



2016 Bioethics Bowl Case Packet

The National Undergraduate Bioethics Conference
*Regenerative Medicine and Biomedical Engineering:
Innovations and the Consequent Controversies*

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Note: This packet contains fifteen cases, with questions following each case. During the Bioethics Bowl, only one question from each case will be selected by the moderator for the teams to debate.

Case 1

Bits and Pieces – Uterine Morcellation

In 1995, the Food and Drug Administration (FDA) approved the uterine morcellator through an expedited 510(k) process since similar devices were already being used in other surgical fields. Essentially, the morcellator allows for large tissue specimens (usually the uterus in gynecology) to be electrically cut into smaller segments and pulled out of the body through a much smaller incision. This allows for surgeries that would otherwise require large incisions and thus, increased intraoperative complications, post-operative recovery times, and overall increased morbidity to remain as minimally-invasive (laparoscopic or robotic) surgeries.

However, recently, the high-profiled case of the tragic morcellation of an occult malignant uterus (thus, potentially spreading the cancerous cells throughout the pelvis and decreasing prognosis), has resulted in a firestorm of impassioned responses via the media, physician groups, hospitals, and the FDA. The FDA has now put a warning on the use of the electric power morcellator in gynecologic surgery, urging physicians to be cautious about its use. Many device manufacturers have stopped production and several large hospital systems have altogether banned its use.

While at first glance this seems appropriate given the risk of upstaging cancer, many researchers and physician groups have argued the opposite point of view. For example, they have argued that the risks of laparotomy (using a big incision to remove the large specimen) far outweigh the risks of minimally-invasive surgery combined with the risks of the morcellator. Occult malignancy, or cancer that is unknown prior to surgery, is rare and occurs with a frequency of 1:3,000 by some estimates, although high quality data are lacking to pinpoint an exact rate. While it is unfortunate that one person in 3000 patients has a worse prognosis due to the use of the morcellator, some believe it is unfair to mandate the known increased risks of laparotomy on the other 2,999 who would not have had such an outcome.

Questions:

1. Should physicians and hospitals continue to use the morcellator for gynecologic surgery? If so, whose decision should it be – the patient's, the physician's, or the hospital's?
2. Do physicians and medicine in general have an obligation to collect data to inform patient decision-making? From where does this obligation arise and how has the lack of information in this case led to the present situation?
3. What is the role of the media and the FDA in protecting the public? How does society balance rare negative outcomes with the obligation to ensure safe, effective care for everyone?

Resources:

American College of Obstetricians and Gynecologists. Power morcellation and occult malignancy in gynecologic surgery: a special report. Available at:
http://www.acog.org/Resources_And_Publications/Task_Force_and_Work_Group_Reports/Power_Morcellation_and_Occult_Malignancy_in_Gynecologic_Surgery.

American Association of Gynecologic Laparoscopists—Tissue Extraction Task Force. Morcellation during uterine tissue extraction. Available at: www.aagl.org/wp-content/uploads/2014/05/Tissue_Extraction_TFR.pdf.

Levitz J. Doctors Eye Cancer Risk in Uterine Procedure. Wall Street Journal. 2013. Available at:
<http://www.wsj.com/articles/SB10001424052702304173704579264673929862850>

Case 2

Little Baby Bloodspots

Newborn screening programs test virtually every baby born in the United States for a number of serious genetic and metabolic health conditions. The founding mission of newborn screening programs was to identify children with inherited life threatening or developmentally devastating medical conditions in order to provide medical interventions that would save lives and/or reduce morbidity. Screening began in the 1960s, and today, health departments in every U.S. state and the District of Colombia have newborn screening programs. The diseases these programs look for have some form of intervention or treatment.

For over 50 years, newborn screening programs have been almost exclusively framed within the context of child welfare. The potential life saving information provided by these programs has been used to ethically justify mandatory screening and the addition of new tests to screening panels. Legally, the state supports mandatory screening on the basis of *parens patriae* power: i.e. the state's inherent authority to act in to promote the child's welfare. In other words, the ethical/legal justification for overriding parents' autonomy stems from the concern that refusing to screen could harm the child. However, while consent is typically not needed for newborn screening, most states do have some options for parents to opt-out of the testing for either religious or philosophical reasons.

When a child is tested through state newborn screening programs, specimen collection is usually obtained at the hospital through a heel stick within 24-48 hours after birth. Blood samples are collected on filter paper and dried for laboratory testing. The bloodspots are then sent to a public health laboratory for testing. Typically, only a small amount of the collected blood is needed for the tests themselves. After screening is completed, many states store the leftover bloodspots for a period of time that ranges from 1 year to indefinitely. These leftover bloodspots have been used for a number of purposes including projects aimed at improving the quality of newborn screening or to add new conditions to the state's screening panel. More recently, there has been an increased interest in using leftover newborn screening bloodspots for more generalized research projects. For example, since these bloodspots contain the DNA of all state residents born in a given year, they represent a potentially important source of representative genetic samples that could be used for studies aimed at untangling the contributions of genetic variants and environmental exposures to disease. Typically when research is conducted using leftover bloodspots, they de-identified so a researcher would not be able to know whom the samples are from.

The potential use of these specimens also raises a number of ethical, legal, and social challenges given that they were originally collected without consent within the context of a mandatory public health program aimed at benefitting individual newborns. Over the last few years lawsuits have been filed in Minnesota, Texas, and Indiana to try and prevent the use of these samples for research. For example, the Texas State Health Department was sued on the basis that the storage and use of newborn screening bloodspots was a violation of constitutional protections against unlawful search and

seizure. The State Health Department settled the case, and as a result 4.5 million blood specimens were destroyed.

These debates have raised critical questions about how the secondary research use of blood or tissue collected within the context of a public health service may fundamentally change the public health mission, as well as the public's perceptions of these programs. Overall, these debates center on whether these samples constitute human subjects research, and thus should require consent for storage and use. Currently, some states have begun to obtain consent for the use of their leftover bloodspots, while others have maintained an opt-out approach in which samples are stored and used unless parents actively contact the health department to have a sample destroyed.

Questions:

1. If the samples are de-identified after collection, do newborn screening programs have an ethical or legal obligation to obtain consent from parents before de-identified leftover bloodspots are stored and used for future research, or is an opt-out approach sufficient?
2. Do newborn screening programs have an ethical obligation to obtain permission from individuals whose samples are stored for research when they reach adulthood if they wish to continue using those specimens for future research studies?
3. Does a state health department's newborn screening program have an ethical obligation to return individualized results of research conducted using newborn screening bloodspots?

Resources:

Botkin, J. R., Goldenberg, A. J., Rothwell, E., Anderson, R. A., & Lewis, M. H. (2013). Retention and research use of residual newborn screening bloodspots. *Pediatrics*, *131*(1), 120-127.

Faden, R. R., Holtzman, N. A., & Chwalow, A. J. (1982). Parental rights, child welfare, and public health: the case of PKU screening. *American Journal of Public Health*, *72*(12), 1396-1400.

Lewis, M. H., Goldenberg, A., Anderson, R., Rothwell, E., & Botkin, J. (2011). State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics*, peds-2010.

Olney, R. S., Moore, C. A., Ojodu, J. A., Lindegren, M. L., & Hannon, W. H. (2006). Storage and use of residual dried blood spots from state newborn screening programs. *The Journal of Pediatrics*, *148*(5), 618-622.

Case 3

Doctor's Orders

Dr. Jones is a 60-year-old physician working at a medium sized for-profit hospital in a large city. His father had died twenty years previously from a cerebral stroke that had left him ventilator dependent and unable to speak or otherwise communicate. Prognosis was dismal. Dr. Jones, the oldest child, had been asked by the hospital staff whether he wanted the ventilator turned off for his father. Dr. Jones was tortured about the decision. His father had given no directions about what he would have wanted in this situation. He chose not to stop aggressive intervention. His father lived for four months without recovering his communicative abilities.

Dr. Jones was determined that he would never place himself and his family in the same position. He knew that strokes run in families. He filled out a living will stating clearly that if he ever had severe brain damage from a stroke and lost the ability to communicate with no chance of recovery, he would want all treatment stopped and be allowed to die with comfort care only.

Dr. Jones was a workaholic. He spent long hours at his office, frequently missing dinner and social events with his wife and two daughters. His wife complained and, after 35 years of marriage began threatening divorce. He also was unhappy with work. A younger physician had been given his administrative responsibilities as head of an important clinical unit. Dr. Jones was generally in good health.

One night, while working in his office next to the hospital, he wrote a DNAR on a series of Post It® notes and pasted them around his office. He then wrote a long suicide note telling his wife and daughters how much he loved them but that he had failed them as a husband and father and now was a “failure” at work. He explained how well he had provided for them financially for the future and explicitly how they could access the considerable amount in his estate. Next, at approximately 10pm, he took a large overdose of barbiturate medications. The cleaning staff found him comatose at 6am the next morning, called 911 and he was emergently resuscitated, including intubation, and admitted to the medical intensive care unit of his own hospital, deeply comatose.

Over the next two days the barbiturates cleared from his system, but he remained unresponsive. His wife brought in his advanced directive and told the physicians to stop the ventilator and all other life-sustaining measures. The physicians refused saying the prognosis was not yet clear. The wife was furious. Four days later, he began to wake up. Ten days later his thinking and speech seemed normal. He regained all motor function. While he was doing physical therapy, he had a major stroke and became aphasic and hemiplegic. His condition had not improved after one year.

Questions:

1. Were the staff and physicians wrong to resuscitate Dr. Jones in the face of all the all the DNAR notes clearly visible to them?

2. When the patient had not recovered after two days of ICU treatment, should the physicians have honored his wife's request to implement his advance directive?
3. If the physicians had honored the advance directive at his wife's request, would they have been assisting in his suicide?

Case 4

A PPACA Controversy

This election cycle, Republican presidential candidates have openly criticized the Patient Protection and Affordable Care Act (PPACA) both in entirety and specifically for including prenatal testing within the range of prenatal care services to be covered by health insurers. In some candidates' view, requiring insurance coverage for prenatal testing, and specifically amniocentesis, is problematic in that it would encourage abortion of pregnancies in which fetal anomalies are detected.

Historically, insurance coverage for abortion services has been restricted, and these candidates' concerns highlight the contentiousness between the increasing availability of prenatal genetic testing modalities with simultaneous limitations on abortion provision in the United States.

Questions:

1. What are the ethical implications of federally mandating insurance coverage for prenatal genetic testing?
2. What role should the state play in regulating prenatal genetic testing?
3. Given the findings in *Burwell v. Hobby Lobby*, what are the implications for the PPACA mandate to require insurance coverage for amniocentesis in the face of conscientious objection?

Case 5

Medical Deportation

Medical deportation is a process by which documented and undocumented immigrants with long-term health care needs and little or no health insurance coverage are transferred from a U.S. hospital to a facility in their country of origin. The practice is also known as “medical repatriation.”

Jose Ramirez is brought to the hospital emergency department following a multi-car accident on a major freeway that left several people dead and several more injured. Mr. Ramirez is unconscious and has sustained severe injuries to his spine. It is unclear whether he will regain consciousness.

After several days in the hospital, it becomes clear to the hospital administration that Mr. Ramirez will need longer-term hospital care. He has been in the U.S. legally from Guatemala, having received a temporary visa to perform seasonal agricultural work for one of the large southwestern U.S. agricultural companies. However, the employer did not provide health care insurance and Mr. Ramirez does not have any. The extent to which emergency Medicaid would be available to cover the costs of his hospitalization remains unclear. Despite the hospital’s efforts to seek coverage on Mr. Ramirez’ behalf, the ultimate determination resides with the state agency. Mr. Ramirez does not have any family or friends in the U.S. who could make health care decisions for him or contribute to the costs of his hospital care.

The hospital administration, together with the facility’s attorneys, are seeking a state court order to allow them to have Mr. Ramirez transported to Guatemala. The hospital will bear the costs of such transport, believing that it pales in comparison with the costs associated with a longer-term hospital stay. They have not determined specifically whether the medical facilities that exist there have adequate equipment and/or skill to provide the requisite care that Mr. Ramirez needs to prevent a deterioration of his condition.

The physicians and nurses who treat Mr. Ramirez on a daily basis are unanimous in their concern for his condition and have advised the hospital administrators that they do believe that such a move will result in a drastic deterioration in Mr. Ramirez’ condition. His health care providers have had little or no training in ethics and are now unable to see any possible course of action apart from compliance with the mandate of a hospital administrator.

Critics of the practice of involuntarily transporting hospital patients to their country of origin have argued that the practice raises significant legal issues. Depending on the specific circumstances, these may include claims of false imprisonment, infliction of emotional distress, violation of the Emergency Medical Treatment and Active Labor Law (EMTALA), violation of Title VI of the U.S. Civil Rights Act of 1964 requiring language assistance and interpretation services, and lack of state court jurisdiction.

Questions:

1. What are the ethical obligations, if any, of Mr. Ramirez' health care providers (physicians and nurses) in this situation? What courses of action, if any, are open to them, apart from complying with the administrators' demand to have Mr. Ramirez transported back to Guatemala?
2. Does the hospital, apart from its health care providers, have a moral responsibility to Mr. Ramirez? If so, what is it and what are its limits?
3. Should Mr. Ramirez' employer and/or the U.S. government bear any moral responsibility for Mr. Ramirez' situation?

Resources:

Huffington Post Live. Deportation while unconscious (video).
<http://live.huffingtonpost.com/#r/segment/unconscious-deportation-medical-repatriation-immigration-/5175c6902b8c2a42af000165>

Lee, P., Sibley, E., Tolin T., and Vader Woud, S. (2012). *Discharge, deportation and dangerous journeys: A study on the practice of medical repatriation*. South Orange, NJ: Seton Hall University. Available at:
<http://law.shu.edu/ProgramsCenters/PublicIntGovServ/CSJ/upload/final-med-repat-report-2012.pdf>

Sontag, D. (2008, August 3). Immigrants facing deportation by U.S. hospitals. New York Times. Available at
http://www.nytimes.com/2008/08/03/us/03deport.html?pagewanted=all&_r=0.

Case 6

Limitless in the ER

Consider the following hypothetical. Drug A has been found to significantly enhance the performance of emergency room physicians. Clinical trials have demonstrated that physicians who have taken this drug 5 days a week (one dose a day at the beginning of their shift), 48 weeks per year for five years show no long-term ill effects. Transient effects while on the drug include mild headache in 10% of users. There is no addiction or withdrawal problem. There is no sleep problem.

Studies have shown definitively that the drug enhances cognitive skills such as ability to focus, process information more quickly, and multitask during 10 hours shifts. Studies have also demonstrated conclusively that the rate of medical error is reduced by 20% and the death rate by 5% when ER physicians take Drug A.

Questions:

1. Which of the following policies should a hospital adopt:
 - (a) Require any physician working in the ER to take Drug A while on duty;
 - (b) Suggest that ER physicians take Drug A but leave it up to them;
 - (c) Remain silent on the issue?

2. If a hospital allows its ER physicians to take Drug A, should the public be made aware of this?

3. Are there any compelling ethical reasons to forbid physicians from using Drug A while working?

Case 7

Japanese Stem Sells

Japan has recently made some major changes to its Pharmaceuticals, Medical Devices and Other Therapeutic Products Act. First, regulators have made “regenerative medicine products” a separate category from drugs, devices, and other biologics. These regenerative medicine products include both multipotent and pluripotent stem cell-based biologics, as well as other human cell and tissue-based products. Next, they have introduced a seven-year-long conditional approval system for any regenerative medicine products that have cleared early safety trials. Under Japan’s conditional approval system, new regenerative medicine products can enter the medical marketplace for seven years, during which time they will be made available for patients with serious medical conditions as efficacy data are collected. Although the efficacy of these conditionally approved products do not have to be proven upon entry to the medical marketplace, patients’ access to these products will be reimbursed through Japan’s universal health care system, a system in which payers and patients split costs 70% to 30%. Lastly, Japan’s conditional approval system for regenerative medicine products extends to products developed by non-Japanese biotech companies.

Proponents of this new policy applaud it for removing burdensome regulatory barriers that have stood in the way of desperate patients seeking new stem cell-based treatments. As long as new stem cell therapies are deemed to be safe, patients should have the right to see if they can benefit from them personally. In addition to meeting patient demand, this policy would also put Japan on the fast track to becoming a world leader in the clinical translation of stem cell research. Recently, the California Institute for Regenerative Medicine (CIRM), a \$3 billion taxpayer-funded stem cell agency, applauded the new Japanese policy in its 2016 strategic plan (CIRM 2.0, p. 10), and called out the U.S. FDA for being too conservative when it comes to approving new stem cell-based therapies.

Critics of Japan’s new policy worry that the country is racing ahead too quickly at the expense of patient welfare and rigorous science. Even if these conditionally approved therapies prove to be safe, they may create opportunity costs by crowding out patients’ interests in pursuing proven standards of care. Additional uncertainties loom. How will companies track and record signs of clinical efficacy in a scientifically rigorous way once these products are released into the medical marketplace? Will the conditional approvals system undermine subject enrollment for stem cell-based clinical trials, ultimately hindering legitimate scientific progress? Issues of social justice also arise. Why should patients and the public have to pay their own money to help for-profit companies establish that their products work? Furthermore, because the conditional approval system and insurance reimbursement will be made available for regenerative products developed by non-Japanese companies, Japan’s new policy has the potential to be exploited by foreign companies who want Japanese patients and taxpayers to pick up the tab for their own product development.

Questions:

1. Should the U.S. emulate Japan's new regulatory approach to regenerative medicine products?
2. Is it unfair for patients and public insurers in Japan to pay for stem cell-based therapies that have not been proven to work?
3. Are there ethically appropriate ways to improve the Japanese conditional approval system for regenerative medicine products, or should the entire plan be rejected?

Resources:

Douglas Sipp, "Conditional Approval: Japan Lowers the Bar for Regenerative Medicine Products," *Cell Stem Cell* 16, 2015: 353-356.

CIRM 2.0: Proposed Strategic Plan 2016 & Beyond. Available at:
https://www.cirm.ca.gov/sites/default/files/files/agenda/151217_Agenda_7_CIRM_Strat_Plan_final_120815.pdf

Case 8

Who's Listening?

Kelly and Mark are a thirty-something couple who have been together five years, but are not married. They recently found out that Kelly is pregnant. The fetus' biological paternal grandmother, Mary, is deaf and several of her brothers and sisters are deaf, although her parents were hearing. When the Kelly is 20-weeks pregnant, the couple, along with Mary, visits a genetic counselor to determine if deafness may be genetic. The genetic counselor, Dr. Cole, advises them that it's possible if there is a mutation with Connexin 26. Lisa also tells them that they would have to test the Mary to verify. Mary is willing, as she is very interested in knowing if the deafness in her family is genetic. Because Mary is the one that is tested, Dr. Cole gives her the results, which are positive for the mutation. Mary advises Dr. Cole that she has no intention of sharing the information with Kelly and Mark because she'll be thrilled if her grandchild is deaf.

Kelly has a normal pregnancy and a normal birth. Alexis, the newborn, subsequently passes a newborn hearing screening test. Because of this, Kelly and Mark never have her retested, although their pediatrician repeatedly expresses concern about her hearing. At 3 years of age, Alexis is diagnosed as completely deaf. Kelly and Mark revisit Dr. Cole to have Alexis tested to see if she is a good candidate for cochlear implants. If Alexis tests positive for the Connexin 26 mutation, then she'll be a good candidate. If she doesn't, then she will not be. Alexis tests positive for the mutation. During the follow-up visit, Dr. Cole learns that Kelly and Mark have a 1-year-old who also has passed a newborn hearing screening test. Dr. Cole suggests that Kelly and Mark also have her tested. Mark agrees, but Kelly declines.

At Kelly's insistence, she and Mark take Alexis to an otolaryngologist, Dr. Kim, to be evaluated for the implants. Dr. Kim advises that Alexis is a good candidate. Kelly is adamant that Alexis get the implants. Mark tells Dr. Kim that Alexis is fine without them and he is unsure as to whether they should go through with the surgery. Dr. Kim learns that Alexis is not getting any education in sign language, even though Mark and Mary both sign, as Kelly is adamant that Alexis not be considered deaf. Kelly has also banned Mary from the house and Alexis' life. Dr. Kim explains to Kelly and Mark that while the implants will be helpful to Alexis, they will not provide her with normal hearing. He advises that whether or not Alexis gets the surgery, she should be learning to sign and to read lips. Kelly states that she will not permit this until after the surgery, if at all, and asks what the next steps are to move forward with the surgery.

A few weeks later, Dr. Cole is surprised to see Mark on her schedule alone. However, when she enters the room, she finds him with his 1-year-old, Hayley. Mark asks Dr. Cole to test Hayley for the Connexin 26 mutation.

Questions:

1. Should Dr. Cole have provided Mary's results to Kelly and Mark?
2. Should Dr. Kim have assisted Kelly and Mark in moving forward with the surgery?
3. Knowing that Kelly did not want Hayley tested, should Dr. Cole test her at Mark's request?

Case 9 **Never Let You Go**

Ms. Smith was a 45-year-old woman diagnosed with a type of lymphoma that carries a very bad prognosis. She was told that the most aggressive chemotherapy could keep her alive for two years at the most. Ms. Smith was a life-long Jehovah's Witness. She was unmarried, had no children and was very close to her loving parents. The aggressive therapy would almost certainly suppress her bone marrow to the point that transfusions would be necessary to preserve her life during treatment. She refused transfusions but requested that the physicians try the aggressive chemotherapy nonetheless. They refused, but offered her a less aggressive chemotherapy that would not suppress her bone marrow but would only provide a very small chance of surviving more than a couple months. She agreed to the weaker chemotherapy.

Things did not go well for Ms. Smith. The lymphoma rapidly spread throughout her body. Her organ systems began to fail and eventually she was admitted to the intensive care unit where she was intubated due to respiratory failure. Her liver, kidneys, intestines and heart also began to fail. Ms. Smith had consistently told her physicians that she wanted to "stay alive as long as possible." Her hematocrit and hemoglobin levels were barely compatible with life (not from the chemotherapy but rather from the lymphoma itself). The inability of her blood to deliver adequate oxygen was in large part responsible for her heart, gut, and brain failure. Her parents were distraught. Themselves Jehovah's Witnesses, Ms. Smith's parents surprisingly asked the physicians in the intensive care unit to give their daughter transfusions saying, "We don't want to lose her." The hospital record and conversations with previous physicians indicated that the patient had never swerved from her wish to refuse blood or blood products.

The physicians denied the family's request. Over the next few days, the patient hovered near death. The physicians recommended that a DNAR order be written. The parents insisted on full resuscitative efforts that, according to the physicians, had no chance of prolonging her life for more than a few minutes. The parents insisted. The physicians called for a clinical ethics consultation saying resuscitation in this case was futile and that they should be allowed to unilaterally refuse resuscitative efforts.

Questions:

1. How much should a consideration of wasting resources be a deciding factor in decisions about Ms. Smith's care?
2. Should the physicians have refused the parents' request to prolong the patient's life by giving her transfusions, knowing that it probably would give her a week or two more life?
3. Is futility a viable concept that allows physicians to unilaterally refuse resuscitation or other potentially life-prolonging interventions

Case 10

Anyone Need a Womb? – Uterus Transplantation

Doctors in Sweden have recently announced the first human livebirth after uterus transplantation after nearly fifteen years of research. Uterine factor infertility affects nearly 9.5 million women in the United States. Previously, there were only two potential treatments – surrogacy or adoption. Uterus transplantation represents a novel third option. Following this success in Sweden, the Cleveland Clinic recently announced it will begin enrolling research subjects for the first uterus transplant clinical research trial in the United States.

In the reported Swedish case, a 61 year-old close family friend donated her uterus to a 35 year-old woman who was born without a uterus. After a ten-hour surgery for the donor and an almost five-hour surgery for the recipient, the recipient was placed on immunosuppressive medication. After several months of waiting to ensure stabilization of the transplant, transfer of an embryo created through in-vitro fertilization previously using the recipient's eggs and her husband's sperm was placed into the transplanted uterus. Over the course of the next eight months, the recipient's pregnancy progressed. Due to medical complications arising from her baseline health and the superimposed risks of pregnancy, she delivered via cesarean section several weeks preterm. Both mom and baby recovered well and are healthy.

Uterus transplantation represents a medical first – both in the reproductive infertility world and the transplant world. It is the world's first ephemeral transplant, that is, intended only for a short time rather than for life-long benefit. After the recipient is done childbearing (she plans on having 2 children), a hysterectomy will be performed so that she does not need to be on immunosuppression for the rest of her life. It also allows for the experience of the gestational component of motherhood, unlike the current options of surrogacy and adoption. However, it is an incredibly costly treatment for infertility and represents an organ transplant done for quality-of-life and not life-saving reasons.

Questions:

1. Organ transplant plans typically have exit strategies – that is, what to do if/when the transplant begins to fail. What are the complexities created by an “exit strategy” for uterus transplantation?
2. Uterus transplantation could be regulated either as an infertility treatment (currently through the free market in the United States) or as an organ transplant (governed by need as defined by the Uniform Network for Organ Sharing). What are the implications and limitations to each method of regulation?
3. Surrogacy, the only alternative for women with uterine factor infertility that preserves the option of raising a genetically-related child, is fraught with its own

ethical difficulties. Compare and contrast the ethical challenges of surrogacy and uterus transplantation.

Resource:

Brannström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, et al. Livebirth after uterus transplantation. *Lancet* 2015;385(9968):607-16.

Case 11

CRISPR Humans

Genetic engineering has come a long way in the last 40 years. The latest laboratory tools – zinc finger nuclease, TALEN, and CRISPR Cas9 – allow researchers to make precise deletions and substitutions along the genomes of any species. Among these tools, CRISPR Cas9 has garnered the most attention in recent months because it offers the fastest and by far the easiest means to edit genes. Anyone can learn to use it in one day.

The CRISPR system is a naturally occurring acquired immune system found in bacteria and archaea. It allows single-cell organisms to cut and deactivate foreign genetic elements introduced by invading viruses and plasmids. Researchers discovered a couple of years ago that CRISPR Cas9 could be used to add, silence, or alter a DNA sequence at any location by using the proper guide RNAs to target the desired sequence. CRISPR Cas9 is so precise that it can even be used to edit a single base pair within a gene.

Lately scientists have been using CRISPR Cas9 and other gene editing technologies experimentally to modify the somatic cell DNA of patients suffering from serious genetic diseases. Most recently, an infant suffering from a rare and aggressive form of leukemia was treated in London using “off the shelf” T cells that were genetically modified using TALEN to enable them to hide from her own immune system. By all accounts, she is doing very well. With such precise gene editing tools at their disposal, scientists are starting to believe that the promise of somatic cell “gene therapy” may be finally around the corner.

In addition to designing experimental somatic cell therapies, some researchers have also become interested in discovering whether CRISPR Cas9 can be used to alter the human germline, i.e., the lineage of cells from which human germ cells (sperm and eggs) are derived. In theory, the human germline could be modified by altering the genes of sperm, eggs, or zygotes. Unlike somatic cell modifications, any changes to the germline would be passed to subsequent generations. The purpose of human germline editing would be (at least initially) to replace known harmful genes, such as the gene responsible for cystic fibrosis, so that parents who are carriers can avoid transmitting genetic harms to their offspring while remaining otherwise genetically connected to their children. For individuals with a family history of serious genetic disease, one perceived benefit of human germline modification would be to remove the threat of the disease for their future descendants.

So far, CRISPR mediated germline editing has been shown to work in a number of different animal species. Transgenic animal models for research can now be generated in just one gestation cycle, as opposed to one year or more using the previous method of cross-breeding stem cell-derived chimeric animals (which has only worked in mice). Before human germline editing can become a reality, however, extensive preclinical research *in vitro* will have to be performed using human reproductive materials. Currently, most researchers believe gene editing would have to be applied to a germ cell

or a single cell embryo *in vitro* in order to avoid genetic mosaicism arising from trying to use CRISPR Cas9 on multiple cells at once. For this reason, the use of surplus fertility clinic embryos (which are stored after the zygote stage) is not likely to provide a resource for preclinical human germline editing research. Instead, scientists will have to create their own research embryos using donated human germ cells, a form of research that cannot be federally funded in the U.S. at this time.

Despite legal restrictions in the U.S. and certain other countries which would preclude the conduct of any preclinical human germline gene editing research, let alone the transfer of any genetically altered embryos into a womb to produce a pregnancy, some researchers in more permissive jurisdictions have reported early research using CRISPR Cas9 to modify human embryos *in vitro*. Recognizing the need for some level of international consensus on using CRISPR Cas9 technology to modify the human genome, particularly with respect to germline modifications, an international summit was called in Washington DC in December 2015. While scientists and bioethicists have barely begun their efforts to draft international guidelines on human gene editing, research teams in permissive jurisdictions continue their research on human germline editing.

Questions:

1. Top tier scientific journals have received manuscripts that detail *in vitro* research on human germline editing. Although international guidance has not yet been issued for this controversial area, the research teams conducting these studies have claimed that they are acting in compliance with all local laws and regulations and that it would be unfair to hold them to any further standards beyond this. As long as the scientific merit of their research is deemed acceptable by peer reviewers and journal editors, should journals publish their findings?
2. Recently, the UK's Human Fertilisation and Embryology Authority (HFEA) decided to permit clinical trials for human mitochondrial replacement research, a modification to human eggs that would result in a permanent change to the germline of any girl born through this technology. Is it ethically consistent to allow germline modifications in this sense while at the same time prohibiting germline changes using CRISPR Cas9?
3. According to many commentators, including the organizers of the International Summit on Human Gene Editing and the developers of CRISPR technology, it is ethically permissible to conduct *in vitro* research on human germ line editing, as long as modified embryos are not transferred to a uterus. Is this an ethically dangerous position to advocate?

Resources:

Edward Lanphier and Fyodor Urnov, "Don't Edit the Human Germ Line," *Nature* 519, 2015: 410-411.

David Baltimore, *et al.*, "A Prudent Path Forward for Genomic Engineering and Germline Gene Modification," *Science* 348, 2015: 36-38.

Jennifer Kahn, "The Crispr Quandary," *The New York Times Magazine*, November 9, 2015: http://www.nytimes.com/2015/11/15/magazine/the-crispr-quandary.html?mwrsm=Email&_r=1.

Andrew Pollack, "A Cell Therapy Untested in Humans Saves a Baby With Cancer," *The New York Times*, November 5, 2015: <http://www.nytimes.com/2015/11/06/business/a-novel-cell-therapy-untested-in-humans-saves-baby-with-cancer.html>.

Sara Reardon, "Global Summit Reveals Divergent Views on Human Gene Editing," *Nature News*, December 8, 2015: <http://www.nature.com/news/global-summit-reveals-divergent-views-on-human-gene-editing-1.18971>

Case 12 **Mom's Genes**

Jane is a 54-year-old divorced female who was diagnosed with ovarian cancer seven years ago. Her treatment included a hysterectomy followed by six cycles of chemotherapy. She has not had a recurrence of that cancer, but was recently diagnosed with stage 4 breast cancer. She has two daughters, 32-year-old Sarah who is her health care power of attorney and 30-year-old Jennifer who is the executor of her will. Sarah has two young daughters and Jennifer recently got married and is planning to start a family. Both Sarah and Jennifer have been very involved in Jane's care and have attended all of Jane's doctor's appointments with her.

Unfortunately, Jane suffered a medical complication, was rushed to the emergency department, and expired unexpectedly with both Sarah and Jennifer at her side.

Immediately after Jane's death, Sarah asks the nurse if Jane's blood can be drawn for genetic testing for a BRCA mutation. She claims that Jane had recently scheduled an appointment with a genetic counselor to get information on being tested for the sake of providing the results to her daughters and granddaughters (and future grandchildren). Jennifer, on the other hand, disagrees and does not think the blood should be drawn. She states that Jane had concerns that her genetic information would not be kept private and so was unsure that she wanted to be tested. According to Jennifer, the appointment with the genetic counselor was only to gain further information into the testing process before Jane made a decision. Jennifer explains that Jane was a very private person, and that although she wanted to help her children and grandchildren, she had serious concerns about leaving her genetic information behind. Sarah adamantly disagrees.

Given that blood must be drawn within hours of the death, the nurse quickly consults a genetic counselor, Dr. Choudhary, to determine how important it is to test the deceased for a genetic mutation in this situation. Dr. Choudhary explains that it is very important because testing an affected individual is the best way of determining whether there is an inherited mutation. If Jane tests positive for a BRCA mutation, then her daughters have a 50% chance of testing positive. If either one, or both, tests positive, then they should seek proper medical management given their increased risk of getting cancer. If Jane tests positive, but her daughters test negative, then her daughters did not inherit the mutation and are not at an increased risk of getting cancer. Dr. Choudhary emphasizes that the problem arises if Jane tests negative or is not tested at all. If Jane and her daughters are all negative for the BRCA mutation, then Dr. Choudhary will ask for more family history in order to determine what other genetic tests to run on Jane to determine if there is another genetic mutation responsible for the cancer. If Jane is not tested and her daughters test negative, then they will not know whether Jane did have a genetic mutation other than a BRCA mutation responsible for her cancer and so they will not know what genetic mutation to look for in her daughters or granddaughters.

Questions:

1. Is there any further information that would be helpful in determining whether to draw the blood or not? If so, what information would be helpful and why?
2. Does one daughter have stronger decision making rights in this situation than the other? If so, which one and why?
3. Should the blood be drawn?

Case 13

Sharing the Wealth

A patient (call him DF) is treated at Dana-Farber Cancer Institute for a rare cancer (Truog *et al.*, 2012). His illness is progressing rapidly, and he is not doing well. He is admitted to the hospital due to increased shortness of breath. His doctors insert a pleural drainage catheter in order to help relieve his symptoms.

During this hospital admission, DF consents to his doctors' request to collect discarded fluid from the catheter so they can isolate a number of his tumor cells for research. Because DF has a rare cancer, these tumor cells, if they can be grown into a cell line in culture, could become a valuable resource for basic science research and for the development of new therapeutics. DF's doctors, who are also scientific investigators, believe that, in the future, DF's cell line could provide a steady revenue stream for Dana-Farber Cancer Institute, as well as provide additional personal income for themselves.

DF's cancer continues to progress, and he eventually dies. The physician-investigators who treated him wonder if they should arrange to have his family receive some financial benefits from any future commercial success of his cancer cell line. They are aware that they are not legally obligated to share down-stream revenues with the family. The U.S. courts have ruled in a number of legal cases that patients do not have property rights over their tissues after they have been removed during treatment, and that they do not have the right to demand royalties from profitable discoveries derived from the use of their discarded tissues. Nonetheless, nothing legally prevents DF's doctors from offering to share revenues with the family.

Questions:

1. Are DF's doctors in this case ethically obligated, permitted, or forbidden from sharing future revenues with DF's family?
2. Would sharing revenues with DF's family set a bad precedent for Dana-Farber Cancer Institute? For physician-investigators in general?
3. Would the ethical considerations being weighed by DF's doctors change at all if DF were alive and in remission?

Resource:

Robert D. Truog, Aaron Kesselheim, Steven Joffe, "Paying Patients for Their Tissue: The Legacy of Henrietta Lacks," *Science* 337, 2012: 37-38.

Case 14

Please Don't Feed Him

The patient is an 84 year-old retired professor who has become progressively more and more demented over the past 7 years. He has now been living in a nursing facility for 4 years. He is nonambulatory, although the staff gets him up in a wheelchair daily. He is nonverbal, and although awake and alert, he does not seem to recognize his family any longer. He can no longer participate in any activities. The patient can no longer feed himself, and must be fed by the staff. He seems to have a good appetite, however, because when food is put up to his mouth he takes it.

The patient has a living will in which he said he would not want artificial nutrition or hydration at end of life. There is a DNAR in place. The family is distraught, because they see their father losing his dignity and he had always said that he wouldn't want to be kept alive in a condition where he could not think, interact, and care for himself. They say that he would be mortified if he "could see himself now." But despite the years of dementia, he is surprisingly strong. He is in a very good nursing facility and does not have bedsores or some of the other problems that come with poor care.

The family has approached the director of the facility and asked that the staff stop feeding their father. They should continue all other care, but not do the hand feedings. They say that if their father could speak, he would definitely ask the same.

The staff, who have grown quite attached to the patient, are horrified and cannot believe that the family would want to starve their father to death. They indicate that they would not follow such an order.

Questions:

1. Does the nursing home staff have an ethically compelling argument to refuse the family's request?
2. Could this conflict have been avoided? How?
3. If the staff and family cannot come to an agreement, what should happen next?

Case 15

Globalization of Genomics Research

In recent years there have been major scientific and technological advances in genomics research. Increasingly, investigators have implemented genomic research internationally including in low income and middle income nations. This case involves genomic research using DNA samples obtained from individuals in Africa.

On September 22, 2015, Reuters (Julie Steenhuisen) reported:

“A company formed by genome pioneer Craig Venter will offer clients of a South African-based insurance company whole genome sequencing – sequencing all protein-making genes in the human genome – at a price that makes yet another dramatic decline in the cost of gene sequencing, the two companies said on Tuesday. Venter’s company, Human Longevity Inc., will provide the tests at a cost of \$250 each through a special incentive program offered by Discovery Ltd, an insurer with clients in South Africa and the United Kingdom.

Venter, the US scientist who raced the US government to map the human genome 15 years ago for a cost of \$100,000, said the \$250 price point per whole exome marks a new low in the price of gene sequencing. ‘It’s our goal to make this (sequencing) available to broad populations,’ he said in a telephone interview. The multiyear deal gives Discovery’s clients access to low-cost whole exome sequencing tests that look only at the protein-making segments of DNA known as exons, which represent 2 percent of the genome but account for 85 percent of disease-causing mutations.

The deal also covers testing for whole genome and cancer genome sequencing services. Financial terms were not disclosed.

Until recently, whole genome sequencing – which maps all of an individual’s 20,500 genes – was prohibitively expensive, costing about \$20,000 just five years ago. As of last year, the average cost of whole genome sequencing fell to \$1,500. Whole genome sequencing costs range from \$400 to \$1,500, plus extra charges for analyzing the results.

For insurance company Discovery, exome-sequencing will be offered through a behavioral wellness program that provides clients with tools and incentives to make lifestyle changes to help them stay healthy.

Discovery clients who choose exome sequencing will receive a comprehensive report detailing their risks for specific diseases and potential strategies to modify those risks. Discovery will provide the reports to clients through a network of physicians and genetic counselors.

Venter’s company, which is based in San Diego, will receive de-identified data from participating Discovery clients, which it will use to build its library of

genetic and health information. Such data is becoming highly prized by pharmaceutical companies as a faster means of drug research.

Last January, Human Longevity signed a multiyear deal to sequence and analyze tens of thousands of genomes for Roche Holding's Genetech unit in an effort aimed at identifying new drug targets and biomarkers.”

In contrast to Venter's entrepreneurial initiative to conduct genomic research to develop pharmaceuticals using de-identified data from Discovery clients (including those from South Africa), the H3Africa Consortium (Human Heredity and Health in Africa) is a publically funded initiative to promote genome science across Africa. The H3Africa Consortium is funded by the U.S. National Institutes of Health and the Wellcome Trust in the U.K. An important goal of H3Africa is to build genomic and biobanking research capacity in Africa through an international collaboration of scientists from Africa nations and elsewhere. An important objective of H3Africa is to advance our knowledge of genetic and environmental determinants of common diseases in Africa and to apply this knowledge to improving the health of African populations.

A key component of H3Africa is the promotion of secondary research through sharing research data and DNA samples to expedite scientific discoveries that could impact disease prevention and treatment for African populations and for populations globally. Currently, the H3Africa Consortium includes 16 funded genomics research projects, 3 biobanking projects, one bioinformatics infrastructure project and three projects that examine ethical, legal and social issues surrounding genomic research. Policies that promote collaboration between local and international scientists have the potential to promote fairness in the production of genomic science.

Questions:

1. Are Venter's deal with Discovery Ltd. and the H3 Africa Consortium equally good for individuals in Africa?
2. What are the main ethical risks of the Venter deal?
3. Which of these two funding models of genomics research is ethically preferable?

Resource:

Web site for H3Africa: www.h3africa.org