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Banking on it: Public policy and the ethics of stem cell research and development

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Abstract

If the therapeutic potential of stem cell-based therapies is ever realized, demand for stem cells and derivative tissues will be tremendous and will create new challenges for health care systems, especially publicly funded health care systems. We propose a framework for the ethical analysis of stem cell research and development that considers the welfare of communities, tissue recipients, and cell sources in relation to a range of stem cell production and distribution options. Ethical desiderata include: equitable access, maximized potential therapeutic benefit across demographic and disease groups, and reasonable cost. Other ethical priorities include the minimization of stem cell line and tissue wastage, risk of immune rejection, risk of transmitting diseases, the use of human embryos, and risk to those contributing source cells. We array plausible sources of stem cells and distribution strategies to characterize 12 potential models for producing and distributing cells and tissues in the future. We describe ''personalized'', ''matched'', and ''universalized'' models, and compare the ethical acceptability of these models. Popular and scientific discourses about stem cells typically emphasize personalized or matched stem cell distribution models. We show that universalized models may ultimately best serve the interest of taxpayers, communities and patients who hold high stakes in the therapeutic success of stem cell science. They are therefore highly worthy of scientific pursuit. This conclusion is provisional and the framework must be reapplied as scientific knowledge, technological capacity and ethical mores evolve.

Keywords: Bioethics; Stem cells; Tissue sharing; Health policy; Resource allocation; Social values; Ethics

Introduction

While stem cell researchers tackle basic science questions concerning the viability and plasticity of stem cells *in vitro* as well as their performance *in vivo* (Kimmelman, Baylis, & Glass, 2006; Robert, 2004), enthusiasts (some of whom are also researchers) extol the therapeutic potential of stem cells for prevalent, intractable conditions such as Alzheimer's disease, Parkinson's disease, diabetes, osteoarthritis, and rheumatoid arthritis. The track from bench to bedside is long, however, and involves many scientific, technological, and social hurdles. As stem cell technology progresses to the clinical setting, health

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care systems—especially publicly funded health care systems concerned with access, fairness, and cost control—will be challenged to derive, expand, and distribute cells and tissues routinely and on a massive scale. Unique ethical, economic, and organizational problems undoubtedly will arise.

In this paper, we propose a framework for the ethical policy analysis of stem cell science. For the sake of argument, we assume that stem cell therapies will be proven adequately safe and effective to qualify as insured health services, and will pose less risk and more certain benefit than they do as investigational technologies (Dawson et al., 2003). Above this coverage standard, however, levels of safety and effectiveness may vary widely across specific treatments and conditions. We further assume that such therapies will be provided through a publicly funded, universal health care system such as Canada's. We map ethical concerns about the welfare of the community, those who receive cell transplants, and those who provide cells or tissues onto two dimensions of stem cell production and distribution: (1) how stem cells and their derivatives are *produced*, and (2) how they are *distributed*. By arraying these production and distribution possibilities, we identify 12 plausible models, and identify the least ethically problematic of these models. The usefulness of the proposed framework lies in its ability to provide a broad view of many complex issues at once, and to highlight goals for stem cell science in the public interest, as well as its potential adaptability in response to developments in stem cell science and ethics.

Basic ethics of stem cell therapeutics

How does a just health care system distribute stem cells and stem cell-based tissues as a mass-produced health care product? From a public policy perspective, the ethical problems of stem cell production and distribution can be divided into three categories: (1) problems concerning the welfare of the community, (2) problems concerning the welfare of individuals who provide the materials for the derivation of stem cells, and (3) problems concerning the welfare of stem cell transplant recipients.

Welfare of the community

With regard to the welfare of the community, two basic concerns arise. The first concern is *equity*: individuals should have fair access to stem cell therapies, based on medical need. Access should not be determined by demographic or economic features such as ethnicity, gender, or wealth. Available tissue types should reflect clinical imperatives and not discriminate incidentally (Greene, 2006). Moreover, individuals who provide the materials for deriving stem cells must be plentiful and diverse in terms of human leukocyte antigen (HLA) types to allow those in need to receive well-matched tissue. Stem cell therapeutics ideally should be available for a range of amenable health problems, and cater to more severe problems where resources are scarce.

Another community concern is with the potential impact of stem cell-based therapies on the fiscal sustainability of health systems (Baylis & Downie, 2005).It is too early to venture an economic evaluation of stem cell therapeutics, but stem cell tissues will surely be expensive. This highlights an ethical imperative to use stem cell resources prudently: tissue production models should not entail the routine wastage of unused stem cell lines or donated cells and tissues. Production methods should generate as few unused or unusable tissue lines as possible. Ceteris paribus, the brief storage of a few lines is preferable to the long-term storage of many lines. Ideally, tissues would be supplied in response to present needs, rather than as insurance against distant needs that may never materialize.

Stem cell and related sciences may have far-reaching impacts on communities; others have identified profound and unsettling possibilities (The President's Council on Bioethics, 2004). Important questions about the impact of the broader sociotechnological agenda and its proper governance remain outside our scope, however. Here, we focus on issues raised by stem cell therapeutics as routinized health services.

Welfare of those providing cells and tissues

A second cluster of ethical concerns centers on the welfare of those providing tissues necessary to derive stem cell lines for transplantation—healthy or diseased humans at all stages of development (embryos, fetuses, infants, children, adolescents, adults). The cell source may be an anonymous provider or the ailing recipient. Some approaches to the collection of cells are invasive, and some put the source's health or even life at risk. Sources that have garnered significant scientific and political

interest include the human embryo (created by *in vitro* fertilization (IVF) or somatic cell nuclear transfer (SCNT)), the post-natal (''adult'') somatic cell donor, and the umbilical cord.

In many jurisdictions, the use of human embryos for research is ethically unacceptable, or marginally acceptable under limited circumstances. In these jurisdictions, the industrial creation of human embryos and their destruction in great numbers to derive stem cell lines for *routine* clinical use would be morally problematic. Another concern with the research use of human embryos focuses not on the moral status of the developing embryo, but on the harms to women who provide ova to create embryos destined to become stem cell sources. With ovarian stimulation there is the risk of ovarian hyperstimulation syndrome (OHSS), mild forms of which involve abdominal discomfort, nausea, vomiting, diarrhea and abdominal distention (The Practice Committee of the American Society for Reproductive Medicine, 2003). More severe, life-threatening forms involve ''…renal failure, acute respiratory distress syndrome (ARDS), hemorrhage from ovarian rupture, and thromboembolism'' (The Practice Committee of the American Society for Reproductive Medicine, 2003, p. 1310). A recent European report confirms that at least six women have died of OHSS (Pearson, 2006). The long-term risks of OHSS are not well studied or understood; a link between ovarian stimulation and ovarian cancer has been suggested (Brinton et al., 2004; Rossing, Darling, Weiss, Moore, & Self, 1994). In addition to these physical harms, there are additional harms of coercion and economic exploitation. These harms, already present in the current research context, would be amplified by routine large-scale embryo donation system for stem cell therapies.

Another source of stem cells is the adult somatic cell donor who gives some of her bodily tissues to develop stem cell lines for transplantation. Tissue collection can be invasive, hazardous, and painful to varying degrees depending upon the tissue type and quantity. Potential psychological harms threaten cell donors (and possibly family members), as they must undergo genetic and other diagnostic screening to minimize the risk of transmitting infection or genetic conditions. The information generated by genetic testing can result in loss of privacy, disrupted familial relations, economic discrimination, and so forth (Lo et al., 2005).

Welfare of those receiving cell-based therapies

Although we assumed at the outset that stem cell-based therapeutics will be basically safe and effective, their health impacts, side effects, and risks can be affected by how tissues are produced and distributed. Well-recognized safety issues that are particularly sensitive to the tissue production and distribution system include preventing immune rejection and preventing the transmission of either infectious or genetic diseases between cell sources and recipients (Dawson et al., 2003).

Summary: ethical imperatives in stem cell therapies

In summary, eight ethical desiderata for stem cell tissue production and distribution are: (1) ensuring equitable access across demographic groups, (2) ensuring as little unmet need as possible across groups that might benefit, (3) ensuring reasonable expense, in the interest of health care system sustainability, (4) minimizing wastage of stem cell lines and tissues, (5) minimizing or avoiding the use of human embryos, (6) minimizing potential harms to those providing cells for the derivation of stem cell lines, (7) minimizing the risk of immune rejection in recipients, and, (8) minimizing the risk of transmitting disease between cell sources and recipients. All of these goals are laudable, but communities may vary in how much they value each goal, whether they are willing to sacrifice one goal for another, and what array of compromises among the various goals would be acceptable. Further, each of these ethical desiderata can be violated to a greater or lesser extent. For example, while it is ideal not to harm any person at all, it is better to harm a few than it is to harm many, and it is better to harm minimally than it is to harm greatly. These magnitudes affect ethical tensions amongst goals and policy imperatives. They are especially salient for a large-scale enterprise that requires the industrial production of cells and tissues for transplantation.

Models of stem cell production and distribution

At this early stage of research and development, the stem cell production and distribution options are many. Nevertheless, a few core visions predominate regarding where stem cells might come from and where the derived tissues might go.

Stem cell production

One source of stem cells is the IVF embryo. This could be an embryo remaining after infertility treatment, or this could be an embryo purposefully created for stem cell derivation. Between the third and fifth day of the IVF embryo's development undifferentiated stem cells are removed, thereby destroying the embryo. A second embryonic source of stem cells is the SCNT embryo created by fusing the nucleus of an adult somatic cell (not sperm) with an enucleated human ovum. This embryo will be a genetic clone of the person supplying the somatic cell, and the resulting cells and tissues will be nearly genetically identical to that person's bodily tissues. As with the derivation of stem cells from the IVF embryo, it is again the case that removing undifferentiated stem cells destroys the embryo. A third source of stem cells is adult somatic tissue. Stem cells at various stages of differentiation are dispersed through many types of adult tissue (e.g., skin, heart, brain, blood, baby teeth) and can be isolated from samples of that tissue, with varying levels of difficulty. Finally, a fourth source of stem cells is the umbilical cord. Blood is drawn from the umbilical cord at medically qualified births, hematopoetic stem cells are extracted and grown into specific blood cells.

These stem cell sources differ from each other in important respects. The two embryonic options involve the destruction of the cell source and require that women consent to the risks of ovarian stimulation and ova retrieval; the other two options do not. With somatic stem cell sources, the source is not destroyed, but tissue collection may be invasive depending upon the body part targeted (e.g., blood is less invasive, muscle or brain more so). Typically, for tissue transplantation, the closer the genetic match between source and recipient, the lesser the risk of immune rejection, but the degree of immune response to genetically unrelated tissue varies by tissue type. And finally, stem cells may be more or less differentiated in their development at the time they are derived. It is currently believed that stem cells can only become more differentiated as they are cultured, which means that more differentiated cells can yield fewer types of tissues for transplantation. The primary appeal of embryonic stem cells is their remarkable ability to differentiate into any tissue. By contrast, cord blood stem cells are able to produce only blood tissues. Researchers debate whether the limited potency and plasticity of somatic stem cells is inherent, or an artefact of current scientific knowledge and practice (Alison et al., 2003; Lakshmipathy & Verfaillie, 2005; Moore & Quesenberry, 2003).

Table 1 summarizes these four sources of stem cells (based on prevailing science) and attendant ethical issues. Embryonic sources are expected to produce stem cells with high plasticity, useful for any disease amenable to stem cell therapy. Demographic equity suffers if embryonic stem cells are sourced from excess IVF embryos in infertility clinics. Wealth, ethnicity, and other demographic factors affect access to IVF (Inhorn & Fakih, 2006). To the extent that infertility or access to IVF correlate with genetic differences, this will affect access to subsequent stem cell lines (Faden et al., 2003). By comparison, somatic and cord blood stem cells are more differentiated and are thus useful for a more limited array of diseases. Bodily access to somatic and cord blood stem cells varies—some are difficult to find or invasive to collect, but neither requires the risky collection of human ova from women, nor the creation and use of human embryos for industrial purposes.

Stem cell distribution

Having established where the cells and tissues for transplant might come from, the next question is where they might go. Many social factors (relationships, social status, economics, etc.) affect access to health care and no doubt to eventual stem cell therapies. Here, we focus on biological factors that would make stem cell-based tissues more or less accessible to patients. A crucial issue in debates about the likely safety and efficacy of stem cell therapies concerns HLA matching between the stem cell tissues and the prospective patients. If tissues are recognized as foreign by the patient's immune system, there is the risk of rejection and associated pathology; this diminishes with HLA-compatible tissues. Whenever foreign tissues enter the body, there is also a risk of inadvertently introducing infectious or genetic disease. Tissues must also be made in sufficient quantity and with sufficient speed to meet the clinical needs of specific patients.

Models for the effective distribution of stem cell-based tissues may be grouped into four categories. A relevant criterion in distinguishing these categories is the degree to which the tissues are immunologically or genetically compatible with the recipient. A second criterion is whether tissues

Table 1
Ethical concerns with the four stem cell production models

Ethical concerns	Sources of stem cells			
	IVF embryonic	SCNT embryonic	Somatic	Cord blood
Welfare of the community				
Demographic equity	Unlikely (if embryos surplus to infertility treatment) Yes (if embryos purposely created for tissue production)	Yes (because embryos are created for tissue production)	Unlikely[a]	Unlikely
Number of treatable diseases	Large	Large	Likely limited	Blood only
Welfare of cell sources				
Use of embryos	Yes	Yes	No	No
Use of ova donors	Yes	Yes	No	No
Use of somatic cell donors	No	Limited[b]	Yes	Yes

Key: shaded cells highlight ethical problems.
[a]Stem cell lines derived from somatic cells require volunteer donors of each bodily tissue and antigen profile, donor demographics are unlikely to represent population demographics. With SCNT (which also relies on somatic cell donors), there is the option of determining the tissue type in the laboratory and not by patterns of goodwill among donors.
[b]We assume that tissue type is not as crucial with SCNT as it is with somatic cell donation, since the SCNT embryo is not differentiated tissue and many useful stem cell lines may derive from a relatively few donors. For somatic cell sources, more donors may be required to produce an adequate supply of all relevant cell types.

are to be created rapidly on demand, or long before anticipated need and stored for future distribution. Risk of rejection and risk of introducing new disease also vary across these four models. The four models are: (1) *personalized* tissues genetically identical to each recipient's own cells but generated on an "*as needed*" basis in response to a specific disease or injury, (2) *personalized* tissues genetically identical to each recipient's own cells, banked for a lifetime "*as insurance*," for treating any amenable disease the individual might develop, (3) banked *matched* tissues where donors and recipients' tissues are genetically unrelated but tissues match adequately to avoid immune rejection complications, and (4) banked *universalized* tissues that are developed to be immunologically compatible with entire populations of individuals despite differences between donors' and recipients' genetics.

Personalized stem cell lines would be derived from SCNT embryos created with nuclear DNA from the prospective recipient's somatic cells and would be genetically identical to the recipients' own bodily tissues. Personalized tissues avoid immunohistocompatibility problems because the identical genetics ensure identical antigen profiles. The risk of transmitting new infectious or genetic disease is negligible. However, if the health problem being treated has a genetic basis, genetic risk may be sustained in the regenerated tissues. In such cases, others' genes may be genetically superior to the recipient's own genes, but this potential benefit is forfeited to the goal of perfect immunohistocompatibility.

There are two possible distribution options involving the use of personalized stem cell lines. A first option would involve creating personalized lines only as needed. This obviates the challenge of banking stem cell lines for the life of the individual, as stem cells would be created on demand to treat specific health problems. In practice, this may be difficult if stem cell derivation and production remain complex and uncertain, or if it takes time to produce adequate volumes of tissue. The longer the delay, the fewer health conditions could be treated effectively on an as-needed basis.

A second option for personalized stem cell lines would involve creating and banking personalized lines as insurance. Healthy individuals (as early as infancy) would bank personalized stem cell lines for future possible use. Each citizen would have his or her own stem cell lines in waiting. The cost, however, would be enormous. Ballpark estimates from Canada illustrate the problem. Canada's population is close to 31 million; about 570,000 new individuals join the Canadian population each year (Statistics Canada, 2004).Canada's publicly funded health plans cover provincial and territorial populations ranging in size from 28,000 to 11.4 million. On average, these plans spend about $2,354

per capita on health care (2002–03 figures). What might it cost to provide every Canadian with a personalized stem cell line as insurance against future possible health needs?

It is not currently known what a single-personalized stem cell line would cost to establish and maintain long-term. Rough (and low) banking costs might be estimated from private cord blood banks, where personalized tissue stores are reserved "as insurance" for the needs of individuals. One private Canadian cord blood bank charges a one-time registration, processing, and diagnostic fee totaling CDN$850, and CDN$125 per year for storage up to 15 years (Lifebank, 2004). At these rates, the initial investment for storing a personalized stem cell line for each Canadian might be CDN$25.5 billion. Thereafter, the annual cost of maintaining the lines would be CDN$4.2 billion per year, plus CDN$484 million per year to establish new lines for new Canadians. This averages to about CDN$141 per capita, equivalent to approximately 6% of the current per capita public expenditure for health care. This is only the cost for storage, not cell culture or differentiation. Many cell lines would be wasted, as disease or injury amenable to stem cell therapy may not occur, and the cell lines of approximately 280,000 Canadians who die or emigrate each year would be decommissioned.

Personalized stem cell lines for hematopoietic tissues could be created with cord blood drawn at birth, but for other tissues, the personalized cell lines would be derived from SCNT embryos created with the help of ova donors. If either harvest of ova or destruction of embryos is ethically questionable in itself, it becomes even more so with the mass production of personalized tissues. For ova donation, it may be easier to secure high quality, informed consent from a few motivated volunteers than from numerous women recruited to the cause. Misinformation and coercion become larger concerns. Further, because of the low probability that the cell lines generated would ever be put to therapeutic use, there is less assurance that potential benefit to recipients would be proportionate to the harms to ova donors. Altruistic organ and tissue donation for strangers is ethically problematic in itself, and more so when recipient benefit is unknown or uncertain (Adams et al., 2002). Some envisioned stem cell uses may be life saving or profoundly restorative (e.g., treating spinal cord injury), others are arguably more frivolous (e.g., treating baldness). One way around this daunting ova donor problem (although not the embryo problem) would be to create a perpetual *in vitro* source of human ova, thereby obviating the need for mass donations. Early research in mice suggests that it may become possible to generate gametes from stem cells (Testa & Harris, 2005; Vogel, 2005).

Personalized stem cell lines may not be necessary, however. The reason typically given for creating personalized lines is to avoid immune rejection. At present, evidence of a rejection problem with embryonic stem cells is lacking, and the possibility is keenly debated among scientists. Stem cell-derived tissues provoke host immunorejection less than other transplantable tissues (Medicetty, Bledsoe, Fahrenholtz, Troyer, & Weiss, 2004; Weiss et al., 2003). Even if there were evidence of an immune rejection problem, this might be addressed in other ways. Two alternatives identified by Thomson, a pioneer of human embryonic stem cell research, are:

> …banking cell lines with defined major histocompatibility complex backgrounds or genetically manipulating ES cells to reduce or actively combat immune rejection. (Thomson, 1998)

The first of these options, banking lines with a range of histocompatibility profiles, we refer to as the "matched" model of stem cell distribution. In this case, donors' and recipients' genetics differ, but stem cell tissues are matched as closely as possible to the recipient's HLA profile to prevent immune rejection. The matched model relies on a collective tissue bank. In much the same way that blood is banked today, stem cell banks could solicit donations from the general public, cultivate a limited number of stem cell lines to represent adequate population genetic variation, and distribute these lines as needed.

A drawback with this approach, however, is that the chance of getting a good match may vary by non-clinical factors, as has occurred with the distribution of organs for transplantation. The chances of an individual getting a good match depend on how many people genetically similar to that individual have donated tissue. People with rare antigen profiles face poorer chances, as do people belonging to groups that have low donation rates for any reason. As with organ transplantation, biological and social inequalities may impair access to appropriate tissues (Wolfe et al., 2000), and greater access may come at the cost of suboptimal

tissue matching, with increased risk of treatment failure (Roberts et al., 2004).

What might be the biologically ideal number of lines? It is not clear exactly how many genetically distinct stem cells lines would be required to meet the health needs of a given population; Taylor et al. have recently estimated the need for the UK population at150 lines (Taylor et al., 2005); Faden et al. for the US estimate a need for 120 lines to serve a range of the country's ethnic groups (Faden et al., 2003).

A second drawback to the matched model is the potential need for immunosuppressive drugs to overcome mismatches with their attendant and serious effects on the health of recipients. A third problem is the possibility of transmitting either genetic or infectious disease from the donor to the recipient via cell or tissue sharing. Stem cell donors and stem cell lines may require extensive diagnostic and genetic testing to prevent this. Diagnostic workups affect the wellbeing of the donors as well as the recipients.

Thomson's second option, genetically manipulating stem cells to reduce or combat immune rejection, is a compelling possibility. We call this distribution model the "universalized" model: all lines would be universally compatible with all potential recipients. Whether rendered universally immunocompatible naturally or artificially, such cell lines would need not be genetically diverse nor banked in large numbers (assuming a large volume of tissue could be grown from relatively few lines). In principle, any individual could safely receive, as needed, tissue derived from virtually any source.

Table 2 summarizes the four stem cell distribution models and relevant ethical issues. Personalized stem cells and tissues require stem cell line production on a grand scale and at formidable cost. Banking personalized lines for individuals' lifetimes as insurance multiplies the costs as well as waste. However, for recipients, personalized lines pose little risk of tissue rejection, infectious disease transmission, or genetic disease transmission (excepting that due to the recipients' own genetic flaws). While matched rather than personalized cells and tissues save costs, matching models also pose problems. They require the banking and sustenance of hundreds of stem cell lines, may result in unequal access by demographic groups with uncommon HLA profiles or low donation rates, probably require the use of immunosuppressive drugs, and involve greater risk of disease transmission from donors to recipients. Universalized stem cell distribution models overcome nearly all of the problems with personalized and matched models: very few lines could serve an unlimited number of people, and these few lines could be cultivated to reduce or actively combat immune rejection and to be free of known genetic defects and pathogens.

Table 2
Ethical concerns with the four stem cell distribution models

Ethical concerns	Models			
	Personalized, as insurance	Personalized, as needed	Matched	Universalized
Welfare of the community				
Demographic equity	Yes	Yes	Unlikely	Yes
Banking expense	Extremely high	High	Moderate	Low
Number of lines	Millions	Up to millions	Hundreds	Few
Duration of each line	Decades	Up to years	Indefinitely	Indefinitely
Wasted lines	Up to millions	Few	Few	Few
Welfare of recipients				
Rejection risk	No	No	Yes	No
Disease transmission risk	Minimal	Minimal	Moderate	Minimal
Welfare of cell sources				
Use of embryos	Yes[a]	Yes[a]	Possibly	Possibly
Use of egg donors	Yes	Yes	Possibly	Possibly
Use of somatic cell donors	Yes (self)	Possibly	Possibly	Possibly

Key: shaded cells highlight ethical problems.
[a]The special case of cord blood banking for hematopoetic tissues is an exception.

Synthesis: 12 stem cell production and distribution models

By arraying the four sources of stem cells against the four distribution models, we identify, in Table 3, 16 stem cell production and distribution models, four of which are implausible (models labeled "1" through "4"). Model 1, the creation of personalized stem cell tissues from IVF embryonic sources as insurance, would be available only to individuals conceived by IVF, at which time a twin embryo would be created—one twin to gestate to term (i.e., the eventual recipient) and the other to be cryopreserved and later cultivated as a stem cell source. Model 2, the creation of personalized stem cell tissues from IVF embryonic sources as needed, like Model 1, would be available only to individuals conceived by IVF, at which time a twin embryo would be created as a stem cell source to treat the other twin during gestation or immediately after birth. Stem cell treatment beyond this time frame would require cryopreservation and would thus be an instance of Model 1. With Model 3, the creation of personalized stem cell lines from somatic tissues as insurance, it would be necessary to derive stem cells from many of the individual's bodily tissues for the unlikely event that these will be needed for treatment—an option too expensive, invasive, and risky to justify the small possibility of benefit. Finally, Model 4, the creation of personalized stem cells from cord blood as needed, is impossible any time after birth (the alternative here is to collect cord blood as insurance, which is possible). As such, there are 12 plausible stem cell production and distribution models. These are labeled "A" through "L".

Table 4 reviews the ethical issues enumerated in Tables 1 and 2 in relation to the models identified in Table 3, thereby broadening the ethical gaze. In some respects this big picture is simplistic, but it usefully shows how moving from one production and distribution model to another solves some ethical problems while exacerbating others. Table 4 also attempts to qualify the degree of ethical concern. This degree is indicated by the number of "x"s appearing in a cell: one x indicates a problem, more "x"s indicate a larger scale problem *within the same ethical category*. How individuals or jurisdictions weigh the moral gravity of *different* ethical problems (not different magnitudes of the same ethical problem) will vary with value systems; these assessments are not reflected in Table 4. Even so, Table 4 allows us to locate more and less ethically problematic models in general, and to identify some specific challenges.

What is the comparative ethical acceptability of the 12 stem cell distribution and production models? The answer will depend on the relative importance of community, recipient and cell source welfare, as well as the degree of ethical violation that is tolerated in each category. Individuals and policy makers who are averse to the use of embryos or ova donors would find Models A, C, E, F, I and J unacceptable, but some may be willing to trade off recipient welfare somewhat (from restricted tissue types) by turning to Models K or L. Those who aim to minimize the use of embryos and ova donors, but who do not see their use as an absolute moral wrong, may find options I or J desirable because they strongly serve community welfare (in terms of high access at affordable costs) and recipient welfare (by supporting a full spectrum of somatic tissue types at minimal risk of immune rejection or new disease). As such, Models I, J, K, and L—involving universalized stem cells—appear to be the least ethically problematic. And yet, these are not the models that dominate current scientific, bioethical and popular discourse.

Table 3
Twelve stem cell production and distribution models

How stem cells are produced	How stem cell tissues are distributed			
	Personalized, as insurance	Personalized, as needed	Matched	Universalized
IVF embryonic	(not plausible #1)	(not plausible #2)	E	I
SCNT embryonic	A	C	F	J
Somatic	(not plausible #3)	D	G	K
Cord blood	B	(not plausible #4)	H	L

Table 4
Nature and degree of ethical concerns with each of the 12 models

	Personalized											
	As insurance		As needed		Matched				Universal			
	SCNT	Cord blood	SCNT	Somatic	IVF	SCNT	Somatic	Cord blood	IVF	SCNT	Somatic	Cord blood
	A	B	C	D	E	F	G	H	I	J	K	L
Welfare of community												
Demographic equity	●	●	●	●	xx	x	x	x	●	●	●	●
Number of treatable diseases	●	xxx	xxx	xx	●	●	xx	xxx	●	●	xx	xxx
Banking expense	xxx	xxx	xx	xx	xx	x	x	x	●	●	●	●
Welfare of recipients												
Rejection risk	●	●	●	●	xxx	xx	xx	xx	●	●	●	●
Disease transmission risk	●	●	●	●	xx	xx	xx	xx	●	●	●	●
Welfare of cell sources												
Uses embryos	xxx	●	xxx	●	xx	xx	●	●	x	x	●	●
Requires ova donors	xxx	●	xxx	●	●		●	●	x	x	●	●
Requires somatic cell donors[a]	●	●	x	xxx	x	x	xx	●	●	x	x	●

Key: shaded cells highlight ethical problems.
● = not particularly ethically problematic, according to criteria applied in this analysis
x to xxx = somewhat to very ethically problematic, respectively. These relative degrees of ethical concern apply *within* the rows only. Comparisons of degree across rows are not valid in the absence of additional ethical analysis.
[a]Autologous (self) donor is indicated by one "x", as is the model of very few unrelated donors; cord blood donation is not counted with somatic cell donation here.

Conclusion

Much current publicity about stem cell science portrays the astonishing nature of stem cells and the promise of personalized cures for individuals. There is no parallel vision of what this technology might look like as a routine health care service provided to millions of people, particularly under public funding. More attention is needed to the ethics of protecting healthy people from undue risk, providing fair access, and sustaining the economic viability and equity of health systems as they accommodate new technologies. The essential tension between progress and equity in medical research (Callahan, 2002) must be considered early and often as stem cell technology evolves. Prospective or "real-time" technology assessment (Guston & Sarewitz, 2002) is essential for innovation toward goals such as the promotion of the public interest or the sustainability of health care systems.

By taking a broader view of the stem cell science and ethics agendas, this analysis has highlighted some ethically promising directions for the science of stem cell therapeutics. A *universalized* distribution model seems to hold the greatest promise for addressing future clinical and health system needs. It is the model of stem cell distribution most likely to promote efficiency and equity. Even if embryonic sources are used, the number required would be small, curbing the risk of countless healthy women being exploited as ova sources. The fewer ova donors required would be more likely to be authentically motivated volunteers and to give truly informed consent. Scientific and technical obstacles to creating universalized stem

cell lines are many, but so too are obstacles to creating personalized stem cell lines by SCNT—the most widely promoted, and far more ethically problematic, alternative.

The personalized distribution model comes at enormous cost to the health care system as it involves creating and banking a unique cell line for each potential recipient. Health payoffs would have to be dramatic to justify publicly funding a technology that may require for example the equivalent of 6% or more of Canada's per capita public spending for health care. It would be wasteful and unaffordable to establish lines for everyone to be held as insurance against any amenable future health problem.

A surprising finding of this analysis is the relative ethical unattractiveness of matched models for stem cell distribution. Matched models resemble most closely our current methods of distributing blood and transplantable organs. They may not suit stem cells and derived tissues, especially in light of the plausible alternative of universalized cells and tissues. Because banking is necessary, matched models would be more expensive than universalized models, although less so than personalized models. Although matched cells and tissues could be quite accessible in principle, effectiveness and risks would vary across demographic groups due to immunohistocompatibility patterns. The inevitable and inequitable mismatching problem would be more pronounced if surplus IVF embryos were used as stem cell sources. However, matched models are likely if universalized models fail to be technically possible.

This analysis illustrates how scientific breakthroughs that may serve sick individuals may not serve diverse populations and economically fragile health systems. At this early stage in the development of stem cell technologies, there is the opportunity to plot a basic research agenda to pursue a viable health service as well as an individual cure. Our analysis shows that perhaps there is a happy juncture between individual and societal interests: the production and distribution of *universalized* stem cell lines. As universalized stem cell lines may best serve the interest of taxpayers, communities and patients who hold high stakes in the therapeutic success of stem cell science, stem cell researchers and funding agencies should target adequate resources and efforts toward this goal. This does not mean that research agendas should pursue one model to the exclusion of all others. Different models may be appropriate for different diseases, populations, or jurisdictions. What is called for, however, is critical attention to the systemic implications of the models in which we invest.

In summary, we have proposed an ethical framework for evaluating options for stem cell research and development that looks beyond the welfare of the *in vitro* embryo or the ailing individual, and considers impact on the health care system. Doing so during the early years of stem cell science is risky but necessary. It is risky in that many assumptions about the scientific and technical possibilities are speculative and even what is not speculative is subject to change. It is nonetheless necessary, insofar as it helps to clarify some of the needs of the health care system and communities in relation to the objectives of stem cell science. Researchers aware of these needs can steer research programs toward stem cell technologies more likely to serve the public interest.

Clearly, as the capacities and future applications of stem cell technologies expand, the proposed ethical framework—which maps a number of ethical concerns onto an even greater number of scientific and technical possibilities—will evolve. For example, scientific breakthroughs in immunosuppression could make matched stem cell lines a more attractive treatment option. Alternatively, future research to derive embryonic stem cells without destroying embryos (Weissman, 2006) could significantly shift the debate about the ethics of personalized stem cell therapeutics, especially if this is accompanied by industrial breakthroughs that dramatically lower tissue production costs. What should remain constant over time, however, are collective worries about avoiding the coercion and exploitation of women as egg donors, ensuring equitable access to stem cell treatments, and the sustainability of health care systems.

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