ELSI IN HUMAN ENHANCEMENT: WHAT DISTINGUISHES IT FROM THERAPY?

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ELSI IN HUMAN ENHANCEMENT: WHAT DISTINGUISHES IT FROM THERAPY?

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Editorial: ELSI in Human Enhancement: What Distinguishes It From Therapy?

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Editorial on the Research Topic

ELSI in Human Enhancement:What Distinguishes It From Therapy?

This ebook is timelier than we could have expected.

While this tome was envisaged more than a year ago, its publication unpredictably closely follows worldwide outrage at the news that two embryos, now children, were genetically enhanced via CRISPR, a genetic engineering technology, with a potential third child on the way.

Among the many justifiable (and some unjustifiable) concerns and considerations associated with this incident was an issue raised in many of the papers herein, and one that continues to confound scientific researchers and ethicists alike: What distinguishes scorned enhancement from celebrated therapy? Is there a clear line that can be drawn that makes one research path acceptable while the other is shunned?

Simplistically, enhancement in the biomedical context could be defined as intervention with the primary aim of overcoming those biological limitations that afflict the average person; these limitations may be inborn or acquired later in life. Some interventions are aimed to radically alter human biology, while others are more superficial.

In contrast, therapy is designed to help those who suffer from afflictions (not necessarily a trivially defined term, as shown in at least one of the papers in this compendium) that are not average, and result often in a standard of living that is below average. Succinctly: Enhancements seek to raise the user beyond the norm, whereas therapy seeks to bring the user up to the norm. A simple-minded example would be LASIK surgery. Eye surgery performed to bring a patient to 20/20 vision would be therapy, whereas surgery meant to provide super-human eyesight would be enhancement.

The LASIK example further importantly illustrates that it is rarely the technology itself that marks the difference between the two. Many factors associated with both therapy and enhancement are also often indistinguishable: Both therapeutics and enhancements can be implemented at any time in life: from pre-conception to near-death, and both can be accomplished via genetic manipulation, pharmaceutical, mechanical, biomechanical, and/or other methodologies. Both can be invasive or non-invasive, they can be permanent, semi-permanent, or temporary. In some instances, both therapies and enhancements can affect the germline of the individual, passing on the changes to their offspring.

Returning to the case of the aforementioned enhanced children, their embryos were altered to provide them with a rare genetic variant that could ostensibly provide some natural immunity against HIV infection. While arguably potentially therapeutic, most ethicists maintained that given the cheap and proven standards methods for preventing HIV infection, the resulting genetic manipulation was effectively more enhancement than therapeutic, and as such, abhorrent.

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We can nearly fit this case into the above proposed definition of enhancement: Whereas the average person could use prophylactics, only the distinctive few, carry a helpful genetic variant. But, here is where the classification breaks down: the helpful genetic variant is by definition not superhuman, it exists in a not insubstantial portion of the population.

This ongoing discussion regarding therapy vs. enhancement is not simply academic: The rate of innovation in this area requires that legal jurisdictions decide what is, and what is not acceptable manipulation of the human body, perhaps sooner than we could have anticipated. In most legal jurisdictions, when restrictions are proposed for genetic manipulations, those restrictions typically will allow for therapeutic intervention, with regulators balking at the thought of enhancement, even when the exact same technology is employed. Thus, while there is no rule of thumb, in general, the closer interventions are to therapeutic goals, the easier they are to be regarded as acceptable. Further confounding this issue: there remain many enhancements, such as those pursued by athletes, military and other commercial industries that nevertheless often receive at least a grudging pass from the relevant regulatory bodies.

To some degree, there will likely never be a bright line distinction, and there will always be a visceral response to many areas of human enhancement technologies, even those that might seem to some as therapeutic: to paraphrase a US Supreme Court judge, many just know it when they see it. In these instances, the populist concerns tend to lean more toward issues related to playing God, not being natural, or how the enhancement somehow threatens an important aspect of the human condition, or simply some undefinable but palpable je ne sais quoi. These fuzzy feelings are legitimate but harder to deal with, particularly by the law. Whereas, other concerns that touch on issues of social justice, agency, regulation, as well as specific concerns attached to the specific populations using such interventions are much more manageable for the regulator.

And as we advance more innovative technologies, the stakes have clearly been raised regarding the many ethical, legal, and social concerns. And while we do not aim to solve this issue, this Frontiers Research Topic provides an overview on the ethical, social, and legal concerns raised by a variety of enhancement modalities, as well as different lenses on the topic from a broad spectrum of scholars in sociology, philosophy, genetics, neuroscience, and ethicists.

Several of the contributions to this e-book challenge other longstanding views in this area as well, and propose new frameworks oriented that can be helpful as we anticipate a lively and longstanding debate regarding human enhancement.

In the following, we provide a brief overview on the content of the e-book on "ELSI in human enhancement."

The paper from Bruynseels et al. looks to the novel idea of incorporating the engineering concept described as Digital Twins. A digital twin is effectively a software version of the original, a computer model that is fed by numerous sensors that provide sufficient data via continuous monitoring to accurately reflect not only the architecture of the organic model (e.g., person) itself but also the real time dynamic of the original: a "data magnifying glass."

According to the authors this is a feasible reality, given for example, the growing availability of a wide variety of wearable sensors. The authors argue that digital twins will be helpful in drawing a useful quantitative distinction between health and disease. This distinction should allow for a more nuanced appreciation of what is therapy and what is enhancement, where therapy relates to the maintenance or restoration to a clearly definable normal, that normal would likely be different in each individual. The predictive powers of such a system would also support therapeutics in asymptomatic individuals as while they are perceptively healthy, the digital twin would suggest otherwise.

The issue about how realistic are the scientific assumptions of the neuroenhancement debate is tackled by Schleim and Quednow. In particular, the authors suggest that all the hype notwithstanding we have yet to witness recent substantial innovation in the area of neuroenhancement drugs. The authors, noting the history of enhancement drugs are especially pessimistic regarding the near-future of this field. Moreover, they suggest that given the less than optimal state of the psychopharmacology field, resources are better used for the sick rather than the otherwise healthy.

Shook and Giordano address the vividly discussed area of moral bioenhancement for social welfare, but with a focus on whether or not civic institutions are ready for dealing with the consequences of such type of enhancement. They argue that if moral bioenhancement is to benefit both oneself and others it need to be conducted hand in hand with enhancement of local social conditions and civic institutions. They provide an hypothetical case of how the criminal justice system would deal with someone who has already received a civic enhancement, an enhancement which "would yield a large and reliable reduction in a person's behavior that could be threatening to other people, or would initiate and escalate violence." Their conclusion is that civic institutions are ill prepared to handle such scenarios, and suggest that neuroethics can help develop answers by working with other disciplines.

Hyun introduces the novel discussion relating to what they call the genetics of ethnicity and diet. In particular this emerging trend could call into question the necessity of the scientific field of anti-doping, as well as highlighting the unintended cultural impacts of this field. Particularly Hyun is concerned with how genetic research in the area of antidoping can have unintended consequences such as the facilitation of uninformed discussions on genetic determination and racism in sports.

So et al. provide one of the most prescient submissions in this collection, focusing specifically on a central question regarding the recent genetic manipulation of three embryos by He Jiankui. As described above, Dr. He ignited an international firestorm when he announced the birth of twin girls, Lulu and Nana who had been modified and possibly enhanced. The two girls, and possibly a third, had their genomes edited with the goal of deactivating the CCR5 gene.

While the twin's father was HIV positive, neither girl was at risk for contracting HIV and as such, many had argued that the genetic modification was an enhancement, not a therapy, even though the results could be construed as providing a therapeutic outcome.

Some of the discussion regarding Dr. He also focused on an issue, not necessarily touched upon in this collection of papers, but nevertheless highly relevant to human enhancement efforts: What about the externalities? The girls' modified CCR5 gene does not confer 100% resistance, and whatever resistance it does confer comes at a price in the form of increased susceptibility to West Nile Virus and the Flu. Moreover, the data suggests a further important caveat, while the intent was to incorporate the delta 32 variant into the girls' genomes, the data suggests that neither girl received that particular known variant: Lulu has a different mutation and Nana has two separate mutations.

In the meantime the girls currently appear to be healthy, however the inexactness of the science would further suggest that these sorts of manipulations be limited to only instances where the health of the child is clearly at risk, not for seemingly trivial enhancements. A further externality of the case, the growing global consensus for a moratorium that could also limit innovation in this area, a moratorium that might have been perceived to be unnecessary had He employed the technology for a clearly therapeutic purpose.

Further, as the authors of this paper point correctly predicted, the use of germline modification by He has led to an outcry against this type of modification and has led to the likelihood that now most efforts to provide resistance to communicable disease (RCD) will be reflexively labeled enhancements and not therapeutics. This paper will continue to be relevant both as the He scandal continues to play out, and likely long after.

Cabrera discusses the ethical importance to reframe human enhancement from its individual-based orientation and reductionist approach to a more inclusive and population-oriented one. She argues that lessons can be learnt from a population health perspective to focus on addressing environmental factors, instead of just individual ones, in order to attain optimal performance and well-ness of individuals at the scale of populations. Cabrera argues that this reframing of enhancement, together with the focus on equitable and accessible interventions, can also be regarded as a reasonable path in addressing social inequalities.

A novel perspective on neuro-enhancement is provided by the "Neuro-Enhancement Practices Across the Lifecourse: Exploring the Roles of Relationality and Individualism" from O'Connor and Nagel. They also argue that relationality, rather than pure individualism, may be a more suitable framework for conceptualizing findings in the empirical literature about everyday engagements with neuroenhancement. The authors focus on two major areas within the neuroenhancement discourse, (1) enhancing children's brains, and (2) preventing age-related cognitive deterioration. Readers gain an insight into how those concerns are essentially relational, and how they shape the ways in which neuroenhancement concepts and technologies unfold in everyday life.

Finally, the contribution of Tamir focuses on considerations of children rights to be genetically enhanced. Like So et al. forewarning submission speaks to one of the issues associated with the aforementioned Dr. He's research, specifically the lack of consent by the children, and their subsequent children regarding the germline genetic modification of the CCR5 gene. Although Tamir refers specifically to the post-natal phase of a child's life, where the lack of consent is most glaring given that the children would actually have a voice, many of the issues are particularly relevant even today, at least to the to the very small subset of individuals who have already undergone prenatal genetic enhancement. A subset that will likely soon grow.

In fact, the two conditions that Tamir sets out as necessary for the wide introduction of post-natal genetic enhancements, are precisely the areas where Dr. He failed in his efforts: The CCR5 gene in question was not perfectly targeted, the children did not obtain the desired delta 32 allele, and the children's genomes were not efficiently modified. At least one of the girls is heterozygous for the desired allele.

It is unlikely that even the uniform outcry associated with Dr. He's work will not prevent future enhancement efforts on both prenatal as well as eventually post-natal children. As such, Tamir's efforts to create a right for children to be or not be genetically enhanced is an important and valuable effort.

Overall, the contributions that form this eBook on ethical legal and societal implications in human enhancement demonstrate the variety of concerns and modalities involve in the quest to enhance humans. It also suggests the importance of inputs coming from regulatory and legal mindset when considering human enhancement, as many of the relevant issues and determinations would benefit from sharp and clear legal definitions and distinctions. We are encouraged to see that researchers from many different disciplines brought different insights into the discussion around human enhancement.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Postnatal Human Genetic Enhancement – A Consideration of Children's Right to Be Genetically Enhanced

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This paper considers children's rights with respect to genetic enhancement (GE). It is focused on the futuristic prospect of postnatal GE, namely, genetic modifications, *in vivo,* of actual existing individuals. More specifically, the paper examines whether, in a future reality where pre- and postnatal human GE is safely and prevalently practiced, a child would have a right to be genetically enhanced by her parents or guardians, as well as the right *not* to be genetically enhanced. It is in fact the *postnatal* phase, inhabited by persons of indisputable moral status, subject of rights against others, which makes the child's putative right (not) to be genetically enhanced a relevant and legitimate subject of exploration. Since postnatal GE is a futuristic technology, an appropriate, concrete, rights-discourse has not yet been developed. In this paper, I therefore attempt to initiate such discourse, by identifying, through legal analysis, potential sources for the child's right to be genetically enhanced, and theorizing about its nature (derivative, or a newly created independent right; positive or negative right). I begin by considering several (mostly) contemporary candidate core rights, from which the child's right to be genetically enhanced could potentially derive; next, I consider the child's right *not* to be genetically enhanced, through ethical analysis; finally, I look into the merits of creating such a novel right of the child. I conclude, that the direct translation of the child's interests in being genetically enhanced, into any kind of recognized positive or negative right – whether derivative or a newly emerging independent right – is unlikely. As per the putative child's right *not* to be genetically enhanced postnatally, I determine that such a right could be recognized as a relative right, balanced against parental autonomy in rearing and shaping one's child.

Keywords: human genetic enhancement, postnatal, prenatal genetic enhancement, children's rights, autonomy, open future

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INTRODUCTION

The year is 2053. Human genetic enhancement (HGE) is safely and prevalently practiced pre- and postnatally, and is part of health care or welfare programs typically managed under the *Ministry of Enhanced Living*. Guy London is a 3-year-old infant. Guys' parents opt to purchase for him the *Deluxe Enhancement Package for Athletic & Sociable Boys*. The package offers a series of genetic modifications that guarantee, to a certain extent, that Guy's personal traits and physical characteristics will be predominantly those of a

promising outgoing, popular athlete. Does Guy have a valid right to be genetically enhanced (including the right NOT to be thus modified)? Would Guy's putative right be deemed any differently if Guy were a 12-year-old boy or a 16-year-old adolescent?

This paper is about children's rights with respect to genetic enhancement (GE). In particular, it examines whether in a future reality where pre- and postnatal HGE is safely and widely practiced, a child would have a right against her parents or guardians to be genetically enhanced by them,[1] as well as the right *not* to be genetically enhanced. The paper initiates a rights-discourse on Guy's and his peers' claims with respect to their *postnatal* HGE (PoGE), by positing and attempting to answer two principal questions. The first, a future-looking question resting on positive (presently applying) law: would it be possible to derive a child's right to PoGE from contemporary core rights? The second is a normative one: should we create or recognize a novel child's right to PoGE?

Arguably, such (putative) rights-discourse can only take place in an uncontentious manner, in the realm of PoGE, where the subjects of GE are actual, presently existing individuals, as opposed to future persons of controversial moral status, e.g., embryos or fetuses, who occupy the realm of *prenatal* GE (PGE).

The scholarly literature on HGE has been typically and predominantly focused on *prenatal* enhancement. The human enhancement debate is overwhelmingly concerned with targeted genetic modification of the embryo *in vitro*, speculating on the implications of inheritable genetic alterations for future generations, for the human species as such, for the soundness of human nature and for society at large [see, e.g., Fukuyama (2002), Habermas (2003), and Sandel (2007)], while largely disregarding *postnatal*, somatic cell (uninherited) genetic modifications *in vivo,* of existing individuals. This paper, however, is concerned with the latter; particularly, with GE – narrowly defined as *purely elective*, i.e., non-therapeutic[2] genetic modification – of children. It offers an original analysis of children's (putative) right to be genetically enhanced postnatally, introducing a fresh perspective on the position of minors with regard to their own GE, and their power to make right claims in this context.

I posit that exploring particular aspects of PoGE, such as children's rights with respect to this technology, is a timely discussion (as well as a beneficial thought experiment), in the sense that such development is anticipated. This assertion hinges on the assumption that in the relatively not-so-distant future (i.e., within a few decades) scientists and technology will be able to surmount the current scientific hurdles that stand in the way of effective postnatal manipulation of desired characteristics through somatic cell modification.

In order for such a targeted genetic intervention to be successful in the postnatal stage, two fundamental capacities are required: (1) the ability to perfectly *target* and correctly *identify* the gene(s) responsible for the traits that are candidates for enhancement and to *decipher* their activity. This will be particularly challenging with respect to *polygenic* traits (i.e., the product of the interaction of multiple genes), or *complex, multifactorial* traits targeted for enhancement (e.g., intelligence, athleticism). Such traits entail variation within multiple genes, and their interaction with behavioral and environmental factors. This, combined with our current *epigenetics ignorance*,[3] undeniably sets further hurdles for the effective enhancement of desirable traits; and (2) the capability to *efficiently* modify the DNA of *each and every cell* specialized for a particular trait elected for enhancement. Both capacities are currently gravely lacking and would present challenging problems for "enhancement-enthusiasts" scientists.

Now, once such obstacles are overcome and the PoGE technology is proved to be safe, I can easily (even if somewhat reluctantly) imagine it becoming simply another parental rearing and shaping tool of one's children. This "tool" could be analogized to several contemporary examples of postnatal biological, or biomedical non-genetic enhancements (i.e., for non-therapeutic purposes), already applied to minors, underpinning various parental (and child) motivations for shaping and improving children. Prominent examples are: elective cosmetic surgery and human growth hormone treatment for ameliorating appearance (thereby potentially boosting the child's self-esteem and social status), and neuroenhancement by performance-enhancing psychotropic drugs (methylphenidate, e.g., Ritalin, and dexamphetamine compounds, e.g., Adderall), for enhancing cognitive abilities of *healthy* subjects (Tamir, 2015, p. 43–56; Tamir, 2016, p. 6–10).

My assumption that the scientific obstacle will eventually be surmounted, thus paving the way to the application of PoGE, is based on two things:

(a) Several emerging indications that science is steadily moving toward postnatal human genetic modification; for instance, scientific advancements such as CRISPR-Cas9,[4] a seemingly promising artificial *genome editing* technology, allowing specific, refined, and precise engineering of the human DNA (De Chant and Nelsen, 2014; Pak, 2014; Organizing Committee for the International Summit on Gene Editing, 2015). It is also "relatively safe, technically accessible, and affordable, essentially bringing about the 'democratization of gene targeting'" (Travis, 2015; Tamir, 2016). This technique uses a Cas9 enzyme that snips through DNA, like a pair of molecular scissors, guided by a small RNA molecule to a specific sequence of DNA to make the cut in a controlled way. It exploits the cell's DNA repair mechanism in humans, animals, and plants, to direct the spread of specific traits throughout a population, primarily in order to eradicate diseases and turn back evolutionary clocks (Brice, 2013; Esvelt et al., 2014). In fact, as recently as February 2016, scientists in the UK were granted permission by the Human Fertilization and Embryology Authority (HFEA) to genetically modify

[1] I have elsewhere also analyzed the putative duty of the state to genetically enhance children, *in lieu* of their parents; see Tamir (2015, p. 241–269) and Tamir (2016).

[2] I intentionally avoid discussing the child's putative right to therapeutic GE (i.e., gene therapy) in this paper, focusing merely on the seemingly "harder" case of *purely elective, voluntary* (social pressure aside) GE.

[3] Epigenetics is the inheritable external influence of lifestyle and environmental factors that does not involve changes to the DNA sequence, through chemical alterations to the epigenome that regulate the activity (expression) of all the genes within the genome (Jablonka and Lamb, 2006; Rothstein et al., 2009).

[4] CRISPR – Clustered Regularly Interspaced Short Palindromic Repeat.

human embryos in the first 7 days after fertilization, using the CRISPR-Cas9 technology for the first time in history, for research purposes of investigating miscarriages in women (Callaway, 2016). Now, although this genome editing technology seems to be more readily associated with therapeutic aims achieved through prenatal genetic modification,[5] there is good reason to assume that such gene-editing tool could be harnessed in the future (perhaps with some modifications) to perform predesigned PoGE, or at the very least – advance our mastery of the targeted genetic manipulation that PoGE requires. Geneticist George Church, a realistic outspoken advocate of CRISPR, indeed anticipates the inevitable spread of its use from therapy to self- and child-enhancement (Perlman, 2015). Potential GE-related somatic cell applications of the CRISPR technology have already been suggested [see Polcz and Lewis (2016)] and

(b) A reasoning based on optimistic academic attitudes accepting the eventual inevitability of GE technologies becoming part of our lives. One example for such an attitude is Nicholas Agar's "pragmatic optimism" approach (Agar, 2004, p. 34–8), which holds that it is better to be prepared with suitable moral argumentation and well laid-out principles for what will eventually mature into existence[6] – presumably, in order to instruct an appropriate legal-social stance – than to be caught unequipped to deal with the ramifications of a novel technology. Another example is Baylis and Robert's Inevitability Thesis (Baylis and Robert, 2004, p. 25), providing us with a more elaborated theory of acceptance of or resignation to the possibility of GE technologies integrating into our life. Their thesis generally suggests that embracing GE technologies is an inescapable consequence of human "*perfectibility* and the biosocial drive to pursue perfection."

And so, in this spirit of optimism, we may reasonably assert that PoGE will emerge as an available shaping tool, making the child's putative claim right to be genetically enhanced, a relevant and legitimate subject of exploration.

Before delving into our analysis, I should make a preliminary note: since the technology of PoGE is a futuristic one and, as such, has hardly been analyzed in the academic literature, I use theoretical legal and ethical analysis of (children's) rights relying, *inter alia*, on *contemporary* legal reality, as reflected in relevant universal conventions and U.S. and UK jurisprudence. I rely on existing legal framework, with the (naïve?) expectation that it will remain pertinent to our envisaged PoGE-future, due to the obvious limitations of accurately predicting the legal landscape in a few decades' time. In short, I am fully aware of the methodological difficulties posed by the futurity of the technology and its hidden (currently unknown) implications, that make such pioneering attempts to lay the foundations for an appropriate child's rights discourse in the context of her PoGE, quite challenging.

The paper is constructed as follows: At the outset, I briefly introduce some of PoGE's distinctive features and suggest two relevant policy considerations for us to bear in mind throughout our analysis. Then, I move on to analyze the core issue of this paper – the child's rights with respect to PoGE. First, I analyze whether a child's putative right to PoGE could be a derivative right of existing core rights, by examining the theoretical suitability of several (mostly) contemporary fundamental rights. Then, I consider the child's right *not* to be genetically enhanced by her parents/guardians, or the state, through an ethical analysis, where I critically address Joel Feinberg's notion of "the child's right to an open future," in the context of PoGE. Finally, I consider through jurisprudential analysis, whether a novel, positive, or negative child's right to PoGE should be recognized or created in the future, given the foreseeable implications of such recognition.

PoGE'S MOST DISTINCTIVE FEATURES

Focusing on GE conducted at the postnatal phase rather than on one conducted prenatally, holds certain advantages, particularly with respect to rights-discourse, which are predominantly attributed to the fact that this phase presents us with *existing actual persons* (children) subject for enhancement, rather than *potential*, *possible* or *future*[7] ones as in the prenatal phase. Unlike pre-natality, post-natality provides us with persons of *indisputable moral status*; subject of *rights* (and duties); individuals with a voice to assent/consent to/reject the enhancement procedure, to make claims (e.g., the right to be genetically enhanced) and express volitions (e.g., *not* to be genetically enhanced), and opinions (with regard to the specific traits chosen for GE by the child's enhancers) – what I have elsewhere termed "the presence benefit" (Tamir, 2016, p. 11). And perhaps, most importantly – post-natality provides us with an identity, which can both guide the enhancement plan and constrict it. That is to say, PoGE allows the enhancer to accommodate the enhancement plan (i.e., the traits targeted for enhancement) to the existing child's apparent identity (an option denied from the *prenatal* genetic enhancer).

Genetically enhancing an existing individual also entails other, more circumstantial unique features. One such feature is the "transparent environment." Namely, owing to the fact that PoGE is performed *in vivo* rather than *in vitro*, "the personal, social, environmental, and political state of affairs at the time the enhancement is carried out, is transparent to us" (Tamir, 2016, p. 11). This confers a further advantage upon both the child candidate for enhancement and the enhancers, which I term "enhancement in context," an advantage that PGE obviously lacks.

[5]See, recent report on the genetic modification of defective human embryos by Chinese scientists, employing the CRISPR-Cas9 gene editing technique (Cyranoski and Reardon, 2015). Various other therapeutic aims of this technology (e.g., treating HIV and cancer) are also presently being researched (Saayman et al., 2015; Liverpool, 2016).

[6]In fact, Agar has speculated, back in his well-known paper *Liberal Eugenics* (1998, p. 139), that "twenty-fifth century genetic engineers may be able to directly intervene in the genomes of existing individuals, splicing in genes for desired traits and snipping out those not similarly favoured."

[7]Heyd (1992, p. 97), defines "*potential* persons" as "people whose existence is dependent on human choice," and "*possible* persons," as "persons who have not yet, and may not ever, come into existence." "Future persons" are "persons who do not yet but will exist," who may be included under the category of actual persons (Roberts and Wasserman, 2009, p. xiii).

Lastly, genetically enhancing *existing* individuals provides us with a relatively "flexible timeframe," for conducting the enhancement. In other words, "since we are in no rush to bring a *particular* (potential) individual into existence… [t]he enhancement plan could… be orchestrated to fit the enhanced child's developmental stages, in order for it to be optimally assimilated into her personality and life in general" (Tamir, 2016, p. 12). Indeed, from a present-day *scientific* perspective, it is possible that there will be a "time window" for the modification of some traits candidate for PoGE in terms of the optimal potential for enhancement, making PoGE time-sensitive, to a certain extent [see Polcz and Lewis (2016), p. 10]. Such recognition of the relative significance of the timing of enhancement in a child's life could potentially constrain the rather flexible timeframe that features PoGE. However, for the sake of argument (and with the possibility that future scientific developments will render such time windows meaningless), I shall assume that said "time windows" will not stand in the way of PoGE as such, but will at most, affect its optimality. Namely, that genetically enhancing selective cognitive skills of 12-year-old guy, will be approximately[8] as effective as the cognitive GE of 3-year-old guy.

From an *identity-centered* ethical perspective, generally speaking, it would seem plausible that the earlier the genetic intervention takes place, the better it is for the child candidate for enhancement, in terms of the enhancement's integration into her identity and the consequent reduced risk of self-alienation, sentiments of inauthenticity and "damage" to her personal identity and self-perception (all feared-results by GE opponents; e.g., Habermas, 2003). On the other hand, from an *autonomy-centered* perspective – PoGE of older children, who possess a more cohesive self-perception, better capacity for autonomy, and are better articulated in voicing their opinion with respect to the (parent- or self-motivated) GE, may be preferable. This perspective will be elaborated further below.

In sum, these features of PoGE not only allow for a proper child rights discourse to take place but will also compel us, as enhancers, to consider the position of the minor on the matter; namely, to be attentive to her preferences, commensurate with her age, and to be mindful to the putative effects of PoGE on her self-perception and narrative identity, particularly, in terms of the identity's "intrusion tolerance" for changes brought on by the act of enhancement.

And so, due to obvious shortcomings of the *prenatal* GE setting (such as non-existence and lack of standing of the subjects of enhancement), considering here the right to PoGE of *existing* children will provide forthright child rights talk that is unparalleled in the prenatal account.

THE RIGHT TO GENETIC ENHANCEMENT – TWO POLICY CONSIDERATIONS

The right to GE essentially means the right to be improved in a targeted manner, *via* the application of a particular technology. However, as PoGE is presently in its theoretical stage, we have no specific child's right to GE nor a pertinent rights-and-duties discourse, to rely on. The existent set of children's rights (to develop and thrive, to wellbeing, health, and well-rounded growth) – closely or *narrowly* construed – seems to refer to children's most essential needs, whereas PoGE obviously far exceeds the threshold of such "basic needs."

We therefore ought to consider whether a right to PoGE makes the case for a distinct, derivative, or a novel, children's right.

But before considering this, I should point out two general policy considerations that must be taken into account, prior to recognizing such a right:

(1) What such a right would entail in terms of desert or entitlement of the child. Arguably, one could follow here the same line of argument of those who oppose the "best interest of the child" criterion: one (even a child) cannot reasonably secure an interest to have the best of most, against the world. After all, we dare not commit parents to much less demanding child-benefiting instruments (e.g., music lessons for musically gifted children), so extending children's rights to include PoGE may seem exaggerated and over-demanding. We could also appeal to a sense of reasonableness or proportionality (i.e., human and financial resources are typically limited and need to be allocated to several other, more pressing objectives); and to one's sense of morality, i.e., humility. But such talk is mostly intuitive.
(2) The potential clash, or conflict, between such a right and parental autonomous discretion in rearing and shaping one's children, specifically – parents' putative autonomy-derived right to genetically enhance their offspring.[9] Also relevant is the way parents' values and prioritization considerations influence their decisions and actions (e.g., parents could afford certain PoGEs for their child, yet *prefer* to otherwise influence her personality). Furthermore, recognizing a child's right to PoGE may coerce parents into shaping children in a manner which is inconsistent with their worldview or personal philosophy.

Having these considerations in mind, let us now attempt to identify potential sources for the child's right to PoGE and theorize about its nature.

CAN A CHILD'S RIGHT TO PoGE BE A DERIVATIVE RIGHT? IN SEARCH OF A SUITABLE CORE RIGHT

The CRC (Convention on the Rights of the Child, 1989) seems like the natural place to begin such a quest even though there is no direct support for, or any indication of, "a child's right to be shaped and enhanced in a targeted manner," in the language of the convention. Arguably, it may be inferred from a core principle of the CRC – devotion to the best interests of the child, or from

[8] See *infra* discussion in footnote 17, about the life-stage-dependent realization of the *potential* for enhancement.

[9] For a comprehensive analysis of parental autonomy and rights in the context of PoGE, see Tamir (2015), p. 137–165.

the spirit of the convention at large, but this would seem all too general and somewhat overreaching, for grounding a child's specific derivative right to PoGE.

Children's rights roughly consist of two main categories – both recognized in the CRC, acknowledging the vulnerability and incapacity of children and their need for safeguarding of their interests: (a) *human and civil rights*, equating children's entitlements to those of adults, e.g., the rights to dignity, autonomy, privacy, etc.; and (b) *protective rights*, such as the rights to nourishment, health care, education, etc.

On its face, a claim right to PoGE cannot be appropriately derived from core protective rights, due to the elective, non-essential, "privileged" nature of enhancement, making children's adult-like human and civil rights, a more plausible source for core rights.[10] Such perception of HGE, however, reflects our *present-day* reality, and it may therefore be inappropriate to rely on in our reference to the future, say, *circa* 2053 (the year of our opening illustrative example). We may therefore assume, that in a time where HGE is safely and widely practiced – PoGE may eventually become the norm, a near-standard tool for rearing and shaping one's child (as well as for self-improvement). This may set the threshold for basic needs somewhat higher than it is presently set. Elsewhere, I have even referred to the possibility of future society deeming certain types of GE a standard *sine qua non* necessity (notwithstanding its non-therapeutic, elective characterization), and hence the objects of children's rights (Tamir, 2016).

Against this background assumption, we can suggest two CRC-based potential candidate core rights: the child's fundamental *rights to participate fully in social and political life,* residing within the adult-like human and civil rights category; and the child's fundamental *rights to develop to the fullest*, residing within the category of children's protective rights. We shall now consider these candidates:

The child's fundamental rights to participate fully in social life and political life ("participatory rights"). Participatory rights are about giving "an active voice" to children (UNICEF[11]), i.e., a say in matters affecting their social, economic, religious, cultural, and political life; entitling them, *inter alia*, to freedom of thought; to the right to express opinions and be heard, and to have access to information; to the right to privacy; etc. (CRC, art. 12–17). Now, assumingly, the spreading of PoGE throughout society may set higher thresholds for participation in social and political life. In other words, given our envisaged "PoGE-inclined social climate," becoming genetically enhanced could be an implied *condition for* participation in social and political life in various respects, in the interest of fairness and equal opportunities. This would make participatory rights, broadly construed, potential core rights for the child's right to PoGE to be derived from. Let us now move on to consider the other CRC-based candidate core right.

The child's fundamental rights to develop to the fullest ("development rights"). Development rights are essentially about the child's right to evolve and flourish, to develop her personality, and cultivate her talents and abilities to their fullest potential. The fundamental right of children to development is generally stated in art. 6 of the CRC (along with the rights to life and to survival). Development rights in more specific contexts are protected under the CRC (art. 6, 18, 23, 27, 29, and 32) with respect to various domains: physical, mental, moral, social, personality, talent, cultural, and spiritual (Peleg, 2013, p. 523). (Since our business here is with domains, which directly correspond with PoGE, the latter two domains are irrelevant to our discussion.) Looking through the lenses of our "future-glasses," children's development could be broadly construed to include personal development through PoGE. Take, for instance, these present references to children's development rights under specific articles of the CRC: (a) parental responsibility "for the upbringing and development of the child" (CRC, art. 18). This may very well include parental responsibility for the child's GE in various domains; (b) directing the education of the child to "[t]he development of the child's personality, talents, and mental and physical abilities to their fullest potential" (CRC, art. 29). This may entail the provision of a cognitive and physical enhancement package, such as the kind sought for guy by his parents, in our illustrative example (the *Deluxe Enhancement Package for Athletic & Sociable Boys*).

Accordingly, the child's right to be genetically enhanced postnatally may indeed be *an instance,* a derivative, of the child's development and participatory rights, broadly construed. Or, rather, the derivative of children's development and participatory rights would be the presently hypothetical and somewhat over-demanding child's "right to be improved by the most up-to-date technologies," making PoGE – a part of a new specific class of improving technologies – a *private case* of such an instance (rather than a derivative right in and of itself). Alternatively, the child's right to PoGE could be considered as an *extension* of the right to be improved by the most up-to-date technologies, though with no independent standing (unlike derivative rights).

Another potential candidate core right for the child's right to PoGE to be derived from, is the universal "right to enjoy the benefits of scientific progress and its applications," embedded in article 15(1)(b) of the International Covenant on Economic, Social, and Cultural Rights (Gran et al., 2013). However, while HGE will definitely qualify as "benefiting, applicable, and scientific progress," deriving the child's specific right to PoGE from this general universal right, seems to be inadequate. This is due to the fact, that it is essentially a form of distributive justice claim vis-à-vis novel goods, relating to their just and fair allocation in a given society. In other words, while the essence of the right to enjoy the benefits of scientific progress and its applications is letting everyone equally to enjoy the fruits of scientific progress, the child's right to PoGE concerns a benefiting privilege for the single child, from an individual, non-social justice perspective.

Finally, I submit a more suitable, seemingly natural candidate for core human right: the "right to personal autonomy" in the sense of *self-determination*. I suggest establishing the *mature* child's putative right to PoGE on an account of minority-constrained (that is, not full-fledged) autonomy, which I shall term "minorautonomy." I shall illustrate the appropriateness of minorautonomy as a core right from which the child's right to PoGE may derive, in the following sections.

[10] Although, according to Julian Savulescu, "…enhancement is no luxury. In so far as it promotes well-being, it is the very essence of what is necessary for a good human life Savulescu (2005 p. 38)."

[11] UNICEF (accessed July 30, 2016). *The Convention on the Rights of the Child – Participation Rights: Having an Active Voice*. Available at: http://www.unicef.org/crc/files/Participation.pdf.

Minorautonomy

The notion of "minorautonomy" is based on the assumption that at a certain stage of minority children too are qualifiedly autonomous to a certain extent. Such autonomy is typically somewhat restrained by parents' (and state's) paternalism. While minorautonomy as a key right in the child's self-shaping and self-determination processes is not necessarily an original concept – its application to the issue of children's PoGE, however, *is*.

Minorautonomy features a dynamic transitory autonomy, in the sense that its limitations are gradually lifted pending adolescence and removed entirely at adulthood when one becomes a fully capacitated individual. The concept of minorautonomy is consistent with the tendency of growing respect for adolescents' autonomy and human dignity. It views late adolescents (17 years and older),[12] as *borderline adults* and *quasi-competent* agents, capable of autonomous reasoning and nearly free authorship (in the sense of being the originators) of their own narrative identity (DeGrazia, 2005, p. 294), to a certain extent. Arguably, younger preteen adolescents (10–16 years) will too be inspired by this notion, which, at the very least, stands to cultivate a sense of autonomy within them. As a result of this positive spill-over effect, they may benefit from an autonomy-promoting environment that allows them to voice their opinion, commensurate with their age and individual maturity; and for their opinion to be taken into account, mainly by their parents who would consider these expressions of early autonomy legitimate and a significant part of their children's developing adult autonomy.

Minorautonomy also serves a general second-order purpose of any liberal society: grooming children into mature, personally and socially responsible right-holders, by supplying them with tools that will gradually advance them from "their childlike state of dependence, vulnerability, and immaturity" toward adulthood (Archard, 2013).

Joseph Raz, lays out his conditions of personal autonomy: (1) *the appropriate mental abilities* to form complex intentions and "plan their execution" (i.e., "minimum rationality"); (2) *an adequate range of (morally acceptable) options*; and (3) *independence* (Raz, 1986, p. 372–8). Arguably, a late adolescent facing the option of PoGE amongst other self-shaping options may satisfy these stipulations to a significant extent.

Support for the notion of minorautonomy may be found in the General Comment to the CRC (Committee on the Rights of the Child, 2005) on the implementation of child rights in early childhood, that is, BELOW the age of EIGHT years. The comment advocates respect for the views and feelings of the young child (sec. 14), perceiving young children as active social agents and right-holders. It also invokes the "child's capacities for autonomous decision-making and comprehension of his or her best interests" (sec. 17).

What further supports the notion of minorautonomy is the charge of *arbitrariness*: it essentially claims that the age of majority, that is, the threshold of adulthood, typically set at 18 in most countries – is simply arbitrary. There is no marked difference between a 17-year-old on the verge of 18 and an 18-and-1-day-year-old young person; at least, not one that justifies the dramatic change in legal status (Archard, 2013). However, it is not strictly biological age, but rather the correlation of age-related cognitive maturity with capacity, which essentially "qualifies one to have rights" (Archard, "Children's Rights"). On the other hand, as life experience has taught us, there is good reason to distinguish adults from minors on grounds of their decision-making capacity.

The CRC (art. 12) has made it a universal rule that a child's voice should be heard and her opinion taken into consideration, with respect to matters affecting the child. The article essentially "insists on the 'visibility' of children in their own right" and "requires that we recognize the value of their own experience, views and concerns" (Lansdown, 2001, p. 1). Children should therefore be encouraged to actively participate in decisions concerning them rather than be mere "passive recipients of adult's decision-making" (Lansdown, 1995, p. 2). Minorautonomy allows for minors capable of voicing their opinion, to participate in decisions such as self-shaping through PoGE.

In fact, minorautonomy already plays a progressively larger part in medical decision-making, where young people are being gradually perceived as *quasi* autonomous, "possess[ing] the capacity to appreciate their medical conditions, and … competent to judge treatment decisions from a fairly young age" (Singh and Kelleher, 2010, p. 7). We are hence called to respect their privacy in matters such as contraceptives, abortions, sexually transmitted diseases, and drug treatment.

The legal doctrine of *mature minor*, developed in *Gillick v. West Norfolk and Wisbech Area Health Authority* (1986), binding in England and Wales (and approved in Scotland, Australia, Canada, and New Zealand), is an indication of such a determination. It has established that a minor *under* the age of 16[13] can consent to contraceptive advice and treatment from a doctor, *without parental consent* or *knowledge*, providing that she can understand what is proposed despite her young age, and that other conditions of the "Fraser guidelines" (so termed after Lord Fraser's opinion in *Gillick*), indicating a high likelihood of her continuing to have sexual intercourse, with or without contraceptive treatment and against her best interests, are met. Notably, since initially introduced, the "Gillick competency" test has been extended beyond the realm of contraceptive advice for girls to adolescents' other welfare and medical decisions (Cornock, 2007; Blyth and Frith, 2009, p. 186).

The statutory or common-law mature minor doctrine is an exception to the rule requiring parental consent to minors' medical treatment. The doctrine is not recognized by all states in the U.S. Where it is recognized, it usually applies to 16-year or older (unemancipated) minors facing medical decisions, sometimes without parental knowledge and typically without parental consent. They are required to prove sufficient maturity

[12] Steinberg and Cauffman (1996) maintain that "[c]ontrasts between adolescents and adults that do not distinguish between older and younger teenagers… are likely flawed." They therefore suggest creating subcategories of adolescents – distinguishing between 16 and younger (early and middle adolescents), and 17 and older (late adolescents).

[13] See the UK's Family Law Reform Act (1969), allowing for minors between 16 and 18 to consent to medical treatment (it even goes as far as to regard any such non-consensual treatment as a trespass upon her person), making parental or guardian consent (where a minor's effective consent was given) redundant.

and understanding with respect to the nature of the specific medical process and its consequences.[14,15] Minorautonomy presumes that late adolescents have the required capacity and therefore the power to *consent* to PoGE (rather than merely assent in addition to parental/guardian consent).

Since we refer to personal autonomy in the sense of *self-determination,* and as we have postulated that minorautonomy can only be attributed to late adolescents on the verge of adulthood, who typically exert more than minimal self-governance, it would seem relatively safe to entrust minorautonomous young persons with such self-shaping decisions.

Nevertheless, the fact remains that minorautonomy is a *relative* right[16] and power constrained by parental autonomy and authority. And so, determining whether a particular minor in a particular setting is qualified to make certain (minor)autonomous decisions, will require a subjective factual determination, on a case-by-case basis.

Minorautonomy is also *issue-relative* in the sense that it is dependent on the particular kind of choice or activity in question and varies accordingly. Namely, minorautonomy would generally apply to decisions regarding matters that are: (a) personality-defining; (b) closely linked to the minor's identity; and (c) if deferred until adulthood, such decisions might lose some of their relevance and force.[17]

Consequently, where more general matters relating to participation in social life are concerned, minorautonomy will typically not apply and full-fledged autonomy will be required, even where the minor is situated on the threshold of majority: for example, a 17-year-old young person wishing to enlist in the U.S. military is required to produce parental consent (essentially rescinding minorautonomy). S/he could enlist without parental consent, as well as vote, at the age of 18, whereas in most U.S. jurisdictions, a young person will not be considered autonomous or legally permitted to consume alcohol before the age of 21.

Scientific Evidence Relating to Adolescent Decision-Making or Maturity of Judgment

The traditional empirical perception is that children and young persons have not yet acquired the decision-making capacity possessed by adults, in terms of cognitive faculties regulating inhibition, risk-assessment, problem solving, etc., and consequently engage in risk-taking behavior and impulsive conduct, making suboptimal decisions that lead to increased incidence of harm (Cherry, 2010, p. 562). This is based on a significant body of neurobiological evidence indicating the ongoing development of the prefrontal cortex, through adolescence and into early adulthood.

Casey and Caudle (2013, p. 83), claim that these are misleading overgeneralizations and that where emotional information can be isolated and the atmosphere is "cool," adolescents are "capable of acting rationally and making optimal decisions" as well as demonstrate impulse-control. In fact, under such conditions, many adolescents perform not only well, but better than adults! Similarly, the common charges against adolescents' flawed risk-assessments are rejected by Reyna and Farley (2006, p. 34), who claim that adolescents do *not* perceive themselves as invulnerable and, in fact, tend to *overestimate* risks such as HIV and lung cancer.

Steinberg et al. (2009, p. 592), suggest that 16-year-old adolescents' decision-making or maturity of judgment does not fall short of that of adults, where emotional information can be isolated; social influences are "minimized or can be mitigated"; consultants "who can provide objective information about the costs and benefits of alternative courses of action" are accessible; and a "deliberative, reasoned decision-making" process – allowed.

It would be highly speculative and difficult to envisage the typical conditions under which adolescents would make decisions regarding their own GE. Parents and professional consultants (such as physicians, geneticists, and psychotherapists) will probably be available for guidance. Social (peer-) pressure and pressing trends, however, will be difficult to escape. In fact, these will probably not only influence the adolescent's decision-making, but inspire and motivate it in the first place.

Notwithstanding this, the evidence (succinctly described here) cautiously suggests that late adolescents should, in principle, be entitled to make decisions concerning their self-shaping through GE.

To conclude this section, given that autonomy is a foundational right, the above analysis may indicate that the child's putative right to PoGE could, *prima facie*, derive from the core right to personal (minor)autonomy or, at least, that minorautonomy may create a supportive climate for the recognition of such a novel right. Purportedly, the same may be true for deriving said right from, or perceiving it as *an instance of* children's development and participatory rights. In fact, should we acknowledge a child's *positive right* to PoGE, such core rights may be more applicable to infants and younger children who cannot yet reside under minorautonomy and are merely lightly influenced by the purported (minor)autonomy-promoting environment.

A CHILD'S RIGHT NOT TO BE GENETICALLY ENHANCED?

Minorautonomy equally entails the right NOT to be genetically enhanced postnatally, to be free from coerced GE. That is, since

[14]"Mature-minor doctrine law & legal definition." *USLegal*. Available at: http://definitions.uslegal.com/m/mature-minor-doctrine.

[15]See the West Virginia Supreme Court ruling in Belcher v. Charleston Area Medical Center (1992), where the court has specified the facts to be determined in establishing a mature minor status.

[16]A relative right is a right, which is not absolute (see *infra* footnote 18), in the sense that it is balanced against other fundamental rights.

[17]This last criterion (c) hinges on the assumption that, for the most part, genetically enhancing a particular trait or several traits merely gives the genetically modified individual a *potential* for enhancement. Presumably, however, in order to realize this potential, one would have to: (a) truly *desire* and *aim* to achieve a particular goal through such enhancement and (b) to be *provided* with the *opportunity* to perfect her genetic-modification-given skills, and to effectively master them to reach the desired goal. So, it is the loss of opportunity, specifically in terms of its timing, that raises concern in this respect. For example: if a highly motivated, competitive minor wishes to enhance her athletic abilities in order to become, through supplemental training, an outstanding athlete – putting such enhancement on hold until she becomes legally mature, say, at the age of 18, will hardly be relevant or effective, as she would have "squandered" away years potentially dedicated to honing her genetically-enhanced athletic skills.

PoGE may also close some options rather than open them, the child – commensurate with her maturity – may opt *against* GE, rather than become a slave to her extraordinary capacity in a specific field through such technology.

GE *proponents* support such a right, on libertarian grounds. GE *opponents* also typically invoke such a right, while employing a different rhetoric. Jürgen Habermas, for one, invokes *the child's freedom* in this respect Habermas (2003, p. 49). He makes the point that "[t]he parents' eugenic freedom is subject to the reservation that it must not enter into collision with the ethical freedom of their children." Such freedom allegedly entails *both* the right to be genetically enhanced, and its negative counterpart – the right *not* to be genetically enhanced. Such freedom is typically constrained by parental authority and autonomy, which routinely determine children's narrative identity to a great extent and chart the path along which they make their early (often defining) steps in life. It is also constrained by the child's limited capabilities for making such resolutions and lack of the financial means necessary for carrying out the enhancement plan. So, speaking of a child's freedom to design herself (including by rejection of the option of PoGE) in absolute terms is somewhat incoherent as well as impractical. For the dominant paternalistic conception is such, that the child is a rather passive recipient of parental dictates with respect to rearing her and shaping her personality. Accordingly, children do not have a right *not* to be educated nor do they have a right *not* to be raised according to a certain religious faith – at least not absolute rights.[18] By the same token, children would not have a right *not* to be genetically enhanced by their parents or guardians (or the state, where applicable). At least, not an absolute one.

Fenton (2006, p. 35, 39), who criticizes Habermas's negative approach to liberal eugenics,[19] powerfully makes the argument that

> … *the parent–child relationship is inherently one of inequality*; even without explicitly choosing a child's characteristics or traits, a parent has considerable control over the development of that child and the range of options open to her for future development (emphasis added – Sivan Tamir).

However, the child's right *not* to be genetically enhanced (i.e., to be free from coerced GE[20]) could seemingly be recognized as a *relative* right, balanced against parental autonomy in rearing one's child, which is itself constrained, in turn, by two principles: (1) the above-considered principle of (minor)*autonomy*; and (2) the principle of the child's *human dignity.* Notably, the principle of human dignity similarly applies to the child's right to *be* genetically enhanced but seems to apply more strongly to its negative counterpart (the child's right *not* to be thus enhanced). A nuanced outlook would suggest that the principle will typically be invoked with respect to the child's right *to be* genetically enhanced, in the contexts of agency and the ability to exercise free will in seeking the GE procedure. However, with respect to the child's right *not* to be genetically enhanced, human dignity will be invoked in the context of respect for the child's will (not to be genetically modified) with regard to the features of the specific enhancement project. Namely, PoGE performed *against* the child's will, the (reasonably foreseeable) outcome of which is socially adverse or personally degrading, or any PoGE that fails to respect the child's present identity-description, is deemed to harm the child's human dignity and is consequently impermissible.

Now, Habermas (2003, p. 22), also speaks of the "right to an unmanipulated genetic heritage," immune from artificial intervention. The Recommendations of the Council of Europe on Genetic Engineering (Parliamentary Assembly, 1982) similarly invoke the "right to inherit a genetic pattern, which has not been artificially changed." Such a purported right seems stifling or indiscriminately inhibiting any benefiting scientific progress that advances the goals of mankind. It also ascribes undue significance to human "genetic heritage" or "pattern," as if it has any relevance independently of an individual's identity or personality. What is more, it seems to naïvely assume that genetics, in itself, is an inviolable, deterministic legacy. Fenton (2006, p. 41), disputing Habermas, provocatively questions whether the "right to a genetic inheritance immune from artificial interference," heralded by enhancement opponents, could not in fact be rejected in favor of a "right to enhance one's genome." (She seems to think that it is quite possible, relying on moral common sense that may perceive human nature as "valuable, but in no way … sacrosanct and inviolable.").

The Child's Right to an Open Future

Feinberg (1980, p. 124–6), has offered an elegant, oft-cited classification of rights. The *child's right to an open future* – the collective term for children's rights-in-trust – belongs to the subcategory of children's rights (C-rights) that appear as adult autonomy rights, but cannot be exercised by the child until her decision-making capacity and other features of maturity are more fully formed. Such rights are saved for her until adulthood since they are prone to violation before the child can effectively exercise them. Other scholars have adopted various versions of the child's right to an open future, as a constraint on parental autonomy in shaping one's children (Dworkin, 1982, p. 205; Buchanan et al., 2000, p. 175; Ouellette, 2010). Some versions (e.g., Buchanan et al.'s) are weaker than Feinberg's at times stricter account of a right to "a maximally open future" (Buchanan et al., 2000, p. 170).

The child's right to an open future has been criticized for various reasons, *inter alia*, for being over-demanding, unrealistic, and conceptually vague (e.g., open to what extent? incomparable different possible futures; and ambiguity as to what makes one future more open than another) (Arneson and Shapiro, 1996, p. 365; Mills, 2003, p. 499; Resnik and Vorhaus, 2006, p. 6; Archard, 2013). I shall note my own reservations here (while my critique is

[18] Absolute rights are such rights that are intrinsic to human beings, as such; ones that it is the duty of everyone to respect. And in the words of Gewirth (1981, p. 2): "A right is absolute when it cannot be overridden in any circumstances, so that it can never be justifiably infringed and it must be fulfilled without any exceptions."

[19] "Liberal eugenics," is the idea of parental freedom in choosing the genetic characteristics or design of their children, and state neutrality in this respect. See Agar (1998, 2004).

[20] Plausibly, *everybody* (not just children) will have a right to freedom from coerced genetic manipulation.

chiefly aimed at the stronger version of the child's right to an open future, it also generally applies to its weaker accounts):

(a) No one's future is truly "open." The future is somewhat unpredictable and inconstant. Things happen that continuously narrow and reformulate our future options. Invoked in the context of GE, the idea of an attainable "open future" assumes perfect control over the results of genetic modification. This seems erroneously deterministic, disregarding epigenetic[21] and environmental effects that assure us that genetic expression can be unpredictable, whether genes are in their natural or modified state.

(b) Even adhering to the most stringent standard of neutrality with respect to the child's future (i.e., refraining from affecting her "unlimited" future life course, one way or another), as stricter accounts may have us do, could detrimentally affect her open future. Take, for example, the adoption of a permissive parenting style. Such forced avoidance, would leave the child unguided, uneducated, in utter confusion with regard to the values she should uphold, and generally neglected and detached. Consequently, it has been argued that it is this non-interfering, open parenting manner that perhaps paradoxically "ends up being autonomy-diminishing" (De Ruyter and Schinkel, 2013, p. 382). The child's autonomy could be reduced by such parental neutrality, in two possible senses: first, since autonomy is, *inter alia*, about having an adequate range of options to choose from, limiting this range in childhood would arguably constrict the child's optional life plans; second, it would go against Raz's requirement that the exercise of personal autonomy must entail a capacity to understand *valuable*, morally acceptable (not neutral) options, from which a capacitated individual is required to choose. This critique obviously does not apply to much less demanding, weaker versions of the child's right to an open future.

(c) The threat to a child's open future may also be invoked with respect to her *current* interests and *presently* realizable rights. Therefore, the claim right to an open future, if recognized, should *not exclusive*ly apply to rights-in-trust, but rather to *all* of the minor's interests that stand to be violated in a manner that might affect her "open" future, requiring the protection of parents/guardians.

(d) The duration of relevancy of children's rights-in-trust, as Feinberg (1980, p. 148–150), himself points out, may in fact be shorter than it initially appears. Also, we lack a clear-cut line beyond which C-rights are replaced by adult (A-) rights. All we have are mere approximations. Feinberg concedes that the point of full maturity or adulthood is *arbitrarily* fixed. In reality, C-rights-in-trust become adult rights much sooner (by the age of 10 or 12). Consequently, children beyond infancy are partly adults. In fact, children influence their own shaping from the very beginning: initially passively, by showing their "rudimentary character," and as they grow older – more actively. Parental shaping is guided by these displays of character and accordingly (at least ideally) strengthens "the basic tendencies of the child as manifested at that stage." I therefore wonder: if this is a true reflection of things, how can parents be expected to discern the actual timeframe within which they are responsible to protect the child's open future? Or, how can parents' decisions or actions to preserve such an open future be distinguished from those of the child's, when they supposedly act *in sync* with the child's own shaping of her future?

(e) Last, a particular reservation concerning the application of the right to an open future to the PoGE setting: the putative right to PoGE is a personal autonomy right, which the child cannot presently exercise (at least, not before becoming "minorautonomous"). Now, putting the exercise of such a right on hold for the child until s/he is an adult, in accordance with Feinberg's account, would self-defeat the entire purpose of PoGE. That is, since the rationale of PoGE is to provide the child with better life opportunities, by honing genetically enhanced traits and skills *throughout childhood*. So, it is in fact, the implementation of PoGE *now* that will open the child's tomorrow, rather than avoiding it now and deferring it until adulthood.

To conclude, significant genetic modification plausibly stands to constrain a child's ideally unfettered horizon, just as education, religious indoctrination, and financial limitations do. However, the child's entitlement to an "open" future is an idealistic notion, a worthy guide to some extent, but largely impracticable for the reasons cited above.

After this rather comprehensive pursuit after a derivative child's right to PoGE (emanating mostly from existing core rights), we shall now turn to examine whether a child's *de novo* right to PoGE is warranted.

SHOULD WE CREATE OR RECOGNIZE A NOVEL CHILD'S RIGHT TO PoGE?

Rights talk seems to have become overly extensive and right claims too easily made nowadays, invoking concern that "the prodigality of rights attributions is damaging to the cause of rights." L.W. Sumner and others critically observe the proliferation of rights with dwindling value and argumentative power Sumner (1987). Sumner (1987, p. 15), rather graphically describes the erosion process that a right goes through, starting out as a "specialized instrument" and gradually (due to political pressures and through the distortion/abuse of the language of rights) becoming a general-purpose one. Consequently, as a right is stretched farther and farther "beyond its proper domain," it is progressively emptied of its distinctive content, thus bringing about "increasing versatility of rights… purchased at the cost of their increasing vacuity." This seemingly calls for a policy of calculated, sparing recognition of novel rights *ex nihilo*,[22] to avoid such diminishing effects (Epstein, 1992).

[21] For a comprehensive account of epigenetics and genetic determinism in the context of PoGE, see Tamir (2015), p. 62–79.

[22] The term "*ex nihilo*" should be broadly construed here in the sense that the foundation for the new right was already laid by existing neighbouring rights but the new right, *per se*, is unprecedented.

Now, although there is talk about "new claims of rights being proliferated daily" (Knowles, 2001, p. 165–6), the reality seems to be that unlike the frequent appearance of such claims, which follow the emergence of new social goods reflecting certain values (such as access to the unprecedented instrument of PoGE), it is not often that new *independent* rights, entrenching such values, are legally recognized. Rather, typically, new values initially tend to be expressed through the lax interpretation or artificial extension of "old" existing rights. (It is only later, and not always, that society matures into explicit, independent acknowledgment of new legal rights.)

The legal acknowledgment of new *positive* rights is a rare occasion. (A rather fresh example is the "right to be forgotten" "in the context of digital memory and/or data retention," i.e., a right against others to have one's personal data actively erased from digital records;[23] Weber, 2011, p. 120.) Such rarity is primarily (but not exclusively) due to the nature of the democratic process, i.e., the many compromises and trade-offs in the legislative body, and the pressure exerted by various stakeholders. Moreover, from a public policy perspective, rights (particularly *new* rights) bear significant costs and burdens when they generate new duties, in terms of informing the general public about these duties, and constructing, financing and regulating new mechanisms for realizing such rights, particularly their enforcement.

In principle, the recognition or creation of a novel positive right of the child to PoGE would also require justification. On a general level, it ought to be taken into account that the recognition of such a right will broaden the scope of presently recognized children's rights, potentially breaching it by (undesirably?) introducing a new category of children's rights (in addition to the already existing ones of the CRC – "human and civil rights," and "protective rights") – that of "improvement rights." On the other hand, seemingly, such a right would promote the interests of individuals in self-determination, self-creation, and self-improvement. Nevertheless, while children deserve to have their basic needs provided for, to thrive and prosper and to have good opportunities in life – it is not clear that they necessarily deserve the *best* or *optimal* opportunities, potentially facilitated by PoGE!

And indeed, Bostrom and Sandberg (2009, p. 333), maintain with respect to cognitive enhancement, that it is not quite clear "whether access to all enhancements should or would be regarded as a positive right"; whereas "[t]he case for at least *a negative right* to cognitive enhancement, based on cognitive liberty, privacy interests, and… capacity for autonomy, *seems very strong*" (emphases added – Sivan Tamir).

I agree that the case for a *negative* right would, in theory, be more plausible than that for a positive one, for the following cumulative reasons, which correlate with the policy considerations mentioned at the outset of this paper: (a) GE will most probably be available on the free market and will not be cost-free (except, perhaps, for a state-funded once-in-a-lifetime basic enhancement package); (b) a *positive right* – either derivative or a newly emerging independent one – will potentially invoke considerably burdening correlative legal (and moral) duties imposed upon parents and the state to supply the demand for this benefiting technology; and (b1) arguably, such duties would, respectively, exceed parental obligations to satisfy the *best interests* of the child, reasonably and proportionally construed – namely, recognizing the limitations of available options, the needs, rights, and interests of others (parents and other siblings), and the fact that family members' lives are intertwined (Kopelman, 1997); as well as state's typically limited resources, additionally bound by principles of distributive justice, which may weigh against such elective expenditure.

So, while the child's interest in being genetically enhanced postnatally may be construed as intrinsically valuable to her (i.e., of *ultimate value*),[24] this is not necessarily sufficient to justify holding others (such as parents and the state) legally duty-bound on this ground (Raz, 1986, p. 189). Consequently, it would be hard to justify a new positive right (be it independent or derivative) based on the child's interests of self-determination and self-improvement.

However, the case for such a *negative* child's right is not compelling either, since particularly young children would typically not be the initiators of such use of shaping technology, and would actually require the active involvement of their parents/guardians in executing and financing the enhancement plan. A non-interfering, stand-off position of the latter, namely, parental/guardian neutrality in this respect, might therefore even *deny* them the promotion of their interests through GE.

Last, another policy consideration, which might bear influence on the strength of the claim for such a child's right, is what we may term the "realizability factor." Whether a child's claim for PoGE is a positive or a negative right, we might have to take into account the prospects of actually realizing it. To put it more straightforwardly, in light of potential epigenetic influences, the genetic modification may be incapable of guaranteeing the fulfilment of the enhancement plan (in part or in full), exactly as originally intended.[25] Policymakers considering the acknowledgment

[23] The "right to be forgotten" "reflects the claim of an individual to have certain data deleted so that third persons can no longer trace them… [it] is based on the autonomy of an individual becoming a right holder in respect of personal information on a time scale" (Weber, 2011, p. 121). The right is recognized in EU law ["the right to erasure ('right to be forgotten')," Regulation (EU) 2016/679, art. 17 and Directive (EU) 2016/680]. Its status, however, is somewhat perplexing. While it may be considered for a status of a new fundamental right within the body of human rights, it could also be merely a derivative right of the fundamental "right of the protection of personal data," recognized in article 8(1) of the Charter of Fundamental Charter of Fundamentalghts Right of the European Union (2012). On the other hand, art. 8 does not specifically refer to the option of erasure of personal data. Also of interest with respect to the nature of this right, is the ruling of the Court of Justice of the European Union in a case brought before it (Google Spain SL v. Agencia Española de Protección de Datos, 2014), where "the Court explicitly clarified that the right to be forgotten is not absolute but will always need to be balanced against other fundamental rights, such as the freedom of expression and of the media (para 85 of the ruling)" (European Commission, 2014). I shall not delve further into this intriguing novel right, as it exceeds the scope of this paper.

[24] Raz (1986, p. 177–180), maintains that a right should be based upon an interest of *ultimate value*, which he defines as one that is "… non-derivative…, intrinsically valuable… independently of one's instrumental value."

[25] This suggestion hinges on the assumption that the understanding and control of epigenetic mechanisms will remain limited as they *presently* are. However, it is not improbable that by the time PoGE will be prevalently practiced, the enigma of epigenetic effects will also be resolved, hence making any such reservations redundant.

of a child's right to PoGE, under any framework, ought therefore also to take into account that rights are too serious a matter to be protecting shaky unrealizable interests.

CONCLUSION

The purpose of this paper was to identify potential sources for- and analyze the nature of a purported child's right to be genetically enhanced postnatally. Due to our epistemic inability to accurately predict the future state of affairs, our analysis has relied on existing law and *presently* prevalent (Western-)liberal morality. I have examined the suitability of several potential fundamental rights to serve as core rights from which the child's right to PoGE may derive. My initial conclusions were that such putative right could, *prima facie*, be a derivative of the right to personal (minor)autonomy, as well as a derivative of children's development and participatory rights, in the case of infants and younger children who cannot yet reside under minorautonomy. Further exploration, however, has shown that the direct translation of any of the child's interests in GE into any kind of recognized positive or negative right – whether derivative or a newly emerging independent right – is unlikely. Such improbability is mainly attributed to the considerably burdening correlative legal (and moral) duties that a positive right to supply the demand for this non-essential technology would impose upon parents and the state; and to the anticipated situation that likely would require the active involvement of parents/guardians in executing and financing the GE plan, which does not conform with a negative right of non-interference.

As per the putative child's right *not* to be genetically enhanced postnatally, I determined that such a right could be recognized as a relative right, balanced against parental autonomy in rearing and shaping one's child.

I believe that conducting such deliberation ahead of time is a worthy thought experiment that would be valuable for forthcoming regulatory debates, by laying down the foundations for an appropriate ethico-legal framework, *before* GE technologies become state-of-the-art techniques.

Naturally, any such analysis that does not grapple with the chief implication of rights – their respective duties – is incomplete. Albeit making some assumptions regarding the burden of such potential duties and its negative effect on the prospect of recognizing such a right, there are still several aspects that require contemplation: first and foremost – whether or not traditional childrearing duties, broadly construed, should encompass a legal duty to genetically enhance one's offspring, postnatally. This weighty issue deserves separate consideration.

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The author confirms being the sole contributor of this work and approved it for publication.

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Neuro-Enhancement Practices across the Lifecourse: Exploring the Roles of Relationality and Individualism

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One key theme in sociological analysis of neuro-enhancement has been the question of whether the drive for enhancement promotes the cultural value of individualism. It has been argued that neuro-enhancement discourses implicitly propagate new responsibilities that oblige individuals to continually "work on" their brain to ensure its health and productivity. However, much of this critique relies on rather abstract analyses of discursive trends, with relatively little consideration of empirical evidence illuminating the role played by more "micro" social dynamics, such as interpersonal relationships, in the logics and practices of neuro-enhancement. This article proposes a novel perspective on neuro-enhancement by reviewing existing empirical literature enlightening everyday engagements with neuro-enhancement, and suggesting that relationality, rather than pure individualism, may be a better framework for conceptualizing these findings. The article advances this argument through a particular focus on two major preoccupations of neuro-enhancement discourses, namely, enhancing children's brains and preventing age-related cognitive deterioration. The article synthesizes the empirical evidence showing that these two concerns are essentially relational in experience and considers how familial relationships and conceptualizations of caregiving shape the ways neuro-enhancement concepts and technologies unfold in everyday life. The article offers insights from the philosophical literature on relationality as a conceptual framework to steer further investigation of neuro-enhancement's impact on contemporary society. A more holistic understanding of the relational dynamics that characterize everyday engagement with neuro-enhancement practices will enable better anticipation of the risks and benefits such practices may entail, due to greater insight into how they are likely to be enacted in context.

Keywords: neuro-enhancement, relationality, pediatric neuro-enhancement, aging, individualization, responsibility

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INTRODUCTION

The meaning of neuro-enhancement, its prevalence and use, and its justification and critiques have evolved over recent decades. Typically, neuro-enhancement refers to the use of technologies such as prescription medication and brain stimulation for the purpose of augmenting normal cognitive or affective function (Parens, 1998; Farah, 2005; Nagel, 2010a, 2014; Lucke and Partridge, 2013). In a wider sense, other interventions such as nutrition and cognitive training can also be

understood as neuro-enhancement (Dresler et al., 2013; George and Whitehouse, 2011; Lumma and Nagel, 2016). While many of the relevant techniques were originally developed for use in clinical populations, they are increasingly proposed as options for persons who are healthy and "normal" across the lifespan. Notably, neuro-enhancement is not only suggested to have the potential to influence cognitive facilities (e.g., memory and attention), but also physical capacities (e.g., muscle strength and sleep), affective states (e.g., moods and emotions) and even social and moral competencies (e.g., moral decision-making) (Nagel, 2010a). There is mixed data on the veracity of these claimed effects (de Jongh et al., 2008; Repantis et al., 2009, 2010; Battleday and Brem, 2015). However, it is important to note that while the effectiveness and scientific validity of many neuro-enhancement applications remain uncertain, their popularity and cultural prominence mean that they merit ethical scrutiny irrespective of whether they actually are effective. This need not contribute to the "hype" (Hasler, 2012) that often surrounds discussion of neuroscientific advances, but instead can help avoid a "phantom debate" (Quednow, 2010) by grounding ethical analysis in reasoned, empirically informed discussion of actual social practice.

The notion that we can affect our neurocognitive performance through deliberate action has many appealing dimensions. It promises a greater degree of control over our futures, and a route to promoting health, happiness, autonomy, and economic success (Harris, 2007; Greely et al., 2008; Bostrom and Sandberg, 2009; Savulescu et al., 2011). However, the topic of neuro-enhancement also raises numerous ethical issues. Neuro-enhancement's implications in relation to standard bioethical principles, such as users' safety and autonomy, have received necessary consideration in the literature (Parens, 1998; Farah et al., 2004; Nagel, 2010a). Yet, neuro-enhancement raises more complex ethical issues than direct threats to the safety and autonomy of the individuals who avail of enhancement technologies. Neuro-enhancement is extensively discussed in the media and increasingly absorbed into public policy (Broer and Pickersgill, 2015; O'Connor and Joffe, 2015). As a cultural phenomenon, neuro-enhancement has potential repercussions for broad societal issues such as justice, equality, markets, and health policies (Singh and Kelleher, 2010; Nagel, 2015; Ray, 2016). Thus, further ethical considerations relate to the type of society that neuro-enhancement reflects and reinforces. As a result, the popularity of new neuro-enhancement technologies has sparked extensive sociological scrutiny. One of the most frequent themes in this analysis has been the question of whether the drive for neurocognitive enhancement promotes the cultural value of individualism (Pitts-Taylor, 2010; Biebricher, 2011; Ortega, 2011; Thornton, 2011; Joldersma, 2016). The current paper seeks to advance understanding of these ideological dynamics by bringing into focus the micro-social dimension of how people engage with neuro-enhancement ideas in real-world social contexts. It reviews empirical research enlightening everyday engagements with neuro-enhancement and argues that relationality, rather than pure individualism, may be a better framework for conceptualizing these findings. It offers insights from the philosophical literature on relationality as a conceptual framework to steer further investigation of neuro-enhancement's impact on contemporary society.

A concern with investigating how neuro-enhancement resonates in ordinary social life requires consideration of how "neuro-enhancement" is to be defined. The extant empirical and conceptual literature on the topic has primarily concentrated its discussion on technological means of enhancement, with a particular focus on psychotropic medication. Such practices are indeed increasingly salient in society at large (Farah, 2015). Yet, sociological research shows that concern with enhancing brains manifests at a much broader level of practice, such as the adoption of daily nutritional and cognitive training regimes specifically oriented toward improving neurocognitive function (Pitts-Taylor, 2010; Thornton, 2011; O'Connor and Joffe, 2015). Again, whether these actually do affect neurocognitive performance is uncertain, yet inconsequential for studying neuro-enhancement as a cultural phenomenon: when the aim is to understand how neuro-enhancement is being configured as a cultural ideal, the key condition for analytic attention is that a particular practice is *experienced* as an act of enhancement. In the current paper, we adopt an inclusive definition of neuro-enhancement, which incorporates any behavior that the actor undertakes with the specific aim of enhancing neurocognitive function. While this is somewhat imprecise, inclusivity is an advantage in an exploratory analysis, as it reduces the chances that some important phenomenon will be overlooked. This is especially pertinent since technological means of neuro-enhancement remain in use by only a minority of the population, who have often been prompted to adopt these technologies by a specific neurological or psychological diagnosis. If logics of neuro-enhancement also manifest in more prosaic everyday behaviors, such as nutrition and leisure regimes, this may be where their impact is most pervasive (Lumma and Nagel, 2016). While such practices are not intrinsically or necessarily enhancements, they can be experienced as such if they are performed with the aim of affording the user a competitive advantage in the culture in which they are operating. Adopting a broad definition of what "counts" as neuro-enhancement thus affords the best chance of capturing the multifarious ways people are engaging with this ideal in their day-to-day lives.

Considering neuro-enhancement in its social context makes clear that the extent and nature of engagement with neuro-enhancement deviates across important social categories such as culture, gender, and class. The current paper seeks to enlighten the micro-social dynamics of neuro-enhancement through a particular focus on the generational dimension of neuro-enhancement experiences. The ethical questions neuro-enhancement raises may vary according to the developmental stage of the population at which it is targeted (Forlini and Racine, 2011). This is reflected, for instance, in the American Academy of Neurology's differing guidelines for use of neuro-enhancement for children and adults, which recommend more conservative practice for children (Graf et al., 2013) than for adults (Larriviere et al., 2009). Children are frequently positioned as vulnerable consumers (Graf et al., 2013). While enhancement in adolescents is often justified with reference to the principle of personal autonomy, enhancement for young children is more difficult to evaluate because their underdeveloped cognitive and legal competence establishes a special vulnerability to any risks

neuro-enhancement technologies might incur (Graf et al., 2013). Just as children need distinct consideration, the group of the elderly is often also positioned as requiring caution in relation to enhancement endeavors. Given that enhancement is usually most relevant to elderly people experiencing or anticipating cognitive decline, questions about personal autonomy and risk again arise when neuro-enhancement is targeted at this population.

In an exploration of the micro-social dynamics of neuro-enhancement, focusing on children and the elderly adds particular analytic value due to the unique social positioning of these populations. Members of both groups have a heightened level of dependence on others, generally within a family context. As such, data enlightening engagement with neuro-enhancement within these populations should offer a particularly direct glimpse of how neuro-enhancement is mediated by personal relationships. The current paper reviews the existing empirical research that illuminates how the ideas and practices of neuro-enhancement manifest in the lives of children and elderly people and considers how these findings resonate with philosophical reasoning on individualism and relationality. With this structure, the paper does not claim to capture the full spectrum of relationships that may mediate neuro-enhancement's social effects. Firstly, it concentrates mostly on familial relationships: relationships rooted in non-domestic contexts, such as educational and medical settings, are undoubtedly also important. Furthermore, in focusing on children and older people, the paper omits direct consideration of the young and middle-aged adults who, in many cases, are those providing the care that children and older individuals require. While these groups doubtlessly also merit attention, they lie outside the scope of the current paper. Here, childhood and aging are adopted as case studies on which to base a preliminary conceptual investigation of the micro-social context of neuro-enhancement ideas and practices.

NEURO-ENHANCEMENT AND INDIVIDUALIZATION

Individualism is an ethos deeply rooted in Western civilization. Many cultural theorists have observed that processes of individualization gathered pace in European and American societies throughout the twentieth century (Lukes, 1973; Sampson, 1988). Beck and Beck-Gernsheim (2002) define individualization as the instantiation of:

> a compulsion, albeit a paradoxical one, to create, to stage manage, not only one's own biography but the bonds and networks surrounding it and to do this amid changing preferences and at successive stages of life, while constantly adapting to the conditions of the labour market, the education system, the welfare state and so on (p. 30).

Beck and Beck-Gernsheim's (Beck and Beck-Gernsheim, 2002) formulation of individualization is characterized by two primary features: the individualization of social risks such as unemployment and environmental degradation, so that social problems are perceived and explained in terms of individuals' flawed behavior, and the rising importance of individual achievement orientation. Whereas in previous epochs, a person's identity was largely "given" by their social positioning, under conditions of individualization fashioning an identity becomes a task with which individuals are charged. Individualization is thus centrally linked with responsibilization: individuals bear practical responsibility for forging their destinies, and moral responsibility for the successes or failures of those efforts.

On the surface, this historically new level of agency is empowering. Presumably, encouraging people to make choices in line with their personal preferences should maximize the number of people who achieve "the good life." However, Beck and Beck-Gernsheim (2002) argue that opportunities for action can quickly become burdens of action. Nagel (2010) draws on evidence from psychology and economics to refute the simplistic assumption that more choice necessarily leads to more well-being: empirical evidence shows that an abundance of choice is often experienced in terms of anxiety, frustration, and anticipated and/or actual regret. One of the primary reasons for this is that "whatever turns out to be a matter of choice and personal control also turns into a candidate for blame and self-blame" (Nagel, 2010, p. 114). This is clearly illustrated in the domain of health, which in recent decades has been increasingly constructed as an outcome of one's lifestyle choices (Rabinow, 1992; Crawford, 2006). While this framing can motivate people to make health-promoting decisions, it can also produce a tendency toward victim blaming when health calamities do befall an individual (Wikler, 1987; Link and Phelan, 1995; Lantz and Booth, 1998; Quinn and Crocker, 1999; Crawford, 2006; Kim and Willis, 2007). The emphasis on individual agency means that the causal influence of uncontrollable biological forces, as well as social factors such as gender, class, and race, are systematically underappreciated in explaining individuals' life outcomes.

An enduring critique of contemporary neuroscience has been that by focusing its gaze inside the human skull, neuroscience perpetuates individualistic modes of explanation (Maasen and Sutter, 2007; Gergen, 2010; Meloni, 2011; Canter, 2012; Joldersma, 2016). Critical theorists' attention has been particularly drawn to the field of neuro-enhancement, due to the parallels between the concept of neuro-plasticity and the neoliberal values of flexibility, mobility, and adaptability (Malabou, 2008; Choudhury et al., 2009; Pitts-Taylor, 2010; Ortega, 2011; Papadopoulos, 2011). The concept of neuro-enhancement implies that aspects of human life previously beyond our control—the biological foundations of cognitive development and decline—are now malleable by deliberate human action. Beck and Beck-Gernsheim's (Beck and Beck-Gernsheim, 2002) theory predicts that in an individualized society, a situation where individuals *can* enhance their brain will fast become a situation where individuals *should* enhance their brain. From this perspective, opportunities for neuro-enhancement mutate into a new form of responsibilization, whereby individuals are obliged to continually "work on" their brain to ensure its health and productivity (Pitts-Taylor, 2010; Biebricher, 2011). Those who fall short of socioeconomic demands for lifelong productivity and self-reliance can be blamed for failing to perform the required neurological self-government.

As Pitts-Taylor (2010) puts it, "Seeing ourselves in neuronal terms may be becoming a duty of biomedical citizenship, since failure to think about our brains in neuroscientific terms, or at all, not only invites risk but may increasingly constitute moral failure" (p. 649). Neuro-enhancement is thus seen as reflecting and reinforcing an increasingly individualistic, competitive culture.

However, understanding of the sociopolitical implications of neuro-enhancement is limited by the fact that much of the existing literature on the topic is speculative in nature. When empirical evidence is included, it is usually restricted to the analysis of media texts or commercial products. While these data contain valuable indicators of how neuro-enhancement is being configured in wider culture, they cannot give direct insight into its manifestation in lived experience. To fully understand the normative implications of new opportunities for neuro-enhancement, we need first to answer the empirical question of how humans do in fact respond to the increased degree of choice and responsibility these technologies entail (Bostrom and Sandberg, 2009; Forlini and Hall, 2016). The research that has investigated how neuro-enhancement ideas are received by the lay public has revealed some unexpected findings: for instance, although people are interested in neuro-enhancement and conscious of normative pressures to engage in it (Cabrera et al., 2014; Fitz et al., 2014; Schelle et al., 2014), actual uptake of neuro-enhancement regimes may be relatively low (Pickersgill et al., 2014; O'Connor and Joffe, 2015). A valid and responsible analysis of neuro-enhancement's cultural implications should be sensitive to its real-life operations, and incorporate the nuances and qualifications that are evident therein.

An inevitable consequence of focusing on real-world human activity is an acknowledgment of the undeniably interdependent state of human existence. An extreme version of the individualist critique of neuroscience suggests that neuroscience promotes a philosophy akin to Sampson's (Sampson, 1977) "self-contained individualism." Under this conceptualization, human life is desocialized to such an extent that the resulting society is comprised of entirely atomized, alienated individuals. Theoretically, neuro-enhancement could contribute to an "each man/woman for him/herself" mentality by encouraging individuals to constantly seek neurocognitive advantage over others. However, a cursory glance at how neuro-enhancement is enacted in contemporary society shows that pure self-interest cannot be the sole driving force. Almost all analyses of media accounts of neuro-enhancement have highlighted a major focus on enhancing children's brains (Thornton, 2008, 2011; Pitts-Taylor, 2010; O'Connor and Joffe, 2013a). The marketing of neuro-enhancement is often directed at parents who are presumably motivated by promoting their children's interests, rather than their own. As we demonstrate below, another major preoccupation of neuro-enhancement discourses, preventing dementia in later life, is underpinned by concerns about the impact dementia would have on one's loved ones, rather than only the directly affected person him/herself. Thus, interpersonal relationships lie at the core of how neuro-enhancement concepts and technologies play out in everyday life. Imperatives for neuro-enhancement are configured in terms of responsibilities to *others*, as well as responsibilities to oneself (Broer and Pickersgill, 2015). Given these diverse felt responsibilities toward others, neuro-enhancement discourse and practice must be understood in terms of individuals' connectedness to other people. As we will argue below, it even specifically targets these relationships as the medium through which neuro-enhancement is to be enacted.

Rose and Abi-Rached (2013) cohere with this framing in their assertion that brains are not understood as totally individualized and isolated; they suggest that quite on the contrary, the brain can be conceived as a new locus of sociality. Scrutinizing the discourse around neuro-enhancement shows that optimizing brains is recommended not just for the benefit of individuals, but for the wider social good (Thornton, 2011; Rose and Abi-Rached, 2013; Broer and Pickersgill, 2015). Adults are exhorted to sculpt their children's brains and prevent their own neurocognitive deterioration, in order to cultivate a productive, entrepreneurial society composed of self-sufficient actors who do not burden social resources. Neuro-enhancement has also been proposed as a tool for improving public health (Shaw, 2014) and reducing social inequalities (Ray, 2016). The political implications of neuroscience's use in social policy have already been the subject of much analysis (Wastell and White, 2012; Macvarish et al., 2014; Munro and Musholt, 2014; Broer and Pickersgill, 2015; Edwards et al., 2015). Less attention, however, has been paid to the role played by more "micro" social dynamics, i.e., interpersonal relationships, in the logics and practices of neuro-enhancement. The current paper seeks to fill this gap by considering what is known about the familial contexts in which neuro-enhancement ideas manifest across the lifecourse, with particular attention to the ways applications are targeted at young children and aging adults.

NEURO-ENHANCEMENT IN CHILDHOOD

One of the most common themes in public discussion of neuro-enhancement is the recommendation of intervention in the first years of life, which are positioned as a critical neurodevelopmental period (O'Connor and Joffe, 2013a). Appropriate stimulation in the brain's early development, it is argued, will lay the foundations for healthy cognitive, social, and emotional outcomes (Allen, 2011). Alternatively, failure to take advantage of this time-limited critical period will result in lifelong neurocognitive disadvantage. Neuroscientific concepts have been appropriated by many toy manufacturers, food producers, pharmaceutical companies, and book publishers to propose a wide range of interventions that purportedly optimize brain development during early life (Thornton, 2011). These recommendations for pediatric neuro-enhancement have been challenged for various scientific and ethical reasons (Singh and Kelleher, 2010; Graf et al., 2013).

Inevitably, commercializations of neuro-enhancement are marketed at parents, who are exhorted to implement the enhancement techniques on their child's behalf. The ways pediatric neuro-enhancement is promoted are therefore closely bound up with prevailing cultural constructions of the parent–child relationship. The discourse that surrounds neuro-enhancement is premised on deeply engrained beliefs about parenting, and more particularly mothering (Gillies et al., 2016). In particular, pediatric neuro-enhancement dovetails with an ethic of "intensive parenting" (Hays, 1996) that encourages parents to invest maximal time, energy, and resources in the "concerted cultivation" (Lareau,

2002) of their child's abilities. Nadesan (2002) argues that family life in the twentieth century was marked by the emergence of a desire among parents for their children to *exceed* the norm in developmental achievements. This competitive mindset became particularly fixated on the domain of intelligence (Nadesan, 2002). Neuro-enhancement clearly chimes with this parental preoccupation. Indeed, it could be argued that the logic of neuro-enhancement in childhood only makes sense within the context of a widespread desire to help one's child attain a level of intellectual achievement that excels beyond that of their peers (Wall, 2010).

Thornton (2011) suggests that more recent years have seen a shift in focus away from cognitive achievement toward a superficially more rounded priority of emotional well-being. This construction of emotional well-being is also mediated through the brain, drawing heavily on ideas from attachment theory and affective neuroscience. Here, the means of neuro-enhancement is day-to-day maternal interaction rather than technological intervention. However, this does not render the enhancement agenda any less burdensome for the caregiver. Although suffused with a "back to basics" ethos that emphasizes "natural" maternal "instinct," this new discursive turn is argued to place subtle but heavy pressures on mothers to monitor and regulate their own affective experience (Thornton, 2011). Mothers are advised to classify and count their facial expressions, vocal utterances, and internal feelings to ensure that the infant's "emotional brain" is receiving optimal input. Neuro-enhancement thus feeds into a cultural encouragement of emotionally intensive forms of caregiving.

The small body of research that has directly asked parents about their experiences of these discourses suggests they can impose a heavy burden. Wall's (Wall, 2010) interviews with middle-class Canadian mothers showed that despite some skepticism about the "now or never" logic of the early years discourse, mothers showed full certainty about their ability to affect their child's life outcomes *via* their brains, and a sense of responsibility to do so in the optimally effectual manner. As one mother put it, "I am constantly aware that everything I do affects how their brains are going to develop" (Wall, 2010, p. 257). This pervasive sense of responsibility was matched by guilt regarding inevitable failures to meet the demanding standards of constant intensive, stimulating one-on-one interaction with one's child. Similar research in a British context suggests that some mothers experience the provision of intensive cognitive stimulation as a mandatory part of the maternal identity (Budds et al., 2016). The mothers interviewed in this study invested great importance in their role as a facilitator of their child's cognitive development. Daily interactions with the infant were construed as opportunities for accelerating cognitive development; and by definition, an opportunity can be exploited or lost. The high stakes thereby embedded in the enhancement agenda fostered a widespread moralization of everyday caring activity. For example, mothers equated brief disengagement from their infants with neglect and condemned their self-adjudicated failure to live up to the demands of being a "good mother." Budds et al. (2016) suggest that lay interpretations of the enhancement agenda function to reinforce the gendered division of labor and tighten the bonds linking women's identity to the domestic sphere.

The motivations behind pediatric neuro-enhancement are thus centrally premised on the forms parent–child relationships take in contemporary society. Pediatric neuro-enhancement finds a market because parents want the best for their child. What constitutes "the best" is determined by the culture in which the family lives. Nadesan (2002) suggests that the vogue for cognitive enhancement is driven by parental consciousness of a labor market demand for "entrepreneurial knowledge-workers." As such, neuro-enhancement plays on the understandable parental desire for their child to be recognized as a valuable member of society and receive the attendant social and material rewards. Additionally, in a society characterized by growing awareness of mental health difficulties, neuro-enhancement discourses promise parents a route to ensuring their child's happiness and emotional well-being.

"Doing the best" for one's child is not an entirely selfless enterprise, however. Wall's (Wall, 2010) interviewees expressed an awareness that their own social status among their peers was contingent on their child's achievements. Producing high-achieving children is a means of enhancing one's own social capital, and perhaps one's material security in old age. Demonstrating awareness of the latest scientific concepts is also a cultural signifier, marking oneself as a knowledgeable, up-to-date, and committed parent (Nadesan, 2002). As such, it is difficult to separate the extent to which pediatric cognitive enhancement is driven by an intrinsic desire to serve the child's welfare versus the secondary benefits that a child's accomplishments lend their parent.

NEURO-ENHANCEMENT IN AGING

Besides enhancing child neurodevelopment, the other dominant focus of neuro-enhancement discourse is preventing age-related cognitive deterioration (O'Connor and Joffe, 2015). Aging populations across the developed world have resulted in dramatic increases in dementia prevalence, and great concern about the social and economic repercussions this entails. In this context, health promotion initiatives and the popular press strongly advocate that middle-aged adults should structure their lifestyle around a dementia-prevention regime that infiltrates the most routine dimensions of daily life, dictating appropriate food choices, behavioral practices, and mental activities (O'Connor and Joffe, 2015). The prominence afforded to these ideas means that among the general lay population, there is now high awareness regarding the supposedly protective effects of crossword puzzles, dietary supplements, and social interaction (Friedman et al., 2009; Kim et al., 2015; O'Connor and Joffe, 2015).

Similar to pediatric neuro-enhancement, there is limited evidence for the efficacy of such methods (Katz and Peters, 2008; Palmour and Racine, 2011). However, they retain a grip on the public imagination due to the fear that dementia commands in contemporary culture. Research shows that aging is often accompanied by high levels of dread about future cognitive decline (Cutler and Hodgson, 1996; Corner and Bond, 2004; Kim et al., 2015). A 2014 US poll conducted by the Alzheimer's Association identified Alzheimer's disease as the public's most feared illness, and the recent increase in dementia prevalence is framed in hyperbolic terms of an "epidemic," "tsunami," or "time-bomb" (Peel,

2014). The anxiety surrounding dementia is absent from many non-Western cultures, where cognitive decline and memory loss are seen as normal aspects of the aging process (Faure-Delage et al., 2012; Perkinson and Solimeo, 2013). In contrast, in highly cognitivized Western societies where intellectual performance is a key marker of personal worth, dementia signals a sharp rupture from one's previous identity (von Faber et al., 2001; Williams et al., 2011; Van Gorp and Vercruysse, 2012; Buckley et al., 2015). Research on public understandings of dementia commonly reveals an idea that with the onset of dementia, the person who previously occupied that body "disappears" or becomes "lost" (von Faber et al., 2001; Corner and Bond, 2004; McParland et al., 2012; Buckley et al., 2015). Dementia thus heralds the symbolic although not the physical end of life, a phenomenon Sweeting and Gilhooly (1997) term "social death." In this context, any hope of a means of preventing this highly feared and still incurable disease is eagerly received by the public and heavily covered in the mass media (Kirkman, 2006; Kang et al., 2010; O'Connor et al., 2012; Van Gorp and Vercruysse, 2012; Peel, 2014).

As with pediatric neuro-enhancement, the drive to prevent dementia through lifestyle choices can be characterized as perpetuating the individualization of health problems. Currently healthy individuals are tasked with structuring their daily routine around maintaining neurocognitive resilience, with the implication that the onset of dementia is attributable to the individual's prior self-disciplinary failings (Peel, 2014). Yet, as with neuro-enhancement in children, relationality is paramount in the lived experience of dementia-prevention discourses. Research shows that much of the fear aging adults express toward dementia is not centered on the repercussions for themselves, but the implications for their loved ones who will be forced into caring roles (Corner and Bond, 2004; Steeman et al., 2006; Buckley et al., 2015). Responsibilities for caring for aging adults traditionally fall on their children, although this became more variable in the late twentieth century due to increased geographic mobility and female workforce participation (Mancini and Blieszner, 1989; Beck and Beck-Gernsheim, 2002). Nevertheless, it is still women who are disproportionately allocated caring responsibilities for aging relatives, which they must balance with their existing occupational, domestic, and childcare labor (Brody, 1981; Stephens et al., 2001). In this context, the dread of becoming a physical and emotional burden on one's loved ones accounts for much of the anguish that oncoming dementia elicits (Steeman et al., 2006; Buckley et al., 2015). Interviews with older people reveal a positioning of family members as the "real victims" of dementia, and a belief that the demented person's confusion protects them from fully appreciating the indignities of their situation (Corner and Bond, 2004).

Given that concerns for other people lie at the heart of the alarm dementia elicits, it is likely that the forces that motivate people to engage in dementia-prevention regimes pertain to these relational concerns, rather than pure self-protection. This appeared to be the case in interviews conducted by O'Connor and Joffe (2014, 2015), which asked laypeople to free-associate around the topic of "brain research." Half of the 48 interviewees introduced the topic of dementia, often in the context of the importance of preventing its onset through neuro-enhancement regimes. Discussion of dementia was permeated with an acute sense of anxiety, especially among older participants. In considering the reasons for this fear, participants often focused not on the intrinsic symptoms of the disorder itself, but on the anticipated loss of important relationships. Especially salient was the specific fear of losing memory of one's children, a prospect that was particularly likely to prey on female participants' minds. The other outcome of dementia that preoccupied people was loss of independence and self-sufficiency. Loss of self-control was seen as compromising the integrity and dignity of the person, such that deterioration of the brain heralded a disintegration of the whole self. Further, damage to the brain was seen as engendering reliance on others. For those who anticipated that caregivers would be family members, the worry focused on the difficulties their loved ones would experience as a result. For those who mentioned reliance on paid caregiving, the primary concerns were vulnerability to exploitation and becoming a drain on public resources.

Thus, a person's unique relational circumstances are pivotal in how they envision life with dementia to unfold, and thus in their motivations to engage with aging-related neuro-enhancement discourses. Adopting neuro-enhancement practices may be driven by the desire to prevent deprivations that would befall one's loved ones rather than oneself.

FROM PERSONAL TO RELATIONAL RESPONSIBILITY: CONSIDERING RELATIONALITY AS KEY TO UNDERSTANDING NEURO-ENHANCEMENT

The evidence reviewed above suggests that to understand the ideological dynamics of current manifestations of neuro-enhancement, we need a conceptualization of how responsibility can be experienced as a relational rather than individual phenomenon. The philosophical literature on responsibility provides some insights in this regard but is surprisingly silent on the relational nature of the everyday experience of responsibility. The notion of responsibility is deeply rooted in Western beliefs about autonomy and morality. Traditionally, responsibility can be understood as either causal or moral responsibility. While causal responsibility only describes the causal relationship between an entity and an event, and therefore does not involve agency (e.g., bacteria's responsibility for a disease), moral responsibility results from an actor's decision to perform a morally significant action, which is characterized by blame- or praiseworthiness (Eshleman, 2016). In the philosophical literature on moral responsibility, there is a long-standing debate regarding whether moral responsibility can be ascribed to groups (collective responsibility) as well as to individuals (individual or personal responsibility) (May and Hoffman, 1991; Sadler, 2006; Björnsson, 2011). These debates focus on the possibility of groups perpetuating morally significant actions, and therefore praise or blame for the collective agent. However, there have been challenges to the notion of associating moral blameworthiness with groups, since moral agency is often understood as an individual property (Sverdlik, 1987).

Recently, a few rare approaches to responsibility have arisen that distance themselves from an individualistic approach.

Gergen (2009, 2011) argues for a relational responsibility that makes individuals care for relationships in order to sustain morality. In what he describes as "second-order morality," humans need to take responsibility for relationships by devoting "attention and effort to means of sustaining the potential for co-creating meaning" (Gergen, 2011, p. 218). Relational responsibility is needed, in which not only the individuals but also the relations are subject to responsibility. In being responsible for relationships, both narcissism and self-negation can be avoided (Gergen, 2011). Similarly, Visse et al. (2012), with recourse to Walker's (Walker, 2007) work on moral understanding, demonstrate how responsibility is a relational and contextual practice. Accordingly, moral responsibilities evolve with interaction; they are relational and collaborative. Understanding responsibilities thus requires attention to prevailing narratives of identity, relationships, and value.

Most philosophical literature on responsibility seeks to determine how responsibility "really is" or how it "should be" allocated. Notably, there has been little philosophical discussion of the role played by human relationships in *subjective experiences* of responsibility (Walker, 2007; Gergen, 2011; Visse et al., 2012). The notion of relational responsibility has received minimal elaboration in the theoretical discourses on responsibility, let alone in deliberations regarding the ethical and social questions around neuro-enhancement specifically. This silence on the question of relationality from philosophers and ethicists working on responsibility leaves us under-equipped to conceptualize the lay perceptions of responsibility discussed above in relation to neuro-enhancement in early and late life. As demonstrated, in both cases, concerns for other people lie at the heart of the endeavors and perceived imperatives.

The discussion of relational responsibility that exists in other scholarly literature is mostly rooted in clinical contexts. The relational dimension of personal health decisions is vividly illustrated in the field of genetic testing, where disclosure of one individual's genetic status necessarily has implications for their genetic relatives. Research with people considering undergoing genetic testing for hereditary cancers shows that the decision is rarely approached by considering the risks and benefits for oneself alone (d'Agincourt-Canning, 2006; Arribas-Ayllon et al., 2008; Kearns et al., 2010). The processes involved in genetic testing are relational at every level: for example, the decision to undergo testing may be motivated more by concern about one's children's risk status than one's own (d'Agincourt-Canning, 2006); some people may feel coerced by relatives to acquire information they would rather not have (ibid); and people may feel an obligation to circulate the results of their own test around their wider kinship network (d'Agincourt-Canning, 2001). These instances of relational responsibilities steering people's health decisions may reflect similar processes in everyday engagement with neuro-enhancement. However, the relational responsibilities that affect neuro-enhancement may also diverge from those evident in medical contexts, since neuro-enhancement is often initiated by a person him/herself without any professional advice or support, and since it is directed at improving baseline functioning rather than addressing an active dysfunction. Further research is required to establish the extent to which empirical accounts of relational responsibility in clinical contexts mirror its specific role in neuro-enhancement activities.

Other work on decision-making processes has elaborated the concept of "relational autonomy." The common view of autonomy expression in health care decision-making can be described as "sterile" autonomy. The clinician bears responsibility to convey the benefits, harms, options, and consequences of treatment options for a presenting problem, from which the patient (or a surrogate speaking for the patient) is expected to choose. In the recent past, feminist and communitarian scholars have developed variants on the alternative concept of "relational autonomy" (Nedelsky, 1989; Friedman, 2000; Christman, 2004; Mackenzie and Stoljar, 2010). Relational accounts of autonomy recognize that when people make decisions, they usually admit input from friends, family, colleagues, or professionals (Nagel and Reiner, 2013). They often do so intentionally, without feeling unduly influenced. Nagel (2015) describes it thus: "Individuals in health care settings who feel overwhelmed or do not perceive themselves as sufficiently qualified might ask for support in a decision process […] professionals could offer support if they perceive that the patient could benefit from it" (p. 50). Such accounts, which consider the interdependencies characterizing our lives, were recently further substantiated by Specker-Sullivan (2016), who suggested "maternalism" as an alternative ethical framework. "Maternalism" avoids the main objections against paternalism while acknowledging that an individual's choices often are influenced by others. Those influences mirror the interdependencies, and the various practices premised on these social dynamics are in the individual's best interest if they follow the individual's values.

The above philosophical and medical discussions are premised on the principle that symbiotic and interdependent relationships are paramount in lived human experience. It is clear that human beings are not atomized, alienated individuals: we are socially embedded in constant interaction with others, both directly and indirectly. This is particularly evident in the early and late phases in life. In childhood, parent–child relationships are essential for survival, and their significance reemerges in later life as parents' increasing needs render them dependent on their offspring. Discussing neuro-enhancement in childhood and old age without consideration of the manifold interdependencies that steer motivations thus risks ignoring a key driving force underlying acceptance or rejection of opportunities for neuro-enhancement. Recognizing the impact of social relations for the values and motivations underlying the pursuit of neuro-enhancement fills a gap in our understanding of how neuro-enhancement practices manifest in everyday thought and action. A more holistic understanding of the relational dynamics that characterize everyday engagement with neuro-enhancement technologies will enable better anticipation of the risks and benefits such technologies may entail, due to greater insight into how they are likely to be enacted in context.

CONCLUDING COMMENTS

Previous discussion of the ideological implications of neuro-enhancement has afforded minimal attention to its relational

dimensions. This may be due to a tendency to premise analysis on a false dichotomy between individualistic and socio-structural conceptual frameworks, which assumes that focusing attention on individual brains necessarily implies neglect of socio-structural factors and *vice versa*. As a result of this rhetorical dynamic, the relational dimension, which stands as an intermediary between the individual and socio-structural levels of explanation, is left unexplored. The above accounts of neuro-enhancement in relation to childhood and aging highlight the importance of human relationships in mediating how neuro-enhancement ideas and practices manifest in real-world experience.

The empirical evidence indicating the significance of relationality warrants a caution against simplistic framings of neuro-enhancement as individualistic in essence. The motives that neuro-enhancement harnesses are not just based on individual self-interest but also individuals' investment in the welfare of those around them. The relationality evident in lay engagement with neuro-enhancement can also be found in political appropriations of neuroscience, as a recent analysis of British social policy shows (Broer and Pickersgill, 2015). Broer and Pickersgill (2015) observe responsibility as a key topic in neuroscientifically informed policy reports: it can be found implicitly in the three themes their analysis identifies, i.e., optimization, self-governance, and vulnerability. Citizens' responsibilities for solving social problems are framed in terms of relationships—parents are responsible for optimizing their children's opportunities, people are responsible for governing themselves so others will not have to, and people are responsible for defending against the exploitation of their own or other's vulnerability. Broer and Pickersgill's analysis concludes that "reports discussing policy across the life course ascribe specific social problems to the functioning of brains, yet the solution that they plea for is often a relational one, where parents have a more loving relationship with their children and understand their teenagers better, and where people care for and understand the behavior of those with dementia" (Broer and Pickersgill, 2015, p. 60). Neuro-enhancement does not deny individuals' connectedness to others; on the contrary it specifically targets these relationships as the medium through which neuro-enhancement is to be achieved.

It is important to note that acknowledging the importance of relationality does not negate arguments that neuro-enhancement can function as a vehicle for neoliberal political and cultural agendas. The "social" that is imbricated in neuro-enhancement is a very narrow form of relationality, based on immediate interpersonal relationships rather than collective bonds (Gillies et al., 2016). In close familial relationships, the psychological separation between "self" and "other" is somewhat blurred. For instance, if children are experienced as an extension of the parent, serving their benefit simultaneously serves the parent's own. In this sense then, acknowledging relationality does not disconfirm arguments that neuro-enhancement exacerbates a cultural ethic of self-interest and competitiveness. Moreover, policy interventions that address social relations, but in these very restricted, narrow forms, can contribute to obscuring the wider macro-structural factors which shape people's lives. There is a strong trend of conservative policymakers using neuroscientifically informed intervention in the socio-emotional lives of "problem families" to discharge their responsibilities to support struggling communities in more material ways (Macvarish et al., 2014; Munro and Musholt, 2014). This notwithstanding, academic analysis that focuses on families' interpersonal relations need not emulate politicians in therefore forgoing consideration of broader social dynamics such as class, gender, and race. Indeed, it is only through daily micro-social relations that the influence of such variables is realized. For instance, exploring the lived experience of neuro-enhancement in childhood and aging reveals the particular burden placed on women, who take a disproportionate share of responsibility in caring for both their children and aging parents.

The above reflections hinge on the premise, well articulated by Forlini and Hall (2016) and Pickersgill (2013), that normative ethical analysis should be closely tied to empirical evidence that enlightens how neuro-enhancement plays out in real-world contexts. A valid ethical analysis of neuro-enhancement must start from a conscientious inspection of how these practices manifest in everyday thought and action. In other words, the priority is on "empirical neuroethics" over "anticipatory neuroethics" (Illes, 2007; Northoff, 2009; Pickersgill, 2013; Fitz et al., 2014). While there is certainly value in preemptive reflection on as-yet-unrealized repercussions of neuroscientific advances, numerous observers have noted that this form of promissory discourse can lean toward collaborating in the "hype" that neuroscience often engenders (Vidal, 2009; Conrad and De Vries, 2011; Pickersgill, 2013). Since neuroscience's profile began to dramatically rise in the late twenty-first century, there have been numerous cases where assertions that neuroscience was inciting transformative societal changes were disconfirmed by empirical evidence (O'Connor and Joffe, 2013b). Extreme versions of the individualist interpretation of neuro-enhancement may be one more such example. The empirical research that has thus far accumulated suggests that far from revolutionizing society, neuroscientific knowledge often perpetuates familiar cultural themes (Hagner and Borck, 2001; Choudhury et al., 2009; Vidal, 2009; Ortega, 2011; O'Connor and Joffe, 2013b). The current paper has argued that neuro-enhancement is premised upon and enacted through existing human relationships, most notably familial bonds. It can therefore reinforce prevailing interpersonal dynamics, whether these are positive or negative in nature. For instance, parental interest in their children's welfare is unarguably a personal and social good. Yet, when cultural trends funnel this natural instinct into practices that place intense and unnecessary pressure on both parent and child, the interests of neither are served. Similarly, intergenerational caring relationships can promote domestic harmony. Yet, many feminist scholars have highlighted the harms of the caring responsibilities delegated to women, who are socialized to subordinate their own needs to those of their kin (Gilligan, 1982; Bartky, 1990; Kittay, 1999; Held, 2006). Neuro-enhancement practices reflect and reinforce these relational dynamics.

The scope of the current paper excludes several potentially fruitful targets of future consideration. First, the extent to which the above considerations are specific to neuro-enhancement or similarly relevant to other forms of bodily enhancement requires

further study of the motivations and practices that characterize both domains. Second, by foregrounding the two life phases of childhood and old age to demonstrate the importance of relationality, our analysis should not suggest that the period "in-between" does not need special attention. To the contrary, it is especially people in this phase of life—being parents of young children and/or children of aging parents—who are delegated the responsibility of overseeing others' neuro-enhancement. Additionally, exhortations to guard against neurocognitive degeneration target people in mid-adulthood as well as those who have already reached senior citizenship (Broer and Pickersgill, 2015; O'Connor and Joffe, 2015). Discussing the specifics of this "middle" generation, which is not even identified by a specific name, is an important task for future research. Finally, another important dimension that this paper leaves untouched is non-familial relationships such as peer and professional interactions. These may be particularly crucial in uses of neuro-enhancement in educational, medical, and occupational settings. We encourage the initiation of further research that expands our understanding of how neuro-enhancement interacts with the manifold forms of relationships that characterize the lives of today's citizenry. Contextualizing neuro-enhancement in light of these relational dynamics is critical for gaining a comprehensive understanding of the promises and perils that new neuro-enhancement technologies are likely to entail.

AUTHOR CONTRIBUTIONS

CO and SN equally contributed to the conceptualization and writing of this manuscript.

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Reframing Human Enhancement: A Population Health Perspective

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The dominant understandings on human enhancement, such as those based on the therapy–enhancement distinction or transhumanist views, have been focused on high technological interventions directly changing biological and physical features of individuals. The individual-based orientation and reductionist approach that dominant views of human enhancement take have undermined the exploration of more inclusive ways to think about human enhancement. In this perspective, I argue that we need to expand our understanding of human enhancement and open a more serious discussion on the type of enhancement interventions that can foster practical improvements for populations. In doing so, lessons from a population health perspective can be incorporated. Under such a perspective, human enhancement focus shifts from changing the biological reality of individuals, to addressing environmental factors that undermine the optimal performance of individuals or that can foster wellness. Such a human enhancement perspective would be consistent with a population health approach, as it pursues more equitable and accessible interventions, on the path to addressing social inequality. Human enhancement does not need to be only about high-technological interventions for a selected group of individuals; rather, it should be a continuous project aiming to include everyone and maximize the public benefit.

Keywords: human enhancement, individualism, social determinants of health, population health, low-tech approaches

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REFRAMING HUMAN ENHANCEMENT

Human enhancement has been a much-debated area in the past decades (Parens, 1998; Buchanan et al., 2001; President's Council on Bioethics, 2003; Lin and Allhoff, 2008; Bostrom and Savulescu, 2009; Coenen et al., 2009; Savulescu et al., 2011; Presidential Commission for the Study of Bioethical Issues, 2015). One of the most common definitions of enhancement in these debates is the biomedical definition, which starts from the premise that there is a distinction between therapy and enhancement. Anything below the established baseline is considered treatment and anything above enhancement. Frequently biomedical definitions include those stating that enhancements are "interventions designed to improve human form or functioning beyond what is necessary to sustain or restore good health" (Juengst, 1997: p. 29) or those beyond the species-typical level or statistically normal range of functioning (Allhoff et al., 2011).

Another common way to conceptualize enhancement has been transhumanist-based definitions. In these cases, human beings are seen as work-in-process, thus such approaches take a more controversial approach in which the goal is the expansion or augmentation beyond species limits (Miah, 2003; Bostrom, 2005). Other definitions of enhancement have suggested *welfare* as the starting point in which the focus is on increases in the chances of leading a good life in the relevant circumstances (Savulescu, 2006). While others see human enhancement as "modification aimed at improving individual human performances and determined by interventions carried out on a

scientific or technological basis on the human body" (Coenen et al., 2009: p. 17).

All of these definitions involve normative concepts such as health, disease, normal, natural, and the good life. All of these concepts have been a matter of continuous philosophical debate (Cabrera, 2015; Kahane and Savulescu, 2015), and in pluralistic societies such as ours those discussions are likely to continue. But there are other important conceptual issues that have been neglected within the human enhancement discussion. On the one hand, the debate on human enhancement has focused on high-technological interventions, such as genetic engineering (Baylis and Robert, 2004; DeGrazia, 2012), pharmacological interventions (Rose, 2002; Bolt and Schermer, 2009; Evans-Brown et al., 2012), nanotechnology (Lin and Allhoff, 2006; Cabrera, 2015), and human/machine interfaces (Warwick, 2014). Yet, strictly speaking even low-tech approaches like drinking coffee, being vaccinated, having a good night's sleep, eating nutritious food, and exercising are human enhancements (Sandberg and Bostrom, 2006; Allen and Strand, 2015). On the other hand, the debate has focused on those interventions that are aimed at changing directly the biological and physical reality of individuals. Human enhancement is mostly seen and discussed as this individual enterprise to augment a physical or mental feature or even add new ones. This reflects a liberal individual perspective, which prioritizes individual preferences and well-being, self-interest, and freedom of choice. Such human enhancement practices politically, economically, and socially seem to benefit only a few and disadvantage or do nothing for the majority. Moreover, the liberal individual view, where the individual is seen as an abstract, rational, self-sufficient, and isolated being, neglects the importance of the different and complex relationships that shape human lives and their well-being (Held, 2006). These features have prevented a critical assessment and deeper exploration of complementary or alternative ways in which human enhancement can be conceptualized and ultimately practiced.

The point here is not to question the potential benefit that individual-based type of enhancement interventions might have; rather, it is to question the assumption that these are the only ways to enhance humans or that these are the enhancement practices that should be prioritized. With this in mind, in this paper, I question the emphasis on such individually focused enhancement interventions and argue that greater attention must be paid to complementary ways in which individuals and society can benefit from enhancement practices. A more inclusive understanding of enhancement is one that acknowledges the relationship between individual–society–environment, and balances social needs with individual preferences. A reframing of the debate can complement and inform ongoing work in science and technology and societal debate.

Such a reframing calls for moving beyond current enhancement perspectives and their individual-based high-tech approaches. In this regard, important lessons can be taken from a population health perspective and scholarship in the social determinants of health (SDH), including acknowledgment that a person's well-being is shaped by a complex net of intersecting social determinants, and the weighing of outcomes is at the population level rather than at the individual one. Integrating these perspectives into the ways in which enhancement is conceptualized could foster the promotion of other types of enhancement interventions that reflect more social values and which are a more pragmatic, politically feasible, and responsible ways to enhance humans.

The suggested reframing offered here is not mutually exclusive with current definitions of enhancement, rather it shows an underexplored perspective than can complement the current ones. It is an attempt to spark further discussion in terms of comprehending the functional character of human enhancement at a population level (Battaglia and Carnevale, 2014). In the next section, I provide an overview on population health and the SDH. Finally, I will make an argument linking the aims of population health with those underlying the human enhancement perspective offered here. This perspective merely scratches the surface in the conceptual and philosophical issues surrounding such an expansive view on enhancement. There will be many issues that need to be addressed, such as how to decide the interventions to be prioritized, or how to decide the group level we are targeting (e.g., a city, a town, and a district), but it serves as a starting point to introduce the reader to expanding concepts of enhancement beyond individualistic and high-technological approaches.

A POPULATION HEALTH PERSPECTIVE AND THE SDH

Considering that some of the most pressing global challenges we face at present are related to the health and well-being of the global community, it becomes clear why population health—which deals with optimizing the health of a population—has become a priority in the international agenda and a core focus in the era of health care reform (Gourevitch, 2014: p. 544).

Population health is generally concerned with "the distribution of health outcomes within a population, the health determinants that influence distribution of care, and the policies and interventions that impact and are impacted by the determinants" (Kindig and Stoddart, 2003). Population health seeks "to eliminate health-care disparities, increase safety, and promote effective, equitable, ethical, and accessible care" (Sidorov and Romney, 2011: p. 4). Such a definition of population health articulates the direction of contemporary public health as a broader model responding to historical failures of the traditional public health approach, including its been too confined with a focus on critical functions of state and local public health departments. In contrast with the narrow understanding of the fundamental causes of disease and health of traditional public health approaches, a population health model offers a more integrated view of the changing patterns of health within communities by grasping "how social and physical environments interact with biology and how individuals 'embody' aspects of the context in which they live and work" (Kelly et al., 2007).

Through policies or programs population health aims to improve the health of individuals and populations by embracing the full range of determinants of health; thus, addressing the underlying social, economic, and environmental conditions in an effort to shift the distribution of health risks. It is these social, physical, and economic environments, in which people are born, grow, live, work, and age, what is commonly referred to as the

SDH. The SDH reflect people's different positions in the social "ladder" (social position) of power, income, resources, status, and services (Blas et al., 2011). Research on SDH has clearly shown that there are other available options to improve individual and population well-being. Quality of education and working conditions, as well as community settings and infrastructure resources in support of community living, is a few determinants now known to shape health across contexts (Healthy People 2020, 2016). A growing body of research also indicates that social stressors (Tost et al., 2015), nutritional patterns (Gómez-Pinilla, 2008), and even television exposure (Blas and Kurup, 2010) are powerful determinants of health working across subgroups.

Clear messages of the SDH and population health scholarship have included a focus on promoting non-biomedical interventions, the intersection of different areas of expertise in order to address health and well-being goals, and a deep commitment to social justice, by improving daily living conditions and tackling inequitable distribution of power, money, and resources (CSDH, 2008; Nash et al., 2011). In addition, both of these approaches bring into their analysis a view in which the individual is not taken to be isolated from others or from his or her environment, but instead is regarded as a relational individual, who is greatly shaped by the interactions he or she has with the social and physical environments. With this overview on population health and the SDH, the next section elaborates on how the complementary enhancement perspective offered at the outset of the paper can take insights from these frameworks to promote more socially relevant enhancement practices.

POPULATION HEALTH AND SDH: TOWARD MORE SOCIALLY RELEVANT ENHANCEMENT PRACTICES

Just as population health emerged as a reaction against the individualistic 20th century biomedical approaches to health, disease, and health promotion, a more comprehensive approach to human enhancement could help address the pitfalls that come with a focus on only individualistic enhancement interventions. Thus, expanding and prioritizing enhancement practices that are focused on the social and contextual aspects that shape individual well-being and that promote more equal access to enabling conditions for people to truly exploit their capabilities, can be very valuable (Cabrera, 2015). This could represent an unprecedented opportunity to improve human lives by enabling the conditions for their development and flourishing.

The dominant understandings of human enhancement have focused on the interests, desires, and values of a reduced group of privileged individuals (mostly Western white men with certain economic advantages). Therefore, highlighting a broader and different set of interests, desires, and values might not only be a new focus but also it brings into the discussion those who historically have been left out of the enhancement discourse. More importantly, it urges us to rethink the assumptions upon which the current discourse is based; and to consider the possibility that far from being a source of enhancement, its principles, values, and criteria actually reinforce patterns of domination and subordination that contribute to the deterioration and worsening of human well-being (Cabrera, 2015).

Reframing human enhancement can promote more engagement and representativeness in the debate of what sort of enhancement practices should be prioritized. In particular enhancement interventions more attuned to the different abilities, biological realities, values, and preferences of individuals in the population should be prioritized. Not everyone embraces radical and controversial enhancements, yet less drastic interventions aimed at improvement of well-being seem to be in the realm of what most individuals would find desirable and acceptable (Cabrera et al., 2015). Such enhancement practices might be better suited to address urgent population needs and current global challenges from multilevel perspectives and with the involvement of different sectors.

While science-based and technological interventions have helped in improving the human condition, it must be acknowledged that human enhancement does not necessarily require novel, high technology interventions, or radical technological interventions, which most often are neither cost-effective nor the best possible/available options. In this regard, one important insight from a population health framework is a focus on environmental and social interventions (Blas and Kurup, 2010), as these enable the conditions needed for people to live the lives they value and the conditions in which individuals and communities can be empowered (CSDH, 2008). This means that enhancement options are neither exhausted by medical solutions or technological gadgets nor by interventions focused on intervening directly in the human body. Environmental and social interventions should also be part of the repertoire of human enhancement practices (Sandberg and Bostrom, 2006; Levy, 2012; Cabrera, 2015), involving, among other things infrastructure and institutional design, nudges (Felsen et al., 2013), and other environmental changes, where there is sufficient evidence regarding their effectiveness, practicality, and amenability to change using available technologies, knowledge, and policies.

Lead paint abatement and interventions to ensure toxin-free workplaces are two examples of enhancement interventions in this more comprehensive enhancement perspective. The use of information technologies to outsource functions, such as memory, is another example of enhancement interventions that are not about changing the biological reality of individuals and which do not necessarily require high-technological interventions. Expanding the human enhancement debate to include this low-tech and more population oriented interventions can be an important step in achieving a more just distribution of enhancement benefits, and addressing the social, economic, cultural, and political realities shaping human lives. It would provide a platform to rethink the values underlying the dominant human enhancement interventions, such as competitiveness, egoism, and self-interest, and instead promote communal values, such as collective action, caring, and cooperation at the foreground of enhancement actions. Evidence from studies on implementing social determinant approaches in real-life situations (Blas and Kurup, 2010) bring hope in that there are things that can be done and that improvement of the sort suggested by such an enhancement perspective can be reached.

THE CHALLENGES

Despite the visibility of these issues and the evidence from research on the SDH, the importance of a population-based perspective within the discourse of human enhancement has not been fully appreciated. There are a few challenges that need to be addressed in order to move forward with such a reframing of human enhancement:

One challenge has to do with the problem of how to determine which interventions would bring about more population benefits compared to other possible interventions. In that regard, it is not clear that environmental interventions, such as painting the walls green for improved concentration, are necessarily better than a pill taken by an individual to enhance concentration, as in both situations not everyone would profit equally from the intervention. However, including the option of painting the wall expands the range of options available, in particular one that is likely safer as well as more economically and politically feasible. Regardless of which enhancement option one is inclined to favor, more empirical research is needed looking at different variables affecting enhancement outcomes.

Another challenge is connected to the idea that for some people expanding enhancement to include these types of interventions would constitute an unnecessary interference from different social actors in processes better left to market forces and individual choice. Yet, one has to remember that individuals are not discrete entities; they are relational. As such, changes to the environment and institutions are not necessarily infringements to individual autonomy but improvements in relational autonomy (Jennings, 2016).

Others might challenge the novelty of this enhancement perspective. The perspective offered here is innovative in that it builds on the population health and SDH frameworks to foster improvements that are responsive to the relational nature of individuals and the social determinants that affect well-being. While other suggestions have been put forward, including a shift from enhancement to enablement (Williams, 2007) or even moral enhancement (Douglas, 2008), the focus is still predominantly high technological individual-based interventions. Much of the moral enhancement literature, for example, is devoted to the ethics of giving people drugs to become, say, more emphatic. Yet, we are still left with a highly individualistic way of thinking about human well-being.

Another challenge stems from the fact that such an enhancement perspective is too broad, rendering almost everything as a form of enhancement. However, a broader perspective is essential for considering both the relative impacts of the pattern of social determinants and their interaction. Thus the importance of reframing the human enhancement debate with such a broader scope is that it urges us to review the concepts underlying the enhancement discussion in the light of the relational nature of individuals and the impact various social determinants play.

Probably the major challenge for such a broaden enhancement perspective comes from finding ways to move it from the philosophical and theoretical to the practical application. A possible reason for this is the lack of motivation toward supporting interventions that although promising to bring large overall benefits for communities seem to bring small advantages to individuals.

These are just some of the challenges that lay ahead. Further research is needed to better understand the ethics of enhancement interventions at a population level. However, the suggested paths of action are feasible and from a population health perspective even desirable.

CONCLUSION

Human enhancement choices are very much about values, ideology, and political will. Consequently, these sorts of considerations will likely shape decisions to be made regarding the kind of human enhancement interventions to be prioritized. Therefore, there is value in trying to explore more inclusive enhancement perspectives. In particular, taking into consideration the current state of the world, there is a need to reframe or complement our current enhancement practices to include enhancement interventions that are safer, more pragmatic, sustainable, as well as politically and economically feasible. The enhancement perspective suggested here could point us to areas of research that might have been underestimated or/and neglected but also to a different set of values than the ones dominating the current enhancement discourse. It can also help capture the imagination, feelings, intellect and will of political decision-makers and the broader public and inspire them to enhancement interventions focused at the population level with benefits for society as well as individuals. A true commitment to the ethos of population health and willingness to address the SDH means we would have taken a major step toward human enhancement as a more just and caring way to improve the human condition.

AUTHOR CONTRIBUTIONS

LC conceived the work and wrote the manuscript.

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Disease Resistance and the Definition of Genetic Enhancement

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Recent gene editing experiments carried out in human embryos have raised the question of whether interventions like the introduction of a CCR5-Δ32 deletion, which could provide heritable resistance to HIV infection, ought to be considered enhancements. Many authors have used the term "enhancement" in different ways, some based on patients' biomedical outcomes and others on their social context. These classifications are often considered overly imprecise. Nevertheless, the concept of "enhancement" could affect the ways in which these applications are regulated in different jurisdictions, the availability of coverage by insurers or public health care, and the force of public opinion in shaping future policy on gene editing. In order to ethically situate resistance to communicable disease with reference to other techniques, this article provides an overview of its similarities and differences with disease gene therapy in embryos, gene therapy in consenting adults, and vaccination. In discussing key ethical features of CCR5-Δ32 deletion (including its frequency in various populations, biological mechanism, benefits for individuals, and use in previous clinical trials) we offer some potential guideposts for the continuing discussion on how to classify "enhancements" in the age of CRISPR gene editing.

Keywords: enhancement, gene editing, gene therapy, CRISPR/Cas9, CCR5, HIV, disease resistance

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INTRODUCTION

Recent scientific advances have heightened the debate over using "gene-editing" technologies like the CRISPR/Cas9 system (Clustered Regularly Interspaced Short Palindromic Repeats; CRISPR-associated protein 9) to make heritable modifications to the human genome. These ongoing international discussions were partly catalyzed by two proof-of-principle experiments performed in China using non-viable human embryos. The first study, published in 2015, attempted to modify the *HBB* gene, which is involved in the genetic blood disorder beta-thalassemia (Liang et al., 2015). The following year, a second Chinese team published the results of a study which, rather than targeting a genetic disease locus, attempted to introduce the *CCR5-Δ32* gene variant, a 32-bp deletion that prevents some strains of HIV from entering white blood cells via the CCR5 receptor protein (Kang et al., 2016).

These two experiments have raised the novel question of whether gene editing aimed at providing resistance to communicable diseases (RCD) ought to be considered similar to therapeutic editing from an ethical perspective, or whether it ought to be classified as a form of "enhancement." In this article, we examine the reasons why this distinction might be important to the uptake of gene editing, and provide examples of biotechnologies that have raised similar ethical concerns. We also discuss the merits and risks of describing traits like HIV resistance as enhancement at this stage in the development of governance for CRISPR.

WHY IS THE CLASSIFICATION OF "ENHANCEMENT" SIGNIFICANT?

For many years, bioethicists have written about the use of genetic engineering to "enhance" human traits, including its consequences for distributive justice, discriminatory social norms, and the preservation of children's autonomy (Parens, 1998). While speculative modifications to intelligence, strength, or attractiveness are more frequently discussed than *CCR5-Δ32* editing, it is possible that they raise similar moral questions and deserve to be classified in the same way. Although the question of different labels for gene editing can seem overly abstract, the loosely defined category of "enhancement" could affect future uses of gene editing technologies through its use in regulation, health policy, and public discourse.

Regulation

Over 40 jurisdictions have written regulations on human germline genetic modification, most of which ban the practice in some form (Araki and Ishii, 2014; Isasi and Knoppers, 2015). For instance, Australia, Canada, France, and Germany have strict laws against altering the human germline. While similarly restrictive approaches have been adopted by countries such as China, India, and Japan, the attendant sanctions are often unclear and may not be legally enforceable (Araki and Ishii, 2014; Isasi et al., 2016). The lack of guidance and oversight in these countries could weaken public trust in science regulation (Caplan et al., 2015).

Many of these policies reflect policymakers' fears of dystopian and disruptive use of technologies such as human cloning (Knowles and Kaebnick, 2007; Knoppers et al., 2017). Their scope is frequently outlined in abstract or subjective language (Isasi et al., 2016): the UN *Declaration on Human Cloning* instructs member states to prohibit techniques "that may be contrary to human dignity" (United Nations, 2005); pan-European regulations on clinical trials prohibit "modifications to the subject's germ line genetic identity"; Israeli law allows genetic interventions only where "human dignity will not be prejudiced" (ISRAEL, 1999; European Parliament, 2014). Regulations from Germany and India also prohibit germline enhancement and express concern about eugenics (Indian Council of Medical Research, 2000; Interdisciplinary Study Group "Gene Technology Report", 2008). Thus, classifying RCD as an enhancement could result in it being more strictly regulated or proscribed in some jurisdictions.

The label of enhancement could also prevent RCD from falling under exemptions in some laws which prohibit germline modification generally but permit interventions for therapeutic purposes (Isasi et al., 2016). Treatment and enhancement are often defined in opposition to one another in the context of genetic modification (Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017). Thus, a preventive "treatment" for HIV might be included in these exemptions, while an "enhancement" might receive stricter scrutiny. As a related example, the Council of Europe's (1997) *Oviedo Convention* states that genomic modification "may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." It is possible that, in some countries, "correcting" a genetic disorder would not count as the introduction of a heritable modification (Ishii, 2015). However, it seems likely that the introduction of an "enhancement" would remain more strictly regulated in these cases.

Health Coverage

Even if gene editing to provide RCD in human embryos is eventually permitted in some jurisdictions, access to such interventions may be restricted by insurers or public health care systems unwilling to subsidize costly "enhancements" (Buchanan et al., 2000). Glybera, the first gene therapy approved in Europe, was introduced at a cost of €1.1 million per patient, making it the world's most expensive medicine and resulting in disputes over insurance reimbursement. The second, Strimvelis, cost €594,000 (Abou-El-Enein et al., 2016). Although RCD for embryos would not necessarily be as expensive, it would have to be performed alongside one or more cycles of IVF (*in vitro* fertilization), incurring further medical, economic, and social costs. Although the ethical ramifications of relying on IVF for gene editing are still poorly understood, it is beyond the scope of this article to outline these issues here (Zimmerman, 1991; Chambers et al., 2013; Werner-Felmayer and Shalev, 2015).

In the same way that cosmetic surgeries are generally excluded from both private insurance policies and public programs like the United States' Medicare and Medicaid, both types of payer might choose to classify ambiguous cases as enhancements in order to justify considering them as elective rather than medically necessary procedures. This could allow them to avoid paying for expensive new technologies which are also likely to be socially controversial (Mehlman, 1999). However, some authors suggest that therapeutic gene editing could help reduce overall health care expenditures as well as the associated costs of caring for people with cystic fibrosis, sickle cell anemia, and other genetic diseases (Zimmerman, 1991; Walters and Palmer, 1997; Resnik et al., 1999). Members of the biotechnology industry may also advocate labeling gene editing as treatment, given their commercial interests in the widespread use of CRISPR and related technologies.

Public Opinion

The development and use of new biotechnologies can be affected by public attitudes, which influence resource allocation, "political policy," and participation rates in experimental clinical studies (McCaughey et al., 2016). It is widely agreed that public consultation is an important step in the present ethical deliberation over the appropriate uses of CRISPR/Cas9 in humans. For instance, the American College of Medical Genetics' Board of Directors have urged "broad public debate" to inform this decision (ACMG Board of Directors, 2017), while the organizers of the International Summit on Human Gene Editing stated that clinical germline editing would require "broad societal consensus about the appropriateness of the proposed application" (Baltimore et al., 2016).

However, societal views are difficult to assess. More public surveys on gene editing have been carried out in the United

States than any other country, yet there is still not enough data to indicate a clear trend. A large number of respondents, although not a majority, generally accept the prevention of inherited genetic diseases. Most respondents draw a much stronger line at modifications aimed at improving or "enhancing" physical or psychological traits (Blendon et al., 2016; Funk et al., 2016). Despite this clear discrepancy, no survey has ever asked a question specific enough to elicit opinions on providing future children with RCD.

This situation has limited experts' ability to make evidence-based theories regarding public opinion on gene editing, as well as policymakers' desire to take societal values into account. It also raises doubts whether most laypeople have sufficient knowledge of genetics to provide an informed opinion at this time, although these beliefs could solidify as the technology becomes more prominent. Labeling ambiguous interventions like *CCR5* editing as "enhancements" could reduce support from the general public, regardless of the validity of these concerns; these opinions may carry significant consequences for policy development.

CAN RESISTANCE TO COMMUNICABLE DISEASES BE CLASSIFIED AS HUMAN "ENHANCEMENT"?

Despite these potential effects, the term "enhancement" is notoriously blurry. Definitions may refer to the procedure's means or its intended outcome. They can also focus on broad social and philosophical issues, or on specific impacts upon individual patients (Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017). In the former framework, authors frequently question whether gene editing would represent a primarily competitive advantage, or an "absolute good" benefiting its recipients independent of their social context (Buchanan et al., 2000; Sandel, 2004; Fox, 2007; Cohen, 2014; Elhauge, 2014; Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017).

In the latter, more individual approaches, health is often considered to follow a continuum with disease on the bottom, "enhanced function" on top, and health falling in the middle (Buchanan et al., 2000). Some consider any intervention which moves someone further up the spectrum to be an enhancement, regardless of the starting point or the endpoint (Walters and Palmer, 1997; Quigley and Harris, 2009). Other authors define enhancement as any change that raises someone into the "better than well" range (Greely, 2008; de Melo-Martín, 2010). However, RCD editing as typically envisioned would prevent a healthy person from potentially falling lower on the spectrum, meaning neither definition would apply.

Parens (1998) suggests simply adding the category of "prevention," but this does not tell us whether RCD would be treated as an enhancement by the actors discussed above unless enhancement, prevention and treatment are mutually exclusive. This assumption may not be useful from a regulatory, normative, or scientific perspective. First, many authors have referred to identical interventions using each of the three terms. Second, reference points on the health continuum depend both on the population and the course of medical progress. Third, genetic interventions could involve very similar methods and outcomes, meaning that treatments intended for disease and enhancements intended for healthy patients might be equivalent from a purely biomedical perspective. And fourth, these categories may not capture relevant social attitudes or realistic policy options (Walters and Palmer, 1997; Mehlman and Botkin, 1998; Elhauge, 2014; Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017). Given these difficulties, it may be more helpful to examine RCD's similarities and differences with interventions about which we are relatively secure in our moral intuitions, including gene therapy in embryos, gene therapy in adults, and vaccination.

Gene Therapy in Embryos

At first glance, the two studies editing *HBB* and *CCR5* in non-viable human embryos seem very similar: the only significant difference in their methods was the design of different guide RNAs for targeting purposes (Liang et al., 2015; Kang et al., 2016). According to the continuum-based definitions cited above, correcting thalassemia would seem to fall squarely within the purview of medicine. Norman Daniels (1985) argues that the only obligatory forms of care are those which restore "species-typical functioning" on a biological level in order to give patients a "normal range of opportunity" in society. While definitions of medical "normalcy" have been widely debated (Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017), that question is beyond the scope of this article, and we believe most people would agree that severe genetic disorders do not represent typical function and result in a restricted range of opportunities compared to "healthy" people. A similar argument could theoretically be made for *CCR5* editing and the limitations on opportunity imposed by HIV/AIDS. In this case, the absence of HIV infection might be considered "normal" or "species-typical."

One objection to this interpretation might be that wild type, HIV-vulnerable *CCR5* alleles should represent normal functioning, since they represent the large majority of people in every ethnic group. In Northern Europe, only up to 14% of the population may have copies of the *CCR5-Δ32* allele, while in East Asian populations, the HIV-resistant population is functionally nil (Stephens et al., 1998). In fact, it has previously been suggested that introducing natural variants of sufficient rarity into an embryo should be considered enhancement. Yet as with the concept of "normalcy," the question of where to draw the line for rarity in a biological population remains somewhat open, and allele frequency itself can change over time or geography (Walters and Palmer, 1997; Parens, 1998; Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017).

RCD could also be compared with interventions which, rather than targeting clear-cut disorders like beta-thalassemia, attempt to reduce genetic predispositions to adult-onset diseases. Just as human behavior interacts with genotype to influence cancer and diabetes risks, *CCR5* editing would also modulate risks dependent on environmental exposure. As such, RCD may represent an

enhancement in that it would allow a future person to live with fewer worries or greater freedom than their peers. While the use of preimplantation genetic diagnosis to avoid severe genetic disorders has many proponents, the selection of embryos based on Alzheimer's risk has been widely criticized by ethicists as an overreach of parental decision-making (Robertson, 2003; Anderson et al., 2015). If there is an ethical boundary between limiting future risks and addressing conditions with well-defined existing etiology, it might be prudent to classify the former as enhancement.

Gene Therapy in Adults

One appeal of the comparison between embryo editing for RCD and gene therapy in adults is that both methods may involve the same genetic "edit." Indeed, somatic *CCR5-Δ32* editing in T cells has already been tested as a treatment for HIV-positive adults (Tebas et al., 2014). These methods are considered ethically acceptable provided they satisfy requirements regarding risk–benefit ratio and informed consent (Lander, 2015; Rodriguez, 2016). However, germline modification raises additional concerns about unpredictable, inherited effects on future generations who would have no say in the decision (Rodriguez, 2016).

It is not clear that consent is relevant to the classification of enhancement. Many theorists differentiate acceptable from unacceptable interventions based on whether they maximize the "open future" of children, providing them with the means to achieve their own projects, or whether they restrict children to lives following their parents' value systems (Feinberg, 1980; Habermas, 2003; Agar, 2004). Yet even philosophers with vastly different views on human gene editing agree that it could prevent many sorts of goals from being sidetracked by illness (Buchanan et al., 2000; Habermas, 2003; Quigley and Harris, 2009). RCD is unlikely to represent the threat to identity or authenticity feared by some of the legislators discussed above.

The second relevant difference lies in these methods' effect on future generations. Assuming people have genuine interests in the health of their immediate descendants, it might be argued that RCD editing represents an enhancement compared to somatic therapy. This possibility, combined with the high price of gene editing, evokes longstanding fears about societal stratification, discrimination against the "genetic underclasses," and political instability (Walters and Palmer, 1997; Parens, 1998; Agar, 2004; Joly et al., 2013). However, broadly subsidized RCD could be seen as a public health measure. Similar to the way in which vaccination creates "herd immunity," reducing the total number of people vulnerable to communicable diseases could help shield those without the protective allele. For instance, South Africa's representative to the International Summit on Gene Editing discussed *CCR5* gene therapy as a potential strategy in dealing with the public health burden of HIV/AIDS in Africa (Moodley, 2015).

Vaccination

Like embryonic *CCR5* editing, vaccination often involves manipulating someone's immune system without their consent in order to boost their resistance to infections. Interestingly, the question of whether vaccines represent enhancement has already been discussed in the literature (Bostrom and Roache, 2007; Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017). Since vaccination is morally accepted by most stakeholders, those who reject enhancement have had to find ways to exclude vaccination from its definition (Douglas, 2013). Daniels (2000), for instance, states that vaccinations "exploit more fully our immune capabilities rather than extending them." However, many ethicists describe vaccination as a clear enhancement beyond species-typical functioning (Walters and Palmer, 1997; Harris, 2007; Quigley and Harris, 2009; Roberts, 2014), and those who support more permissive uses of human gene editing often cite it as proof that enhancement is already being widely practiced (Parens, 1998).

In response, it could be argued that RCD in the form of *CCR5-Δ32* editing does not actually represent a functional upgrade to immune activity the way vaccination does. It merely changes the structure of the CCR5 receptor in a way that limits HIV entry into host cells (Lopalco, 2010). Furthermore, this allele appears to be associated with a significant increase in susceptibility to West Nile virus (Glass et al., 2006; Moodley, 2015). On second glance, even a successful *CCR5-Δ32* deletion might be viewed not as an objective enhancement so much as a deliberate trade-off, with both advantages and disadvantages depending on the medical context (Lander, 2015; Gyngell et al., 2016).

CONCLUSION

Recent experiments involving human embryos have raised ethical and legal questions about the editing of genes like *CCR5* in order to promote disease resistance. Given the longstanding bioethical debate over human "enhancement," the labeling of these techniques could have significant effects on their eventual clinical uses. First, regulations in many jurisdictions refer to subjective concepts which could be used to exclude enhancements. Second, both insurance companies and public health care systems could make or interpret policy in order to avoid paying for such interventions. Third, ethics deliberation and political decision-making could be influenced by public fear—whether rational or irrational—of dystopian futures following from genetic enhancement.

Although the concept of enhancement is nebulous, confusing, "freighted with erroneous assumptions and ripe for abuse" (Parens, 1998), it seems too entrenched in our language to be ignored or replaced. While actual consensus about its definition would represent an important breakthrough (Hotze et al., 2011), we are not suggesting a new definition in this article. Rather, our investigation of RCD has demonstrated a number of ways in which using the ambiguous label of "enhancement" as a guiding principle can be limiting for the bioethical debate. Arguments for or against new interventions should appeal to more concrete ethical concerns, such as the provision of competitive advantages against other members of society. Regulators should also consider using more specific language in governance documents. In the present context, however, we suggest that ambiguous cases be more

pragmatically classified as enhancement or non-enhancement based on considerations of the public good. While germline gene editing does not seem efficient as a public health measure, it also does not appear to raise significant ethical issues beyond the other techniques discussed above. Therefore, we do not see a strong case for considering it an enhancement in the present context.

For the purposes of this article's more philosophical arguments, we have assumed the eventual safety and efficacy of embryonic gene editing. However, the technology is currently agreed to be unsafe for clinical use (Liang et al., 2015; Baltimore et al., 2016; Kang et al., 2016; Committee on Human Gene Editing, and National Academies of Sciences, Engineering, and Medicine, 2017). Given our lack of experience with these technologies, the use of CRISPR in a human embryo at this stage would be more likely to produce mosaicism and off-target effects than the desired enhancement. Modifications capable of being inherited by future generations must also be held to especially rigorous safety standards. The risk of introducing disorders into the germline of a healthy embryo, or of providing RCD to some diseases at the cost of increased vulnerability to others, ought to be taken into account in the calculus of labeling interventions as enhancements.

It should also be noted that many ethicists argue against editing human embryos regardless of whether it represents enhancement. They express concern that any intervention represents a slippery slope toward more problematic forms of gene editing (Annas et al., 2002). Further dialog on this topic can help us avoid inadvertently facilitating morally blurry interventions. We should endeavor to predict conflicts which could arise from different perceptions of these technologies, while continuing to examine the relation between our ethical and regulatory frameworks and stakeholders' views on the concept of enhancement.

AUTHOR CONTRIBUTIONS

DS conceived the article subject, wrote one-third of the first draft, and performed final edits on each draft. EK wrote one-third of the first draft and edited the manuscript. ST wrote one-third of the first draft and edited the manuscript. YJ oversaw the writing and edited the manuscript.

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Geneticizing Ethnicity and Diet: Anti-doping Science and Its Social Impact in the Age of Post-genomics

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While gene doping and other technological means of sport enhancement have become a topic of ethical debate, a major outcome from genomic research in sports is often linked to the regulation of doping. In particular, researchers within the field of anti-doping science, a regulatory science that aims to develop scientific solutions for regulating doped athletes, have conducted genomic research on anabolic-androgenic steroids. Genomic knowledge on anabolic-androgenic steroids, a knowledge base that has been produced to improve doping regulation, has caused the 'geneticization' of cultural objects such as ethnic identities and dietary habits. Through examining how anti-doping genomic knowledge and its media representation unnecessarily reify cultural objects in terms of genomics, I argue that Ethical, Legal, and Social Implications (ELSI) research programs in human enhancement should include the social impacts of anti-doping science in their discussions. Furthermore, this article will propose that ELSI scholars begin their academic analysis on anti-doping science by engaging with the recent ELSI scholarship on genomics and race and consider the regulatory and political natures of anti-doping research.

Keywords: human enhancement, anti-doping science, sports doping, geneticization, genomics and race, regulatory science

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INTRODUCTION

While the use of science for doping detection in sports has long been a hotspot of ethical debate, an increasing number of social and ethical concerns have been raised by new genomic knowledge in relation to sport enhancements. Recent developments in genetics and genomics create new technological possibilities for enhancing sports performance on the molecular level. In particular, with the rise of gene therapy since the early 2000s, scientists have begun to worry about the misuse of gene therapy for sport enhancement (Baoutina, 2011). Since then, the World Anti-Doping Agency (WADA), the international organization coordinating and monitoring the illegal use of drugs in sports, has proactively implemented preventative strategies on gene doping; for example, in 2003, WADA added gene doping to the list of banned practices (WADA, 2009). Along these lines, bioethicists have discussed the social and ethical impacts of genetic modification in sports performance in doping practices (Miah, 2004; Sandel, 2009).

Ironically, major outcomes of genomic research in relation to doping in sports tend to be linked to doping regulation rather than to doping itself. In particular, since 2003 new genomic knowledge on anabolic androgenic steroids (AAS) has vastly increased because WADA has

encouraged scientific researchers to find new doping detection methods for preventing gene doping and other unknown techniques (Miah, 2011). Anti-doping scientists, who aim to develop scientific and technological solutions for regulating doped athletes and who are mainly funded by international and national anti-doping agencies, have conducted genomic research on AAS. The scientific outcomes of their research play an important role in controlling international and national sports contests, because their findings are immediately introduced into doping regulation practice through WADA and national anti-doping agencies. Furthermore, the genomic knowledge they have produced has strongly influence popular thinking on sports performance, nutrition, and other topics, via news media on international matches like the Olympic Games and FIFA World Cup. Despite the importance of anti-doping science, few discussions of the social and ethical implications of this science exist (Hyun, 2016).

In this article, I argue that Ethical, Legal, and Social Implications (ELSI) research programs in human enhancement should consider the social impact of anti-doping science, particularly in relation to genomics. This paper examines the case of genomic research on the relationship between a uridine glucuronosyl transferase 2B17 (*UGT2B17*) gene and testosterone metabolism. By doing that, this paper shows how genomic research originally produced for strengthening doping regulations and the media's hype on the implication of their research have caused the reification of cultural objects—ethnic identities and diet customs—in terms of genomics. This reification has led elite athletes and the lay public to understand their cultural differences as genetic differences. Due to this unnecessary reification, some athletes may face unjustified accusations of doping.

To investigate the social impact of anti-doping science in relation to genomics, this article conducts two analyses: content analysis of scientific journals and content analysis of news media. I used various sources to search for scientific articles and news reports related to anti-doping genomic studies. My first analysis is a content analysis of anti-doping genomic research. In order to collect this data, I first sought genomic research projects that received research funds from WADA between 2001 and 2016. This literature review of WADA-funded genomic research led me to recognize the association research between the *UGT2B17* and testosterone metabolism as a main research subject in anti-doping science. For this reason, I chose anti-doping research on *UGT2B17* as a case study of content analysis. I then collected scientific articles related to this subject on Google Scholar, using the terms "*UGT2B17*," "testosterone," "doping," and "genomic research." I also conducted a supplementary search to find *UGT2B17* research that might not have been identified by Google Scholar, specifically identify scientific reports on *UGT2B17* and testosterone metabolism that were uploaded as web resources on 34 WADA-accredited anti-doping laboratories.

My second analysis is a content analysis of media reports on anti-doping genomic research. Since many of scientific reports on *UGT2B17* and testosterone metabolism highlighted the genetic specificity of East Asians in relation to *UGT2B17*, I included news articles published in East Asian countries in my analysis. As a result, I examined four languages (English, Chinese, Japanese, and Korean) papers that reported anti-doping scientists' *UGT2B17* research from January 1, 2001 to December 31, 2016. I used news meta-search engines to identify these articles: Google News (UK and US news articles), Baidu News (Chinese news articles), Yahoo Japan News (Japanese news articles), and Naver News (Korean news articles).

This article consists of three sections. In the first section, I introduce the current status of genomic research in relation to doping regulations. In the next section, I describe two "geneticization" cases with respect to genomic knowledge of *UGT2B17* and testosterone metabolism. Then, in the discussion section, I propose that the social impact of anti-doping science should be seriously considered in ELSI programs in human enhancement and genomics. Finally, through engaging with recent ELSI studies on genomics and race, I investigate the ways in which ELSI scholars may begin meaningful analysis of anti-doping science.

HISTORICAL BACKGROUND: DOPING REGULATION AND GENOMIC RESEARCH

Ever since the International Olympic Committee (IOC) established its Medical Commission in 1967 and installed the Subcommision on Biochemistry and Doping in Sport in 1980, the field of scientific research for doping regulation has grown rapidly. One of the most important charges for doping regulation was to develop biochemical tests to detect AAS. As early as 1971, the IOC president Avery Brundage had asked the IOC Medical Commission for a method of detecting AAS (Dimeo, 2007, p. 112). Pioneering anti-doping scientists, like British pharmacologist Dr. Arnold Beckett at the University of London and German biochemist Dr. Manfred Donike at the German Sport University Cologne, sought to find an AAS screening method under the sponsorship of the IOC during the 1970s. The outcome of their biochemical and pharmacological research on AAS was the invention of a basic testing method: the testosterone/epitestosterone (T/E) ratio test. A major rationale of this test was that administrating exogenous testosterone does not affect the concentration of urinary epitestosterone glucuronide; if the ratio of testosterone glucuronide to epitestosterone glucuronide in urine is high, it should indicate the injection of exogenous testosterone. In 1982, the IOC introduced the T/E ratio test to deter AAS doping and set a T/E ratio in excess of 6.0:1 as a criterion for evidence of the injection of exogenous testosterone (Krieger, 2016).

Discovering detection methods of AAS continued into the 2000s. This effort to develop detection methods was partially due to the limitation of the T/E ratio test, given that test results were sometimes inconclusive. For example, doped athletes could avoid detection by taking low-dose AAS or suspending the use of AAS before the test. WADA, the new international anti-doping foundation established in 1999, tightened the doping test by adopting use of isotopic ratio mass spectrometry for AAS detection, in which an urinary T/E ratio of greater than or equal

to 4.0 was considered indicative of doping; however, this new rule did not fully resolve the problem (Saudan et al., 2006).

Anti-doping scientists began to start genomic research on doping in sports by raising concerns about the limitations of the T/E ratio test. Since most anti-doping scientists were mainly experts in the fields of biochemistry, clinical chemistry, and pharmacology, their genomic research was naturally related to pharmacogenomics. They conducted pharmacogenomic studies of AAS that sought to understand AAS metabolism in the body with respect to environmental and genetic influences, and to find alternative detection methods.

In 2001, for instance, Drs. Anders Rane and Mats Garle at the Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute began a research project titled "Human Androgen Metabolism, Kinetics and Excretion: Genetic and Ethnic Determinants of Variation," under financial support from WADA. In their research proposal, they proposed that the T/E ratio test "is probably affected by inter-individual and ethnic genetic differences and variation" and planned to identify polymorphisms in androgen metabolizing enzyme genes (Rane and Garle, 2001). Over the course of a decade, their group discovered that polymorphisms in several enzyme genes, like *UGT2B17*, cytochromes P17 (*CYP17*), and phosphodiesterase 7B (*PDE7B*), substantially influence the results of the T/E ratio test (Rane and Ekström, 2012). They contended personalized surveillance strategies in doping tests were needed to account for genetics-related individual differences in the T/E ratio test; for example, longitudinal monitoring of the T/E ratio of individual athletes would provide better results than a single T/E ratio test for all participants (Rane and Garle, 2001). Their proposal on individual surveillance strategies in doping tests supported WADA's new anti-doping programs such as the Athlete Biological Passport program (ABP), which collects a longitudinal record of biological markers in individual athletes and detects doping violations when the recent biomarker results show large changes from the previous records.

In sum, the beginning of anti-doping genomic research was simultaneous to changes in AAS doping management practices. Given the limitations of the traditional T/E ratio test, anti-doping authorities and scientists began to seek alternative ways of regulating athletes. They developed more personalized surveillance on the biological status of each athlete; pharmacogenomic research highlighting genetic variability in testosterone metabolism contributed to introducing AAS to doping detection practices. No one regarded the social implications of genomic research with respect to doping in sport. Yet as we will see, the outcome of their research would deeply influence the way athletes thought about their profession.

GENETICIZING CULTURES AND BIOLOGICAL DETERMINISM

Twenty-five years ago, sociologist Dr. Abby Lippman coined the term "geneticization," defining it as "an ongoing process by which differences between individuals are reduced to their DNA codes, with most disorders, behaviors and physiological variations defined, at least in part, as genetic in origin" (Lippman, 1991, p. 19). Lippman's idea is quite old but remains useful in describing how the scientific results of genomic research with respect to doping in sports, with its media representations, reify cultural differences as genetic differences. Though genomic scientists reject the conception of a gene as a blueprint, the ways that anti-doping scientists have adopted of speaking on the scientific results of genomic research have contributed to the development of genetic determinism on cultural activities related to sports. Media reports on their research, in turn, strengthen the gene-deterministic picture on cultural activities.

In this section, I describe how anti-doping scientists and media representations on their research reify ethnicity and diet as genetic beings, through the lens of geneticization. This rough sketch will provide the basis for further discussions on the social impacts of anti-doping science.

The Geneticization of Ethnicity

As I showed in the previous section, anti-doping scientists have conducted pharmacogenomic research on the metabolism of AAS since the early 2000s. In particular, they have been interested in the effect of genetic variations in the metabolism of AAS in the body and the resulting T/E ratio test. By so doing, they wanted to show the existence of intra-individual differences in the T/E ratio and to problematize traditional doping test methods. For example, the Karolinska research group found that a deletion polymorphism in *UGT2B17* prevents encoding of the UGT enzyme to catalyze the glucuronidation of testosterone. They reported that research subjects who have this deletion polymorphism (del/del) in *UGT2B17* only excreted a small amount of testosterone glucuronide in their urine and had a T/E ratio test that was lower than threshold, despite an injection of AAS (Schulze et al., 2008). In addition, they discovered that the T > C polymorphism of the *CYP17* gene is related to urinary glucuronide levels of epitestosterone and ultimately affects the results of the T/E ratio test. Lastly, a genome-wide association study found that research subjects who were homozygotes of the G-allele in the *PDE7B* gene and who were injected with AAS had a lower T/E ratio than others who had an A-allele in *PDE7B* gene (Ekström et al., 2011).

UGT2B17 is a fascinating genetic marker precisely because of AAS regulation research. It has been an important research topic for many anti-doping scientists around the world, including researchers at the Swiss Laboratory for Doping Analyses (hereafter, SLDA). Dr. Pierre-Edouard Sottas, the director of SLDA, designed experiments on the effect of *UGT2B17* that were similar to the Karolinska group's experiments, whereby soccer players were screened for binary polymorphisms of *UGT2B17* (Strahm et al., 2009). The SLDA and Karolinska groups were convinced that they had discovered scientific grounds to problematize the traditional T/E ratio test and introduce a new doping practice—ABP. Indeed, Sottas pointed to the outcome of the *UGT2B17* study as scientific proof of the limitation of the T/E ratio test and later took the position of ABP Manager at WADA.

The study of *UGT2B17* contributed to the introduction of new regulation programs like ABP into doping detection practices. The problem, however, is that anti-doping scientists designed

their experiments to employ the category of "ethnicity" as a variable used to identify genetic differences among research subjects. In 1999, the United States Institute of Medicine recommended that the nation's National Institutes of Health focus on "ethnic groups" rather than "racial groups" in their cancer surveillance program. In this recommendation, the Institute of Medicine defined racial groups as groups related by biological commonalities and ethnic groups as groups related by cultural and behavioral commonalities (Oppenheimer, 2001). According to this definition, anti-doping scientists should have classified their research subjects into several cultural or social groups who did not *necessarily* have biological commonality. In fact, human geneticists have employed the category of ethnicity when labeling populations in terms of similarities and differences in common cultures (Panofsky and Bliss, 2017, p. 64).

In research designations, however, anti-doping scientists instead revitalized racial classifications that connote biological ties among people by employing the category of ethnicity. For example, Schulze et al. (2008) categorized their research subjects—Swedes and Koreans—into Caucasians and Asians. Furthermore, the Karolinska group was convinced that the deletion polymorphism of *UGT2B17* is "common in East Asians but relatively rare in Caucasians" (Schulze et al., 2009, p. 368). The SLDA group also adopted "ethnic origin" as a variable used to identify the metabolic effects of the *UGT2B17* genotype among research subjects: they reported that the distribution of the *UGT2B17* deletion polymorphism and T/E ratio threshold varied among "African, Caucasian, Asian, and Hispanic" participants and contended that Asians' genetic characteristics allowed them to pass the T/E ratio test by lowering their T/E ratio threshold to below 4:1 (Strahm et al., 2009). Based on these studies, Karolinska and SLDA researchers have concluded that "ethnicity," as "an endogenous factor," plays a significant role in "connection to androgen metabolism" in the evaluation of an individual steroid profiling (Schulze et al., 2009; Rane and Ekström, 2012; Kuuranne et al., 2014). In consequence, they made ethnicity not a cultural status, but a genetic one. According to their works, ethnicity determines athletes' androgen metabolism and thus allows specific ethnic groups to avoid the T/E ratio test genetically.

The media reports worsened this misuse of group categories, by which they misrepresented the outcome of *UGT2B17* studies as being implied to racist statements. *Reuters* reported that "steroid doping tests currently used ... ignore vital ethnic differences in hormone activity." The rapporteur stated, "individuals with a deletion of certain genetic "letters" on this [*UGT2B17*] gene —notably Asian men— excrete less testosterone in their urine" (Hirschler, 2009). Sports writer David Epstein wrote that genetic variations of *UGT2B17* benefit some athletes "to dope with impunity" in *The Sports Gene*. Epstein stated, "Two-thirds of Koreans have the genes that confer immunity to T/E ratio testing," whereas only "about 10% of people with European ancestry have" (Epstein, 2013, p. 148). Nick Harris, sports news writer of *Mail on Sunday* criticized Asian athletes who are "born to cheat." Harris exaggerated the implication of *UGT2B17* studies by saying that "a landmark Swedish study [of the Karolinska group] found that 'doping with impunity' gene variant [—the *UGT2B17* deletion polymorphism—] occurs in 66.7% of Asian populations and almost 10% of Caucasians" (Harris, 2013). Harris defined Asian athletes as those who "have a license to dope" and contended, "certainly official WADA statistics show that certain major accredited labs in some Asian countries are returning many fewer negatives than counterparts elsewhere" (Harris, 2013). By so doing, Harris suggested that readers consider Asians to be innately dishonest.

The way in which anti-doping scientists conflated "ethnicity" with "race" in their genomic research allowed the media to make racist arguments about sports doping. Byrd and Hughey (2015) claim that genetic determinism—race is genetically inherited—is one of the ideological double helix that shapes beliefs about racial inequality. This case demonstrates their argument well. A cultural category (ethnicity) became a biological category (race) in anti-doping research on *UGT2B17*; ethnic groups became understood as ones who shared a genetic inheritance; finally, this categorical change was utilized to make racist arguments in the popular media.

The Possible Future of Epigeneticizing Diet

Although the case of ethnicity in *UGT2B17* studies and its media reports appears to be a typical example of geneticization and genetic determinism, the case of dietary habits and doping that I will examine in this subsection seems to be an atypical example, because of its epigenetic characteristics. In fact, epigenetic research has been considered a main opponent of genetic determinism. Recent sociologists of science, however, suggest that the epigenetic framework can be compatible with genetically deterministic views and some epigenetic explanations in both scientific practices and popular journals are narrated as deterministic (Waggoner and Uller, 2015). A similar trend is found in genomic research on doping and nutrition. This new current of anti-doping research aims to find the epigenetic influence of dietary habits in doping practices. By focusing on the role of environment in changing genetic regulatory mechanisms, the genomic research on doping and nutrition seems to steer anti-doping authorities and athletes away from the tendency to view genetic traits as deterministic of doping outcomes. This subsection will show how these new trends of research and their media representations may instead strengthen genetically deterministic views on doping and nutrition, rather than liberating people from genetic determinism.

In 2012, Declan P. Naughton and colleagues at the UK's Kingston University reported that dietary green tea may lower the T/E ratio by suppressing testosterone glucuronidation. Under the sponsorship of WADA, they discovered that the catechin compounds included in green tea inhibit the enzyme UGT2B17 and thus may affect the relative ratio of testosterone glucuronide in urine (Jenkinson et al., 2012). This endocrinal effect of catechins on the human body was very inconclusive because it was merely an *in vitro* study.

The outcome of this study immediately invoked a strong reaction from anti-doping officials and scientists, however. At

the beginning of the 2012 London Olympics, WADA officials, such as the scientific director Olivier Rabin, interpreted the result as a sign to introduce ABP into doping regulation practice in lieu of the traditional T/E ratio test. Also, a well-known anti-doping scientist, Charles Yesalis at Pennsylvania State University, expressed a deep concern that, "there are already lots of athletes out there drinking loads of green tea" to avoid doping detection (Cheng, 2012). Further, anti-doping scientists who took part in ABP programs quickly picked up dietary green teas as "exogenous factors," influencing steroid profiling in relation to AAS detection (Kuuranne et al., 2014).

As with the case of the role of ethnic differences of the *UGT2B17* genetic polymorphism and its impact on doping tests, the mass media hyped and misrepresented the biological effect of drinking green teas on AAS screening. *The Guardian* ran a news report titled, "Green tea could hide testosterone." *Daily Mail* also delivered this news using the title, "Green tea could help cheats;" *USA Today* had a similar title, "Green tea could cloud Olympic doping tests" (Associated Press, 2012; Cheng, 2012; Sportsmail Reporter, 2012). These sensationalist news title lines underplayed the point that Jenkinson et al. (2012) was just a preliminary *in vitro* study.

In fact, anti-doping studies that showed a remarkably different results from Jenkinson et al. (2012)'s study were completely ignored by WADA and the mass media. In 2013, the Karolinska group reported that the *in vivo* testing on non-steroidal anti-inflammatory drugs in 23 healthy males showed those drugs had no influence on the T/E ratio in urine. Based on this result, they argued that speculation on the inhibitory effect of drinks like green tea that were only based on *in vitro* studies should be seriously reconsidered (Lundmark et al., 2013, p. 6). Neither news reports nor WADA announcements accompanied this negative finding of dietary effects of green tea on real doping practice.

Meanwhile, the epigenetic effects of green tea catechins have simultaneously been investigated in relation to the rise of nutritional epigenetics among anti-doping scientists since that time. Nutritional epigenetics hypothesizes that food is a key environmental factor in altering the genetic regulatory mechanism of the human body (Landecker, 2011). Green tea intake is hypothesized to help prevent several tumors; epigallocatechin gallate, a type of catechin, is thought to block methylation of tumor-promoting genes (Yiannakopoulou, 2015). Though most studies on the epigenetic influence on nutrition have focused on carcinogenesis, in recent years anti-doping scientists have begun to focus their attention to the role of nutrition—including catechin components—on DNA methylation and its implications on doping practice (Schwarzenbach, 2011). In this context, the concept of epigenetic doping testing is proposed to identify behavioral and environmental factors that influence both epigenetic profiling and doping test outcomes (Diel et al., 2015; Andrèn-Sandberg, 2016, p. 4379). Under this new scientific vision on doping and nutrition, dietary activities—like drinking green tea—become an epigenetic action that influences the genetic regulatory mechanism of the human body.

Meloni and Testa (2014) anticipate that the epigenetic vision of life will reorder social norms as well as living phenomena. According to them, epigenetic findings will blur the distinction between natural and social inequalities through revealing the fact that societal factors such as class inequalities can modify biological endowments. With blurring boundaries between natural and social inequalities between human populations, the epigenetic vision will move to redefine cultural and social subpopulations as biological groups that can be identified with epigenetic markers. Furthermore, this epigenetic reordering of social populations will require new social norms for these populations. A specific subpopulation is expected to have an advantageous or disadvantageous genetic regulatory mechanism due to an epigenetic effect on their social and cultural activities; they might be restricted in their activities by social policy and discourse. For example, the US government's fish consumption regulations based on studies on epigenetic effect of methylmercury exposure much more focus on controlling the dietary habits of Native Americans (Mansfield, 2012).

This possibility of epigeneticizing cultural and social groupings and making new social norms through epigenetic facts have already been seen in the case of drinking green tea and doping practices. Indeed, different consumption patterns of dietary green teas among different social groups affect the lives of individuals along cultural lines; some individuals who maintain drinking teas as a part of their lifestyle begin to worry about the *biological* implications of their *cultural* activity. Although the biological effect of green tea is not limited to specific cultural groups, the social and political context of sports doping forces particular ethnic groups to be more anxious about its biological implications than other ethnic groups.

For several years, a strong concern about tea drinking customs has been raised in the sports communities of East Asian countries such as China, Japan, and South Korea. Green teas are daily necessities in these countries; drinking tea, which is sometimes called a tea ceremony (*chayi* in Chinese, *chado* in Japanese, and *dado* in Korean), is one of the most distinctive East Asian cultural customs. Yet, due to criticism of green tea drinking as a potential crime because it can mask illegal uses of AAS, athletes and coaches in East Asian countries have suppressed their own cultural customs. In fact, a UK news media outlet implicitly connected Chinese athletes with drinking green tea when reporting the news of tea intake as a way to hide doping: "Chinese Gold medal winners at the Beijing games were given this [green] tea as a special present to recognize their achievements at the Beijing Olympics. But Olympic doping officials are now faced with the conundrum that this green tea may be used as a way of masking elevated levels of testosterone" (AP Television, 2012).

While English-written news reports did not consider about the possibility of incautious misuse of green tea in order to avoid doping detection among athletes in their own nations, East Asian newspapers dealt with the possibility very seriously. The Chinese news journal *Fenghuang Web* delivered the news by saying, "*Qing Ming Jie*, which falls on April 4–6, is the time to deliver new tea products into the [Chinese] market; yet who could imagine that neat, elegant green teas have been

an umbrella for hiding AAS?" (Chen, 2012a). Other Chinese journalists also wrote: "Experts say that green tea works as an umbrella to hide doping and that [2012] London Olympic medalists shall be reexamined," "athletes hope to drink green tea to hide their doping," or "green tea became the subject for anti-doping monitoring because a scientific study discovered that this tea contains banned substances" (Chen M., 2012; Chen, 2012a,b). In Japan and South Korea, news writers reported this news in a tone similar to that of their Chinese colleagues. Their news reports made East Asian athletes very anxious. Chinese sports athletes were curious about whether green tea is a doping substance or not. In the Online Q&A Forum of the Korean Anti-doping Agency, one can easily find Korean athletes who continuously ask about whether drinking green tea and functional products containing green tea is considered a doping activity or not (Korean Anti-Doping Agency [KADA], 2016). In Japan, a Japanese drinking company Kirin's new tea "*Harecha*," which contained green teas and geranium, provoked controversy among Japanese athletes who suspected that this new product contained banned substances (Netorabo, 2015).

With the rise of epigenetic doping testing and the growing interest in epigenetic studies on doping and nutrition among anti-doping scientists, one can anticipate that more and more athletes will develop an epigenetic determinism of doping and nutrition—a belief that a specific diet pattern alters genetic regulatory mechanisms to help hide doped experiences. It is plausible that a popular racist discourse connoting epigenetic determinism might appear, due to epigenetic findings on doping and nutrition and due to the media's misrepresentation on these findings.

Millard Baker, who is the founder of MESO-Rx.com, one of the largest AAS information websites, provides an example of how racist arguments can appear in relation to anti-doping genomic research. In a web article titled, "Green Tea Helps Steroid-Using Athletes Beat Anti-doping Test," Baker contended that, in 2008, he realized that "genetically gifted" athletes, mostly "Asians," have a doping advantage through the genetic effect of the *UGT2B17* deletion polymorphism. He wrote that "an athlete's ethnicity may give them a doping advantage," citing statistics on the percentage of *UGT2B17* deletion polymorphism among different human groups like "66.7% East Asian," "29.1% Black," "3.5% White Caucasian." His diction of "genetically gifted" is not value-neutral, because it implied that Asians have "genetically unfair traits." Since then, he had suspected the existence of a pharmaceutical drug blocking the UGT2B17 enzyme. Discovery of green tea's endocrinal effect on the UGT2B17 enzyme in 2012 convinced him that drinking green tea as a method to avoid detection was "common knowledge in some elite athletes" (Baker, 2012).

Although Baker did not explicitly define who "some elite athletes" are, one can easily suppose that he tried to connect drinking green tea as a method for hiding doping with *genetically gifted Asian* athletes, through use of *UGT2B17* as a connector. The rise of epigenetic determinism due to anti-doping research is still in the future, yet it is genuinely possible.

DISCUSSION: ANALYZING THE SOCIAL IMPACTS OF ANTI-DOPING SCIENCE

Sports doping has received extensive academic attention in the ethical literature on human enhancement (Tolleneer et al., 2012). The use of biomedical interventions to improve the physical performance of athletes in sports has served a paradigm case to ethical discussions on unnaturalness and unfairness in human enhancement.[1] In this context, bioethicists and sport sociologists struggle with whether doping is unfair and unnatural or not, and try to create a role for new genetics in doping by only focusing on the unnaturalness of an unfulfilled enhancement technology—gene doping (Miah, 2004; Murray, 2012). For them, anti-doping science is a timid, minor subject. Furthermore, bioethicists who think performance enhancements are unnatural as well as unfair contend that anti-doping science should be pursued (Murray, 2012). On the contrary, critical sport sociologists who suspect that ethical values such as fairness and naturalness are social constructs believe that anti-doping science is just a scientific instrument to control and monitor the behaviors of sport athletes around the world (Park, 2005). Both sides do not consider anti-doping science a part of the social, ethical discussion in relation to human enhancement.

However, ELSI scholars in sport enhancements and genomics needs to pay attention to the rapid growth of regulatory research against sports enhancement over two decades, particularly in terms of genomics. Anti-doping scientists preemptively developed regulatory knowledge and technologies for expected doping technologies. Under WADA's official systematic support, genomic research for regulation developed prior to the advent of a new gene doping. What's more, anti-doping science has considerable power to change popular beliefs on the human body, sports, and nutrition through global sports contests such as the Olympic Games and FIFA World Cup. The scientific results of anti-doping science are more widely shared among the public—particularly athletes and coaches—than other academic sciences because of its global influence through international and national sports games.

In this paper, I described the social impact of anti-doping science in relation to its recent genomic research on AAS. Two cases of geneticization—ethnicity and dietary habits—show anti-doping science's influential power on society, particularly in relation to thoughts concerning human enhancement. It indicates that ELSI scholars need to include this science in their analysis if they want to thoroughly investigate which ethical and societal problems will be raised with respect to the topic of sports enhancements and genomic science.

In this section, I analyze the social and ethical problems of anti-doping science in further detail. To do this, I engage with the ELSI literature regarding genomics and race. This detailed analysis provides insight into how the social impact of anti-doping science can be investigated as a part of ELSI research.

The ELSI scholarship exploring the topic of genomics and race shows that research practices and media representations

[1]For an extensive review of the ethical problems of human enhancement, see Allhoff et al. (2011).

cause biological reification of race and the rise of genetic determinism. First, in relation to research practices in genomics, ELSI scholars illuminate that how biomedical research has been racialized in terms of genomics, such that race has both been reconceived in genomic terms and has appeared as a biological essence (Fujimura et al., 2008). Particularly, their empirical studies reveal that labeling the activities of human populations and differences in genomic research plays a crucial role in making race a biological essence in terms of genomics (Fullwiley, 2007; Montoya, 2007; Fujimura and Rajagopalan, 2011; Panofsky and Bliss, 2017). Even though some genomic scientists consciously avoid the use of racial categories and adopt alternative concepts such as geographic or genetic ancestry, they rely on racial concepts when clustering genomic databases (Bolnick, 2008; Fujimura and Rajagopalan, 2011). In many cases, labeling activities in genomic research is strongly influenced by genomic scientists' local understanding of groupings among human populations. As a result, local social categories of human groups—particularly racial categories in the U.S.—are reified as biological essences in the process of labeling practices in genomic research (Gannett, 2014). This biological reification of race in genomic research contributes to the rise of genetic determinism (Gannett, 2004).

Second, ELSI scholars reveal how media representations of genomic research on race strengthen genetic determinism (Nelkin and Lindee, 1995; Phelan et al., 2013). They show that news articles "distort" explanations about scientific outcomes in original press releases and play a vital role in "science hype" in relation to genomic research (Brechman et al., 2011; Caulfield and Condit, 2012). This problem of science communication and misrepresentation in the media is closely linked to journalistic norms (Nelkin, 1996). In contrast to scientists, journalists write for diverse readers that vary in their interest and knowledge levels. As a result, journalists often must simplify the implications of scientific outcomes. For instance, journalists will report that scientists discovered "a fat gene" instead of "a meaningful marker that may predispose an individual to obesity" (Nelkin, 1996, p. 1602). The media's oversimplification of scientific results misrepresents modest genomic research on different human groups as a racial study implying genetic determinism and racist arguments (Phelan et al., 2013).

The problem of labeling practices in scientific research practice and the simplification of research results in media representations are similarly identified with the case of the geneticization of ethnicity and dietary habits in anti-doping genomic research. Indeed, in the case of ethnicity in *UGT2B17* research, the misuse of ethnicity can be understood in light of the problem of labeling practices. And in both cases (i.e., ethnicity and dietary habits) relating to *UGT2B17* studies and their media reports, simplification of scientific research created genetically deterministic and racist explanations on the association between sports doping and cultural identities and habits.

Meanwhile, one can identify different factors influencing the biological reification of race in anti-doping genomic research and other genomic sciences. Those differences are mainly due to the distinctive characteristics of anti-doping science. Anti-doping genomic research is clearly separated from academic genomic sciences in two ways: its regulatory and political aspects (**Table 1**). First, anti-doping science is a regulatory science that seeks to improve the regulation of doping in sports, rather than expand general knowledge of the natural world. As science scholar Sheila Jasanoff highlights, regulatory scientists are more focused on improving regulation methods than creating scientifically rigorous research outcomes (Jasanoff, 1990). This regulatory-oriented research approach allows anti-doping researchers to ignore research protocols and guidelines that scientists in academic-oriented disciplines have developed.

Second, anti-doping science is directly influenced by anti-doping politics. Due to its regulatory nature, anti-doping science already takes a specific stance in anti-doping politics. Anti-doping scientists conduct their research with support from WADA's anti-doping policy and share the political position as WADA: sports doping and doping-related works and traits are inherently unfair and should be eradicated (Kayser et al., 2007). This political involvement with WADA's anti-doping policy influences the view of anti-doping scientists with respect to the useful aspects and implications of their research. The news media also share this political view of the unfairness of sports doping. This unfairness-focused concern of anti-doping research and its media representations often leads anti-doping scientists and the mass media to fail to recognize that they sometimes deliver ethically unjustified statements on specific groups.

Those two characteristics of anti-doping science are closely related to the influential power of athlete communities worldwide. Indeed, anti-doping scientists play a crucial role in exerting doping control over athletes. Their research outcomes are directly applied in regulatory practices in near-future international sports. For this reason, elite athletes and their coaches are strongly responsive to new information regarding state-of-the-art anti-doping research and are easily harmed by news reports on anti-doping studies, regardless of the correctness of media representations. In this respect, though its public is quite limited to athlete communities, anti-doping research and its media reports have a much greater impact on the public than other general academic sciences.

We can use this understanding of anti-doping science to examine the process of geneticization of ethnicity and dietary habits. First, the regulatory nature of anti-doping science makes labeling practices in anti-doping genomic research more problematic. Anti-doping scientists only concentrate on research outcomes that improve doping regulations, and are not concerned about the connotations of their scientific research. For example, they conflated "ethnicity" with "race" without serious consideration to the debate of grouping categories in human

TABLE 1 | Two characteristics of anti-doping science.

Anti-doping science	
Regulatory nature	**Political nature**
Regulatory science	Anti-doping policy
Regulatory-oriented	Unfairness-focused
Doping control of athletes	

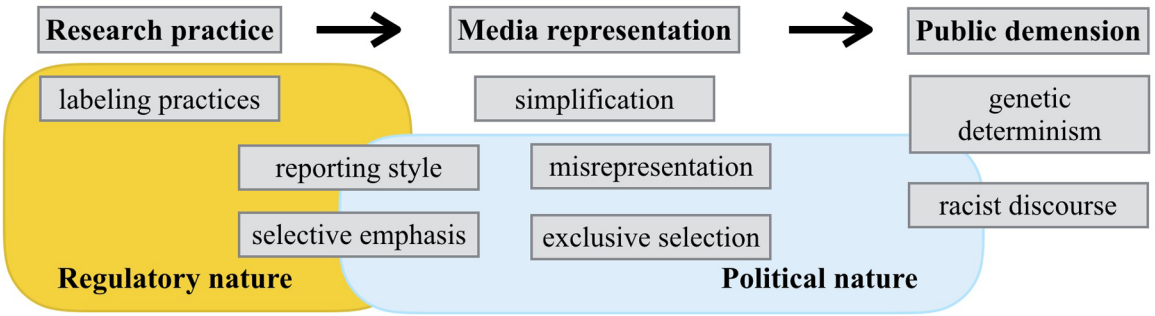

FIGURE 1 | The process of geneticization in anti-doping science.

genomics research. Indeed, "ethnicity" has been a proposed alternative for replacing the term "race" in genomic research, yet anti-doping scientists did not consider this effort that had been occurring in the field of academic genomic sciences (Sankar and Cho, 2002). Panofsky and Bliss (2017) have shown that grouping categories within the human population remain unstandardized and ambiguous, yet most academic genomic scientists recognize the problem of using racial categories and thus try to avoid racial connotations. Anti-doping researchers failed to recognize the research protocols and guidelines developed by the academic genomics communities, and thus labeled their research populations using racial classifications.

Second, the political nature of anti-doping science, with its regulatory nature, influences anti-doping scientists' reporting style and selective emphasis on research outcomes. In contrast to general academic sciences like genomic cancer research, a biased explanation on the research outcome is produced from the very early stages of the press release (Brechman et al., 2011). Using the moral judgment that sports doping is unfair and harmful, anti-doping scientists report the unfair aspects of some genetic variations and metabolic mechanisms in their research outcome. Harm reduction and protecting athlete health are two important rationales in anti-doping policies, yet those aspects are ignored when anti-doping scientists report their research outcomes (Kayser et al., 2007). Also, this regulatory nature strengthens this selective emphasis tendency when reporting their research outcomes. For anti-doping scientists, regulatory priority is emphasized to a greater degree than the sufficient accumulation of scientific evidence. For this reason, results that help the regulatory regime are selectively emphasized and the scientific contestation of their research outcome is often ignored. As I showed, WADA and anti-doping scientists focused on the misuse of green tea to avoid doping regulation, even though the supportive research was merely an *in vitro* study. In contrast, the negative *in vivo* study on the misuse of green tea was ignored by WADA officials and the wider anti-doping scientist community.

Third, in the mass media, socially problematic arguments are easily justified because of the political nature of anti-doping science. News media reports often use the moral judgment that sports doping is unfair and harmful when framing their articles, and thus reports anti-doping research outcomes by referencing possible "doping allegations" and future "scandals." In order to prevent or criticize possible unfair situations in sports games, news reporters are allowed to make socially problematic arguments like Asian athletes are "genetically born to cheat" and have "a gene for doping with impunity." By adopting this moral judgment on sports doping, news journalists do not adhere to the "objectivity" norm in journalism, that is, reporting and balancing conflict claims (Nelkin, 1996). This paper, for example, identified zero news articles that reported on the contradictory *in vivo* study questioning the ability of green tea misuse to avoid doping detection.

Most importantly, contrary to academic genomic sciences, anti-doping research and its media reports have a powerful impact on a specific lay group—athlete communities. As ELSI scholars of genomics and race reveal, most of the lay public is less influenced by the media coverage on genomics and race than some of critical racial scholars claimed. The lay public does not believe the media's misrepresentation on academic genomic research and actively assesses the content of news articles using their complex view on race (Condit et al., 2004). In other words, the media representation of results in academic genomic sciences has a relatively limited influence to the public dimension. On the contrary, anti-doping research and its media representations immediately affect the lives of athletes. Regardless of the scientific concreteness of the claims, athletes and coaches worldwide can be enforced to change their cultural customs, like drinking green tea. Given their subordinate relationship within WADA's anti-doping control system, athletes and coaches easily accept and internalize the genetic determinism and racist discourse generated by the media representations.

In sum, the process of geneticization in relation to anti-doping science shows both similarities and differences with cases of academic genomic sciences that ELSI scholars in genomics and race have studied (**Figure 1**). Cases of anti-doping genomic research share similar problems with other genomic studies regarding labeling practices in research practice and outcomes simplification in media representation. At the same time, due to the regulatory and political natures of anti-doping science, anti-doping genomic research and its media reports more easily facilitate genetic determinism and racist discourse in the public dimension. By understanding such distinctive characteristics of

anti-doping science, ELSI scholars can begin to apply a more critical analysis on the social impact of this science in the context of genomics and human enhancement.

CONCLUSION

In this article, I tried to show the social impact of the genomic knowledge that anti-doping scientists have produced and that the news media has propagated. I pointed out the geneticization of cultural objects such as ethnic identities and dietary habits by anti-doping science, and proposed the need for increased attention to this science by ELSI scholars who explore human enhancement and genomic science. Furthermore, I engage with the ELSI scholarship on genomics and race to suggest that an understanding of the regulatory and political natures of anti-doping science is a possible starting point for including anti-doping science in ELSI programs in human enhancement and genomics.

The ethical debates on the implications of gene doping and other potential doping technologies remain important. At the same time, however, one should recognize the fact that the realization of doping technologies is still in the future whereas the social impact of anti-doping science is in the present. For this reason, ELSI scholars should include this regulatory science in their analysis if they want to thoroughly investigate which ethical and societal problems are raised with respect to the topic of sports enhancements and genomic science.

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The author confirms being the sole contributor of this work and approved it for publication.

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Moral Bioenhancement for Social Welfare: Are Civic Institutions Ready?

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Positive assessments of moral enhancement too often isolate intuitive notions about its benefits apart from the relevance of surrounding society or civic institutions. If moral bioenhancement should benefit both oneself and others, it cannot be conducted apart from the enhancement of local social conditions, or the preparedness of civic institutions. Neither of those considerations has been adequately incorporated into typical neuroethical assessments of ambitious plans for moral bioenhancement. Enhancing a person to be far less aggressive and violent than an average person, what we label as "civil enhancement," seems to be quite moral, yet its real-world social consequences are hardly predictable. A hypothetical case about how the criminal justice system would treat an offender who already received civil enhancement serves to illustrate how civic institutions are unprepared for moral enhancement.

Keywords: morality, enhancement, neuroscience, genetics, neuroethics, genethics

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Speculations about if and how modifications of genotype and/or phenotype could help someone be more moral have stimulated philosophical, scientific, sociological, and political discussion and debate. Studies of putative neurological structures and functions involved in moral cognition and behavior have become part of the field known as neuroethics (Glannon, 2017). Importantly, the discipline also addresses the questions and problematic issues arising from the broader implications to neuroscientific research and potential neurotechnological applications. But, if moral bioenhancement should benefit both oneself and others, then, we argue that it cannot be conducted apart from the enhancement of local social conditions, or the preparedness of civic institutions. Often, such considerations have not been adequately incorporated within typical neuroethical assessments of ambitious plans for moral bioenhancement.

People lacking in morality might look like a problem needing a technological solution. Some neuroethical assessments of moral enhancement hardly get beyond saying, "It's moral, so it has to be good for you and everyone too," as if adjusting a person's moral capacity always bears intrinsic worth. Other kinds of cognitive enhancement have been treated in a similarly simplistic manner [an overview of perspectives on cognitive enhancement is Jotterand and Dubljević (2016)]. Cognitive enhancement is unrealizable without due regard for the real-world contexts in which Cognitive abilities contribute to measurable performance improvements (Shook and Giordano, 2016a).

Three different ideas about moral improvement compete for attention in people's minds when they hear about "moral enhancement." The first idea is to instill some degree of moral capacity and responsibility in someone who has never had it, which is better labeled as "moral habilitation." (And restoring lost moral capacity would hence be "moral rehabilitation.") The second idea occurs if enhancement is taken to mean an improvement of already-existing moral capacity toward

society's standards of good moral conduct. This idea of enhancement as "moral normalization" is probably what first comes to mind and initially earns approval because that goal is already the aim of morality itself: each person behaves in accord with moral standards that everyone is expected to follow. Finally, the third idea of enhancement is improvement above regular requirements of common morality, which might be called "surpassing enhancement." This third idea has received the most attention in academic discussions, yet, it is more difficult to analyze and less straightforward to justify (Shook and Giordano, 2016b,c). Only surpassing enhancement is the topic of this discussion.

Another distinction is also crucial. The label of "moral bioenhancement" applies to technological interventions employed for directly controlling some aspect of human neurocognitive functioning that is viewed as instrumental to moral thought and/or behavior. Such technologies are new; controlling human behaviors is not. Although specialized social means, such as education and law, can be improved by technology, they are not essentially invasive or reconstructive (unless they resort to such things as bioenhancement). Only impactful events in the local environs of a person (e.g., hearing a narrative, suffering a punishment, receiving a reward, and so on) are involved with mundane means of socialization, correction, and so forth. Any lasting change to one's behaviors and habits is accompanied by some redistribution or reorganization of neurological activity. The distinction between "bioenhancement" and "enviroenhancement" is instead based on the nature of the method. Technology also permits a third category, "selection-enhancement," when an embryo or fetus is chosen for birth because it meets preset genetic or developmental criteria. We shall not consider selection-enhancement here.

We must disagree with those who insist on a sharp dichotomy to firmly separate efforts at moral bioenhancement apart from efforts at moral enviroenhancement [e.g., Sparrow (2017)]. There is a deep connection between utilizing bioenhancement and enviroenhancement to foster morality, not as regards their role as distinctive means, but rather with the realization of their common end. That connection is revealed through a pragmatic assessment of the conditions needed for their moral effectiveness. Allowing that dichotomy to stand unchallenged would permit assessments of bioenhancement to proceed in an unrealistic manner and potentially arrive at rashly optimistic judgments.

In order to justify labeling an adjustment to human abilities as a "moral enhancement," a framework of prior judgments must be premised. First, it will be important to define what is meant by "morality." Clearly, this opens broad and deep discourse, if not debate. What emerges from such discourse is that society establishes what is considered (at any given time) to be "moral." Thus, moral cognitions and actions are internal processes that occur in, and reflect external contexts (MacIntyre, 1998, 1999; Giordano et al., 2016; Jotterand, 2016). Second, criteria must be applied for empirically confirming when a physiological/neurological intervention shifts personal conduct in a desired moral direction (Shook, 2016). Third, distinguishing episodic from enduring adjustments is necessary. An episodic adjustment made as situations arise is moral in a limited sense (e.g., "he did a morally good deed"), while an enduring adjustment, such as an non-reversible alteration of the brain or a genetically engineered modification, would be moral in a broader sense (e.g., "she is a more moral person"). Additionally, expectations should be established about what may constitute good outcomes for morally enhanced people as they function in a society in which most people are not morally altered. A further layer of envisioned prospects for morally enhanced people as they interact with important civic institutions, especially law enforcement and governing agencies, should also be evaluated. The final section of this paper offers a hypothetical example illustrating why the civic practicality to a moral enhancement cannot be taken for granted.

In what follows we shall only consider surpassing and enduring moral enhancements, which includes genetically engineered modifications for above-average moral conduct. Anything called a "moral enhancement" should at least deliver something that anyone could verify and want for themselves. What do people realistically expect from so much more morality? For example, is it more moral to be less selfish? If an alteration is supposed to keep one's overall selfishness at a lower level, for example, what specific course of conduct during a salary negotiation, or a dispute between parents, would count to prove its effectiveness? Hence, what percentage wage increase shall the less-selfish female employee accept from her male supervisor? How many household duties should the less-selfish parent take over from the other parent? Such practical scenarios should make readers feel uncertain and perhaps a bit uncomfortable. In the real world, each person wants *other* people to act less selfishly toward them, while acting as self-interested as one already happens to be. If morality involves some sacrifice, who shall be among the first?

There won't be a realistic way to simultaneously enhance millions or billions of people or to control all social interactions to guarantee universally fair results (that is why fanciful moral utopias are barely distinguishable from totalitarianisms.) A realistic framework allows (and accepts) that moral enhancers will not be uniform in either distribution or manifestation, given that: (a) the large majority of social interactions would involve at most one morally enhanced individual and (b) morally enhanced people would probably not see similar consequences of their engagements within social groups.

Unrealistic frameworks, by contrast, isolate one "obvious" moral virtue—altruism or empathy are frequently selected, for example—and then presume that such a good thing must always be good no matter the circumstances. By that framework, there's no conceivable harm simply from living a more altruistic life, since human nature is meant to be, and deserves to be, more kind and generous. Only the technological means of achieving that end, and not the moral end itself, needs to be scrutinized (DeGrazia, 2016). Although objections raised against these assumptions are rarely heard [but see Marshall (2014); Carter (2015); and Casal (2016)], we agree with their concerns that large-scale and long-term social dynamics should be empirically investigated rather than reflectively intuited.

It should be first noted that morality is not necessarily contrary to self-interest.[1] Most moral deeds can be beneficial to all parties, as the practices of cooperativeness, trustworthiness, civility, etc., are conducive to everyone's welfare. The question is not whether conducting oneself in accord with common moral standards is beneficial. When enhancement asks for above-average moral

behavior, we question how uncommon morality would fare in the real world of ordinary moral expectations.

If this issue is to be treated as an empirical matter, any intuitive generalization about above-average moral people is probably unsound. What could be reliably predicted from dramatically enhancing the morality of any randomly chosen person somewhere in the world today? It seems quite dubious that being more moral than average could ensure that one's status, income, relationships, or life prospects are affected in some predictable way, much less re-directed in the same way as other morally enhanced individuals. None of these framing presumptions, common to positive assessments of moral enhancement, can be trusted:

> The overall welfare of a person can be predictably increased by morally enhancing that person.
> Social affairs within a group can be reliably improved with the moral enhancement of even a few individuals.
> The overall welfare of a group can be predictably increased by a moral enhancement to a portion of its members.
> The improvement of social relations within group can be reliably accomplished by selecting a moral rule that an individual can follow, and enhancing many individuals into conformity with that rule.

These tenets are unreliable because the intuitive calculations behind them take morality to be isolable and individualizable. That permits speculation to imagine that morality's goodness must aggregate to improve society no matter what else may be happening. Concepts about morality in their abstract purity are poor guides when compared with the collective experiences of an entire society.

That said, which behavioral modifications already regarded as moral would actually be conducive to widely welcomed social benefits? Taking morality to be as social as the general welfare it is supposed to yield, and evaluating changes to people's morality in terms of empirically confirmable results for society, opens the entry to the field of *social ethics*. Connecting public morals to social welfare and civic improvement is an approach to social theory inherited from Cicero, Seneca, and Plutarch, and pursued by Western political thinkers, both liberal and conservative, from medieval times to the twentieth century. Eastern philosophy is also replete with this kind of moral and social theorizing. Even modern libertarians, opposed to government encroachment upon private liberties, argue that freer citizens are the kind of virtuous citizens who are essential to a good society. However, this is not without contention; one needs only to recall Mandeville's *Fable of the Bees* for poetic illustration of problems that can arise when attempting to mitigate "private vices for public benefit."[2]

But given that humans are social animals, the capacity to behave morally enables engagement with productive social relationships and institutions. It is, as philosopher Owen Flanagan has noted, an essential part of human ecology (Flanagan, 2007). Just as public morals are evidently tied to social welfare, it is difficult to deny the social nature of individual well-being:

> … a person's well-being is shaped by a complex net of intersecting social determinants, and the weighing of outcomes is at the population level rather than at the individual one (Cabrera, 2017).

The overall connection is becoming clear: the relationship between one's individual well-being and one's moral conduct with others is mediated by environing social conditions. How one's morality affects oneself, as well as others, depends on the social contexts making behavior meaningful, effective, and productive. For social ethics, improving individuals morally is foremost about the social contexts in which conduct occurs. Morality is not simply about what a person prefers to do; how a person *can* behave is largely dependent on environing obstacles or opportunities. This is as true of morality as it already is for any desirable improvement of personal conduct. Enhancing what people can do has little to do with them individually; empowerment requires social opportunity. This approach has been defended by Laura Cabrera:

> Under such a perspective, human enhancement focus shifts from changing the biological reality of individuals, to addressing environmental factors that undermine the optimal performance of individuals or that can foster wellness. Such a human enhancement perspective would be consistent with a population health approach, as it pursues more equitable and accessible interventions, on the path to addressing social inequality. Human enhancement does not need to be only about high-technological interventions for a selected group of individuals; rather, it should be a continuous project aiming to include everyone and maximize the public benefit (Cabrera, 2017).

For example, if recycling cans and bottles is a good thing to do, few people could actually do this until a recycling industry is assembled and public infrastructure is in place to allow many people to easily recycle some of their household garbage. Asking, "Who is a good recycling person?" makes no sense until many people can recycle when they want to; motivating people to be good recyclers is pointless until society provides for recycling. In general, for social ethics, the right social context allows good deeds to happen, which in turn benefit society. Adjusting social conditions where people are expected to act morally is far more intelligent and productive for social welfare than just making some people decide to behave better. Philosophically stated, "ought" implies "can": when and where people are to do what they *ought*, conditions are to be arranged so they *can*.

Social conditions cannot be left out of account; they shape morality as much as morality guides society. Unless it is supposed that one's morality is uncorrelated with one's overall well being, or it is imagined that one's well being is achievable, no matter what society is like, how a society functions largely explains the moral capacities of its members.

What does this perspective from social ethics imply for any practical mode of moral enhancement? We offer two initial recommendations. First, to re-iterate, a sharp dichotomy between moral bioenhancement and moral enviroenhancement is unsound in both concept and practice. Effective and large-scale bioenhancement should include enviroenhancement in tandem as a unified strategy. Moral bioenhancement pursued without due regard for appropriate moral enviroenhancement may satisfy purely conceptual notions about individualized morality, but it will not satisfy real-world plans for human welfare. Second, moral enviroenhancement should only be pursued while

anticipating how established social institutions should adjust in order to appropriately deal with morally enhanced individuals. This recommendation is especially the case for enduring moral enhancements. The final portion of our essay enlarges upon this thesis.

Moral bioenhancements that afford enduring effect in order to produce above-average cooperativeness and congeniality (and below-average tendencies toward conflict and aggression) may be labeled as "civil enhancers (CEs)." By definition, a functional CE would yield a large and reliable reduction in a person's behaviors that could be threatening to other people, or would initiate and escalate violence. We are not talking about moral rehabilitation or normalization, which at most improves morality up to society-wide standards. Civil enhancement produces people who are morally abnormal, by being much less likely than the average person to ever engage in threatening or aggressive behavior.

What would happen if civil enhancement were enacted while leaving civic institutions unaltered? Let us consider a specific example: how might a civic institution, such as a society's legal system, handle issues of criminal intent and responsibility for persons modified by civil enhancement? Setting aside the ethical issues attached to the idea of mandatory neurotechnological treatment of offenders [consult Focquaert (2014)], we simply try to predict the fate of a hypothetical person already civilly enhanced for whatever reason.

Consider this imaginary legal case—a hypothetical person P was provided with a CE, which dramatically reduces the likelihood of choosing to indulge in aggressive or abusive conduct. P has been using CE as supervised by a competent clinician. On a certain day, P is arrested for getting into a violent fight and is accused of instigating the violence. The legal defense for P argues during the trial that, in light of conflicting witnesses and ambiguous evidence about who started the violence (e.g., no video surveillance), the additional fact that P was properly using the CE should be admitted as evidence tending to show that P was probably not the instigator. After all, as the legal defense would point out, surely the purpose of a reliable CE is to reduce criminal intent, and hence to reduce the chances of criminal responsibility.

Our questions about this hypothetical situation ensue. Should P's use of CE be admitted as evidence under such circumstances? If admitted, how should the evidence be presented/explained to the jury? Are any special jury instructions needed for their deliberations? And if P is convicted on some charge, should the same evidence be available for sentencing deliberations? How should P's use of CE affect sentencing, if at all? Three basic options seem available. Option (A): P is *less* blameworthy, since P is less responsible for bad behavior, which was not sufficiently moderated by the weak CE (and thus, P is entitled to, and perhaps also requires, a stronger CE). Option (B): P is *equally* blameworthy as anyone, for P is just as responsible for intentional conduct, regardless of enhancement (and P needs a stronger CE, too). Option (C): P is *more* blameworthy, since P is more responsible for bad behavior, which was caused by P's deeper viciousness despite the use of the CE (and, therefore, P is sentenced to use a stronger CE as well).

Additional questions arise. Could contemporary law and legal theory determine a ranking of A, B, and C? Is there any amount of possible neurological information to directly determine whether A, B, or C is the correct option? These questions, and the premises upon which they are based, are not esoteric, but rather are becoming ever more realistic as the law seeks to engage the brain sciences [The area of neurolaw has emerged at this intersection; see Morse and Roskies (2013)]. To be sure, some neurological determination would be convenient, but it turns out that neuroscience alone cannot yet provide such information, or accomplish such a normative task (Shats et al., 2016). Perhaps neuroethics can proactively develop answers by working in tandem with the other disciplines already mentioned. In the meantime, needless to say, the civic institutions for law, criminal justice, and corrections are at present unprepared for these kinds of issues.

One additional question can be asked to narrow the issue to genetic/developmental means to accomplish moral bioenhancement. If P had received this reliable CE treatment during conception or gestation, should this person be treated differently (option A or C) from other people who never had any form of CE? We leave the reader to their own thoughts about possible answers and their implications, for both this particular issue and the overall trajectory and consequences of bioenhancement in society.

NOTES

1. There often is an egoistic component to an altruistic action, since some aspect of that act (something about its results, or its meaning, or the evoked responses from others, and so on) must be reinforcing to the actor in some way (Avram et al., 2014; Giordano et al., 2016).
2. Physician-philosopher Bernard Mandeville's poem "The Grumbling Hive, or Knaves Turn'd Honest," included in his 1724 book *The Fable of the Bees: Private Vice; Publick Benefits*, explored the respective roles and proper balancing of personal moral conduct and public economic and social gain [consult Goldsmith (1985)].

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this article.

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How Realistic Are the Scientific Assumptions of the Neuroenhancement Debate? Assessing the Pharmacological Optimism and Neuroenhancement Prevalence Hypotheses

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Since two decades, neuroenhancement is a major topic in neuroethics and still receives much attention in the scholarly literature as well as in public media. In contrast to high hopes at the beginning of the "Decade of the Brain" in the United States and Europe that we subsume under the "pharmacological optimism hypothesis," recent evidence from clinical neuroscience suggests that developing drugs that make healthy people smarter is even more difficult than finding new treatments for patients with mental disorders. However, cognitive enhancing drugs even for patients with impaired intellectual performance have not been successfully developed yet and new drugs that might have a disruptive impact on this field are unlikely to be developed in the near future. Additionally, we discuss theoretical, empirical, and historical evidence to assess whether cognitive enhancement of the healthy is common or even epidemic and if its application will further increase in the near future, as suggested by the "neuroenhancement prevalence hypothesis." Reports, surveys, and reviews from the 1930s until today indicate that psychopharmacological neuroenhancement is a fact but less common than often stated, particularly in the public media. Non-medical use of psychostimulants for the purpose of cognitive enhancement exists since at least 80 years and it might actually have been more common in the past than today. Therefore, we conclude that the pharmacological optimism hypothesis and neuroenhancement prevalence hypotheses have to be rejected and argue that the neuroenhancement debate should take the available evidence more into account.

Keywords: smart drugs, study drugs, cognitive enhancement, neuroenhancement, stimulants, modafinil, methylphenidate, amphetamine

INTRODUCTION

Since the late 1990s, scientists, ethicists, and legal scholars debate the issue of neuroenhancement – the improvement of healthy people's cognitive functioning on the neural level, for example by psychopharmacological means (Whitehouse et al., 1997; Farah et al., 2004). Other possible strategies, such as brain stimulation or genetic modification, are presently being investigated and discussed as well (e.g., Hamilton et al., 2011). However, because of the higher prevalence and longer history of psychopharmacological approaches, we focus on stimulant drugs in the present paper, particularly methylphenidate, modafinil, and amphetamine. The scholarly interest in neuroenhancement has steadily increased since the 1990s, as reflected by the number of annual publications (**Figure 1**). It is also a revenant topic in the media communication about brain research: The broad public or at least the decision-makers of the popular press address "brain optimization" even more frequently than mental disorders (O'Connor et al., 2012). The vast majority of such reports describes neuroenhancement as common, increasing, or both (Partridge et al., 2011), but we also noted many scientific publications doing so (Quednow, 2010; Schleim, 2010; Schleim and Quednow, 2017).

The sustained enthusiasm about and interest in pharmacological neuroenhancement is frequently based on three assumptions, (1) that intellectual performance can putatively be improved by drugs, (2) that pharmacological neuroenhancement is already done commonly by healthy people, and (3) that it will be used increasingly in the future. If neuroenhancement were impossible, at least in the short- to mid-term, or if almost nobody used drugs for such purposes, the debate would probably lose much of its public relevance, although there would be still other ethical issues for discussion. We would like to coin the first assumption the "pharmacological optimism hypothesis" and summarize the two latter ones to the "neuroenhancement prevalence hypothesis." With theoretical considerations, reviewing recent surveys on prevalence of neuroenhancement including historical evidence from Germany, Switzerland, the Netherlands, and the United States, we will assess both hypotheses in this paper to provide a better evidence base for the ethical neuroenhancement debate.

THE PHARMACOLOGICAL OPTIMISM HYPOTHESIS

Essential support for our arguments is coming from the so-called funding crisis in psychopharmacology that arose in ca. 2010[1] and from past and current reports on the consumption patterns of psychostimulant users and the low prevalence of their use as neuroenhancers. Optimistic expectations to find better treatments for neurodegenerative or psychiatric disorders were central to the "Decade of the Brain" proclaimed by the U.S. Government and the European Commission (Bush, 1990; Pandolfi, 1993), but also to influential political initiatives that prioritized funding of that research area. The German manifesto on the future of brain research published by eleven influential neuroscientists (Monyer et al., 2004) and the Human Brain Project[2], funded by the European Research council since 2013, are further examples for the confidence regarding new treatments developed by clinical neuroscience. Similarly, a major aim of the fifth edition of the Diagnostic and Statistics Manual (DSM-5) of the American Psychiatric Association published in 2013 was the discovery of neuroscientific biomarkers that are reliable targets particularly in the brain or genome for diagnosis and treatment of psychiatric disorders (Kupfer et al., 2002; Hyman, 2007). In spite of these efforts and an unprecedented increase in scientific publications and knowledge, the high expectations in terms of translations to clinical applications were not met yet (Schleim and Roiser, 2009; Schleim, 2014a; Frisch, 2016). The failure to discover even a single reliable biomarker for any of the hundreds of DSM-5 classifications lead to the introduction of a new research paradigm, the Research Domain Criteria (RDoC), whose scientific superiority remains unclear at the present moment (Kirmayer and Crafa, 2014).

In accordance with the high expectations of the 1990s and early 2000s regarding clinical neuroscience, the neuroenhancement literature was optimistic that new drugs for dementia or attention disorders could also be used for improving cognitive functioning in healthy people (Whitehouse et al., 1997; Farah et al., 2004). In contrast to these hopes, the funding crisis of psychopharmacology became evident around 2010: On the one hand, governmental changes in the funding structures of many countries made scientists in this area more dependent on collaborations with the pharmaceutical industry (Stanford, 2008; Hendrie, 2010). On the other hand, a lot of pharmaceutical companies closed their respective laboratories and rather invested in other fields because of the lack of successes of newly developed compounds resulting in high business risks regarding the introduction of new medications (Miller, 2010; Nutt and Goodwin, 2011; van Gerven and Cohen, 2011).

From this perspective it is not surprising that a major part of the psychopharmacological neuroenhancement literature (Smith and Farah, 2011; Weyandt et al., 2013; Busardo et al., 2016) covers well-known stimulant drugs that have been discovered a long time ago, like amphetamine, already synthesized at the end of the 19th century, methylphenidate, a discovery of the 1940s, and modafinil, synthesized in the 1970s. All of these drugs were or are still prescribed for some psychiatric indications with some differences between countries related to, e.g., the substances' abuse potential.[3] However, that the molecules have been known and investigated for a long time does not mean that they do not pose scientific challenges any more. Amphetamine, by far the oldest of the three compounds, still keeps scientists busy

[1]For example, *nature news* featured "Psychopharmacology in crisis" in June 2011 (http://www.nature.com/news/2011/110614/full/news.2011.367.html). We will address more scholarly sources below.

[2]https://www.humanbrainproject.eu/

[3]For a comparison of legislations within Europe, see information provided by the European Monitoring Centre for Drugs and Drug Addiction http://www.emcdda.europa.eu/html.cfm/index146601EN.html

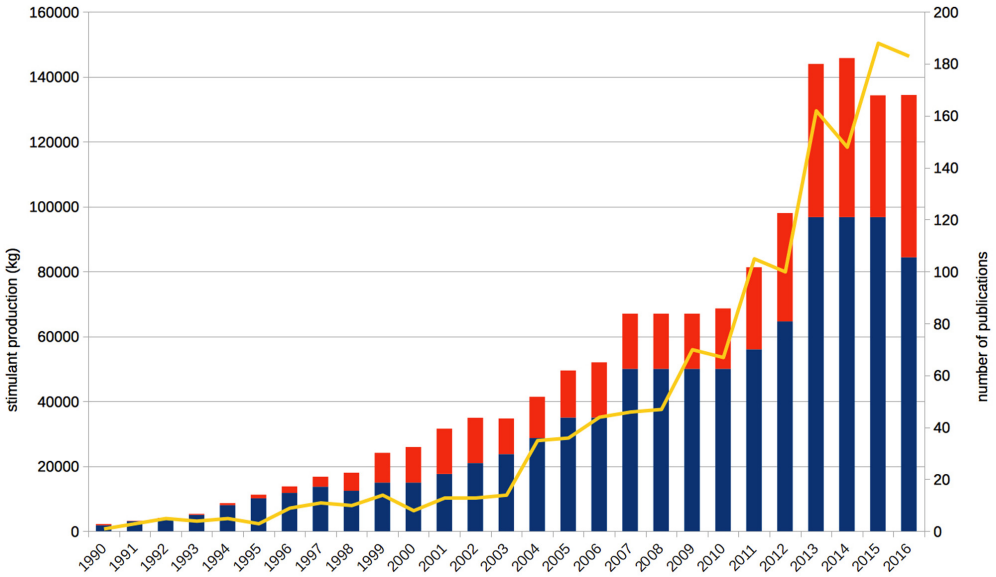

FIGURE 1 | Annual publications on enhancement have grown steadily since the early 1990s (yellow line, right axis), in parallel to the annual production quotas of methylphenidate (blue bars) and amphetamine (red bars; both left axis). "Cognitive enhancement" is by far the most common term with 1,065 hits for the whole period, followed by "neuroenhancement," which was mentioned first in 2004, achieving a total of 180 hits so far. Based on data from the ISI Web of Science topic search for cognitive, affective, mood enhancement, and neuroenhancement as well as the US Drug Enforcement Agency and the US Federal Register.

who want to understand the precise mechanism of action in the animal and human brain (Sulzer et al., 2005). A recent Cochrane meta-analysis of the available clinical studies on amphetamine for attention-deficit/hyperactivity disorder (ADHD) treatment found that most trials were at a high risk of bias, provided low to very low quality evidence, and should be longer in duration to learn more about long-term side effects of the treatment (Punja et al., 2016). The latter point is of particular interest when neuroenhancement in the healthy is performed not just for a particular event, like an exam period, but to increase performance continuously.

These observations demonstrate that psychopharmacological research is complex, challenging, and difficult even in the case of neurological and psychiatric disorders, where the treatment outcome is clear, such as a reduction of symptom severity associated with an improvement of social and occupational functioning. Moreover, the ethical issue of intervening in the brain chemistry is justified by patients' suffering, but might be disputable in healthy people. In the case of cognitive-emotional disturbances in mental disorders, clinically validated and reliable neuropsychological tests are available to measure the treatment's outcome; however, most of the so far tested substances have very limited effects on disturbed cognitive functions in neurological and psychiatric patient populations (Dekkers and Rikkert, 2007; Chou et al., 2012; de Jongh, 2017). In contrast to these clinical standards, it is much less clear what the outcome of neuroenhancement in the healthy would be and how it could be measured. Employing the same neuropsychological tests as in clinical studies would carry the risk of the fallacy that what helps patients must also help the healthy (Schleim, 2014b). That this reasoning is not necessarily true can be shown with many examples, such as insulin which is essential for patients with diabetes but would not help and even harm people without the disease. According to an influential definition, human enhancement is "[a]ny change in the biology or psychology of a person which increases the chances of leading a good life in the relevant set of circumstances" (Savulescu et al., 2011). This could be virtually everything and the meaning of "a good life" can be expected to strongly vary across people (Schleim, 2014b). Either way, the evidence is still low that so far discussed drugs in fact broadly enhance cognitive performance in the healthy (de Jongh et al., 2008; Quednow, 2010; Wood et al., 2014). We assume that if the situation of psychopharmacology were more positive, with a high availability of clinically validated new treatments for neurological and mental disorders, optimism concerning psychopharmacological neuroenhancement might be justified. However, in the present situation we have to reject the pharmacological optimism hypothesis, which does not amount to sheer pessimism but rather a pharmacological realism considering the evidence discussed above (Schleim and Quednow, 2017).

THE NEUROENHANCEMENT PREVALENCE HYPOTHESIS

As already summarized in the introduction, public media often describe ways to improve one's brain and pharmacological neuroenhancement as common, increasing, or both (Partridge et al., 2011; O'Connor et al., 2012). A detailed analysis has shown that scientific sources are often quoted as evidence for such statements (Partridge et al., 2011), which is in line with

our own perception of the scholarly literature. At first glance, stimulant production figures seem to support this finding: The aggregate production of methylphenidate and amphetamine combined in the United States was about 100.000 kg in the 1990s, 500.000 kg in the first decade of the 2000s and already more than 800.000 kg in the 7 years from 2010 to 2016 (**Figure 1**). Thus, the amount deemed sufficient during a *whole decade* in the 1990s is surpassed *annually* since 2013 with 134.000–146.000 kg of just these two psychostimulants produced per year. According to the neuroenhancement prevalence hypothesis, one would expect a similar increase of the prevalence of non-medical prescription stimulant consumption, for example, on college or university campuses. In contrast, this is not what the data show: Although the reported prevalence rates vary from nearly 0% to more than 30% in individual studies, the most recent and most comprehensive reviews found that the methodologically best studies (e.g., comprising the largest and most representative samples) frequently reported prevalence rates well below 10% (Smith and Farah, 2011; Weyandt et al., 2013). Importantly, consumption generally operationalized as non-medical use often included other motives beyond cognitive performance enhancement, such as recreational/lifestyle use in order to have fun, to party, or to lose weight, and often referred to lifetime or last year prevalence, which does not provide more information than that users have consumed such substances at least once during long periods of time. For example, one study, which reported a lifetime prevalence of 16.2%, found that only 15.5% of this subsample, or 2.5% of the original sample, were regular users who took prescription stimulants non-medically at least two or three times per week (White et al., 2006).

One of the first surveys in Germany showed that the lifetime prevalence of the use of neuroenhancers was only 1.3% in a large sample of pupils and students (Franke et al., 2011). A more recent nation-wide survey among students reported low prevalence rates for specific neuroenhancement use of prescription drugs (1.7%, methylphenidate, modafinil, or beta blockers; at least "sometimes") or illicit drugs (1.3%, e.g., cocaine) in the Netherlands (Schelle et al., 2015). Similarly, a nation-wide survey among university students in the United Kingdom and Ireland reported that 0.8, 3.4, or 0.3% were current users of methylphenidate, modafinil, or amphetamine, respectively, for the purpose of neuroenhancement (Singh et al., 2014). Finally, also in Swiss students the lifetime prevalence rates of using methylphenidate (3.7%), modafinil (0.3%), amphetamine (0.4%), and cocaine (0.2%) exclusively for cognitive enhancement purposes were rather low and clearly non-epidemic (Maier et al., 2013).

Of course it is debatable how high the percentage of consumers needs to be to properly speak of a "common" or even "epidemic" use. However, there is currently no evidence, to our knowledge, that the numbers have really been increasing in the past 20 years. The situation is further complicated by different inclusion criteria (e.g., general non-medical vs. specific neuroenhancement use) and outcome measures (e.g., once-in-a-lifetime vs. regular use) of the studies. By contrast, the evidence more likely suggests that many of the consumers responding positively in the surveys are young people trying out prescription stimulants for neuroenhancement or other non-medical and recreational use just once or only a few times – and then stop doing so (Sussman et al., 2006; Schleim and Quednow, 2017). It is well known that college students have a high likelihood of experimenting with different kinds of illicit drugs and dangerous behaviors (Dennhardt and Murphy, 2013) but that they usually stop this behavior when they leave the college (Johnston et al., 2005). Summarizing all of the above, it is thus highly likely that the increase in psychostimulant production in the United States (**Figure 1**) and many other countries largely reflects an increase in medical use induced by a change in prescription patterns of physicians as it was shown for the increase of methylphenidate production during the 1990s and 2000s in Germany (Ferber et al., 2001; Schubert et al., 2010). However, such prescriptions are usually excluded in surveys on the prevalence of non-medical stimulant use, in accordance with the basic assumption of the ethical neuroenhancement debate that treatment has to be distinguished from enhancement (Council on Bioethics, 2003).

In fact, the frequency of diagnosing ADHD for which methylphenidate and, in some countries, also amphetamine are commonly prescribed, has been increased since the 1970s and is estimated to have reached 7.2% of children and adolescents presently on the basis of a large meta-analysis (Thomas et al., 2015). The rate of children and adolescents prescribed with ADHD medication has increased accordingly, approaching 4% in the Netherlands and the United States, 2% in Denmark and Germany, but remaining at only 0.5% in the United Kingdom (Bachmann et al., 2017), partially explaining the increase of stimulant production seen in **Figure 1**. In summary, these data make plausible why we only see an increase of prescription stimulants in production quotas, but not in surveys investigating the prevalence of neuroenhancement. Given the high availability of the drugs because of medical prescriptions, one might have expected even higher prevalence rates of non-medical use. For the time being, we consider the presented arguments as sufficient justification to reject the neuroenhancement prevalence hypothesis.

HISTORY OF NEUROENHANCEMENT

In addition to this evidence concerning the present situation, we can also present historical sources to support our arguments even further. Rasmussen (2008) already has drawn insightful parallels between medical use of psychostimulants in the early 2000s and before the 1970s. We identified publications documenting the use of amphetamine as study drugs, thus non-medically as neuroenhancement, as early as in the 1930s. For example, an editorial in the *Journal of the American Medical Association* of 1937 stated that "*. . .this information* [about the psychological outcomes of an amphetamine experiment at the University of Minnesota] *was disseminated to the student body by word of mouth and the drug has been and still is being obtained by the students from drug stores for the purpose of avoiding sleep and fatigue when preparing for examinations*" (Goodman and Gilman, 1937). A follow-up editorial a year later contained a

general warning about the substance and stated that "*news that it could be obtained for keeping one awake while 'cramming' for final examinations spread from campus to campus*" (Anon, 1938). The Dutch physician Meerloo (1937) wrote that three of his patients, all of them students who had taken amphetamine to study longer at night, suffered from unwanted side-effects or test anxiety. In Germany, an experiment carried out in September 1938 with students at the Military Academy of Berlin is documented in which placebo, caffeine,and amphetamine were compared when students learned under conditions of sleep deprivation (Ohler, 2015).

Psychostimulant use for neuroenhancement purposes occurred even after the "War on Drugs" was proclaimed in the early 1970s, which introduced harsh punishments for amphetamine usage: "*The occasional use of amphetamine to remain alert or enhance one's performance is widespread. Students cramming for exams, drivers on extended nonstop trips, athletes attempting to excel, and military personnel on prolonged operations are some of the groups involved*" (Cohen, 1975). We documented elsewhere that surveys carried out in the 1960s, 1970s, and 1980s found similar and in some cases even higher prevalence rates for stimulant consumption than those discussed above, particularly for amphetamine, including instrumental use to stay awake and/or to study, thus which would be called "neuroenhancement" nowadays (Schleim and Quednow, 2017). The combined historical evidence from the 1930s to the 1980s makes our case for the rejection of the neuroenhancement prevalence hypothesis even stronger.

CONCLUSION

Psychopharmacological neuroenhancement – or cognitive enhancement – exists at least for more than 80 years. Only the concept is new; and the surge in related publications documented in **Figure 1**. But even before the contemporary debate, some scholars raised ethical and theoretical issues concerning stimulant consumption long before so-called "neuroethics" came into existence. Smith and Blachly (1966) already asked, whether subjects really perform better or just perceived themselves so, in how far socioeconomic status affects consumption, why so many students rather consume the drugs occasionally than regularly, whether medical students are at a higher risk, or to what extent the practice is influenced by the pharmaceutical industry. Unfortunately for those patients who are waiting for better treatments, psychopharmacological research turned out to be more difficult than suggested during the very optimistic 1990s and early 2000s in which also the present ethical neuroenhancement debate has its roots. We have argued that if it is even challenging to develop new treatments, then finding drugs which are suitable for improving cognitive functioning of the healthy with acceptable long-term side-effects is even more difficult, for theoretical, pharmacological, and ethical reasons. Therefore we clearly reject the pharmacological optimism and neuroenhancement prevalence hypotheses as explained above.

The neuroenhancement debate has been called a "myth" (Zohny, 2015), a "bubble" (Lucke et al., 2011), and a "phantom debate" (Quednow, 2010) independently by various authors. From our perspective, the already common phenomenon of students' drug use was re-framed as a new ethical and epidemiological problem in academic discourses, making use of exaggerated promises and prevalence rates. We do not say that scientists, ethicists, or legal scholars should stop debating neuroenhancement, but that this debate should rest on correct theoretical, empirical, and historical evidence in order to avoid unrealistic expectations in the general public (Forlini and Racine, 2009; Forlini and Hall, 2016). Other authors criticized the repetitiveness of this debate since the 1990s (Brenninkmeijer and Zwart, 2017). Furthermore, as psychopharmacology is in a funding crisis, relocation of resources for improving the already healthy probably would imply further negative consequences for many patients. Meanwhile, if the modification of biopsychological factors to improve people's chances of leading a good life (Savulescu et al., 2011) turns out to be more difficult than expected, we propose a shift to the environmental and social factors affecting people's well-being as an alternative (Schleim, 2014b).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm

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Personalized medicine uses fine grained information on individual persons, to pinpoint deviations from the normal. 'Digital Twins' in engineering provide a conceptual framework to analyze these emerging data-driven health care practices, as well as their conceptual and ethical implications for therapy, preventative care and human enhancement. Digital Twins stand for a specific engineering paradigm, where individual physical artifacts are paired with digital models that dynamically reflects the status of those artifacts. When applied to persons, Digital Twins are an emerging technology that builds on *in silico* representations of an individual that dynamically reflect molecular status, physiological status and life style over time. We use Digital Twins as the hypothesis that one would be in the possession of very detailed bio-physical and lifestyle information of a person over time. This perspective redefines the concept of 'normality' or 'health,' as a set of patterns that are regular *for a particular individual*, against the backdrop of patterns observed in the population. This perspective also will impact what is considered therapy and what is enhancement, as can be illustrated with the cases of the 'asymptomatic ill' and life extension via anti-aging medicine. These changes are the consequence of how meaning is derived, in case measurement data is available. Moral distinctions namely may be based on patterns found in these data and the meanings that are grafted on these patterns. Ethical and societal implications of Digital Twins are explored. Digital Twins imply a data-driven approach to health care. This approach has the potential to deliver significant societal benefits, and can function as a social equalizer, by allowing for effective equalizing enhancement interventions. It can as well though be a driver for inequality, given the fact that a Digital Twin might not be an accessible technology for everyone, and given the fact that patterns identified across a population of Digital Twins can lead to segmentation and discrimination. This duality calls for governance as this emerging technology matures, including measures that ensure transparency of data usage and derived benefits, and data privacy.

Keywords: therapy, ethics of human enhancement, digital twins, privacy in healthcare technologies, value sensitive design in healthcare technologies, ethics of biomedical data, personalized medicine, virtual self

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PERSONALIZED MEDICINE – THERAPY AS DIGITALLY SUPPORTED ENGINEERING

Personalized medicine starts from the assumption that refined mathematical models of patients, fuelled by big biodata, will drive more precise and effective medical interventions. Instead of basing medical interventions on the responses of the average person, digital models now even carry the promise to tailor healthcare to the anticipated responses of *individual* patients.

The availability of molecular readout technologies and of sufficient computational power increasingly makes it possible to build such personalized models, and to complement them with continuously tracked health and lifestyle parameters. This eventually can result in a digital representation of an individual patient – a 'virtual patient' or even an 'in-silico-self.' Such strategy was proposed as a venue for European healthcare: "realistic computer models that are built and validated upon experimental big data collected by the most advanced technologies from molecular to macroscopic scales" (Lehrach et al., 2016). This manifesto projects vast health improvements, reduction of health care costs, and an increased personal freedom in dealing with our own biology.

Provided such 'virtual patients' indeed become available, they will take the current engineering practices in health care to a different level. In this paper, we elaborate on the striking similarities between these emerging trends in health care, and the emerging concept of Digital Twins in engineering. A Digital Twin in engineering consists of a particular artifact and a computer model that closely reflects the state of that artifact. The artifact – for instance the engine of an airplane – and its model are closely coupled via a multitude of sensors. Such dynamic computer models prove to be very instrumental when doing predictive maintenance or engineering of real-world artifacts. At the instrumental level, a 'virtual self' of a patient conceptually is on a same par with a Digital Twin of a complex and mission critical artifact. Digital Twins therefore provide a conceptual instrument to analyze the impact of these novel engineering practices on core concepts in current debates on health care, like health, disease, preventative care, and enhancement. One can analyze these health care concepts in analogy with engineering concepts of 'normal functioning,' 'malfunctioning,' 'predictive maintenance,' 'performance optimization,' and the 'implementation of new functionality.'

Engineering approaches in general are ubiquitous in modern medicine. In current health care practices, one engineers a vascular bypass to restore the blood flow in case of atherosclerosis, repairs a heart valve, or replaces and old lens in the eye of a patient suffering from cataract. These engineering practices are rooted in the explanatory power and practical successes of the mechanical philosophy that has gradually emerged since the Renaissance. For instance, the drainage of the Low Countries provided significant improvements in the understanding of pumps, valves and hydraulic systems. These evolutions resonated in the work of contemporaries that studied vascular anatomy and the working of the heart (Novell, 1990). The description of the heart as a pump with one-way valves eventually opened the route to engineering actions like heart valve replacement. The engineering perspective developed into an important paradigm in current health care and therapy. Many Technical Universities in the world now train and educate engineers in clinical technology curricula, and doctors routinely work with engineers with a range of different backgrounds.

This engineer's point of view also forms the hidden premise in many debates about human enhancement. When it is possible to replace broken parts in the body, and to tweak, fine tune, and optimize them, it is in principle also possible to extend this body with new functionalities. Neural implants can for instance be used for visual prosthetics for blind people, but they also open the route toward capabilities going beyond normal human sight and give access to a range of normally inaccessible parts of the electromagnetic spectrum. Drugs like Ritalin can be used to help ADHD patients to focus, but can also be applied to boost mental performance in people that don't suffer from ADHD. The engineer's perspective becomes especially striking in the case of human germline editing with the aid of CRISPR/cas (Liang et al., 2015). In therapeutic applications, one could consider the editing of the nucleotides that give rise to severe Mendelian diseases, thereby preventing a lot of human suffering. With the same engineering approach, one can potentially bring in traits that go beyond current human capabilities. For example, one could consider engineering human hemoglobin to be more like shark-hemoglobin, thereby allowing humans to store more oxygen in the blood. Substantial engineering of traits will though be very difficult if not unfeasible. The engineering approach to health in contemporary medicine is confronted with the sheer complexity of the human body and its operations. Here a purely mechanistic approach proved to be insufficient. It is for instance very difficult or impossible to precisely predict the efficacy of a drug and its side effects in a concrete patient. A large quantity of the massively prescribed blockbuster drugs therefore has suboptimal effects. Complex multifactorial diseases prove to be very hard to tackle via an engineering approach. Along these lines, human enhancement will require the engineering of complex and interconnected traits. This might well be impossible to achieve with current medical engineering approaches.

To get a better grip on this complexity, large initiatives are established to generate detailed molecular data of patients and healthy research subjects. Publicly funded initiatives like Genomics England (The 100.000 Genomes Project, 2017) or the US precision medicine (PMI Working Group, 2015), and private initiatives like Human Longevity Inc. and the Mayo Clinic Centre for Individualized Medicine gather genomic information on large numbers of individuals. These initiatives ultimately aim at the development of digital models of certain aspects of patients, allowing for more targeted health care interventions. Instead of using an overall scheme of the average human body and its responses, personalized medicine starts from the premise that health care can vastly benefit from detailed molecular and life style data of each individual patient. In the case of picking the right drug to treat a cancer, the efficacy of this approach already has been proven. Genotyping an individual's tumor tissue provides clues on which drug will result in the biggest impact and the smallest side effects (Kummar et al., 2015). Personalized medicine also carries the promise to lead to predictive medicine, where diseases can be predicted and thereby also preventatively treated. All these initiatives constitute steps in the direction of 'virtual patients': data-driven mathematical models of patients that allow for more precise and effective medical interventions. The modalities of how and where such patient models will reside, who will own these models and who will be able to access them, these all need to be determined as this emerging technology evolves. The choices made will have strong impacts on health care related values like data privacy and patient autonomy. Among

the current implementations for instance are private/academic partnership where the company, and not the research subject owns the data, and in which research subjects are allowed a certain level of access to their data (Project Baseline, 2017).

The analogy with Digital Twins, as elaborated in this paper, provides a conceptual tool to pinpoint where the engineering paradigm holds true, and where it differs in case of personalized models of individuals. The detailed information contained in virtual selves will allow for a quantitative underpinning of medical engineering actions. But in contrast to the relation between an artifact and its digital representation, a person's 'virtual self' does not only relate to the physicalist realm, but also to the realm of language and meaning. The handling of an artifact's Digital Twin and a person's 'virtual self' diverges at the point where meanings get attributed to features identified in the virtual representations. This will make that besides a quantitative aspect, also conceptual and ethical aspects come into play. We will analyze what implications a Digital Twin engineering paradigm in health care can entail.

DIGITAL TWINS IN ENGINEERING PRACTICES, AND THEIR RELEVANCE FOR DATA- AND MODEL-DRIVEN HEALTHCARE

Digital Twins-based practices in civil engineering provide a good conceptual framework, when analysing the impact of a data- and model-driven healthcare on concepts of health, disease, and enhancement.

Unlike traditional engineering models, Digital Twins reflect the particular and individual, the idiosyncratic. Traditional engineering models reflect the generic: they apply to multiple instances. A Computer Aided Design model of an airplane jet engine reflects the structure of all the jet engine instances that are built based on this model. A Digital Twin though tightly connects the physical system (e.g., one particular machine) with its computer model, so that the latter closely reflects the architecture, the dynamics *and* the actual state of this one particular system. Sensors that allow for continuous monitoring of technical systems increasingly make it possible to create such individualized dynamic models. This type of model has been termed 'Digital Twin,' since it closely represents the inner state of the physical twin object. Digital Twin models are used in predictive maintenance, where they are used to identify anomalies long before parts actually break down. Digital Twins are also used to simulate the outcome of technical interventions like fixes and upgrades. The Digital Twin concept for instance was applied by NASA in the development of aerospace vehicles that last longer and endure more extreme conditions. In this context, they were defined as "an integrated multi-physics, multi-scale, probabilistic simulation of an as-built vehicle or system that uses the best available physical models, sensor updates, fleet history, etc., to mirror the life of its corresponding flying twin. . . . By combining all of this information, the Digital Twin continuously forecasts the health of the vehicle or system, the remaining useful life and the probability of mission success. The Digital Twin can also predict system response to safety-critical events and uncover previously unknown issues before they become critical by comparing predicted and actual responses" (Glaessgen and Stargel, 2012). The concept emerges also as a key element in Industry 4.0 strategies. It was termed "a living model of the physical asset or system" that allows to "continually adapt to changes in the environment or operations and deliver the best business outcome" (Infosys Insights, 2016), a "digital copy that is created and developed simultaneously with the real machine" (Siemens, 2015), "the bridge from the physical to the digital worlds, providing understanding of each unique asset over time" (General Electric, 2017). Digital Twins have been applied to optimize the operations of power plants, wind turbine parks, critical jet engine components, etc.

The emerging data-driven personalized health care practices bear striking resemblances to Digital Twins driven engineering in industry. These novel engineering approaches to health care also build on dynamic and high resolution digital models of genetic, biochemical, physiological and behavioral aspects of individual persons. Digital Twin based medicine is far from being an established fact yet. Various initiatives nevertheless pave the path by gathering detailed molecular data from individual patients (The 100.000 Genomes Project, 2017), (Telenti et al., 2016). Closer to the engineering of artifacts, attempts are currently already undertaken to develop Digital Twin models of the heart (Scoles, 2016).With the availability of high throughput sequencing technologies and of wearable devices, multi-dimensional molecular pictures of normal patterns can be developed at the individual's level. Examples in this direction are a project by a Google spin-off that will track ten thousand healthy American individuals for their genome, microbiome, physiological parameters captured by a wearable device, life style and well-being (Project Baseline, 2017).

The concept of Digital Twins therefore provides a very viable conceptual instrument for analysing the impact of individualized *in silico* models on key concepts in healthcare. It does so for multiple reasons. Firstly, the perspective taken in contemporary medicine is that of rational maintenance, optimization and even design of (very complex) bio-physical systems. Interventions in both engineering and medicine can be considered as engineering actions. Probabilistic models of human individuals in personalized medicine aim at supporting the engineering of a healthy status. This includes an approach analogous to predictive maintenance in industry. Molecular biomarkers can provide an early identification of upcoming disease states, even before the disease is manifest. Interventions can then be done to restore the system to a healthy state. Further along the same lines, human enhancement scenarios implicitly assume that humans are (eventually amongst other things) biophysical system of which the components and the functioning can potentially be understood in terms of mechanistic processes, and are therefore amenable to engineering of current features, and the engineering of novel ones. Secondly, these activities in both fields are guided by big data and by mathematical models that represent *one individual* person or artifact. In both engineering and medicine there is a strong belief that interventions will be more precise and

effective, when individualized mathematical models are used that capture the actual status of one particular artifact or person over time. Models of artifacts are evidently much more comprehensive than models of an organ or of the metabolic status of a person. Artifacts have building plans and are much less complicated than human beings. Models in medicine are still very partial and coarse grained, but nevertheless already show effectiveness, as can be seen in the field of cancer treatment. By combining various types of omics-levels one can anticipate that a much higher level of predictivity can be achieved than when using only single data types, like genomic data.

DIGITAL TWINS AND THE CONCEPTS OF THE NORMAL

Digital Twin approaches in health care have the potential to vastly increase the resolution and the comprehensiveness at which one can define normality and disease. The 'virtual self' models will provide a detailed map that allows to better pinpoint deviations from the normal. This 'normal' or healthy state can be defined at a high resolution and in multiple data-dimensions, using molecular, phenotypic and behavioral level over a person's life time. Natural variation amongst individuals, which make it otherwise difficult to pinpoint what is exactly normal, can be mapped in this high dimensional space. Heterogeneity in data acquisition is replaced by regular measurement of parameters over one's life time. Such approach will allow to obtain a much sharper statistical definition of the normal or healthy state, and likewise of disease states or disease susceptibilities. Confounding factors like age, lifestyle, and genetic background can be take into account in such models.

High resolution models of what is normal or healthy constitutes the cornerstone of upcoming personalized medicine approaches. A detailed picture of the healthy assumedly allows for a better identification of potential or actual disease states that need to be remediated. For example, assessment of which particular chemical is optimal to treat a cancer in a specific patient requires classification of that cancer by its driver mutations. This implies a precise understanding of how a healthy genome looks like, and which deviations from this normal situation are harmful. The approaches though often base the concept of the normal on the population, not yet on the individual. Early initiatives like the Framingham Health Study used physical examinations and lifestyle interviews on a set of healthy individuals. These studies played an important role in understanding the impact of lifestyle on cardiovascular diseases (Framingham Heart Study, 2017). Population genomics studies sequence large amounts of citizens to infer genetic diseases, and by consequence build a picture of a healthy genome. Initiatives like the Metagenomics of the Human Intestinal Tract (MetaHIT), the Human Microbiome Project (HMP), and Chinese diabetes consorts reported on microbiomes of healthy individuals (Lloyd-Price et al., 2016). Multi-dimensional molecular pictures of healthy individuals are being pioneered (Project Baseline, 2017).

Next to being defined at high resolution, the normal will also be truly *personalized*. It will be based on both the disease and healthy statuses of a particular individual. To the extent that physicians already tailor treatments to the medical history and actual status of their patients, one can say that medicine has always been personalized (Brenner, 2012). This personalization though relies on coarse grained categories, plus a picture of the past *disease* states of a particular person. Digital twin approaches in health care will heavily rely on a detailed picture of the *healthy* state of an individual, not merely on a record of disease states. 'Normal' in this context refers to the typical molecular, physiological and behavioral patterns observed in the individual, interpreted against the backdrop of the patterns observed in the entire population. Blood pressure readouts provide a simple illustration of this point. The sphygmomanometer is available for more than 100 years, nevertheless there is not yet a clear understanding of what is a 'normal' blood pressure. One of the reasons is that this cuff-based blood pressure determination method results in sparse measurements over a person's lifetime. (Steinhubl et al., 2016). This makes it impossible to assess the impact of day or night, age, caffeine consumption, stress conditions, and so on. The result is improper management of hypertension in many cases. Wearable devices nowadays can monitor an individual's blood pressure continuously. A "virtual medical assistant" has been proposed that uses machine learning to mine these data streams and identify the blood pressure trends that are unique to that particular person. Such information can provide an individualized concept of what is a normal blood pressure, against the backdrop of trends observed in people with similar age, life style, etc. (Steinhubl et al., 2016). Similar approaches are relevant for molecular biomarkers. Identification of the risk to chronic heart failure can benefit from serial measurements of biomarkers over time, rather than from single values (Miller and Jaffe, 2016). The Digital Twin approach is in contrast with current normal function accounts that define a normal or healthy state based on statistics derived from large cohort studies. As is clear from the example of blood pressure, the ability to define what is normal based on an *individual*'s detailed history results in a very different concept of the 'normal' as derived from population studies. Digital twin models will be continuously fed with all types of information during the lifetime of a person. This will allow to determine what the statistically normal patterns are *for that person* for a manifold of parameters. These normal patterns for the individual might well lie out of range when compared to the ones observed in population studies. The normal will be individualized.

Thirdly, Digital Twin models will make an individual's molecular and physiological makeup – which is currently hard to gain access to – transparently accessible. This will allow for comparing normal patterns across individuals with much greater ease and in great detail. The multidimensional space of properties across Digital Twins can be used to cluster similar individuals. Currently comparison with the normal range is mainly based on age and gender. One can expect that a high-resolution picture will lead to a great heterogeneity of types of human beings, each of them characterized by their own normal patterns. This effect already becomes apparent at the genomic level. High resolution genomic sequence data of multiple individuals revealed that human genomic variation was larger than originally

anticipated (Telenti et al., 2016). Variation in genomics regions that were previously perceived as junk seemed to have functional significance when having more data at hand. Similarly, it has been suggested that there might be a manifold of healthy states in human microbiomes, and therapy entails moving the composition of the microbiome toward one of these healthy attractors (Lloyd-Price et al., 2016).

Digital Twins therefore will not only result in a better quantitative resolution when defining health and disease. The fact that Digital Twins reflect the status of individuals, and allow for a transparent comparison of these individuals, leads to a conceptual change in the distinction between health and disease. The transparency in the heterogeneity of what is normal raises the question on whether natural levels are optimal and are prone to engineering (Kahane and Savulescu, 2015). What previously was regarded as healthy, i.e., the absence of any obvious disease indications, can lose its unproblematic character in view of this transparency. Gradations in levels of 'healthy' will become pronounced against the backdrop of this data landscape. The healthy state can now potentially be perceived as a suboptimal condition, when compared to others in the population. A condition that requires remediation. Next to this, the healthy state can become a state of 'symptomless illness,' because the data allow to infer likelihoods of developing diseases. Individuals with a ApoE-4 allele for instance have a higher likelihood of developing Alzheimer's disease (though they might never develop the disease during their lifetime). The statistical character of these inferences can transform 'health' into a series of disease susceptibilities, some of which can be mitigated given modifications in life style or given medical interventions. Last but not least, against the background of a Digital Twin model, the healthy state does not appear as the unproblematic natural state, but rather as an arbitrary configuration, out of many possible configurations. The engineering paradigm that comes with Digital Twins will sharply raise the question whether the healthy – normal – state indeed is optimal. It implicitly carries the question whether certain properties should be optimized or enhanced. In current health care practices, one mainly consults a physician when the normal becomes problematic and calls for action. For instance, when a disease gets manifest (e.g., experiencing a sharp pain in the stomach), or when one belongs to a certain category or has certain coarse grained indications (e.g., preventative measures to reducing the risk to osteoporosis in elderly women). In Digital Twins based health care practices, the normal may call for action.

DIGITAL TWINS AND THE CONCEPTS OF THERAPY, PREVENTATIVE CARE, AND ENHANCEMENT

The distinction between therapy, preventative care, and enhancement – though intensely debated – is instrumental in decisions in health care. The distinction between therapy and enhancement was proposed as means to identify those actions that require special moral consideration, because they change the constitutive aim of our medical interventions, which is to cure. (Daniels, 2000; President's Council on Bioethics, 2003). This viewpoint is reflected in one of the common definitions of enhancement, namely enhancement as the improvement of general abilities "beyond the species-typical level or statistically normal range of functioning" of a human being (Daniels, 2000; President's Council on Bioethics, 2003; Allhoff et al., 2009; Menuz et al., 2013).

The concepts of therapy, preventative care and enhancement bear a striking analogy with engineering concepts, and thus offer a relevant perspective on the question whether and how Digital Twins changes concepts in health care. Engineering actions on existing systems always aim at either restoring the functioning of a system, or at modifying a system. These actions can be classified as either repair, maintenance, or improvement. In repairs the modifications address a problem, and aim at restoring a system to the normal functioning. Maintenance actions make sure that the operational life time of an artifact is optimized. Improvement actions like 'souping up the engine of a motor' bring an existing functionality beyond the normal, or they introduce a novel functionality. Given the strong analogies with the distinctions between therapy, preventative care and enhancement, one can expect a significant impact of Digital Twin-based engineering practices on these distinctions in health care.

Digital Twins change the existing engineering paradigm. Main elements in this paradigm shift are the high transparency of the inner status and workings of an artifact, and the centrality of each individual artifact. This changes how repair, maintenance and improvement can be done. Similarly, when a Digital Twin approach would be applied to health care, a shift in related concepts can be expected. The individualized character of the approach for instance will impact the already problematic distinction between therapy and enhancement. Such distinction namely depends on the reference taken. In the engineering cases, it is 'the normal' as defined in the certification or classification (e.g., of a ship or the weight of a payload, stress, torque) which helps to define the boundary between systems maintenance and problem remediation versus improvement. In a similar way, the normal in the biological realm defines the boundaries between therapy and enhancement in "species typical normal functioning" accounts (Daniels, 2000). This definition of normal functioning is often based on population statistics. When taking the individual's normal patterns as reference in a Digital Twins approach, therapy entails the maintenance or restoration of this *individualized* normal state. It is well possible that an individual performs well in a certain trait when benchmarked against her individualized normal state, but underperforms vastly when compared to the rest of the population. In analogy with a wind turbine park, one can tune a poorly performing wind mill toward the average mills in that park, instead of bringing it back to its twin's definition of regular performance. Or even more, one could decide to take measures to get it to the best performing mills in the park. So, even given the high-resolution picture on normal performance that can be derived from Digital Twins, the distinction between maintenance and upgrade crucially depends on the reference or baseline that is chosen, so that this distinction contains an important normative element. In the case of medical actions on humans, as has often been pointed out (Hofmann, 2017), the

distinction between therapy and enhancement will not result only from a detailed observation of the state-of-affairs but also from their interplay with the realm of language and meaning. ADHD for instance has only been categorized as a diseased state in recent times (Lange et al., 2010). Nature does not come with clear categories, and is often is characterized by gradients rather than by crisp clear joints at which one conceptually can cut. As pointed out along these lines by Bostrom and others, the concept of "disease" may not refer to any natural kind and depends on the perspective taken (Bostrom, 2008). In a 'promiscuous realism' perspective, the human interest together with the patterns found in nature will determine where one will "carve nature at its joints" (Dupré, 1993). Along these lines, categories like therapy and enhancement do not solely reflect patterns found in the data of patients. They also reflect our normative interests and conventions.

A Digital Twin approach will lead to a high level of transparency of an individual's molecular and physiological constitution. The impact of this molecular and physiological information is not constrained to a purely instrumental value. In the case of wind mills and jet engines, the virtual representation is purely instrumental. In the case of human begins, such transparency will make that moral distinctions can be grafted on this information. Some important moral distinctions concerning humans are rooted in, or depend on the physicalist state-of-affairs (Burms and Vergauwen, 1991). Some morally important distinctions are made based on grounds that are morally irrelevant, but are based on a material link or 'inner structure' (Singer, 1974). These authors illustrate the point with the example of 'speciesism.' Humans have the strong tendency to attribute a special moral status to human beings over animals. When having a closer look though, such fundamental moral distinction cannot be made on grounds of differences in morally relevant criteria. Animals for instance also have the capacity for suffering, and in some cases their capacity for reasoning in certain areas surpasses those of mentally retarded people or infants. The conclusion drawn from this observation is that biological origin defines who belongs to the human community, in other words the hidden inner structures and the relations of descendance that define a being as part of the natural kind "human." Along the same lines, the growing body of knowledge on biomarkers and genes shows that data on the molecular and physiological constitution of a person can give rise to moral distinctions, when connected to properties like intelligence, entrepreneurship, susceptibility to diseases like dementia, etc. This moral load is one important reason for data privacy.

The cases exemplify that some important moral distinctions are *grafted* on structures deeply embedded in nature. If this is the case, then it is reasonable to expect that in a hypothetical scenario in which high resolution data on genetics, metabolism, life style, etc. is available for persons, and their individualized high-resolution pictures are offered by Digital Twins, we may witness changes in what we consider to be health, disease, therapy and enhancement. Consider for instance the emerging class of 'asymptomatic ill.' This class consists of healthy people with molecular patterns indicative of a high susceptibility to a disease, though they did not develop that disease yet (Plümecke, 2016). Now, assuming one takes some (medical) steps to prevent the disease to develop, one may wonder whether this intervention would qualify as therapy. Conceptually, it seems unwarranted to define therapy an intervention done on a healthy individual. In this respect, such preventive care interventions resemble more what from an engineering perspective would be called a maintenance intervention. However, this wouldn't be simple maintenance, due to the specific goal for which it is done. This goal is to prevent one very specific and statistically uncommon malfunctioning or disease to occur via a targeted (medical) intervention, where the occurrence of this specific potential disease has been predicted based on a high resolution picture of the individual subject. The subject is healthy according to current health care practices, but her Digital Twin indicates a certain likelihood of developing a disease later on, therefore making that the person "is not ok." Namely, predictions derived from an accurate digital model, being very closely intertwined with the person and her identity, will have a different load than generic observations derived from population studies. An accurate digital model of a person will not be merely instrumental in better decisions in health care interventions, but will also be part of that person's identity. Predictions derived from such digital models will impact both the persons self-perception, and eventually societal perceptions about that person.

On the other hand, defining these interventions as forms of enhancement due to them being done on a (currently) healthy individual and/or due to them being based on information in a digital representation of the subject rather than on her actual conditions and/or being done via complex and costly interventions would not sound convincing either. After all, it is a disease that we are fighting. It may therefore well be that personalized medicine and Digital Twins will force us to further stretch or revise what we consider therapy. For instance, by accepting the idea of something being a therapy, even if done on a healthy individual based on a critical condition of her Digital Twin, insofar as the intervention is done in order to address a potential illness of the individual which is highly probable to occur. In fact, it is to strike this balance that some already use the apparently paradoxical label of "preventive medicine." Needless to say, this is not only a conceptual but also a moral issue. Depending on whether these interventions are considered as daily care, therapy, or enhancement, different conclusions may be drawn on the question as to what extent and under which conditions they should be provided and their costs covered by a public healthcare system.

A second example of a possible shift in what we consider to be health, disease, therapy and enhancement would be life extension via anti-aging medicine. There is a high interest to develop ways to prolong the human life span, as in Google's spinoff Calico LLC or Venter's Human Longevity Inc. The rationale that is often used to support this type of research is a therapeutic one. Preventing diseases by making people growing old in a healthy way is better than curing diseases only when they happen to arise. Life style and genetics already result in considerable differences in life span among people, so one can expect that there are mechanisms that can be engineered in order to extend people's life-span. Some people seem to have

a constitution or habits that result in a long and healthy life. With the availability of Digital Twins, such naturally occurring people with an extremely long life-span might end up in a dedicated medically salient category. A combination of certain features in genetic makeup and lifestyle as displayed in someone's Digital Twin namely might allow to reasonably predict their life-span. Such ability to cluster based on Digital Twins data would lead to new medically relevant distinctions between healthy persons, even without the presence of enhancement technologies. One would be able to classify a set of people as prone to lead a long and healthy live, and sets of people with normal or with short life expectancies. This medically relevant distinction between persons, again, will be grafted on top of the (statistical) patterns that are found in the population of Digital Twins.[1] Such clustering is not possible if detailed data on the *individuals* are not available. Now, let's imagine that, thanks to Digital Twins we come to discover with some precision which life-styles are typical of people in the class of long-livers, for instance a certain diet or a certain regime of physical activity. Let's also assume that based on this knowledge one would gradually manage to move more people into this class. This could be done for instance via the advertisement, possibly the nudge or any other set of psychological or economic incentives to live according to these healthier life styles. Again, the question arises as to whether a life extension achieved in this way would count as therapy or enhancement. On the one hand, one may not categorize this as human enhancement. The deviation from the norm can be for the individual, and still be in the normal life expectancy range of the human species as a whole. Moreover, if a group of people starts to live whatever happens to be the life-extending life-style and thereby lives longer, this would hardly be considered enhancement. Living a healthy life is the paradigm of a health improvement that does not qualify as an enhancement (or therapy, for that matter). However, one may argue that there is a crucial difference between this scenario and the scenario that involves Digital Twins and an explicit policy of incentives. Here it can be said that a certain individual's or group's life extension has been achieved *by design*; because of the kind of knowledge provided by the data of the Digital Twins (high resolution, etc.), and because of the systematic, deliberate targeted policy that this knowledge has allowed for. The intertwinement of Digital Twins with a person's identity will add to this: the transparent model allows for design operations, that then get reflected in the person via medical or life style modifications. In other words, whereas the means used to achieve life extension – food, physical activity – clearly fall into the field of natural remedies, the broader process of scientific acquisition of data and of (social) design of which they are part may turn the process into a form of engineering, and therefore, arguably, of human enhancement. In fact, if the same group of people would obtain the same life extension effect, but this time because they have the financial means to access some complex biotechnological interventions, intuition would probably lead us to classify this as enhancement. The reason is not merely that such a radical intervention surpasses a normal range derived from the distribution over the entire population. The reason to categorize this as enhancement has to be, first of all, with the *explicitly* engineering nature of this intervention. The Digital Twin type of data-driven enhancement is to a certain extend an extrapolation of the intensive follow up of professionals in sports. In the case of these athletes, measuring and tracking of all types of parameters, and the resulting continuous optimizations of life style, diet and supplements, can provide a vast competitive advantage over other athletes.

Certainly, the fact that such life extension would be achieved via *costly* technologies, would also have a symbolic boundary surpassed. It would impact the way we think about humans and aging in general. It is a vastly rooted principle in human societies that the wealthy and the poor face the same facts of life: they grow old and die. Access to health care, nutrition, housing, etc. evidently can contribute to a longer life. But biologically speaking mortality *per se* is indifferent from human action. This biological fact is rooted in culture and society since the dawn of mankind. Technological modification of this process would not only result in a biological quantum leap, but also in a quantum leap in meaning. The concept of what it is to be human may fundamentally change by means of advanced life extension technologies (Temkin, 2011). The premise that "all humans are mortal" then will not hold true for all men to an equal extend anymore. Some will be less mortal than others due to technical means, eventually because of their financial means. In this case, the transgression that determines whether a modification is an enhancement therefore is not just a quantitative change in a certain feature, but also a transgression in the domain of meaning, that is grafted on a technological modification of biology. This fact holds true whether or not it concerns radical transformations, although radical transformations probably carry a higher likelihood to affect existing symbolic distinctions more harshly.

DIGITAL TWINS AND THE ETHICS OF HUMAN ENHANCEMENT

So far, we have used human Digital Twins – the assumption that one is in the possession of a data magnifying glass, that gives a detailed account of the molecular, phenotypic and life-style history of persons – as a conceptual tool to understand an existing trend in medicine, and to start a reflection on the potential conceptual implication of this trend on our understanding of the categories of health, disease, and enhancement. In this last section, we use Digital Twins to explore some possible ethical and societal implications of this trend.

A popular line of argumentation in favor of the *prima facie* moral acceptability of human enhancements starts from the observation that humans already use enhancement techniques, albeit low-tech ones. Athletes for instance improve their performance via physical exercise, a special diet, and a regular life style. With the introduction of wearable health monitoring devices this type of improvements becomes supported by real time data from the individual athlete. The improvement

[1] Some ethical implications of such scenarios are discussed in the last section.

obtained by training and dietary schemes might be the same as the improvements obtainable via pharmaceutical means, both based on these early stage Digital Twins. The aims and the factual outputs are similar, maybe even at the molecular level, which might lead to the welfarist position that therapy and enhancement are equally acceptable means to increase welfare (Giubilini and Sanyal, 2015). As outlined above though, the acceptability of the approach is not merely rooted in the data, but in the distinctions made at the level of meaning. Human enhancement achieved via technological means or programs based on Digital Twins may be seen as specifically problematic because of this. By using pharmaceutical means, an athlete may transgress a certain symbolic boundary that is institutionalized in her sport for a long time. It is exactly the transgression of this symbolic boundary that makes the athletes act problematic, not merely the result in performance. Let's assume that a society rethinks a marathon, now entailing the usage of tailored pharmaceuticals based on the runner's Digital Twins, as a means to boost runners performance. One might consider the resulting contest as morally acceptable if no transgression at the level of meaning would be involved. But the participants of this activity would engage in something that is different from what we now call a marathon. The constitutive rules are changed. We could also think about introducing a rule in chess (and leave other rules unchanged), that allowed a knight to jump twice in one turn. Since many human activities are defined by their point and meaning and embedding in a practice that is governed by formal or informal rules, they would engage in a very different type of activity (Whitehouse et al., 1997; Santoni de Sio et al., 2016). This is a general point that goes beyond the sports example.

Egalitarian concerns constitute one of the main bioconservative arguments to caution enhancement. The fear is that human enhancement technologies might lead to different classes of people, and therefore have a disruptive effect on our democratic institutions (Fukuyama, 2002). Along these lines, human enhancement technologies can be thought of as increasing the already existing diversity among human beings. People already differ in strength, health, intelligence or longevity. When such differences would be available as quantified properties in a person's digital representation and available to the entire community for consulting, that evidently in itself carries the danger of discrimination and of the constitution of novel classes. This may create a crucial complication for the realization of the ideal of human enhancement as a social equalizer. Consider, for example, cognitive enhancement. Enhancers, unlike natural talent and capacities, would be at least in principle available to everybody in the same way. One therefore can argue that enhancers are potential social equalizers, counterbalancing the individual differences that are randomly assigned by the natural and social lottery (Savulescu et al., 2004). However, it turned out that individual differences matter also for the functioning of enhancers (Husain and Mehta, 2011). This doesn't necessarily mean that cognitive enhancers may not work for a certain category of people (though it may well be the case). But it certainly means that a big quantity of individual data is needed to fine-tune the treatment or the enhancement. Digital Twins have therefore great potential to make enhancements more precise and effective, if the assumptions behind personalized medicine prove to be correct. This holds true not only for cognitive enhancement, but for all sorts of therapy and enhancement. This necessity of acquiring a massive amount of data about the individuals may introduce new issues of equality that may counterbalance the desired equalizing effect.

It hints at the fact that not the enhancements themselves, but rather the sheer availability of a vast amount of data like those of Digital Twins coupled with the human tendency to attribute meaning to patterns in data may give more concerns for equality. Digital Twins thus can sharply raise the question of distributive justice. One needs to determine whether the development of costly digital representations will be purely market driven, or whether compensation mechanisms need to be implemented for the least well off. One also needs to define which resulting possible health care interventions (be it therapeutic, preventative or enhancement actions) will be supported. Next to this, governance mechanisms will be needed for safeguarding the rights of persons that have Digital Twins. Such governance mechanisms can draw from how for instance biobanks or medical databases are designed, regulated, inspected, etc. The governance structures should for instance ensure transparency on how the Digital Twins are used, protection of the data, and a fair distribution of the benefits derived from people's personal biological information. Data protection will be a key instrument to mitigate some of the potentially negative effects. Privacy concerns that were raised in the context of genomics will be even more relevant in the case of Digital Twins, since the combination of multiple layers of biological and behavioral data will be much more telling about a person than genomics data alone. Given also the engineering analogy that is closely related to Digital Twins, privacy will be instrumental in avoiding that persons will be on a same par as designed objects, *vis a vis* their twins. In other words, privacy will avoid blunt comparison of human Digital Twins and therefore the grafting of symbolic distinctions on top of these data.

However, this may create a trade-off or even dilemma between equality of capabilities of people to lead the lives of their choice, versus equality of privacy. In order to grant everyone access to medical treatments, distributing pills or medical devices may not be enough. In this 'virtual patient' scenario it is a prerequisite to collect everybody's data and to create a Digital Twin for everybody. Personalized medicine will probably increase the cost at the individual level, when compared to off-the-shelf pills. Next to that, there will be differences in people's capacity to protect their data, due to differences in information about the risks, and differences in their contractual position in the "negotiation" about the use of their data. This is a concern for the standard reasons about (medical) data protection (van den Hoven, 2008). But it also raises a new, specific, issue. Bioconservative fear of a class of biologically privileged persons might realize without any technological intervention; the mere existence and knowledge of one's Digital Twin may create discrimination of the real people of which the twins are a digital representation. Self-fulfilling prophecy mechanisms similar to the ones active in the financial sector can come into play: the mere fact that other people or institutions think that you are going to be sick or weak or short-lived may make you sick, weak or short-lived.

Much in the same way in which the mere fact that you are thought to be insolvent may eventually leave you broke. This marks an important difference between the use of Digital Twin in engineering and in medicine. The social and symbolic dimension in the human realm create a new layer of complication and potential ethical issues. A Digital Twin for a human may be not just a powerful tool to improve one's physical condition. It may also be a second self who can – metaphorically speaking – rise up against its biological counterpart; or, more prosaically and realistically, being the source of serious moral damage for the real person. In this way, it may be the case that the only way to achieve equality of capabilities would be by creating data which may in turn be used to penalize some groups or to create new forms of discrimination.

The engineering approach that is inherent to Digital Twins also sheds a new light on current health care values, and opens the route to a whole new range of values. In current health care, where in most cases only a low-resolution picture of the disease trajectory of a patient is available, regular health care values that apply are autonomy, beneficence, non-malfeasance and justice (Timmermans et al., 2011). All these values will face different concretizations in case Digital Twins become available. Distributive justice for instance will be challenged due to the high resolution with which one can suddenly identify differences in constitution and capabilities among people. It will sharply raise the question on which conditions are to be treated in order to compensate for bad luck in the natural lottery. The value of autonomy will have to be implemented in view of a strong dependency of a digital model. Given a close link between the digital model and the corresponding individual, question is to which extend the patient will be able to make autonomous decisions on what is good or bad for her, and to which extend this is determined by the algorithms that claim to propose the most optimal solution based on the data at hand. 'Dataism' in this context might become a new form of medical paternalism. Patients thus will have to develop a proper relation toward their Personal Digital Twin, and develop the capacity to make informed decisions in view of strong data-driven personalized models.

Moreover, with the availability of detailed molecular data of novel engineering methods to impact biological systems (e.g., engineering germlines or somatic cells via CRISPR/cas), a whole range of values need to be decided upon. Examples are the efficiency of the engineering actions, the effectiveness of the design, the competitiveness of the design versus other designs. The question is then which enhancements to favor, and how to make the engineering decisions. Engineering in general requires decisions on which values to include in the design or the optimization of a system, and which values to maximize (van den Hoven et al., 2012). Value-sensitive design approaches in engineering make explicit which values are implied in the technical development of an artifact, and try to overcome moral dilemmas by design. Given the analogies with engineering, this approach can also provide relevant insights in the field of personalized medicine and Personal Digital Twins. The trade-off between equality of access to (personalized) medicine and risks of data-based discrimination is one example of a challenge that value-sensitive design may face in this domain.

Next to this, the results of medical engineering actions are intrinsically positional, as they are in the economic context of engineering artifacts. It is not the available quantity of the services that determines their value in the market, but the extent to which others have *no* access to them. If a small group of people has access to life extension products, these products will have a much higher value to them than in the case all members of a society have equal access, since in the first case it provides them a significant competitive advantage over others. The rationales for pursuing enhancements will be colored by this positional character. Individuals for instance can aim at enhancements with personal flourishing as underpinning motif (e.g., ability to even more enjoy their swimming experience), but more likely they will be driven by competitive motifs (outperform others that score less on the swimming property). A different effect is that enhancement actions may lead to an impoverishment, by focusing on certain traits and neglecting others. Since enhancement can be considered to be an engineering optimization problem, one needs to decide which optimizations to pursue. It might well be that improving an athlete's performance will for instance lead to a decrease in longevity, or that an improved feeling of contentment leads to a decrease in entrepreneurship. Digital Twins have the potential to make these tradeoffs transparent.

Rationality has limits, and this point is often pivotal in bioconservative perspectives on human enhancement (Giubilini and Sanyal, 2015). Reason proves to be an instrument with very limited capabilities when it boils down to predicting the future. Predicting the consequences of radical enhancements is therefore merely impossible. It even proved to be difficult to assess the demographic effect of simple and un-invasive technologies like the prenatal determination of a child's sex (Fukuyama, 2002). Hottois (1996) stressed the point that our complex bio-physical world *brings about* the future, and that these dynamics can only be captured to an extremely limited extend via reason and via our systems of language and meaning. In this perspective, one cannot fully anticipate the future impact of current human enhancements, whether they are disruptive or gradual. This lack of long term predictability not necessarily implies that enhancement actions should be banned. One can accompany the process of making bio-physical modifications, with deliberation about meaning, value, risks, etc. Since Digital Twins constitute a bridge between the bio-physical world and the world of language and meaning, they can become an important technical platform for enabling such techno-moral accompaniment. The data in Personal Digital Twins reflect the operational character of reality. These data are read-outs of the metabolic composition of the blood at a given point in time, the genomic code, the history of blood pressure and of physical movements of the body, and so on. As such, these data are an intermediate stage between the operational realm of the biophysical reality, and the realm of symbols, language, and meaning. Availability of these data provides us with a substrate to graft symbolical distinctions and meaning on structures that are present in the bio-physical world. Digital Twins, be it as conceptual tool or as emerging technology, can therefore be a tool for moral accompaniment

of technological evolutions. They can be one element, among many others, in an effort to realize a Responsible Innovation in this domain, and aid both in understanding and in shaping the continuous interactions between engineering actions in the bio-physical world, and the world of values and meaning.

CONCLUSION

The Digital Twins concept provides a solid thought instrument to analyze conceptual and ethical aspects of future healthcare and human enhancement. It does so by putting enhancement against the backdrop of individualized high-resolution data of people's molecular constitution, physiology, life style, and dietary habits. Next to that, Digital Twins are an emerging field in medicine, that has the potential to become the playfield where therapy and enhancement are explored. Comparison between Digital Twins in entire populations allows to get a much sharper idea on health versus disease, and by consequence sharpen the debate on therapy versus enhancement. Digital Twins have the potential to be a rich source for identifying novel and effective engineering routes, both for therapy and enhancement. As such, Digital Twins can allow to identify physical well-being parameters that one would prefer. Digital Twins also have the potential to impact a person's identity, since meaning can be assigned to the patterns in the data. The engineering paradigm inherent to a Digital Twins based health care will raise novel ethical, legal and social issues for therapy and enhancement. Digital Twins for instance can challenge equality, even without the application of enhancement technologies. The differences between persons can be sharply defined and made extremely transparent based on the differences in their compiled information, leading potentially to segmentation and discrimination. Personal Digital Twins are an asymptotically data-intense scenario that clarifies the importance of governance concerning the production and use of personal biological and life style data.

AUTHOR CONTRIBUTIONS

KB and JvdH conceived of the presented approach. KB took the lead in writing the manuscript. FSdS provided contributions to the sections on the ethics of enhancement and the distinction between therapy and enhancement. All authors discussed the approach and contributed to the final manuscript. JvdH supervised the work.

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