

# Regulating Genetic Advantage

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<b>INTRODUCTION</b>	<b>3</b>
<b>I. BACKGROUND</b>	<b>7</b>
A. Choosing our Genetics	7
B. Genetic Modification for Performance Enhancement in Sports	11
C. WADA's Ban on Genetic Modification for Performance Enhancement in Sports	14
D. Minimizing the role of luck	21
<b>II. EXPERIMENTAL STUDIES</b>	<b>23</b>
A. Methodology of Study 1	23
B. Results of Study 1	27
Reactions to the Base Case Scenario	27
Demographic differences	28
Comparison to attitudes towards doping	28
C. Methodology for Study 2	28
D. Results of Study 2	31
Challenging the idea that the genetics you are born with should confer protected privilege	31
Effect of language in attitudes to performance enhancement in sports	32
Robustness of our results to concerns of equality of access and to modification type	33
<b>III. DISCUSSION</b>	<b>34</b>
A. Support for gene doping	34
B. Choice of language impacts public perception	34
C. Genetics at birth not deserving of competitive protection	35
D. The Self-Authoring Vision of the Spirit of Sport	37
E. Limitations and Future Directions	39
<b>IV. CONCLUSION</b>	<b>40</b>

*The regulation of genetic modification is generating urgent international debate.*

*Development of new technologies means not only new therapies, but new possibilities for enhancement. The only area with existing regulation concerning genetic enhancement is sports, where adoption is seen as imminent. “Gene doping” is banned by the World Anti-Doping Agency (WADA), and enforced at considerable cost, on the basis that biological innateness is essential to what is valuable in sports. As both the first and a highly visible mover, WADA’s ban is set to disproportionately affect other domains.*

*We present a normative analysis of current regulation and the first experimental study (n=1000) on US attitudes towards gene doping. Through a series of ten scenarios, we find respondents view gene doping as fundamentally different than other forms of enhancement: 79% support allowing athletes modified to have an advantage competing alongside those born with that advantage; 54% support allowing modified athletes to compete alongside unmodified athletes; 34% endorse creating a separate competitive category. This leaves only a small minority supportive of an outright ban. These results are inconsistent with the protection of biological innateness. WADA need to acknowledge that genetic modification calls into question the foundations of their prohibition decisions.*

*Our results are consistent both with increasing acceptance of genetic modification, and with theoretical and empirical work that equality of opportunity is best achieved through minimizing the role of luck. In this view, genetic modification is a tool to reduce the inequities of the natural lottery. The development of regulation in other areas should proceed with this in mind.*

## INTRODUCTION

Some things in life we have no control over; they are the result of luck. The natural lottery has traditionally been the quintessential example of a realm where luck reigns. But our awareness of the inner workings of biological fortune and misfortune is accelerating. Science is uncovering new links between genes and attributes that predict achievement, illuminating how our genetics define the outer boundaries of possibility for our lives.<sup>1</sup> But what if it were possible to change our genetics even after we are grown? Long a staple of science fiction plots, this has recently become possible through a new wave of techniques, particularly CRISPR.<sup>2</sup> Applications of the technology are developing rapidly. The genetic modification of adults, particularly for reasons other than medical treatment, poses real questions for contemporary society.<sup>3</sup> These questions stand apart from concerns with designer babies, even though the latter have grabbed more headlines to date. These adult enhancement applications have disruptive potential for both public and private domains: education, the job market, the marriage market, combat, disability rights, criminal justice, and the sports and entertainment industry, among others.

The one domain with regulation already in place, as it foresees an early influx of adults who choose genetic modification, is sports. In 2003, the international oversight authority on the

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<sup>1</sup> For advances in complex traits relevant to disease, *see, e.g.*, Peter M. Visscher et al., *10 Years of GWAS Discovery: Biology, Function, and Translation*, 101 *AM. J. HUM. GENETICS* 5 (2017), available at <https://www.sciencedirect.com/science/article/pii/S0002929717302409>; for intelligence, *see, e.g.*, Suzanne Sniekers et al., *Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence*, 49 *NATURE GENETICS* 1107 (2017), available at <https://www.nature.com/articles/ng.3869>.

<sup>2</sup> CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and the protein Cas9 form a system that can be used for genetic modification. *See e.g.*, Jennifer A. Doudna & Emmanuelle Charpentier, *The new frontier of genome engineering with CRISPR-Cas9*, 346 *SCIENCE* (2014).

<sup>3</sup> Sarah Polcz & Anna Lewis, *CRISPR-Cas9 and the non-germline non-controversy*, 3 *J. L. & BIOSCIENCES* 1 (2016).

use of drugs in sports, the World Anti-Doping Agency (WADA), stepped outside its primary sphere of substances to preemptively ban from competition athletes who have undergone genetic modification,<sup>4</sup> branding such procedures as “gene doping”.<sup>5</sup> WADA’s motivation for the ban is the protection of natural talent, which it equates with ensuring a level playing field.

<sup>6</sup> Its response to the perceived threat of adult genetic modification involves not only imposing prohibitions, but also setting an agenda of moral education to shape public attitudes. Their rush to regulation has ramifications from a broader societal perspective: with a new technology, decisions by early, influential movers can have ripples to other domains.

In contrast to WADA’s top-down approach, the scientific establishment is actively making calls for urgent and widespread public engagement around the uses of these new technologies.<sup>7</sup> Their motivations include promoting transparency, conferring legitimacy, and

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<sup>4</sup> WORLD ANTI-DOPING AGENCY, *WORLD ANTI-DOPING CODE (2003)*, available at [https://www.wada-ama.org/sites/default/files/resources/files/wada\\_code\\_2003\\_en.pdf](https://www.wada-ama.org/sites/default/files/resources/files/wada_code_2003_en.pdf) [hereinafter 2003 WADA Code].

<sup>5</sup> Consider remarks made in 2015 by then WADA director general David Howman on challenges to the integrity of sport:

[W]hen the curtain is drawn, what is revealed is a social problem of steroids in schools and amongst our security forces; the presence of the criminal underworld in trafficking prohibited substances; an unregulated supply of non-sanitized drugs through the internet and from profit-making opportunists (including many in local gyms); amateur athletes doping in recreational sports events; young people taking steroids in a bid to look good; and, an overall challenge to the values of sport and its integrity through allied activities such as spot- or match-fixing, bribery and corruption. None of these matters really fall under WADA’s express mandate of elite sport, but evidence of all have come to our attention.

*Speech by WADA Director General, David Howman, Challenges to the Integrity of Sport, Melbourne, WORLD ANTI-DOPING AGENCY (Oct. 15, 2015)*, <https://www.wada-ama.org/en/media/news/2015-10/speech-by-wada-director-general-david-howman-challenges-to-the-integrity-of-sport>.

<sup>6</sup> See *Athletes*, WORLD ANTI-DOPING AGENCY, <https://www.wada-ama.org/en/athletes> (last visited Apr. 15, 2018) (“WADA strives to establish a level playing field, to allow them to concentrate on the pursuit of athletic excellence through their natural talent – “playing true”).

<sup>7</sup> U.S. National Academy of Sciences (NAS) and the National Academy of Medicine (NAM) have argued for public engagement to be incorporated into the policy-making process for human genome editing. See NAT’L ACAD. SCI. & NAT’L ACAD. MED., *HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE* (2017). “The potential for rapid advance of this approach, and the pressure to apply it clinically, should not be underestimated. The ACMG Board of Directors strongly encourages broad public debate regarding the clinical

improving policy making. They fear a public backlash may sabotage hopes of advancing these technologies to alleviate human suffering. WADA, on the other hand, do not have the same motivations to ensure a full dialogue with the public, as the benefits of the technology fall outside of their domain. The value of mapping public judgments is to equip regulators contemplating action with information about the potential reception of different regulatory regimes.

Part of the challenge of public engagement is that the lines drawn by the scientific community are often a function of technological technique and in important instances fail to capture socially meaningful distinctions. One of the only surveys of public opinion of genetic modification found that the distinction the public thought most meaningful was between applications designed to cure disease versus enhancement applications. This is not the same as the distinction the scientific establishment has been devoting most time to discussing, which is whether or not a modification is heritable.<sup>8</sup> In this paper, we investigate a distinction that is socially meaningful by probing sentiment about advantageous modifications which give people genes that already exist within the human species but are unevenly distributed. This allows us to decouple such questions from applications we might expect to be more problematic, but which popular culture – for example, the X-men – has brought into the lay concept of genetic modification. This would include modifications which some could feel erode what it means to be human and consequently overestimate public opposition to enhancement more narrowly construed. Two reasons that are often given for opposition to genetic enhancement that could hold in the case we focus on are the concern that social

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application of genomic editing.” ACMG Board of Directors, *Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics*, 19 *GENETICS IN MED.* 723, 724 (2017), available at <https://www.nature.com/articles/gim2016195.pdf>

<sup>8</sup> The somatic versus germline distinction. See Background, Section A.

inequities may be exacerbated if cost barriers are high, and the fear that those who would otherwise choose not to use the technology would feel compelled to do so. An empirical approach allows us to investigate the extent to which these concerns are felt.

We experimentally probe the evaluative judgments of 1000 US-based individuals through a series of experiments based on gene doping. We find that whereas the public see doping as rightfully prohibited, they do not see genetic modification for performance enhancement in the same way. With the unlevel playing field of inherited genetic advantage laid bare, people do not support protecting natural talent – it is clear this amounts instead to the protection of at-birth genetic advantages. Genetic modification can be a tool for broadening equality of opportunity; a means to level the bumpy playing field of inherited genetic advantage. WADA’s attempt to simultaneously promote natural talent and to defend the ideal of the level playing field has always been strained, but has now hit breaking point: our data suggest the public view these two principles as in fundamental tension with each other. In banning genetic modification for performance enhancement, WADA simply extended their rationale governing traditional ways of boosting performance to encompass genetic modification. But they need to instead acknowledge the fundamental challenge genetic modification raises for the philosophical foundations of their regulation. Our results are consistent with a worldview that seeks to minimize the role of luck, and instead reward excellence produced through choice.<sup>9</sup> As the role of genetics becomes clearer, and with the prospect of being able to change aspects of our genetics, genetic modification becomes a tool to promote equality of opportunity.

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<sup>9</sup> This is an idea that appears in several schools of thought, including branches of egalitarianism and economics. *See* Background, Section D.

In Section I, our Background, we provide context on genetic modification, why sports has been the first area to be regulated, the reasoning behind the ban, and the broader context of perceptions of fair outcomes. This sets the scene for our own experiments probing perceptions of fairness concerning gene doping, which we introduce in Section II. Section III contains our Discussion and Section IV our Conclusions.

## I. BACKGROUND

### A. Choosing our Genetics

For the vast majority of people, genetics is determined at the moment of conception, meaning the only deliberate impact a parent can have on the genes of their offspring is through their choice of mate. But opportunities to expand genetic choice are already arising. Parents using donated sperm or eggs are now able to select donors based directly on their genetics.<sup>10</sup> And it has become a routine part of an IVF cycle to genetically screen embryos before they are transferred to the womb.<sup>11</sup> In the US, there are currently no legal barriers to choosing an embryo to implant based on genetic testing.<sup>12</sup> While today genetic screening is typically performed only for a handful of conditions, the technology is already mature enough to

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<sup>10</sup> For example, the Seattle Sperm Bank allows customers to select donors based on athleticism and lists evidence of athletic achievement such as “Division I” athlete and “professional soccer player.” *Top Athletes*, SEATTLE SPERM BANK, <https://www.seattlespermbank.com/athletes/> (last visited Jan. 18, 2017). GenePeeks allows for predicting “Virtual Progeny,” with those selecting a sperm or egg donor a target market. GENEPEEKS, <https://www.genepeeks.com> (last visited Jan. 22, 2017).

<sup>11</sup> Robert Klitzman et al., *Preimplantation Genetic Diagnosis (PGD) on In-Vitro Fertilization (IVF) Websites: Presentations of Risks, Benefits and Other Information*, 92 FERTILITY & STERILITY 1276 (2009), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2950118/> (revealing that by 2008 70% of IVF clinics were advertising Preimplantation Genetic Diagnosis).

<sup>12</sup> Preimplantation Genetic Diagnosis has been used to select embryos based on gender, as well as by parents with disabilities who desire children with the same conditions, such as deafness or dwarfism, a practice which is not permitted in certain other nations. See Michelle J. Bayefsky, *Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism*, 3 REPROD. BIOMED. & SOC’Y ONLINE 41 (2016).

screen for any genetic variant.<sup>13</sup> In *The End of Sex*, Hank Greely argues that in 20 years, people in developed countries will regularly use genetic testing in combination with embryo selection in order to maximize the chances their child will have the traits they desire.<sup>14</sup>

Beyond our ability to select an embryo comes our much more recently developed ability to modify genetics. This can be done at the embryo stage or later. Modification of human embryos is an example of a *germline modification*, i.e. a change which enters the gene pool as it can be passed onto offspring. Adults can also be genetically modified, however their modifications cannot be inherited. These changes are referred to as *somatic modifications*.<sup>15</sup> The early promise of somatic genetic modification is that it is a way to treat individuals with genetically caused diseases. Clinical research started in the 1980s, and by November 2017, there had been nearly 2600 gene therapy clinical trials.<sup>16</sup> It was not until 2003 that the first gene therapy was approved, in China.<sup>17</sup>

In the last five years, the genetic engineering field has been revolutionized by a new technology called CRISPR.<sup>18</sup> First demonstrated as a genome-editing technology in human cells in 2013,<sup>19</sup> the technology enables precise genetic changes to be made at more or less any location on a DNA molecule, by making molecular-level scissor-like snips. CRISPR is

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<sup>13</sup> See Brock A. Peters et al., *Detection and phasing of single base de novo mutations in biopsies from human in vitro fertilized embryos by advanced whole-genome sequencing*, 25 GENOME RES. 426 (2015), available at <http://genome.cshlp.org/content/25/3/426.full?sid=d792542d-2090-4f59-a75a-ffedfb6cae7a>. In practise this would be very costly.

<sup>14</sup> HENRY T. GREELY, *THE END OF SEX AND THE FUTURE OF HUMAN REPRODUCTION* (2016).

<sup>15</sup> More precisely, germline cells are those whose DNA can be passed on to the next generation, and somatic cells are all non-germline cells.

<sup>16</sup> J. Gene Med., *Gene Therapy Clinical Trials Worldwide*, ABEDIA (NOV. 2017), <http://www.abedia.com/wiley/phases.php>.

<sup>17</sup> Sue Pearson et al., *China approves first gene therapy*, 22 NATURE BIOTECHNOLOGY 3 (2004), available at <https://www.nature.com/nbt/journal/v22/n1/full/nbt0104-3.html>.

<sup>18</sup> Its first reported use in human cells appears in Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819 (2013).

<sup>19</sup> Pearson et al., *supra* note 17.

widely regarded as revolutionary in part because it is much cheaper, more accurate and more technologically straightforward than earlier technologies.<sup>20</sup>

Clinical trials for somatic applications using CRISPR have already started.<sup>21</sup> On the germline side, the first successful editing of a human embryo was announced by a team of Chinese researchers in 2015, and in 2017 US researchers repeated the feat.<sup>22</sup> These advances ignited a heated debate over the appropriate ethical and regulatory framework for such research.<sup>23</sup> The American College of Medical Genetics made an official statement in January 2017 advising that the “potential for rapid advance of this approach, and the pressure to apply it clinically, should not be underestimated.”<sup>24</sup> While to date germline applications (“designer babies”) have been at the center of this debate as they stand to introduce changes to the human gene pool,<sup>25</sup> there has been acknowledgement that policy attention should also be directed towards uses of this technology to enhance the genetics of adults. Many stakeholders have recently made calls for urgent public engagement to inform the policy-making process for human

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<sup>20</sup> See Antonio Regalado, *Engineering the Perfect Baby*, MIT TECH. REV. (Mar. 5, 2015), <https://www.technologyreview.com/s/535661/engineering-the-perfect-baby/>.

<sup>21</sup> The first clinical trial involving CRISPR started in China in October 2016, and the first trial in the US is due to start in 2018. David Cyranoski, *CRISPR gene-editing tested in a person for the first time*, NATURE (Nov. 15, 2016), <http://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988>; Sara Reardon, *First CRISPR clinical trial gets green light from US panel*, NATURE (June 22, 2016), <http://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137>.

<sup>22</sup> Puping Liang et al., *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, 6 PROTEIN & CELL 363 (2015). In 2016, Chinese researchers announced editing the genome of a human embryo for a second time, to make it resistant to HIV infection. Xiangjin Kang et al., *Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing*, 33 J. ASSISTED REPROD. & GENETICS 581 (2016). Hong Ma et al., *Correction of a pathogenic gene mutation in human embryos*, 548 NATURE (2017). Whereas the Chinese researchers were editing non-viable embryos, these US researchers edited viable embryos, and reported substantial accuracy improvements compared to the previous work.

<sup>23</sup> See Polcz & Lewis, *supra* note 3.

<sup>24</sup> Editorial, *Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics*, GENETICS IN MED. (Jan. 26, 2017), <http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2016195a.html>.

<sup>25</sup> See Polcz & Lewis, *supra* note 3, at 415-7.

genome modification, particularly for enhancement applications, including from the National Academies of Science and Medicine.<sup>26</sup>

These calls for engagement are made against a background of a near total absence of relevant studies. A 2015 review of human enhancement public opinion surveys concluded that the area is understudied.<sup>27</sup> On the topic of genetic modification for human enhancement, none of the papers that met the review's broad inclusion criteria covered the United States. Since then, there have been two public opinion surveys of note. The first was commissioned by Pew and covered 4726 US-based individuals. When participants were asked for their attitudes on gene editing to reduce babies' chances of disease, they were 42% supportive if the babies would be far healthier than any known human, 52% supportive if they would be much healthier than the average human today, and 54% supportive if they would be always equally healthy as the average human today.<sup>28</sup> The National Academies of Science and Medicine, in their commissioned report on this topic, referenced this work: "the Pew study and many others suggest that policy in this area needs to be developed with full attention to public attitudes and understandings."<sup>29</sup> The second study was conducted by YouGov in early 2017 and covered 1600 US-based individuals. They found higher acceptance for genetic

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<sup>26</sup> NAT'L ACAD. SCI. & NAT'L ACAD. MED., *supra* note 7. "RECOMMENDATION 6-2. Government bodies should encourage public discussion and policy debate regarding governance of somatic human genome editing for purposes other than treatment or prevention of disease or disability." *Id.*, at 159. "RECOMMENDATION 7-3. Public participation should be incorporated into the policy-making process for human genome editing and should include ongoing monitoring of public attitudes, informational deficits, and emerging concerns about issues surrounding "enhancement." *Id.*, at 178.

<sup>27</sup> Anne M. Dijkstra & Mirjam Schuijff, *Public opinions about human enhancement can enhance the expert-only debate: A review study*, 25 PUB. UNDERSTANDING SCI. 588 (2015), available at <http://pus.sagepub.com/content/early/2015/01/19/0963662514566748>.

<sup>28</sup> Cary Funk et al., *U.S. Public Wary of Biomedical Technologies to 'Enhance' Human Abilities*, PEW RES. CTR. (Nov. 2, 2016), <http://www.pewinternet.org/2016/07/26/u-s-public-wary-of-biomedical-technologies-to-enhance-human-abilities/>.

<sup>29</sup> NAT'L ACAD. SCI. & NAT'L ACAD. MED., *supra* note 7, at 143.

modification than previous surveys: acceptance or indifference towards somatic gene editing for therapy was ~83%, and for enhancement ~65%.<sup>30</sup> They also found that whereas the major distinction discussed to date has been between concerning heritable changes (i.e. the germline/somatic distinction), individuals when questioned distinguish more between changes designed to be therapeutic versus enhancing.

## **B. Genetic Modification for Performance Enhancement in Sports**

Eero Mäntyranta was a champion Finnish cross-country skier competing in the 1960s, winning three Olympic golds, two world championships, and setting records as one of the greatest Olympians ever to compete in his sport. He was found to have an abnormally high red blood cell count which allowed his blood to carry more oxygen, in turn giving him a competitive edge. This led to accusations of cheating, and his victories were viewed with suspicion.<sup>31</sup> His name was only cleared two decades later when his family was selected for a genetic study which revealed that his elevated red blood cell count – 50% more than average – was due to a rare genetic variant.<sup>32</sup> Two other members of his family who carry the same genetic variant also went on to be champion skiers.<sup>33</sup>

Mäntyranta's case illustrates the important role genetics plays in athletic ability. Athletes tend to have specific physiological attributes, and are often from the same families.<sup>34</sup> Stephen Hsu

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<sup>30</sup> Dietram A. Schufele et al., *U.S. attitudes on human genome editing*, 357 *SCIENCE* 553 (2017).

<sup>31</sup> See generally David Epstein, *Magic Blood and Carbon-Fiber Legs at the Brave New Olympics*, *SCI. AM.* (Aug. 5, 2016),

<https://www.scientificamerican.com/article/magic-blood-and-carbon-fiber-legs-at-the-brave-new-olympics/>.

<sup>32</sup> See Albert de la Chapelle et al., *Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis*, 90 *PROC. NAT'L ACAD. SCI.* 4995 (1993), available at

<http://www.pnas.org/content/90/10/4495.full.pdf> (identifying the variant segregating in his extended family).

<sup>33</sup> Epstein, *supra* note 31.

<sup>34</sup> See Van Jensen & Alex Miller, *Why Basketball Runs in the Family*, *WALL ST. J.*, June 13, 2016,

<http://www.wsj.com/articles/nba-basketball-runs-in-the-family-1464130236> (reporting that 49% of NBA players are related to an elite athlete).

argues that the “whole enterprise of competitive athletics has been, in effect, a search algorithm for genetic outliers.”<sup>35</sup> Genetic variation in dozens of genes – over 120 individual genetic differences – has been linked to sports performance.<sup>36</sup> Table 1 lists some representative examples which demonstrate that our genetics influence a range of relevant traits including endurance ability, muscle performance, how the body regenerates after injury, how energy metabolism is regulated, how blood flow is controlled, how pain is perceived, how the body responds to stress, and when sexual development takes place.<sup>37</sup> Our understanding of the genetics underlying traits which predict athleticism is rapidly evolving and expanding as new genetic sequencing technologies make large-scale studies feasible.<sup>38</sup>

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<sup>35</sup> Stephen Hsu, *We Are Nowhere Close to the Limits of Athletic Performance*, NAUTILUS (Aug. 11, 2016), <http://nautil.us/issue/39/sport/we-are-nowhere-close-to-the-limits-of-athletic-performance> (“Bolt’s times weren’t just faster than anyone else in the world. They were considerably faster even than those of a world-class runner from the previous generation that was using performance-enhancing drugs.”).

<sup>36</sup> See e.g., Giuseppe Lippi et al., *Genetics and sports*, 93 BRIT. MED. BULL. 27 (2010), available at <https://academic.oup.com/bmb/article/93/1/27/306419/Genetics-and-sports>; Daniel G. MacArthur & Kathryn N. North, *Genes and human elite athletic performance*, 116 HUM. GENETICS 331 (2005), available at <http://link.springer.com/article/10.1007%2Fs00439-005-1261-8>; Jim L. Rupert, *The search for genotypes that underlie human performance phenotypes*, 136 COMP. BIOCHEMISTRY & PHYSIOLOGY PART A: MOLECULAR & INTEGRATIVE PHYSIOLOGY 191 (2003), available at <http://www.sciencedirect.com/science/article/pii/S1095643302003495>. The 120 figure appears in Ildus I. Ahmetov & Olga N. Fedotovskaya, *Current Progress in Sports Genomics*, 70 ADVANCES IN CLINICAL CHEMISTRY 247 (2015), available at [https://www.researchgate.net/profile/Ildus\\_Ahmetov/publication/274735844\\_Current\\_Progress\\_in\\_Sports\\_Genomics/links/55294fcb0cf29b22c9b1ee2.pdf](https://www.researchgate.net/profile/Ildus_Ahmetov/publication/274735844_Current_Progress_in_Sports_Genomics/links/55294fcb0cf29b22c9b1ee2.pdf). While there have been no large scale studies regarding the heritability of sports performance, there have been some that confirm the high heritability of sports participation. A study of over 37,000 pairs of twins from seven countries found heritability of exercise participation to be 48-71%. Janine H. Stubbe et al., *Genetic Influences on Exercise Participation in 37,051 Twin Pairs from Seven Countries*, PLOS ONE 1 (Dec. 20, 2006), available at <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000022>. An earlier study found that genetic factors account for ~29–62% of the variance in daily exercise behavior and 35–83% of the variance in sports participation. Gaston Beunen & Martine Thomis, *Genetic determinants of sports participation and daily physical activity*, 23 INT’L J. OBESITY S55 (1999), available at [https://www.researchgate.net/profile/Martine\\_Thomis/publication/12931043\\_Genetic\\_determinants\\_of\\_sports\\_participation\\_and\\_daily\\_physical\\_activity/links/54aa64300cf200447b258b60.pdf](https://www.researchgate.net/profile/Martine_Thomis/publication/12931043_Genetic_determinants_of_sports_participation_and_daily_physical_activity/links/54aa64300cf200447b258b60.pdf).

<sup>37</sup> For a review of how genetic linkages are ascertained, and some of the complexities involved, see João Guilherme et al., *Genetics and sport performance: current challenges and directions to the future*, 28 REVISTA BRASILEIRA DE EDUCAÇÃO FÍSICA E ESPORTE 177 (2014), available at [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S1807-55092014000100177](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-55092014000100177). The underlying genetics is not straightforward, with both common and rare variants contributing

<sup>38</sup> In January 2017 the leading genetic sequencing company, Illumina, announced that it would soon be possible to sequence an entire human genome for \$100. Meghana Keshavan, *Illumina says it can deliver a \$100 genome — soon*, STAT (January 9, 2017), <https://www.statnews.com/2017/01/09/illumina-ushering-in-the-100-genome/>.

Attempts to develop products around these genetic links have begun in earnest,<sup>39</sup> with Uzbekistan announcing it will use the results of genetic testing to select individuals as young as 10 for its Olympic training team.<sup>40</sup>

Many of the genetic targets for gene therapy align with potential targets for genetic modification for sports performance enhancement (see Table 1).<sup>41</sup> For example, the gene therapy Neovasculgen, already approved in some countries,<sup>42</sup> is a candidate for gene doping because of its role in generating new blood vessels (see Table 1, gene VEGF). Another potential gene doping method, inhibition of Myostatin (MSTN, see Table 1) is a gene therapy target for diseases that cause muscular atrophy because it promotes muscle development. Bioviva, a biotechnology company, is developing a gene therapy involving Myostatin

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<sup>39</sup> A number of genetic testing companies provide information on genetic predisposition for sports injuries, and identifying individuals with desirable genetics. For a review of the availability of tests that help reduce injury, see Gabrielle T. Goodlin et al., *The Dawning Age of Genetic Testing for Sports Injuries*, 25 *CLINICAL J. SPORTS MED.* 1 (2015). For reviews of tests that help identify talented individuals, see Ahmetov & Fedotovskaya, *supra* note 36; Guilherme et al., *supra* note 37; Marios Kambouris et al., *Predictive Genomics DNA Profiling for Athletic Performance*, 6 *RECENT PAT. DNA & GENE SEQUENCES* 229 (2012).

<sup>40</sup> See Ron Synovitz & Zamira Eshanova, *Uzbekistan Is Using Genetic Testing to Find Future Olympians*, *ATLANTIC* (Feb. 6, 2014), <http://www.theatlantic.com/international/archive/2014/02/uzbekistan-is-using-genetic-testing-to-find-future-olympians/283001>. In 2015, there were at least 39 companies offering genetic tests directly to consumers, though there is no or little evidence that they actually help prevent injury or select star athletes. M. Alison Brooks & Beth A. Tarini, *Genetic Testing and Youth Sports*, 305 *JAMA* 1033 (2011), available at <http://jamanetwork.com/journals/jama/fullarticle/645993>. A group of world experts issued a consensus statement asserting that “[t]he general consensus among sport and exercise genetics researchers is that genetic tests have no role to play in talent identification or the individualised prescription of training to maximise performance.” Nick Webborn et al., *Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement*, 49 *BRIT. J. SPORTS MED.* 1486 (2015), available at <http://bjsm.bmj.com/content/bjsports/49/23/1486.full.pdf>. Such testing raises multiple ethical concerns, including over eugenics and the treatment of minors. See Guilherme et al., *supra* note 37.

<sup>41</sup> See David Gould, *Gene doping: gene delivery for olympic victory*, 76 *BRIT. J. CLINICAL PHARMACOLOGY* 292 (2013), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3731603/>. For a list of potential gene modifications in sports, see Ewa Brzeziańska et al., *Gene Doping in Sport – Perspectives and Risks*, 31 *BIOLOGY OF SPORT* 251 (2014), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4203840/>.

<sup>42</sup> *Neovasculgen*, HUM. STEM CELL INST., <http://eng.hsci.ru/products/neovasculgen> (last visited Jan. 17, 2017) (announcing approval in Russia).

inhibition, and reports successful results on its first test subject, their CEO.<sup>43</sup> In October 2017 biohacker Josiah Zayner announced that he was the first human to have CRISPRed himself – he has been self-injecting to inhibit Myostatin, and is selling the key component to allow others to do this at home for \$20.<sup>44</sup>

The overlap between genes of interest for diseases that will be early targets for gene therapy, and genes of interest for sports performance enhancement, is one reason to anticipate that athletes may be early adopters of genetic modification. Another reason is that athletes have shown themselves to be risk takers when it comes to gaining a competitive edge.<sup>45</sup> WADA agree, stating in their St. Petersburg Declaration that

[T]he financial and personal rewards for enhanced performance in sport indicate that sport will be one of the areas in which gene-based enhancement is first likely to arise. The world of sport therefore serves as a very effective setting in which to examine broad societal issues of enhancement and the unclear boundary between treatment and enhancement.<sup>46</sup>

### **C. WADA's Ban on Genetic Modification for Performance Enhancement in Sports**

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<sup>43</sup> *Dual Gene Therapy Has Beneficial Effects On Blood Biomarkers And Muscle Composition*, BIOVIVA (2016), <http://bioviva-science.com/blog/dual-gene-therapy-has-beneficial-effects-on-blood-biomarkers-and-muscle-composition>.

<sup>44</sup> There is no evidence that his muscles have actually bulked up as a result. See Tom Ireland, *I want to help humans genetically modify themselves*, GUARDIAN (Dec. 24, 2017), <https://www.theguardian.com/science/2017/dec/24/josiah-zayner-diy-gene-editing-therapy-crispr-interview>. The key component is "Human Myostatin Knock-Out Targeting CRISPR-Cas9 Plasmid," which is being sold by his startup The Odin.

<sup>45</sup> See Polcz & Lewis, *supra* note 3, at 422.

<sup>46</sup> *WADA St. Petersburg Declaration*, WORLD ANTI-DOPING AGENCY (June 11, 2008), [https://www.wada-ama.org/sites/default/files/resources/files/WADA\\_StPetersburg\\_Declaration\\_2008.pdf](https://www.wada-ama.org/sites/default/files/resources/files/WADA_StPetersburg_Declaration_2008.pdf).

WADA banned genetic modification for performance enhancement in 2003 and clarified that this extended to technologies such as CRISPR in 2017.<sup>47</sup> They justified the ban on the basis that it would be “contrary to the spirit of sport even if it is not harmful.”<sup>48</sup> WADA has taken several practical steps towards enforcing this ban. It invests a considerable portion of its budget attempting to develop methods to detect gene doping,<sup>49</sup> and will test athlete samples collected during the 2016 Rio Olympics for EPO gene doping.<sup>50</sup> In February 2018, it announced that it was considering mandatory whole genome sequencing for athletes in order

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<sup>47</sup> *The World Anti-Doping Code: International Standard: Prohibited List January 2018*, WORLD ANTI-DOPING AGENCY (Jan. 1, 2018), [https://www.wada-ama.org/sites/default/files/prohibited\\_list\\_2018\\_en.pdf](https://www.wada-ama.org/sites/default/files/prohibited_list_2018_en.pdf). The following was added: “The use of gene editing agents designed to alter genome sequences and/or the transcriptional or epigenetic regulation of gene expression.”

<sup>48</sup> 2003 WADA Code, *supra* note 4, art. 4.3.2. Comment. “[T]he use of genetic transfer technology to dramatically enhance sport performance should be prohibited as contrary to the spirit of sport even if it is not harmful.” *Id.*

<sup>49</sup> Since 2001 WADA has spent more than \$70 million on research, of which a “significant portion” has been dedicated to gene doping detection research, with the justification that “the size of the effort is appropriate for the size of the threat to sport.” *USADA Funded Research*, U.S. ANTI-DOPING AGENCY, <http://www.usada.org/science/research/usada-funded-research/> (last visited January 17, 2017). A review of approaches to gene doping detection is given in E. Brzeziańska et al., *supra* note 41.

<sup>50</sup> As announced by the IOC’s medical and scientific director Richard Budgett. Sarah Everts, *Athletes at Rio Olympics face advanced antidoping technology*, CHEMICAL & ENGINEERING NEWS, Aug. 8, 2016, at 25, available at <http://cen.acs.org/articles/94/i32/Athletes-Rio-Olympics-face-advanced.html>. The test will look for minor differences between the structure of the introduced gene and the naturally occurring one; similar strategies have been proposed elsewhere. A. Baoutina et al., “Implementation of method for erythropoietin gene doping detection in WADA accredited laboratories”, WORLD ANTI-DOPING AGENCY, [https://www.wada-ama.org/sites/default/files/resources/files/final\\_report\\_13c36ab\\_dr\\_baoutina.pdf](https://www.wada-ama.org/sites/default/files/resources/files/final_report_13c36ab_dr_baoutina.pdf) (last visited Jan. 17, 2017); Liping Chung et al., *Novel Biomarkers of Human Growth Hormone Action from Serum Proteomic Profiling Using Protein Chip Mass Spectrometry*, 91 J. CLINICAL ENDOCRINOLOGY & METABOLISM 671 (2006), available at <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2005-1137>; Françoise Lasne et al., “Genetic Doping” with erythropoietin cDNA in primate muscle is detectable, 10 MOLECULAR THERAPY 409 (2004), available at [http://www.cell.com/molecular-therapy-family/molecular-therapy/pdf/S1525-0016\(04\)01358-9.pdf](http://www.cell.com/molecular-therapy-family/molecular-therapy/pdf/S1525-0016(04)01358-9.pdf). It is unclear how reliable this testing will be, and whether it will require muscle biopsies. It should be noted that WADA have been under criticism for not allowing their tests to be statistically validated and on at least one occasion one of their tests was found invalid by the Court of Arbitration for Sports. *Veerpalu v. Int’l Ski Fed’n*, CAS 2011/A/2566 (Ct. Arb. Sport 2013), available at [http://www.tas-cas.org/fileadmin/user\\_upload/Bulletin\\_2013\\_2\\_complete.pdf](http://www.tas-cas.org/fileadmin/user_upload/Bulletin_2013_2_complete.pdf). See also Donald A. Berry, *The science of doping*, 454 NATURE 692 (2008), available at <http://www.nature.com/nature/journal/v454/n7205/full/454692a.html> (“The processes used to charge athletes with cheating are often based on flawed statistics and flawed logic.”); Arne Ljungqvist et al., *Doping: world agency sets standards to promote fair play*, 455 NATURE 1176 (2008), available at <http://www.nature.com/nature/journal/v455/n7217/full/4551176a.html> (offering WADA’s response); Editorial, *A level playing field?*, 454 NATURE 667 (2008), available at <http://www.nature.com/nature/journal/v454/n7205/full/454667a.html> (“Drug testing in sport aims to promote fair play, but the science behind the tests needs to be more open.”).

to enable detection of gene doping.<sup>51</sup> The addition of an enhancement method to WADA's List is tantamount to a sports-industry-wide ban,<sup>52</sup> and the penalties for violations are often career ending for athletes.

WADA's self-proclaimed *raison d'être* is to defend the spirit of sport by establishing a level playing field.<sup>53</sup> Their prohibition decisions are designed to support this aim: the principal criterion they use to justify banning an enhancement method is "conflict with the spirit of sport".<sup>54</sup> The spirit of sport is defined in terms of the "dedicated perfection of each person's natural talents."<sup>55</sup> WADA is not required to justify its decisions, nor can these decisions be legally challenged on the grounds that WADA erred in applying its own criteria,<sup>56</sup> though this

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<sup>51</sup> See Eric Niiler, *Olympics Could Require Athletes' Genetic Code To Test For Doping*, WIRED (Feb. 5, 2018), <https://www.wired.com/story/olympics-could-require-athletes-genetic-code-to-test-for-doping/>.

<sup>52</sup> In 2014, inter-organizational harmonization led the NCAA, which covers nearly half a million student athletes, to amend its bylaws to prohibit gene doping. Consequently, as a result of the collegiate to professional athlete pipeline, many professional athletes will be subject to WADA's gene doping prohibition early in their careers. *2016-2017 Banned Drugs*, NAT'L COLLEGIATE ATHLETIC ASS'N, [https://www.ncaa.org/sites/default/files/2016\\_17\\_%20Banned\\_%20Drugs\\_%20Educational\\_%20Document\\_20160531.pdf](https://www.ncaa.org/sites/default/files/2016_17_%20Banned_%20Drugs_%20Educational_%20Document_20160531.pdf) (last visited Jan. 17, 2017). See also *Division I Proposal - 2014-9*, NAT'L COLLEGIATE ATHLETIC ASS'N, <https://web3.ncaa.org/lstdbi/search/proposalView?id=3150> (last visited Jan. 17, 2017) ("[A] student-athlete under a drug testing suspension from a national or international sports governing body that has adopted the WADA code shall not participate in NCAA intercollegiate competition for the duration of the suspension. Such suspensions are only applicable to drugs and procedures that are also banned by the NCAA."). An additional signatory is the International Military Sports Council, which has over 130 member states and is the second largest multi-discipline sports organization after the IOC. This means that all military personnel competing as part of US Armed Forces Sport are subject to the Code. Armed Forces Sports, *Anti-Doping*, U.S. DEP'T DEF., <http://armedforcessports.defense.gov/Portals/19/Documents/2015%20SOP/Appendix%20L%20Antidoping%20brief.pdf> (last visited January 22, 2017).

<sup>53</sup> WORLD ANTI-DOPING AGENCY, *supra* note 6.

<sup>54</sup> 2003 WADA Code, *supra* note 4, art. 4.3.1.

<sup>55</sup> WORLD ANTI-DOPING AGENCY, WORLD ANTI-DOPING CODE 14 (2015), available at <https://www.wada-ama.org/sites/default/files/resources/files/wada-2015-world-anti-doping-code.pdf>.

<sup>56</sup> Decisions from other adjudicative forums in which doping violations have been litigated offer little guidance on the spirit of sport or related concepts to which to turn. See Josephine R. Potuto & Matthew J. Mitten, *Comparing NCAA and Olympic Athlete Eligibility Dispute Resolution Systems in Light of Procedural Fairness and Substantive Justice*, 7 HARV. J. SPORTS & ENT. L. 1, 44 (2016). Moreover the NCAA effectively precludes judicial review through its Restitution Rule. See Stephen F. Ross, Richard T. Karcher & S. Baker Kensinger, *Judicial Review of NCAA Eligibility Decisions: Evaluation of the Restitution Rule and a Call for Arbitration*, 40 J.C. & U.L. 79 (2014). Among the cases which stand as exceptions none address the inclusion of substances on the banned list. Case law from both Canada and Germany implicitly appeals to the intuition that doping rules are normatively justified in excluding substances that would interfere with sports as a test of biological potential, but with inadequate theoretical elaboration. See, e.g., *Johnson v. Athletics Canada*, [1997] O.J. 3201, para.29

may conceivably change.<sup>57</sup> Nonetheless, WADA have made attempts to identify an organizing principle under which to unify their judgments of impermissibility. Two of these have been *naturalness* and *normalcy*, both of which we argue below neither work in theory, nor have been applied systematically in practice.

What would count as “the dedicated perfection of each person’s natural talents”? Blood that has more EPO has higher oxygen carrying potential, and can increase performance. But several things can increase EPO levels: training at high altitude, sleeping in a hyperbaric tent, extracting your own blood at an earlier date and injecting it at a later date, or injecting synthetic EPO. The first two are not prohibited; the last two are. Surgical interventions, including performance enhancing interventions, are also not banned.<sup>58</sup> The concept of natural has not been applied by WADA in a consistent way. Moreover, the International Olympic Committee (IOC) have taken issue with equating natural with fair, through insisting that some female athletes suppress their natural hormone levels pharmacologically to be allowed to compete in the Olympics.<sup>59</sup>

More recently, in their 2017 update to the gene doping ban, WADA has relied on the concept of normalcy in justifying their position: genetic modification for therapeutic purposes will be

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(arguing it is “necessary to protect the right of the athlete, including Mr Johnson, to fair competition, to know that the race involves only his own skill, his own strength, his own spirit and not his own pharmacist”); *Krabbe v. Int’l Amateur Athletic Fed’n*, Oberlandesgericht München [OLG M] [Munich Region Court of Appeal] Mar. 28, 1996, *Zeitschrift für Sport und Recht* [SpuRt] 133, 134, 1996 (Ger.) (asserting that doping regulations further “the establishment of equal starting and competing conditions.”).

<sup>57</sup>A case from the European Court of Justice, *Case C-519/04, Meca-Medina v. Comm’n*, 2006 E.C.R. I-6991, suggests courts could determine whether the prohibition of a method is excessive, beyond what can be justified to achieve the proper conduct of competitive sport.

<sup>58</sup> See *DORIANE LAMBELET COLEMAN ET AL., CTR. FOR SPORTS L. & POL’Y, POSITION PAPER: WHETHER ARTIFICIALLY INDUCED HYPOXIC CONDITIONS VIOLATE “THE SPIRIT OF SPORT”* 1, 4 (2006), *available at* <https://www.law.duke.edu/features/pdf/hypoxiaresponse.pdf>.

<sup>59</sup> See also *IOC Regulations on Female Hyperandrogenism*, INT’L OLYMPIC COMM. (June 22, 2012), [https://stillmed.olympic.org/Documents/Commissions\\_PDFfiles/Medical\\_commission/2012-06-22-IOC-Regulations-on-Female-Hyperandrogenism-eng.pdf](https://stillmed.olympic.org/Documents/Commissions_PDFfiles/Medical_commission/2012-06-22-IOC-Regulations-on-Female-Hyperandrogenism-eng.pdf).

allowed provided that the modification does not produce an “enhancement beyond a return to normal”.<sup>60</sup> However, what is normal can depend on factors such as one's age and ethnicity. For example, a genetic variant that is found in 9% of Swedish males but 67% of Korean males is associated with considerably lower natural testosterone levels.<sup>61</sup> Moreover, Olympic athletes are genetic outliers – would one include what was normal for an average human, or for an athlete, or for an internationally competitive athlete? Between non-banned therapeutic applications and banned enhancements, there is also a gray area of preventative measures, for example genetic modification to lower cholesterol levels to below the average in the population.<sup>62</sup>

The National Academies of Science and Medicine, in their report on applications of genetic modification, critique reliance on concepts of the natural and normalcy in this domain:

Unless one assigns great importance to fate, it is difficult to tease out enhancements that allow individuals to fairly match the capacities of others from those that are “unnatural,” “abnormal,” or “excessive.” Furthermore, any attempt to relate enhancement to what is “normal” or “average” risks categorizing efforts to combat

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<sup>60</sup> Michael Le Page, *Anti-doping agency to ban all gene editing in sport from 2018*, NEW SCIENTIST (Oct. 9, 2017), <https://www.newscientist.com/article/2149768-anti-doping-agency-to-ban-all-gene-editing-in-sport-from-2018/> (“Generally, performance enhancement implies enhancement beyond a return to normal, although you may appreciate that this is not always easy to prove definitively”).

<sup>61</sup> Jenny Jakobsson et al., *Large Differences in Testosterone Excretion in Korean and Swedish Men Are Strongly Associated with a UDP-Glucuronosyl Transferase 2B17 Polymorphism*, 91 J. CLINICAL ENDOCRINOLOGY & METABOLISM 687 (2006), available at <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2005-1643>; *Impact of UGT2B17 gene deletion on the steroid profile of an athlete*, 3 PHYSIOLOGICAL REP. 1 (2015), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4760435/>.

It is likely that the threshold value for testing positive for testosterone abuse will be based on genotype in the future. For suggestions on how to make testing thresholds dependent on genetics, see Larry D. Bowers, *Testosterone Doping: Dealing with Genetic Differences in Metabolism and Excretion*, 93 J. CLINICAL ENDOCRINOLOGY & METABOLISM 2469 (2008), available at <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2008-0977>, and Jenny Jakobsson Schulze et al., *Substantial advantage of a combined Bayesian and genotyping approach in testosterone doping tests*, 74 STEROIDS 365 (2009), available at <https://www.ncbi.nlm.nih.gov/pubmed/19056415>.

<sup>62</sup> This example is given in NAT'L ACAD. SCI. & NAT'L ACAD. MED., *supra* note 7, at 112.

widespread “normal” but undesirable aspects of life (e.g., age-related declining eyesight, hearing, and mobility) as a form of “enhancement,” with all the pejorative connotations implied by the word.<sup>63</sup>

WADA’s attempts to date to define a grounding principle to unify prohibition decisions have failed. Others have proposed less aspirational lines along which to distinguish which enhancements to prohibit. One possible argument is to focus entirely on anti-doping policy as a tool to protect the economic value of sports as an entertainment industry. Richard Posner has argued that the question of sports doping should be approached as a matter of audience preferences, and the theoretical project of defining the spirit of sport in grander terms should be rejected.<sup>64</sup> For Posner, doping prohibitions may be justified and necessary to assure an economically efficient sports market. Other commentators have arrived at the same position,<sup>65</sup> which is also supported by pre-WADA rulings in Germany and England.<sup>66</sup> This view can be generalized to the proposition that institutions are legitimate to the degree to which they fulfil their main purpose as understood by their relevant constituency. Operating under this model, audience preferences should be central to prohibition decisions, making the ascertainment of these preferences key to developing policy. To date, WADA’s prohibition policies have not been based on data concerning public and consumer judgments of permissibility.

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<sup>63</sup> NAT’L ACAD. SCI. & NAT’L ACAD. MED., *supra* note 7, at 113.

<sup>64</sup> Richard Posner, *In Defense of Prometheus: Some Ethical, Economic, and Regulatory Issues of Sports Doping*, 57 DUKE L.J. 1725 (2008).

<sup>65</sup> See Antonio Rigozzi et al., *Doping and Fundamental Rights of Athletes*, 3(3) SWEET & MAXWELL INT’L SPORTS L. REV. 39, 43 (2003).

<sup>66</sup> See *Krabbe*, SpuRt 1996 at 134 (linking doping to damage to the public image of sports); *Gasser v. Stinson*, (June 15, 1988) Unreported, Queen’s Bench Division (Scott J.).

There have yet to be any public attitude studies published on gene doping. There are two studies surveying athletes: an unpublished study of 115 US student athletes from 2005 found that 60% thought gene doping was ethically equivalent to steroid use;<sup>67</sup> a survey of 81 Dutch athletes and 52 Kinesiology professors found a high level of support for the proposition that gene doping formed a serious threat to fair play.<sup>68</sup> Even more surprisingly, we have been unable to find any scholarly studies examining public attitudes toward doping (of any kind) in sports in the US, though there have been several opinion polls conducted, which show strong disapproval for doping, with some evidence that attitudes may be becoming more lenient.<sup>69</sup> There have been scholarly studies performed outside the US, showing the same trends<sup>70</sup>

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<sup>67</sup> *Results from Oregon College Athlete Gene Doping Survey*, GENEFORUM (2005), <http://www.geneforum.org/node/489>.

<sup>68</sup> Kris Dierickx et al., *The Ethics of Gene Doping: A Survey of Elite Athletes and Academic Professionals*, 3 J. CLINICAL RES. & BIOETHICS 136 (2012), available at <https://www.omicsonline.org/the-ethics-of-gene-doping-a-survey-of-elite-athletes-and-academic-professionals-2155-9627.1000136.php?aid=8190>.

<sup>69</sup> In an opinion poll conducted in 2016, 61% of US respondents stated that doping by some athletes decreased the attention they paid to the Olympics by “a lot” (41%) or “some” (20%). BBC World Serv., *Doping a Problem but Olympic Success Remains a Driver of National Pride: Global Poll*, GLOBESCAN (Jul. 26, 2016, 11:01 PM), [http://globescan.com/images/images/pressreleases/bbc2016-olympics/BBC\\_Olympics\\_Pride\\_Poll\\_Press\\_Release\\_July\\_25.pdf](http://globescan.com/images/images/pressreleases/bbc2016-olympics/BBC_Olympics_Pride_Poll_Press_Release_July_25.pdf). Examples from baseball: *AP/AOL Poll: More Than Half Of Baseball Fans Say The Sport Hasn't Done Enough To Curb Use Of Steroids*, IPSOS (Apr. 24, 2006), <http://www.ipsos-na.com/news-polls/pressrelease.aspx?id=3059> (showing 84% of respondents cared); *Baseball And Steroids*, CBS NEWS / N.Y. TIMES (Mar. 30, 2008), <http://www.cbsnews.com/htdocs/pdf/March31-a-baseball.pdf> (showing 82% of respondents who were at least somewhat interested in baseball cared); GfK Roper Public Affairs & Media, *The AP-GfK Poll*, GREENBOOK (Feb. 17, 2009), [https://www.greenbook.org/Content/GfK/AP-GfK\\_Poll\\_Baseball\\_Topline.pdf](https://www.greenbook.org/Content/GfK/AP-GfK_Poll_Baseball_Topline.pdf) (showing 79% of respondents cared); *Washington Post Poll*, WASH. POST (Jan 6. 2016), [http://www.washingtonpost.com/wp-srv/politics/polls/postpoll\\_20130106.html](http://www.washingtonpost.com/wp-srv/politics/polls/postpoll_20130106.html) (showing 53% of respondents cared).

<sup>70</sup> For a survey of Norwegian sports fans showing no tolerance for doping, see Harry A. Solberg et al., *Doping in elite sport - do the fans care? Public opinion on the consequences of doping scandals*, 11(3) INT'L J. SPORTS MARKETING & SPONSORSHIP 2 (2010). See also Stephen Moston et al., *Perceived incidence of drug use in Australian sport: a survey of public opinion*, 15 SPORT IN SOC'Y 64 (2011), available at <http://www.tandfonline.com/doi/abs/10.1080/03031853.2011.625277> (finding low support for doping amongst the Australian public); Hanspeter Stamm et al., *Attitudes towards doping - A comparison of elite athletes, performance oriented leisure athletes and the general population*, 11 EUR J. SPORT & SOC'Y 171 (2014), available at <http://www.tandfonline.com/doi/abs/10.1080/16138171.2014.11687939> (showing lack of support for doping among Swiss respondents); Hanspeter Stamm et al., *The public perception of doping in sport in Switzerland, 1995 - 2004*, 26 J. SPORTS SCI. 235 (2008), available at <http://www.tandfonline.com/doi/abs/10.1080/02640410701552914> (recording similar findings for an earlier period). A Belgian study of students' opinions of doping found that this demographic's opinion may be shifting

#### D. Minimizing the role of luck

The main angle from which WADA consider the regulation of an enhancement method is fairness, understood as maximizing equality of opportunity. It is no coincidence that we get the very term “level playing field” from the arena of sports. This idea has been explored by several schools of thought outside the realm of sports, and there is empirical evidence suggesting that humans do indeed conceive of fairness in this way.

The level playing field ideal is advocated for by Ronald Dworkin and other thinkers within the *luck egalitarianism* tradition.<sup>71</sup> From this perspective, a just system is one where there is equality of opportunity. Dworkin introduced the distinction between *endowments* and *ambitions*.<sup>72</sup> He argues that distributive inequalities are only just when they flow from one’s choices (ambitions) rather than factors over which one has no control (endowments). The idea that the role of luck should be minimized is not unique to luck egalitarianism. Rawlsian *relational egalitarianism*<sup>73</sup> contends that a society in which the “natural lottery” plays a large role is immoral, and that when we can structure society to minimize the role of the natural lottery, we should.

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from zero-tolerance to a more lenient approach. Hans Vangrunderbeek & Jan Tolleneer, *Student attitudes towards doping in sport: Shifting from repression to tolerance?*, 46 INT’L REV. SOCIOLOG. SPORT 346 (2010), available at <http://journals.sagepub.com/doi/pdf/10.1177/1012690210380579>.

<sup>71</sup> Luck egalitarianism has been expounded and extended upon in the philosophical literature e.g., RONALD DWORKIN, *SOVEREIGN VIRTUE: THE THEORY AND PRACTICE OF EQUALITY* (2000); Richard J. Arneson, *Equality and Equal Opportunity for Welfare*, 56 PHILOSOPHICAL STUDIES 77 (1989); G.A. Cohen, *On the Currency of Egalitarian Justice*, 99 ETHICS 906 (1989).

<sup>72</sup> Ronald Dworkin, *What is Equality? Part 2: Equality of Resources*, 10 PHIL. & PUB. AFF. 283 (1981), reprinted in DWORKIN, *supra* note 71, at 65.

<sup>73</sup> Rawls introduced the metaphor of the natural lottery in this context in his *A Theory of Justice*. For a summary of his appeal to luck, see Carl Knight & Zofia Stemplowska, *Responsibility and Distributive Justice: An Introduction*, in *RESPONSIBILITY AND DISTRIBUTIVE JUSTICE* 1, 2-9 (Carl Knight & Zofia Stemplowska eds., 2011).

Similar ideas drive lines of research in economics, where ongoing empirical work tracks individuals' decisions on redistributing winnings gained under various scenarios.<sup>74</sup>

Contemporary results include those coming from Konow,<sup>75</sup> who varied the amount of effort that went into determining outcome. He found that when outcomes were independent of effort even distributions of winnings were preferred, but when outcomes depended on effort, distribution according to effort was preferred. Other empirical work supports beliefs that individuals across cultures are more likely to hold others responsible if they had control over a situation.<sup>76</sup> A recent study found that redistribution of gains was much higher if outcomes were the result of endowments (“brute luck”) rather than when choice/ambition played a role.<sup>77</sup> From these empirical observations the *accountability principle* has been put forward:<sup>78</sup> an individual's fair allocation should be proportional to relevant variables they can influence, and not those variables they cannot influence. These results suggest that individuals' fairness preferences often seek to minimize the role of luck in reward.<sup>79</sup>

To summarize the background necessary to contextualize our empirical work: our ability to modify genetics is imminent and there have been urgent calls for public engagement in shaping a regulatory response; sports will be one of the first application areas for enhancement, reflected in the fact that it is the only area to date with existing regulation; the

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<sup>74</sup> James Konow & Lara Schwettmann, *The Economics of Justice*, in HANDBOOK OF SOCIAL JUSTICE THEORY AND RESEARCH 83, 92-97 (Clara Sabbagh & Manfred Schmitt, eds., 2016).

<sup>75</sup> James Konow, *Fair Shares: Accountability and Cognitive Dissonance in Allocation Decisions*, 90 AM. ECON. REV. 1072 (2000).

<sup>76</sup> See, e.g., Erik Schokkaert & Kurt Devooght, *Responsibility-sensitive fair compensation in different cultures*, 21 SOC. CHOICE & WELFARE 207 (2003).

<sup>77</sup> Gustav Tinghog et al., *Are Individuals Luck Egalitarians? – An Experiment on the Influence of Brute and Option Luck on Social Preferences*, 8 FRONTIERS IN PSYCHOL. 1 (2017), available at <https://www.frontiersin.org/articles/10.3389/fpsyg.2017.00460/pdf>. The study was designed to probe fairness preferences of 226 Swedish based individuals involving real incentives.

<sup>78</sup> Konow & Schwettmann, *supra* note 74.

<sup>79</sup> But see, Merve Akbaş et al., *When Is Inequality Fair? An Experiment on the Effect of Procedural Justice and Agency*, SSRN (Mar. 9, 2016), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=2474368](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2474368).

technology's use for enhancement has been banned, though the grounds for the ban are questionable; there have been no studies of public opinion on whether genetic modification for performance enhancement should indeed be banned; prior work, both theoretical and empirical, highlights that minimizing the role of luck promotes a fair and just society. As we will go on to discuss below, not only does this help contextualize our results, it also suggests a useful lens for exploring the regulation of this new technology in other areas.

## II. EXPERIMENTAL STUDIES

In order to assess public attitudes towards “gene doping” we designed a study based on a scenario inspired by the case of Eero Mäntyranta (see Background, section B). To better understand the results of this first study, we designed a second study that allowed us to investigate the role of several factors in shaping public opinion.<sup>80</sup>

### A. Methodology of Study 1

Our methodology was based around seeking reactions to the following Base Case scenario:

*Scientists have discovered Gene Z relates to success in long distance competitive running. Gene Z enables more oxygen to be carried in the blood. Gene Z is not enough on its own; hard work, training, and diet are important contributing factors to winning.*

*It is well known that scientists can now give Gene Z to people who are not born with it, at low cost. Some people will experience side effects, including higher likelihood of injury.*

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<sup>80</sup> Our data is publicly available at <https://osf.io/c96v7/>.

*Many race winners in the past 50 years have had Gene Z. A person without Gene Z would be less likely to win, even with hard work, training, and the right diet.*

Our choice of enhancement was designed to closely model a real example of genetic variation naturally occurring in other humans. As discussed in the Introduction, this choice is significant as it allows us to decouple this type of application from more extreme examples of, for example, modification to include a gene coming from an animal. It was also chosen to not affect outward appearance, so that we could disentangle the question of attitudes to genetic modification for performance enhancement from attitudes towards genetic changes that alter appearance. We designed the Scenario to be realistic in its emphasis that genetic endowment is not the sole determinant of athletic performance, that results are probabilistic, and that there would be a chance of some side effects. The latter was based on some pilot study data which suggested people's views were unaltered compared to it being a riskless process. Although in this scenario we mention that the enhancement would be available at low cost, in a subsequent scenario we also test a high cost setting. We should stress with reference to our scenario that the genetics underlying sports performance are complicated.<sup>81</sup> Although this genetic advantage was based on an example caused by a single genetic difference, in general traits are influenced by differences in many genes.

Our experiments asked participants to react to statements concerning the scenarios on a 7 point Likert scale (Strongly Disagree, Disagree, Somewhat Disagree, Neither Agree nor

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<sup>81</sup> Guilherme et al., *supra* note 37. Our use of the term "Gene Z" is itself a simplification to align with colloquial use of the term, and should more accurately read "Genetic variation within gene Z."

Disagree, Somewhat Agree, Agree, Strongly Agree). We asked for reactions to two statements.

*SOURCE OF ADVANTAGE: People who have chosen to acquire Gene Z should be permitted to race with people who were born with Gene Z.*

This statement probed whether subjects cared about the source of a given genetic advantage – the natural lottery of birth or an elective procedure. Because this scenario makes the unlevel playing field of natural talent salient, we hypothesized that subjects might not object to this type of procedure.

The second statement aimed to directly capture reactions to gene doping, by asking whether individuals who choose to acquire this performance advantage should still be able to race alongside those who have not chosen not to get it and therefore lack this performance advantage:

*CHOOSING ADVANTAGE: People who have chosen to acquire Gene Z should be permitted to race with people who have chosen not to acquire Gene Z*

Subjects were asked to explain their responses by stating their support for a series of reasons. We chose these reasons based on pilot data, and also provided an open text option.

Additionally, we asked a randomly selected half of the subjects for their reactions to the statement *Athletes should be allowed to dope* and the other half for their reactions to *Athletes should be allowed to take performance enhancing drugs*. We also asked whether they watched more than one hour of sports per week, and whether they considered themselves religious.

Our base case scenario was answered by 400 US-based individuals, with representation designed to reflect census data across age (18-55), gender, and education level.<sup>82</sup> The study was run on the Prolific survey platform.<sup>83</sup> Use of this platform gave us access to several dozen demographic data points. Participants were paid through this platform at a rate of \$0.50.

To assess the precision of our estimates we used the bootstrap procedure, which is a resampling approach.<sup>84</sup> This is as recommended by the American Association of Public Opinion Research.<sup>85</sup> Hypothesis testing was also performed using bootstrapping.<sup>86</sup>

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<sup>82</sup>We performed strata based sampling using ten strata. The size of each stratum was determined based on US 2010 Census data. We used the following strata, separately for men and women: 18-23 year olds, 24-34 year olds with college level education, 24-34 year olds without college level education, 35-55 year olds with college level education, 35-55 year olds without college level education.

<sup>83</sup> Prolific is an Oxford University Innovation company. PROLIFIC, <https://www.prolific.ac> (last visited Jan. 22, 2017). Participants are prescreened according to researcher specified criteria.

<sup>84</sup> James G. MacKinnon, *Bootstrap Hypothesis Testing*, in HANDBOOK OF COMPUTATIONAL ECONOMETRICS 183-213 (David A. Belsley & Erricos John Kontoghiorghes eds., 2009). We generated 100,000 independent "resamples" by randomly selecting 400 respondents with replacement from the original survey data set. Resamples were formed using the same 10 strata as our survey, such that we matched the same number of respondents from each stratum in each subsample. For our 100,000 resamples, we computed the statistic of interest (in this case the proportion of respondents who agreed or were indifferent to the question), and used the variability in these estimates as the basis of the confidence intervals reported. The confidence interval assumes that our estimates are approximately unbiased.

<sup>85</sup> *AAPOR Guidance on Reporting Precision for Nonprobability Samples*, AM. ASS'N PUB. OPINION RES. (Apr. 22, 2016), [http://www.aapor.org/getattachment/Education-Resources/For-Researchers/AAPOR\\_Guidance\\_Nonprob\\_Precision\\_042216.pdf](http://www.aapor.org/getattachment/Education-Resources/For-Researchers/AAPOR_Guidance_Nonprob_Precision_042216.pdf).

<sup>86</sup> For two cases we wished to compare (e.g. women's responses versus men's, or answers to one question versus answers to a variant question), the null hypothesis is that the responses come from the same distribution. Let the size of the first sample be  $N$  and the second  $M$ . We created 100,000 samples of the combination of the two cases, and calculated the difference between the proportion of agreed and indifferent of the first  $N$  of each subsample and the proportion of agreed and indifferent in the final  $M$  of each subsample. We then compared the observed difference in proportion of agreed and indifferent to the list of 100,000 bootstrapped differences, and report as the p-value the fraction of times the bootstrapped difference had a greater magnitude than the observed difference.

## **B. Results of Study 1**

### ***Reactions to the Base Case Scenario***

In response to the Source of Advantage statement, 79% of subjects agreed or were indifferent, upholding our hypothesis that the source of genetic advantage – birth or procedure – does not matter. Of those who agreed, the reason with most support was *You either have a gene or you don't, doesn't matter how you got it* (79%). There was also broad support for the two other statements presented, *Sports would be a fairer test if the biological playing field were more level* (67%), and *It would be hard to test whether someone was born with a gene or had it added later, so it would be pointless to try and prevent this happening* (68%). Of the minority who disagreed, 54% (9% overall) endorsed the view that *Humans shouldn't interfere with genetics under any circumstances*.

For the Choosing Advantage statement, 54% agreed or were indifferent. The 46% minority who disagreed were asked to react to the following two statements: *People who have acquired Gene Z should not be permitted to race at all* (39% agreed, which is 18% overall) and *There should be a separate category for those who do not have Gene Z* (74% agreed, 34% overall).

The 18% who thought there was no room for genetic modification in sports is not much higher than the 9% who would not accept genetic modification under any circumstances.

### ***Demographic differences***

In our sample size of 400, we found more support for both statements among younger people. This is not surprising given that younger people tend to view biotechnology more favorably.<sup>87</sup> We found no statistically significant difference between men and women, between Republicans and Democrats, or between those who self-reported as religious and those who did not. We did find that those who reported watching an hour or more sports per week were less supportive than those who did not for the Source of Advantage Statement (74% compared to 84%,  $p=0.006$ ), though not for the Choosing Advantage statement.

### ***Comparison to attitudes towards doping***

In reaction to the statement *Athletes should be allowed to dope*, 17% of our participants agreed or were indifferent. For the statement *Athletes should be allowed to take performance enhancing drugs*, 23% agreed or were indifferent. These numbers are very different from the 54% for our Choosing Advantage statement. In order to understand why acquired genetic advantage is viewed more positively than advantages acquired from substances, and in order to test the robustness of our results under different conditions, we designed a second study.

## **C. Methodology for Study 2**

We had two hypotheses as to what might account for this difference. First, that the genetic modification scenario would be more supported because the prospect of genetic modification questions whether it is fair to protect the genetics you happen to be born with. And second, that branding something as “doping” or even as a “drug” would prime people with negative

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<sup>87</sup> George Gaskell et al., *Europeans and Biotechnology in 2002*, EUR. COMM’N (Mar. 21, 2003), available at [http://ec.europa.eu/public\\_opinion/archives/ebs/ebs\\_177\\_en.pdf](http://ec.europa.eu/public_opinion/archives/ebs/ebs_177_en.pdf).

associations. We made small modifications to our base case scenario in order to test these hypotheses.

To test the first hypothesis, we designed three Scenarios. The first was a “No Genetic Enhancements” scenario (i.e., one that represents the world today), identical to the base case except without mentioning the possibility of changing whether or not someone had Gene Z. This was designed to enable us to test the impact of genetic mutability through comparison to the base case. We asked for reactions to the following two statements:

*PERMIT NATURAL ADVANTAGE: People who were born with Gene Z should be permitted to race with people who were not born with Gene Z*

*GENETIC SEGREGATION: People who were born without Gene Z should have a race category in which people who were born with Gene Z cannot compete.*

The other two Scenarios were similarly designed to allow us to probe the effect of making clear that some athletes have an innate biological advantage. Our “Biomolecule, natural differences” scenario referred to *Biomolecule V*, and mentioned that *Different individuals’ bodies naturally produce differing amounts of biomolecule V*. Our “Biomolecule, no natural differences” scenario referred to Biomolecule V but made no mention of naturally occurring differences.<sup>88</sup> Use of the term “biomolecule” also allowed us to probe the second hypothesis, around the role of language. We additionally designed a scenario with the word *Biomolecule* replaced with the word *Drug*, our “Drug, no natural differences” scenario.

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<sup>88</sup> A biomolecule is a molecule that is present in living organisms.

Alongside testing these two hypotheses for explaining the higher level of support for performance-enhancing genetic modification versus doping, we were interested in the robustness of our result to two factors: concerns about equality of access, and the type of genetic modification. Because concerns over equality of access could be a potential reason to oppose this form of performance enhancement in sports, we were interested in how changing the cost described in our scenario would affect respondent judgments. We designed a “High Cost” scenario, identical to our base case with the exception that the procedure was available at a cost of \$100,000 rather than at *low cost*, as is mentioned in our base case. All the scenarios mentioned so far were based on the same underlying enhancement to increase the oxygen carrying capacity of an athlete's blood. To assess whether our results were robust to the type of enhancement, we designed a scenario affecting psychological properties, “Psychological Enhancement”: *Gene Z helps athletes feel a sense of reward after training and therefore helps them stick to a more intense training regime.*

We were also interested in public judgments when the individual undergoing the modification was a minor, because of the existence of a developmental window for modifications to take effect.<sup>89</sup> One might have anticipated low support for the genetic modification of minors, owing to issues of informed consent, but this is not what we observed. As our results were in line with the more general case, we do not discuss these experiments in the main text.<sup>90</sup>

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<sup>89</sup> For example, genetic variation linked to being taller would not produce extra height if introduced after someone had finished growing.

<sup>90</sup> We designed a scenario with three variants. The main scenario involving minors read:

Jamie is 11 years old and wants to be a long-distance runner. Jamie was not born with Gene Z. Those who have Gene Z before they go through puberty will develop more efficient muscles and go on to have an advantage in long distance running over those who did not have Gene Z during puberty. (If Gene Z is introduced after puberty it gives no advantage). Both Jamie and Jamie's parents would like for Jamie to be given Gene Z before puberty.

To avoid participants' answers for any one study being unduly influenced by previous questions, we divided these six scenarios across three groups of 200 people (n = 600 in total). The quota was the same as for the base case, except the older age bracket extended to age 40 instead of 55.<sup>91</sup> Participants were paid at a rate of \$0.80.

## D. Results of Study 2

### *Challenging the idea that the genetics you are born with should confer protected privilege*

For our “No Genetic Enhancements” Scenario, 14% of individuals disagreed with the Permit Natural Advantage statement. These subjects thought that some natural advantages should preclude athletes from competition. There is precedent for some natural advantages being seen as “too much.” Caster Semenya has dominated the women’s sprinting scene on the occasions when she has been allowed to compete without taking hormone suppressants. A sprinter who has raced alongside Caster, Paula Wright, has said: “I don't like the idea of anyone being excluded... but we have to keep our sport fair, which means deciding where the

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It is well known that scientists can now give Gene Z to people who are not born with it (including minors), at low cost. Some people will experience side effects, including higher likelihood of injury.

The three versions were

- I. Development window: as above
- II. No development window: as above, but without any mention that the change needs to happen before puberty
- III. Scholarship: as (II), but with the following addition, *Many students who have won athletic scholarships to college in the past 50 years have had Gene K. A student long distance runner without Gene K would be less likely to win an athletic scholarship to college, even with hard work, training, and the right diet.*

We asked for the degree of support for the following statement: *Jamie should be permitted to acquire Gene Z.* Each of the three groups of participants in our second study received one of these scenarios.

We found that 75% of our respondents agreed or were indifferent to the statement *Jamie should be permitted to acquire Gene Z.* 53% of those who disagreed (13% overall) see issues with genetic modification of minors. We found no statistically significant difference in level of support to the other two variants of the scenario.

<sup>91</sup> When we compared our base case scenario to the other scenarios we subsampled the base case respondents to match the same age range.

genetic and performance advantage is too much.”<sup>92</sup> Lynsey Sharp, who finished sixth to Caster’s first in the Rio 800m said “Everyone can see it’s two separate races,” while Polish Joanna Jozwik, who finished fifth, said “I’m glad I’m the first European, the second white”.<sup>93</sup>

In response to the Genetic Segregation statement, 43% agreed or were indifferent to introducing separate categories for those born with the named genetic advantage. In response to a modified Choosing Advantage statement, 63% agreed or were indifferent in the “Biomolecule, natural differences” scenario, and 56% in the “Biomolecule, no natural differences” scenario. Our finding of lesser support for the second scenario ( $p = 0.05$ ), supports the hypothesis that making salient the natural lottery may play a role in support for performance enhancement via genetic modification.

### ***Effect of language in attitudes to performance enhancement in sports***

In the two scenarios which differed only in use of the term Biomolecule versus Drug, 56% versus 29% agreed or were indifferent to the Choosing Advantage statement. This difference is statistically significant ( $p < 10^{-5}$ ). From our first study, we had observed that 17% of respondents agreed or were indifferent to the statement *Athletes should be allowed to dope*. This is significantly less support than for *Drug V* ( $p < 10^{-5}$ ), again highlighting the importance of framing language.

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<sup>92</sup> Tim Layden, *Is it fair for Caster Semenya to compete against women at the Rio Olympics?*, SPORTS ILLUSTRATED (Aug. 11, 2016), <http://www.si.com/olympics/2016/08/11/caster-semenya-2016-rio-olympics-track-and-field>.

<sup>93</sup> Tom Morgan, *Caster Semenya wins 800m: beaten GB finalist Lynsey Sharp criticises rule changes over 'obvious' hyperandrogenous women*, TELEGRAPH (Aug. 21, 2016), <http://www.telegraph.co.uk/news/2016/08/21/lynsey-sharp-criticises-obvious-hyperandrogenous-women-having-been/>; Mark Critchley, *Rio 2016: Fifth-placed Joanna Jozwik 'feels like silver medallist' after 800m defeat to Caster Semenya*, INDEPENDENT (Aug. 22, 2016), <http://www.independent.co.uk/sport/olympics/rio-2016-joanna-jozwik-caster-semenya-800m-hyperandrogenism-a7203731.html>.

### ***Robustness of our results to concerns of equality of access and to modification type***

We found no statistically significant difference in the level of support for the High Cost scenario compared to our base case (low cost) scenario. This result seems surprising. There are at least three different factors that we think may contribute. The first is that people may view equality of access to sporting success as already intractably subject to cost barriers: increased chances of success are bought by the quality of the coaching, precision diets, the quality of facilities, the access to a broader team of support staff, all of which are a function of money. Second, this form of equality of access is in tension with the unequal opportunity produced by the genetics you are born with. And third, US-based individuals are accustomed to living in a society where people can spend their money as they choose; for example, in a pay-to-access healthcare system high cost is normalized for both necessary and elective procedures.

We found our results remained consistent when testing a different sort of genetic modification: 86% agreed or were indifferent to the Source of Advantage statement, and 66% to the Choosing Advantage statement for the psychological enhancement scenario. Indeed, we found more support for this modification for both statements ( $p = 0.04$ ,  $p = 0.01$ ). Why this difference? The psychological change is less directly related to what the competition (long distance running) is testing, and this may be why it has more support. This result – more support for psychological rather than physical modification – is consistent with the findings of the recently published survey of public attitudes to genetic modification more generally.<sup>94</sup> The public will likely have different attitudes towards different genetic

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<sup>94</sup> Dietram A. Schufele et al., *Supplemental Materials for U.S. attitudes on human genome editing*, NATURE (Aug. 11, 2017), at 6, available at [http://science.sciencemag.org/content/sci/suppl/2017/08/09/357.6351.553.DC1/aan3708\\_Schufele\\_SM.pdf](http://science.sciencemag.org/content/sci/suppl/2017/08/09/357.6351.553.DC1/aan3708_Schufele_SM.pdf)

modifications because the social consequences and meanings of different traits are varied. We think the differences in attitudes to different types of genetic modification represents a rich vein of possible future research.

### **III. DISCUSSION**

#### **A. Support for gene doping**

We designed a series of experiments to probe public judgments and isolate the impact of several variables of interest. Experimental participants were 1000 US-based individuals, with proportional representation based on US census data across age (18-55), gender, and education level. We found that 54% (physical scenario) and 66% (psychological scenario) agreed or were indifferent to genetic modification for enhancement of athletic performance. These numbers are within the ballpark of recently established figures for overall support for somatic modification for enhancement (65%<sup>95</sup>). This was in stark contrast to the 17% of people who agreed or were indifferent to athletes being allowed to dope. Why the high level of support? We considered and tested two hypotheses.

#### **B. Choice of language impacts public perception**

One hypothesis was that the choice of language can have a large impact on public perception. Our data strongly supported this: figures for those who agreed or were indifferent were 17% for “doping,” 29% for a “drug,” and 56% for a “biomolecule.” This highlights the significance of WADA’s preemptive move to ban any form of genetic engineering, including

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(finding more support for enhancement of "a person’s mental abilities, such as memory" than for enhancement of "a person’s physical features, such as improving eyesight to beyond perfect vision”).

<sup>95</sup> The survey of 1600 US based individuals published in August 2017 found that 65% were in favor of (39%) or indifferent to (26%) somatic modification for enhancement. Schufele et al., *supra* note 30.

the introduction of the term “gene doping.” An explicit part of WADA's mission is to educate the public that its definitions as to what constitutes doping are important to maintaining the spirit of sport.<sup>96</sup> WADA’s moves to shape the debate contrast with consistent calls to seek public input at such moments when potentially game-changing technology emerges. The National Academies of Science and Medicine have made a clear and urgent call for the public to be engaged in plotting the path forward, on the basis that “[m]eaningful engagement with decision makers and stakeholders promotes transparency, confers legitimacy and improves policy making.”<sup>97</sup> If the public are not primed to think of genetic modification as doping, our data shows support for its use.

### **C. Genetics at birth not deserving of competitive protection**

The other hypothesis to explain why what WADA call “gene doping” had a much higher level of support than “doping” was the following: the prospect of genetic modification causes us to question whether the genetics we are born with are worthy of competitive protection. We have at least three lines of evidence suggestive of this. First, it does not matter whether a genetic advantage comes from birth or a procedure: 79% agreed or were indifferent to our Source of Advantage statement (*People who have chosen to acquire Gene Z should be permitted to race with people who were born with Gene Z*), suggesting that genetic advantages at birth are not seen as entitlements worthy of protection in competition. The corresponding number for the psychological enhancement scenario was 86%. Indeed, of those people who agreed, 67% agreed or were indifferent to the statement *Sports would be a fairer test if the biological playing field were more level*, suggesting that genetic modification

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<sup>96</sup> *WADA Ethics Panel: Guiding Values in Sport and Anti-Doping*, WORLD ANTI-DOPING AGENCY (Oct. 2017), [https://www.wada-ama.org/sites/default/files/resources/files/wada\\_ethicspanel\\_setofnorms\\_oct2017\\_en.pdf](https://www.wada-ama.org/sites/default/files/resources/files/wada_ethicspanel_setofnorms_oct2017_en.pdf).

<sup>97</sup> NAT'L ACAD. SCI. & NAT'L ACAD. MED., *supra* note 7, at 4.

is seen as a tool to promote equality of opportunity. Second, drawing attention to the existence of biological differences that affect performance leads to more support for enhancement. For our Biomolecule scenarios which differed only in whether or not the existence of natural differences between individuals were mentioned, there was majority support for enhancement in both cases, with even more support if the differences were mentioned (63% agreed or indifferent versus 56%,  $p = 0.05$ ). Third, respondent approval for enhancement increases with the possibility of choosing to improve our genetics. From our first study, of those who disagreed with our Choosing Advantage statement (*People who have chosen to acquire Gene Z should be permitted to race with people who have chosen not to acquire Gene Z*), 74% supported separate categories. When no possibility of genetic enhancement was mentioned (“No Genetic Enhancement” scenario), 43% supported separate categories of competition. We should anticipate that as people become more aware of the possibility of changing our genetics, they will be less likely to view the genetics we are born with as worthy of privilege and protection. Our findings echo prior work in other areas that has found that individuals’ preferences align with minimizing the role of unearned advantage (see Background, Section D).

As discussed in the Background, WADA’s judgments of what counts as cheating rely on the idea of promoting natural talent. When faced with the possibility of genetic modification, our respondents do not necessarily see the promotion of natural talent as fair. They do not see genetic endowments as advantages worthy of competitive protection. Insofar as our respondents do equate promoting natural talents with fairness, they may be conceiving of natural talents as character-based traits or intangibles. Fairness can mean equality of opportunity. Our scenario presents a powerful way in which equality of opportunity can be

enhanced – by offsetting the inequities of the natural lottery. Genetic modification in such contexts may prove to be a means of furthering equality of opportunity with the potential for bipartisan support, as a feature of this method is that it is one way of leveling opportunity that does not require resource redistribution.

#### **D. The Self-Authoring Vision of the Spirit of Sport**

Our results are consistent with an alternative vision of the spirit of sport. WADA's concept of the spirit of sport is an essentialist view, equating talent worthy of protection with at-birth biological potential.<sup>98</sup> Our unfolding understanding of how luck in the genetic lottery shapes our abilities (see Background, Section B) calls this premise into question. So does the prospect of our formerly fixed genetics becoming mutable through genetic modification. If the alignment between the spirit of sport and natural talent is severed, what replaces it? An alternative vision we have touched on prizes choice, or judgment – rather than luck (see Background, Section D). In this “Self-Authoring” vision, excellence produced through judgment and choice is rewarded, and the rewards for non-choice factors, such as inherited genetic advantage, are minimized.<sup>99</sup>

This Self-Authoring vision of the spirit of sport can accommodate different categories for competition based on comparative physical attributes. Precedent for separate categories

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<sup>98</sup> For an argument that current anti-doping policy rests on dubious claims as to what is natural or normal, see Bengt Kayser et al., *Current anti-doping policy: a critical appraisal*, 8 BMC MED. ETHICS 2 (2007). See also Savulescu et al., *Why we should allow performance enhancing drugs in sport*, 38 BRIT. J. SPORTS MED. 666 (2004) (arguing that the view of sports as finding the person with the most biological potential was “the old naturalistic Athenian vision of sport: find the strongest, fastest, or most skilled man.”).

<sup>99</sup> Savulescu et al., *supra* note 98, at 666 (“Humans are not horses or dogs. We make choices and exercise our own judgment. We choose what kind of training to use and how to run our race. We can display courage, determination, and wisdom. We are not flogged by a jockey on our back but drive ourselves. It is this judgment that competitors exercise when they choose diet, training, and whether to take drugs. We can choose what kind of competitor to be, not just through training, but through biological manipulation. Human sport is different from animal sport because it is creative.”).

already exists at the Olympic level. Most notably there are separate categories for men and women, some with different sub-events and rules.<sup>100</sup> Other categories include weight, for martial arts and for rowing. With some degree of success, biological categories have been created to reflect the diversity of athletes' physical endowments for the Paralympics. Akin to the genetic case, crisp categorical distinctions often prove elusive in these instances; nevertheless, lines have been drawn which are workable. Factors including muscle tone, short stature, balance, and limb length are all used.<sup>101</sup> The case of female hyperandrogenism is an example of the IOC's willingness to use underlying biology to define categories, through use of testosterone levels to determine who should be permitted to compete in the female category.<sup>102</sup> It may be that in years to come, genetic advantage is added to the list of categorical differentiators.

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<sup>100</sup> For example, the events that female and male gymnasts compete in are different. *Gymnastics Artistic*, INT'L OLYMPIC COMM., <https://www.olympic.org/gymnastics-artistic> (last visited Jan. 22, 2017). There are also differences in required elements for figure skating. *Judging System: Technical Panel Handbook: Single Skating*, INT'L SKATING UNION (July 24, 2016), available at <http://www.usfigureskating.org/content/2016-17%20TPHB%20Singles.pdf>.

<sup>101</sup> *Layman's Guide to Paralympic Classification*, INT'L PARALYMPIC COMM., [https://www.paralympic.org/sites/default/files/document/120716152047682\\_ClassificationGuide\\_2.pdf](https://www.paralympic.org/sites/default/files/document/120716152047682_ClassificationGuide_2.pdf) (last visited Jan. 18, 2017); *Raza Point score table for IPC Athletics*, INT'L PARALYMPIC COMM. (Jan. 20, 2011), [https://www.paralympic.org/sites/default/files/document/120719101234998\\_2011\\_01\\_20\\_Raza\\_Point\\_score\\_table\\_for\\_IPC\\_Athletics\\_2011\\_-\\_Explanation.pdf](https://www.paralympic.org/sites/default/files/document/120719101234998_2011_01_20_Raza_Point_score_table_for_IPC_Athletics_2011_-_Explanation.pdf).

<sup>102</sup> Before the London 2012 Olympics the IOC declared that it would be testing testosterone levels to determine who was permitted to compete in the female category. *IOC Regulations on Female Hyperandrogenism*, INT'L PARALYMPIC COMM. (June 22, 2012), [https://stillmed.olympic.org/Documents/Commissions\\_PDFfiles/Medical\\_commission/2012-06-22-IOC-Regulations-on-Female-Hyperandrogenism-eng.pdf](https://stillmed.olympic.org/Documents/Commissions_PDFfiles/Medical_commission/2012-06-22-IOC-Regulations-on-Female-Hyperandrogenism-eng.pdf). This approach was abandoned for the Rio Olympics in 2016 following a 2014 ruling by the Court of Arbitration for Sport, partly because of the underlying biological complexity. Talha Khan Burki, *Hyperandrogenism rule no longer in play at Rio Olympics*, 4 LANCET DIABETES & ENDOCRINOLOGY 820 (2016). Part of the overturn rested on the overlap between the distributions of testosterone levels in men and women. The case involved additional biological complexity, as high levels of testosterone were acknowledged to only confer an advantage in the presence of working androgen receptors, which many of the athletes in question did not have. *Chand v. Athletics Fed. of India*, CAS 2014/A/3759, ¶ 547 (Ct. Arb. Sport 2015), [http://www.tas-cas.org/fileadmin/user\\_upload/AWARD\\_3759\\_FINAL\\_\\_\\_REDACTED\\_FOR\\_PUBLICATION\\_.pdf](http://www.tas-cas.org/fileadmin/user_upload/AWARD_3759_FINAL___REDACTED_FOR_PUBLICATION_.pdf). The International Association of Athletics Federations has indicated it will challenge this ruling. *Sebastian Coe indicates IAAF will challenge female testosterone ruling*, GUARDIAN (Aug. 11, 2016), <https://www.theguardian.com/sport/2016/aug/11/caster-semenya-sebastian-coe-iaaf-cas-testosterone-olympics>.

## E. Limitations and Future Directions

Applications of new technologies often have global consequences. The availability of medical tourism means that one country's permissive regulatory regime can limit the effectiveness of more restrictive frameworks implemented in other jurisdictions.<sup>103</sup> There is good reason to expect a diversity of international perspectives on the applications of genome modification. For example, the Chinese<sup>104</sup> and Russians<sup>105</sup> may be less concerned about the spectre of eugenics than their European and North American counterparts. Specifically in the case of athletic competition at the international level, a global enterprise involving nation states as well as the private sector, a diverse array of public opinion is relevant. Our study is limited in its focus on US-based individuals. Other differences may exist in terms of concerns over equity of access. While we found that our respondents were not influenced by high cost barriers to access, this may be because US-based individuals are used to pay-to-access healthcare. Those who live in societies where this is not the case may think differently.

We designed our study to capture preferences concerning modifications to genetic difference present in the human gene pool. The example we presented was based on a real case, and our scenario explicitly stated that some athletes have this genetic variation. It is unclear how responses would change if instead the modification was to include genes only found in non-human animals. There may additionally be preference differences depending upon how

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<sup>103</sup> See R. Alta Charo, *On the Road (to a Cure?) — Stem-Cell Tourism and Lessons for Gene Editing*, 374 NEJM 901 (2016), available at <http://www.nejm.org/doi/full/10.1056/NEJMp1600891>.

<sup>104</sup> See Geoffrey Miller, 2013: *What \*Should\* We Be Worried About?*, EDGE, <https://www.edge.org/response-detail/23838> (last visited Jan. 18, 2017) (arguing for the importance of Chinese eugenic ambitions).

<sup>105</sup> A study found that 40% of Russians and 7% of Britons approve of genetic modification ("changing genes") to enhance "special skills." Lev Gudkov et al., *Human Genetic Improvement: a comparison of Russian and British public perceptions.*, 134 BULL. MED. ETHICS 20 (1998). By way of comparison, 55% of Russians and 29% of Britons approve of vitamin supplements for the same purpose. *Id.*

commonly a gene is found in other humans. Professional sports is an interesting test case, because extremes of ability are already the norm. The extension of this work to other domains, for example to education or the military, may reveal socially meaningful boundaries other than species-level variation on which regulatory attention ought to be focused.

#### **IV. CONCLUSION**

Genetic modification, and particularly CRISPR, is a game-changing new technology that has the potential to positively impact society in many ways. This impact will be shaped by regulation. Many public bodies have called for urgent interaction with, and assessment of, public attitudes to this powerful new tool. WADA was the first to ban genetic modification as a condition for participation in a valued social domain. This is not surprising as athletes are known to be early adopters of technologies offering a competitive edge. As an early and highly visible mover, WADA's negative attitude and may have a disproportionate effect on public perception and regulation in other areas. Indeed, we found that the condemning language of "doping", in contrast with neutral descriptions of the same underlying substance, influenced public judgments of ethical permissibility. Sports, with its defined rules and clear outcomes, also happens to provide a highly accessible framework for assessing impact and for rolling out policy in other areas. Our study is the first to investigate public preferences for the regulation of genetic enhancement in sports. There are several reasons for WADA to take into account the preferences of the public. One is that doing so confers legitimacy upon their institutional pronouncements. Another is to protect the economic value of sports, an aim which is furthered by incorporating consumer preferences into their prohibition decisions.<sup>106</sup>

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<sup>106</sup> See Posner, *supra* note 64. Representative samples of individuals are a strong proxy for the market.

WADA aims to protect the spirit of sport, defined as “the dedicated perfection of each person’s natural talents.”<sup>107</sup> Even before the advent of genetic modification, relying on this idea was problematic: WADA permits many means of bolstering natural endowments (for example, surgeries); naturalness is being challenged as fair – for example in the case of females with naturally higher levels of testosterone. The prospect of genetic modification may be the death knell for the use of naturalness as an organizing principle. As our results show, the public does not necessarily see the genetics one happens to be born with as worthy of competitive protection. Our results suggest that, at least in the United States, the public’s opinion does not align with WADA’s on the boundaries of the spirit of sport. Insofar as the ban on genetic modification for performance enhancement is based on its incompatibility with the spirit of sport, we conclude that the ban is not justified. The lifting of the ban should be discussed by WADA as part of a broader conversation necessary in moving on from the use of naturalness as an organizing principle. They could instead adopt a vision of the spirit of sport where athletes are deserving of glory for the choices they make and the self-authorship of their victories. This could be combined with sensible precautions to protect athlete health.<sup>108</sup>

We are currently faced with decisions on how to balance the potential gains of CRISPR against threats, perceived or otherwise. Our data reflect increased acceptance of genetic modification, which raises questions about the necessity of a blanket prohibition in the case of sports. This illustrates the opportunity for more narrowly tailored and evidence-based regulatory approaches. Our findings are consistent with those perspectives in distributive

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<sup>107</sup> WORLD ANTI-DOPING AGENCY, *supra* note 55, at 14.

<sup>108</sup> As part of his argument for allowing doping in general in sports, Julian Savulescu encourages a focus on safety rather than prohibition. A similar focus for genetic modification in particular could perhaps be developed in a consistent way to protect athlete health. Savulescu et al., *supra* note 98, at 668.

justice which consider a fair system as one in which the role of unearned advantages, notably birth endowments, is minimized, and in which individuals are rewarded based on their efforts and ambitions as expressed through their choices.<sup>109</sup> Genetic privileges are just some of the many inherited privileges, social and biological, of which one can be a beneficiary. Inherited privileges have long gated access to positions and goods valued by society, and in many cases these gates have collapsed under the force of changing public opinion. Genetic privilege for access may also be so challenged – particularly in a world where we both understand how particular genetic differences lead to advantages, and where those differences can become unshackled from the roll of the dice at birth.

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<sup>109</sup> See Background, Section D. We suspect that some of our readers may view the prospect of genetic modification as a *reductio ad absurdum* on the luck egalitarianism theory, even if it is a theory that coheres with individual preferences.

## FIGURES AND TABLES

**Table 1: Genes related to performance enhancement in sports, and their strong overlap with targets for gene therapy**

*Genetic variation in several genes is relevant to gaining a performance edge in sports. There is a high overlap between these genes and those that are targets for gene therapy.*

Gene	Role of Gene	Example genetic variation	Work related to gene therapy
EPOR	Determines red blood cell count	Variant that enables blood to carry >50% more oxygen <sup>110</sup>	Animal studies motivated by treatment for anemia associated with chronic renal failure and thalassemia <sup>111</sup>
COL5A1	Part of collagen, the main component of connective tissue	Variant associated with likelihood of Achilles tendon injuries <sup>112</sup>	
SLC6A4	Control of serotonin levels	Variant that produces more serotonin more common in athletes than non-athletes <sup>113</sup>	

<sup>110</sup> Chapelle et al., *supra* note 32.

<sup>111</sup> S. Zhou et al., *Adeno-associated virus-mediated delivery of erythropoietin leads to sustained elevation of hematocrit in nonhuman primates*, 5 GENE THERAPY 665 (1998), available at <https://www.ncbi.nlm.nih.gov/pubmed/9797871>; B. Gavish et al., *Adiabatic compressibility of globular proteins*, 80 PROC. NAT'L ACAD. SCI. 750 (1983), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC393457/>.

<sup>112</sup> G. G. Mokone et al., *The COL5A1 gene and Achilles tendon pathology*, 16 SCANDINAVIAN J. MED. & SCI. SPORTS 19 (2006), available at <https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1600-0838.2005.00439.x>.

<sup>113</sup> E.V. Trushkin et al., *Association of SLC6A4 Gene 5-HTTLPR Polymorphism with Parameters of Simple and Complex Reaction Times and Critical Flicker Frequency Threshold in Athletes during Exhaustive Exercise*, 150 BULL. EXPERIMENTAL BIOLOGY & MED. 471 (2011).

VEGF	Involved in growing new blood vessels	Variant that gives higher oxygen uptake before and after aerobic training <sup>114</sup>	Human trials for treatment of chronic critical leg ischemia <sup>115</sup>
IGF	Involved in muscle repair and growth	Genetic variation associated with more of this gene product is more common in power athletes <sup>116</sup>	Animal studies to demonstrate utility for those recovering from injury and for the elderly <sup>117</sup>
PPAR	A regulator of metabolism	Genetic variant associated with endurance performance <sup>118</sup>	Animal studies for treatment of atherosclerosis <sup>119</sup>
BDNF	Involved in neural development	Variants that affect psychological response to stress and motivation to exercise <sup>120</sup>	Animal studies motivated by improving progression of Huntington's disease <sup>121</sup>
MSTN	Myostatin; inhibits muscle	Variants that reduce levels of myostatin lead to muscle growth <sup>122</sup>	Animal studies and human trials for those with muscle diseases and

<sup>114</sup> Steven J. Prior et al., *DNA sequence variation in the promoter region of the VEGF gene impacts VEGF gene expression and maximal oxygen consumption*, 290 AM. J. OF PHYSIOLOGY-HEART & CIRCULATORY PHYSIOLOGY H1848 (2006), available at <http://ajpheart.physiology.org/content/290/5/H1848.full.pdf+html>.

<sup>115</sup> Kou-Gi Shyu et al., *Intramuscular vascular endothelial growth factor gene therapy in patients with chronic critical leg ischemia*, 114 AM. J. MED. 85, available at [http://www.amjmed.com/article/S0002-9343\(02\)01392-X/pdf](http://www.amjmed.com/article/S0002-9343(02)01392-X/pdf).

<sup>116</sup> Sigal Ben-Zaken et al., *Can IGF-I polymorphism affect power and endurance athletic performance?*, 23 GROWTH HORMONE & IGF RES. 175 (2013), available at <https://www.ncbi.nlm.nih.gov/pubmed/23850449>.

<sup>117</sup> Sukho Lee et al., *Viral expression of insulin-like growth factor-I enhances muscle hypertrophy in resistance-trained rats*, 96 J. APPLIED PHYSIOLOGY 1097, available at <https://www.physiology.org/doi/pdf/10.1152/jappphysiol.00479.2003>.

<sup>118</sup> I.I. Ahmetov et al., *Association of a PPAR $\delta$  polymorphism with human physical performance*, 41 MOLECULAR BIOLOGY 776 (2007), available at <http://link.springer.com/article/10.1134/S002689330705010X>; Vihang A. Narkar et al., *AMPK and PPAR $\delta$  agonists are exercise mimetics*, 134 CELL 405 (2008), available at [http://www.cell.com/cell/pdf/S0092-8674\(08\)00838-6.pdf](http://www.cell.com/cell/pdf/S0092-8674(08)00838-6.pdf).

<sup>119</sup> G. Li et al., *Hematopoietic knockdown of PPAR $\delta$  reduces atherosclerosis in LDLR $^{-/-}$  mice*, 23 GENE THERAPY 78 (2016), available at <http://www.nature.com/gt/journal/v23/n1/abs/gt201578a.html>.

<sup>120</sup> Muaz Belviranli et al., *The relationship between brain-derived neurotrophic factor, irisin and cognitive skills of endurance athletes*, 44 PHYSICIAN & SPORTS MED. 290 (2016), available at <http://www.tandfonline.com/doi/full/10.1080/00913847.2016.1196125>; A. Pokrwa et al., *Genes in Sport and Doping*, 30 BIOLOGY SPORT 155 (2013), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3944571/pdf/JBS-30-1059606.pdf>.

<sup>121</sup> B. Connor et al., *AAV1/2-mediated BDNF gene therapy in a transgenic rat model of Huntington's disease*, 23 GENE THERAPY 283 (2016), available at <http://www.nature.com/gt/journal/v23/n3/full/gt2015113a.html>; H. Fukui et al., *BDNF gene therapy induces auditory nerve survival and fiber sprouting in deaf Pou4f3 mutant mice*, SCI. REP. 2 (Nov. 12, 2016), <http://www.nature.com/articles/srep00838>.

	differentiation and growth		as a protection against muscle loss with age <sup>123</sup>
ACTN3	Component of the contractile apparatus in fast skeletal muscle fibers	Elite sprinters are more like to carry a certain variant <sup>124</sup>	
HBB	Haemoglobin; enables blood to carry oxygen	Variants that affect cardiorespiratory adaptation <sup>125</sup>	Animal studies and human trials for treatment of Beta Thalassemia <sup>126</sup>

<sup>122</sup> Markus Schuelke et al., *Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child*, 350 NEW ENG. J. MED. 2682 (2004), available at <http://www.nejm.org/doi/10.1056/NEJMoa040933>.

<sup>123</sup> *Dual Gene Therapy Has Beneficial Effects On Blood Biomarkers And Muscle Composition*, BioVIVA (2016), <http://bioviva-science.com/blog/dual-gene-therapy-has-beneficial-effects-on-blood-biomarkers-and-muscle-composition>; Janaiah Kota et al., *Follistatin Gene Delivery Enhances Muscle Growth and Strength in Nonhuman Primates*, 1 SCI. TRANSLAT'L MED. 6ra15 (2009), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2852878/pdf/nihms187428.pdf> (examining Follistatin in the same pathway).

<sup>124</sup> Nan Yang et al., *ACTN3 Genotype Is Associated with Human Elite Athletic Performance*, 73 AM. J. HUMAN GENETICS 627 (2003), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180686/pdf/AJHGv73p627.pdf>.

<sup>125</sup> Z. He et al., *Polymorphisms in the HBB gene relate to individual cardiorespiratory adaptation in response to endurance training*, 40 BRIT. J. SPORTS MED. 998 (2006), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2577474/pdf/998.pdf>.

<sup>126</sup> Zhanhui Ou et al., *The Combination of CRISPR/Cas9 and iPSC Technologies in the Gene Therapy of Human  $\beta$ -thalassemia in Mice*, SCI. REP. 6 (Sep. 1, 2016), <http://www.nature.com/articles/srep32463>; *Genome Editing for Hemophilia: A Next Step in Genetic Therapy*, CHILD. HOSP. PHILA. (Apr. 4, 2014), <http://www.chop.edu/pages/genome-editing-hemophilia-next-step-genetic-therapy>.