Prospectus

Designing a Novel Device for Femoral Socket Preparation in ACL Reconstruction
(Technical Topic)

Constraining Omnipotence: How CRISPR Must be Regulated in the Coming Age
(STS Topic)

By

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Background

In the United States, approximately 200,000 Anterior Cruciate Ligament (ACL) ruptures occur annually, with numbers rising due to an increasingly active population (Samitier et al., 2015; Hosseini et al., 2011). Up to 15% of these patients will eventually require complete revision surgery due to postoperative complications, wherein the ligament must again be completely replaced and the surgery repeated. Unfortunately, repeated surgeries can compromise the structural integrity of other components of knee, and thus these revision surgeries maintain a significantly lower satisfaction rate of 76% relative to the 97% satisfaction of primary surgeries (Samitier et al., 2015). Most of these patients will then never return to pre-injury levels of function following revision. This resulting reduction in athletic capability has been observed to have tangible effects on mental health, with as many as 42% of ACL reconstruction (ACLR) patients experiencing clinically diagnosable depression following the surgery (Wu et al., 2016). Since 15-25 year-olds are known to have the highest incidence of ACL injury, and are simultaneously at the highest risk of depression induced suicide, the physical effect of postoperative complications from ACLR pose a significant threat to the mental wellbeing of this segment of the population.

As someone who similarly suffered post-operative complications following a career ending injury, I have personally experienced the sense of hopeless after surgery. As such, I have decided to utilize my technical background as an undergraduate engineer to develop a novel surgical tool that will aid with the success rate of primary ACL reconstruction. This device will serve to improve satisfaction rates following surgery via technical modifications to current technology, but is moreover significant as it will also allow patients maintain their quality of life and reduce the prevalence of resultant psychiatric comorbidities from unsatisfactory results.

Specifically, this instrument will enhance drilling trajectory during arthroscopy and increase the fidelity of the placement of the new ligament. While the technical portion of this investigation will be centered on orthopedic devices, the second half of this paper addresses the ethics of genetic engineering.

Femoral Tunnel Misalignment Leads to Graft Impingement

While the etiologic classification of ACLR failure remains complex and multifactorial, Noyes and Barber-Westin (2001) have presented specific indications of the need for revision surgery: (1) a complete graft tear with > 6 mm of anterior tibial displacement as compared to the healthy knee; (2) a positive pivot shift test graded +2 or +3 compared to the healthy knee, with or without knee pain or inflammation, or subjective sensation of instability or functional limitations for daily life and/or sports activities (Samitier et al., 2015). Literature has approximated that nearly 70% of such primary reconstruction failures can be attributed to technical errors (ibid). Among those failures, femoral tunnel malposition was reported to be the most common technical failure at 80% followed by tibial tunnel malposition at 37% (denominator is greater than 100% as surgeons were instructed to check all that apply) (Hosseini et al., 2012). The femoral and tibial tunnels are the holes that are drilled into the femur and tibia during surgery that serve to anchor the newly introduced ligament, called a graft. In other words, the majority of ACL reconstruction failures, as defined by the widely recognized standards set by Noyes and Barber, can be attributed technical errors by surgeons, with the most common being faulty drilling of the tibial and femoral tunnels that work to anchor the new ligament within the knee.

Even small changes in the placement of the femoral tunnel towards the tibial center of rotation may impact the kinematics of the knee (Carson et al., 1998; Hosseini et al., 2012; Samitier et al., 2015; Vergis et al., 1995; Vergis et al., 1975). With regards to the sagittal plane, overly anterior femoral tunnels may lead to tightened grafts during flexion, reducing a patient's range of motion, or can lead to graft stretching and resultant laxity (Bylski-Austrow et al., 1990; Good, Odensten, Gillquist, 1994; Hoogland, Hillen, 1984). When the femoral tunnel is too posterior, the graft may tighten in knee extension and have laxity on flexion, similarly leading to failure (Samitier et al., 2015). If, however, the graft does not break, then the knee may adapt to this circumstance by creating a knee flexion contracture with a deficit of complete extension. The biomechanical effect of this could impair the gait and cause anterior knee pain due to overload of the patello-femoral joint (ibid). With regards to the coronal plane, a centered and vertical femoral tunnel may restore anteroposterior stability but produce a rotational instability with a positive pivot shift test and increase biomechanical demand during rehabilitation (Wang, Fleischli, Zheng 2013; Kim et al., 2013; Streich, Reichenbacher, Barié, Buchner, Schmitt, 2013). Ultimately, these data demonstrate that even slight alterations to the placement of the tunnels can lead to grave biomechanical effects, underscoring the importance of accurate (described as "anatomical", since the accuracy of drilling is relative to the individual physiology of the patient) tunnel placement. Such developments have been recorded across all of the major ACL reconstruction techniques.

At the present time, there exist 4 commonly used drilling techniques, each with distinct advantages and disadvantages: transtibial (TT), anteromedial (AM), outside-in (OI) and retrograde drilling (RD), see Figure 1 below. While benefits and drawbacks of each technique are numerous, they can be generally summarized as the following: (1) TT- surgical familiarity,

but increased risk of nonanatomic placement due to constrained tibial drilling; (2) AM- unconstrained anatomic placement, but technically demanding with risk of short tunnels or sockets as well as posterior-wall blowout; (3) OI- unconstrained anatomic placement, but 2 incisions are required; (4) RD- unconstrained anatomic placement and all-epiphyseal drilling in skeletally immature patients, but fluoroscopy is needed for all-epiphyseal drilling (Robin et al., 2015). While each approach has its merits, they all fundamentally all rely on a single, real time visualization of the procedure. To this end, producing an instrument that allows for real time visualization of the intra-articular space from multiple angles would help surgeons in locating osseous landmarks to facilitate femoral portal drilling. The implications of such improvement would dramatically increase patient satisfaction, and thereby surgeon satisfaction. Moreover, a more operationally efficient tool would prove beneficial for the surgeon as it would maximize their operative capacity in a given time frame.

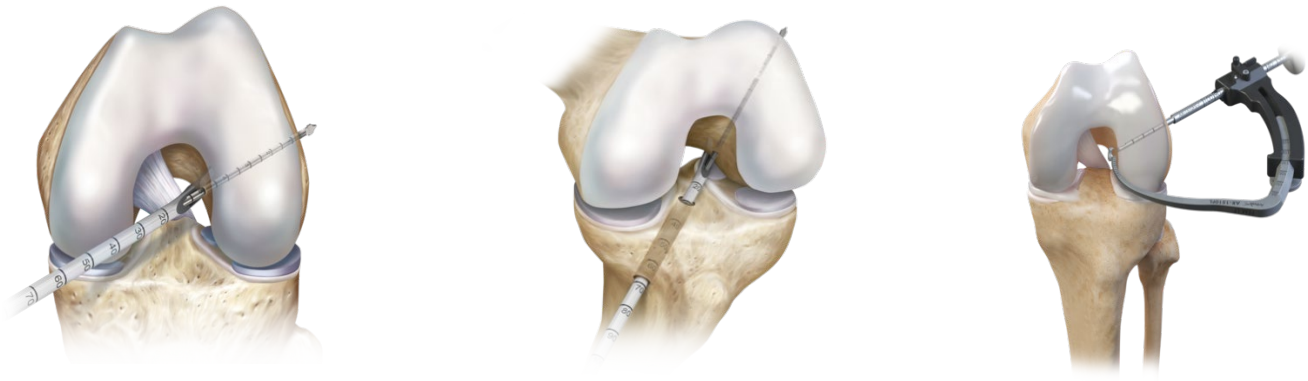

Figure 1. Images of three techniques to operate on the ACL. Left image shows representation of the TT technique. Center image depicts AM technique and right-hand image shows OI technique.

Although the technical portion of this capstone will be centered on orthopedic devices, as a biomedical engineer I would be remiss if I did not mention perhaps the most influential piece of technology not only within our field but even to our species as a whole: genetic engineering. As such, this portion of the prospectus diverges and focuses on the genetic editing aspect of clinical care and examining how the technology should be regulated as scientists rapidly refine the procedure.

Exploring CRISPR and its Significance

With 6% of all births having a serious defect of genetic origin and 35% of all deaths under 70 arising from chronic diseases (such as cancer and diabetes), such technology stands to benefit billions of humans across the globe (Savulescu, Pugh, Douglas, 2015). CRISPR-Cas9 (short for Clustered Regularly Interspaced Short Palindromic repeat DNA sequences) is the latest

iteration of [more precise descriptor] technology and considered to be the "hallmark of a bacterial defense system" (Tomlinson, 2018, p. 443). CRISPR itself is a naturally occurring molecule found in bacteria, but is often used as a catchall term for systems that enable researchers to program the CRISPR molecule to make precise cuts along a cell's genome (Broad Institute 2020). The system is facilitated via a guide RNA (gRNA) molecule which identifies particular portions of the DNA strand to initiate precise cleavage, allowing for the insertion or deletion of an entire genomic sequence, as well as more passive intervention by activating or suppressing a gene without completely adding/removing it (Redman et al., 2016; Adli, 2018). Scientists around the world have continually refined CRISPR technology to make it even more precise, with current techniques being described as "editing a sentence with a word processor to delete words or correct spelling mistakes" (Tomlinson, 2018, p. 446; Cohen 2016). These capabilities differentiate CRISPR from other contemporary gene editing techniques, as current treatments only target somatic cells, which are not inherited and unique to an individual (NIH, 2017). CRISPR, however, can alter germline cells that are heritable and become passed down lineages (ibid). This capacity to permanently alter heritable traits could thus lead to the complete eradication of both hereditary and chronic diseases that currently have no treatment (Tomlinson, 2018).

Is the Research Unethical?

While applications of CRISPR are numerous, the technology has proven an incredibly contentious topic for scientists and philosophers alike. Following the publication of the first study to successfully utilize the technique in human embryos by Liang et al. in 2015, many called for a moratorium of the research (Lanphier et al., 2015). Leading scientists expressed

much apprehension in the safety of the technique, noting several failures in Liang's initial investigation (Lanphier et al. 2015). Consequently, many refuted further research on the grounds that intentionally subjecting human embryos to such imprecise modifications was incredibly dangerous given the prevalence of inaccurate editing (Lanphier et al., 2015; Iyer et al., 2015; Baltimore et al., 2015). Moreover, many argued that even successful cases yielded unpredictable effects on future generations (as germ-line modifications would pass down through bloodlines) rendering it "ethically unacceptable" (ibid).

Conversely, proponents of the field such as Savulescu and Singer maintain that there is a "moral imperative" to continue this research, positing that intentionally refraining from such "life-saving" research is to be "morally responsible for the foreseeable, avoidable deaths of those who could have benefitted" (Savulescu, 2015, pp. 476-480; Singer 1993). They argue that current techniques such as *in vitro* fertilization (IVF) and pre-implantation genetic diagnosis (PGD) are not sufficiently practical alternatives. In such techniques, multiple embryos are genetically tested with only disease-free embryos selected for implantation. However, unless vast numbers of embryos are created (hundreds of thousands), it remains impossible to avoid complex multigenic disease using IVF and PGD. Consequently, diseases that have been identified to have a polygenic contribution will not be treatable without a more flexible method of genetic engineering (Bourne, Douglas, Savulescu, 2012). Additionally, Iyer and co-authors demonstrated that much research on gene editing can be accomplished according to stringent safety guidelines by utilizing tripronuclear (3PN) zygotes that occur naturally in ~2%–5% of zygotes during IVF clinical trials (Savulescu, 2015; Iyer et al., 2015). Since these zygotes never develop normally *in vivo*, they are never viable for implantation and make great candidates to further CRIPR research (Munné and Cohen, 1998). Furthermore, many supports of genetic engineering also cite

reproductive embryos as another alternative. Specifically, those embryos that were created for reproductive purposes, but that now exist in surplus and are to be destroyed. In this regard, these embryos are in a sense "bound to die", and thus there are no ethical qualms in science benefiting from their inevitable destruction (Outka, 2002). Trialing CRISPR with these zygotes thus provides the opportunity to refine research from a naturally occurring mechanism with no chance of a live birth, thereby bypassing the aforementioned ethical concerns.

Procreative Beneficence

From these arguments, Savulescu has designed a framework with which to evaluate procreative concerns. His principle of Procreative Beneficence (PB) adheres to a "common-sense" morality, where parents should always choose what they believe will create the best life for their children (Savulescu, 2009, p. 276). He applies this principle to a host contemporary procreative decisions, citing how parents with the choice of raising the same exact children under financial duress or as millionaires will always choose the latter in an effort to better support their children. In this regard there is a financial incentive to wealth as it *can* (but does not always guarantee to) provide children with a better life. Similarly, parents will always choose to raise children while they are emotionally stable rather than when they are under severe emotional duress (assuming all else equal), demonstrating the emotional incentive of mental wellbeing. Savulescu thus argues that there is a parallel moral incentive to raise children with the best chance of life via genetic engineering, and that this component is to be weighed equally against other procreative decisions. Henceforth PB recognizes the "genetic endowment" by parents to a child in a similar manner to their financial or emotional endowment while raising children, and procreative decisions require a delicate and contextual balance of these competing forces.

Specifically, he states that should a couple decide to have a child, they have "significant moral reason" to choose of the "possible" children, the one who would be most likely to experience the "greatest wellbeing", be the "most advantaged child", or otherwise have the "best chance" at life (Kahane, Savulescu, 2009, p. 274). In the following sections, these core pillars of PB will be further analyzed before utilizing the framework to evaluate several relevant case studies to ultimately develop a comprehensive picture as to how genetic engineering technologies such as CRISPR must be moderated in the future.

First, in labeling PB as a "moral reason" rather than an absolute obligation, Savulescu has succeeded in making this principle compatible with the natural decision making of parents. When possible, few would argue that couples should not wait to be able to financially or emotionally stable enough to support a child in order to give them a better chance of life within the couple's means. PB is simply an extension of this natural philosophy, highlighting how while couples should not be forced in choosing to have children with the best possible chance of wellbeing, there is a significant reason to do so via whatever tools are available. There has just been relatively few ways to accomplish this. CRISPR represents a new tool available to parents who wish to be able to support their children beyond emotional, financial, and personal means. Since many already fundamentally adhere to such a principle, applying PB to genetic engineering does not inherently deviate from the current social standard

Furthermore, the emphasis on selecting the "most advantaged" child lends it flexibility as its understanding of wellbeing is entirely contextual. While there exist several equally valid definitions of what constitutes a better or best life, Savulescu is neutral in this debate. PB's understating of wellbeing is "plural" and "open-ended". In this regard, it does not specifically delineate any particular understanding of wellbeing, but rather asks parents to apply their own

definition. PB's relegation of responsibility to the perception of parent is thus compatible with any situation, and its understanding of the contextual divergence of wellbeing prevents it from being constrained by normative, social, or genetic denotations of the term.

This stress on context is further seen in PB's understanding of disability, which Savulescu writes is critical in the aforementioned determination of wellbeing. Whereas many ethicists use either a biologically normative definition of disability or a purely socially constructed definition of the term, PB highlights the shortcomings of each. Savulescu explains how erectile dysfunction, for example, is considered a disability by most if not all members of society. However, according to normative inquiry, such deficiency is to be expected and does not deviate from the species norm (males are genetically designed to lose function with age). Henceforth, normative inquiries fail to recognize disabilities that may be inherent to species. Similarly, while a purely socially constructed term of disability is useful in capturing the notion of social prejudice limiting an individual's wellbeing (and thus also highlights the contextual nature of disability as it is contingent on a given society's values), it also is not always applicable. Indeed, Savulescu highlights that in some contexts, having perfect health can be a disadvantage, such as in Russia in the 1800s, where men of good health meant 15 years' service in the army, with a significant chance of being killed (Kahane, Savulescu, 2009). Deafness, for example, would be incredibly useful in a world of constant, cacophonous noise. These are a prime examples of socially constructed disabilities that only exists within the confines of their particular contexts. However, such social constructions are not always adequate in capturing the inherent disabilities in life. Few would argue that there is any benefit to debilitating joint pain regardless of any social context. Savulescu labels this as an "instrumental badness" that can be described to some extent via a biological normative inquiry but can be completely overlooked

with a constructionist theory. Moreover, although a constructionist theory lends itself to recognizing contextual markers, it still only does so from a broader social context. That is it say there is no consideration for personal disabilities. For example, in current times color blindness is hardly seen as a disability given that technology has advanced to the state where those afflicted can still live incredibly functional and fulfilling lives. It is at most a mild disability if even to be considered one at all. Henceforth, the relevant social forces prevent color blindness from being a debilitating disability for society as a whole. However, should a master painter suddenly fall colorblind, many would agree that to be incredibility debilitating for that individual. Neither a biological normative nor socially constructed definition would accurately depict such an event. As such, PB utilizes a hybrid of the two, recognizing some of the biological qualities that transcend social norms while simultaneously recognizing the contextual forces, both socially and personally, that contribute to an understanding of disability

Ultimately, PB is a useful framework with which handle the complex questions surrounding the regulation of genetic engineering as its delegation as a moral reason allows us to better balance the competing forces that may exist when raising children. Moreover, its commitment to only altering possible children restrains the limits of the technology enough such that it can be digested from a regulatory standpoint (making laws around technology Is much easier when the bounds of the technology have been clearly defined). Additionally, its understanding of wellbeing and disability as a combination of socially constructed forces, inherent biological forces, and context and person dependent forces lends it much flexibility in mediating the more subjective factors that regulate procreative decisions as is currently seen now with child-related legislation. As such, I plan to utilize PB as the foundational moral framework with which to investigate how CRISPR should be regulated in the age of genome editing

Regulatory Implications on Society

The current state of the technology in the US has allowed the research to continue under private donations but banning US government funding. As a result, such privately funded studies are subject to neither federal oversight nor state regulations, providing the government with limited control regarding the research plans of these studies (Tomlinson 2018). Consequently there exist no clearly defined ramifications for researchers who choose to ignore consensus-driven ethics in the field of genomic editing (ibid). Tomlinson further describes the United States' current regulatory regime for biotechnology as "woefully ineffectual" and, despite recent efforts to modernize this process, "outdated and inefficient" (ibid, p. 458). Non-therapeutic uses of the technology could create "classes of individuals" defined by the "quality of their engineered genome" (ibid, p. 459). Henceforth, the focus of this investigation will be utilizing PB to evaluate case studies of genetic modification in an effort to propose how the technology should be regulated in the coming age.

Research Methods

The proposed research will address the question: How CRISPR should be moderated in the coming age? In doing so, I will utilize a PB framework, drawing upon Savulescu's definitions of disability and wellbeing to evaluate the various case studies in the topic. As such this paper will draw evidence from prior literature from Savulescu in an effort to further advance his ideas into a more comprehensive moral scaffold. I will also explore some of philosopher Peter Singer's work regarding practical ethics in society, where he takes a somewhat stronger stance than Savulescu in that he believes refraining from such genetic engineering is ethically

reprehensible. These two works in particular will provide the moral and ethical backbone from which the capstone will draw upon to modulate regulations of CRISPR, supplementing Savulescu's initial paper describing of PB. Given that this will be largely a review of sources I have already encountered, I expect this phase of literature review to be completed by mid-January.

I will then turn my focus to identifying relevant case studies within the field of genetic engineering. I plan on finding at least three highly controversial and complex instances of some sort of genetic modification (or lack thereof) that will be analyzed. Though all of cases have not been identified, I plan on referring to the famous case of Sharon Duschneau and Candy McCullough, a deaf lesbian couple that deliberately created a deaf child by using sperm from a deaf male donor. In my evaluation, I will identify the given disability and its contribution to the subject's wellbeing, weigh it against other identifiable procreative decisions (financial/ emotional status) and determine morality of the choice against a PB backdrop. The outcomes of these evaluations will serve as the foundation from which I determine how genetic engineering technology should be regulated in the future. Given that this will require intense research into the topic regarding very challenging and morally ambiguous case studies and will essentially be the core of my prospectus, I believe this will take more time to complete relative to the first portion, and expect to finish in in mid-March.

Conclusions

The technical deliverable of this investigation will be a surgical tool that improves the accuracy of femoral tunnel drilling. This device will allow for more anatomical tunnel placement, reducing detrimental stresses on the ACL graft and thereby failure rates of primary

reconstruction. More effective surgeries will increase patient satisfaction rates, allowing them to better return to active lifestyles as well optimize surgeon's operating time. The STS deliverable, however, will pivot slightly from orthopedics and will focus on designing a framework for how modern gene editing technologies should be regulated in the near future. It will accomplish this by evaluating the PB lens and overlaying that with current disparities in access to healthcare a framework for regulation of gene editing will provide an initial foundation from which to build upon as such technology inevitably becomes refined enough to be used in a clinical setting.

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