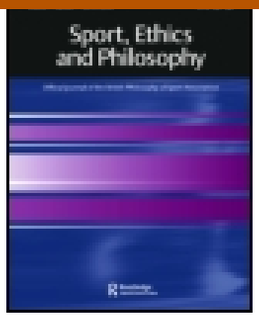

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Ethics, Genetic Technologies and Equine Sports: The Prospect of Regulation of a Modified Therapeutic Use Exemption Policy

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ABSTRACT

This article critically reviews the current availability and selected use of genetic technologies for horses, before undertaking an ethical evaluation of current practice and regulatory positions in comparative relation to debates surrounding genetic testing, pre-implantation genetic testing and gene editing in humans. We argue that genetic testing for hereditary disorders is not only justified but should be encouraged on welfare grounds and that genetic testing for performance traits is ethically permissible based on a restricted imperative to genetically edit horses and horse embryos to reduce genetic predisposition to disease and injury. Given the current state of the science, where the effects of gene editing on health and welfare are currently undetermined, space is created for an analytical distinction between equine gene editing for 'treatment' and for 'enhancement'. Gene editing is only justified for purposes of correcting/preventing disease and injury. Current regulation is challenged by apparently conflicting welfare-based ethical imperatives with respect to welfare-based gene editing. We propose modifications to the blanket bans on gene editing with a case-by-case assessment of applications to permit gene editing, based on best welfare interests underwritten by the aim of facilitating fair sport that adapt WADAs International Standard for Therapeutic Use Exemptions, adding an important reporting element. We reject the use of gene editing to obtain currently prohibited competitive advantages. In order to safeguard the welfare of human and equine athletes, we argue that regulatory institutions should urgently collaborate to develop cross-sport international regulations for the use of gene editing, including obligatory reporting of data about the health and welfare of genetically edited horses.

KEYWORDS

Equine sport; ethics; genetic testing; gene editing; equine welfare

Introduction

The use of genetic technologies within the equine industries has become increasingly common since the horse genome was published in 2009 (Wade et al. 2009). Testing for genes coding for disease in adult horses is common clinical practice (Brosnahan, Brooks, and Antczak 2010), whilst testing of equine embryos was first reported in 2010 (Harper

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2010) and is now available as a commercial service (Choi, Penedo, and Hinrichs 2015). Identification of 'candidate genes' which might be associated with desirable performance characteristics (Schroder, Klostermann, and Distl 2011) has been used to develop commercial tests which purport to inform breeding and competition decisions (Hill et al. 2010a). Recently, there has been increasing interest in equine gene editing. This initially centred around the possibility of using genetic editing therapeutically, to correct injury and disease (Finno and Bannasch 2014; Finno, Spier, and Valberg 2009; Webbon 2012). In 2017 the first report was published of non-therapeutic gene editing of equine embryos aimed at enhancing performance in the absence of injury or disease (Vichera et al. 2019).

Opinion on whether available genetic technologies should be adopted is divided within the equine world. Some sectors, for example, the polo industry, have adopted all of them with enthusiasm. Others, for example, the World Arabian Horse Organisation (WAHO) and the Federation Equestre Internationale (FEI) (which regulates all Olympic and additional international horse competitions) have prohibited gene editing but allow genetic testing. Yet other organisations, for example, the International Federation of Thoroughbred Breeding Associations (IFTBA) have been hesitant about embracing even genetic testing.

This article critically reviews the current availability and selective use of genetic technologies for horses, as a precursor to an ethical evaluation of the *status quo* in comparative relation to current discourse and debates surrounding genetic testing, preimplantation genetic testing and genetic editing in humans. We consider these arguments in relation to both the general and athlete human and horse populations. We explore the extent to which arguments relating to athlete autonomy and welfare, and sports ethics more generally, apply to horses as they do to humans. We conclude that testing for inherited diseases is an important tool for improving equine health and welfare and that testing to identify genes coding for desirable traits (including athletic performance) is merely a refinement of existing selective breeding practices. Thus, we argue that such testing is not ethically problematic in non-human animal populations providing that welfare protection is a guiding principle, but hold that transparency about genetic testing at the time of sale is a necessary part of good commercial and governance practices. More positively, we note that gene editing has the potential to improve equine welfare by reducing the expression of diseases and injuries that have a genetic basis. Nevertheless, our support for gene editing is not absolute. We note that the effects of gene editing on health and welfare, particularly when combined with other techniques such as cloning, are at present undetermined. This makes gene editing ethically distinct from genetic testing. Gene editing has the potential to adversely as well as positively affect the health and welfare not only of individual animals but also—if a permanent alteration to the genome is made through genetic editing of embryos—of future generations. It has been recently suggested (Naylor 2019) that gene editing in horses will be used as a model for gene editing in human athletes, both by regulators and by those who might seek to use the technology to obtain a (prohibited) competitive advantage. We argue that in order to safeguard the welfare of human as well as equine athletes, the equine industries should collaborate with urgency to develop cross-sport international regulations for the use of gene editing and should include obligatory reporting of data about the health and welfare of genetically edited horses. An opportunity currently exists to drive ethical consensus and subsequently to implement such systems before the use of

gene editing in horses becomes widespread, to provide an evidence base for ongoing ethical decision-making about the use of these technologies.[1]

Section 1. How are Genetic Technologies Currently Being Used in Horses?

Genetic Testing to Detect Heritable Disease

Testing of Postnatal Horses

Attempts to identify the genetic basis of equine diseases began in the 1990s and intensified after the publication of the equine genome sequence in 2009 (Brosnahan, Brooks, and Antczak 2010; Finno, Spier, and Valberg 2009). As of 2019, 237 equine traits or disorders with a genetic basis have been catalogued (University of Sydney 2019). Genetic testing may be used in horses to identify 'carriers' and thereby avoid heritable disease (Brosnahan, Brooks, and Antczak 2010). These are animals that appear normal and do not suffer from the disease themselves, but carry a recessive abnormal gene which is inherited via an autosomal genetic mechanism. In order for the disease to occur, an animal must inherit two copies of the defective gene, one from each parent. If carrier animals are crossed with other carrier animals there is a 1:4 chance of their offspring inheriting two abnormal copies of the gene and thus suffering from the disease. If they are 'crossed' with non-carrier animals no offspring will suffer from the disease, although 50% of them will carry the abnormal gene.[2]

Genetic testing is also used to identify genetic abnormalities that are inherited via a dominant autosomal mechanism. In these cases, only one copy of the abnormal gene need to be inherited for the disease to be expressed. In some cases, the expression of the disease is not always apparent, either because it occurs at different levels of severity or because its physical effects become obvious only under certain circumstances. For example, hyperkalemic periodic paralysis (HYPP) of Quarterhorses is an autosomal dominant disease caused by point mutation in the SCN4A gene (Naylor 1994) giving rise to signs ranging from mild muscle tremors through temporary paralysis to collapse and death. Those horses which have inherited two copies of the defective gene often exhibit more severe disease than those which have inherited one copy. Malignant Hyperthermia Disorder (MH) of Quarterhorses, Paint horses and Appaloosas is an autosomal dominant disease caused by mutation in the ryanodine receptor 1 (RYR1) (Aleman, Nieto, and Magdesian 2009). It can cause a hypermetabolic state, which is triggered particularly by stress and by the use of halothane anaesthesia. Testing for such autosomal dominant abnormalities helps to identify those horses that carry the defective gene but show only mild (if any) symptoms, in order to avoid crossing them with similar animals and giving rise to more severe disease in offspring.

The adoption of equine genetic testing has been largely voluntary, incentivised by economic loss associated with foals which express the disease. Thus, the WAHO's website, for example, states 'WAHO very strongly supports the concept of voluntary testing and disclosure'. Some breed registries now insist upon genetic testing for certain diseases. Examples include the American Quarterhorse Association (AQHA) whose rules make it mandatory for all stallions to have a DNA profile on record, and to have been tested for five genetic diseases[3] (AQHA 2019a; Jefferies 2019). Furthermore, the AQHA have recently amended their regulations so that from 1 January 2020 the registration of

foals which are homozygous positive (Gb/Gb) for GBED; homozygous positive (MH/MH) or heterozygous (N/MH) for MH; heterozygous positive (N/H) for HYPP or homozygous positive (HRD/HRD) for HERDA will not be permitted (AQHA 2019b). Many Warmblood horse breeders and registries now encourage testing of all breeding stock for Warmblood Fragile Foal Syndrome (for example, SHB (GB) 2019, Hector 2019), whilst some studbooks such as The Royal Dutch Sporthorse Association (KWPN) and Hannoveraner Verband have made such testing mandatory for breeding stallions (KWPN 2019; Verband 2019). Some of the constituent members of the WAHO (for example, the German Arabian Horse Organisation) have opted to make genetic testing for cerebellar atrophy and severe combined immunodeficiency syndrome compulsory in all breeding animals (WAHO 2019a).

Testing of Embryos

Testing equine embryos for heritable disease involves flushing embryos out of the mare's uterus, biopsying embryos *in-vitro*, and testing the embryonic cells thus obtained for genetic disease (Choi et al. 2010, 2015, Guignot et al. 2015). Only those embryos that are not carrying abnormal genes coding for the disease of concern are selected for transfer back into a mare, to develop to term. Transfer may be immediate, or the embryos may be vitrified (frozen) whilst the results of genetic analysis are awaited. This commercially available process is equivalent to pre-implantation genetic diagnosis in humans. Because the testing takes place *in-vitro* and thus involves embryo flushing and embryo transfer, it can only be used in those breeds whose studbooks allow the registration of foals resulting from embryo transfer. Since the studbooks that register racing Thoroughbreds internationally do not permit embryo transfer, genetic testing of embryos of racing Thoroughbreds is not currently permissible.

Genetic Testing for Desirable Traits

In both postnatal horses and equine embryos, genetic testing is also carried out for reasons other than the detection of disease. The aim is to identify animals or embryos carrying genes coding for traits which breeders find desirable. This includes identification of sex in embryos (Herrera et al. 2014, 2015; Hinrichs 2018; Hinrichs and Choi 2012) and of genes coding for coat colour or white markings in embryos and adults (Guignot et al. 2015; Negro et al. 2017; Rieder 2009). The sex of embryos is of interest to those breeders who consider that one sex performs better than the other in the competition (for example, anecdotally, polo players favour mares, whereas event riders often favour (castrated) males). Identification of coat colour is often undertaken simply for commercial reasons, but in some breeds there exist colour-linked genetic diseases, so that testing for colour and for disease is combinable. For example, in the American Paint Horse, a breed genetic mutation (overo lethal white foal syndrome) occurs, which causes complete white colour and pink skin and also causes an abnormal lack of ganglion cells in the large and small intestines. This results in severe intestinal tract abnormalities and early death (Finno, Spier, and Valberg 2009). Since the disease is an autosomal recessive trait, animals are only affected if they inherit two copies of the defective gene. Genetic testing thus serves the dual purpose of identifying coat colour and identifying animals carrying the overo lethal white foal gene in order to avoid crossing them.

Particular interest has developed in the possibility of testing adult horses for genes associated with athletic performance. Such testing can be used to inform decisions about which animals to breed together, or which races (speed or stamina) to select animals for. Initial research involved the investigation of variations in myostatin gene expression in racing Thoroughbreds. Myostatin inhibits skeletal muscle growth, and polymorphisms in the myostatin gene have been found to account for much of the genetic basis of race distance aptitude in racehorse (Hill et al. 2010a, 2010b, Hill, Ryan, and MacHugh 2012a, 2012b, McGivney et al. 2012; Tozaki et al. 2012). An alternative approach claims to correlate mitochondrial DNA genes with aptitude for speed or stamina (Harrison and Turrion-Gomez 2006). Groups of genes associated with the control of substrate utilisation, insulin signalling and muscle strength have now also been shown to be of relevance to performance and to gait in non-Thoroughbred horses (for example, Finno and Bannasch 2014; Kristjansson et al. 2014; Sole et al. 2017).

Gene Editing

The sequencing of the equine genome (Brosnahan, Brooks, and Antczak 2010) has facilitated research to identify the genetic causes of various diseases (Finno and Bannasch 2014; Webbon 2012), including those relevant to athletic performance such as disorders of the musculoskeletal (Diesterbeck and Distl 2007; Distl 2013; Mickelson and Valberg 2015; Naccache, Metzger, and Distl 2018) respiratory (Gerber, Tessier, and Marti 2015) and neurological (Aleman et al. 2018) systems. The development of gene-editing techniques has provided a means 'of making targeted interventions at the molecular level of DNA or RNA function, deliberately to alter the structural or functional characteristics of biological entities' (Nuffield Council of Bioethics 2016). Foremost amongst current gene-editing techniques is the 'CRISP- Cas9' system first reported in 2012 (Jinek et al. 2012), which uses guide strands of RNA to identify particular, pre-determined DNA sequences of interest within a genome, and then uses an endonuclease protein which is attached to the guide RNA strand to cut the DNA at the target site (Nuffield Council of Bioethics 2016). This provides a method of permanently introducing or eliminating specific genes from the genome. CRISPR-Cas9 systems can also be modified to perform functions other than cutting; for example, performing epigenetic modifications to switch target genes on or off (rather than adding or removing genes). Such refinements to the CRISPR-Cas9 system allow the possibility of altering gene expression in individuals without making a heritable change to their genome (Nuffield Council of Bioethics 2016).

The applicability of CRISP-Cas9 systems to equine medicine is limited by the fact that many equine diseases have a polygenic basis and are strongly influenced by non-genetic variables such as environment and nutrition. Nonetheless, the possibility of using genetic editing to influence the expression of disease in horses—whether through modification of the genome of post-natal animals or of equine embryos—is rapidly increasing.[4] The potential to 'knock out' genes which control so-called 'disabling disorders' in equine athletes is of particular interest. Furthermore, evidence of genetic variation for fracture risk (Blott et al. 2014) and heritability of tendon injuries in horses (Welsh et al. 2014) raises the possibility that genetic editing might be used to reduce the incidence of injury in equine athletes.

Recently, scientists at the Kheiron and Lian laboratories in Argentina collaborated to use CRISPR-Cas9 gene-editing and whole animal cloning techniques (Anon 2017; Argentinian Government 2018). CRISPR-Cas9 was used to knock out the myostatin gene (that negatively regulates muscle mass) in fibroblast cells, and the modified fibroblast cells were then used to create cloned equine embryos by somatic cell nuclear transfer (cloning) (Vichera et al. 2019). This use of genetic editing goes beyond correction of disorders and instead aims to enhance physiological limits beyond 'normal'—a possibility that is facilitated by increasing understanding of the genetic control of equine performance (Harrison and Turrion-Gomez 2006; Hill et al. 2010a, 2010b, Hill, Ryan, and MacHugh 2012a, 2012b, McGivney et al. 2012).[5]

The main international regulators of equine competition (excepting *inter alia* polo) do not allow genetic editing for purposes either of disease correction or 'enhancement'. The FEI (F. E. I. 2019) prohibits horses competing following any non-therapeutic use of gene-editing techniques, or following 'any form of genetic modification' (Article 1004 c,d). Similarly, the International Federation of Horseracing Authorities' (IFHA's) Agreement on Breeding, Racing and Wagering effectively prohibits genetic editing through Section 12, 'Definition of a Thoroughbred' that precludes the registration of any foals 'produced by … any form of genetic manipulation' (IFHA 2019). Nevertheless, Section 6A of that agreement states that horseracing authorities have the discretion to 'allow or disallow' the racing of horses or their offspring after the administration of genetic therapy'. No such permission has yet been granted, meaning that the practical *status quo* is that genetic editing is not currently allowed for any reason. This is broadly in line with the position in human sport, where the World Anti-Doping Agency (WADA) prohibits the use of gene editing for any purpose (Le Page 2017). The enforcement on such bans is, however, dependent upon the ability to detect genetic editing of an athlete, and such work is underway in equine doping (Teruaki et al. 2019; Tozaki et al. 2018).

Section 2. A Comparative Ethical Analysis of the Use of Genetic Technologies in Horses and Humans

Having briefly reviewed the use of genetic technologies in equine sport, we turn now to consider a range of ethical issues comparing and contrasting human analogues. For the purposes of this argument, we assume the justifiability of human sporting use of animals providing that the positive welfare of sentient animals is maximised, and welfare harms minimised (Campbell 2013a, 2013b, 2016, 2019). We now turn to arguments concerning genetic testing for health limiting conditions and performance enhancement and later gene editing, before critically presenting the case for the ethical salience of the distinction.

Ethical Arguments Surrounding Genetic Testing for Inherited Disease

The sequencing of the human genome has made it possible to predict the risk of disease; identify carriers of disease; and establish pre-natal and clinical diagnoses and prognoses. Such testing[6] of adult and embryonic humans is fraught with ethical problems, which we do not have space to discuss here but which are reviewed in (Burgess 2001; Nuffield Council of Bioethics 1993, 2006). Major ethical considerations include:

(1) Issues of personal autonomy. For example,
   - the possibility to give '*informed* consent' for genetic testing given the complexities surrounding the reliability of such testing and the implications of its results, despite genetic counselling;
   - issues surrounding the testing of minors who are unable to consent;
   - The possible existence of 'a right to know' and, conversely a 'right not to know' and its application for those who do or do not opt for such tests (including family members); and
   - Issues surrounding confidentiality and disclosure—for example, to insurance companies.

(2) Issues of impact. For example,
   - difficulties in assessing individual health risks associated with test results;
   - difficulties in assessing the psychological impacts of testing, particularly if no treatment is available should the test prove positive;
   - impact on those identified as carriers, particularly in terms of life chances andreproductive choices?;
   - potential stigmatisation and/or discrimination?

(3) Concerns about a 'slippery slope' to eugenic selection.

(4) 'Rights' of embryos. For example,
   - If pre-implantation genetic testing reveals defective genes those embryos could be 'discarded'.

Some of these concerns, such as psychological consequences, clearly do not apply directly to the genetic testing of horses. Nor are horses capable of consent, though it can be assumed that their owners are likely to understand the relevant information and thus act as proper proxies. Other issues are, however, directly applicable to horses. The power of genetic data is considered exceptional in human medicine (Bains 2010), and is likely to be so also in the equine sphere. Issues of confidentiality, disclosure and impact that make human genetic data so powerful are analogous to issues of transparency in equine medicine. If an owner chooses to have a horse tested (a) questions arise as to proper access to the data, and claims by various interested parties to have this disclosed; and (b) adverse results are likely to have an impact on the commercial value of breeding animals. The use of genetic data to discriminate against certain human individuals or groups can affect access to healthcare (Geelen et al. 2012). In equine sport, the provision of health care—including the preventative measure of not crossing two carrier animals—is likely to be improved by transparent disclosure of genetic testing information to potential purchasers and to the breeding community more generally. The revelation that a stallion is a carrier of a disease gene, for example, enables not only prospective purchasers of that stallion's breeding services but also existing owners of that stallion's progeny which may have inherited the deleterious gene to avoid crosses that may result in the expression of disease (AQHA 2019a; KWPN 2019; SHB (GB) 2019; WAHO 2019b). Assuming that equine welfare is paramount, the (potential) economic harm of loss of commercial value as the result of the disclosure of genetic testing results is outweighed by the potential positive welfare impact upon future generations of animals. Transparent disclosure of genetic testing results should, therefore, be encouraged and may be facilitated by breed registries introducing mandatory systems of genetic testing. Selective breeding, as we discuss

below, is not a problematic concept in horse breeding and 'slippery slope' arguments about eugenics do not appear to apply here (though an extension to more general loss of species variety cannot be ruled out). The imperative to protect the welfare of animals under our care (Campbell 2019; RCVS 2012), appears to support the use of genetic technologies to select against disease.

One of the main concerns surrounding the use of technique of pre-implantation genetic testing in humans is that it can facilitate discrimination against and even the killing of 'disabled' embryos (Sparrow 2008). This is problematic if one believes that embryos have moral status (Robertson 2003). Nonetheless, its use to select against disease is allowed and/or regulated for in many jurisdictions (Bayefsky 2017). For example, nearly 400 conditions can be tested for using PGD under the regulation of the Human Fertilisation and Embryology Authority in the UK (HFEA 2019). For reasons which have been previously explained (Campbell (2018)) we do not believe that the moral status of equine embryos is such that it protects them from humane death, and that, combined with the fact that they are incapable of suffering, makes killing them ethically permissible. Furthermore, whereas using genetic testing of adults to identify carrier animals in order to cross them only with non-carrier animals still results in a 50% chance of producing carrier foals, genetic testing of embryos allows the selection only of those embryos which have two normal copies of the disease gene of concern. If such genetic testing of embryos was adopted by an entire breed, it would allow the elimination of the undesirable disease gene in one generation (Hinrichs and Choi 2012). Selecting against and destroying equine embryos carrying genes which code for the disease is thus not only permissible but should be encouraged, for the same welfare-promoting reasons as genetic testing of adult horses should be adopted.

Ethical Arguments Surrounding Genetic Testing for Performance-limiting Genes

In human sport, testing for genetic predisposition to disease that limits performance is undertaken on the grounds of harm protection. Examples include testing for genetic predisposition to Achilles tendon and anterior cruciate ligament injury (Posthumus et al. 2010); to sudden cardiac arrest (Anderson, Exeter, and Bowyer 2012; Tiziano et al. 2016); and to exertional rhabdomyolosis associated with sickle cell anaemia (Taranto et al. 2018). Such testing is ethically complicated, since tensions exist between the desire to protect athletes from injury and the protection of athletes' autonomy; privacy and their right to informed consent. Whilst some have argued in favour of mandatory testing programmes[7] (Ferrari et al. 2015), others argue that non-voluntary testing is unjustifiably paternalistic (Anderson, Exeter, and Bowyer 2012; Savulescu 2005). Such arguments are complicated by the fact that there is no absolute link between genetic predisposition to disease or injury and the actual risk of harm in an individual (Magavern et al. 2017; McNamee et al. 2009).

It is thus important that test results be interpreted by and discussed with medical professionals (Taranto et al. 2018) and not simply made available upon demand directly to consumers (Vlahovich et al. 2017; Webborn et al. 2015). Furthermore, testing under-determines what action should follow—ranging from exclusion from competing (e.g. for potentially fatal conditions), or the facilitation of informed risk-taking (Magavern et al. 2017; Williams, Wackerhage, and Day 2016). Additional issues occur surrounding

whom data should be shared with, and under what conditions, which press hard on the principle of confidentiality in relation to employers with a commercial interest in such data.

Genetic testing for predisposition to disease and injury in equine athletes lags far behind the use of such techniques in human athletes. Nonetheless, a significant genetic variation for risk of fracture in Thoroughbred racehorses has been identified (Blott et al. 2014), and the traits which are associated with athletic durability investigated (Sole et al. 2017; Velie, Hamilton, and Wade 2016). The genetic basis of equine exertional rhabdomyolosis has also been studied (Norton et al. 2016). This is in some ways analogous to the work on sickle-cell anaemia-related exertional rhabdomyolosis in humans, and will be of relevance to the welfare of endurance (Nagy, Murray, and Dyson 2014) as well as of racehorses.

When applied to the relationship between equine athletes and their physicians (veterinarians), the principle of paternalism is less contentious than it is when applied to human sports medicine. The primary obligation of a veterinarian is to protect the health and welfare of the animals under their care (RCVS 2012). There appears to be a moral imperative for veterinarians to protect equine athletes, incapable of autonomy, by testing for genetic predisposition to injury or disease (Webbon 2012), and by limiting an animal's activities in the face of adverse results. Yet just as the contract between a sports physician and an employer may rest with both them and the individual athlete (Anderson and Gerrard 2005), the contract exists between a veterinarian and the horse owner, not the equine athlete. This is complicated even further by the fact that the horse owner may be represented by an intermediary, for example, the trainer or rider (Campbell 2013a, 2013b).

Ethical Arguments Surrounding Genetic Testing for Desirable Traits

We have argued that genetic testing of adult and embryonic horses for the heritable disease is ethically desirable. We now wish to consider whether there is any ethical difference between genetic testing of horses for disease, and for desirable traits.

In human medicine, the idea of allowing testing—particularly of embryos—for desirable but non health-linked traits is controversial. Savulescu (2001) argued that parents should not merely be allowed to choose those characteristics which they wish to be expressed in their children but that they were obliged to choose the best futures for them. Critics argued that this had echoes of eugenic experiments, and concerns about discrimination and promotion of inequality in society have resulted in a body of work arguing that such selection should not be permitted (Roberts 2002; Wilkinson 2006, 2008). Genetic testing of existing children to determine their aptitude for various sports—which one might argue maximises a child's life opportunities (Camporesi and McNamee 2016)—has been criticised not only on the grounds that it is currently an unreliable indicator of athletic ability (Webborn et al. 2015) but also on the grounds that it may interfere with a child's 'right to an open future' and prevent them from exploring other meaningful activities (Camporesi 2013; Camporesi and McNamee 2016). Such autonomy-based concerns are not relevant to decision-making about genetic testing in horses. In animals, the notion of 'selective breeding' for non-health related desirable characteristics (e.g. meat production, or competitive ability) is centuries old. Using genetic testing is merely an extension of selective breeding. The harms of testing adult animals (taking a hair or blood

sample for DNA analysis) are minimal. As we have argued above, consent and autonomy-based considerations that apply to human patients are irrelevant, and concerns about the moral status of embryos are inapplicable. Providing that transparency about testing at the time of sale or breeding is insisted upon, there are therefore no convincing ethical reasons to prohibit genetic testing for desirable characteristics in horses. Enabling breeders to select for characteristics that make foals more saleable may in the long term reduce the number of unwanted foals and their abandonment less likely (Leadon, O'Toole, and Duggan 2012; Snellow 2008).

In a sporting context, similar potential positive welfare effects exist. For example, Swedish studies across several equine breeds report positive correlations between specific, identified genes and performance (Kristjansson et al. 2014; Schaefer et al. 2017; Velie et al. 2018). The aim of such research is to align genetic make-up with use and to improve welfare by avoiding horses being trained in disciplines in which they are bound to fail. The success of such programmes is predicated upon the validity of the assumption that equine athletic performance is at least reasonably significantly determined by genetics (Asadollahpour Nanaei, Ayatollahi Mehrgardi, and Esmailizadeh 2019; Schroder, Klostermann, and Distl 2011). International organisations overseeing breeding and racing of Thoroughbred racehorses have been hesitant to promote this use of genetic testing (EFTBA 2016), based on the validity of claims to genetic precursors of superior athletic performance (EFTBA 2016). Similar arguments are made in relation to humans for athletic aptitude (Roth (2012), Loland 2015, Webborn et al. 2015, Jacob et al. 2018). In equine sport, examples are given of a Melbourne Cup (long distance) winner whom it is reputed would, on the basis of genetic testing, be identified as suitable for sprinting, and of 'one of the best (sprinting) stallions in the world … [who is] believed to be a ….predominantly stamina (genetic) type' (EFTBA 2016). Such hyperbole undermines welfare-based ethical arguments in favour of genetic testing for desirable characteristics since such testing may provide owners with information which misinforms decision-making about horses' athletic careers. This may actually have adverse welfare consequences, either through causing owners to aim horses at competitions for which they are not suited, or by destroying the market for animals with the 'wrong' genetic make-up (EFTBA 2016). This could result in a surplus of unwanted, low-value animals whose welfare is likely to be compromised (Snellow 2008). Furthermore, the selection on the basis of performance-related genes could lead to a situation whereby only a relatively small number of horses with a particular genetic make-up were being bred from. This has the potential to reduce genetic diversity within a breed (Binns et al. 2012). Thus, whilst genetic testing for desirable athletic traits may have the potential to improve equine welfare, this prospect is countered by the uncertain correlation between genetic factors and performance (EFTBA 2016; Guth and Roth 2013; Webborn et al. 2015), and also by possible unintended welfare consequences.

Ethical Issues Surrounding Genetic Editing in Horses

A recent conference presentation concerning the gene-editing of human embryos in order to prevent disease provoked public outcry (Cyranoski 2019) and criticism from the academic community (Li et al. 2019). Although Savulescu et al. (2015) have argued in favour of allowing continuing research on gene editing of human embryos, others have advocated extreme caution (Baltimore et al. 2015; Lanphier et al. 2015). Ethical concerns centre around

economic inequality; absence of consent; opposition to the use of embryos based on their moral status; and the fact that the safety of gene editing of embryos is unproven and that off-target effects (edits in the wrong place) and mosaicism (when some cells carry the edit but others do not) may occur and be passed on to future generations.

In horses, two potential applications of gene editing are clear at this time: (1) gene editing an existing post-natal animal or (2) gene editing an equine embryo. In both scenarios—as discussed above—gene editing could be undertaken in order to 'correct' a genetic predisposition to disease or injury, or to 'enhance' performance beyond 'normal' to give a competitive advantage. Notwithstanding the scientific limitations around achieving either of these goals discussed above, it is foreseeable that more reliable gene editing of the equine genome in order both to reduce predisposition to disease or injury, and to positively affect performance will develop. We, therefore, discuss now the ethical issues surrounding such developments, in order to facilitate proactive regulatory discussion. Given that the main international regulators of equestrian sport prohibit gene editing of horses for any reason, we consider whether this stance is ethically justifiable.

The Principle of Justice Applied to Editing the Equine Genome

In sport, the principle of justice (Beauchamp and Childress 2009) is thought critical to preserve fair play or a 'level playing field' (Bloodworth and McNamee 2017; Murray 2017): the idea that athletic excellence should be determined primarily by merit (Loland and Hoppeler 2012). Within the philosophy of sport, this is known as the fair equality of opportunity principle. Complete equality of opportunity is neither necessary nor feasible given tolerable differences in, for example, luck, performance conditions, skill, wealth, etc. Equestrian sport does not provide an exception to this framework, but racing may indeed reduce some inequalities by its handicapping systems. Despite the recognised impossibility of delivering complete equality of opportunity, the notion of 'fair competition' permeates equestrian sport. The FEI website, for example, states that the creation of 'A universal and level playing field' is one of its core values, whilst the website of the British Horseracing Authority (BHA) claims that part of the BHA's role is to 'encourage (…) the honest majority to do the right thing, and prevent. the dishonest minority from gaining an unfair advantage, thus ensuring a level playing field for all'(BHA 2019). In both human and equine sport part of the argument around considerations of justice involves also those who might bet on the result, and the need to protect them by ensuring that competitions are not deceitfully influenced either by the use of prohibited performance-enhancing substances or methods, or by event manipulation (i.e. 'fixing'). The combination of gene-editing techniques having the potential to improve performance whilst being prohibited by sports' regulatory bodies would make data about a horse's genome economically valuable, and give those with access to it (through legitimate or illegitimate means) an unfair advantage in a betting marketplace. Gene editing may elicit criticisms of unfairness in access to technologies. Neuhaus and Parent (2019) have argued that the use of gene editing is unfair because such technologies will inevitably be expensive, and not all breeders or owners will be able to afford them. Whilst it is true that gene editing is likely to be expensive, such concerns are not decisive since access to top stallions in the marketplace is already a major factor: only those who can afford the highest stud fees use the best stallions. Since considerable economic inequalities are already tolerated, the argument that gene editing is unfair or unjust on economic grounds is diminished.[8]

In terms of the 'fair equality of opportunity', one could argue that proper competition between animals who have been edited and those who have not requires an outright ban, as seems to be the position of the IFHA (IFHA 2019) and the FEI (F. E. I. 2019). We note whilst the reasoning behind such regulation is based in the ethical principle of justice, the application of the principle—through enforcement of regulation—is necessarily predicated on the availability of reliable tests for gene editing that is nascent in scientific terms (Teruaki et al. 2019; Tozaki et al. 2018).

One alternative approach to satisfying the principle of fair equality of opportunity, often mooted in doping debates, would be to run separate races for genetically edited animals and non-edited animals. Such a proposal falls foul of the validity and reliability arguments above. It would require complicated classification systems and result in reduced numbers in races, possibly making them economically unviable or reducing their appeal to spectators. Moreover, the argument as to whether a horse ought to be in one category not the other might be difficult and expensive to validate.

A third approach to satisfying demands of fair equality of opportunity would be to waive the blanket ban on gene editing in favour of a blanket permission. This is analogous to familiar pro doping arguments. While promoting fairness it risks other ethically desirable protections around athlete welfare and widespread paternalistic concerns around excessive risk-taking by sports institutions such as WADA, the International Olympic Committee, and international sport federations that fall under their jurisdiction.

It is evident from a consideration of these possible solutions that the principle of fair equality of opportunity could be satisfied by either acceptance or prohibition of gene editing. We turn, therefore, to welfare-based consequential harm: benefit analysis to deliver decisive ethical solutions.

A harm-benefit analysis of the Ethical Issues Surrounding Editing the Equine Genome

The welfare of the horses being used for competitive sport is a matter of increasing public concern worldwide (for example, Anon 2013; Doherty et al. 2017; McLean and McGreevy 2010; Mullane 2010; von Borstel et al. 2009). If the uncontentious claim that the dominant ethical concern here is with equine health and welfare is accepted, then it follows that a harm: benefit analysis is appropriate. Certainly, equine welfare is the priority of the equine industries and regulators of equestrian sport, and an outright ban on using safe gene-editing techniques that could enhance equine welfare would run counter to that priority. Equally, genetic editing has the potential to improve equine welfare by reducing hereditary predisposition to disease and injury. There are a number of performance-affecting equine diseases which are already known to have a hereditary basis—for example, equine exertional rhabdomyolosis (Norton et al. 2016) and osteochondrosis dissecans (Naccache, Metzger, and Distl 2018). It is also possible that some injuries which occur during racing (e.g. fractures) may have a hereditary component, or at least a genetic predisposition to them (Blott et al. 2014). One might initially conclude that the use of gene-editing technologies that improve health, reduce injury and thus improve welfare are ethically justified.

Despite its appeal, such a conclusion is permissive, since it fails to account for the potential adverse consequences of gene-editing techniques concerning 'off target' effects, i.e. unanticipated somatic events (Harrison and Hart 2018), including possible mutagenesis (Gupta et al. 2019). Such effects might be reduced using the CRISPR-Cas9

system compared to earlier methods of gene editing (Gupta et al. 2019) yet concerns remain (Cyranoski 2018). The currently unpredictable nature and extent of 'off target' effects present a problem in terms of ethical decision-making around the use of gene editing in horses. Whilst a blanket ban on gene editing potentially prevents or delays improvements in equine health and welfare, so too might gene editing result in negative (or potentially negative) welfare impacts. Suppose 'corrective' gene editing is permitted, and an individual animal is treated for some genetically determined physiological abnormality (a so-called 'disabling disorder') that limits athletic performance. Depending on the method used and its targeting, gene editing can result in an alteration to the musculoskeletal system that may not give rise to heritable genomic changes. The horse's own performance levels then might exceed its pre-intervention ability, and it might consequently become an attractive breeding prospect. Nevertheless, subsequent progeny would inherit the 'disabling disorder', not the genetic 'correction', thus either perpetuating the persistence of such disorders within a breed or making gene editing inevitable for generations of horses to come. Both outcomes have negative welfare impacts. Thus, if our primary concern is to improve equine welfare any relaxation of the current regulations to allow gene editing 'corrections' in post-natal horses should be accompanied by a ban on breeding from animals who have been 'treated' in such a way.[9]

Where gene editing occurs at the embryonic stage, changes to the genome would very likely be heritable. In a harm:benefit analysis, the use of gene-editing techniques in equine embryos to reduce a genetic disposition to disease or injury, therefore, appears to be justified for future equine generations. It must be noted, however, that the opposite may also be true: off-target effects will be more serious when editing embryos than when editing post-natal horses, because of heritability.

Is There an Ethical Distinction between Gene Editing for 'Correction' and for 'Enhancement'?

One temporary solution would be to allow the use of the technique and then properly evaluate it. In a harm: benefit analysis, one could argue that off-target risks are worth taking if we are gene editing in order to treat or prevent disease or predisposition to injury rather than aiming at performance or economic benefits. This argument has been made in relation to gene editing in humans (Vlahovich et al. 2017; WADA 2008) eliciting arguments about the boundaries of 'normality', and thus what constitutes 'correction' and what 'enhancement'.

Any regulatory distinction between 'gene therapy' and 'gene doping' is problematic given that correction of any disease state which had negative physiological consequences is likely to enhance athletic performance. Furthermore, although we know in broad terms what 'normal function' of a species or even a breed is, huge individual variations retain. It is thus very difficult to distinguish with certainty between gene editing which simply returns an animal to a 'normal' level of performance ('correction/therapy') and gene editing which enhances performance beyond 'normal' ('doping'). Such conundrums in sports ethics stretch beyond the equine sphere and beyond gene editing. Consider, for example, a situation in which a child of short stature was treated with growth hormone in the absence of a growth

hormone deficiency, in order to enhance their growth to a height which is 'normal' for their population. For many sports, the athletic capability of that person as an adult would have been improved by having been treated with growth hormone as a child. Has the treatment thus conferred an unfair advantage? The adult person is 'normal' in population terms, but has arguably been enhanced beyond what would have been 'normal' for that individual. This is precisely the question asked of the Argentinian footballer Lionel Messi, who received such treatment for (an alleged) idiopathic short stature (Sonksen, Cowan, and Holt 2016). Arguably, all therapies might be considered 'enhancements' both of an individual and from that individual's perspective (Holm and McNamee 2011).

Within a regulatory framework, one way of dealing with the conceptual problems around 'normality' is to avoid the 'treatment' (i.e. correction)/'enhancement' distinction. This, however, may facilitate either a blanket prohibition (the current *status quo* in human and most equine sport), or a blanket permission. The ethical importance of the distinction between 'treatment' and 'enhancement' (e.g. doping) lies in the notion that 'gene doping' (but not gene therapy) contradicts the aims of protecting the integrity of sport and of maintaining meaningful competition that does not descend into a biotechnological arms race. This is not a viewpoint adopted by all authors. Miah (2004) has argued that genetic editing to enhance performance may be seen as a type of innovation analogous to the use of new equipment, rather than as a type of doping analogous to the use of prohibited drugs. On similar lines, Savulescu, referenced by Skipper (2004) has argued that in fact 'gene doping' is entirely consistent with the 'spirit of sport' and with a centuries long tradition of trying to optimise performance by any means necessary or available. Underlying such arguments is an assumption that athletes should be allowed to exercise unconstrained autonomy when deciding to subject their bodies, and coerce athletic competitors, to medical or genetic treatments, and that the fulfilment of the principle of autonomy outweighs any concerns on the part of others about harms to the athlete.

Without evaluating the de/merits of these permissive postures (Loland and McNamee 2016), these arguments do not apply with the same force to equine sport, since animals are incapable of exercising autonomy concerning such interventions. Veterinarians, animal owners and breeders ought to act in the best interests of equine athletes (Campbell 2013a, 2013b) but it is far from certain what this would look like or whether indeed they do. It follows that significant weight should be accorded to the likelihood of deleterious effects of gene editing. In terms of benefits, we reject Neuhaus and Parent's (2019) claim that gene editing to enhance performance could also improve equine welfare by reducing 'wastage rates' (i.e. retirement or euthanasia rates) due to suboptimal performance. That argument is unconvincing since the limit of what is 'inadequate' would merely continue to shift upwards as equine athletes became increasingly genetically modified, thus diminishing any potential positional advantage. In such a scenario, wastage rates due to suboptimal performance remain unaffected.

We conclude that welfare-based harm:benefit analysis, recognising the currently unpredictable likelihood of off-target and deleterious effects of existing gene-editing techniques, supports the ethical salience for the distinction between genetic correction and genetic enhancement in equine sport in the present case.

A Modified Therapeutic Use Exemption Policy: Permit 'Therapy' While Prohibiting 'doping'

Notwithstanding the acknowledged conceptual challenges, we have argued for the recognition of an ethical distinction between 'corrective' and performance enhancing gene editing. Regulators are currently challenged by simultaneous, welfare-based ethical imperatives to allow gene editing in order to improve equine welfare and to prohibit gene editing in order to protect equine welfare. Such a conundrum is the product of the uncertain and incomplete state of the science of gene editing. How then should regulation around gene editing and equine sport be structured in order to best protect equine welfare in the face of such uncertainty?

One possible solution would be to augment the current blanket ban on gene editing with a case-by-case assessment of applications to permit gene editing, based on an analysis of best welfare interests and underwritten by the aim of facilitating fair sport. This would effectively be a modified form of WADAs International Standard for Therapeutic Use Exemptions (TUE) (WADA 2019a) apt to regulate gene editing. The TUE systems are well established for the use of medicinal drugs in human sport, where the primacy of an athlete's right to treatment is acknowledged. The TUE process is controversial (Bloodworth, Cox, and McNamee 2018; Fitch 2012) and prone to abuse (Cox, Bloodworth, and McNamee 2017), such that some authors suggest its abolition on the grounds of fairness (Dimeo and Møller 2017, 2018). In enabling treatment under a TUE, the World Anti-Doping Agency (WADA) aims to allow athletes with a genuine disease state to return to their 'normal' functioning levels (WADA 2019b). Some equine regulators, for example, the FEI, allow the limited use of certain specified drugs in equine athletes during competition. Other regulators, for example, those governing racing, insist that equine athletes should be free of the effects of drugs on competition days. Nevertheless, something like a TUE process might provide a regulatory mechanism of distinguishing between 'correction' and 'enhancement' at an individual level, that currently seems to be impossible at a species (or even breed) level for the reasons explained above. In order to be effective, compliance with such a TUE system would need to be enforced via effective testing methods for undeclared, unauthorised gene editing. Granted such a system will depend on the trustworthiness of the veterinarian who approves the TUE certificate, as it relies on the trustworthiness of doctors in human sport.

The TUE system for gene editing in equine athletes would require rigorous provision for obligatory short, medium and long-term reporting of the health and welfare status of animals who have been genetically modified, and for independent collection and analysis of that data. This would have the indirect benefit of facilitating longitudinal health and welfare data for horses analogous to studies of the health of children conceived using assisted reproductive techniques (e.g. Fauser et al. 2014; Hansen et al. 2005), promoted in the UK by the reporting function contained within the Human Fertilisation and Embryology Act (1990, as updated in 2008). By adopting this rather cautious,' individual TUE plus reporting' approach, regulators may manage to simultaneously promote and protect equine welfare. Finally, such a 'TUE plus reporting' system would provide an evidence base for ethical decision-making concerning future gene editing in equine athletes.

Conclusion

Many of the ethical issues surrounding the use of genetic technologies in humans and human athletics, most obviously those concerning consent and autonomy, do not apply to horses or equine athletes. Nevertheless, in light of the fact that horses as complex, sentient animals are deserving of moral consideration, genetic testing for disorders is not only justified but should be encouraged on welfare grounds. Whilst testing for performance traits to inform breeding decisions is an extension of historic selective breeding in non-human animals, caution should be exercised in its use due to the possibility of indirect adverse welfare consequences of 'wastage' or abandonment.

The same ethical imperative which should encourage us to test for the heritable disease should also cause us to genetically edit horses and horse embryos to reduce genetic predisposition to disease and injury. This positive ethical intervention ought not to extend permissively as in some slippery slope position. The effects of gene editing on health and welfare, particularly when combined with other techniques such as cloning, are at present undetermined. This makes genetic editing ethically distinct from genetic testing.

Given the current state of science, there is an ambiguous but valuable distinction between equine gene editing for 'treatment' and for 'enhancement'. Given possible unpredictable and poorly understood off-target and deleterious effects, we have argued that gene editing is only justified for purposes of correcting/preventing disease and injury. As and when the science develops and is refined to abolish negative effects on health and welfare, genetic editing of horses for enhancement of performance may become ethically acceptable, based in a harm: benefit analysis. In the meantime, the welfare of equine athletes and of human athletes for whom equine athletes and sport may serve as models should be protected by the development of international regulation and reporting systems akin to WADAs International Standard for Therapeutic Exemptions for genetic editing in horses.

Notes

1. We acknowledge that the ethical discussion on genetic technologies is hostage to broader debates around animal welfare. Specifically, ethical arguments about the acceptability of the use of genetic technologies in horses are inevitably dependent upon one's view of the moral status of horses and hence the justifiability of their use by humans. We do not have space here to consider alternative philosophical views of the moral status of animals, reviewed by GRUEN, L (2010) The moral status of animals. The Stanford Encyclopaedia of Philosophy. Available at http:/plato.stanford.edu/archives/fall2010/entries/moral-animal (Accessed 12.02.2020). Throughout our arguments, we adopt a view of the moral status of animals that has been previously described (CAMPBELL, M.L.H. (2019) How we think about animals. Ch 1 in Animals, Ethics and Us. 5 M publishing, Sheffield, 1–9): animals are recognised as sentient beings with interests in having their own welfare protected but whose moral status is ultimately inferior to that of humans due to animals' lack of a sense of future. Humans are expected to pay virtuous attention to animals' welfare needs—to minimise harms and to maximise benefits—but human benefits may sometimes be allowed to trump animal harms.
2. Examples of testing for recessive genes which can cause equine disease include testing for Hereditary Equine Regional Dermal Asthenia Disorder (HERDA) in Quarterhorses (ZÖLDÁG, L. (2011). Current and relevant genetic diseases of horses. Literature review. *Magyar Állatorvosok Lapja* **133**(8): 451–463); Severe Combined Immunodeficiency Disorder (SCID) in

Arabian horses (ALEMAN, M. FINNO, C.J. WEICH, K. AND PENEDO M. C. T. (2018). Investigation of Known Genetic Mutations of Arabian Horses in Egyptian Arabian Foals with Juvenile Idiopathic Epilepsy. *J Vet Intern Med* **32**(1): 465–468); and Fragile Foal Syndrome (WFFS) in Warmblood breeds (Dias, N. M.,. de Andrade, D. G. A Teixeira-Neto, A.R., Trinque, C.M., Oliveira-Filho, J.P., Winand, N.J., Araujo, Jr. J.P and Borges A.S. (2019) Warmblood Fragile Foal Syndrome causative single nucleotide polymorphism frequency in Warmblood horses in Brazil. *Vet J* **248**: 101–102).

3. The five diseases are HYPP; MH; Glycogen Branching Enzyme Deficiency Disorder (GBED); Hereditary Equine Regional Dermal Asthenia Disorder (HERDA) and Polysaccharide Storage Myopathy Disorder (PSSM).
4. This is evidenced by the use of the techniques in other large animals such as pigs and cattle West, J. and W. W. Gill (2016). Genome Editing in Large Animals. *Journal of Equine Veterinary Science* **41**: 1–6.
5. At the time of writing, no report of foals being born from the embryos which were genetically edited in the Kheiron and Lian Laboratories has been published.
6. In human medicine, a distinction is made between 'genetic testing', i.e. of an individual in whom disease is suspected on clinical grounds and 'genetic screening', i.e. genetic testing which is carried out when there is no prior evidence of disease in an individual.
7. For example, the National Collegiate Athletic Association (NCAA) in the USA has a mandatory testing programme for sickle cell anaemia trait.
8. In human sport, it has been argued on egalitarian grounds that gene editing levels the playing field Tamburrini, C. M. (2007). 'What's wrong with genetic inequality? The impact of genetic technology on elite sports and society.' Sport, Ethics and Philosophy **1**(2): 229–238.
9. We accept in making this argument that the same argument could be applied to breeding from animals who have had 'corrective surgeries' for conditions with a plausible hereditary component, for example, recurrent laryngeal neuropathy Gerber, V., C. Tessier and E. Marti (2015). 'Genetics of upper and lower airway diseases in the horse.' Equine Vet J **47**(4): 390–397, Draper, A. C. E. and R. J. Piercy (2018). 'Pathological classification of equine recurrent laryngeal neuropathy.' Journal of veterinary internal medicine **32**(4): 1397–1409.

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References

ALEMAN, M., C.J. FINNO, K. WEICH, and M.C.T. PENEDO. 2018. Investigation of known genetic mutations of Arabian horses in Egyptian Arabian foals with juvenile idiopathic epilepsy. *Journal Of Veterinary Internal Medicine / American College of Veterinary Internal Medicine* 32 (1): 465–68. doi:10.1111/jvim.14873.

ALEMAN, M., J.E. NIETO, and K.G. MAGDESIAN. 2009. Malignant hyperthermia associated with ryanodine receptor 1 (C7360G) mutation in quarter horses. *Journal Of Veterinary Internal Medicine / American College of Veterinary Internal Medicine* 23: 329–34. doi:10.1111/j.1939-1676.2009.0274.x.

ANDERSON, L., D. EXETER, and L. BOWYER. 2012. Sudden cardiac death: Mandatory exclusion of athletes at risk is a step too far. *British Journal of Sports Medicine* 46 (5): 331–34. doi:10.1136/bjsports-2011-090260.

ANDERSON, L.C. and G.F. GERRARD. 2005. Ethical issues concerning New Zealand sports doctors. *Journal of Medical Ethics* 31: 88–92. doi:10.1136/jme.2002.000836.

Anon. 2013. UAE horse dies in 120km endurance ride. Available at:http://www.horseandhound.co.uk/news/uae-horse-dies-in-120km-race-412468 (accessed 10 December 2019)

Anon. 2017. Sport horses with genetic edits will be with us soon, say researchers. Available at https://www.horsetalk.co.nz/2017/12/28/sport-horses-genetic-edits-researchers/ (accessed 9 September 2019)

AQHA. 2019a.. Genetic test roundup. Available from https://www.aqha.com/-/genetic-test-roundup (accessed 9 December 2019).

AQHA. 2019b. AQHA Rulebook. Available at https://www.aqha.com/aqha-rulebook (accessed 9 December 2019).

Argentinian government. 2018. Caballos clonados con genes editados, otra hazaña de científicos argentinos.Available at https://www.argentina.gob.ar/noticias/caballos-clonados-con-genes-editados-otra-hazana-de-cientificos-argentinos (accessed 9 December 2019).

Asadollahpour Nanaei, H., A. Ayatollahi Mehrgardi, and A. Esmailizadeh. 2019. Comparative population in genomics unveils candidate genes for athletic perfomance in Hanoverians. *Genome*. 62 (4):279–85.

BAINS, W. 2010. Genetic exceptionalism. *Nature Biotechnology* 28 (3): 212–13. doi:10.1038/nbt0310-212b.

BALTIMORE, D., P. BERG, M. BOTCHAN, D. CARROLL, R.A. CHARO, G. CHURCH, J.E. CORN, G.Q. DALEY, J.A. DOUDNA, M. FENNER, H. T. GREELY, M. JINEK, G.S. MARTIN, E. PENHOET, J. PUCK, S.H. STERNBERG, J.S. WEISSMAN, and K. YAMAMOTO. 2015. Biotechnology. A prudent path forward for genomic engineering and germline gene modification. *Science (New York, N.Y.)* 348 (6230): 36–38. doi:10.1126/science.aab1028.

BAYEFSKY, M.J. 2017. Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism. *Reproductive Biomedicine & Society Online* 3: 41–47. doi:10.1016/j.rbms.2017.01.001.

BEAUCHAMP, T.L. and J.F. CHILDRESS. 2009. *Principles of biomedical ethics*. New York: Oxford University Press.

BHA. 2019. About integrity. Available at https://www.britishhorseracing.com/regulation/integrity/ (accessed 9 December 2019).

BINNS, M.M., D.A. BOEHLER, E. BAILEY, T.L. LEAR, J.M. CARDWELL, and D.H. LAMBERT. 2012. Inbreeding in the Thoroughbred horse. *Animal Genetics* 43 (3): 340–42. doi:10.1111/j.1365-2052.2011.02259.x.

BLOODWORTH, A., L. COX, and M. MCNAMEE. 2018. What to do with the TUE process? Bradley Wiggins, therapeutic use, and data sharing, chapter 16. In *Doping in cycling: interdisciplinary perspectives*, edited by B. Fincoeur, J. Gleaves, and F. Ohl. London: Routledge: 220–33.

BLOODWORTH, A.J. and M. MCNAMEE. 2017. Sport, society, and anti-doping policy: An ethical overview *Medicine and Sport Science*. 62: 177–85.

BLOTT, S.C., J.E. SWINBURNE, C. SIBBONS, L.Y. FOX-CLIPSHAM, M. HELWEGEN, L. HILLYER, T.D. PARKIN, J.R. NEWTON, and M. VAUDIN. 2014. A genome-wide association study demonstrates significant genetic variation for fracture risk in Thoroughbred racehorses. *BMC Genomics* 15: 147. doi:10.1186/1471-2164-15-147.

BROSNAHAN, M.M., S.A. BROOKS, and D.F. ANTCZAK. 2010. Equine clinical genomics: A clinician's primer. *Equine Veterinary Journal* 42 (7): 658–70. doi:10.1111/j.2042-3306.2010.00166.x.

BURGESS, M.M. 2001. Beyond consent: Ethical and social issues in genetic testing. *Nature Reviews Genetics* 2 (2): 147–51. doi:10.1038/35052579.

CAMPBELL, M.L.H. 2013a. The role of veterinarians in equestrian sport: A comparative review of ethical issues surrounding human and equine sports medicine. *The Veterinary Journal* 197 (3): 535–40. doi:10.1016/j.tvjl.2013.05.021.

CAMPBELL, M.L.H. 2013b. When does use become abuse in equestrian sport?. *Equine Veterinary Education* 25 (10): 489–92. doi:10.1111/eve.2013.25.issue-10.

CAMPBELL, M.L.H. 2016. Freedoms and frameworks: How we think about the welfare of competition horses. *Equine Veterinary Journal* 48 (5): 540–42. doi:10.1111/evj.12598.

CAMPBELL, M.L.H. 2019. *Animals, ethics and us: A veterinarian's view of human: animal interactions*. Oxfordshire: 5M Publishing.

CAMPBELL, M.L.H. 2018. Equine embryo research ethics – Should we worry? *Equine Veterinary Journal* 50 (3): 384–85. doi:10.1111/evj.12816.

CAMPORESI, S. 2013. Bend it like Beckham! The ethics of genetically testing children for athletic potential. *Sport Ethics Philos* 7 (2): 175–85. doi:10.1080/17511321.2013.780183.

CAMPORESI, S. and M.J. MCNAMEE. 2016. Ethics, genetic testing, and athletic talent: Children's best interests, and the right to an open (athletic) future. *Physiological Genomics* 48 (3): 191–95. doi:10.1152/physiolgenomics.00104.2015.

CHOI, H.Y., C. PENEDO, and K. HINRICHS. 2015. Genetic testing of equine embryos. Paper presented at International Embryo Transfer Society Equine Reproduction Symposium, Paris.

CHOI, Y.H., A. GUSTAFSON-SEABURY, I.C. VELEZ, D.L. HARTMAN, S. BLISS, F.L. RIERA, J.E. ROLDÁN, B. CHOWDHARY, and K. HINRICHS. 2010. Viability of equine embryos after puncture of the capsule and biopsy for preimplantation genetic diagnosis. *Reproduction* 140 (6): 893–902. doi:10.1530/REP-10-0141.

CHOI, Y.H., M.C. PENEDO, P. DAFTARI, I.C. VELEZ, and K. HINRICHS. 2015. Accuracy of preimplantation genetic diagnosis in equine in vivo-recovered and in vitro-produced blastocysts. *Reproduction, Fertility, and Development* 28: 1382–89. doi:10.1071/RD14419.

COX, L., A. BLOODWORTH, and M. MCNAMEE. 2017. Olympic doping, transparency, and the therapeutic exemption process *Diagoras: International Academic Journal on Olympic Studies*. 1: 55–74.

CYRANOSKI, D. 2018. Baby gene edits could affect a range of traits. *Nature*. *Nature (news)*. Available at https://www.nature.com/articles/d41586-018-07713-2 (accessed 9 September 2019). doi:10.1038/d41586-018-07713-2.

CYRANOSKI, D. 2019. The CRISPR-baby scandal: What's next for human gene-editing. *Nature* 566: 440–42. doi:10.1038/d41586-019-00673-1.

DIESTERBECK, U. and O. DISTL. 2007. Review of genetic aspects of radiological alterations in the navicular bone of the horse. *Deutsch Tierarztl Wochenschr* 114 (11): 404–11.

DIMEO, P. and V. MØLLER (2017). Elite sport: Time to scrap the therapeutic exemption system of banned medicines. *The Conversation*. Available at http://theconversation.com/elite-sport-time-to-scrap-the-therapeutic-exemption-system-of-banned-medicines-89252 (accessed 9 December 2019).

DIMEO, P. and V. MØLLER. 2018. *The anti-doping crisis in sport: Causes, consequences, solutions*. London: Routledge.

DISTL, O. 2013. The genetics of equine osteochondrosis. *Veterinary Journal (London, England : 1997)* 197 (1): 13–18. doi:10.1016/j.tvjl.2013.03.036.

DOHERTY, O., V. CASEY, P. MCGREEVY, and S. ARKINS. 2017. Noseband use in equestrian sports - An international study. *PloS One* 12 (1): e0169060. doi:10.1371/journal.pone.0169060.

EFTBA (2016). Communique: Recent racing news and events and equine genomics. Available at https://www.eftba.eu/news.php?id=28 (accessed 9 December 2019).

F. E. I. (2019). Veterinary regulations. Available at https://inside.fei.org/sites/default/files/2019%20VRs%20final%20-%20Clean.pdf (accessed 9 December 2019).

FAUSER, B.C., P. DEVROEY, K. DIEDRICH, B. BALABAN, M. BONDUELLE, H.A. DELEMARRE-VAN DE WAAL, C. ESTELLA, D. EZCURRA, J. P. JGERAEDTS, C.M. HOWLES, L. LERNER-GEVA, J. SERNA, and D. WELLS. 2014. Health outcomes of children born after IVF/ICSI: A review of current expert opinion and literature. *Reproductive Biomedicine Online* 28 (2): 162–82. doi:10.1016/j.rbmo.2013.10.013.

FERRARI, R., L.S. PARKER, R.E. GRUBS, and L. KRISHNAMURTI. 2015. Sickle cell trait screening of collegiate athletes: Ethical reasons for program reform. *Journal of Genetic Counseling* 24 (6): 873–77. doi:10.1007/s10897-015-9849-1.

FINNO, C.J. and D.L. BANNASCH. 2014. Applied equine genetics. *Equine Veterinary Journal* 46 (5): 538–44. doi:10.1111/evj.12294.

FINNO, C.J., S.J. SPIER, and S.J. VALBERG. 2009. Equine diseases caused by known genetic mutations. *Veterinary Journal (London, England : 1997)* 179 (3): 336–47. doi:10.1016/j.tvjl.2008.03.016.

FITCH, K. 2012. Proscribed drugs at the olympic games: Permitted use and misuse (doping) by athletes. *Clinical Medicine* 12 (3): 257–60. doi:10.7861/clinmedicine.12-3-257.

GEELEN, E., K. HORSTMAN, C.L.M. MARCELIS, P.A. DOEVENDANS, and I. VAN HOYWEGHEN. 2012. Unravelling fears of genetic discrimination: An exploratory study of Dutch HCM families in an era of genetic non-discrimination acts. *European Journal of Human Genetics: EJHG* 20 (10): 1018–23. doi:10.1038/ejhg.2012.53.

GERBER, V., C. TESSIER, and E. MARTI. 2015. Genetics of upper and lower airway diseases in the horse. *Equine Veterinary Journal* 47 (4): 390–97. doi:10.1111/evj.12289.

GUIGNOT, F., F. REIGNER, C. PERREAU, P. TARTARIN, J.M. BABILLIOT, B. BED'HOM, M. VIDAMENT, P. MERMILLOD, and G. DUCHAMP. 2015. Preimplantation genetic diagnosis in Welsh pony embryos after biopsy and cryopreservation. *Journal of Animal Science* 93 (11): 5222–31. doi:10.2527/jas.2015-9469.

GUPTA, D., O. BHATTACHARJEE, D. MANDAL, M.K. SEN, D. DEY, A. DASGUPTA, T.A. KAZI, R. GUPTA, S. SINHAROY, K. ACHARYA, D. CHATTOPADHYAY, V. RAVICHANDIRAN, S. ROY, and D. GHOSH. 2019. CRISPR-Cas9 system: A new-fangled dawn in gene editing. *Life Sciences* 232: 116636. doi:10.1016/j.lfs.2019.116636.

GUTH, L.M. and S.M. ROTH. 2013. Genetic influence on athletic performance. *Current Opinion in Pediatrics* 25 (6): 653–58. doi:10.1097/MOP.0b013e3283659087.

HANSEN, M., C. BOWER, E. MILNE, N. DE KLERK, and J.J. KURINCZUK. 2005. Assisted reproductive technologies and the risk of birth defects: a systematic review. *Human Reproduction* 20 (2): 328–38. doi:10.1093/humrep/deh593.

HARPER, A. 2010. Breakthrough in genetic testing of embryos. *The Horse* (April 18). Available at https://thehorse.com/154294/breakthrough-in-genetic-testing-of-embryos/ (accessed 10 December 2019).

HARRISON, P.T. and S. HART. 2018. A beginner's guide to gene editing. *Experimental Physiology* 103 (4): 439–48. doi:10.1113/eph.2018.103.issue-4.

HARRISON, S.P. and J.L. TURRION-GOMEZ. 2006. Mitochondrial DNA: An important female contribution to thoroughbred racehorse performance. *Mitochondrion* 6: 53–66. doi:10.1016/j.mito.2006.01.002.

HECTOR, C. (2019). WFFS sweeps the breeding world. *The Horse Magazine*. Available at https://www.horsemagazine.com/thm/2019/03/wffs-sweeps-the-breeding-world/ (accessed 10 September 2019).

HERRERA, C., M.I. MORIKAWA, B. BELLO, M. VON MEYEREN, J. EUSEBIO CENTENO, P. DUFOURQ, M.M. MARTINEZ., and J. LLORENTE (2015). Embryo sexing followed by implantation. Paper presented at International Embryo Transfer Society Equine Reproduction Symposium, Paris.

HERRERA, C., M.I. MORIKAWA, M.B. BELLO, M. VON MEYEREN, J.E. CENTENO, P. DUFOURQ, M.M. MARTINEZ, and J. LLORENTE. 2014. Setting up equine embryo gender determination by preimplantation genetic diagnosis in a commercial embryo transfer program. *Theriogenology* 81 (5): 758. doi:10.1016/j.theriogenology.2013.12.013.

HFEA (2019). Pre-implantation genetic diagnosis. Available at https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/pre-implantation-genetic-diagnosis-pgd/ (accessed 9 December 2019).

HILL, E.W., J. GU, S.S. EIVERS, R.G. FONSECA, B.A. MCGIVNEY, P. GOVINDARAJAN, N. ORR, L.M. KATZ, and D. MACHUGH. 2010a. A sequence polymorphism in MSTN predicts sprinting ability and racing stamina in thoroughbred horses (Speed gene in racehorses). *PloS One* 5 (1): e8645. doi:10.1371/journal.pone.0008645.

HILL, E.W., B.A. MCGIVNEY, J. GU, R. WHISTON, and D.E. MACHUGH. 2010b. A genome-wide SNP-association study confirms a sequence variant (g.66493737C>T) in the equine myostatin (MSTN) gene as the most powerful predictor of optimum racing distance for Thoroughbred racehorses. *BMC Genomics* 11: 552. doi:10.1186/1471-2164-11-552.

HILL, E.W., D.P. RYAN, and D.E. MACHUGH. 2012. Horses for courses: A DNA-based test for race distance aptitude in thoroughbred racehorses. *Recent Patents on DNA & Gene Sequences* 6 (3): 203–08. doi:10.2174/187221512802717277.

HINRICHS, K. 2018. Assisted reproductive techniques in mares. *Reproduction in Domestic Animals = Zuchthygiene* 53 (Suppl 2): 4–13. doi:10.1111/rda.13259.

HINRICHS, K. and Y.-H. CHOI. 2012. Equine embryo biopsy, genetic testing, and cryopreservation. *Journal of Equine Veterinary Science* 32 (7): 390–96. doi:10.1016/j.jevs.2012.05.005.

HOLM, S. and M. MCNAMEE. 2011. Physical enhancement: What baseline, whose judgment? In *Enhancing Human Capacities*, edited by J.S. Ter, R. Meulen, G. Kahane, and N.J. Hoboken. Oxford: Jon Wiley and Sons. 291–303.

IFHA. 2019. International federation of horseracing authorities' international agreement on breeding, racing and wagering. Available at https://www.ifhaonline.org/resources/ifAgreement.pdf (accessed 9 December 2019).

JACOB, Y., T. SPITERI, N.H. HART, and R.S. ANDERTON. 2018. The potential role of genetic markers in talent identification and athlete assessment in elite sport. *Sports (Basel)* 6 (3): pii E88. doi:10.3390/sports6030088.

JEFFERIES, A. 2019. Genetic tests for horses. *Equus Magazine*. Available at https://equusmagazine.com/horse-world/appliedgenetics (accessed 10 September 2019).

JINEK, M., K. CHYLINSKI, I. FONFARA, M. HAUER, J.A. DOUDNA, and E. CHARPENTIER. 2012. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 337 (6096): 816–21. doi:10.1126/science.1225829.

KRISTJANSSON, T., S. BJORNSDOTTIR, A. SIGURDSSON, L.S. ANDERSSON, G. LINDGREN, S.J. HELYAR, A.M. KLONOWSKI, and T. ARNASON. 2014. The effect of the 'Gait keeper' mutation in the DMRT3 gene on gaiting ability in Icelandic horses. *Journal of Animal Breeding and Genetics = Zeitschrift Fur Tierzuchtung Und Zuchtungsbiologie* 131 (6): 415–25. doi:10.1111/jbg.2014.131.issue-6.

KWPN. 2019. Warmblood fragile foal syndrome. Available at https://www.kwpn.org/kwpn-horse/selection–and-breedingprogram/breeding/wffs (accessed 9 December.2019).

LANPHIER, E., F. URNOV, S.E. HAECKER, M. WERNER, and J. SMOLENSKI. 2015. Don't edit the human germ line. *Nature* 519 (7544): 410–11. doi:10.1038/519410a.

LE PAGE, M. 2017. *Anti-doping agency to ban all gene editing in sport from 2018*. New Scientist online Available at https://www.newscientist.com/article/2149768-anti-doping-agency-to-ban-all-gene-editing-in-sport-from-2018/#ixzz62VvNlcc1 (accessed 5 March 2020).

LEADON, D., D. O'TOOLE, and V.E. DUGGAN. 2012. A demographic survey of unwanted horses in Ireland 2005–2010. *Irish Veterinary Journal* 65. *Ir Vet J* 65: 3. Available at https://irishvetjournal.biomedcentral.com/articles/10.1186/2046-0481-65-3. doi:10.1186/2046-0481-65-3.

LI, J.-R., S. WALKER, J.-B. NIE, and X.-Q. ZHANG. 2019. Experiments that led to the first gene-edited babies: The ethical failings and the urgent need for better governance. *Journal of Zhejiang University. Science* B20 (1): 32–38. doi:10.1631/jzus.B1800624.

LOLAND, S. 2015. Against genetic tests for athletic talent: The primacy of the phenotype. *Sports Medicine (Auckland, N.Z.)* 45 (9): 1229–33. doi:10.1007/s40279-015-0352-5.

LOLAND, S. and H. HOPPELER. 2012. Justifying anti-doping: The fair opportunity principle and the biology of performance enhancement. *European Journal of Sport Science* 12 (4): 347–53. doi:10.1080/17461391.2011.566374.

LOLAND, S. and M. MCNAMEE. 2016. Anti-doping, performance enhancement, and 'the spirit of sport': A philosophical and ethical critique In *Doping and public health*, edited by N. Ahmadi, A. Ljungqvist, and G. Svedsäter. Abingdon: Routledge. 111–23.

MAGAVERN, E.F., L. BADALATO, G. FINOCCHIARO, and P. BORRY. 2017. Ethical considerations for genetic testing in the context of mandated cardiac screening before athletic participation. *Genetics in Medicine : Official Journal of the American College of Medical Genetics* 19 (5): 493–95. doi:10.1038/gim.2016.146.

MCGIVNEY, B.A., J.A. BROWNE, R.G. FONSECA, L.M. KATZ, D.E. MACHUGH, R. WHISTON, and E.W. HILL. 2012. MSTN genotypes in Thoroughbred horses influence skeletal muscle gene expression and racetrack performance. *Animal Genetics* 43 (6): 810–12. doi:10.1111/age.2012.43.issue-6.

MCLEAN, A. and P. MCGREEVY. 2010. Ethical equitation: Capping the price horses pay for human glory. *Journal of Veterinary Behavior: Clinical Applications and Research* 5 (4): 203–09. doi:10.1016/j.jveb.2010.04.003.

MCNAMEE, M.J., A. MULLER, I. VAN HILVOORDE, and S. HOLM. 2009. Genetic testing and sports medicine ethics. *Sports Medicine (Auckland, N.Z.)* 39 (5): 339–44. doi:10.2165/00007256-200939050-00001.

MIAH, A. 2004. *Genetically modified athletes: Biomedical ethics, gene doping and sport*. London: Routledge.

MICKELSON, J.R. and S.J. VALBERG. 2015. The genetics of skeletal muscle disorders in horses. *Annu Rev Anim Biosci* 3: 197–217. doi:10.1146/annurev-animal-022114-110653.

MULLANE, L.A. (2010). Beasts of Burden: What happens to thoroughbred racehorses after retirement. *Washington Post*. Available at http://www.washingtonpost.com/wp-dyn/content/article/2010/05/21/AR2010052103337.html (accessed 10 December 2019).

MURRAY, T.H. 2017. A moral foundation for anti-doping: How far have we progressed? Where are the limits? *Medicine and Sport Science*. 62: 186–93.

NACCACHE, F., J. METZGER, and O. DISTL. 2018. Genetic risk factors for osteochondrosis in various horse breeds. *Equine Veterinary Journal* 50 (5): 556–63. doi:10.1111/evj.12824.

NAGY, A., J.K. MURRAY, and S.J. DYSON. 2014. Horse-, rider-, venue- and environment-related risk factors for elimination from Fédération Equestre Internationale endurance rides due to lameness and metabolic reasons. *Equine Veterinary Journal* 46 (3): 294. doi:10.1111/evj.12170.

NAYLOR, J.M. 1994. Equine hyperkalemic periodic paralysis: Review and implications. *The Canadian Veterinary Journal. La Revue Veterinaire Canadienne* 35 (5): 279–85.

NAYLOR, T. (2019) Doping in horse racing. Presentation at 'Doping in Sport' meeting of the Sports Management Professional Interest Network, London. Organised by Liverpool University.

NEGRO, S., F. IMSLAND, M. VALERA, A. MOLINA, M. SOLE, and L. ANDERSSON. 2017. Association analysis of KIT, MITF, and PAX3 variants with white markings in Spanish horses. *Animal Genetics* 48 (3): 349–52. doi:10.1111/age.12528.

NEUHAUS, C.P. and B. PARENT. 2019. Gene doping-in animals? Ethical issues at the intersection of animal use, gene editing, and sports ethics. *Cambridge Quarterly of Healthcare Ethics : CQ : the*

International Journal of Healthcare Ethics Committees 28 (1): 26–39. doi:10.1017/S096318011800035X.

New scientist 9th October (3147). Available at https://www.newscientist.com/article/2149768-anti-doping-agency-to-ban-all-gene-editing-in-sport-from-2018/#ixzz62VvNlcc1 (accessed 10 September 2019).

NORTON, E.M., J.R. MICKELSON, M.M. BINNS, S.C. BLOTT, P. CAPUTO, C.M. ISGREN, A.M. MCCOY, A. MOORE, R.J. PIERCY, J. E. SWINBURNE, M. VAUDIN, and M.E. MCCUE. 2016. Heritability of recurrent exertional rhabdomyolysis in standardbred and Thoroughbred racehorses derived from SNP genotyping data. *The Journal of Heredity* 107 (6): 537–43. doi:10.1093/jhered/esw042.

Nuffield Council of Bioethics. 1993. Genetic screening ethical issues. Available at http://nuffieldbioethics.org/wp-content/uploads/2014/07/Genetic_screening_report.pdf (accessed 9 December 2019).

Nuffield Council of Bioethics. 2006. Genetic screening: A supplement to the 1993 report by the nuffield council on bioethics. Available at http://nuffieldbioethics.org/wp-content/uploads/2014/07/Genetic-Screening-a-Supplement-to-the-1993-Report-2006.pdf (accessed 9 September 2019).

Nuffield Council of Bioethics. 2016. Genome editing: An ethical review. Available from http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf (accessed 9 September 2019).

POSTHUMUS, M., M. COLLINS, J. COOK, C.J. HANDLEY, W.J. RIBBANS, R.K. SMITH, R.P. SCHWELLNUS, and S.M. RALEIGH. 2010. Components of the transforming growth factor-beta family and the pathogenesis of human Achilles tendon pathology–a genetic association study. *Rheumatology (Oxford, England)* 49 (11): 2090–97. doi:10.1093/rheumatology/keq072.

RCVS (2012). Declaration. Availabale at http://www.rcvs.org.uk/advice-and-guidance/code-of-professional-conduct-for-veterinary-surgeons/#declaration (accessed 9 December2019).

RIEDER, S. 2009. Molecular tests for coat colours in horses. *Journal of Animal Breeding and Genetics = Zeitschrift Fur Tierzuchtung Und Zuchtungsbiologie* 126 (6): 415–24. doi:10.1111/j.1439-0388.2009.00832.x.

ROBERTS, J.C. 2002. Customizing conception: A survey of preimplantation genetic diagnosis and the resulting social, ethical, and legal dilemmas." *Duke Law and Technology Review* July 23.E1. Available at https://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1053&context=dltr (accessed 5 March 2020).

ROBERTSON, J.A. 2003. Extending preimplantation genetic diagnosis: The ethical debate: Ethical issues in new uses of preimplantation genetic diagnosis. *Human Reproduction* 18 (3): 465–71. doi:10.1093/humrep/deg100.

ROTH, S.M. 2012. Critical overview of applications of genetic testing in sport talent identification. *Recent Patents on DNA & Gene Sequences* 6 (3): 247–55. doi:10.2174/187221512802717402.

SAVULESCU, J. 2001. In defense of selection for nondisease genes. *The American Journal of Bioethics* 1 (1): 16–18. doi:10.1162/152651601750078907.

SAVULESCU, J. 2005. Compulsory genetic testing for APOE Epsilon 4 and boxingIn *Genetic technology and sport: Ethical questions*, edited by C.M. Tamburrini and T. Tannasjo. London: Routledge: 136–46.

SAVULESCU, J., J. PUGH, T. DOUGLAS, and C. GYNGELL. 2015. The moral imperative to continue gene editing research on human embryos. *Protein & Cell* 6 (7): 476–79. doi:10.1007/s13238-015-0184-y.

SCHAEFER, R.J., M. SCHUBERT, E. BAILEY, D.L. BANNASCH, E. BARREY, G.K. BAR-GAL, G. BREM, S.A. BROOKS, O. DISTL, R. FRIES, C. J. FINNO, V. GERBER, B. HAASE, V. JAGANNATHAN, T. KALBFLEISCH, T. LEEB, G. LINDGREN, M.S. LOPES, N. MACH, A. DA CAMARA MACHADO, J.N. JMACLEOD, A. MCCOY, J. METZGER, C. PENEDO, S. POLANI, S. RIEDER, I. TAMMEN, J. TETENS, G. THALLER, A. VERINI-SUPPLIZI, C.M. WADE, B. WALLNER, L. ORLANDO, J.R. MICKELSON, and M.E. MCCUE. 2017. Developing a 670k genotyping array to tag ~2M SNPs across 24 horse breeds. *BMC Genomics* 18 (1): 565. doi:10.1186/s12864-017-3943-8.

SCHRODER, W., A. KLOSTERMANN, and O. DISTL. 2011. Candidate genes for physical performance in the horse. *Veterinary Journal (London, England : 1997)* 190 (1): 39–48. doi:10.1016/j.tvjl.2010.09.029.

SHB (GB) (2019). Statement: Warmblood fragile foal syndrome. Available from http://www.sporthorsegb.co.uk/sports-horse-news-article.asp?$=113&o= (accessed 9 September 2019).

SKIPPER, M. 2004. Gene doping: A new threat for the Olympics? *Nature Reviews Genetics*. 5: 720. doi:10.1038/nrg1461.

SNELLOW, L. 2008. Overbreeding. *The Horse*. Available at http://www.thehorse.com/articles/22039/overbreeding (accessed 9 December.2019).

SOLE, M., M. VALERA, M.D. GOMEZ, J. SOLKNER, A. MOLINA, and G. MESZAROS. 2017. Heritability and factors associated with number of harness race starts in the Spanish Trotter horse population. *Equine Veterinary Journal* 49 (3): 288–93. doi:10.1111/evj.12632.

SONKSEN, P.H., D. COWAN, and R. HOLT. 2016. Use and misuse of hormones in sport. *The Lancet Diabetes & Endocrinology* 4 (11): 882–83. doi:10.1016/S2213-8587(16)30218-2.

SPARROW, R. 2008. Genes, identity, and the expressivist critique In *The sorting society*, edited by L. Skene and J. Thompson. Cambridge: Cambridge University Press. 111–32.

TARANTO, E., M. FISHMAN, H. BENJAMIN, and L. ROSS. 2018. Genetic testing by sports medicine physicians in the United States: Attitudes, experiences, and knowledge *Sports (Basel)*. 6: 4.

TERUAKI, T., O. AOI, T. MASAKI, K. MIO, K. HIRONAGA, H. KEI-ICHI, K. KANICHI, and N. SHUN-ICHI. 2019. Droplet digital PCR detection of the erythropoietin transgene from horse plasma and urine for gene-doping control *Genes*. 3: 243.

TIZIANO, F.D., V. PALMIERI, M. GENUARDI, and P. ZEPPILLI. 2016. The role of genetic testing in the identification of young athletes with inherited primitive cardiac disorders at risk of exercise sudden death. *Front Cardiovasc Med* 3: 28. doi:10.3389/fcvm.2016.00028.

TOZAKI, T., S. GAMO, M. TAKASU, M. KIKUCHI, H. KAKOI, K.-I. HIROTA, K. KUSANO, and S. NAGATA. 2018. Digital PCR detection of plasmid DNA administered to the skeletal muscle of a microminipig: A model case study for gene doping detection. *BMC Research Notes* 11 (1): 708–708. doi:10.1186/s13104-018-3815-6.

TOZAKI, T., E. HILL, W. HIROTA, K. KAKOI, H. GAWAHARA, H. MIYAKE, T. SUGITA, S. HASEGAWA, T. ISHIDA, N. NAKANO, and M. KUROSAWA. 2012. A cohort study of racing performance in Japanese Thoroughbred racehorses using genome information on ECA18. *Animal Genetics* 43 (1): 42–52. doi:10.1111/j.1365-2052.2011.02201.x.

University of Sydney (2019). Online mendelian inheritance in animals. Available at https://omia.org/home/ (accessed 9 December 2019).

VELIE, B.D., K.J. FEGRAEUS, M. SOLE, M.K. ROSENGREN, K.H. ROED, C.F. IHLER, E. STRAND, and G. LINDGREN. 2018. A genome-wide association study for harness racing success in the Norwegian-Swedish coldblooded trotter reveals genes for learning and energy metabolism.". *BMC Genetics* 19 (1): 80. doi:10.1186/s12863-018-0670-3.

VELIE, B.D., N.A. HAMILTON, and C.M. WADE. 2016. Heritability of racing durability traits in the Australian and Hong Kong Thoroughbred racing populations. *Equine Veterinary Journal* 48 (3): 275–79. doi:10.1111/evj.12436.

VERBAND, H. (2019). Statement from the board of the Hannoveraner Verband regarding WFFS. Available from http://hanoverian-gb.org.uk/drupal/?q=node/118 (accessed 9 September 2019).

VICHERA, G., D. VIALE, R. OLIVERA, V. ARNOLD, A. GRUNDNIG, J. BASTON, S. MIRIUKA, and L. MORO. 2019. 20 Generation of myostatin knockout horse embryos using clustered regularly interspaced short palindromic repeats/CRISPR-associated gene 9 and somatic cell nuclear transfer. *Reproduction, Fertility and Development* 31 (1): 136–136. doi:10.1071/RDv31n1Ab20.

VLAHOVICH, N., P.A. FRICKER, M.A. BROWN, and D. HUGHES. 2017. Ethics of genetic testing and research in sport: A position statement from the Australian institute of sport. *British Journal of Sports Medicine* 51 (1): 5–11. doi:10.1136/bjsports-2016-096661.

VON BORSTEL, U., I. DUNCAN, A. SHOVELLER, K. MERKIES, L. KEELING, and S. MILLMAN. 2009. Impact of riding in a coercively obtained Rollkur posture on welfare and fear of performance horses. *Applied Animal Behaviour Science* 116 (2): 228–36. doi:10.1016/j.applanim.2008.10.001.

WADA (2008). Levelling the playing field. Play True(3). Available at https://www.wada-ama.org/sites/default/files/resources/files/PlayTrue_2008_3_Levelling_the_Playing_Field_EN.pdf (accessed 9 September 2019).

WADA. 2019a. International standard for therapeutic use exemptions. Available at https://www.wada-ama.org/en/resources/therapeutic-use-exemption-tue/international-standard-for-therapeutic-use-exemptions-istue (accessed 26 February 2020).

WADA. 2019b. Therapeutic use exemptions. Available at https://www.wada-ama.org/en/what-we-do/science-medical/therapeutic-use-exemptions (accessed 9 September 2019).

WADE, C., S. M. GIULOTTO, E. SIGURDSSON, M. ZOLI, S. GNERRE, F. IMSLAND, T.L. LEAR, D.L. ADELSON, E. BAILEY, R.R. BELLONE, H. BLOCKER, O. DISTL, R.C. EDGAR, M. GARBER, T. LEEB, E. MAUCELI, J.N. MACLEOD, M.C. PENEDO, J.M. RAISON, T. SHARPE, J. VOGEL, L. ANDERSSON, D.F. ANTCZAK, T. BIAGI, M.M. BINNS, B.C. CHOWDHARY, S.J. COLEMAN, G. DELLA VALLE, S. FRYC, G. GUERIN, T. HASEGAWA, E.W. HILL, J. JURKA, G. KIIALAINEN, A. LINDGREN, J. LIU, E. MAGNANI, J.R. MICKELSON, J. MURRAY, S. G. NERGADZE, R. ONOFRIO, S. PEDRONI, M.F. PIRAS, T. RAUDSEPP, M. ROCCHI, K.H. ROED, O.A. RYDER, S. SEARLE, L. SKOW, J. E. SWINBURNE, A.C. SYVANEN, T. TOZAKI, S.J. VALBERG, M. VAUDIN, J.R. WHITE, M.C. ZODY, E.S. LANDER, and K. LINDBLAD-TOH. 2009. Genome sequence, comparative analysis, and population genetics of the domestic horse. *Science* 326 (5954): 865–67. doi:10.1126/science.1178158.

WAHO (2019a). Report from the WAHO Conference: Germany. Available from http://www.waho.org/germany-2/ (accessed 9 December 2019).

WAHO (2019b). Genetic disorders in Arabian horses. Available at http://www.waho.org/genetic-disorders-in-arabian-horses-current-research-projects/ (accessed 10 December 2019).

WEBBON, P. 2012. Harnessing the genetic toolbox for the benefit of the racing Thoroughbred. *Equine Veterinary Journal* 44 (1): 8–12. doi:10.1111/j.2042-3306.2011.00465.x.

WEBBORN, N., A. WILLIAMS, M. MCNAMEE, C. BOUCHARD, Y. PITSILADIS, I. AHMETOV, E. ASHLEY, N. BYRNE, S. CAMPORESI, M. COLLINS, P. DIJKSTRA, N. EYNON, N. FUKU, F.C. GARTON, N. HOPPE, S. HOLM, J. KAYE, V. KLISSOURAS, A. LUCIA, K. MAASE, C. MORAN, K. N. NORTH, F. PIGOZZI, and G. WANG. 2015. Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement. *British Journal of Sports Medicine* 49 (23): 1486–91. doi:10.1136/bjsports-2015-095343.

WELSH, C.E., T.E. LEWIS, S.C. BLOTT, D.J. MELLOR, A.J. STIRK, and T.D. PARKIN. 2014. Estimates of genetic parameters of distal limb fracture and superficial digital flexor tendon injury in UK Thoroughbred racehorses. *Veterinary Journal (London, England : 1997)* 200 (2): 253–56. doi:10.1016/j.tvjl.2014.03.005.

WILKINSON, S. 2006. Eugenics, embryo selection, and the equal value principle. *Clinical Ethics* 1: 46–51. doi:10.1258/147775006776173408.

WILKINSON, S. 2008. Sexism, sex selection and family balancing. *Medical Law Review* 16: 369–89. doi:10.1093/medlaw/fwn013.

WILLIAMS, A.G., H. WACKERHAGE, and S.H. DAY. 2016. Genetic testing for sports performance, responses to training and injury risk: Practical and ethical considerations *Medicine and Sport Science*. 61: 105–19.

ZÖLDÁG, L. 2011. Current and relevant genetic diseases of horses. Literature review. *Magyar Állatorvosok Lapja* 133 (8): 451–63.