augmentations classify as 'cheating', the literature generally recognized doping as a form of cheating. See, eg, Sigmund Loland, 'The Varieties of Cheating–Comments on Ethical Analyses in Sport', (2005) 8(1) *Sport in Society* 11, 12-3.

6 Mike Rowbottom, *Foul Play: The Dark Arts of Cheating in Sport* (Bloomsbury, 2013) 2. See also Piers Edwards, 'The Gain Game: Why Do Sports Stars Cheat?', *CNN News* (11 December 2012) <https://www.cnn.com/2012/12/11/sport/sport-cheats-suarez-cazorla/index.html>.

7 See Deborah Healey, 'The Myth of the Level Playing Field in Sport' in Ulrich Haas and Deborah Healy (eds), *Doping in Sport and the Law* (Hart, 2016).

8 Louis M Solomon, David S Mordkoff, and Rebekka C Noll, 'Physical Enhancement of Human Performance: Is Law Keeping Pace with Science?' (2009) 6(1) *Gender Medicine* 249.

9 Don H. Catlin and Thomas H. Murray, 'Performance-Enhancing Drugs, Fair Competition, and Olympic Sport' (1996) 276(3) *JAMA* 231. See generally John Gleaves and Thomas Hunt (eds), *A Global History of Doping in Sport: Drugs, Policy, and Politics* (Taylor & Francis, 2015).

10 Karen Crouse, 'Swimming Bans High-Tech Suits, Ending an Era', *New York Times* (24 July 2009) <https://www.nytimes.com/2009/07/25/sports/25swim.html>; Emma Dorey, 'Does Nanotechnology Offer Athletes More than a Sporting Chance?', *The Guardian* (8 May 2012) <https://www.theguardian.com/nanotechnology-world/does-nanotechnology-offer-athletes-more-than-a-sporting-chance>; Sean Ingle, 'Nike's Lightning Shoes Hint at Power of Technology to Skew Elite Competition', *The Guardian* (22 July 2018) <https://www.theguardian.com/sport/2018/jul/22/nike-shoes-vaporfly-sport>.

11 See Mehmet Unal and Durishevar Ozer Unal, 'Gene Doping in Sports' (2004) 34(6) *Sports Medicine* 357.

12 National Academies of Science, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Report, February 2017) 1 <https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance>.

13 Mazhar Adli, 'The CRISPR Tool Kit for Genome Editing and Beyond' (2018) 9 *Nature Communications* 1911:1–13, 2.

14 Jennifer A. Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR-Cas9' (2014) 346(6213) *Science* 1077, 1077.

sequences to cut away viral DNA that inserted itself into the normal bacterial genome.[15] In 2012, Doudna and Charpentier illustrated how to 'program' these CRISPR associated ('Cas') proteins to target and edit a DNA sequence of interest,[16] thus sparking a torrent of scientific activity. Collectively these efforts, and those of others, illustrate the flexibility and ease of use of CRISPR. In consequence, CRISPR has arisen as the scientific community's primary gene editing tool.[17] Recent breakthroughs using CRISPR and other tools for precision gene editing have brought closer the possibility of augmenting adult bodies through genetic manipulation, and/or designing heritable traits into humans.[18]

While the focus of the scientific community to date has centred on therapeutic applications, we argue that CRISPR and associated techniques hold substantial disruptive potential in sport, where genetic factors create a ceiling for potential athletic performance.[19] While the ethics of human gene editing remain controversial,[20] recent research demonstrates a growing capacity to design and engineer select genetic traits for both adult or embryonic applications.[21] Considering the significant role that emerging technologies play in the geopolitics of athletic performance,[22] we postulate that gene editing will likely have a profound influence on future athletic performance, whether carried out under an international ethical and legal framework, or at the borders of acceptable practices.[23]

While acknowledging that so-called 'gene' or 'genomic doping' remains a hypothetical possibility at this time,[24] we contend that these advanced gene editing technologies will likely materialize as a major disruption in the realm of sports. The technology has the potential to provide the scientific foundation for athletes who wish to enhance their physical abilities and capacity to win, or organisations who wish to foster individuals with superior athletic abilities, while simultaneously testing the governance frameworks under which competition occurs. As we highlight here, adult athletes aided by the scientific community can theoretically already engage in somatic cell 'gene doping'. Moreover, we

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15 Edze R. Westra, Angus Buckling, and Peter C. Fineran, 'CRISPR-Cas Cystems: Beyond Adaptive Immunity' (2014) 12(5) *Nature Reviews* 317, 317.

16 Martin Jinek et al, 'A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptative Bacterial Immunity' (2012) 337(6096) *Science* 816.

17 See Michal Boettcher and Michael T McManus, 'Choosing the Right Tool for the Job: RNAi, TALEN, or CRISPR' (2015) 58(4) *Molecular Cell* 575, 583.

18 See David Cyranoski, 'Baby Gene Edits Could Affect a Range of Traits', *Nature News* (12 December 2018) <https://www.nature.com/articles/d41586-018-07713-2>.

19 Ross Tucker and Malcolm Collins, 'What Makes Champions? A Review of the Relative Contribution of Genes and Training to Sporting Success' (2011) 46(8) *British Journal of Sports Medicine* 555, 555.

20 *Human Genome Editing* (n 12) 1.

21 Prashant Mali et al, 'RNA-Guided Human Genome Editing via Cas9' (2013) 339(6121) *Science* 823.

22 Scarlett Cornelissen, 'The Geopolitics of Global Aspirations: Sport Mega-Events and Emerging Powers' (2010) 27(16) *The International Journal of the History of Sport* 3008.

23 Matthias Braun, Hannah Schickl, and Peter Dabrock, 'An Introduction' in Matthias Braun, Hannah Schickl, and Peter Dabrock (eds) *Between Moral Hazard and Legal Uncertainty: Ethical, Legal and Societal Challenges of Human Genome Editing* (Springer, 2018) 6–9.

24 Even recent scholarship on gene doping in sport has expressly declined to consider the social and legal dimensions of germline editing. See James Brown, 'Genetic Doping: WADA We Do About the Future of "Cheating" in Sport?' (2019) 6(12) *International Sports Law Journal* 1, 2.

argue the first generation of embryonically gene-edited athletes, designed from gestation, may appear on the track, in the gym, or on the court within the next two to three decades, in a bid to gain future personal, political, and economic benefits for those involved. While such predictions may sound farfetched, the history of sporting competitions and scientific advancement support such a contention.

The manner in which national and global communities prepare for the potential impacts of gene editing on sport will depend critically on understanding the potential 'legal' and 'illegal' uses of this technology, the possible risks to individuals and communities, the likely impacts of its use on sport, and pathways toward the ethical and legally responsible use of gene editing for enhanced athletic performance.[25] This article seeks to examine each of these issues and does so against the backdrop of doping in sport more generally. Part II begins with an historical overview of doping in sport. Part III considers familiar and unique governance challenges presented by somatic and germline uses of gene editing to bolster athletic performance. Part IV follows by assessing conditions which may drive individuals, parents, or states to consider using gene editing techniques on adult athletes or human embryos. We conclude, in Part V by arguing that it is inevitable that professional and non-professional athletes alike will leverage the advantages offered by somatic and, especially, germline gene editing tools. Anti-doping bodies such as WADA must begin to conceptualize the dynamic governance arrangements that will be needed to address the unique challenges posed by the realities of gene doping and begin rolling out such frameworks within the next 12-24 months.

History of Doping in Sports – Part II

The use of performance enhancing substances in sports dates back to Greek Olympians and Roman gladiators.[26] The use of such substances for pain relief and enhancement presented real or perceived benefits to athletic performance.[27] Coinciding with the rise of contemporary medicine, more modern applications of drug-use in sports began in the late 19th century, when French cyclists and lacrosse players drank wine mixed with cocoa leaves to fight fatigue and hunger.[28] The practice of athletes creating different concoctions for enhancement continued uncontested until marathoner Thomas Hicks collapsed and almost died at the 1904 Olympics.[29] No prohibitions on either of the substances found in his system, strychnine and brandy, existed at the time.[30] His collapse, however, generated significant attention and, in turn, appears to have been a driver for greater oversight over the use of performance enhancing substances by athletes.

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[25] See generally Bob Goldman and Robert Klatz, *Death in the Locker Room: Drugs & Sports* (Elite Sports Medicine Publications, 1992).
[26] Gary L Wadler and Brian Hainline, *Drugs and the Athlete* (FA Davis Company, 1989).
[27] Ibid.
[28] Thomas H Murray, 'The Coercive Power of Drugs in Sports' (1983) 13(4) *Hastings Center Report* 24, 24.
[29] Terry Todd, 'Anabolic Steroids: The Gremlins of Sport' (1987) 14(1) *Journal of Sport History* 87.
[30] Ibid at 87.

In the aftermath of Hicks' collapse, the International Association of Athletics Federations ('IAAF'), the governing body for track and field, made a fundamental shift from focusing not only on the rules of games, to also concentrating on doping as a mechanism for cheating. As such, in 1928, they became the first international sporting federation to prohibit doping by athletes.[31]

However, as the IAAF was developing new rules on doping in sport, the next iteration in performance enhancement was emerging. Specifically, the 1930s gave rise to a new era in the use of anabolic steroids such as testosterone. Anabolic steroids lead to increased muscle mass, which is of particular interest to weightlifters.[32] Reports suggest synthetic testosterone first came into competitive use by Russian weightlifters in the 1952 Helsinki Summer Olympics, who dominated all classes that year.[33]

During the 1950s, anabolic steroids were not only legal, but under development as a therapeutic drug. In 1958, the United States ('US') Food and Drug Administration ('FDA') approved the synthetic anabolic steroid methandienone (Dianabol), which was invented by Dr John Zieglar, the US Olympic weightlifting team physician at the time. As a result, the US weightlifting team served as Zieglar's personal experimental cohort.[34] Within two years, almost all world class athletes became aware of the performance enhancement potential of anabolic steroids, and research suggests that many of these athletes appeared willing to experiment upon themselves in their quest to win.[35]

While anabolic steroids increased physical strength, other athletes in the late 1950s began to turn to central nervous system stimulants such as amphetamines to bolster wakefulness, reaction times, and mood.[36] The death of Danish cyclist Knut Jensen during the 1960 Rome Olympics prompted increased anti-doping oversight for amphetamines.[37] Initial reports attributed Jensen's death to heat stroke, but his autopsy revealed traces of the amphetamine Ronicol – a substance not banned at the time.[38] In response to the death, in 1961 the International Olympic Committee ('IOC') formed a medical committee for the purposes of instituting drug testing at the 1968 Summer and Winter Olympics.[39]

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31 Handbook of the International Amateur Athletic Federation, 1927-1928

32 American Psychological Society, 'Anabolic Steroids Provide a Competitive Edge in Power Lifting Years After Doping Has Ended', *ScienceDaily* (3 October 2008) <https://www.sciencedaily.com/releases/2008/09/080925072430.htm>.

33 John McCloskey and Julian Bailes, *When Winning Costs Too Much: Steroids, Supplements, and Scandal in Today's Sports World* (First Taylor Trade Publishing, 2005) 8.

34 Justin Peters, 'The Man Behind the Juice', *Slate* (18 February 2005) <http://www.slate.com/articles/sports/sports_nut/2005/02/the_man_behind_the_juice.html>.

35 Todd (n 30) 87, 94-5. See also Terry Todd 'The Steroid Predicament' (1983) 59(5) *Sports Illustrated* 62.

36 See Lidia Avois et al, 'Central Nervous System Stimulants and Sport Practice' (2006) 40(Suppl 1) *British Journal of Sports Medicine* i 16, i 16–7.

37 David Maraniss, *Rome 1960: The Olympics That Changed the World* (Simon & Schuster, 2008) 111.

38 Ibid.

39 Ibid 142.

The IOC issued its first list of banned substances in 1967, identifying narcotic painkillers and central nervous system stimulants but excluding anabolic steroids.[40] Despite the broader sporting community beginning to suspect the use of anabolic steroids for enhancement purposes, no method for testing existed to prove this suspicion, resulting in the exclusion of steroids from the original IOC banned substance list.[41] Robust testing methods for anabolic steroids did not appear until the 1972 Munich Olympics.[42] While new testing measures only covered narcotic analgesics and three classes of stimulants, they offered more comprehensive screening tools than previous regimes.[43] In 1975, development efforts yielded a test considered reliable enough to screen for anabolic steroids. Only then did the IOC add anabolic steroids to their list of banned substances.[44] Over the next two decades, the IOC added several more compounds to the banned substance list including beta-blockers, diuretics, and insulin.[45]

This advance in testing, though, was short-lived. A paradigm shift in doping occurred in 1980 when Finish long-distance runner Kaarlo Maaninka received legal transfusions of two pints of blood before winning medals in both the five and ten-kilometre races.[46] In 1984, the US cycling team revealed that a third of the team, including five medal winners, had undergone blood transfusions prior to their Olympic events.[47] These blood transfusions marked the advent of doping without using isolated drugs or compounds; not surprising, the IOC moved to ban blood doping as a 'doping method' in 1985.[48] Yet, while their regulations prohibited it, the scientific community lacked an accurate test to identify the practice.[49] Additionally, cyclists began to use a different form of blood doping using the substance erythropoietin ('EPO')[50] which, when given to athletes, stimulates red blood cell production, thereby increasing capacity for

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[40] David R Mottram, 'Banned Drugs in Sport: Does the International Olympic Committee (IOC) List Need Updating?' (1999) 27(1) *Sports Medicine* 1, 1–2.

[41] Michelle Verroken and David R Mottram, 'Doping Control in Sport' in David R Mottram (ed), *Drugs in Sport* (Routledge, 2005) 339.

[42] The standards set during the Munich Olympics were subsequently adopted by numerous national and international federations. Many of these regulations are still used, including the requirements that laboratories provide reports within 24 hours and that every testing procedure must have analysis of four control samples. Furthermore, the IOC intended to create internationally approved standards and their efforts represent a turning point in drug testing. See Michael F. Krüger, Stefan Nielsen, and Christian Becker, 'The Munich Olympics 1972: Its Impact on the Relationship Between State, Sports and Anti-Doping Policy in West Germany' (2012) 32(4) *Sport in History* 526, 529–30, 543–5. See also eg 'Athlete Reference Guide to the 2015 World Anti-Doping Code', *World Anti-Doping Agency* (2015) 10 <https://www.wada-ama.org/sites/default/files/resources/files/wada-reference-guide-to-2015-code-nocode.pdf>; 'International Standard for Laboratories', *World Anti-Doping Agency* (2004) 14 <https://www.wada-ama.org/sites/default/files/resources/files/WADA_International_Standard_Laboratories_v.4.0_FINAL.pdf>.

[43] Verroken and Mottram (n 41) 339.

[44] Ibid.

[45] Ken Fitch, 'Proscribed Drugs at the Olympic Games: Permitted Use and Misuse (Doping) by Athletes' (2012) 12(3) *Clinical Medicine* 257.

[46] Alex Hoyt, 'Blood Doping Goes Back to the Future', *The Atlantic* (2 Nov 2010) <https://www.theatlantic.com/technology/archive/2010/11/blood-doping-goes-back-to-the-future/65508/>.

[47] Ibid.

[48] Mottram (n 41) 2.

[49] Kenneth Reich, 'U.S. Cycling Federation Prohibits Blood Doping', *Los Angeles Times* (19 January 1985) <http://articles.latimes.com/1985-01-19/sports/sp-8183_1_federation-boar>.

[50] EPO is a naturally occurring glycoprotein hormone produced in the kidneys in response to cellular hypoxia. Dominic J Wells, 'Gene Doping: The Hype and the Reality' (2008) 154(3) *British Journal of Pharmacology* 623, 626.

carrying oxygen. This technological shift and onset of doping methods not using readily identifiable compounds highlighted the need for a more strategic and streamlined approach to doping prevention and culminated in the establishment of WADA in 1999.[51]

Importantly, the benefits of doping can come with very real and often significant risks. Acne, baldness, liver damage, stunted growth in adolescents, cardiovascular disease, and aggressiveness among many other symptoms, have been associated with taking substances to boost performance.[52] While the desire for athletes to risk their health for competitive advantage may seem foreign to non-athletes, this reality has critical repercussions. Physician Robert Goldman captures this phenomenon in a construct termed the 'Goldman dilemma'.[53] Here, when asking elite athletes if they would pursue sporting success through an undetectable performance enhancing drug, but would die in 5 years, 52% reported they would take it.[54] Although more recent studies suggest these results are inflated,[55] the concept highlights the pressure and extreme desire to win at all costs that many athletes face.

In the following section, we introduce gene doping and gene editing techniques as potential new frontiers in doping and highlight the revolutionary advances ongoing with new gene editing tools. In our view, this emerging scientific field presents substantial new challenges as athletes, scientists, and states weigh up the benefits and risks of gene-based approaches to cheating in sport.

Regulatory Challenges with Gene Doping and Gene Editing – Part III

Each new iteration of biological cheating techniques has confounded the governance of sports for decades. Genetic and other biological interventions hold notable potential to augment athletic performance,[56] heightening the temptation to pursue and deploy emerging methods of cheating. Exacerbating such regulatory challenges, WADA – with its mission to promote, coordinate and monitor the fight of drug use in sports[57] – and other anti-doping institutions, face a pacing problem similar to public institutions confronting the impacts of

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51 'Who We Are', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/who-we-are>. Originally initiated by the IOC, this international and independent agency focuses on 'scientific research, education, development of anti-doping capabilities and monitoring of the World Anti-Doping Code ('Code'). See 'World Anti-Doping Code 2015: With 2018 Amendments', *World Anti-Doping Agency* (2018) <https://www.wada-ama.org/sites/default/files/resources/files/wada_anti-doping_code_2018_english_final.pdf> ('Code'). WADA applies a strict liability to situations in which urine or blood samples produce evidence of doping, in these cases the athlete's results are automatically invalidated. 'Strict Liability in Anti-Doping', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/questions-answers/strict-liability-in-anti-doping>.

52 'Effects of Performance-Enhancing Drugs', *US Anti-Doping Agency* (Web Page) <https://www.usada.org/substances/effects-of-performance-enhancing-drugs/>.

53 Goldman and Klatz (n 25).

54 Ibid.

55 James Connor and Jason Mazanov, 'Would You Dope? A General Population Test of the Goldman Dilemma' (2009) 43 (11) *British Journal of Sports Medicine* 871, 872.

56 These factors create a ceiling for performance, so methods of lifting the ceiling hold promise. See Tucker and Collins (n 11) 555.

57 'Who We Are' (n 51).

nascent technologies more generally.[58] With progress in biomedical technologies advancing rapidly, next generation cheating methods have begun to outpace the regulatory and enforcement capacity of WADA and analogous agencies. The power and potential of CRISPR for embryonic editing will likely open a third wave of concerns and anti-doping governance challenges in the coming years.

Gene Therapy and Gene Editing Technologies

Issues surrounding the use of gene editing technologies related to doping first arose from applications in bacteria, and not directly in humans. Recombinant DNA techniques pioneered in the 1970s enabled experts to leverage existing cellular machinery in bacteria to integrate foreign sequences of DNA into the cell's genome.[59] Early applications of recombinant DNA included inserting genetic sequences associated with human insulin production into bacteria, allowing for the biomanufacturing of insulin for clinical use.[60] However, recombinant DNA technologies also enabled the production of proteins that included human growth hormones and EPO for use in doping.[61] Over time, existing methods of anti-doping screening began to capture biomolecules formed using recombinant DNA-based methods, and concerns shifted towards the potential use of genetic modification directly in adult human bodies.[62]

Somatic gene therapy represents the therapeutic use of recombinant DNA and related techniques to introduce beneficial genetic factors directly into the human body.[63] Such therapies promises the ability to treat disease by modifying the genome of adult human cells to correct for genetic defects, often by using a virus to inject desirable genetic material into cells.[64] However, gene therapy methods lack precision, as the techniques used lead to random insertion of the desired sequence through the genome.[65] These techniques can be applied directly in the body, or on cells or tissue withdrawn from the body and subsequently reinserted.[66] Gene therapies classify as somatic treatments because they act on adult human cells not involved in reproduction, rather than creating heritable gene edits by modifying the human 'germline'.[67] Despite some disillusionment over the potential of gene therapy in the late 20th century, the Human Genome

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58 See Gary E Marchant, 'The Growing Gap Between Emerging Technologies and the Law' in Gary E Marchant, Braden R Allenby, and Joseph R Herkert (eds), *The Growing Gap Between Emerging Technologies and Legal-Ethical Oversight* (Springer, 2011) 19, 19–20, 22–3.

59 Institute of Medicine, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of Recombinant DNA Advisory Committee* (Final Report, 2014) 23 <https://www.nap.edu/catalog/18577/oversight-and-review-of-clinical-gene-transfer-protocols-assessing-the>.

60 Irving S Johnson, 'Human Insulin from Recombinant DNA Technology', (1983) 219(4585) Science 632, 632.

61 Hassan ME Azzazy, Mai MH Mansour, and Robert H Christenson, 'Doping in the Recombinant Era' (2005) 38(11) *Clinical Biochemistry* 959, 959–61. See also eg 'EPO Detection', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/questions-answers/epo-detection>.

62 Azzazy, Mansour, and Christenson (n 61) 961.

63 Institute of Medicine (n 59) 22.

64 Eugene H Kaji and Jeffrey M Leiden, 'Gene and Stem Cell Therapies' (2001) 285(5) JAMA 545, 545.

65 Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review' (Final Report, 2016) 7 <http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf>.

66 Ibid.

67 See Edward Lanphier et al, 'Don't Edit the Human Germ Line' (2015) 519(7544) *Nature* 410, 410.

Project, which mapped out the full human genome in the early 2000s, offered renewed hope of somatic cell treatments for heritable disease.[68] Others posited pragmatic somatic treatments would lead to athletic enhancement through the nontherapeutic use of gene therapy[69] – a practice termed 'gene doping'. Rather than aiming to remedy genetic defects, gene doping would use the same underlying mechanisms as gene therapy to insert genes believed to heighten athletic performance.[70]

Myostatin inhibitors exemplify this troubling shift to gene doping.[71] In 2008, WADA prohibited drugs prior to market release which artificially build muscle mass by inhibiting myostatin levels in the body,[72] but discoveries of naturally occurring genetic elements which perform the same function as the drugs raised the spectre of gene doping.[73] Scientists have discovered a child who was abnormally muscular, even in infancy, was found to carry mutations in both copies of the myostatin gene, demonstrating a genetic control for natural myostatin production.[74] His mother, a former professional athlete, carried one defective copy of the gene.[75] While myostatin inhibitors are extremely promising for muscle wasting diseases, they are also tempting for use by athletes. Here, WADA has mechanisms to test for doping with drugs but no clear tools to detect genetic manipulation achieving the same goal. Somatic gene therapies have continued to develop, though at a slower rate than initially anticipated. The first gene therapies for cancer applications obtained regulatory approval in 2017.[76] Early successes in 2019 led to somatic therapies based on zinc finger gene editing tools.[77] Active clinical trials using CRISPR for somatic modification exist in China and the US.[78]

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[68] See Francis Collins, 'Implications of the Human Genome Project for Medical Science' (2001) 285(5) *JAMA* 540, 542–3.

[69] Theodore Friedmann and Johann Olav Koss, 'Gene Transfer and Athletics–An Impending Problem' (2001) 3(6) *Molecular Therapy* 819, 819.

[70] Wells (n 50) 623–5.

[71] These compounds work by blocking myostatin, a protein in the body that stops skeletal muscle growth. See Dimitrios D Nikolopoulos, Chara Spiliopoulou, and Stamatios E Theocharis, 'Doping and Musculoskeletal System: Short-Term and Long-Lasting Effects of Doping Agents' (2011) 25 *Fundamental & Clinical Pharmacology* 535, 539, 554.

[72] World Anti-Doping Agency, *The World Anti-Doping Code: The 2008 Prohibited List*, (January 2008) 4–5 <https://www.wada-ama.org/sites/default/files/resources/files/WADA_Prohibited_List_2008_EN.pdf>.

[73] Matthew N Fedoruk and Jim L Rupert, 'Myostatin Inhibition: A Potential Performance Enhancement Strategy?' (2008) 18(2) *Scandinavian Journal of Medicine and Science in Sports* 123.

[74] Markus Schuelke et al, 'Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child' (2004) 350(26) *New England Journal of Medicine* 2682.

[75] See, eg, 'FDA Approves CAR-T Cell Therapy to Treat Adults with Certain Types of Large B-Cell Lymphoma', *US Food and Drug Administration* (18 October, 2017) <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm581216.htm>.

[76] See, eg, 'FDA Approves CAR-T Cell Therapy to Treat Adults with Certain Types of Large B-Cell Lymphoma', *US Food and Drug Administration* (18 October, 2017) <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm581216.htm>.

[77] See Marilynn Marchione, 'Tests Suggest Scientists Achieved 1st "In Body" Gene Editing', *Associated Press News* (7 February 2019) <https://www.apnews.com/d728f86d70d94ce68dd4fedffe58d03f>.

[78] Cormac Sheridan, 'Go-Ahead for First In-Body CRISPR Medicine Testing', *Nature Biotechnology News* (14 December 2018) <https://www.nature.com/articles/d41587-018-00003-2>; Preetika Rana, 'China Pushes Ahead with Human Gene-Editing Trials', *The Wall Street Journal* (28 April 2017) <https://www.wsj.com/articles/china-pushes-ahead-with-human-gene-trials-1493380057>.

Emerging gene editing tools offer a more precise approach to modification than recombinant techniques used in gene therapy and doping. Zinc finger nucleases, TALENS, and now CRISPR-Cas systems enable scientists to identify a specific site in the genome to edit and, ideally, modify only that site.[79] The precision of these gene editing instruments makes them better candidates for germline editing, which involves modifications leading to heritable changes in the genome.[80] Germline modifications in an early human embryo can change the course of development or the attributes of the individual by altering various sites in the genome and epigenome, or factors overlaying the DNA which control when and which cells express genes.[81] Recombinant DNA methods can only add new sequences at largely unpredictable genetic sites, creating unacceptable risks to a child born from such alterations. In contrast, gene editing systems can, in principle, insert, eliminate, or substitute genetic sequences or individual nucleotides at specific locations in the genome, offering a degree of control and discretion unavailable in recombinant techniques.[82]

CRISPR has drawn particular attention for their application in human adults and embryos due to several advantages over other gene editing tools, including flexibility, low cost, and ease of use.[83] CRISPR-Cas systems use a guide RNA molecule to locate and act on a specific genetic locus, which lowers the risk of off-target edits.[84] The Cas enzyme can use any guide RNA molecule of appropriate length, rendering the technique readily customizable and relatively cheap to prepare.[85] CRISPR-Cas systems also offer more modes of editing than other gene editing tools, such as allowing for modifying multiple loci simultaneously, or changing individual nucleotides rather than full sequences.[86]

Feasibility and Risks of Somatic and Germline Modification

Technical barriers and safety concerns will provide significant pragmatic and normative obstacles to gene doping and gene editing for athletics. Adequate efficacy of both somatic and embryonic interventions will require identifying appropriate genetic sites to target. In the gene doping context, experts have pointed to a handful of potential genomic pathways for targeting, including those regulating the production of human growth factor and EPO.[87] However, no single genetic locus exists for height, strength, or stamina.[88] Instead, physical attributes depend on nuanced interactions of genomic, epigenomic,

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79 Nuffield Council on Bioethics (n 65) 4, 8–10.
80 Lanphier et al (n 67) 410.
81 National Academies of Science, Engineering, and Medicine (n 12) 1, 3–4.
82 Nuffield Council on Bioethics (n 65) 4, 8–10.
83 See Boettcher and McManus (n 17) 583
84 Jennifer A. Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR-Cas9' (2014) 346(6213) *Science* 12580961:1–9, 1–4.
85 Doudna and Charpentier (n 14) 1077.
86 Nuffield Council on Bioethics (n 65) 9, 14.
87 Azzazy, Mansour, and Christenson (n 61) 961–2.
88 See Sarah Tishkoff, 'Strength in Small Numbers' (2015) 349(6254) *Science* 1282, 1282.

environment, social, and behavioural factors.[89] While some direct-to-consumer genetic testing services allege to offer insights into sports capabilities, the claims made about these products undergo few regulatory checks and have received sharp criticism.[90] Despite progress in human gene editing, many technical barriers remain before such techniques could yield broad, predictable performance advantages.

The sheer complexity of the influence of the human genome on health exacerbates the risks and uncertainties of modification, particularly where unintended modifications occur. Traditional gene therapy involves random insertion of the desired gene into the genome, which can disrupt the existing genomic structure and result in cancer or other conditions.[91] Similarly, off-target effects in CRIPSR applications merit specific attention. Though the CRISPR-Cas system can be programmed to seek out specific sections of DNA, natural errors in the search process can result in the enzyme editing undesired and unanticipated sites in the genome.[92] Unexpected errors or modifications in somatic and germline applications could yield potentially dangerous results, including cancer or iatrogenic genetic diseases.[93]

Both somatic and embryonic editing also present risks of mosaicism, where variations in editing success yield an individual with different genomes in different regions of the body. This can exacerbate the risk of developing various diseases.[94] Particular concerns arise in germline editing, based on findings that embryonic cells which successfully respond to CRISPR modification may have increased susceptibility to cancer.[95] The human immune system can react

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[89] See, eg, Fatimah LC Jackson, Mihai D Niculescu, and Robert T Jackson, 'Conceptual Shifts Needed to Understand the Dynamic Interactions of Genes, Environment, Epigenetics, Social Processes, and Behavioral Choices' (2013) 103(S1) *American Journal of Public Health* S33, S33; Sonia Shah et al, 'Improving Pheontypic Prediction by Combining Genetic and Epigenetic Associations' (2015) 97(1) *American Journal of Human Genetics* 75, 75.

[90] See, eg, Nicole Vlahovich et al, 'Ethics of Genetic Testing and Research in Sport: A Position Statement from the Australian Institute of Sport' (2017) 51(1) *British Journal of Sports Medicine* 5, 8.

[91] Boris Fehse and Ingo Roeder 'Insertional Mutagenesis and Clonal Dominance: Biological and Statistical Considerations' (2008) 15(2) *Gene Therapy* 143, 146–7.

[92] Xiao-Hui Zhang et al, 'Off-Target Effects in CRISPR/Cas9 Mediated Genome Engineering' (2015) 4 Molecular Therapy–Nucleic Acids e264:1–8, 1. Even less invasive variants of CRISPR techniques, designed to modify individual nucleotides instead of larger genetic sequences, have raised recent concerns for off target effects. See, eg, Shuai Jin et al, 'Cytosine, But Not Adenine, Base Editors Induce Genome-Wide Off-Target Mutations in Rice' (2019) *Science* aaw7166:1–6, 1; Erwei Zuo et al, 'Cytosine Base Editor Generates Substantial Off-Target Single-Nucleotide Variants in Mouse Embryos' (2019) *Science* aav9973:1–6, 1.. See also Sharon Begley, 'CRISPR Base-Editing, Known for Precision, Hits a Snag with Off-Target Effects', *Stat News* (28 February, 2019) <https://www.statnews.com/2019/02/28/crispr-base-editing-off-target-mutations/>.

[93] Eric S Lander, 'Brave New Genome' (2015) 373(1) *New England Journal of Medicine* 5, 5–7. See also Editorial, 'Keep Off-Target Effects in Focus' (2018) 24 *Nature Medicine* 1081, 1081; Grégoire Cullot et al, 'CRISPR-Cas9 Genome Editing Induces Megabase-Scale Chromosomal Truncation' (2019) 10 *Nature Communications* 1136:1–14, 2.

[94] Leslie G Biesecker and Nancy B Spinner, 'A Genomic View of Mosaicism and Human Disease' (2013) 14(5) *Nature Reviews Genetics* 307, 307.

[95] See Emma Haapaniemi et al, 'CRISPR-Cas9 Genome Editing Induces a p53 Mediated DNA Damage Response' (2018) 24(7) *Nature Medicine* 927, 930; Robert J Ihry et al, 'p53 Inhibits CRISPR-Cas9 Engineering in Human Pluripotent Stem Cells' (2018) 24(7) *Nature Medicine* 939, 945.

to gene therapy vectors and may react to CRISPR-Cas enzymes, potentially introducing a degree of immune-mediated safety risks for somatic CRISPR uses.[96]

Experts continue to debate the extent to which CRISPR tools produce off-target mutations or mosaicisms, complicating risk assessments for human application in therapy or enhancement.[97] Early studies of CRISPR-Cas editing on human embryos not used to create pregnancies reported both off-target and mosaic effects.[98] While certain technical approaches may mitigate harmful side-effects,[99] they will likely not obviate the risk. Ongoing work has produced novel tools that may assist in diagnosing off-target effects,[100] potentially allowing for corrections to off-target mistakes or guiding more precise gene editing approaches. Some unavoidable level of risk or uncertainty may generate greater contention over germline editing applications than somatic ones, as unintended edits to the germline become heritable and could pose additional risks to subsequent generations.[101]

Beyond potential health risks, genomic edits can blur established boundaries between therapy and enhancement. For example, addressing issues of poor muscle development could involve gene editing to increase muscle production.[102] This, however, raises normative and ethical questions around defining the 'normal' human state, whether this case falls below that 'normal', and whether the intervention should raise muscle gain to a 'normal' level or beyond.[103] Similarly, edits targeting one human attribute may impact other biological functions. For example, the genomic modifications to twins recently born in

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[96] Natacha Bessis, FranciscoJose Garcia Cozar, and Marie-Christophe Boissier, 'Immune Reponses to Gene Therapy Vectors: Influence on Vector Function and Effector Mechanisms' (2004) 11 *Gene Therapy* s 10, s 10; Julie M. Crudele and Jeffrey S. Chamberlain, 'Cas9 Immunity Creates Challenges for CRISPR Gene Editing Therapies' (2018) 9 *Nature Communications* 3497:1–3, 2–3. However, some experts have already suggested potential solutions to Cas9 immunity, including using a different Cas enzyme. See Andrew Joseph, 'CRISPR Hits a Snag: Our Immune Systems May Attack the Treatment', STAT News (8 January 2018) <https://www.statnews.com/2018/01/08/immunity-crispr-cas9/>.

[97] See, eg, Vivek Iyer et al, 'No Unexpected CRISPR-Cas9 Off-Target Activity Revealed by Trio Sequence of Gene-Edited Mice' (2018) 14(7) *PLoS Genetics* e1007503:1–17; Michael Kosicki, Kärt Tomberg, and Allan Bradley, 'Repair of Double-Stranded Breaks Induced by CRISPR-Cas9 Leads to Large Deletions and Complex Rearrangements' (2018) 36(8) *Nature Biotechnology* 765. One paper in Nature reporting significant off-target effects was retracted after several months of methodological criticism. See Kellie A. Schaefer et al, "Unexpected Mutations After CRISPR-Cas9 Editing in Vivo' (2017) 14 *Nature Methods* 547–8. An editorial was subsequently issued to apologize for publishing the paper. Editorial, 'CRISPR Off-Targets: A Reassessment' (2018) 15 *Nature Methods* 229–30.

[98] Puping Liang et al, 'CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes' (2015) 6(5) *Protein & Cell* 363, 364; Lichun Tang, 'CRISPR/Cas9-Mediated Gene Editing in Human Zygotes Using Cas9 Protein' (2017) 292(3) *Molecular Genetics and Genomics* 525, 532.

[99] Michelle L. Kimberland et al, 'Strategies for Controlling CRISPR/Cas9 Off-Target Effects and Biological Variations in Mammalian Genome Editing Experiments' (2018) 284 *Journal of Biotechnology* 91, 93–8. Further work has begun to explore techniques for limiting and estimating the risk of off-target effects. See Megan Molteni, 'Gene Editing Is Trickier than Expected–But Fixes Are in Sight', *Wired* (28 February 2019) <https://www.wired.com/story/precise-gene-editing-is-trickier-than-expected-but-fixes-are-in-sight/>.

[100] These include the recently developed 'genome-wide off-target analysis by two-cell embryo injection' (GOTI). See Zuo et al (n 151) 1.

[101] National Academies of Science, Engineering, and Medicine (n 12) 6-7, 112.

[102] Ibid 9.

[103] Ibid; Nick Bostrom and Rebecca Roache, 'Ethical Issues in Human Enhancement', in Jesper Ryberg, Thomas Petersen, and Clark Wolf (eds), *New Waves in Applied Ethics* (Pelgrave Macmillan, 2008) 121, 121–3.

China aimed to protect against HIV infection but may also confer cognitive advantages[104] and reduce lifespan.[105] Uncertainty over the health consequences of genomic intervention worsen for germline editing, where heritable edits could lead to unforeseen intergenerational health risks.[106]

Despite these barriers, steady advances in biotechnology and bioinformatics suggest an approaching future when experts will hold sufficient knowledge to enhance human traits with somatic or embryonic gene editing. The costs of sequencing DNA, even a whole human genome or exome, continue to fall with advances in next generation sequencing techniques.[107] The corresponding increases in the availability, quantity, and quality of human genomic data continue to bolster researchers' ability to correlate biological attributes with genetic factors.[108] Public big data endeavours including the US 'All of Us' project will create massive databases of genomic, health, and behavioural data, supporting efforts to understanding how various genetic elements lead to health outcomes and interact with external factors.[109] The increasing generation of human genome data and analysis will likely build knowledge over time on which multiple and inter-related genetic factors can be correlated with increased physical and athletic performance.

Given the complexity of the genome, information technologists have pursued advances in artificial intelligence (AI) tools such as machine learning to accelerate new biomedical insights. Technologists have deployed deep learning to explore current knowledge and data, seeking connections between genetic factors and human health.[110] Private technology firms have become more involved in using AI in genomics, including a new high-profile collaboration between IBM and the Broad Institute at MIT and Harvard.[111] The convergence of AI and biomedicine could provide the requisite expertise to select specific genomic edits which accurately yield desired physical enhancements in humans.[112] Sufficiently guided gene editing in the somatic or germline context

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[104] Antonio Regalado, 'China's CRISPR Twins Might Have Had Their Brains Inadvertently Enhanced', *MIT Technology Review* (21 February 2019) <https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/>.

[105] Xinzhu Wei and Rasmus Nielsen, 'CCR5-Δ32 Is Deleterious in the Homozygous State in Humans' (2019) 25 *Nature Medicine* 909, 909.

[106] Niklaus H Evitt, Shamik Mascharak, and Russ B Altman, 'Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework' (2015) 15(12) *The American Journal of Bioethics* 25, 26–7.

[107] Katharina Schwarze et al, 'Are Whole-Exome and Whole-Genome Sequencing Approaches Cost-Effective? A Systematic Review of the Literature' (2018) 20(10) *Genetics in Medicine* 1122, 1122.

[108] Antonio Regalado, 'Forecasts of Genetic Fate Just Got a Lot More Accurate', *MIT Technology Review* (21 February 2018) <https://www.technologyreview.com/s/610251/forecasts-of-genetic-fate-just-got-a-lot-more-accurate/>.

[109] 'About the *All of US* Research Program', *National Institutes of Health* (Web Page) <https://allofus.nih.gov/about/about-all-us-research-program>.

[110] *See* James Zou et al, 'A Primer on Deep Learning in Genomics' (2019) 51(1) *Nature Genetics* 12, 12; Michael Wainberg et al, 'Deep Learning in Biomedicine' (2018) 36(9) *Nature Biotechnology* 829, 829.

[111] IBM, 'IBM Watson Health and the Broad Institute Launch Initiative to Help Clinicians Predict the Risk of Cardiovascular Disease with Genomics and AI' (Press Release, 13 February, 2019) <https://newsroom.ibm.com/2019-02-13-IBM-Watson-Health-and-the-Broad-Institute-Launch-Initiative-to-Help-Clinicians-Predict-the-Risk-of-Cardiovascular-Disease-with-Genomics-and-AI>. *See also* 'Platform', Deep Genomics (Web Page) <https://www.deepgenomics.com/platform/>.

[112] See Zou et al (n 110) 16–7.

may enable the 'optimization' of human bodies for athletic performance.[113] Overall, however, while such future advances in biomedical and information technology may provide the capacity to use gene editing for predictable athletic enhancement, these capabilities remain outside the realm of possibility given current levels of precision and certainty.

Governance Responses to Gene Doping from WADA

Experts at the turn of the 21st century began to express concerns over the approaching possibility of athletes using gene therapy methods for non-therapeutic enhancement. Particular anti-doping concerns arose over the lack of adequate diagnostics to accurately identify potential gene doping in athletes.[114] The first articulable concerns over gene doping addressed therapies that enable the body to produce higher levels of natural compounds advantageous for performance, including human growth factors and EPO.[115] Ideal genetic modifications, and the biomolecules they produce, would replicate or approach the natural version of the genetic factor and molecule, thus creating challenges for distinguishing natural and doped genes.[116] In this instance, gene doping effects should remain localized to the targeted tissue, potentially avoiding anti-doping diagnostics by not releasing metabolites into the blood, urine, or saliva, and likely requiring costly and intrusive muscle biopsies to detect.[117] Diagnostics could instead search for the inserted gene in an athlete's genome rather than test for metabolites, but the complexity of the genome and high price of DNA sequencing through the 2000s encumbered efforts to create such screening tools.[118] Furthermore, somatic interventions also have legitimate potential therapeutic uses, including rebuilding muscle, controlling pain, and managing diabetes.[119] Gene therapy and doping therefore induce difficult questions around the line between therapy and enhancement, and how to determine a meaningful difference between the two with diagnostics or other screening tools.

Against this backdrop, WADA held its first workshop on gene doping in 2002 and established an expert group on the topic in 2004.[120] The first WADA Prohibited List in 2004 described gene doping as a 'prohibited method' involving 'the non-therapeutic use of genes, genetic elements and/or cells that

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[113] Walter Johnson and Eleonore Pauwels, 'How to Optimize Human Biology: Where Genome Editing and Artificial Intelligence Collide' (Report, October 2017) 7–9 <https://www.wilsoncenter.org/sites/default/files/how_to_optimize_human_biology_0.pdf>.
[114] Friedmann and Koss (n 69) 819–20.
[115] See Unal and Unal (n 11) 358–9. EPO induces the body to produce more red blood cells for oxygen circulation. Ibid.
[116] Anna Baoutina et al, 'Gene Doping Detection: Evaluation of Approach for Direct Detection of Gene Transfer Using Erythropoietin as a Model' (2010) 17(8) *Gene Therapy* 1022, 1022.
[117] Anna Baoutina et al, 'Developing Strategies for Detection of Gene Doping' (2008) 10(1) *The Journal of Gene Medicine* 3, 4–5.
[118] See ibid 5; Erika Check Hayden, 'The $1,000 Genome' (2014) 507(7492) *Nature* 294, 294–5.
[119] See, eg, David Gould, 'Gene Doping: Gene Delivery for Olympic Victory' (2013) 76(2) *British Journal of Clinical Pharmacology* 292, 293–5.
[120] 'Gene Doping', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/gene-doping>.

have the capacity to enhance athletic performance'.[121] The definition appears to identify nucleic acids themselves as the prohibited tool for enhancement, rather than focusing regulatory attention on genomic modification more broadly. Additionally, the definition arguably captures substances produced through recombinant biomanufacturing as well, as modifying bacteria with recombinant DNA requires the application of nucleic acids.[122] The scope of WADA's 2004 definition reflects the focus of the scientific and medical communities on somatic applications of gene therapy at that time. WADA's official periodical in 2005 explained gene doping specifically as a form of somatic gene therapy used for enhancement-only purposes rather than therapeutically.[123]

In the 2008 St. Petersburg Declaration, WADA highlighted safety, detection, and social issues in the regulation and monitoring of gene doping.[124] Biological passports represent one method WADA developed in 2009 to combat future gene doping and the issues of detection.[125] An Athlete Biological Passport (ABP) constitutes an individual record which profiles various athlete biomarkers over time, giving a baseline to compare against future samples.[126] Statistical discrepancies found in a future sample indirectly implicate the use of doping, including potential gene doping, and may allow for more targeted anti-doping tests.[127] WADA conditions participating in competitions on possessing a valid ABP and now records ABP and other data in the online Anti-Doping Administration & Management System (ADAMS), enabling broad access to athlete passports and tests.[128] Stakeholders have heralded ABPs as an effective intervention,[129] however empirical evaluations of their effectiveness against gene doping specifically are currently unavailable. Notably, ABPs will fail to capture gene doping undertaken prior to establishing a baseline.[130] Moreover,

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[121] World Anti-Doping Agency, *The World Anti-Doping Code: The 2004 Prohibited List*, (March 2004) 6 <https://www.wada-ama.org/sites/default/files/resources/files/WADA_Prohibited_List_2004_EN.pdf>.

[122] Ewa Brzeziańska, Daria Domańska, and Anna Jegier, 'Gene Doping in Sport – Perspectives and Risks' (2014) 31(4) *Biology of Sport* 251, 251.

[123] 'Gene Doping' [2005] (January) *Play True: An Official Publication of the World Anti-Doping Agency* 2, 3–4 <https://www.wada-ama.org/sites/default/files/resources/files/PlayTrue_2005_1_Gene_Doping_EN.pdf>.

[124] 'Saint Petersburg Declaration', *World Anti-Doping Agency* (11 June 2008) <https://www.wada-ama.org/sites/default/files/resources/files/WADA_StPetersburg_Declaration_2008.pdf>.

[125] 'Athlete Biological Passport', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/athlete-biological-passport>.

[126] Ibid. Since 2009, WADA has issued regular ABP guidelines with updated information, though they do not specifically address gene doping. See 'Athlete Biological Passport Operating Guidelines: Version 6.1', *World Anti-Doping Agency* (23 July 2018) <https://www.wada-ama.org/sites/default/files/resources/files/guidelines_abp_v61_2018_jul_en.pdf>.

[127] 'A Closer Look: The Athlete Biological Passport', *US Anti-Doping Agenc*y (26 August 2015) <https://www.usada.org/closer-look-athlete-biological-passport/>; Thijs Devriendt et al, 'Do Athletes Have a Right to Access Data in Their Athlete Biological Passport?' (2018) 10(5) *Drug Testing and Analysis* 802, 802-806.

[128] 'Athlete Biological Passport', *World Anti-Doping Agency* (Web Page) <https://www.wada-ama.org/en/athlete-biological-passport>; Susan Gilbert, 'The Biological Passport' (2010) 40(2) *Hastings Center Report* 18, 18–9.

[129] See, eg, Neil Robinson et al, 'The Athlete Biological Passport: An Effective Tool in the Fight Against Doping' (2011) 57(6) *Clinical Chemistry* 830, 830; Pierre-Edouard Sottas et al, 'The Athlete Biological Passport' (2011) 57(7) *Clinical Chemistry* 969, 969.

[130] See Joe Fore, 'Moving Beyond "Gene Doping": Preparing for Genetic Modification in Sport' (2010) 15 *Virginia Journal of Law and Technology* 76, 81.

the serious sanctions resulting from gene doping may render indirect methods of anti-doping screening like ABP normatively less desirable.[131]

Over the last decade, WADA has continued to invest in research to develop genetic diagnostic tools to screen athletes for sequences suggestive of gene doping.[132] With the falling costs of genome sequencing, WADA has begun to seriously consider adding whole athlete genomes to their ABPs.[133] Biological passports with genomic data would enable detection of gene doping, either by monitoring for changes in the genome or by recognizing sequences connected to enhanced performance, opening new possibilities for detection previously limited by high sequencing costs. However, genomic screening will likely not overcome existing concerns over distinguishing between intentional enhancement, legitimate therapy, or a naturally present genetic factor. Moreover, privacy norms and advocates may balk at the proposal of a mandated genomic passport component.

New breakthroughs in human germline editing now challenge the scope of WADA prohibitions on gene doping. The possibility of athletes with their genomes modified at the embryonic stage would likely escape the prevailing somatic conceptualization of gene doping. The WADA Prohibited List definition of gene doping has continued to evolve over time but has retained its focus on somatic applications. The 2019 Prohibited List definition addresses not only nucleic acids and modified cells but forbids 'gene editing agents designed to alter genome sequences and/or the transcriptional, post-transcriptional or epigenetic regulation of gene expression.'[134] This more recent definition represents an increase in scope from the original 2004 prohibition, now emphasizing the need to control not only nucleic acids but also gene editing tools which alter any stage of gene expression. However, the definition continues to implicate somatic modification through its emphasis on the 'use' of these methods,[135] as athletes can elect to use gene editing on themselves, but individuals modified at the embryonic stage did not 'use' these tools on themselves. Rather, the parents or other guardian would have elected to perform the germline modification from which an edited athlete may subsequently benefit. This lack of consent or exercise of autonomy by an athlete with an edited germline would strain the enforcement capacity of WADA and purpose of its rules,[136] as forbidding those individuals from participating under the gene doping prohibitions may create perceived unfairness or regulatory overreach.

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131 Anna Baoutina et al (n 116) 4.

132 See, eg, 'Generation Sequencing', *World Anti-Doping Agency* (26 May 2017) <https://www.wada-ama.org/sites/default/files/resources/files/16e05ab_dr._baoutina_final_report.pdf>; 'Gene Doping Detection by Next Generation Sequencing', *World Anti-Doping Agency* (26 May 2017) <https://www.wada-ama.org/sites/default/files/resources/files/16e12hh_dr._haisma_summary.pdf>.

133 Eric Niller, 'Olympics Could Require Athletes' Genetic Code to Test for Doping', *Wired* (5 February 2018) <https://www.wired.com/story/olympics-could-require-athletes-genetic-code-to-test-for-doping/>.

134 World Anti-Doping Agency, *The World Anti-Doping Code: The 2019 Prohibited List* (January 2019) 6 <https://www.wada-ama.org/sites/default/files/wada_2019_english_prohibited_list.pdf>.

135 Ibid.

136 See Code (n 51).

Defining more appropriate 'sanctions' than outright banning modified athletes from competing may present inflammatory governance issues as well. Illustrating one potential approach, the Court of Arbitration for Sport (CAS) recently upheld IAAF rules requiring some female runners who naturally produce high levels of testosterone to take medication to lower their levels to an acceptable threshold, dismissing arbitration requests by Caster Semenya.[137] This approach offers a case where regulators mandated athletes use pharmaceuticals to suppress a perceived advantage arising from genomic factors, which could set a precedent for requiring germline edited athletes to use technologies which undercut their perceived advantages. The CAS's justification of the IAAF rules as necessary and proportional – even while clarifying Semenya bore no personal liability[138] – could extend to the context of athletes with modified germlines as well, where athletes had no choice in their editing but may perform at a higher level as a result. However, the CAS decision sparked controversy over who can or should make decisions about what constitutes a perceived 'advantage' and what biases underpin such perceptions,[139] which would likely render this approach similarly contentious if applied to germline edited athletes. Additionally, this regulatory practice leaves those athletes with naturally occurring genetic advantages vulnerable.[140] Would this new standard require the technological suppression of all athletes considered to have a naturally occurring genetic advantage? Would the future of sport require only participation at an average level, and who then would set those standards?

Moreover, detection of embryonic doping creates new governance challenges. Assuming gene editing replaces inherited alleles with only natural variants of the gene and no off-target effects occur, the individual's genome may appear entirely 'natural' or unmodified. Even using synthetic variants of a gene[141] during embryonic editing could go undetected should anti-doping authorities not know to screen for or how to interpret the variant. Further research will be required to determine if new diagnostic methods could detect edits to the human germline. Registries of individuals with edited germlines could potentially bolster monitoring efforts. The WHO has expressed interest in establishing a registry of active research on human gene editing, enforced with non-state governance mechanisms including, for example, scientific journals

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[137] *Mokgadi Caster Semenya v International Association of Athletics Federation & Athletics South Africa v International Association of Athletics Federation* (Award and Opinion, Court of Arbitration for Sport, Case No 2018/O/5794 & 2018/O/5798, 30 April 2019) <https://www.tas-cas.org/fileadmin/user_upload/CAS_Award_-_redacted_-_Semenya_ASA_IAAF.pdf>.

[138] Court of Arbitration for Sport, 'Executive Summary 5794' (30 April 2019) 6 <https://www.tas-cas.org/fileadmin/user_upload/CAS_Executive_Summary__5794_.pdf>.

[139] See Katelyn Burns, 'Caster Semenya and the Twisted Politics of Testosterone', *Wired* (11 May 2019) <https://www.wired.com/story/caster-semenya-and-the-twisted-politics-of-testosterone/>.

[140] For example, a 'functional polymorphism' of the angiotensinogen ('AGT') gene is far more common in elite power athletes than the general public. See Aleksandra Zarębska et al, 'Association of rs699 (M235T) Polymorphism in the AGT Gene with Power but Not Endurance Athlete Status' (2013) 27(10) *Journal of Strength & Conditioning Research* 2898.

[141] See David Ewing Duncan, 'The Next Best Version of Me: How to Live Forever', *Wired* (27 March 2018) <https://www.wired.com/story/live-forever-synthetic-human-genome/>.

agreeing to make publication contingent on compliance with the registry.[142] The Nuffield Council on Bioethics and National Academies have recommended government-supervised registries and follow up programs for any child born with an edited germline in the United Kingdom or US.[143] Providing WADA access to such public or public-private registries could provide another route to monitoring or enforcement for germline modification, though the use of registries raises significant privacy and perceived legitimacy and transparency concerns and would not capture unregistered individuals. Overall, detection of embryonic genomic alterations and determining appropriate sanctioning structures, if any, will likely pose significant anti-doping governance challenges.

The Potential for Gene Editing in Competitive Sport – Part IV

The question turns then to whether individuals, communities, or even states, will likely pursue gene editing in some form to gain a competitive sports advantage. Based on precedent, we predict a strong interest in genomic enhancement in athletics will emerge, as illustrated by past primitive attempts to utilise genetic engineering. In 2005, journalist Brook Larmer revealed, in the novel 'Operation Yao Ming', the coordinated governmental effort expended by China on creating professional basketball player Yao Ming.[144] Officials tracked Ming's family for two generations following the discovery of his grandfather, one of Shanghai's tallest men.[145] Ming's father was then paired with, and encouraged to marry, a tall athletic partner.[146] Ming began compulsory basketball training at an early age and consumed an unknown mixture of compounds to allegedly increase his height.[147] While these interventions appear rudimentary by today's standards, they represent an early use of genetic manipulation in order to gain dominance within the sporting community. These early attempts at genetic manipulation, when considered with China's history of alleged state sanctioned doping and interest in conveying strength through the Olympics,[148] suggest state actors may have sufficient motivation to explore germline editing to gain competitive edge. While China stands out as a leader in human germline editing, actors in any developed or developing state eager to signal political, cultural, or technical

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[142] Jon Cohen, 'WHO Panel Proposes New Global Registry for All CRISPR Human Experiments', *Science News* (19 March 2019) <https://www.sciencemag.org/news/2019/03/who-panel-proposes-new-global-registry-all-crispr-human-experiments>.

[143] National Academies of Science, Engineering, and Medicine (n 12) 190; Nuffield Council on Bioethics, 'Genome Editing and Human Reproduction' (Final Report, July 2018) 140 <http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf>.

[144] See generally Brook Larmer, *Operation Yao Ming: The Chinese Sports Empire, American Big Business, and the Making of an NBA Super Star* (Gotham, 2005).

[145] Ibid 3–4.

[146] Ibid.

[147] Ibid 68, 87.

[148] See Sean Ingle, 'China "Compulsorily Doped" Athletes in 1980s and 90s, Claims Whistleblower', *The Guardian* (22 October 2017) <https://www.theguardian.com/sport/2017/oct/22/china-compulsory-doping-olympic-athletes-claims-whistleblower-athletics>; Pang Zhongying, 'The Beijing Olympics and China's Soft Power', *Brookings* (4 September 2008) <https://www.brookings.edu/opinions/the-beijing-olympics-and-chinas-soft-power/>.

prowess via success in international competitions[149] may also seriously consider means to enhance future athletes at the embryonic stage.

Controversy and ethical conundrums have surrounded the use of gene editing in viable human embryos, though progress has occurred in China.[150] In 2015, Chinese scientists reported editing the genomes of non-viable human embryos – a global first.[151] Despite the embryos not being viable, the achievement ignited significant ethical debates. In November 2018, Chinese scientist He Jiankui went further, claiming to have altered the genomes of twin baby girls born shortly before the announcement.[152] Jiankui altered the embryos at conception during fertility treatments; he introduced a rare, natural variation that makes it more difficult for HIV to infect white blood cells.[153] Such edits aimed to protect the infants from infection of HIV later in life and the notable stigma attached to HIV status in China.[154] The surprise announcement received pointed criticism from public entities in both the Western and Chinese scientific communities.[155] While the Chinese government responded harshly towards Jiankui, some evidence suggests public actors in China may have funded and facilitated the work.[156] Other CRISPR experts in China have signalled their pursuit of safer gene editing tools for near-term use in the clinical setting.[157] While understanding and contextualizing the fallout from this event will invariably take time, more attempts at germline modification may soon follow.

The desirability and pressures for competitive germline editing will likely vary by state, subject to corresponding sociocultural, political, and historical factors.

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[149] For an overview of how states can communicate power through the Olympics, see Christopher J Finlay and Xin Xin, 'Public Diplomacy Games: A Comparative Study of American and Japanese Reactions to the Interplay of Nationalism, Ideology and Chinese Soft Power Strategies Around the 2008 Beijing Olympics' (2010) 13(5) *Sport in Society* 876, 877–8.

[150] Nicholas Wade, 'Scientists Seek Moratorium on Edits to Human Genome that Could Be Inherited', *The New York Times* (3 December 2015) <https://www.nytimes.com/2015/12/04/science/crispr-cas9-human-genome-editing-moratorium.html>.

[151] Liang et al (n 98).

[152] Antonio Regalado, 'Chinese Scientists Are Creating CRISPR Babies', *MIT Technology Review* (25 November 2018) <https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/>.

[153] Dennis Normile, 'CRISPR Bombshell: Chinese Researcher Claims to Have Created Gene-Edited Twins', *Science News* (26 November 2018) <https://www.sciencemag.org/news/2018/11/crispr-bombshell-chinese-researcher-claims-have-created-gene-edited-twins>.

[154] Ibid. See Sharon Begley, 'He Took a Crash Course in Bioethics. Then He Created CRISPR Babies', *Stat News* (27 November 2018) <https://www.statnews.com/2018/11/27/crispr-babies-creator-soaked-up-bioethics/>.

[155] See, eg, Francis S Collins, 'Statement on Claim of First Gene-Edited Babies by Chinese Researcher' *US National Institutes of Health* (28 November 2019) <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-claim-first-gene-edited-babies-chinese-researcher>; 'Statement by the Organizing Committee of the Second International Summit on Human Genome Editing', *National Academies of Sciences, Engineering, and Medicine* (29 November 2018) <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b&_ga=2.167301561.64562508.1543818590-2134740216.1542142257>; John Ruwitch, 'In Open Letter, Scientists in China Say Baby Gene ¬-Editing "Crazy"', *Reuters* (26 November 2018) <https://www.reuters.com/article/health-china-babies-genes-letter/in-open-letter-scientists-in-china-say-baby-gene-editing-crazy-idUSL4N1Y21C7>.

[156] Jane Qiu, 'Chinese Government Funding May Have Been Used for "CRISPR Babies" Project, Documents Suggest', *Stat News* (25 Feburary 2019) <https://www.statnews.com/2019/02/25/crispr-babies-study-china-government-funding/?utm_content=buffer1d4d6&utm_medium=social&utm_source=twitter&utm_campaign=twitter_organic>; Julia Belluz, 'CRISPR Babies: The Chinese Government May Have Known More Than It Let On', *Vox* (4 March 2019) <https://www.vox.com/2019/3/4/18245864/chinese-scientist-crispr>.

[157] Stephen Chen, 'China's Race to Test "Mutation-Free" Gene-Editing Technology on Cancer Patients', *South China Morning Post* (11 March 2019) <https://www.scmp.com/news/china/science/article/2189395/chinas-race-test-mutation-free-gene-editing-technology-cancer>. See also Zuo et al (n 92).

Current national laws and rules regarding human germline editing vary widely, from lenient to prohibitive – where such policies exists at all.[158] Public and media entities in China tend to celebrate rapid innovation in biotechnology,[159] which may have contributed to motivations for the recent CRISPR modification of embryos taken to term in China.[160] The Russian scientists openly seeking state authorization to conduct similar germline editing clinical trials may reflect similar sentiments.[161] South Korea and other states have also shown a favourable disposition towards the possibility of gene editing in humans, with strong social and political support for innovation in biotechnology.[162] Yet, states such as Germany sharply disapprove of human embryonic genomic manipulation and have placed legal barriers to such research or clinical work.[163] Other jurisdictions such as the US take a more moderate approach, where human germline editing remains nominally lawful but relevant agencies are functionally forbidden from funding research or approving clinical trials.[164] This diversity in sociocultural and regulatory approaches to embryonic modifications may result in a setting where some parents or states have access to these interventions for future children, while others face barriers to seeking them. Access to germline editing will likely also vary by research resources and funding available in each state, and any scientific or clinical collaborations with other nations.[165]

Divergent state policies on genetic modification may also give rise to unsupervised interventions or medical tourism, where individuals barred from obtaining genetic modification services in one jurisdiction may seek them out in others with more relaxed oversight.[166] Rising trends in biohacking could also enable athletes to seek out somatic gene doping in unsupervised nonclinical settings. So-called 'do-it-yourself" gene editing materials remain accessible to consumers, disregarding national regulators expressing safety concerns over the kits.[167] The availability of these kits has already enabled individuals to attempt somatic gene therapy on themselves without regulatory approval

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[158] Rosario Isasi, Erika Kleiderman, and Bartha M Knoppers, 'Editing Policy to Fit the Genome?' (2016) 351(6271) *Science* 337, 337-8.

[159] See Lijing Jiang and Hallam Stevens, 'Chinese Biotech Versus International Ethics? Accounting for the China – America CRISPR Ethical Divide' (2015) 10(4) *Biosocieties* 483, 484-6.

[160] Rob Schmitz, 'Gene-Editing Scientist's "Actions Are a Product of Modern China"', NPR (5 February 2019) <https://www.npr.org/2019/02/05/690828991/gene-editing-scientists-actions-are-a-product-of-modern-china>.

[161] See David Cyranoski, 'Russian Biologist Plans More CRISPR-Edited Babies', *Nature News* (10 June 2019) <https://www.nature.com/articles/d41586-019-01770-x>.

[162] Joseph Wong et al, 'South Korean Biotechnology – A Rising Industrial and Scientific Powerhouse' (2004) 22 *Nature Biotechnology* DC42.

[163] Isasi, Kleiderman, and Knoppers (n 158) 337.

[164] Provisions barring public funds for funding and regulatory review of germline editing projects have become boilerplate language for appropriation bills in the US. See, eg, *Department of Defense and Labor, Health and Human Services, and Education Appropriations Act*, Pub L No 115-245, § 508, 132 Stat 2981, 3118; *Consolidated Appropriations Act, 2019*, Pub L No 166-6, § 731, 133 Stat 13, 81.

[165] For example, emerging international clinical trial collaborative structures could provide a model for increasing access to such techniques. See, eg, 'MRFF International Clinical Trial Collaborations (ICTC) Program', *Australian National Health and Medical Research Council* (Web Page) <https://www.nhmrc.gov.au/funding/find-funding/mrff-international-clinical-trial-collaborations-ictc-program>.

[166] R Alta Charo, 'On the Road (to a Cure?) – Stem-Cell Tourism and Lessons for Gene Editing' (2016) 374(10) *New England Journal of Medicine* 901, 901–3.

[167] 'Information About Self-Administration of Gene Therapy', *US Food and Drug Administration* (21 November 2017) <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm586343.htm>.

or oversight.[168] Athletes self-administering performance-enhancing genomic interventions, or seeking out such services in a nonclinical setting, may become possible with developments in the technology.

Medical tourism involving parents seeking advanced assisted reproductive technologies has already occurred. The use of mitochondrial replacement performed by a US doctor for a Jordanian couple at a clinic in Mexico resulted in a live birth in 2016.[169] While the US FDA later barred the physician from offering these services,[170] it appears likely that authorities in none of the three nations involved had advanced notice of the procedure. Incidents of medical tourism for mitochondrial replacement have now occurred in other jurisdictions, including the Ukraine and Greece.[171] These cases of reproductive medical tourism illustrate the willingness of parents to expend significant effort and resources to obtain access and the difficulty of preventing medical tourism for embryonic modification techniques and, instead relegating regulators to reactionary or deterrent roles.[172]

The interest levels of individual athletes also presents a significant driver towards somatic gene doping. Gene therapy expert H Lee Sweeney received innumerable requests from athletes to experiment on them during the 2004 and 2008 Olympics,[173] demonstrating both athletes' awareness and interest in gene doping. Empirical research suggests an individual athlete's propensity to engage in doping reflects the intersection of personal, social, and environmental influences including desire to win, social norms among peers, and the accessibility of doping materials.[174] Athletes generally understand the potential to increase performance and the possible health and career consequences of doping, while doubting the capacity of anti-doping authorities to discover performance enhancement.[175] Influence from parents or coaches also mediate

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[168] Emily Mullin, 'Biohackers Disregard FDA Warning on DIY Gene Therapy', *MIT Technology Review* (17 December 2017) <https://www.technologyreview.com/s/609568/biohackers-disregard-fda-warning-on-diy-gene-therapy/>.

[169] John Zhang et al, 'Live Birth Derived from Oocyte Spindler Transfer to Prevent Mitochondrial Disease' (2017) 34(4) *Reproductive BioMedicine Online* 361, 361–2. See Gina Kolata, 'Birth of Baby with Three Parents' DNA Marks Success for Banned Technique', *The New York Times* (27 September 2016) <https://www.nytimes.com/2016/09/28/health/birth-of-3-parent-baby-a-success-for-controversial-procedure.html>.

[170] Warning Letter to Dr John Zhang, *US Food and Drug Administration* (4 August 2017) <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM570225.pdf>.

[171] See Rob Stein, 'Clinic Claims Success in Making Babies with 3 Parents' DNA', NPR (6 June 2018) <https://www.npr.org/sections/health-shots/2018/06/06/615909572/inside-the-ukrainian-clinic-making-3-parent-babies-for-women-who-are-infertile>.

[172] See Glenn Cohen, 'Circumvention Medical Tourism and Cutting Edge Medicine: The Case of Mitochondrial Replacement Therapy' (2018) 25(1) *Indiana Journal of Global Legal Studies* 439, 452.

[173] Christen Brownlee, 'Gene Doping: Will Athletes Go for the Ultimate High?' (2004) 116(18) *Science News* 280, 280; Melinda Wenner, 'How to be Popular During the Olympics: Be H. Lee Sweeney, Gene Doping Expert', *Scientific American* (15 August 2008) <https://www.scientificamerican.com/article/olympics-gene-doping-expert/>.

[174] Andrea Peróczi and Eugene Aidman 'Psychological Drivers in Doping: The Life-Cycle Model of Performance Enhancement' (2008) 3 *Substance Abuse Treatment, Prevention, and Policy* 7:1–12, 3–4. Luca Mallia et al, 'Doping Use in Sports Teams: The Development and Validation of Measures of Team-Based Efficacy Beliefs and Moral Disengagement from a Cross-National Perspective' (2016) 25 *Psychology of Sport and Exercise* 78, 78–9.

[175] Jaime Morente-Sánchez and Mikel Zabala, 'Doping in Sport: A Review of Elite Athletes' Attitudes, Beliefs, and Knowledge' (2013) 43(6) *Sports Medicine* 395, 395.

doping behaviours in athletes,[176] so external pressure from these or other actors could encourage gene doping. Athletes may also have particular interest in somatic gene doping given the potential permanence of the intervention.[177]

When considering germline athletic enhancement, parents rather than the athletes themselves may serve as the individuals driving these practices. Gene editing may gain favour given its capacity to bolster parents' reproductive autonomy and yield healthier children,[178] but extending such rationales could embolden parents seeking to select traits,[179] or even enhance the athletic abilities of future children. Previous polls in the US and China have shown a high degree of support for gene editing to prevent heritable disease and have also indicated a substantial minority of respondents are comfortable with using the technology for enhancement.[180] Public, private, and civil society groups have released many ethics statements expressing a variety of concerns and conclusions on how or if parents and guardians could appropriately use germline modification.[181] These statements represent critical steps towards defining early guiding norms and ethical principles for germline editing, resembling the codes of conduct seen in early governance efforts around other emerging technologies.[182] However, few contain sport-specific analysis or consider guidance around competitions potentially involving athletes with edited genomes.

More generally, the recent actions by Jiankui in China highlighted an aggressive international response against human germline editing, even for ostensibly therapeutic modifications. The scientific community expressed particular concern,[183] with leading scientific voices such as the US National Institutes of Health ('NIH') Director Francis Collins calling Jiankui's work 'deeply concerning' and reiterating NIH disapproval of gene-editing technologies in human embryos at this time.[184] The Southern University of Science and Technology terminated Jiankui's associate professorship after flagging him as

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[176] See, eg, Justine Allen et al, 'Precipitating or Prohibiting Factor? Examining Coaches' Perspectives of Their Role in Doping and Anti-Doping', *World Anti-Doping Agency* (Final Report, 2012) 6 <https://www.wada-ama.org/sites/default/files/resources/files/allen-final-2012-eng_0.pdf>; Kelsey Erickson, Susan H Backhouse, and David Carless, 'Doping in Sport: Do Parents Matter?' (2017) 6(2) *Sport, Exercise, and Performance Psychology* 115, 125.

[177] See Fore (n 130) 80.

[178] Giulia Cavaliere, 'Genome Editing and Assisted Reproduction: Curing Embryos, Society or Prospective Parents' (2018) 21(2) *Medicine, Health Care and Philosophy* 215, 218, 221.

[179] Bonnie Steinbock, 'Designer Babies: Choosing Our Children's Genes' (2008) 372(9646) *The Lancet* 1294, 1294-5.

[180] Robert J Blendon, Mary T Gorski, and John M Benson, 'The Public and the Gene-Editing Revolution' (2016) 374(15) *The New England Journal of Medicine* 1406, 1407–9; Jiang-Hui Wang et al, 'Public Attitudes Toward Gene Therapy in China' (2017) 6 *Molecular Therapy Methods & Clinical Development* 40, 41.

[181] Carolyn Brokowski, 'Do CRISPR Germline Ethics Statements Cut It?' (2018) 1(2) *The CRISPR Journal* 115.

[182] See Diana M Bowan and Graeme A Hodge, 'Counting on Codes: An Examination of Transnational Codes as a Regulatory Governance Mechanism for Nanotechnologies' (2009) 3(2) *Regulation and Governance* 145, 148.

[183] Carolyn Y Johnson and Gerry Shih, 'Scientists Call for a Halt to Reproductive Uses of Gene Editing, Rebuke Chinese Researcher', *Washington Post* (29 November 2018) <https://www.washingtonpost.com/national/health-science/scientists-call-for-a-halt-to-genetically-editing-embryos-rebuke-chinese-researcher/2018/11/29/16d5b602-f328-11e8-bc79-68604ed88993_story.html?utm_term=.1d10f1c7f58c>.

[184] See Collins (n 155).

a 'rogue' individual.[185] In response, experts including CRISPR pioneers Feng Zhang and Emmanuelle Charpentier have called for an immediate moratorium on all editing of the human germline.[186] The NIH has already declared support for a global moratorium[187] and WADA banned all gene editing in sport in 2018.[188] While this case highlights the power of a rapid and global professional and institutional response to human germline editing, it also demonstrates the power that individual scientists and research groups have in extending the application of CRISPR technologies. Future 'rogue' actors could pursue germline editing for enhancing athletes, even if against international or public consensus.

Conclusion – Part V

The disruptive potential of somatic and germline doping poses vexing problems for the governance of sports. Somatic gene doping continues to present anti-doping concerns now, though the slow progress in underlying gene therapy technologies has prevented these fears from manifesting to date. Unlike the slow start for gene doping, the fundamental technology for conducting germline editing already exists and recently delivered on a proof-of-concept demonstration. Though the international scientific community quickly mobilized to condemn Dr Jiankui's germline editing work, at least one fertility clinic in Dubai contacted Jiankui for technical assistance shortly after the November 2018 press release,[189] indicating quiet interest in scaling up these efforts. The Russian scientist now seeking state legitimation to conduct similar clinical experiments[190] could accelerate conversations about conducting germline editing without the stigma of a 'rogue' actor label. Should rapidly advancing embryonic gene editing techniques yield children with the potential for enhanced athletic abilities within the next 10 to 15 years, these athletes could reach minimum competition age by 2040 to 2050.

The inevitability of athletes with germline modifications seeking to compete creates urgency for WADA and other anti-doping institutions begin to consider their governance options for managing the future of sport. Anti-doping regulation has historically struggled to keep pace with innovations in doping and regulators

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185 David Cyranoski, 'CRISPR-Baby Scientist Fired by University', *Nature News* (22 January 2019) <https://www.nature.com/articles/d41586-019-00246-2>.

186 Eric Lander et al, 'Adopt a Moratorium on Heritable Genome Editing' (2019) 567(7747) *Nature* 165, 165. See also Editorial, 'Set Rules for Germline Gene Editing' (2019) 567(7747) *Nature* 145, 145.

187 Francis S Collins, 'NIH Supports International Moratorium on Clinical Application of Germline Editing', *US National Institutes of Health* (13 March 2019) <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-supports-international-moratorium-clinical-application-germline-editing>; see also Carrie D Wolinetz and Francis S Collins, 'NIH Pro Germline-Editing Moratorium' (2019) 567(7747) *Nature* 175, 175.

188 Michael L Page, 'Anti-Doping Agency to Ban All Gene Editing in Sport From 2018', *New Scientist* (9 October 2017) <https://www.newscientist.com/article/2149768-anti-doping-agency-to-ban-all-gene-editing-in-sport-from-2018/>.

189 Sharon Begley, 'Fertility Clinics Around the World Asked "CRISPR Babies" Scientist for How-To Help', *Stat News* (May 28, 2019) <https://www.statnews.com/2019/05/28/fertility-clinics-asked-crispr-babies-scientist-for-how-to-help/>.

190 Cyranoski (n 185).

including WADA will find themselves in difficult positions when faced with the potential of athletes leveraging human somatic and, especially, germline gene editing tools. Continuously evolving gene editing technologies, most recently CRISPR-Cas methods, pose unique challenges with their precision, low costs, and detection issues, confounded by the reality of approved therapeutic usages that offer enhancement under the right circumstances. Beyond continued surveillance for gene doping, anti-doping institutions should begin to consider whether and how to screen for germline editing in athletes, how to respond appropriately to a positive result, and what standards should apply.

The need to open conversations about anti-doping regulation and germline editing becomes even more salient when acknowledging that germline doping may occur against the international consensus or moratoria on the clinical use of embryonic gene editing. Private or public actors willing to accept the risks of germline doping may pursue embryonic gene editing soon in the hopes of long-term rewards. Moving to ban athletes with germline edits from international competitions – especially if they represent only a minority of nations – could provoke political toxicity and ethical quarrels, so early adopters of germline doping may be rewarded with favourable rulings to avoid the turmoil of prohibitions. Further, states that invest early in scientific work towards germline editing in sport could drastically outpace regulators for the foreseeable future. These political gambles, overlaying health risks and ethical concerns, may tempt some private or public actors to push forward in germline enhancement efforts. As competitive sports can instil motivations for individuals and state actors to push the boundaries of health technologies, sports may offer one of the earliest opportunities for directly addressing the legal and societal implications of clinical interventions manipulating the human germline. As such, anti-doping and other sports governance institutions may face some of the first decisions regarding significant concerns around human gene editing centred around safety, equity, consent, social justice, and concepts of what it means to win. Anti-doping and sport governance institutions may soon find themselves at the vanguard of human gene editing policy and regulation, making decisions with far reaching ethical, social, and legal implications. The time has come to open conversations about the role sports governance entities will play in this emerging and transformative movement towards human genomic enhancement.