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# The Future of Stem Cell Research and its Clinical Translation in Canada: Exploring Questions of Governance and Policy Options

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**Abstract**

Stem cell research is a promising area of biomedical research with tremendous potential for increasing our understanding of human development and for improving clinical treatment options across a range of serious conditions. However, it has historically also been a complex field, both scientifically and ethically. It raises numerous policy tensions including those related to the acceptability of different forms of research in the field and, more recently, regarding how to respond to the rapidly growing private market for clinical applications that lack broadly accepted forms of evidence of safety and efficacy. Using the Canadian market for unproven stem cell interventions as a case study, this review paper identifies questions of governance and policy options as they relate to the future of stem cell research and its clinical translation in Canada. Key areas of inquiry include the roles and influence of evidence, scientific and clinical imperatives, and public pressure on policy decisions, as well as the role of regulation in managing risks and uncertainty in fast moving fields of biomedicine. Examining these questions in a Canadian context is particularly timely at present given the emerging domestic private market for stem cell-based interventions coupled with scientific developments in the field that are highlighting ambiguities and other challenges with our current regulatory framework.

**Keywords**

Stem cell · Policy · Ethics · Regulation · Governance · Unproven interventions

## 1 Introduction

Regulating fast moving fields of science, like stem cell research, is no simple feat. One challenge policy makers face is that it can be difficult to predict with any accuracy both the potential benefits and also the potential risks of new technologies and avenues of research (Butenko and Larouche 2015; Harmon et al. 2013). However, understanding benefits and risks is critically important when it comes to trying to balance diverse and sometimes competing policy priorities. For example, in the stem cell field (as is true in others), there are a number of both pushes and pulls relevant to policy choices including, though certainly not limited to, the desire to stimulate economic growth, create jobs, encourage biomedical developments likely to improve clinical treatment options, respond to

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pressure from the public, patients or other stakeholder groups, address ethical, moral, and/or other concerns, and be responsive to international pressures. Although not always clearly delineated or directly acknowledged, it is important to be cognizant of these various potential influences on decision-making with respect to science and innovation policy (Phillips and Schmeiser 2017) – including in the context of stem cell research – when identifying and considering policy options.

It can also be difficult for regulators to identify what tools or strategies are the best fit for a given area or issue in order to achieve their desired objectives while limiting negative or unintended effects. In many cases, hard law approaches such as criminalization are ill-suited to regulate fields that are changing quickly. Their inflexible nature can make it difficult to adapt to unanticipated developments in the regulated field, risking legal ambiguity and/or unintended consequences when the law does not keep pace with scientific realities (Ogbogu et al. 2018b). Legal authority is also generally restricted by jurisdiction. Indeed, limited jurisdictional reach for regulators is a growing concern, particularly when considering issues with international implications that include cross-border and internet-based activities, such as markets for stem cell-based interventions (Shalev 2010; Sipp et al. 2017).

In this review paper, I will identify questions of governance and policy options as they relate to the future of stem cell research and its clinical translation in Canada, using the market for unproven stem cell interventions as a case study. To set the stage for this discussion, I will begin by framing the relevant regulatory context and by introducing what I suggest are governance challenges in this space, drawing on current examples from the field of stem cell research to highlight specific issues. I will then use the market for unproven stem cell interventions as a case study to illustrate these governance challenges, and to serve as a foundation for an exploration of future strategies. The paper will conclude with a brief discussion of policy options and governance strategies, with a view to contributing to future research strategies in this area.

## 2 Stem Cells: Promises, Pitfalls and Policy Challenges

### 2.1 Context – Regulation and Governance of Stem Cell Research in Canada

Stem cell research is a promising area of biomedical research with tremendous potential for increasing our understanding of human development and for improving clinical treatment options across a range of serious conditions. However, it has historically also been a complex field, both scientifically and ethically. It raises numerous policy tensions including those related to different avenues of stem cell research. For example, early debates about the acceptability – or lack thereof – of research involving the destruction of human embryos and concerns about different kinds of applications such as reproductive cloning, shaped much of the early policy discourse in the field and featured prominently in public forums including the media (Caulfield et al. 2010) and Canadian parliamentary debates (Caulfield and Bubela 2007).

In many ways, the current governance of stem cell research in Canada is a product of those early debates, with a long history of controversy. It is beyond the scope of this paper to provide a fulsome account of that history here (see Cattapan and Snow 2017). The work of the Royal Commission on New Reproductive Technologies, established in 1989, was particularly influential. Its 1993 report, *Proceed with Care – Final Report of the Royal Commission on New Reproductive Technologies* (Baird 1993), called for the regulation of a wide range of activities related to reproductive technologies, including research using human embryos. This report was followed by a number of failed legislative initiatives, ultimately leading to the passing of the *Assisted Human Reproduction Act* (S.C. 2004, c. 2) (AHRA) in 2004. The AHRA was federal legislation that purported to govern aspects of reproductive technologies as well as particular avenues of research. It did so by way of creating two categories of activities – those that were

controlled (relating to activities involved in assisted human reproduction), and those that were prohibited. The prohibited procedures related primarily (though not exclusively) to research activities, and included the following:

> 5 (1) No person shall knowingly
> (a) create a human clone by using any technique, or transplant a human clone into a human being or into any non-human life form or artificial device;
> (b) create an in vitro embryo for any purpose other than creating a human being or improving or providing instruction in assisted reproduction procedures;
> (c) for the purpose of creating a human being, create an embryo from a cell or part of a cell taken from an embryo or foetus or transplant an embryo so created into a human being;
> (d) maintain an embryo outside the body of a female person after the fourteenth day of its development following fertilization or creation, excluding any time during which its development has been suspended;
> (e) for the purpose of creating a human being, perform any procedure or provide, prescribe or administer any thing that would ensure or increase the probability that an embryo will be of a particular sex, or that would identify the sex of an in vitro embryo, except to prevent, diagnose or treat a sex-linked disorder or disease;
> (f) alter the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants;
> (g) transplant a sperm, ovum, embryo or foetus of a non-human life form into a human being;
> (h) for the purpose of creating a human being, make use of any human reproductive material or an in vitro embryo that is or was transplanted into a non-human life form;
> (i) create a chimera, or transplant a chimera into either a human being or a non-human life form; or
> (j) create a hybrid for the purpose of reproduction, or transplant a hybrid into either a human being or a non-human life form.

Contravening any of these provisions is associated with significant criminal sanctions, including a fine of up to $500,000 and/or imprisonment for up to 10 years (AHRA, s. 60).

The AHRA was controversial from the beginning, for a number of reasons (Caulfield 2002). For example, some people viewed it as being overly restrictive in terms of the limits it placed on scientific research; others noted its lack of clarity and responsiveness to emerging avenues of research (Ogbogu and Rugg-Gunn 2008; Rugg-Gunn et al. 2009); still others objected to what they saw as an inappropriate intrusion of the federal government into an area of provincial jurisdiction – that of regulation of the practice of medicine. This division of powers issue ultimately came before the Supreme Court of Canada (SCC) in the *Reference re Assisted Human Reproduction Act*, 2010 SCC 61. In this reference case, the Attorney General of Quebec challenged the constitutionality of provisions of the law which it suggested were an attempt to regulate the practice of medicine and research related to assisted reproduction. The SCC determined that the impugned provisions did indeed exceed the legislative authority of the federal government (see Ogbogu 2013). It is important to note for the purpose of this discussion that the impugned provisions related only to the use of assisted human reproductive technologies. The prohibitions outlined above (AHRA, s.5) relating to research using human reproductive materials were not challenged and remain in force. As will be discussed below, they have their own criticisms at present related in part to the evolution of the field.

The AHRA is not the only relevant source of authority with respect to stem cell research and its applications in Canada. To the contrary, there are various actors – both governmental and non-governmental – that have power and responsibility in this area. Federal regulators such as Health Canada play a key role in regulation of advanced medicinal products, including cell-based therapies (Chisholm et al. 2019). Research involving human participants, including clinical experiments and research using human tissues or health information is subject to research ethics oversight. The Tri-Council Policy Statement (TCPS) (CIHR 2014) governs all research funded by any of the Tri-Council agencies in Canada (Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC)). It specifically addresses "research involving materials related to human reproduction" – which includes

various avenues of stem cell research – and is intended to compliment (i.e. operate alongside) legal requirements, including those contained within the AHRA. Although the TCPS is not hard law, because of its implications for future funding eligibility for both individual researchers and their institutions, its reach in Canada is broad and powerful.

Professional regulatory bodies also have an important role to play in terms of establishing the parameters of professional and ethical standards, providing guidance to their members, and with respect to the investigation and discipline of members who engage in unprofessional conduct (Zarzeczny 2017). Accordingly, regulated healthcare professionals – such as physicians – must also be concerned with their professional obligations when engaging in both research with human participants and clinical practice. In Canada, physicians have the privilege of self-regulation, which carries an obligation – in some cases enshrined in the empowering legislation – to act in the public interest (Collier 2012). As will be discussed in greater detail below, the value and potential influence of professional regulation in current, but more importantly the future, governance of stem cell research and its clinical applications should not be underestimated.

## 2.2 Governance Challenges – Examples from the Field

There are a number of current examples one can point to in stem cell research and related fields that highlight different governance challenges associated with emerging areas of biomedicine. For the purpose of this discussion, the term governance will be used to capture "the pattern or framework within which the exercise of power occurs" (Fairburn et al. 2015 at 5) as well as "steering" activities that "influence, shape, regulate or determine outcomes" (Gamble 2000 at 110). Governance provides a useful lens through which to explore tensions in the field of stem cell research because it contemplates the roles of different actors operating in complex contexts, using various policy instruments (Le Galès 2011).

For example, recent debates about how to respond to gene editing technologies such as CRISPR-Cas 9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9), that allow for purportedly faster, more efficient and more accurate changes to the genome, are attracting attention and highlighting the complex balancing of interests engaged by emerging technologies that offer potential advantages (e.g., elimination disease), alongside potential controversies (e.g., eugenics) (Bosley et al. 2015; Sugarman 2015; Isasi et al. 2016). Both research and clinical applications that involve potentially heritable alterations made to human embryos or somatic cells are controversial. Indeed, a 2018 review highlights 61 statements issued over the previous 3 years by the international community addressing related questions (Brokowski 2018) and the World Health Organization has convened an expert panel tasked with developing global standards of governance and oversight (WHO 2018).

Leaving aside some of the bigger questions surrounding the ethics of potential clinical applications of this technology, many of which are discussed in the statements reviewed by Brokowski (2018), in Canada it is currently unclear whether or not some of these avenues of genetic research are even legal. As outlined above, s. 5(1) of the AHRA provides "No person shall knowingly . . .(f) alter the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants". However, the meaning of "capable" is debatable in this context and there are different potential interpretations. One interpretation is that genetic alterations to a human embryo are permissible, as long as the embryo is intended for research uses only and will never be implanted (Master and Bedford 2018). Another interpretation is that any alteration that could potentially be passed down to future generations, regardless of whether or not an affected embryo is ever intended to be implanted in a woman, is prohibited by the AHRA (Knoppers et al. 2017;

Health Canada 2014). At present, it is unclear which of these interpretations will prevail which makes it difficult for scientists to identify with certainty where the boundaries of the law lie with respect to their work, which has implications for various avenues of both research and clinical use (Cohen et al. 2019).

There are also debates about how section 5(1)(b) of the AHRA should be interpreted. This section makes it illegal to "create an *in vitro* embryo for any purpose other than creating a human being or improving or providing instruction in assisted reproduction procedures" (AHRA). In recent years, researchers in other countries have been honing techniques for developing structures *in vitro* that share some features with human embryos (Warmflash et al. 2014; Harrison et al. 2017). Referred to by some as synthetic human entities with embryo-like features (SHEEFs) (Aach et al. 2017), these two-dimensional structures are seen by many as a valuable research tool that may help develop understandings of early embryo development and developmental disorders, albeit while raising their own ethical issues (Pera et al. 2015). However, although the similarities between these entities and actual human embryos remain slight, and although there is no suggestion these entities would be viable even if implanted into a womb, at present it is not clear whether or not they would be considered "embryos" under Canadian law and therefore be illegal to create. An "embryo" is defined in the AHRA as "a human organism during the first 56 days of its development following fertilization or creation, excluding any time during which its development has been suspended, and includes any cell derived from an organism that is used for. . .creating a human being" (s.3). This definition does not incorporate viability as a criterion and leaves room for entities created through means other than traditional fertilization of a sperm and egg. Accordingly, it very well may preclude Canadian scientists from creating SHEEFs for research purposes – but this interpretation is far from certain.

These are only two examples of emerging forms of research that currently fall into ambiguous or grey areas in the Canadian legal landscape, but they serve as helpful illustrations of some of the governance challenges outlined above. In particular, they demonstrate the difficulty criminal law can have with keeping pace with scientific developments and the ensuing lack of clarity that can result. In the absence of judicial consideration or interpretative guidance from Health Canada, scientists wishing to work in these areas do so at risk of criminal liability. This uncertainty risks serving as a chill on science, to the potential detriment of the Canadian research community and its stakeholders, which include patients and the public. Concerns about the implications of these areas of legal uncertainty have shaped calls for legal reform, including changes to the AHRA and – potentially – to the governance of this area of research more broadly (Bubela et al. 2019; Ogbogu et al. 2018b; Knoppers et al. 2017; Knoppers et al. 2017b).

Together with a multidisciplinary group of scholars and other experts, I have argued previously for a principled approach to policy making in this area. Specifically, we have suggested that:

> Research policy limits should be *proportional*, with appropriate balancing of risks and benefits, as well as of possible penalties for harm. They should be *guided by evidence*, rather than speculation about hypothetical risks. They should be *consistent*, so that like activities are treated similarly and exceptionalism is avoided. They should be *responsive* rather than static, and amenable to flexible interpretation as circumstances change. They should be *clear* and supported by substantive criteria guiding how to interpret and apply them. Finally, they should be grounded in recognition of the *value of scientific discovery* and the *interests of citizens* in benefiting from science and its applications. (Ogbogu et al. 2018b)

Although likely not without its own challenges, such an approach would respond – at least in part – to common criticisms that law is often largely reactive to scientific developments. Building on the work of Harmon (2016) and others, I would also suggest there is a need to examine and characterize current and past governance decisions in respect to emerging areas of biomedical science, with a view to understanding how we might work towards more coherent, consistent and effective strategies in future.

Regardless of the approach taken, there are salient contextual factors in the policy making context surrounding stem cell research that need to be recognized and accounted for in order for a governance strategy to succeed. Alongside the ethical and legal debates that permeate different aspects of the field, there continues to also be a tremendous amount of interest and expectation surrounding stem cells. Indeed, the attention the field draws has grown to a degree now commonly referred to as "hype" (Caulfield et al. 2016; Kamenova and Caulfield 2015). Although an in-depth discussion of the role and impact of hype is beyond the scope of this paper, it must be acknowledged that it is part of the context in which policy makers operate and make decisions, and that it permeates the public sphere with the potential to shape public expectations about what the field should be delivering in terms of clinical applications.

A related contextual factor is the apparent growing patient-driven push for access to experimental and unproven medical interventions. This trend is perhaps best exemplified in the "Right to Try" movement. Under the umbrella of the Right to Try movement, patients are advocating for early and expanded access regimes that permit access to therapeutic interventions that have not yet been approved. While not without its critics and limitations, this movement has gained considerable traction in the United States (US), where it has been implemented by law at both federal and state levels (Zettler and Greely 2014). Though not limited to stem cell interventions, the Right to Try movement has implications for this sphere as with other unproven and experimental treatments (Servick 2016; Shah and Zettler 2010). More broadly, it is arguably reflective of a growing public interest in, and demand for, access to experimental and unproven medical interventions – many of which are available on growing private, direct-to-consumer markets.

In the section that follows, I will use the market for unproven stem cell-based interventions as a case study to further illustrate the governance challenges introduced above, and to ground a discussion of how we might approach policy choices going forward in fast-moving and complex fields of biomedicine, such as stem cell research.

## 3 Case Study – The Market for Unproven Stem Cell Interventions

### 3.1 Overview: A Murky Market

As noted above, stem cells are widely thought to have the potential to improve clinical options for a number of different diseases and conditions. Indeed, there are a growing number of promising avenues of clinical exploration occurring around the world (Li et al. 2014) that may someday improve the lives of many individuals for whom existing treatment options are lacking. However, the clinical translation of stem cell research is a highly complex, and potentially high risk, process. Identifying treatment protocols that are effective and do not cause inappropriate risk to patients takes time and rigorous science (Daley 2017). The potential treatment paths also vary by condition, as do the timelines around when new treatment options may be ready for application in humans. At present, there are only a small number of stem cell-based treatments that are part of a routine standard of care (e.g., bone marrow transplants for leukemia).

However, notwithstanding this relatively early stage of much clinical research into stem cell treatments, a robust private market has developed where a wide range of stem cell-based interventions are advertised directly to patients. This market has been documented for some time, with the first studies analyzing the content of private market provider websites published a decade ago (Lau et al. 2008; Regenberg et al. 2009). Operating on a direct-to-consumer basis, where products and services are sold directly to individuals without the need for a medical referral, this market relies heavily on online marketing and the use of websites to promote products and services, and as an entry contact point for prospective patients (Connolly et al. 2014). The early research on this market found a strong clinic presence in jurisdictions including China, India and Mexico (Lau et al. 2008; Regenberg et al. 2009). More recent work in the field has revealed a remarkable expansion of this market into the

US, Australia and Japan (Turner and Knoepfler 2016; Berger et al. 2016; McLean et al. 2015; Fujita et al. 2016; Munsie et al. 2017).

Gathering robust data on the market for unproven stem cell-based interventions has proven to be a considerable challenge, and researchers have had to engage in a range of creative strategies to gather information. What is known about this market has been drawn from systematic analyses of clinic websites (Connolly et al. 2014; Ogbogu et al. 2013), studies of media reports (Zarzeczny et al. 2010) and patient blogs (Rachul 2011), interviews with patients and their supporters (Petersen et al. 2013), interviews with healthcare providers (Levine and Wolf 2012), and studies of social media (Robbillard et al. 2015; Kamenova et al. 2014), among other approaches. In many cases, clinics offering unproven stem cell interventions on the private market purport to treat a dubiously broad range of conditions (e.g., from aging to orthopedic injury to degenerative diseases such as ALS), often with a lack of specificity and/or a 'one size fits all' treatment approach (Berger et al. 2016). Patients are generally required to pay the often considerable costs associated with these treatments out of pocket, because they are not covered by public or private health insurance (McLean et al. 2015; Turner 2018). For example, in one informal poll of over 500 individuals, participants most often reported having paid between $2500 and $7500 USD (Knoepfler 2018). Patients are increasingly turning to crowdfunding as a means to support their interest in pursuing these interventions (Snyder et al. 2018).

It is important to be clear that not all private market providers can or should necessarily be painted with the same brush. Indeed, as is discussed in more detail below, practices vary and some may be bona fide forms of clinical innovation (Lindvall and Hyun 2009; Sleeboom-Faulkner 2016). However, in many cases the lack of transparency and clarity regarding the nature of the services provided in private clinics offering stem cell-related interventions makes it difficult to ascertain how they fit within current regulatory and practice standards (Zarzeczny et al. 2018). Notwithstanding the challenges with drawing firm lines between different categories of providers/practices, there are a number of general concerns associated with different activities occurring within this market.

In many cases, traditional forms of medically accepted evidence of safety and efficacy are lacking (Lau et al. 2008). There is often limited to no information available about quality control, purification procedures, cell processing mechanisms or facility standards. There also often appears to be minimal patient follow-up by the clinics providing the treatments, which is particularly concerning when patients later require care (sometimes urgently) as a result of adverse events (Bauer et al. 2018). There is no mandatory reporting system (unlike with clinical trials, for example) for adverse event reporting, which limits the ability of these activities to advance scientific knowledge in the field. The overwhelmingly positive portrayals of the clinic offerings on their websites also calls into question whether the standards of informed consent are being met (Lau et al. 2008; Ogbogu et al. 2013). Although valuable work is being done to develop professional standards for informed consent in the context of stem cell therapies (Sugarman et al. 2019; ISSCR 2019), enforcement seems likely to prove challenging among private market providers.

Finally, one of the most important concerns surrounding the wide range of allegedly stem cell based interventions offered in the private market concerns physical risks to patients. Reports of tumours, lesions, infections and vision loss, among other issues, associated with unproven stem cell interventions of one form or another (e.g., Kuriyan et al. 2017; Saraf et al. 2017; Thirabanjasak et al. 2010; Bauer et al. 2018) highlight that the risks of stem cell related interventions are not insignificant. There are different kinds and degrees of risk, depending on the types of cells used, what has been done to the cells (i.e. whether and how they have been manipulated/processed) and how they are administered. Unfortunately, these important distinctions often appear to be lost in many of the products and services currently advertised on the private market (Zarzeczny et al. 2018).

Indeed, in addition to the data limitations noted above, as I have argued elsewhere with colleagues, there are policy challenges stemming from terminology tensions and a lack of clarity in this space (Zarzeczny et al. 2018). As the market grows and diversifies it is becoming increasingly difficult to draw firm boundaries between practices of responsible medical innovation and inappropriate administration of ineffective and/or potentially harmful interventions. This murkiness exists at various levels in the current marketplace; including (though not limited to): what kinds of cells are being used; what processing procedures are used (and whether they are used consistently); what training and experience the providers have; what standard of care applies; where the appropriate line falls between research and clinical practice; what patients are told about these treatments, including whether they have the necessary information about both known risks, and regarding what is currently unknown/uncertain to provide truly informed consent, among many other key issues. This lack of clarity presents a considerable policy challenge, particularly if one accepts that regulation requires a clear understanding of what exactly is being regulated, and how existing laws and policies will apply – all of which is increasingly difficult in this dynamic and rapidly growing area.

## 3.2 An Unfolding Story: Stem Cells for Sale in Canada

Until fairly recently, there was no evidence to suggest the presence of a significant market for unproven stem cell-based interventions available in Canada. Canadians participated in international markets by seeking these interventions in other jurisdictions, which raised questions about what pre-procedure and post-procedure care obligations Canadian physicians have when working with patients who are interested in pursuing these interventions, and/or who return from stem cell treatment elsewhere requiring some form of follow-up care (emergent and otherwise) (Zarzeczny and Clark 2014). However, this situation is changing quickly and the market is growing in Canada. Media stories have drawn attention to Canadian involvement in the market for unproven stem cell interventions (Crowe 2017; Blackwell 2017), including via links to American providers that have come under scrutiny by the United States Food and Drug Association (FDA) (Crowe 2018).

The expansion of the Canadian market noted in these media reports has also been documented in recent research. In their 2016 study, Berger et al. noted 6 clinics in Canada (Berger et al. 2016). In a review of online offerings published in 2017, Chisholm et al. found 11 clinics advertising cell therapies in Canada (Chisholm et al. 2017). Following a study in 2017, Ogbogu et al. report on 15 clinics offering some form of unproven stem cell intervention in Canada, with representation from Ontario, Saskatchewan, Alberta, British Columbia, Quebec and Nova Scotia (Ogbogu et al. 2018a). Another study conducted between 2017 and 2018 identified 30 Canadian companies marketing stem cell treatments at 43 different clinic locations (Turner 2018). The Canadian market, as captured by these various reports, is currently small in comparison to other jurisdictions such as the US. However, the Canadian market appears to be growing quickly and if the US is any indication, is likely to continue to spread and diversify if left unchecked. As is discussed below, Health Canada has recently engaged directly with this issue from a regulatory perspective but how that activity will impact the market's long term trajectory remains to be seen.

## 3.3 Policy Options – Opportunities & Challenges for Canada

Notwithstanding the various concerns and risks outlined above, the market for unproven stem cell interventions has continued to expand and diversify in countries around the world for over a decade. This expansion is arguably reflective of regulatory failure and/or insufficient governance – perhaps related at least in part to the types of governance challenges noted earlier (Sipp 2011). Its more recent spread into Canada presents an

opportunity for decision-makers at various levels in this country to be proactive and exercise leadership by pursuing a deliberate and coordinated governance strategy in order to curtail problematic practices, while protecting the long term health of this promising field. In this section, I will address several specific strategies that could –with appropriate implementation and coordination – provide a solid foundation for an effective governance regime.

As is true of stem cell research and its clinical applications more generally, the market for unproven stem cell-based interventions arguably falls under a distributed governance regime. Health Canada is the federal body with responsibility over pharmaceuticals, medical devices and therapeutic products pursuant to the *Food and Drugs Act* (R.S.C., 1985, c. F-27) and its regulations. It plays an important role in protecting the safety of the public through this regulatory mandate. Although jurisdiction over health-related areas is a complex topic in Canadian law due to our Constitutional framework, it is sufficient for the purpose of this discussion to acknowledge that provincial and territorial ministries of health also have important responsibilities related to the administration of healthcare within their jurisdictions, including regulation of healthcare providers, healthcare facilities and healthcare insurance (Klein 2017). In addition, as identified earlier, regulated healthcare professions are also subject to the authority of their regulating bodies. For example, the practice of medicine is a self-regulating profession in Canada governed by provincial colleges of physicians and surgeons. In general, the colleges have responsibilities for setting educational requirements and standards of practice as well as over licensing conditions and disciplinary processes (Zarzeczny 2017). Accordingly, when it comes to the provision of stem-cell related interventions, whether as established standard of care treatments or unproven alternatives, there are various potential forms of oversight over the facilities where treatment is provided, over the professionals providing the intervention, and over the products themselves.

The distributed nature of governance of this market leads to various possible routes when it comes to policy options for responding to the concerns it raises, each of which offers different merits and challenges (Caulfield and Murdoch 2019). Although it is beyond the scope of this paper to engage in a fulsome analysis of these options, identifying some of the most promising alternatives is an important first step towards developing a robust strategy. At the state level, countries have responded in different ways to this burgeoning market, and there are various examples of attempts to rein in concerning practices. By way of early examples, German authorities pursued a particularly high-profile clinic following the death of a child in the context of an unproven stem cell intervention and ultimately forced the clinic to close (Vogel 2011). China, an early world leader as a destination for stem cell 'tourists' given its large and initially unregulated market, has been working on tightening regulations for the last several years – though questions remain regarding their implementation and enforcement (Rosemann and Sleeboom-Faulkner 2015). More recently, Australia has been taking an increasingly proactive approach to update its regulatory regimes, in an apparent effort to resolve ambiguities and provide clarity around how different kinds of stem cell-based interventions are to be approached in research and clinical contexts (e.g., Australian Government 2017). The FDA has also responded to the rapid growth of the market in the US (Turner and Knoepfler 2016) in a fairly public manner. For example, it provided guidance regarding how relevant regulations are to be interpreted and applied to the kinds of services provided in the growing private market (FDA 2017b, c). It was also took enforcement action including clinic inspections and warning letters for non-compliance (FDA 2017a, d, 2018a), and via the department of justice seeking permanent injunctions against two stem cell clinics (FDA 2018b).

Looking to these international examples is helpful in terms of informing a discussion about how decision makers in Canada might respond to the concerning and particularly risky aspects of

the market growing within our boarders. However, it will also be important that any such response account for relevant factors specific to Canada including – though not limited to – our constitutional division of powers, how our health care providers are regulated, the organization and administration of our health care systems including the largely public nature of their financing, and our existing legal frameworks. With these considerations in view, the following three policy options may have particular value, especially if approached in a deliberate and coordinated manner: (i) regulatory clarification and enforcement from Health Canada; (ii) rigorous enforcement of existing truth in advertising and consumer protection legislation, and (iii) maximization of the power of professional regulation (Caulfield and Murdoch 2019).

Health Canada did not initially engage in this issue as publicly as its American counterpart and analyses of existing regulations, including more specifically those relating to how minimally manipulated autologous cell therapies for homologous use are regulated, suggested there are ambiguities that require clarification so as to prevent private market offerings taking advantage of regulatory grey areas (Chisholm et al. 2017). In the spring of 2019, Health Canada issued a policy position paper clarifying regulatory questions about autologous cell therapies in Canada relating to their risks, how they fit within existing federal product safety rules, and therapy development activities (Health Canada 2019). More specifically, Health Canada clarified that all cell therapies are considered "drugs" for the purpose of regulation and thus are subject to regulation pursuant to the *Food and Drugs Act*. The Government of Canada issued a related public safety advisory (Government of Canada 2019), and there have been subsequent reports of enforcement activities by Health Canada against individual clinics (Crowe 2019). This situation is evolving rapidly and at the time of writing, it remains to been seen what impact this regulatory clarification and accompanying enforcement efforts will have on the future of the market for unproven stem cell-based interventions in Canada.

Canada also has strong consumer protection and truth in advertising standards in place. In Canada, business conduct is regulated primarily via the *Competition Act* (R.S.C. 1985, c. C-34), a federal statute that includes both civil and criminal provisions that deal with false or misleading representations and deceptive marketing practices. Although there are recognized enforcement challenges in this area, consumer protection legislation has considerable potential to be used to restrict false or misleading claims being made to consumers regarding private market offerings of stem cell-based interventions (Ogbogu 2016; von Tigerstrom 2017). Indeed, many of the claims made on clinic websites, including those found in the studies referenced above, are likely to run afoul of Canada's *Competition Act* provisions (Murdoch et al. 2018). The *Competition Act* is enforced by the Competition Bureau, which has a wide range of enforcement options at its disposal including not only both criminal and civil law routes, but also education and other soft-law approaches (Competition Bureau 2019). Although we have yet to see robust enforcement action by the Competition Bureau against problematic stem cell-related marketing in Canada, at least a public level, the availability of this diverse set of responses is a regulatory strength.

Professional regulation is another potentially powerful though as-yet underutilized tool for addressing particularly concerning elements of this market (Zarzeczny et al. 2014). Physicians have been found to play a prominent role as providers of unproven stem cell based interventions (Murdoch et al. 2018; Ogbogu et al. 2018a). Accordingly, professional regulatory bodies – including the colleges of physicians and surgeons in Canada – could play a central role in curtailing problematic practices by their members and, in so doing, restrict the unchecked spread of potentially high risk and/or deceptive practices (Zarzeczny et al. 2014; Murdoch et al. 2019). There are a few examples of initial activity in this realm. For example, the College of Physicians and Surgeons of Alberta recently issued Standards and Guidelines for Stem Cell Regenerative Therapy (CPSA 2018). However, arguably considerably more could be

done to provide clarity to physicians across the country regarding acceptable standards of practice with respect to stem cell-related interventions and with regard to enforcement activities to address unprofessional conduct.

The courts may offer another potential avenue for redress when individuals suffer harm in relation to the provision of unproven stem cell-based interventions. For example, a patient who is injured by a stem cell-based intervention may have an action in negligence against the provider of the intervention and/or their employer (through vicarious liability). Individuals who suffer financial loss may also have claims related to fraud or other heads of liability (Horner et al. 2018; Caulfield and Murdoch 2019). There has been limited litigation in this area to-date and one significant concern with civil law actions, particularly as a remedy for medical harms, is the burden (financial, emotional and otherwise) they often place on individual plaintiffs who may already be in a vulnerable position. Nonetheless, the remedies available through civil litigation and the role it can have in deterrence give it a place worth considering within the broader governance matrix.

There are also an ever-growing collection of information-based responses led by diverse stakeholder groups including scientific organizations, patient advocacy groups, policy researchers and others (e.g., ISSCR 2016; Master and Caulfield 2014). These efforts typically focus on supporting patients (or their substitute decision-makers) in making informed decisions based on accurate and balanced information. Although they arguably have considerable value, the limitations of communication strategies that rely largely on information deficit models are well-recognized; nonetheless, they remain persistent in science communication, likely for various reasons (Simmis et al. 2016). Encouragingly, there is valuable work being done in numerous health-related fields to enhance understanding of different ways to engage and empower patients, including via online mechanisms that could inform future communication strategies (Fagotto et al. 2019). With the proliferation of misinformation online and the use of forums such as YouTube as a marketing strategy for unproven stem cell-based interventions (Hawke et al. 2019), it is increasingly important for efforts seeking to provide patients and the public with accurate and balanced information to explore new modes of engaging their audience, such as the creative use of narratives (Caulfield et al. 2019).

As this brief review of a small sample of options highlights, addressing policy challenges in the field of stem cell research – including the private market for unproven stem cell-based interventions – does not necessarily require dramatic regulatory change. Clarifying and enforcing our existing laws and regulatory structures is arguably a logical first step to responding to the concerns associated with the Canadian market for unproven stem cell-based interventions (Zarzeczny et al. 2018; Caulfield and Murdoch 2019). Doing so will not necessarily require new policies or regulation (although these may ultimately be useful), but rather as a starting point could focus on bringing renewed vigour to those that are already in place. This strategy may or may not provide a complete answer, but we will arguably not be able to reliably identify problematic gaps and ambiguities until we give full effect to existing controls. The market in Canada is in its early stages, meaning we have an opportunity at present to 'get it right' from a regulatory perspective, ideally before too much harm is done – whether to individual patients or to the reputation of the field of stem cell research and regenerative medicine. Indeed, there is a risk that the public may come to lose trust and hope in this field of research if ineffective and potentially harmful interventions are permitted to proliferate in advance of the science (Cossu et al. 2018).

## 4 Implications & Future Agendas

As the case of the market for unproven stem cell-based interventions demonstrates, there are clear and present governance challenges when it comes to arriving at effective policy solutions that address complex issues in the multi-faceted field of stem cell-related research and its clinical applications.

Although some of the issues raised in the case discussed in this paper are specific to the particular area of stem cell-based interventions (e.g., interpretive questions regarding how current regulations apply to autologous cell therapies), many are shared with other avenues of regenerative medicine and more broadly with different areas of biomedical innovation.

For example, when fields develop quickly and/or unpredictably, regulation can struggle both with particulars such as clear and unambiguous definitions and with larger questions about regulatory fit. Legitimate excitement about the potential of cutting-edge research can also easily lead to hype and unrealistic expectations from the public, which may underpin demand for early access to a technology – even though it may not be ready for routine use outside of a research context. Questions about what level and type of evidence of safety and efficacy should be required before access to it is permitted, facilitated (e.g. via public funding), or both, can also be contentious.

Going forward, there is a strong imperative to consider what the growing patient-driven demand for access to experimental and unproven medical interventions means for health system governance and regulation in Canada, and what an effective, consistent and coordinated approach to regulation might look like. The fast-moving nature of these fields may benefit from anticipatory governance strategies (Quay 2010; Barben et al. 2008), taking into account the value of a principled and responsive approach that is proportional, guided by evidence, clear and consistent (Ogbogu et al. 2018b). Notwithstanding the numerous limitations associated with efforts to predict where medical innovations are headed, some form of legal foresighting may prove useful in efforts to support law's relevance and role in shaping science and innovation (Laurie et al. 2012).

In addition to understanding biomedical science and its potential, other important areas of inquiry will need to include the roles and influence of evidence (in different forms), scientific and clinical imperatives and of public pressure on policy decisions. The appropriate role of regulation in managing risks as well as scientific and clinical uncertainty in fast moving fields of biomedicine is a closely related issue that also bears focused consideration. It is important to stress that law is but one tool in a broader governance framework. Indeed, we sometimes hear competing allegations that law is failing to keep pace with scientific advancements, or that it is leaping ahead of science and imposing unnecessary or ill-fitting restrictions on its development. Establishing an appropriate balance between these two extremes can be a difficult challenge, particularly given the different and sometimes competing objectives that inform the policy making process including, but not limited to, protection of the public, promotion of various agendas – political, moral, religious, economic – and the desire to encourage innovation in science and health technology.

These challenges underscore the importance of scientists and policy makers working together, and of exploring how key stakeholders – including the public – can have a meaningful voice in the policy process. They further highlight the value of both hard and soft regulatory strategies (Harmon et al. 2013) and of arriving at governance strategies that facilitate deliberate coordination between them. This agenda is far from simple, but is important to the larger goal of facilitating biomedical innovation while managing and mitigating its risks in a manner suited to the Canadian context.

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