Behavioral Genetics: The Quest for an Ethical Genome

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Case Vignette #1

In his last days of life, Reuven's father confessed to his son the difficulty he had controlling his violent outbursts that resulted in physical abuse of Reuven's mother and older brothers. He advised Reuven to do whatever possible to overcome what he feared was a genetic tendency. This confession frightened Reuven because he also had difficulty controlling his temper. Reuven has read the recent studies from the National Institutes of Health that a gene, called the L version of MAO-A, affects neural circuitry in specific regions of the brain and influences the tendency for violent behavior.[1] Reuven and his wife of two months, Sarah, want to have "normal" children and are planning to engage in preimplantation genetic screening (PGSc) to select an embryo that does not carry those genes reported to predispose violent behavior.

Case Vignette #2

Leah and Ethan are committed to Orthodox Judaism but have parents who are atheists and do not observe the religious tenets of Judaism. Leah and Ethan have been married for 4 years and unlike Reuven and Sarah, they have had fertility problems. After their physician suggested that they undergo In Vitro Fertilization (IVF), Leah and Ethan want to use PGSc to select an embryo that possesses genetic elements that are reportedly associated with high spirituality. They have read the numerous reports on the web[2] and the cover issue of October 17th 2004 Time Magazine[3] that the "God gene", VMAT2, reportedly plays an important role in expressing human spirituality. Leah and Ethan want to select children with a greater tendency to accept an Orthodox way of life as opposed to the atheistic life style of their grandparents.

would halachic authorities permit genetic intervention to alter normal psychological, educational, and environmental forces that control behavior

How should halachic authorities respond to the plans and needs of these two families? Specifically, would halachic authorities permit genetic intervention to alter normal psychological, educational, and environmental forces that control behavior? The innate role of genetics in human behavior is recognized by the Torah. For example, the physical characteristics of Esau at birth were an omen of his murderous tendencies.[4] Moreover, the Talmud[5] discusses how inborn behavioral determinants influence moral behaviors of individuals.

This paper first outlines the general scientific principles of PGSc and the rabbinic response that focuses on the use of PGSs to prevent the transmission of genetic diseases. The paper will then discuss halachic considerations in the potential use of PGSc to select embryos that contain genes or gene

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1 Frazzetto G, Di Lorenzo G, Carola V, Proietti L, Sokolowska E, Siracusano A, Gross C, Troisi A. Early trauma and increased risk for physical aggression during adulthood: the moderating role of MAOA genotype. PLoS ONE. 2007;2(5):e486l; Beaver KM, Wright JP, DeLisi M, Walsh A, Vaughn MG, Boisvert D, Vaske J.A gene x gene interaction between DRD2 and DRD4 is associated with conduct disorder and antisocial behavior in males. Behav Brain Funct. 2007; 3:30; Viding E, Frith U. Genes for susceptibility to violence lurk in the brain. Proc Natl Acad Sci U S A. 2006;103(16):6269-74.

2 http://www.uncommondescent.com/biology/the-god-gene/

3 http://www.time.com/time/covers/1101041025/.

4 Rashi Genesis 25:25.

5 Babylonian Talmud Shabbat 156a.

variants associated with behavioral enhancement.[6] Finally, this paper address new biotechnologies that are in development that may offer couples halachic options to better ensure that their children do not have severe or lethal genetic diseases.

The Science of PGSc

PGSc is a multistep process involving ovarian stimulation, egg extraction, In Vitro Fertilization (IVF), cell biopsy, genetic analysis, and embryo transfer (see a short video of this in reference[7]). It is a powerful technology that can be used to screen preimplanted embryos for the genes responsible for severe illnesses and lethal diseases.

The first step in this process involves hormonally stimulating a woman to obtain 10-20 mature human eggs. The infertility physician then uses various methods (e.g., intracytoplasmic sperm injection)[8] to fertilize each egg with the husband's sperm. In this way all the human eggs from the woman are fertilized and allowed to divide in the laboratory into an eight-stage embryo. The eight-cell embryo is then placed under a microscope, immobilized, and one or two cells are gently detached from each embryo without harming the other cells and without affecting potential future fetal development of the embryos.[9] The DNA from the cells obtained from each embryo are genetically screened within 24-48 hours, to assess which embryos express the specific inherited and diseased genotypes and which do not. Once the genetic profile of each embryo is established, one or two of the screened embryos that do not express the "defective genes" are transplanted back into the woman's uterus[10] to allow for normal fetal development. PGSc is being used by more married couples with a family history of genetic diseases in part because this technology is extremely effective and because these procedures are relatively simple to implement. In 2007 alone, over a thousand healthy babies were born using PGSc.[11]

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PGSc is not only used by families with a history of a severe genetic illness. Parents with genetic-based disabilities, such as deafness and dwarfism, have used PGSc to select for children that have *similar* disabilities or conditions because they feel they are better able to bring up children with disabilities like themselves. One study reports that three percent of infertility clinics surveyed have enabled couples to use PGSc to select for those kinds of disabilities.[12] Some families use PGSc to have a baby who is an immunological match for an existing seriously ill child in order to use the new baby's cord blood for stem cell transplantation. PGSc also can be used to select the sex of an embryo — either to avoid a genetic disease caused by a mutation on the X chromosome (X-linked disease) or simply to satisfy the gender preferences of the future parents. In 2005, PGSc clinics reported that 9% of their cases were done for nonmedical sex selection.[11] Recent advances in the genetic screening of pre-implanted fetal cells and post-implanted fetal cells have enabled geneticists to interrogate the human genome in ways never imagined fifty years ago.

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[6] In order to simplify this discussion, we focus on couples in which sperm is obtained from the husband and the egg from the wife, thereby avoiding the halachic issues of maternity, paternity, and surrogate motherhood.

[7] Pre-implantation Genetic Screening (PGSc) is often referred to as Pre-implantation genetic diagnosis (PGD). The term preimplantation genetic screening is used to denote procedures that do not look for a specific disease but use PGD techniques to identify embryos at risk. Pre-implantation genetic diagnosis is a poorly chosen phrase because, in medicine, to "diagnose" means to identify an illness or determine its cause. An oocyte or early-stage embryo has no symptoms of disease. They are not ill. Rather, they may have a genetic condition that could lead to disease. To "screen" means to test for anatomical, physiological, or genetic conditions in the absence of symptoms of disease. Therefore, this paper uses the term Pre-Implantation Genetic Screening for what is commonly referred to as PGD.

[8] Intracytoplasmic sperm injection (ICSI) is often used in cases for PGD for single gene disorders, regardless of whether or not there is any evidence of male factor infertility. Using ICSI will avoid DNA contamination due to the presence of surplus sperm (and their DNA) in the embryo cultures.

[9] For a short video showing this process see: http://www.youtube.com/watch?v=pocZGO8wJ38&feature=PlayList&p=1201525DBF541A14&playnext=1&index=2.

[10] In some cases the women are given progesterone or other drugs to facilitate their uterus to receive and retain the implanted embryo.

[11] Bruce Goldman, Reproductive medicine: The first cut, Nature 445:479-480, 2007.

[12] Baruch S, Kaufman D, Hudson KL. Genetic testing of embryos: practices and perspectives of US in vitro fertilization clinics. Fertil Steril. 2008;89(5):1053-8.

Specifically, these genetic technologies have been used to identify three broad categories of gene alterations.

The first category includes gene alterations inherited in a Mendelian fashion that cause severe, and even lethal diseases, such as Tay Sachs, cystic fibrosis, muscular dystrophy, or Fragile X syndrome that occur early in life.[13] PGSc may also be used to screen for genes that cause diseases that are expressed late in life such as Huntington's disease and certain types of Alzheimer's disease. The second category includes gene alterations that may not directly cause a disorder, but increase the probability that an illness will occur at some point in the life cycle. Examples in this category are genes associated with autism, diabetes, atherosclerosis, heart disease, and various cancers.[14] The third category includes gene alterations that influence behavioral and/or physical traits of a person such as violence, spirituality, intelligence, body stature, hair color, eye color, sexual orientation, promiscuity, or athleticism. We refer to this third category as behavioral/physical trait enhancement genes.

Screening the genes of preimplanted embryos via PGSc is not 100% accurate.[15] There are several reasons to explain how an embryo identified as healthy, by PGSc, can produce a child with an affected genetic disease. Sometimes, this can occur by a biological process called genetic mosaicism,[16] which denotes the presence of two populations of cells with different genotypes in one embryo that developed from a single fertilized egg. Mosaicism may result from a mutation during development that is propagated to only one subset of the adult cells. Therefore, assessing one cell of an embryo may not reveal, with 100% accuracy, the genetics of the other cells of the preimplanted embryo. To overcome these errors in screening, many infertility centers will also test the DNA of the polar bodies of the mature egg.[17] The polar bodies contain genes and chromosomes that the egg expels (the underlying technology used to assess the genetics of a polar body in PGSc is beyond the scope of this paper[18]). In addition, most infertility centers recommend that a woman undergoing IVF and PGSc employ fetal monitoring during pregnancy, including amniocentesis and chorionic villus sampling (see a short video of this procedure in reference #[19]) to ensure that the implanted fetus does not express the defective gene. However, for religious families, amniocentesis and chorionic villus sampling are generally not done because aborting a diseased fetus is not an halachic option. Most halachic authorities do not permit the termination of pregnancy after the embryo has gestated for longer than 40 days

There are medical risks associated with PGSc that need to be evaluated

[13] Down's syndrome can also be screened using PGSc but there is no evidence that there is a genetic predisposition (i.e. family history) for this condition.

[14] Geneticists also divide the first two categories into three subgroups. For example, in category one (gene alterations that cause severe or lethal illnesses), some of the conditions, such as phenylketonuria (PKU), are treatable that allow the individual to live a relatively healthy life. The second subgroup include disorders, such as cystic fibrosis, where treatments help maintain the health of the affected individual for decades but in the end these individuals will not have a normal life span. A final subgroup in this category includes disorders that are currently not treatable such as Tay Sachs, Fragile X, and Huntington's disease. These three types of sub-grouping can also been applied to genes alterations of the second category –those genes that impact the probability of developing a disease sometime in one's lifetime.

[15] As of 2008 there are only a few reports assessing human error in performing these genetic analysis but most laboratories engage in procedures to minimize inaccuracies due to human error. One study claimed that the risk for misdiagnosis due to allele drop-out or partial amplification relates directly to the type of genetic disorder for which testing is performed. The estimated risk of transferring an affected embryo mistakenly identified as normal by PGD is approximately 2% for recessive disorders and 11% for dominant disorders. Such errors can be reduced significantly if linked markers also are analyzed [see C.M. Lewis, T. Pinel, J.C. Whittaker and A.H. Handyside, Controlling misdiagnosis errors in preimplantation genetic diagnosis: a comprehensive model encompassing extrinsic and intrinsic sources of error, Hum Reprod 16 (2001), pp. 43–50]. The true risk for obtaining a clinically relevant false negative result can be determined only by further genetic testing of all conceptions after PGD, but no such studies have been reported as of 2009.

[16] Huang A, Adusumalli J, Patel S, Liem J, Williams J 3rd, Pisarska MD. Prevalence of chromosomal mosaicism in pregnancies from couples with infertility.Fertil Steril. 2008.

[17] Some infertility and PGSc clinics will remove two cells from the embryo to decrease the risk or error.

[18] Renbaum P, Brooks B, Kaplan Y, Eldar-Geva T, Margalioth EJ, Levy-Lahad E, Altarescu G.
Advantages of multiple markers and polar body analysis in preimplantation genetic diagnosis for Alagille disease. Prenat Diagn. 2007 Apr;27(4):317-21. See http://www.pgd-baby.com/pgd-process.html, http://www.care-life.com/embryo_screening.htm

[19] See http://www.youtube.com/watch?v=0XUZsvTkEnw for a short video showing this technique.

(approximately 6-7 weeks using the conventional classification of gestation).[20]

There are medical risks associated with PGSc that need to be evaluated. In general, these risks are related to the hormonal ovarian stimulation that the woman must undergo in order to obtain mature eggs. Hormonal hyperstimulation of the ovaries is necessary to generate eggs that are ripe for fertilization. This process involves a seven to ten day regimen of medications[21] that are similar to hormones that a woman produces during her menstrual cycle and pregnancy, but given in much larger doses. These prescribed hormones are self-injected to stimulate the woman to simultaneously produce 10-20 mature eggs from her ovaries.[22] Without these medications, most women will only produce one mature egg per month during a menstruation cycle. Women undergoing hormonal hyperstimulation have their blood hormone levels regularly monitored, their temperature monitored daily, and undergo periodic ultrasound assessment of their ovaries. These tests indicate when the eggs in the ovaries are ripe for egg retrieval. When mature eggs are detected, the woman is given a light anesthesia, and the eggs are collected using a thin needle that is guided through the vaginal wall by ultrasound.

Future technologies are emerging that might eliminate the need for women to undergo ovarian hyperstimulation

While only a few percent (3-10%) of the women experience some sort of medical problems with hormonal hyperstimulation, it is still important to delineate all the known medical risks. For example, this procedure can produce ovarian hyperstimulation syndrome (OHSS) in the woman, which can cause life-threatening complications including blood clots, kidney failure, shock, and fluid buildup in the lungs. In a small number of cases, women experiencing OHSS might need to have their ovaries removed.[23] Clinical experience of infertility experts indicates that women, who undergo hormonal hyperstimulation for the first time without complications, will rarely experience complications in future hormonal hyperstimulation treatments.

However, women engaging in multiple cycles of hormonal hyperstimulation of the ovaries may be at increased risk of breast or ovarian cancer.[24] The link to an increased cancer risk has not been firmly established but it is important for reproductive specialists to study the long-term effects of fertility drugs now that their use is so commonplace in IVF practice. Even though over 3.5 million babies have been born via IVF as of 2008, there are only a few studies in the literature that report the incidence of cancer in women who have had repeated cycles of hyperstimulation of the ovaries.[25] It is important to recognize that researchers have had only about a decade to study the potential risk of cancer in a significant numbers of women who have had hormonal hyperstimulation, since these cancers often do not appear until ages 50 or 60. However, the unknown potential cancer risks and the chance that IVF – generated siblings will marry each other, has led many infertility centers to limit hyperstimulation of a woman to 5-6 times in her lifetime.

There are also short-term, but even less common, medical risks associated with the surgical procedures and anesthetics involved in IVF and egg retrieval. These risks include an increase rate of infections, hemorrhage, and psychological effects. While the incidence of these short-term and long-term medical risks vary from clinic to clinic, infertility clinics claim that most women undergoing these procedures do not experience these medical risks and the babies

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[20] Steinberg, Avraham, Enclyclopedia of Jewish Medical Ethics, (Feldheim Publishers, Jerusalem, Israel, 2005) pgs, 422,571-586.

[21] Medications include one or more of the following hormones: gonadotropin-releasing hormone, follicle-stimulating hormone, human menopausal gonadotropin, and human chorionic gonadotropin.

[22] Tarlatzis BC, Bili H. Safety of GnRH agonists and antagonists. Expert Opin Drug Saf. 2004 Jan;3(1):39-46.

[23] http://www.health.state.ny.us/community/reproductive_ealth/infertiliy/eggdonor.htm

[24] Some scientists believe this link is associated with infertility and not ovarian hyperstimulation.

[25] atz D, Paltiel O, Peretz T, Revel A, Sharon N, Maly B, Michan N, Sklair-Levy M, Allweis T.
Beginning IVF treatments after age 30 increases the risk of breast cancer: results of a case-control study. Breast J. 2008 Nov-Dec;14(6):517-22.

produced by either IVF or PGSc are almost always healthy.[26]

Future technologies are emerging that might eliminate the need for women to undergo ovarian hyperstimulation and further reduce many of the medical risks associated with PGSc. For example, scientists are becoming more proficient in retrieving immature eggs from hormonally unstimulated women and subsequently, maturing the eggs in the laboratory.[27] Currently, the success rate of producing a child using immature eggs is significantly lower than using mature eggs. Hopefully this rate will improve in the future. Overall, the success rate of producing a child using current IVF technologies is higher with younger women and in clinics that have a high volume of patients.[28] Most of the major clinics in the United States and Israel report a clinical pregnancy rate per IVF procedure of about 30-40%. The medical risks to the IVF/PGSc generated child appear to be minimal but more studies are being done to examine this aspect in greater detail.

Most halachic authorities permit discarding non-implanted embryos carrying genes that either cause disease or are highly associated with increasing the likelihood of a disease

Halachic permissibility of engaging in PGSc in couples with a history of hereditary diseases.

Most halachic authorities in the United States and in Israel allow PGSc when a family's genetic history indicates a risk of having a baby with a genetic disorder (screening of gene variations that directly causes disease – see page 16). There is no difference whether the embryo is screened for a genetic disease that will affect the child in his or her early years, such as Tay Sachs or late-onset diseases such as Huntington's disease, Alzheimer's disease, or diabetes. In all such cases, halacha will allow married couples to use PGSc to select an embryo that does not contain the heredity determinants that causes these diseases. There are few halachic responses discussing the use of PGSc to select embryos that do not express gene variations in category two, (i.e., gene alterations that are associated with an increased risk of disease). It seems appropriate that when there is a family history of such category-two gene variants, PGSc may be an acceptable medical procedure when the relative risks and benefits are properly evaluated.

In Judaism, the use of PGSc in preventing or reducing the likelihood of genetic diseases is a moral imperative as is the treatment of an illness.[29] An important philosophical concept related to the obligation to heal is found in Bava Batra 10a. Rabbi Akiva states that human beings do not prevent Divine intent when they help the poor or to heal the sick. In Judaism, human beings are directed to partner with God to improve the world.[30] Genesis Rabba 11:6 states that a philosopher asked Rabbi Hoshaya for the reason for circumcision. Rabbi Hoshaya responded saying that God did not create either the world or human beings in a perfect state and as a result, human beings can partner with God in the creation process.[31] Ramban further states that the God-human partnership is reflected in the Bible's use of the phrase "and have dominion" that charges the human race to use scientific knowledge and technologies to improve the world.[32] Finally, this theme is incorporated by several mussar authorities—the Zohar and Peskei Rabbati—who suggest an alternate translation of the Kiddush

[26] ttp://www.medicalnewstoday.com/articles/139400.php

[27] Rao GD, Tan SL. In vitro maturation of oocytes. Semin Reprod Med. 2005, (3):242-7; Suikkari AM, Söderström-Anttila V. In vitro maturation of eggs: Is it really useful? Best Pract Res Clin Obstet Gynaecol 2007; 21: 145–155.

[28] As women age, fewer mature eggs can be produced via ovarian hyperstimulation and the rate of embryo implantation also decreases.

[29] Maimonides, M., Mishnah Commentary on Nedarim 4:4 and Nedarim 38b. The Biblical verse "and heal he shall heal" [Exodus 21:19.] is interpreted by halachic authorities from Talmudic times to mean that authorization is granted by God to the physician to heal. In fact, the Rambam following the discussion in the Talmud, states that the law of restoring lost property includes also the restoration of health. If a person has "lost his health" and the physician is able to restore it, he or she is Biblically mandated to do so.

[30] Sa'adiah Gaon, in his Arabic translation of the Torah, explains the term "God's image" as meaning the ability to conquer and rule. Just like G-d rules over all of creation, man rules over the animal world.

[31] Sefer Hachinuch on circumcision.

[32] See Ramban on Genesis 1:28

blessing (Genesis 2:1-3) said every Friday night.[33] The classical translation of Genesis 2:3 states, "And God blessed the seventh day, and hallowed it"; because that in it He rested from all His work "*asher bara elokhim la'asot* (**which God had created – to do**)." The alternate translation of the word *la'asot* is that it is the responsibility of human beings, not God, "to do"—to complete the doings of his creation (*tikkun olam*). The use of science and medicine in the service of humankind is a fulfillment of this Divine mandate.

virtual unanimity of rabbinical authorities in prohibiting the use of PGSc just for sex selection

There are also many halachic sources that support a mandate to practice proper health measures and prevent illness. Rambam,[34] and Tur,[35] both cite the verse in Deuteronomy (4:9): "Duly take heed to yourself and keep your soul diligently" as the biblical directive to preserve health.[36] Protecting a child from illness can be classified under the rubric of the moral obligation to preserve health and to prevent illness.[37] Netziv[38] applies this halachic principle to the infertile couple in his analysis of the descriptions in the Torah about the infertility of Sarah, Rebecca, Rachel and Hannah. For example, Rachel declared to Jacob: "Give me children, otherwise I would rather die."[39] Netziv explains that this statement signifies that infertility can be viewed as a critical disease.[40]

Halacha also recognizes that there is a predisposition to genetic disease and warns the individual not to marry someone from a family with a history of genetic disease. Yevamot 64b and several halachic works[41] states that one should not marry into a family of lepers or epileptics. Rashi expands this category to include any hereditary disease.[42] This warning certainly means that individuals should also not create families with genetic diseases. In the past, some halachic authorities advised couples who are both carriers of genetic diseases such as Tay Sachs to divorce.[43] However, this response was written before PGSc was fully developed in the 1990s. Today, married couples who are carriers of genetic diseases can have healthy children and should consider PGSc as a mandatory procedure to preserve health and avoid producing a child or family with a severe genetic illness.

Halacha does not demand that an infertile couple engage in ART (artificial reproductive technologies) and expose themselves unnecessarily to known and unknown health risks.[44] However, a modicum of

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33 Pesikta Rabbati 94.
34 Mishna Torah Rotzeach 11:4.
35 Shulchan Aruch Chosen Mishpat 427:8.
36 Steinberg, Avraham, Enclyclopedia of Jewish Medical Ethics, (Feldheim Publishers, Jerusalem, Israel, 2005) pg 830-834
37 Tendler MD. Responsa of Rav Moshe Feinstein. New York: Ktav, 1996, p. 57.
38 Natziv Shiltos, Parsha Naso.
39 Genesis 30:1.
40 Rashi on Genesis 30:1.

41 Mishneh Torah, Hil. Issurei Biah 21:30; Shulchan Arukh, Even Ha-Ezer 2:7;Chatam Sofer 137; Peri Hasadeh part 2 #26; Chazon Ish Yorah De'ah 152;2.
42 Rashi on Yebamot 64b
43 Rabi Y Zilberstein, Halacha U' Refuah Vol 2, 5741 (1981) pg 111.
44 Does the principle that under certain circumstances God will "protect the simple" (*Shomer petayim Hashem* -Psalms 116:6) discharge Jews from taking a proactive medical stance? In fact, the underlying philosophy of *shomer petayim Hashem* is often misunderstood. Avodah Zarah (30b) states that "R. Eliezer claims that one may eat grapes or figs at night and need not fear [that a poisonous snake had bitten into them], for it is written, *Shomer petayim Hashem*." A similar concept is found Niddah (31a): "We have learned [that] if one has relations with his pregnant wife on the 90th day after conception, it is as if he were killing [the fetus]... Abbaye says: 'He may act normally (e.g. engage in marital relations), because of the dictum *shomer petayim Hashem*.'" The Tosefot Rid (Avoda Zarah 30b) derives an important insight from these Talmudic statements suggesting that the principle of *Shomer petayim hashem* applies only when the dangers are rare occurrences or unusual. Given that the permissibility of eating grapes and figs at night is based upon the principle of *shomer petayim Hashem*, the Tosefot Rid reveals that it was implemented only because the risk is rare. Rashi on Ketubot (39a) states that only if there is a minimal risk of danger then one may rely on *shomer petayim Hashem*, but if a safe alternative exists, one should not rely on *shomer petayim Hashem*. Ramban (Exodus 22:15) states that the term petayim refers to individuals whose intelligence is insufficient to understand various matters or understand concepts very superficially and whose hearts are easily misled. The Terumat HaDeshen (Chapter 211) goes so far as to claim that the principle of *Shomer petayim Hashem* does not apply to educated individual (i.e., *talmidei chachamim).* Therefore, when a situation is known to be hazardous and yet people regularly disregard it, *shomer petayim Hashem might not apply*. In the case of a couple where both members are carriers for a genetic disease such as Tay Sachs, there is a probability that 25% of their children will develop Tay Sachs and die within 6 years. This does not constitute a rare occurrence or a minimal risk and the

medical risk may be assumed by a couple to fulfill the biblical commandment to procreate (*pirya v'rivyah*).[45] Since PGSc has been demonstrated to be so successful in generating healthy children from couples who are both carriers of genetic diseases, there is an obligation for families with a genetic history of disease to utilize PGSc to produce healthy children and not to create a family with genetic diseases. In addition, if a strong emotional bond exists between two individuals who are both carriers for a genetic disease such as Tay Sachs or cystic fibrosis, they may still marry because they have the option to use PGSc to produce healthy children. However, such a couple should consult a rabbinical authority before they marry to discuss the halachic and medical consequences of a long life that requires the use of contraception.

There are other potential halachic considerations associated with PGSc related to moral status of the unused and non-implanted embryos. Normally, non-implanted embryos that carry defective genes are discarded by most fertility clinics. Is this halachically acceptable? An artificially produced microscopic embryo comprised of 8 cells created outside a woman's body does not have the equivalent moral status of an implanted human embryo or fetus. However, even an embryo that has developed for less than forty days is not halachically insignificant. Ramban, states that one may engage in *melachot* on Shabbat to save a fetus that is even one day old.[46] However, many halachic authorities state that an embryo that has gestated less than 40 days can be terminated if there are compelling maternal medical concerns. Most halachic authorities permit discarding non-implanted embryos carrying genes that either cause disease or are highly associated with increasing the likelihood of a disease.

Another halachic consideration in PGSc is the Biblical injunction against masturbation or "wasting of male seed". Men who are being tested for infertility must provide semen for fertility analysis. The halachic issue associated with procuring semen has led religious professionals to establish a hierarchy of preferred methods of diagnosing infertility. Today, since 50% of all infertility is caused by male infertility, the first medical test that should be done is a post-coital examination where a fertility physician removes cervical fluid from the woman the morning after the couple had marital relations to assess sperm density and motility. If the man's sperm appears normal, it may still be necessary to assess his seminal fluid by use of a specially designed condom that does not injure the sperm or affect the seminal fluid composition. Only as a last resort would halachic authorities allow the physician to mechanically or electrically stimulate the man to obtain semen or allow him to self-masturbate into a receptacle for semen collection. In addition, semen may be procured during relations and cryopreserved under conditions when artificial insemination has to be done at a time when intercourse is prohibited by Jewish law (when the woman is in a state of ritual impurity). Consultation between the infertility specialist, the couple, and their rabbi is essential in determining which method of sperm procurement would best apply to the needs of the specific couple undergoing IVF and PGSc.

In Judaism, the use of PGSc in preventing or reducing the likelihood of genetic diseases is a moral imperative as is the treatment of an illness

Since timing is a critical element in the whole process of IVF and PGSc (especially procuring mature eggs from the woman), careful planning should be employed to avoid scheduling medical procedures on Shabbat or religious holidays (*Yom Tov*). However, if such appropriate scheduling cannot be accomplished, then it is permissible to engage in these medical procedures on Shabbat and

principle of *shomer petayim Hashem should not apply*. Furthermore, there is a relatively safe and effective alternative available to eliminate that risk, namely PGSc that is recognized by fertility experts around the world. In addition, the principle of *dashu bei rabim* (the multitude are accustomed to it) presented in Shabbat 129b may allow individuals to assume known medical risks in order to achieve medical benefit. In contrast, smoking that was assumed to be of minimal medical risk in the 1960's is now prohibited by Jewish law in view of all the established medical dangers of smoking.

See p. 45-47 of this JME issue -editor

[45] Steinberg, Avraham, Enclyclopedia of Jewish Medical Ethics, (Feldheim Publishers, Jerusalem, Israel, 2005).

[46] The Ramban (*Torat ha-Adam, sha'ar ha-meihush, inyan sakkana)* based this ruling on the premise that it is better to violate one Shabbat in order for the fetus to be saved to celebrate many shabbatot in the future.

Yom Tov using a gentile physician who is not governed by the laws of Shabbat and Yom Tov.

PGSc for non-medical reasons

There are situations in which halachic authorities have deliberated the use of PGSc for non-medical conditions.[47] Some rabbis[48] have allowed couples to engage in PGSc in the non-medical situation where an infertile husband is a kohen (of the priestly tribe), and donor sperm is used to produce a child. The husband and wife may choose IVF to select a female embryo to avoid the social consequences of a kohen whose son is not a kohen.[49] If sex selection were not employed, this scenario might cause embarrassment to the couple and would violate the family's right to privacy since the couple's friends and community would recognize that the baby boy born from the woman is a product of IVF using donor sperm. This example is one in which some Halachic authorities rely on specific humanitarian reasons in allowing PGSc for sex selection.[50] There is virtual unanimity of rabbinical authorities in prohibiting the use of PGSc just for sex selection.[51] However, in couples where PGSc is necessary to select an embryo that does not carry a genetic disease it is permissible at the same time to select the gender from the pool of "healthy" embryos.

Another important halachic consideration with respect to sex selection is summarized by the Rambam[52] where he states that the Biblical duty to procreate and give birth to at least one son and one daughter is fulfilled when one engages in marital relations until children are produced. There is no obligation for a couple to engage in heroic medical interventions to produce a child,[53] much less to select the gender of a child to fulfill the biblical mitzvah of procreation. Engaging in marital relations is within the power of human beings but the gender of the child rest in the hands of God. The birth of both a son and daughter only signifies a point in time when the mitzvah of procreation has been fulfilled.

In countries where the government limits the number of children, there is an increased tendency to utilize various means to produce more boys than girls. For example, the boy to girl ratio in some countries is approaching 120 boys to every 100 girls born. This creates an unnatural biological environment where there are not enough girls for marriage. Such a situation must not be allowed to develop within the Jewish community.

PGSc for genes that affect behavior

There are many reasons why it may be halachically and medically inappropriate or illogical to use PGSc to select embryos with specific behavioral traits:

as of 2009, it is inappropriate and halachically improper to engage in IVF/PGSc to select for behavior enhancement traits

A panoply of genes influences behavioral traits. Screening for one or two gene alterations undermines the complexity of this whole process and fails to take into account the scientific evidence that environment is a critical component in shaping behavior. Judaism believes that all individuals have behavioral tendencies that may cause them to sin. Moreover, God created all individuals with the ability to overcome inappropriate behavioral urges. Thus, for most Jews there is no medically compelling reason to utilize PGSc to select embryos with enhanced behavior traits. Nonetheless, it

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47 Rabbi Broyde also permits parents to utilize PGSc to have a child that genetically matches another family member who requires a bone marrow transplant. Broyde MJ. Pre-implantation genetic diagnosis, stem cells and Jewish law. Tradition. 2004.

48 Ibid 20.

49 If the couple did not utilize sex selection via PGSc, and had a boy, halachically the child would not be the son of a Kohen and would not be allowed to recite the Priestly Blessing, would not receive the Kohen *aliyah* and the parents would not be obligated to perform the mitzvah of redemption of the first born [*Pideyon Haben*- if the sperm donor were Jewish].

50 There is also some controversy whether one is permitted to use PGSc to select an embryo whose cells obtained from the cord blood will be compatible to treating a sick sibling. See *Nishmat Avraham* (publisher: Schlesinger Institute, Jerusalem, new edition - 2007) vol. 4, *Choshen Mishpat*, 243:1.

51 See Grazi, Richard V. *Be Fruitful and Multiply; Fertility Therapy and the Jewish Tradition* (Jerusalem:Genesis Jerusalem Press, 1994), pg 186.

52 Moreh Nevuchim 15:1.

53 Shabbat 31a.

is critical for halachic authorities to consider those rare instances where one or both parents express an abnormal behavioral trait such as violence (documented by psychological testing) and a family history of violent behaviors. Under those conditions, PGSc would be an appropriate procedure when empirical medical data confirms that selecting those embryos lacking those specific genes would in fact dramatically reduce the violent tendencies in the offspring. At this time, there is no reported evidence that PGSc would in fact select for embryos that will grow up being less violent or would develop into more religiously committed Jews. Therefore, as of 2009, it is inappropriate and halachically improper to engage in IVF/PGSc to select for behavior enhancement traits. Equally important, halachic authorities would prohibit the use of a "full service" fertility clinic, such as fertility institutes, that encourages couples to sign up for embryo screening to choose the gender, eye color, hair color, and complexion.[54]

DNA, science, and some elements of halacha are all liable to change in response to internal and external events

Historical and scientific evidence highlight the effectiveness of environment in overcoming many of the unwanted behavioral traits. Judaism places a high value on the impact of education and environment (family life, school, and community) in helping to mold the moral character of a child. Therefore, the first line of defense to combat undesired behavior is to properly educate the child in the ways of the Torah and to create an environment to help the child learn to control normal biological urges. Resorting to PGSc will not exempt the parents from the obligations to educate their children about proper moral conduct.

While the moral status of preimplanted embryos are not equal to that of a 40 day old implanted fetus or a child at birth, nonetheless, such embryos should be treated respectfully and not wasted unnecessarily because they do have the potential to create human life. Therefore, unused non-implanted embryos should not be discarded but rather cryopreserved, or donated to other couples. If this is not feasible then they should be donated for medical research.

Finally, there is an important societal, biological, and medical concern that wide scale embryo screening for behavioral enhancement traits could affect genetic diversity, a critical evolutionary element of human development. Such genetic manipulations, even if restricted to local communities, could render a population more susceptible to unknown or emerging catastrophic infections and other disorders that may be enhanced by the very DNA sequences associated with the behavioral genes being selected.

Analysis of the Two Case Vignettes

In analyzing the two cases presented in the beginning of this article, halachic authorities might only allow Reuven and Sarah to utilized PGSc only under specific conditions. If genetic analysis of Reuven establishes a clear and significant correlation with psychological testing that confirms his violent tendencies and documentation that he has already engaged in as abusive acts then Reuven and Sarah would be allowed to use PGSc.

With respect to Leah and Ethan, if they were using PGSc to select an embryo that did not have the gene for a medical disease such as Tay Sachs, then they would be permitted to select from a pool of "healthy" embryo for one that also expressed gene variations associated with high spirituality and they could also select the gender of the baby from this pool. However, halachic authorities would not permit the use of PGSc solely for behavioral trait enhancements in situations where there is no family history or genetic predisposition to disease, even if the association between genetics and spirituality could be proven scientifically.

Future Technologies

DNA, science, and some elements of halacha are all liable to change in response to internal and external events. Scientific principles change as more research is generated to understand the biology of

[54] http://www.fertility-docs.com/index.phtml.

life, disease and death. In contrast, the halachic process provides established guidelines how and when halacha should respond to internal religious demands or to external events such as emerging technologies. Halacha recognizes that science and religion often collide, philosophically and practically. Yet, the halachic process possesses intrinsic mechanisms by which such collisions are transformed into practical applications.

Any discussion on genetic screening of pre embryos or embryos must present emerging technologies that would require a re-evaluation of their halachic ramifications. Currently several US medical centers, including Columbia University College of Physicians and Surgeons are exploring a new technology in which normal vaginal secretions can be collected into a modified tampon from a woman who is less than 4 weeks pregnant. These vaginal secretions contain cells that are shed from both the woman and the developing embryo. If the embryonic cells can be separated from the maternal cells, they can be accurately analyzed to genetically determine whether the embryo is affected with a genetic disease such as Tay Sachs or cystic fibrosis. These tests can be done within 24 hours after obtaining the sample and will provide the couple with an affected embryo (less than 40 days old) the choice whether or not to terminate the pregnancy. When this technology becomes more established it would allow a pregnant woman, from a couple where both partners are carriers for a genetic disease such as Tay Sachs, to genetically test the cells obtained from the fetus. If the fetus has gestated less than 40 days and was found to have either Tay Sachs or cystic fibrosis, then the couple should choose termination to prevent the creation of genetically diseased children.[55]

Conclusions

In summary, our understanding of the genetic predisposition for behavioral traits is in its early stages. The relative importance of genes that are associated with behavioral traits such as spirituality, intelligence, sexual orientation, or excessive violent behavior will require much more research. This is especially important since environmental factors can play a critical role in behavior. However, if this knowledge and technology does develop credibility in the future, Halachic authorities would revisit the issues presented above.

PGSc is continuing to improve as a means to accurately assess whether a pre-implanted embryo carries common and less common gene mutations or variants that would confer diseases such as Tay Sachs, cystic fibrosis, Canavan disease, Gaucher disease, Familial dysautonomia, Niemann-Pick disease, Fanconi anemia, Bloom syndrome, and Mucolipidosis Type IV, and late onset diseases such as Huntington's disease and Alzheimer's disease. The principle of *chamira sakanta me'isura* (a situation of possible danger demands more stringency than in the case of a halachic prohibition[56]) provides the appropriate incentive to engage in medical procedures, such as PGSc, in order to produce a healthy child, even though the procedure may involves some potential halachic concerns. Since IVF and PGSc are relatively safe procedures, we would encourage those rabbis who discourage an emotionally committed couple from getting married if both are carriers for a genetic disease to re-evaluate their halachic positions. These rabbis were concerned about the high probability of two carriers to produce children with the affected disease. However, the emerging success of IVF and PGSc in producing healthy children affords a couple that carries the defective gene the option to marry and produce healthy children.

[55] Whether termination should be done via a dilatation & curettage or use of oral drugs requires the consultation with the couple's rabbi and physician.

[56] Hulin 10a.