Ethics of Stem Cell (and other high technology) Manipulations
Topical Seminar
Ray ONeill, PhD, Seminar Leader
April 5, 2019

Introduction: There are many types of ultramodern medical treatments that are often in the news and that generate interest in patients, their families, and the public. Research scientists are proficient in discovering medical treatments, but the government, the health insurance, health care delivery industries and the public are needed to provide oversight, both about financial costs and ethical issues involved in their use. Although organ transplants and conception through artificial fertilization *in vitro* (*ex vivo*) have been available at a substantial financial cost for decades, several newer technologies have greatly exacerbated the need for general understanding and informed oversight.

Science behind the Technologies: *Tables 1 and 2* below are works in progress and categorize according to the various technologies, and highlight some cost and ethical issues the group may want to discuss.

The first technology listed in Table 2 identifies the numerous types of transplants. One familiar major type is Organ Transplant (https://en.m.wikipedia.org/wiki/Organ_transplantation).
Another type is Cell transplant. The cell transplants we hear about in the news are transplants of **Stem Cells** (https://en.m.wikipedia.org/wiki/Stem_cell, and for therapy https://en.m.wikipedia.org/wiki/Stem-cell_therapy).
The stem cell therapies open the possibly of future advances in remediating many diseases, including:

- Diabetes[79]
- Rheumatoid arthritis[79]
- Parkinson's disease[79]
- Alzheimer's disease[79]
- Osteoarthritis[79]
- Stroke and traumatic brain injury repair[80]
- Learning disability due to congenital disorder [81]
- Spinal cord injury repair [82]
- Heart infarction [83]
- Anti-cancer treatments [84]
- Baldness reversal [85]
- Replacing missing teeth [86]
- Repairing hearing [87]
- Restoring vision [88] and repair damage to the cornea[89]

- Amyotrophic lateral sclerosis [90]
- Crohn's disease [91]
- Wound healing

One example of Stem Cell therapy that I have heard about from neighbors who are patients, is worn out knee joints. One source of autograft or isograft cells such as adipose liposuction material would be treated in tissue culture with growth and deprogramming factors for some number of days, then injected into the knees. Technically, this would need FDA investigational approval for on- label use from an application that would have preliminary data from animals concerning safety and effectiveness. Once the FDA approves a subsequent marketing submission with convincing data from the human investigational studies, then the procedure would be released to the public through doctors for on-label use. Some doctors could also individually prescribe injection of the stem cells and inject other joints or patients that didn't meet the inclusion criteria for the marketing submission.

Controversy regarding the ethics of stem cell therapy: mainly is focused on Embryonic Stem cells ESC (https://en.m.wikipedia.org/wiki/Embryonic stem_cell), and (https://en.m.wikipedia.org/wiki/Embryonic_Stem_Cell_Research_Oversight_Committees).
An alternative to using human ES cells is the creation and adaptation of Induced Pluripotent Stem Cells iPSCs
(https://en.m.wikipedia.org/wiki/Induced_pluripotent_stem_cell).

The second category of technologies in Table 2 are Genetic technologies.

The third category of technologies in Table 2 are Biologics/Immunotherapy**.**

The fourth and last category in Table 2 is Germline (sperm, egg, embryo) technologies. These are BY FAR the most controversial ethically since they affect not just the patient employing them but also their children and even human evolution. Ray and this Topical Seminar Group discussed this specifically in 2018. The handout is at (http://nebula.wsimg.com/ba46e8d69ec3871cf5c8af0605aeee89?AccessKeyId=8493E27C6DC9900FFC7C&disposition=0&alloworigin=1)

There was a very important development later in 2018 and recently in 2019. A Chinese team led by Dr. He used CRISPR technology to produce live human twins with altered CCR5 genes that should make them resistant to developing AIDS, possibly smarter, but more susceptible to West Nile virus

(https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/). Although portrayed by Dr. He and his team as a "correction" since many cells of this particular father carry the HIV provirus, most outside commentators see resistance to AIDS as an "enhancement" (which are considered far less ethical than genetic corrections). In 2019 there is intense debate in the scientific community about the ethics and regulation internationally of germline modification. Some recent articles are

Https://www.nature.com/magazine-assets/d41586-019-00726-5/d41586-019-00726-5.pdf

https://www.nature.com/magazine-assets/d41586-019-00673-1/d41586-019-00673-1.pdf

https://www.statnews.com/2018/11/28/chinese-scientist-defends-creating-gene-edited-babies/

https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/

https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-claim-first-gene-edited-babies-chinese-researcher

Consideration of Financial Costs: For an introduction see (https://en.m.wikipedia.org/wiki/Health_technology_in_the_United_States)

For a background perspective, the US budget is 4 trillion dollars yearly. The categories of spending include: Medicare at $1.1 trillion (28% of budget), defense at $590 billion (15%), interest on government debt at $263 billion (6.7%), NIH research at $32 billion (0.88%), and DARPA at $3 billion (.075%). The Defense budget is 4% of our GDP (which is more than the next 13 countries combined).

AHRQ provides data on healthcare outcomes, affordability and quality (MEPS.ahrq.gov). Eighteen percent (18%) of the U.S. GDP goes for health care, paid for by many partners. There are tremendous variations in health care costs per person. One (1%) of persons use 22% of the health care dollars (averaging $110,000/yr/person for this group). An additional 5% use 50% of the health care dollars (averaging $50,000), and 15% did not use any health care dollars.

Wikipedia says that health care cost averages $9000 per capita, with 64% coming from the government mainly through Medicare and Medicaid. U.S costs are the world's highest and would need to be cut by a third to be comparable with most other countries. U.S. life expectancy is 79 years of birth which ranks 42nd of 224 countries. The prohibitively high cost of health care is the number one problem preventing access for the 27 million that have insufficient insurance. This roughly translates to 45,000 excess annual deaths per year. It has been estimated that a kidney transplant in U.S. costs at least $100,000 but in the rest of the world costs $2000-$70,000. A liver transplant in the U.S. cost

approximately $250,000 and a heart transplant $860,000 with other countries charging less than $160,000.

The CBO in March 2017 found that healthcare cost inflation and an aging population are the primary drivers of increasing budget deficits with the Federal share being 6% of the GDP in 2017 growing to 9% in 2047. The CBO in 2008 found that 38% to 65% of the long-term rise comes from healthcare systems using new services made possible by technological advances.

FYI, the Federal government provides insurance to protect public health goals that companies are unwilling to assume. Two examples are the HRSA National Vaccine Injury, and the biodefense Countermeasures programs. Organ donation is overseen (organdonor.gov).

There are many pessimistic views on how future medical costs could bankrupt Medicare. As the US population's average age increases, and if our expectations for end-of- life attempts at cure increase, these budget-busting scenarios become more likely. Pressure on the production of global Food as the population has a longer lifespan will greatly depend on the fertility rate and the ecological per capita footprint in each country. Individually, if we live routinely to 120 years, it is likely most of us would have multiple marriages in many careers that would need reeducation every few decades. It is instructive to keep in mind that if a societal goal is life longevity to be a centenarian with compressed morbidity, only 15% of today's centenarians "escape" any serious disease before the last couple years before death. The largest groups are divided between those people who "delay" until after age 80 having any serious diseases (43%), and "survivors" (42%) who had at least one serious disease before age 80 and survived.

For a treatment that alleges a medical benefit, FDA approval is needed specifically for the treatment and indication first at the investigative and later at the marketing stage. Insurance company executives then decide when and under what circumstances their policyholders are covered for both on-label and off-label use. For elders and disabled people, Medicare and Medicaid policies apply. Like it or not, financial constraints require the existence of procedures that can be pejoratively called "death panels." For example several new drugs cure 85% of patients chronically infected with hepatitis C virus. However, the cost of almost $100,000 per patient over several weeks of once in a lifetime treatment can't be borne for all infected patients in any one year by Medicaid or state sources.

For one optimistic view in 2012 of the projected national cost for MRI and PET imaging, see: (http://news.mit.edu/2012/advanced-medical-imaging-and-health-care-costs-0727)

WHO GETS TO DECIDE? The over-arching question is whose rights take precedence: either an individual patient or two parents and their team of doctors, or society at large? Who should pay for these high-tech technologies? Must every patient or parent have equal access despite unequal abilities to co-fund it?

HOW SHOULD THE DECISIONS BE ENFORCED? How many types of Stakeholders will want/deserve a place at the debate? Should there be new laws, regulations, FDA Guidelines, FDA Guidance? Civil suits, Criminal charges, Physician licensing and societies? Other ideas?

The possibility that any one citizen's voice may be heard may seem remote. However, remember the green ecological movement **deflected** the course of political opinion and subsequent laws and regulations regarding the environment over the course of the last decades. On the other hand, if other countries start successfully using a variety of stem cells and designer babies that are smarter workers or "supersoldiers", will there be a catch-up stampede induced in the USA? Remember Yuval Harari has predicted that plagues, famines and wars are now largely manageable; but bodies, brains and minds are where mankind will be challenged and likely progress in the 21st century.

QUESTIONS about Costs and Ethics to ponder that are fleshed-out below:

1. If there are mistakes or unintended consequences, what do we do about the suffering?
2. When the suspected consequences of a procedure could be catastrophic, will it be possible to err on the side of caution (precautionary principle)?
3. How do we strengthen international cooperation and governance of the technologies?
4. Who gets to decide how the enhanced and the non-modified people in the future relate to one another?
5. If we made access to health care universal, how would the U.S. and the states pay for the cost of these new bio-technologies?
6. How do we prevent radical unequal access to these new technologies?

Selected References:
See Clinicaltrials.gov for current or future FDA-approved investigations in humans. (NIH-based investigations are often free to patients but those sponsored by companies can charge.)

Glossary for nuanced words:
Gene - think of a gene as a script like Romeo and Juliet. In different cells at different times, Shakespeare's original idea can be presented as different movies (as a result of epistasis and splicing and epigenetics etc).

Allele - one of hundreds of flavors of a gene with a different ATGC sequence. Most changes are harmless but useful as SNPs for following paternity and ancestry. Very few new alleles arise each generation, and deleterious ones (mutations) can be recessive or dominant.

Note: Background material used in THE Designer Babies 2018 seminar is available at
http://nebula.wsimg.com/ba46e8d69ec3871cf5c8af0605aeee89?AccessKeyId=8493E27C6DC9900FFC7C&disposition=0&alloworigin=1

Table 1 Correction versus Enhancement in Somatic versus Germline cells

	SOMATIC (liver, blood etc)	***GERMLINE (sperm, eggs, embryos)***
CORRECTION	Ethically OK Medicine Most people favor Insurance usually pays Most Stem Cell therapies	Debatable as "Medicine" in future Current debate Who will pay?
xxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
ENHANCEMENT	Example is plastic surgery Little need for consensus Insurance seldom pays Some Stem Cell Therapies	Laws, regulations restrict in most countries Most people disfavor "eugenics" Would usually be privately funded Designer babies

Table 2 Stem Cell and other High-Tech Technologies

	Technical terms/ Examples?	Side effects?	Paid for?	Ethics?
1. TRANSPLANTS				
Solid Organ	Lens 1949, kidney 1954, Liver 1963, heart 1967	shortages, rejection	Fed and insurance	Xenografts from modified animals
Cell	Blood, Bone Marrow decades		Fed and insurance	
ESC Embryonic Stem Cells				From IVF discards or abortions?
iPSC Induced Pluripotent Stem Cells		worrisome		
SC Somatic Stem Cells	SCT 1998	rejection if not an auto- or isograft, effective?	varies	
2. GENETIC				
Somatic Gene Therapy by viral vectors	1980s on	variety, effective?	varies	
Somatic Gene Therapy by CRISPR, Talens, ZFNs	2017 on	off target effects?	varies	
Personalized Medicine	2000s on	effective?	cutting edge	loss of privacy
3. BIOLOGICS/IMMUNOTHERAPY				
Mab Monoclonal Antibodies	Rh Arthritis, Autoimmune diseses		varies	
Immunologic T and B cells	Cancer therapy 1990s on		varies	
4. GERMLINE				
IVF In vitro fertilization	IVF1959, PGD 1989		usually privately	
	ICSI 1992		varies	
Designer Babies	2018 in China		parents	**HUGE DEBATE**

Nanotech