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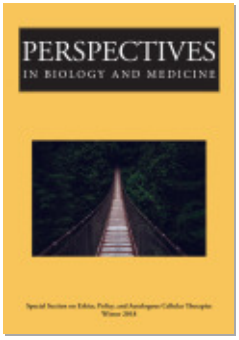

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Perspectives in Biology and Medicine, Volume 61, Number 1, Winter 2018, pp. 90-105 (Article)

Published by Johns Hopkins University Press
DOI: *https://doi.org/10.1353/pbm.2018.0029*

The Need for Beneficence and Prudence in Clinical Innovation with Autologous Stem Cells

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ABSTRACT The term *innovation* is frequently used as a justification for allowing clinicians to offer unproven autologous stem cell-based interventions (SCBIs) to their patients. Proponents of this kind of innovation (which we refer to as "clinical innovation") argue that physicians should be free to administer whatever interventions they choose, and informed consumers should be free to receive them. This article refutes the notion that clinician autonomy and consumer demand are a sufficient justification for offering patients unproven autologous SCBIs. We argue that, while clinician and consumer preferences need to be taken seriously, access to unproven SCBIs can only be fully justified when it is based on a commitment to beneficence and prudence. We also argue that there is a need for a clearer distinction between the *definition* of

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Research related to this article has been funded by the Australian Research Council (LP150100739).
The paper was originally presented at a research symposium on "Autologous Cellular Therapies: Defining the Scope and Obligations of Clinical Innovation" in Singapore on May 24, 2017. This symposium was supported with funding from the National University of Singapore Office of the Deputy President (Research and Technology)–Humanities and Social Sciences Research Fund (WBS: R-171-000-055-646) and the Stem Cell Society, Singapore. Professor Jeremy Sugarman, Johns Hopkins Berman Institute of Bioethics, provided an oral commentary on the paper at the symposium, and the paper was revised following review from the guest editors and Professor George Agich, Bowling Green State University.

Perspectives in Biology and Medicine, volume 61, number 1 (winter 2018): 90–105.

clinical innovation with autologous stem cells, which is morally neutral, and its *justification*, which entails a commitment to beneficence and prudence. Finally, we argue that regulation of clinical innovation with autologous stem cells needs to be based on a bioethics of innovation that attends to beneficence and prudence alongside other ethical principles.

In recent years, there has been a rapid growth in the use of autologous stem cell-based interventions (SCBIs) to treat a wide range of medical conditions, including those for which there is limited evidence of safety and efficacy. One justification for this growth in the use of unproven interventions is that clinicians should be free to innovate, as long as consumers are adequately informed about risks and benefits. In this essay, we systematically refute the strong claim that consumer and clinician autonomy provide sufficient justification for clinical innovation with autologous stem cells. While we do not deny the importance of consumer and clinician autonomy, we argue that equal consideration needs to be given to other ethical principles—most notably beneficence and prudence. We then discuss the need for greater clarity regarding the moral status of clinical innovation with autologous stem cells, and for regulation of such innovation that systematically attends to beneficence and prudence alongside other ethical principles.

The Clinical Use and Marketing of Autologous Stem Cell Interventions

Autologous SCBIs involve collecting stem cells—cells that have the capacity for self-renewal and the ability to differentiate into multiple cell types—from a patient's body and then re-administering them to the same patient. Autologous stem cells have an established, and growing, role in bone marrow transplantation or hematopoietic stem cell transplantation for the treatment of a range of malignant, metabolic, immunological, or genetic diseases. In recent years, however, a new market has emerged for autologous SCBIs for a number of other conditions, including osteoarthritis, motor neuron disease, autism, asthma—uses that are not supported by good quality evidence of safety or efficacy (Berger et al. 2016; McLean, Stewart, and Kerridge 2014; Sipp et al. 2017). Public and private clinics selling such interventions now operate around the globe, in both high- and low-income countries, including the United States, Ireland, Australia, Germany, Japan, China, India, and Mexico (Berger et al. 2016), and there is a flourishing stem cell tourism industry for those who cannot access or afford local interventions (Gunter et al. 2010).

One way of conceptualizing these various uses of autologous stem cells is that some are part of standard clinical practice (for example, their use in transplantation for the treatment of haematological malignancies), some are part of formal clinical research (for example, clinical trials of transplantation for the treatment

of multiple sclerosis), and some are being used as clinical innovation. We define "clinical innovation" as the use, outside of formal clinical research, of interventions that differ from standard practice, and that have not been shown to be safe or effective according to the usual standards of evidence-based medicine. In this essay, we are concerned with the clinically innovative uses of autologous stem cells.

ARGUMENTS FOR CONSUMER-DRIVEN CLINICAL INNOVATION WITH AUTOLOGOUS STEM CELLS

While there is broad agreement that clinical innovation offers a means of translating novel stem cell interventions into practice (Sugarman 2012; Taylor 2010), there is sustained disagreement as to when and how this pathway should be used. Some argue that clinicians should be free to administer unproven SCBIs, and that informed consumers should be free to receive them if they so choose (Salter, Zhou, and Datta 2015). Others, however, claim that clinical innovation is justified only in certain circumstances and with specific processes and safeguards in place, and that SCBIs should not be marketed or made freely available until they have been tested and registered according to the accepted standards of evidence-based medicine (McLean, Stewart, and Kerridge 2015).

In a 2016 *Social Science and Medicine* article, the political scientist Brian Salter and colleagues examined consumer demand for access to unproven autologous stem cell interventions through a process that they referred to as medical innovation. According to them, medical innovation is innovation that is "embedded in practice" (160) and is distinct from scientific innovation, which is the formal process of evidence generation through "basic research, clinical experimentation, product development, clinical trials, product approval and clinical application" (156).

On one level, Salter, Zhoue, and Datta's idea of medical innovation appears to be very similar to what we have defined above as clinical innovation. However, Salter and colleagues' definition of medical innovation does not just capture its context (clinical practice), it also frames it in terms of a sociological critique of medical power. Specifically, they describe Western science and medicine as a hegemonic force that is hostile to innovation, and they view medical innovation as part of a consumer-driven counter-hegemonic movement aimed at a "redefinition of the innovation model itself, its rules and its values" (156).

At the political level, the Salter article draws two key distinctions between scientific innovation and medical innovation. First, while scientific innovation aims for definitive demonstration of an intervention's efficacy, medical innovation requires it to be merely "scientifically based and safe" (160). Second, while scientific innovation allows regulators and the medical profession to decide what forms of innovation are, and are not, appropriate, medical innovation emphasizes

the role of the informed consumer in making such decisions: "At the center of the model is the informed health consumer who assumes she/he has the right to make their own choices to buy treatment in a health care market which is another form of mass consumption" (159). According to this view, it is largely irrelevant whether consumers' decisions would be considered "rational" from the perspective of external observers, because

> the characteristics of a particular disease condition, the proximity of pain and/or death, and the limits of local treatment . . . generates a calculation of risks and benefits with its own internalist rationality and values. Such a subjective rationality may be at odds with the rationality of the external observer, be they scientist, bioethicist or policy maker, and generate a robust demand with limited responsiveness to negative information about stem cell therapies and a high tolerance of health risk. (159–60)

Specifically with regard to autologous stem cell interventions, Salter and colleagues argue that the autologous stem cell market has grown in response to consumer demand, which has been stoked by "affordable travel, facilitating agencies, internet based advertising and information and investment by governments keen to access foreign revenue" (159). They emphasize the ways in which the democratization of biomedical information—particularly access to the internet—enables consumers to bypass the informational barriers that medicine and regulators put in place:

> [Consumers] reflect on information about their condition and appropriate treatment drawn from a wide range of sources which include not only the formally approved outlets of science and state but also the burgeoning information banks of the internet. The latter has proved to be particularly important to consumers of stem cell therapies given that the advice of the national and transnational hegemonic institutions of biomedicine is hostile towards the stem cell therapy clinics consumers often want to access. (159)

In this way, Salter and colleagues frame consumer demand for SCBIs as a counter-hegemonic force, with consumers advocating for a new kind of innovation—medical innovation—that eschews traditional demands for evidence of efficacy and safety.

Salter and colleagues are not alone in advocating for consumer-driven access to stem cell interventions with only minimal standards of safety and efficacy required. The International Society for Cellular Therapy (ISCT), for example, claims that "Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed. There is a place for both paradigms in the cell therapy global

community" (Gunter et al. 2010, 966). Although Salter and colleagues do not go as far as to claim that consumers have a right to access unproven interventions, many others do make such claims. The ISCT, for example, argues that patients: "should have the right to seek treatment for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patient" (Gunter et al. 2010, 966).

Challenging Consumer-Driven Clinical Innovation with Autologous Stem Cells

There are four assumptions at the core of arguments in favor of consumer-driven clinical innovation with autologous stem cells: (1) that clinical innovation and research innovation are distinct enterprises; (2) that consumers who want access to autologous stem cells are actively and deliberately challenging an anti-innovative biomedical hegemony; (3) that consumers will be sufficiently protected by minimal standards of safety and scientific validation; and (4) that informed consumers have the right to make informed decisions about access to unproven SCBIs. Each of these assumptions is contestable.

Clinical Innovation and Research Innovation Are Distinct Enterprises

The first assumption underpinning arguments for consumer-driven clinical innovation is that a neat distinction can be drawn between clinical innovation and research (or scientific) innovation. In this regard, Salter and colleagues (2015) describe medical innovation and scientific innovation as two models that are "informed by the contrasting values of medicine and science. Hence, whereas for the former the goal is the benefit of the individual patient, for the latter the goal is scientifically generalizable results achieved through the application of the scientific method" (160). According to Salter, these models are not only morally distinct, but also operate according to different epistemic standards. While *medical* innovation requires an intervention to be merely "scientifically based and safe" (160), *scientific* innovation aims for definitive demonstration of an intervention's efficacy: "through the lengthy innovation process of basic research, clinical experimentation, product development, clinical trials, product approval and clinical application" (156).

There is, however, a problem with Salter and colleagues' attempts to distinguish between scientists—who are allegedly committed to the advancement of knowledge for the benefit of future patients—and clinicians, whose only concern is patient care. First, these are often not separate groups of people with "separate professional responsibilities" (161), but rather the same people occupying a multiplicity of roles (such as the clinician-researcher). Second, while it is true that researchers are concerned about benefiting future rather than current patients, and might therefore be tempted to use patients merely as a means to an end, clinicians

also have competing interests that may dilute their commitment to patient care. As Patrick Taylor (2010) observes, "the conflict of interest of a therapeutic innovator is not simply theoretical," partly because of the fees that doctors charge, and partly because innovative therapies "create new product opportunities" (292, 291). Given the degree of overlap between scientific and clinical innovation, it makes little sense to argue that completely different moral and epistemic standards apply to each (Faden et al. 2013; Kass et al. 2013).

Consumers Are Challenging an Anti-Innovative Biomedical Hegemony

The second, paired, set of assumptions underpinning arguments for consumer-driven clinical innovation with autologous stem cells are that there is an established biomedical hegemony that is anti-innovative. and there is an increasingly powerful consumer-driven counter-hegemonic movement. With respect to the first part of this assumption, Salter and colleagues (2015) claim that "practice based innovation is condemned as unproven, unsafe and illegitimate by supporters of the orthodox science based model of stem cell innovation" (157). While it might be the case that the over-hyping of SCBIs is being condemned, and that there is resistance to certain forms of use (such as the use of adipose-derived stem cells for neurological disease), medicine as a whole is actually highly supportive of innovation in general, and even stem cell innovation if conducted prudently. In all of the jurisdictions of which we are aware, medical negligence law is structured in such a way that clinicians are free to offer autologous SCBIs and will not be censured for doing so as long as their practice would be condoned by at least some of their peers. Furthermore, in some countries, such as Australia, autologous stem cells are exempt from medical product regulations because they are biological entities that are administered to the same patient from which they were derived. This is hardly an environment that could be considered hostile to all forms of clinical innovation with autologous stem cells.

With respect to Salter and colleagues' claim that consumers who want SCBIs are "activating medical innovation through the registering of their demand in the market of medical practice" (160), there is good evidence to suggest that it is the advertised claims of innovation, and the borrowing of scientific tokens of legitimacy, that fuels consumer demand, rather than the reverse (Sipp et al. 2017). Petersen and colleagues (2017) explore the "political economy of hope" that drives patients to seek stem cell interventions. Citing Thaler and Sunstein, they note that, in this economy, there are various "choice architects" who "seek to steer patients' and carers' conduct along certain preferred treatment paths" (5). These choice architects, who include scientists, clinicians, patients, the biotech industry, and governments, not only shape consumer demand, but also determine whether, when, and how clinical innovation occurs. It is therefore not only, or even primarily, consumer demand that determines the supply of autologous SCBIs.

Consumers Will Be Sufficiently Protected by Minimal Epistemic Standards

The third assumption underpinning calls for consumer-driven clinical innovation with autologous stem cells, and for minimizing regulation of such innovation, is that consumers will be sufficiently protected as long as innovative practices are considered to be safe and scientifically validated by the clinicians who wish to offer them. To see why setting the bar so low is problematic in the stem cell context, one needs to look no further than the growing list of reported adverse events—including deaths—caused by SCBIs. Despite claims about safety, autologous SCBIs are highly invasive, with cells administered intravenously (into the blood stream), intrathecally (into the fluid around the brain and spinal cord), and directly into organs such as the eyes, heart, and brain. There have been several deaths reported internationally, including the death in Germany of an 18-month-old child with cerebral palsy, whose autologous bone marrow–derived stem cells were injected into the brain, and the death in Ecuador of a 27-year-old British patient who developed intracranial hypertension after an unspecified stem cell intervention to treat a spinal injury. Other deaths have occurred in Australia, Japan, China, and the United States (Lysaght et al. 2017). Other harms that have been reported include blindness following injection of stem cells into the eye, and tumor growth at the site of stem cell infusion (Marks, Witten, and Califf 2017). The procedures for obtaining stem cells, such as bone marrow aspiration or liposuction, are also not without risk, as evident in the tragic case of Sheila Drysdale, who died in Australia in 2013 as a result of bleeding from the liposuction procedure that was being used to harvest stem cells to treat her dementia (Lysaght et al. 2017).

Importantly, serious adverse events and deaths related to autologous SCBIs have occurred in countries with otherwise robust health-care systems, such as Australia, the United States, Germany and Japan (Lysaght et al. 2017). This demonstrates that the problem lies in the standards that are being set by those administering SCBIs, rather than with the health systems in which they are embedded. It also calls into question the view that medical tourism to unregulated locations is the primary threat to patients seeking SCBIs (Gunter et al. 2010).

Furthermore, harms may be not only physical but also psychological (for example, stemming from false hope) and financial. In this regard, it is noteworthy that clinicians offering unproven SCBIs work within private health-care markets and charge whatever the market will bear. For example, stem cell providers in the United States charge from US$5,000 to $100,000 for a course of therapy, and many patients travel internationally as stem cell tourists, bearing the costs of travel and payment for follow-up treatment for complications that occur upon their return. Many patients mortgage their houses or seek funds from charities, their communities, or their families, which can have significant psychological ramifications and prevent funds being used for other purposes (Lee et al. 2017).

Consumers Have a Right to Make Informed Decisions

It could be argued that while harms to patients who receive unproven autologous SCBIs are unfortunate, they are morally acceptable because informed consumers have knowingly and willingly subjected themselves to risk. This brings us to the fourth set of assumptions, which is that SCBIs are commodities that clinicians have a right to sell and that informed consumers have a right to purchase. There are four problems with this set of assumptions.

First, while it is obviously wrong for those purchasing stem cell interventions to be portrayed as naïve or ignorant, it is just as wrong to believe that they are fully autonomous—that their choices are fully informed and not influenced by their relationships with clinicians, family members, or others who might have an interest in the patient seeking treatment. The reality is that there are major information asymmetries in the context of any kind of medical practice, which are made worse by the subset of clinicians who flout advertising regulations and make misleading and deceptive claims about the safety and efficacy of autologous stem cells, and the fact that those pursuing SCBIs are often desperate and may lack the ability to differentiate between treatments that have been tested according to rigors of the scientific method and those that have not (McLean, Stewart, and Kerridge 2014, 2015).

In this regard, it is noteworthy that those who think that consumers can be fully informed expect a staggering amount of expertise and effort on the part of these consumers. The ISCT, for example, claims that consumers should (among other things) "evaluate evidence from peer-reviewed publications, professional society presentations and scientific recognition," "be encouraged to seek multiple professional opinions and have all questions answered to their satisfaction," and "consider the reputation of the investigator and clinic, as well as the record of disciplinary activities against these entities" (Gunter et al. 2010, 966). These expectations would be challenging even for those with training in clinical medicine and stem cell science, so it is difficult to see how consumers could possibly fulfil them.

Second, even if consumers could be adequately informed, and the marketing of stem cells was evidence-based, this would not necessarily give consumers the right to access these interventions. This is partly because there is no corresponding duty for anyone to provide access to unproven therapies, and partly because dominant accounts of rights based on autonomy (such as the right to non-domination and the right to non-interference with other rights) either don't apply or fail to account for the imbalances of power and the vulnerability that occurs in the context of illness (Lysaght, Richards, and Muralidharan 2017). Furthermore, rights to access therapies are heavily constrained and context dependent, such that "healthcare providers are not legally or morally obligated to provide a treatment when considerations of cost and distributional fairness are taken into account" (Lysaght, Richards, and Muralidharan 2017, 57).

Third, while the structures of capitalism and the values of libertarianism and neoliberalism suggest that the law should have a limited role in the market, including the health-care market, the reality is that no market is completely unconstrained, and there are legal limits to what one can consent to. In health care,

> one can only consent to a serious bodily medical intervention when that intervention is clinically justified by, for example, a tangible therapeutic benefit. The implication is that if a medical intervention has no therapeutic benefit, it cannot be consented to, and any "informed consent" will be vitiated. Such "treatments" are regarded in the common law as assault and/or battery. (Lysaght et al. 2017, 744)

Indeed, even outside health care, the common law recognizes that people cannot consent to serious bodily injuries unless the behavior causing those injuries is justified by a recognized public interest, such as privacy in sexual activity, religious freedom, or participation in sporting activity (Fovargue and Mullock 2016).

Finally, and perhaps most significantly from a moral perspective, health care is not simply "another form of mass consumption" (Salter, Zhou, and Datta 2015, 159), and health-care professionals are not simply purveyors of goods and services. Rather, health care is a distinctly normative space, and health professionals fulfil ethically profound social roles and construct their practices around notions of duty, virtue, respect, and care. This raises the question of what it means to provide care in the context of clinical innovation with autologous stem cells.

Beneficence and Prudence in Clinical Innovation with Autologous Stem Cells

If we accept that health care does not operate solely in the marketplace, but also in a moral place, and also that clinician and consumer autonomy is not sufficient justification for clinical innovation with autologous stem cells, then we must ask what (other) principles are required to justify this kind of clinical innovation. We believe that there are two key principles that matter in this context: beneficence—the commitment to providing benefit—and prudence—acting with caution and discretion where there is the possibility of harm.

Defining Beneficence and Prudence

What counts as benefit in this context is a complex question, because there are many stakeholders who could potentially benefit from clinical innovation with autologous stem cells, including patients (by providing physical or psychological benefits) health-care professionals (by improving efficiencies or reducing risks to medical staff), or the health-care system more generally (by reducing costs, improving efficiencies, or even by improving the sum total of knowledge). For an individual patient, while beneficence would most obviously be achieved if there

was a positive clinical outcome, such as improved survival or quality of life, even the provision of hope may provide benefit.

Because objective benefits are, by definition, unclear in the context of clinical innovation, and because there is always the possibility of physical or psychological harm (by, for example, providing false hope), a commitment to beneficence is deeply intertwined with a commitment to acting in ways that do not cause harm. These commitments are enacted through prudence, which, in the context of clinical innovation with autologous stem cells, entails recognizing explicitly that every intervention is an experiment (rather than a treatment) and ensuring that harms are minimized by paying attention to (among other things) the specific indications for the intervention, the expertise and (conflicts of) interest of the clinicians who will be carrying it out, the adequacy of health service support and insurance systems in the case of complications, and the appropriateness of fees (ISSCR 2016, 25).

In addition, for reasons of both beneficence and prudence, rigorous and objective scientific peer review should always take place. Data collection should also be a compulsory component of clinical innovation with autologous stem cells, and wherever possible, innovation should occur in parallel with high-quality formal clinical research rather than being used as an excuse to avoid "the costly and time-consuming burdens of research and formal registration" (Richards et al. 2015, 3). In this regard, it is noteworthy that some clinics offering autologous SCBIs claim to be doing research while also offering the interventions as treatments, but the research is often poorly designed, used as a marketing tool, and—contrary to the norms of clinical research—patients are often asked to pay to participate (Bianco and Sipp 2014).

Support for Beneficence and Prudence as Guiding Principles

The idea that clinical innovation with autologous stem cells requires consideration of beneficence and prudence (as well as autonomy) would likely have resonance among many who have written about clinical innovation with autologous SCBIs. These principles are, for example, evident in Taylor's (2010) assertion that: "Innovative therapy is the name we give to novel medical interventions, radically different from the standard of care, *provided in order to benefit a patient*, rather than to acquire new knowledge" (286, emphasis added). Taylor also observes that

> to avoid being simply reckless or superstitious, innovative therapy must be grounded in medical reality, even though it may not be compelled by existing evidence. It must also be linked to a community of mentors and peers who are equally familiar with the practical or theoretical framework which makes a proposed innovative therapy plausible if uncertain so that less personally interested clinicians than the therapeutic innovator evaluate the idea. (296)

The International Society for Stem Cell Research, likewise, is concerned with beneficence, arguing that "the main goal of innovative care is to improve an individual patients condition" (ISSCR 2016, 25). Their guidelines encourage clinical innovation but recommend that careful consideration be given to indications, with clinical innovation being used only for "a small number of . . . seriously ill patients," as well as planning, peer review, consent, institutional oversight, data collection, concurrent research, and marketing (25). Even the ISCT, which is strongly pro-innovation and heavily focused on the informed consumer, acknowledges the need for prudence in the form of compliance with good clinical practice (GCP) and other regulatory standards, responsibility for advertising, reporting of adverse events, disclosure of conflicts of interest, and patient follow-up (Gunter et al. 2010)

Two Caveats

There are two important caveats to our assertion that clinical innovation with autologous stem cells can only be justified with regard to beneficence and prudence. First, in saying that we reject the idea that clinical innovation can be justified solely on the basis of clinician and patient autonomy, we are not suggesting that autonomy is unimportant. Clinicians' views and patients' preferences should most certainly be taken into consideration when deciding whether a particular act of stem cell innovation is justified, and consent should be as informed as possible. However, autonomy is just one prima facie principle, and it should be balanced against other, potentially competing, principles.

Second, a commitment to beneficence and prudence in clinical innovation with autologous stem cells is not an extreme or inflexible position. For example, to say that there should ideally be some evidence of benefit beyond proof of concept is not to say that this evidence needs to be as rigorous as that used as the basis of, for example, pharmaceutical marketing approvals. Indeed, if this were the requirement, then we would no longer be in the realm of clinical innovation but rather standard evidence-based practice.[1] As with beneficence, prudence can and should be enacted in a nuanced and flexible way. The degree and types of prudence that need to be exercised depends on the likelihood of benefit and other factors, such as risk, patient preference, and the availability of clinical support structures (Sugarman 2012; Taylor 2010). High levels of prudence, therefore, would be needed to justify interventions that sit close to the proof of concept end of the evidence spectrum or that are extremely risky, while standards could be relaxed for other interventions.

[1]In this regard, it is important to state that we do not have an idealized view of "standard" clinical practice: we recognize that no intervention is ever really proven, and that many well-accepted interventions in Western medicine are not evidence-based at all. This does not, however, change our overall argument—it just suggests that large parts of standard medical practice need to be acknowledged to be forms of (uncontrolled) clinical innovation that just happen to have been normalized.

Defining versus Justifying Clinical Innovation with Autologous Stem Cells

If we accept that clinical innovation with autologous stem cells can only be justified if those who want to engage in it demonstrate a commitment to some form of beneficence and prudence, then it becomes important to distinguish clearly between *definitions* of clinical innovation and *justifications* of such innovation. Specifically, we think that clinical innovation with autologous stem cells should be defined neutrally, and solely in terms of its novelty and context. The justification for such innovation, on the other hand, is normative, and it entails demonstrating a commitment to beneficence and prudence (alongside other relevant principles, such as autonomy and justice). Therefore, we would reject, for example, the ISCT's definition of innovation as "*the ethical and legitimate* use of non-approved cell therapy by qualified health care professionals in their practice of medicine" (Gunter et al. 2010, 966, emphasis added; also cited in Salter et al. 2016). This distinction is important—not only for the obvious reason that clinical innovation with autologous stem cells can often be harmful, but also because weaving positive meanings into its definition makes it easier for those with vested interests to use the term as a rhetorical device to justify the availability, sale, and clinical use of unproven technologies, which can compromise critical evaluation of innovation.

In this regard, it is noteworthy that many clinics offering unproven autologous SCBIs make use of the term *innovation* to sell their services. One Australian group has given itself the name Cell Innovations (2017) and promises other doctors that it will "provide an innovative and promising . . . therapy to your valued patients"; the Swiss Medica Clinic (2017), which claims that "more than 60 diseases can be treated with stem cells," touts itself as "an excellent centre that offers patients the most innovative therapies"; and the Face Body Wellness (2017) clinic proclaims that at its "just-for-women practice, one of the most innovative skin rejuvenation therapies we offer involves the use of stem cells." In each of these cases, the term *innovative* is clearly being used for rhetorical and commercial purposes.

Governing Clinical Innovation with Autologous Stem Cells

Thus far we have argued that clinical innovation with autologous stem cells can only be justified if those who wish to engage in the practice can demonstrate a commitment to two prima facie principles, beneficence and prudence. These are certainly not the only relevant normative principles. For example, respect for autonomy requires that clinicians' and patients' freedoms and preferences be taken seriously. Likewise, attention to distributive justice is central where innovative interventions (or their complications) are to be paid for by public or private insurers. Attention to equity is crucial where the weight of evidence suggests that

innovative technologies should be disseminated into practice and made widely accessible. And principles such as integrity and transparency cannot be overemphasized in academically competitive and commercialized health-care systems. This raises two questions: who should be responsible for the regulation of clinical innovation with autologous stem cells, and how can ethical principles—including beneficence and prudence—be operationalized as part of this regulation?

We do not advocate here for any particular form of regulation. The mechanics of biomedical regulation cover a wide spectrum, from the most basic form of self-regulation via professional standards through to highly regulated licensing schemes and institutional processes such as ethics review boards, quality assurance committees, or specialized innovation review panels (Sugarman 2012; Taylor 2010).

Which regulatory mechanisms (or group of mechanisms) are chosen will depend upon a number of factors, not least of which is the willingness of various bodies to assume responsibility for the governance of clinical innovation with autologous stem cells. In this regard, it is noteworthy that in some jurisdictions, such as Australia, oversight by health technology regulatory agencies is constrained by the way that biological projects administered in the context of health care are defined. For example, the fact that stem cells are biological products rather than devices or drugs and may be administered autologously by a medical practitioner changes the way in which they are regulated. At the same time, professional and legal bodies may be reluctant or unable to consider issues regarding scope of practice and standards of care because they lack resources to do so, because they require evidence of widespread public concern or demonstrated harm, or because they are conflicted due to a commitment to professional autonomy, consumer independence, and the facilitation of innovation.

Regardless of how one chooses to regulate clinical practice innovation, our argument is that any individual or group that seeks to justify clinical innovation with autologous stem cells must demonstrate some form of commitment to beneficence and prudence. The question then becomes how these and other moral principles can be operationalized as part of regulation. This is not an easy question to answer, because there is currently no such thing as a "bioethics of innovation" (Lipworth and Axler 2016), and, as such, "an adequately coherent normative model for medical innovation is wanting" (Sugarman 2012, 949). There have, however, been policy tools developed to conceptualize "responsible innovation" more generally, and these could be applied to the regulation of clinical innovation with autologous stem cells. For example, Stilgoe and colleagues' (2013) influential formulation of responsible innovation operationalizes it according to four dimensions: *anticipation*—considering possible futures of the technology and its governance; *reflexivity*—engaging in moral reflection about the technology and its governance; *inclusion*—bringing new voices into the process and governance of science and innovation; and *responsiveness*—adjusting innovation and its

TABLE 1 QUESTIONS FOR REGULATORS TO ASK ABOUT A PROPOSED INNOVATIVE USE OF AUTOLOGOUS STEM CELLS

Anticipation	• What is the goal of the proposed intervention? Is it to provide an expected clinical benefit, or is it to provide hope, generate knowledge, or achieve economic benefits? Who is most likely to enjoy these benefits (and who will be excluded)? How will these goals be achieved? How likely are they to be achieved? What are the likely barriers to achieving them? What promises are being made and how realistic are they?
	• What harms are possible? Are these clinical (physical or psychological) harms, economic harms, or epistemic harms (e.g., stifling formal research)? How likely are these harms? Who is most likely to be adversely affected? What steps can be taken to minimize the risk of harm? For example, has there been explicit consideration of:
	  • the patient groups to whom the intervention is offered (which should be clearly defined and justified);
	  • clinician expertise (which should be of the highest level so that "experimentation" is as safe as it can possibly be);
	  • health service support and insurance systems (which are needed in case of complications);
	  • marketing (which should be minimal and factual); and
	  • payment (which should be limited to cost recovery)?

Reflexivity	• What ethical, social, political, and economic concerns been taken into account in the decision to administer autologous stem cells through clinical innovation, and in the specific processes being proposed (e.g., for patient consent)? Has attention explicitly been paid to beneficence, prudence, autonomy, justice, and integrity? • What concerns have been overlooked? For example, are libertarian values, such as clinician and patient autonomy, being valorized and social values, such as care, relational autonomy, solidarity, and system sustainability, being downplayed? Whose interests might be behind this (e.g., commercial, political, or professional groups)? • What (if any) codes of ethics or practice have been considered? • What scientific paradigms are being privileged and de-privileged (e.g., evidence-based medicine vs. clinical innovation) by those proposing the intervention?
Inclusion	• Who has been involved in the decision to engage in clinical innovation? Have patients and communities (e.g., patient advocacy groups) been involved in the decision? How have they been involved (e.g., membership of committees, deliberative processes, focus groups)? Has this been done in a manner that accounts for differential power structures (e.g., the difference in power between regulators or the stem cell industry and patients with life-threatening diseases)? • Have other stakeholders been consulted, such as other clinicians, insurers, regulators? • Has there been an independent process of scientific peer review?
Responsiveness	• If the intervention was approved, how would its outcomes be followed up? Would a registry be established and, if so, how would it be administered? Would results be disseminated and, if so, how? • How would the current intervention be adapted in response to the outcomes of this intervention and in the context of other emergent technologies?

governance as findings emerge from the other domains. These dimensions could be a useful guide for those regulating clinical innovation with autologous stem cells at any of the regulatory levels described above. Regulators might ask themselves the series of questions outlines in Table 1 when considering prospectively whether to license or otherwise permit the clinical use of unproven stem cell interventions. The questions could also be rephrased to be used retrospectively—if, for example, a complaint about a clinician is made to a professional regulatory body. These questions incorporate attention to ethical principles such as beneficence, prudence, autonomy, justice, and integrity, but they also place these issues in a broader teleological, procedural, and sociopolitical context.

Conclusion

Our proposal for a commitment to beneficence and prudence (alongside other ethical principles) in the use of clinical innovation with autologous stem cells would likely be resisted both by those who would regard it as an unreasonable constraint on innovation, and by those who would view it as a reassertion of medical hegemony. Nonetheless, to divorce this kind of clinical innovation from notions of beneficence and prudence, and to rely solely on the values of the market, the rationality of consumers, and the progressive value of science may result in serious harm to patients and health systems and undermine trust in the medical system. Claims to be able to offer unproven autologous stem cell interventions without demonstrating a commitment to beneficence and prudence should have no normative force and should be rejected.

References

Berger, I., et al. 2016. "Global Distribution of Businesses Marketing Stem Cell-Based Interventions." *Cell Stem Cell* 19 (2): 158–62.

Bianco, P., and D. Sipp. 2014. "Sell Help Not Hope." *Nature* 510 (7505): 336–37.

Cell Innovations. 2017. http://www.cell-innovations.com.au/.

Face Body Wellness. 2017. http://fbwnaturale.com/our-treatments/stem-cell-therapy/.

Faden, R. R., et al. 2013. "An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics." *Hastings Cent Rep* 43 (S1): S16–S27.

Fovargue, S., and A. Mullockeds. 2016. *The Legitimacy of Medical Treatment: What Role for the Medical Exception?* Oxford: Routledge.

Gunter, K. C., et al. 2010. "Cell Therapy Medical Tourism: Time for Action." *Cytotherapy* 12 (8): 965–68.

International Society for Stem Cell Research (ISSCR). 2016. "Guidelines for Stem Cell Research and Clinical Translation." http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4.

Kass, N. E., et al. 2013. "The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight." *Hastings Cent Rep* 43 (S1): S4–S15.

Lee, T., et al. 2017. "Regulating the Stem Cell Industry: Needs and Responsibilities." *Bull WHO* 95: 663–64.

Lipworth, W., and R. Axler. 2016. "Towards a Bioethics of Innovation." *J Med Ethics* 42 (7): 445–49.

Lysaght, T., B. Richards, and A. Muralidharan. 2017. "Exploring the Boundaries of Autonomy and the 'Right' to Access Innovative Stem Cell Therapies." *Asian Bioeth Rev* 9 (1–2): 45–60.

Lysaght, T., et al. 2017. "The Deadly Business of an Unregulated Global Stem Cell Industry." *J Med Ethics* 43 (11): 744–46.

Marks, P. W., C. M. Witten, and R. M. Califf. 2017. "Clarifying Stem-Cell Therapy's Benefits and Risks." *N Engl J Med* 376 (11): 1007–9.

McLean, A. K., C. Stewart, and I. Kerridge. 2014. "The Emergence and Popularisation of Autologous Somatic Cellular Therapies in Australia: Therapeutic Innovation or Regulatory Failure?" *J Law Med* 22 (1): 65–89.

McLean, A. K., C. Stewart, and I. Kerridge. 2015. "Untested, Unproven, and Unethical: The Promotion and Provision of Autologous Stem Cell Therapies in Australia." *Stem Cell Res Ther* 6: 33.

Petersen, A., et al. 2017. *Stem Cell Tourism and the Political Economy of Hope*. London: Palgrave Macmillan.

Richards, B., et al. 2015. "The Medical Innovation Bill: Still More Harm than Good." *Clin Ethics* 10 (1–2): 1–4.

Salter, B., Y. Zhou, and S. Datta. 2015. "Hegemony in the Marketplace of Biomedical Innovation: Consumer Demand and Stem Cell Science." *Soc Sci Med* 131: 156–63.

Sipp, D., et al. 2017. "Marketing of Unproven Stem Cell–Based Interventions: A Call to Action." *Sci Transl Med* 9 (397): eaag0426.

Stilgoe, J., R. Owen, and P. Macnaghten. 2013. "Developing a Framework for Responsible Innovation." *Res Policy* 42 (9): 1568–80.

Sugarman, J. 2012. "Questions Concerning the Clinical Translation of Cell-Based Interventions under an Innovation Pathway." *J Law Med Ethics* 40 (4): 945–50.

Swiss Medica Clinic. 2017. http://www.startstemcells.com/anti-aging-treatment-naturally.html.

Taylor, P. L. 2010. "Overseeing Innovative Therapy Without Mistaking It for Research: A Function-Based Model Based on Old Truths, New Capacities, and Lessons from Stem Cells." *J Law Med Ethics* 38 (2): 286–302.