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Inheritable genetic modification: clinical applications and genetic counseling considerations

Joan A. Scott

It is entirely speculative at this point whether technologies to alter the human germ line will develop to the point where they are deemed safe and effective enough to be made available to prospective parents, much less considered ethically acceptable. But even the possibility that such profound technologies might be used has prompted intense debate. The scientific, ethical, moral, and social issues raised by these technologies have been debated in this volume and elsewhere. What has been missing in the discussion thus far, however, has been the perspectives of the couples or individuals who might consider the use of such technologies, consideration of the clinical or research setting in which these technologies might be offered, and the impact of that setting on couples, or the perspectives and concerns of the health professionals and researchers who may be in the position of counseling the families and providing the services. Additionally, the public has not yet been invited into the discussion in any meaningful way. In the interest of extending the debate, this discussion will try to anticipate some of the patient, genetic counseling, and application aspects of technologies developed to alter the human germ line and articulate the need to include many more voices and perspectives in the debate. Some may consider this discussion premature, perhaps even inappropriate at this point in time, but given the speed with which scientific progress is made, it seems prudent to at least introduce these issues into the debate.

12.1 The application of inheritable genetic modification technologies to humans

When will bench and animal research have progressed to the point that human clinical trials of inheritable genetic modification (IGM) might be considered ethically justifiable, at least from the technical standpoint? Some believe that there will never be enough data to feel confident of the safety of IGM in humans. In the 2000 report of the American Association for the

Advancement of Science on IGM, the working group made the following recommendation:

> Human trials of inheritable genetic changes should not be initiated until techniques are developed that meet agreed upon standards for safety and efficacy. In the case of the addition of foreign genetic material, the precise molecular change or the changes in the altered genome should be proven with molecular certainty, probably at the sequence level, to ascertain that no other changes have occurred. Furthermore, the functional effects of the designed alteration should be characterized over multiple generations to preclude slowly-developing genetic damage and the emergence of an iatrogenic genetic defect. In the case in which attempts at IGM involve precise correction of the mutant sequence and no addition of foreign material, human trials should not begin before it can be proven at the full genome sequence level that only the intended genetic change, limited to only the intended site, has occurred. If it is shown at the full genome sequence level that the sequence of a functionally normal genome has been restored, there will likely be no need for multigenerational evaluation. [1]

For the purpose of this discussion, let us assume that we are at some time in the future and that these technical issues have been addressed – techniques have advanced to the point where animal studies demonstrate that one gene can cleanly replace another, without leaving any footprint behind, and that the introduced gene is under appropriate control so that it is expressed in the right tissues at the right time. Additionally, the techniques of adding genes have developed to the point that in animal studies the added genes can be demonstrated to be stable over multiple generations. The rest of this chapter will examine issues related to offering the first IGM trials in humans – who might be candidates for such technologies; in what setting and under what circumstances IGM might be made available and by whom; the comparable risks and benefits that would need to be weighed by the individual or couple considering IGM versus alternative options; what the counseling issues might be that are specific to this situation; and why an individual or family might consider the use of such powerful technologies.

12.2 Candidates for IGM

There is considerable debate about who will be the first candidates for IGM. Some believe that the first clinical applications for IGM will be for couples at risk for having a child with a serious genetic condition. One of the strongest arguments against IGM in these circumstances, however, is that there are relatively few genetic situations for which IGM would be the *only* technology available for such a couple and that other, less risky reproductive options would be more appropriate.

12.2.1 Alternatives to IGM

Depending on the mode of inheritance of the particular disorder in question, some of the reproductive alternatives available for at risk couples to prevent the birth of a child with a genetic condition include adoption, conceiving using

donor egg or sperm, prenatal diagnosis followed by termination of an affected pregnancy, or *in vitro* fertilization (IVF) followed by preimplantation genetic diagnosis (PGD).

Opponents argue that the availability of these alternatives make it unethical, or at least inappropriate, to offer IGM with its potentially greater risks and unknowns and ethical dilemmas. However, while it may be true that these alternatives do exist, it would be a disservice to the families faced with these decisions to minimize or trivialize the physical or psychologic burden each poses, or the difficulty couples may have in deciding which option is best for them. Adoption can be a lengthy and stressful process as can conception using donor gametes. Prenatal diagnosis involves invasive procedures that carry risks of miscarriage. Additionally, if the purpose is expressly to prevent having an affected child, prenatal diagnosis implies that the couple would at least entertain the possibility of terminating an affected pregnancy. Pregnancy termination poses a significant psychologic burden and many find it to be a morally unacceptable option.

PGD is the method most cited as the obvious alternative to IGM. In this procedure, eggs retrieved from a woman who has undergone hormonal hyperstimulation are fertilized using well-established IVF techniques. At the 6- to 8-cell stage, one cell is removed from each of the embryos that are produced and tested for the gene in question. Only those embryos that demonstrate the desired genetic characteristic are selected for transfer. By testing and selecting only "normal" embryos for transfer, a couple can initiate a pregnancy knowing they would not be faced with the difficult decision to terminate. However, PGD is also not without its moral dilemmas, technical difficulties, and risks. PGD requires the creation of many embryos. Only those with the desired characteristics are selected for transfer. Some find the notion of "picking and choosing" offspring by whatever selection criteria, even to prevent a serious genetic disease, problematic, as well as the fate of the unselected embryos, whether they are selected because they do not have the right genotype or because they are "surplus," normal embryos. Because of the technical difficulties in performing genetic analysis on a single cell, there is also the risk of misdiagnosis and implanting an affected embryo. Finally, there is some question as to whether the techniques of IVF and PGD themselves carry an increased for producing birth defects or congenital abnormalities.[2]

12.2.2 Genetic situations for IGM

However problematic these options may be, they are available and thus there are relatively few genetic situations that have been put forward where IGM would be the *only* option for a couple of having an unaffected child that is genetically related to them. David Resnik *et al.*, propose several situations:

1. both parents homozygous for an autosomal recessive gene,
2. one parent homozygous for an autosomal dominant mutation or the mother homozygous for an X-linked dominant mutation,

3. father carries an X-linked dominant mutation,
4. parents heterozygous for multiple alleles.[3]

In the first scenario, both parents would be affected with an autosomal recessive condition and therefore have only the recessive gene to pass on to their offspring. One hundred percent of their children would be affected – like both of the parents. Having both parents affected with an autosomal recessive condition is certainly a rare situation and one could rightly question whether the investment in research for such an uncommon situation is justifiable, but as treatments for genetic conditions improve and more individuals survive to reproductive age, it is perhaps a plausible scenario. The example that is frequently used is cystic fibrosis (CF). Better therapies make the life expectancy of CF such that this scenario is not inconceivable.

The second scenario is similarly quite rare. In this case, the affected parent has only the dominant allele to give to his or her children, so again 100% of his or her children would be affected.

If we approach IGM with the presumption that it is, at least initially, offered only to individuals who have no other options of having an unaffected child that is genetically related, the third situation would not be an appropriate application of IGM. As Resnik correctly states, all of the female offspring of a man who carries an X-linked dominant gene would inherit his X-chromosome and the abnormal gene. However, all of his sons would inherit his Y-chromosome and be unaffected. This couple would have the alternative option of PGD or prenatal diagnosis and of selecting only male embryos and fetuses.

In the fourth scenario it is suggested that PGD is not a practical option because the parents produce various combinations of unaffected embryos, embryos that carry one or more of the recessive mutated genes like the parent, and embryos affected with one or more of the recessive genetic conditions, making it unlikely to get the right combination of genes in an embryo. For example, consider a situation in which both parents are carriers of mutations causing CF and Tay-Sachs disease. IVF followed by PGD and embryo selection would be available; however, Resnik argues that statistically only 1 of 16 embryos would be homozygous normal for both conditions and available for transfer. Given the large numbers of embryos that would have to be produced to get the right combination of genes and the low success rate of IVF and PGD, he suggests that PGD as an approach to prevent the birth of an affected child becomes unlikely. However, if the intent is to prevent having a child affected with Tay-Sachs, CF, or both, then transferring heterozygous embryos is certainly appropriate. Over half of the embryos produced would be homozygous normal or carriers for one or both abnormal alleles. Since everyone in the population carries an estimated 6 to 8 lethal, recessive alleles, these embryos would not carry a genetic burden that exceeds populational norms.

The above situations assume that the reason for considering IGM is to prevent a serious condition in an offspring. Because the genetic situations described

are so exceedingly rare, however, many believe that it will be parents seeking enhanced characteristics for their offspring that will ultimately drive the development and utilization of IGM. The enhancements sought could be for health-related reasons, for example parents seeking to add genes that will boost immunity in their offspring. Or they may be for purely aesthetic or performance reasons – genes to enhance physical characteristics or increase musical talent, for example.[4] Although in some respects the counseling issues will be the same regardless of the intent of the IGM – discussion of safety and risks, for example – the motivational factors, not to mention the broader societal implications, will be entirely different. This chapter focuses primarily on IGM in the context of genetic disease conditions.

12.3 Setting and oversight mechanisms for IGM studies in humans

The first use of IGM, assuming agreed upon medical safety and efficacy standards have been met, will likely occur in a research setting. Although the intent of this chapter is not to review the regulatory climate for IGM, the setting and oversight mechanisms will pose additional challenges for couples who might avail themselves of this technology as well as confound the counseling issues; thus some discussion is warranted.

The specifics of the oversight mechanism will vary from country to country, but in the U.S.A., the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER) has authority over gene transfer technologies and regulates both the gene and the vector used to deliver the gene.[5] Any investigator wishing to test a gene transfer product, therefore, must first submit an Investigational New Drug (IND) application, which includes the scientific and animal data justifying its use in humans and documents that an Institutional Review Board (IRB)-approved protocol, discussed in more detail below, is in place. The FDA can also step in and stop a trial if adverse events are reported that indicate unacceptable risks.

The Recombinant DNA Committee (RAC) of the National Institute of Health (NIH) Office of Biotechnology Activities (OBA) also provides some oversight of gene therapy trials in the U.S.A. The RAC reviews all federally-funded somatic cell gene transfer (SCGT) trials or trials taking place at federally-funded institutions. Only protocols that raise novel issues are required to go through full public RAC review. Novel issues identified that could warrant a public review include:

1. a new vector/new gene delivery system,
2. a new clinical application,
3. a unique application of gene transfer,
4. other issues considered requiring further discussion.[6]

Although the RAC is not a regulatory body and cannot ultimately approve or reject protocols, local Institutional Biosafety Committees (IBCs) cannot give final approval of a protocol until the RAC has reviewed the protocol or determined that the protocol raises no new issues and full RAC review is not needed. The advantage of RAC reviews are that they are public, so new issues can be brought to a public forum for discussion. The RAC has stated:

> Public discussion of human gene transfer experiments (and access to relevant information) shall serve to inform the public about the technical aspects of the proposals, meaning and significance of the research, and significant safety, social, and ethical implications of the research. RAC discussion is intended to ensure safe and ethical conduct of gene transfer experiments and facilitate public understanding of the novel area of biomedical research.[7]

The local IRB, which must approve all federally-funded research involving humans and protocols submitted with IND applications to the FDA, also plays a role in oversight. Federal requirements stipulate that the informed consent documents approved by the IRB contain information about the purpose of the study, a description of what is involved by participating in the trial, the potential risks, potential benefits and alternatives to participating in the research, a statement about the confidentiality of records, a statement about compensation for injury, a contact person to whom questions can be directed, and a statement that participation is voluntary. [8]

The oversight of SCGT studies in the U.S.A. has not been without controversy.[9] The tragic death of Jesse Gelsinger in 1999 led to renewed scrutiny of regulatory procedures and uncovered significant gaps in the current oversight system[10] and steps were taken to rectify deficiencies in the system. Although some complain about duplication of effort and sometimes confusing instructions from both agencies, there are some advantages to the oversight by both the FDA and the RAC. The FDA, regardless of funding source, must review and approve all gene transfer trials. However, FDA reviews are not public. The RAC's reviews are all public; however, privately-funded protocols are not required to submit be to the RAC.

With regard to IGM specifically, the RAC has stated that they will not entertain protocols involving germ line gene transfer (GLGT) at this time.[11] And although the FDA has not explicitly made the same statement, it stopped fertility clinics in the U.S.A. from performing ooplasm transfer as a method of treating infertility in 2001, citing safety concerns. In this procedure, ooplasm from a normal donor egg is injected into the egg of a woman who had previous failed *in vitro* attempts due to poor embryo development. The theory behind the procedure is that the ooplasm from the donor introduces some unknown beneficial components into the recipient's oocytes. As a result of this procedure, the embryo had three genetic parents – the nuclear DNA from the two parents (as is normal), and the mitochondrial DNA from the mother and the donor of the ooplasm. The authors of the major research paper on the technique cited this as "the first case of human

germ line genetic modification resulting in normal children."[12] The FDA sent a letter to all fertility clinics in the U.S.A. stating that the FDA has jurisdiction over "the use of human cells that have received transferred genetic materials by means other than the union of gamete nuclei."[13] Additionally, the FDA stated that:

> The FDA feels further public discussion is necessary to: 1) evaluate the potential risks of this procedure, 2) recommend how safety should be monitored, 3) assess how efficacy might best be determined, and 4) determine what further non-clinical data will be needed to support additional human clinical trials.

Thus both agencies have acknowledged the need for public discourse regarding gene transfer studies. What would constitute adequate background research such that the FDA or the RAC would consider a human IGM trial is not clear at this point since neither group has issued any guidance. But the assumption is that, at least in the U.S.A., clinical trials of IGM could not occur without prior approval of at least the FDA (and the RAC if federally funded), and an IRB-approved informed consent process in place, and some public discourse. It is worth noting that IRBs will likely vary considerably regarding their expertise and knowledge about IGM, calling into question the robustness of the informed consent process. Julie G. Palmer has developed a draft consent form for a hypothetical IGM trial illustrating how complex the information and consenting process could be.[14] Thus it will be important for an individual or couple considering IGM to understand that they are participating in a research protocol with all that involves. There will likely be a team of health care professionals, researchers, and scientists with whom the couple will interact. There may be follow-up studies that are required to monitor outcomes or psychologic impact.

Who will provide the information needed by a couple to make an informed decision about proceeding with IGM? The principal investigator in a research protocol is ultimately responsible for the conduct of a clinical trial; however, most researchers are not trained in the skilled communication processes that counseling for IGM will likely require, as discussed more fully below. Additionally, the relationship between researcher and subjects in any clinical trial can be complex and sometimes conflicting. Whereas the researcher has a vested interest in the research itself and in furthering scientific and medical information, the subject is motivated by an entirely different set of factors and expectations. A health care professional not directly involved in the research project who can provide complex technical and risk information in a context that is meaningful, and who has the counseling and communication skills necessary to provide support throughout the decision-making process would be more helpful to the couple or individual.

12.4 Counseling issues in IGM

Individuals or couples who might consider the use of IGM will need extensive information and counseling in order to make an informed decision about

participating in an IGM trial. There will be a great deal of factual information that will need to be understood and numerous personal issues resolved. First, an at-risk couple, will need to fully understand their genetic situation and their risks of having an affected child. Given the risks of their particular situation they will need to know all of the alternative reproductive options available to them including adoption, conceiving using donor gametes, prenatal diagnosis, and PGD. The relative risks, benefits, burdens, merits, and limitations, both physical and psychologic, of each option will need to be weighed against IGM. The couple will need to weigh the possibility of future treatments for the disorder they are trying to prevent, including the possibility of SCGT for their child, against intervening or trying to prevent the disorder in the first place. If the individual or couple considers IGM as a viable alternative, they should understand the ethical and moral dilemmas that have been raised. Even if they do not adhere to any one position or find a particular option morally objectionable, as potential early adopters of a controversial experimental procedure, they should be aware of what the public perceptions are and what the public discourse has been. They also must clearly understand that they are participating in research rather than receiving a proven therapeutic technique.

Additionally, before participating in an IGM trial, the individual or couple must have full disclosure of the risks and benefits of the procedures they are considering. Theoretically, there are several ways one could introduce a gene into the germ line and the relative risks, benefits, and limitations that a couple will need to consider will depend on which approach is being proposed, as well as the supporting technologies that might be employed. For example, IVF, PGD, or follow-up prenatal diagnosis could be recommended depending on the technique in question; the risks involved with those procedures also must be factored in.

Clearly this is a great deal of information to impart and for a couple to digest and process. These discussions are likely to require multiple sessions that may extend over a long period of time, depending on how much knowledge and previous experience the couple has at the beginning of this process.

12.4.1 Techniques involving embryo manipulation

Some feel the most straightforward approach technically to altering the human germ line will be to introduce the gene into egg or sperm cells, a fertilized egg, or preimplantation embryo. For example, one way this might be approached is that eggs retrieved from a woman who has undergone hyperstimulation could be fertilized using standard IVF procedures. The new genetic material could be injected directly into the fertilized egg or at very early stages of cell division. Alternatively, the embryos might be grown in culture until they reach the blastocyst stage, at which point embryonic stem (ES) cells are removed and the gene introduced. The modified ES cells could then be induced to differentiate into

gametes used for fertilization or the nucleus of a modified ES cell could be inserted back into an egg cell with its own nucleus removed and the resulting embryo transferred into a woman's uterus to initiate a pregnancy.[15]

Regardless of the specific approach, most advocate that IGM should not be considered until techniques to replace one gene cleanly with another, without leaving any trace behind, are developed. By cleanly replacing one gene for another, the introduced gene will, presumably, insert into the genome at the place where it will be under appropriate regulatory control, resulting in normal gene expression. How accurately and consistently this can be accomplished, however, is uncertain.

Other approaches envision adding one or more genes into the embryo via an artificial chromosome.[16] It has even been suggested that these could be engineered with regulatory features that would enable the recipient child to decide at a later time whether to activate the added genes or not, thus avoiding some of the criticism of IGM regarding the lack of informed consent of the recipient.

IGM techniques that involve manipulation of gametes or embryos allow some opportunity to test for unanticipated outcomes. Follow-up testing of an embryo using PGD could prevent an embryo from being transferred that had not incorporated the new gene or chromosome correctly. Prenatal diagnosis and monitoring the pregnancy with ultrasound might provide additional opportunities to look for obvious problems. However, PGD and prenatal diagnostic techniques are limited in their ability to detect genetic abnormalities, and ultrasound can detect only the most obvious structural fetal defects. Thus, an error introduced by IGM may very well not be detected until its effect made itself known, which is potentially not for some time. In addition to the risks of IGM are the risks of the supporting assisted reproductive technologies including IVF, embryo cryopreservation, intracytoplasmic sperm injection (if it is performed), and PGD.

12.4.2 SCGT approaches

Theoretically, a gene could be delivered to the reproductive tissue of the parent using the same techniques that are currently being employed to deliver genes to other tissues in SCGT trials. The major problem with this approach is that it is subject to all of the technical difficulties and risks inherent in SCGT – selecting and designing a vehicle that delivers the gene and its regulatory elements to the targeted tissue, without widespread dissemination to other tissues, but with a high enough efficiency that most of the reproductive tissue incorporates the gene, and achieving stable gene expression and maintenance. Many feel that the technical challenges and risks of the SCGT approach will be difficult to overcome. However, some who may want to consider IGM, but object to the approaches outlined above because they involve manipulating embryos, may be more amenable to SCGT.

In summary, all of the techniques proposed for IGM are fraught with significant technical difficulties and risks, and many require supporting technologies that in and of themselves have inherent risks. Whether IGM involves gene replacement or gene addition, the potential risks and unknowns are considerable. An error in gene replacement could result in an undetected mutation whose effect may not be apparent until the child that resulted from that procedure become an adult, or perhaps not even until a later generation. Techniques that involve adding genes, whether they insert into the resident genome or reside in artificial chromosomes, involve additional risks due to the difficulty of ensuring the appropriate gene regulation and stability across generations. Although this discussion began with the assumption that IGM technology had advanced to the point in animal studies where clinical trials in humans could be ethically offered, animal studies can never completely predict risk in humans. Any individual or couple considering IGM would have to be willing to accept the risks of the IGM procedure, as well as all of the supporting and follow-up technologies. How well-known those risks are or whether they can be quantified in any reasonable or helpful way is questionable. Thus, the couple or individual will also need to be able to accept a considerable level of uncertainty.

12.4.3 Decision-making and IGM

How will individuals or couples weigh their options? They will come to this decision with diverse psychologic and moral frameworks and rich personal histories. Understanding these frameworks will be critical in helping individuals and couples work through decision-making in choosing between reproductive alternatives. Decision-making around *any* pregnancy, childbirth, and parenthood is laden with biologic, psychologic, and social significance,[17] even without the additional burden of being at risk of having a child affected with a severe disorder or of making decisions about complex and controversial technologies. Reproductive decision-making in the context of a risk for an abnormality is influenced by an individual's view of self, previous experience, family and social environments, experience with the disorder, ethnic and cultural background, the value and meaning placed on parenthood and family, coping strategies, problem-solving abilities, and religious and moral beliefs. It is a complex process that occurs over time and is made even more difficult when all of the outcomes of the available options are not knowable or foreseeable, as in the case of IGM.

Do we have any experience in reproductive decision-making in other arenas that provide some guidance as to how couples faced with the decision to undergo IGM may respond? An extensive body of literature has developed over the 30 years that prenatal diagnosis has been available which documents the complexity of the issues related to reproductive decision-making. Various studies have shown that direct experience with a disorder, the magnitude of the perceived risk, the perceived severity of a disorder, the desire to have more children, the

availability of prenatal diagnosis, and the acceptance of termination as an option all influence reproductive decisions and the acceptance of prenatal diagnosis.[18] Once a decision has been made the couple may experience additional anxiety or distress. For example, P.G. Frets *et al.*, found that the availability of prenatal diagnosis influenced the decision to have children for at-risk couples.[19] However, of significance is that those couples for whom prenatal diagnosis was available reported their decision-making as being more burdensome than those couples without this option. Thus, prenatal diagnosis did not provide an "easy way out."

PGD is the technique most similar to proposed IGM techniques. However information about decision-making for PGD is scant. PGD is not a simple procedure; it involves hormonal stimulation to retrieve multiple eggs, complex analysis of the embryos, and cryopreservation of excess embryos, yet results in a low "take home" baby rate. Even in the best hands, the probability of achieving a live birth from a combined IVF/PGD attempt is only about 20%. Undertaking IVF and PGD therefore requires considerable dedication and resources on the part of the family and the team of clinicians and scientists providing the services. A very small study of clients who had undergone PGD, half of whom had prenatal diagnosis in a previous pregnancy and 36% of whom had a previous pregnancy termination, found that PGD was an acceptable alternative to prenatal diagnosis, but it was by no mean an easy solution. In fact, 35% of clients who had had both prenatal diagnosis and PGD found PGD *more* stressful than prenatal diagnosis.[20] In 2003, the Genetics and Public Policy Center at Johns Hopkins University conducted interviews with selected key informants about the development and use of reproductive technologies, including IGM. Included were 10 women who had had PGD for a single gene disorder. Although very supportive of the technology, these women expressed surprise at the low success rate of IVF – they had assumed that because they were fertile, they would have greater success in achieving a pregnancy – as well as dismay at the failure rate of being able to make a diagnosis based on a single cell. Once a pregnancy was achieved, these women expressed significant reluctance in putting the pregnancy at additional risk by doing confirmatory prenatal diagnosis.[21]

People's perceptions of their own risk will influence their reproductive choices.[22] How an individual views her risks and the value and weight given to alternatives solutions is not at all straightforward. Risk perception is not just an understanding of objective, numeric information, but a more qualitative process of how that number is internalized and understood.[23] Factors that can influence risk perception include previous experience, how readily possible outcomes can be brought to mind, the implications of those outcomes, and how optimistic or pessimistic a person is, to name a few. For example, 35 is the commonly accepted age to offer prenatal diagnosis because it is at that age that the risk of miscarriage from the procedure begins to equal the risk that a woman will have a live birth with a chromosome abnormality. These guidelines assume, however, that women value these two adverse outcomes equally. In fact, some studies have shown that

when women consider just these two outcomes, on average, women considering prenatal diagnosis view chromosome abnormalities as 22% worse than miscarriage[24] and that when other possible outcomes are added, the value that women place on information outweighs all other risks,[25] thus calling into question the rationale for age 35 as the cut-off for offering prenatal diagnosis.

Personal experience with a disorder can also significantly influence an individual's views of reproductive options. In the hypothetical genetic situation that we have been considering – a couple both of whom are affected with an autosomal recessive condition or one parent homozygous for a dominant gene – the couple will come to this situation with a lifetime of complex experiences related to their own conditions, including whether if they even consider it to be something that needs "preventing." This will significantly impact their perceptions of the risk of having a child with a condition similar to theirs, balanced against future medical options for that child. Studies evaluating the attitudes of affected patient populations toward reproductive technologies have found conflicting results. In 2001, Lidewij Henneman *et al.*, found that adults with CF and parents of affected children considered prenatal diagnosis an acceptable reproductive option in general, but would have found it difficult to make a personal decision to abort.[26] Similarly, Diane Beeson and Theresa Doksum reported on interviews with families with an individual affected with either CF or sickle cell anemia. When addressing the availability of carrier testing and prenatal diagnosis, they described what they call "experiential resistance":

> Family members become unwilling to equate the meaning of the life of a person with a genetic disorder to their disease, or even the suffering that may accompany it. They are unable to avoid seeing many other fulfilling dimensions of the life of an affected person.[27]

Another important aspect of their research was that this resistance was not fully articulated until some probing by the interviewer; thus simple surveys of the population or even cursory genetic counseling will miss the "essential elements of rational thought, moral concerns, and lived experience upon which counselees' resistance is based."[28]

These and other studies have been limited to examining carrier testing, prenatal diagnosis, or PGD, not specifically the use of IGM. There has been little research into how at risk families would view such technologies. Among the informants in the 2003 study conducted by the Genetics and Public Policy Center were adults affected with a genetic condition and parents of affected children.[29] One woman with achondroplasia said about the hypothetical use of IGM to prevent having a similarly affected child:

> I would not be for that. Nothing wrong with being a dwarf. It goes along the same lines of having these limbs lengthened. A dwarf is a dwarf … It's going to wipe out a lot of things. I mean, there's no such thing as the perfect world, but it sounds like these scientists are trying to make it a perfect world. There's no such thing as a perfect human being.

But a man with achondroplasia was more accepting of IGM:

I would say that would be a decision based on personal belief. Would I do that? No. But I would find it acceptable if somebody else did it … You know, you never know what battles people have internally, and you never know what it is like. So although I may disagree personally with some decisions, it's not my responsibility to put that on somebody else.

And from a woman with a teenage daughter with CF, regarding IGM to prevent CF:

I think it's fine; it's wonderful … If they could do something to fix the CF gene, it would just be remarkable the way it would just change the lives of 30,000 people we have living here in the United States, some of whom are truly suffering and not only they are, the families are.

A man with Marfan's who has affected children said about IGM for Marfan syndrome:

… I think that this could be something wonderful. If we could eliminate the genetic loci from any future generations, that would just be absolutely amazing. It would be truly beyond words.

How common are these sentiments? We really do not know. These individuals represented a small group of patients who self-selected to participate in this study. Additionally, a full discussion about the risks and limitations of IGM technologies was not provided as part of the interview. So although *conceptually* there was general support of the idea of eliminating destructive genes from the population, the question of *at what cost* was not fully explored in this study. Much more needs to be done to determine how these technologies are viewed in the patient population and how likely they are to avail themselves of them. It is also important to remember that what people *say* they will do when questioned, and what they will *actually* do when faced with the situation and full disclosure of the risks, can be two very different things. Before the gene for Huntington disease was identified, for example, studies showed a high interest in presymptomatic testing. However, the uptake of testing since the gene has been identified has, in fact, been low.

12.4.4 Counseling approaches

How does one approach counseling individuals or couples in this situation? Historically, there have been two basic approaches to providing genetic counseling in the reproductive context. One has been the teaching approach, which holds that the client is there for information only and the counselor's role is to educate. It assumes that decisions are made on the basis of a rational understanding of the information and that the client is able to make a decision if the information is presented in a factual and neutral way.[30] The second is the counseling or psychologic approach, in which it is believed that decisions are based

on complex interactions between the information and the subjective meaning of that information. Here the role of the counselor is to help the client work toward understanding the information in a meaningful way and as such the counselor is an active participant in the counseling session.[31] This approach provides a better opportunity for informed decision-making. Given the complexities of IGM and the many issues that an individual or couple would need to consider, it seems a better model to consider.

The central ethos of the counseling approach has been that the counselor is non-directive. This concept has been misunderstood as meaning that the counseling is value-neutral or that the counselor is prohibited from giving advice or being directive. A broader, and more correct interpretation, however, is that non-directive counseling is an approach that promotes client autonomy, and that counselors actively participate in the counseling session by utilizing various counseling models and techniques appropriate to the situation to foster decision-making. The key tenets of non-directive counseling – respect for the client, providing a safe and supportive environment, addressing emotional and psychologic issues, and utilizing interventions that support the client's autonomous decision-making skills – are certainly relevant in the context of providing counseling for IGM.[32]

Again, the clinical and counseling situations we have been considering presume that the reason for the IGM is to prevent a serious genetic defect in a child. In this situation the couple or individual faced with the decision will most likely be very familiar with the disorder and have had a lifetime of experience with the health care system. If IGM were being considered for enhancement purposes, however, it is clear that the experiences and motivations of candidate couples would be completely different. Trying to anticipate and develop an understanding of the experiential and psychologic framework that would motivate a couple to consider the use of such powerful technology for these reasons is more difficult, and providing appropriate guidance and counseling would be potentially infinitely more complicated.

12.4.5 Attitudes of researchers and health care professionals about IGM

How do the health care professionals caring for these families or who would provide the services feel about IGM? Isaac Rabino surveyed members of the American Society of Human Genetics on their attitudes about gene therapy. Although there was less support than for somatic cell therapy (64% as compared to 96% support for somatic cell therapies), the majority of respondents supported the use of IGM – with the caveat that it was proven safe and effective, and used to prevent serious disease but not for enhancement purposes.[33]

This was similar to findings in the 2003 interviews conducted by the Genetics and Public Policy Center that included PGD providers.[34] Among this

small group, there was general support for IGM although the need for a safe procedure was repeatedly emphasized. As one provider stated:

… I would not do it if the technique is not safe. It has to be super, super safe. But once it's safe, no, I wouldn't draw a line. I think it's up to the couple what they want to do with their babies, provided, obviously, that the baby's going to be accepted by society … [When discussing the future of IGM] Again, I don't know where society is going to be 10 years from now. I think 20 years ago people would not have been as accepting of sex selection as they are now. Society changes, and our feelings towards things change. And I think as science changes those boundaries, people tend to open up … I think people get comfortable with technology.

12.4.6 Attitudes of the general public about IGM

In addition to the key informant interviews, the Genetics and Public Policy Center conducted 21 focus groups in five locations around the U.S.A. in 2003 about what the public thinks, knows, and feels about reproductive genetic technologies, including IGM.[35] In contrast to the health care providers and even some of the patients interviewed and quoted above, a more cautionary tone was notable. Although support for the idea of eradicating serious diseases was frequently voiced, the potential downsides were well-recognized and articulated. One woman said about the possibility of correcting the gene for sickle cell anemia:

… treat the child so that they don't have sickle cell and their kids don't have sickle cell. … I think that is a good thing. I think I would recommend it.

But another woman discussing CF stated:

I like the idea of this one thing [CF], and maybe a few other life threatening, horrible disease kinds of things, but I know it would never stop.

This concern about a technology and its practitioners careening out of control was raised by many; for example:

It's all or nothing. If you've gone down this road at all, you've gone down completely. You can talk about matters of degree, but you're playing God.… if we can actually do it, I think that's great. But there is a lot of downside that goes with it. We're talking about the best intentions of medicine, and assuming that this is all going to be for good. But how many movies have we seen [with] so many nightmare scenarios of people manipulating this. So opening that door at all means its open, regardless of the degree.

The issue of social inequities was raised repeatedly:

I mean, obviously this is not going to be available to everybody, regardless of whether it's subsidized by insurance or whatever. There are going to be some people that are able to have super kids, or improved kids, and a lot that aren't.

And finally the larger question of how we view ourselves and our place in the world was expressed:

> People get caught up in making the perfect child. You are trying to create the perfect life and making the perfect child, and that is not synonymous.
>
> We are not meant to have a planet of complete, perfect individuals that are going to live to 100 years old.

When evaluating reproductive genetic technologies, including IGM, participants considered 6 key factors in determining the appropriateness of the technology:

1. whether embryos would be destroyed,
2. the nature of the disease or trait being avoided or sought,
3. technologic control over "natural" reproduction,
4. the value of suffering, disability, and differences,
5. the importance of having genetically-related children, and
6. the kind of future people desire.

That the public is deeply ambivalent about these technologies and concerned about the wider societal impact was also demonstrated in a survey done by the Genetics and Public Policy Center in 2004 of 4834 members of the general public.[36] Americans were much less approving of IGM than PGD or prenatal diagnosis to prevent the birth of a child with fatal disease and very few supported its use to have children with selected traits. Participants also expressed a high level of concern for some societal implications of all of these technologies.

12.5 Summary

This chapter began by acknowledging the hypothetical nature of the scenarios discussed. Indeed, there are those who would argue that the risks involved with IGM are such that even if technical issues are satisfactorily addressed (and that is a major qualifier in some people's minds), the larger ethical issues would preclude any use of IGM. Undoubtedly, IGM in humans will bring with it numerous questions, not the least of which is "for what purpose is it permissible?". This chapter does not address the very complex issues of parents seeking IGM for enhancement purposes. There are also large gaps in our knowledge of where stakeholder groups and the general public stand on the issues that IGM raises. More studies and public dialogue is needed to fully explore attitudes about IGM and the values that shape those attitudes.

If the debate about the use of IGM is to be meaningful, it should be grounded in real applications, not speculation. As the science moves forward, we should foster discussion about who might be a potential recipient of IGM, for what purpose and under what circumstances, in what setting, and at what cost. This

debate should be conducted in a public arena that includes not just scientists and ethicists, but the families who may be impacted, the health professionals who care for these families, policymakers who must address the many policy implications, and the general public.

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NOTES

1 Mark S. Frankel and Audrey R. Chapman, *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues,* prepared by the American Association for the Advancement of Science, Washington, DC, September 2000, http://www.aaas.org/spp/sfrl/projects/germline/report.pdf (last accessed 29 March 2005).

2 Christine Gicquel, Veronique Gaston, Jacqueline Mandelbaum, *et al.*, *In vitro* fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCN1OT gene, *American Journal of Human Genetics* 72 (2003), 1338–41; Roger Gosden, Jacquetta Trasler, Diana Lucifero, *et al.*, Rare congenital disorders, imprinted genes, and assisted reproductive technology, *Lancet* 361 (2003), 1975–7.

3 David B. Resnik, Holly B. Steinkraus and Pamela J. Langer, *Human Germline Gene Therapy: Scientific, Moral and Political Issues.* Austin, TX: R.G. Landes Company (1999); David B. Resnik and Pamela J. Langer, Human germline gene therapy reconsidered, *Human Gene Therapy* 12 (2001), 1449–58.

4 Genetics and Public Policy Center, Johns Hopkins University, Human germline genetic modification: issues and options for policymakers, 2005, http://www.dnapolicy.org (last accessed 31 March 2005).

5 U.S. Food and Drug Administration, Human gene therapy and the role of the Food and Drug Administration, September 2000, http://www.fda.gov/cber/infosheets/genezn.htm (last accessed 29 March 2005).

6 National Institutes of Health (NIH), Guidelines for research involving recombinant DNA molecules, April 2002, http://www.od.nih.gov/oba/rac/guidelines/guidelines.html, (last accessed 29 March 2005).

7 NIH, Guidelines for research involving recombinant DNA molecules.

8 Kennith Cornetta and Franklin O. Smith, Regulatory issues for clinical gene therapy trials, *Human Gene Therapy* 13 (2002), 1143–9.

9 LeRoy Walters, The oversight of human gene transfer research, *Kennedy Institute of Ethics Journal* 10 (2000), 171–4.
10 Cornetta and Smith, Regulatory issues for clinical gene therapy trials; Lynn Smith and Jacquelione F. Byers, Gene therapy in the post-Gelsinger era, *JONAS Healthcare, Law, Ethics, and Regulation* 4 (2002), 104–10.
11 NIH, Guidelines for research involving recombinant DNA molecules.
12 Jason A. Barritt, Carol A. Brenner, Henry E. Malter, *et al.*, Mitochondria in human offspring derived from ooplasmic transplantation, *Human Reproduction* 16 (2001), 513–16.
13 U.S. Food and Drug Administration, Biological Response Modifiers Advisory Committee (BRMAC), Ooplasm transfer as method to treat female infertility, briefing Document for Day 1, 9 May 2002, http://www.fda.gov/OHRMS/DOCKETS/ac/02/briefing/3855B1_01.pdf (last accessed 29 March 2005).
14 Julie Gage Palmer, Appendix A. Consent form for participating in a study of inheritable germline modification. In: Audrey R. Chapman and Mark S. Frankel (eds.), *Designing our Descendants: The Promise and Perils of Genetic Modifications.* Baltimore, MD: Johns Hopkins University Press (2003).
15 LeRoy Walters and Julie G. Palmer, *The Ethics of Human Gene Therapy.* New York: Oxford University Press (1997); Resnik, Steinkraus, and Langer, *Human Germline Gene Therapy*; Frankel and Chapman, *Human Inheritable Genetic Modifications*; Resnik and Langer, Human germline gene therapy reconsidered.
16 Gregory Stock and John Campbell (eds.), *Engineering the Human Germline.* New York: Oxford University Press (2000).
17 Jon Weil, *Psychosocial Genetic Counseling.* New York: Oxford University Press (2000).
18 E.E. Ekwo, J.O. Kim and C.A. Gosselink, Parental perceptions of the burden of genetic disease, *American Journal of Medical Genetics* 28 (1987), 955–63; P.G. Frets, H.J. Duivenvoorden, F. Verhage, *et al.*, Model identifying the reproductive decision after genetic counseling, *American Journal of Medical Genetics* 35 (1990), 503–9; P.G. Frets, H.J. Duivenvoorden, F. Verhage, *et al.*, Factors influencing the reproductive decision after genetic counseling, *American Journal of Medical Genetics* 35 (1990), 496–502; Weil, Psychosocial genetic counseling; Kenneth P. Tercyak, Suzanne B. Johnson, Shearon F. Roberts, *et al.*, Psychological response to prenatal genetic counseling and amniocentesis, *Patient Education and Counseling* 43 (2001), 73–84.
19 P.G. Frets, H.J. Duivenvoorden, F. Verhage, *et al.*, Analysis of problems in making the reproductive decision after genetic counseling, *Journal of Medical Genetics* 28 (1991), 194–200.
20 S.A. Lavery, R. Aurell, C. Turner, *et al.*, Preimplantation genetic diagnosis: patients' experiences and attitudes, *Human Reproduction* 17 (2002), 2464–7.
21 A. Kalfoglou, J. Scott, and K. Hudson, PGD patients' and providers' attitudes about the use and regulation of PGD, *Reproductive BioMedicine Online* 11 (2005), in press.
22 Bonnie S. LeRoy and A. Walker, Genetic counseling: history, risk assessment, strategies, and ethical considerations. In: Richard A. King, Jerome I. Rotter, and Arno G. Motulsky (eds.), *The Genetic Basis of Common Diseases.* New York: Oxford University Press (2002), 87–102; see also Rosemarie Tong, Traditional and feminist bioethical

perspectives on gene transfer: is inheritable genetic modification really *the* problem? (Chapter 9, this volume), and Jackie Leach Scully, Inheritable genetic modification and disability: normality and identity (Chapter 10, this volume).

23 Weil, Psychosocial genetic counseling.

24 Ryan A. Harris, A. Eugene Washington, David Feeny, *et al.*, Decision analysis of prenatal testing for chromosomal disorders: what do the preferences of pregnant women tell us? *Genetic Testing* 5 (2001), 23–32.

25 Miriam Kuppermann, David Feeny, Elena Gates, *et al.*, Preferences of women facing a prenatal diagnostic choice: long-term outcomes matter most, *Prenatal Diagnosis* 19 (1999), 711–6; Miriam Kuppermann, Robert F. Nease, Lee A. Learman, *et al.*, Procedure-related miscarriages and Down syndrome-affected births: implications for prenatal testing based on women's preferences, *Obstetrics and Gynecology* 96 (2000), 511–6; Harris, Washington, Feeny, *et al.*, Decision analysis of prenatal testing for chromosomal disorders.

26 L. Henneman, I. Bramsen, T.A. Van Os, *et al.*, Attitudes towards reproductive issues and carrier testing among adult patients and parents of children with cystic fibrosis (CF), *Prenatal Diagnosis* 21 (2001), 1–9.

27 Diane Beeson and Theresa Doksum, Family values and resistance to genetic testing. In: Barry C. Hoffmaster (ed.), *Bioethics in Social Context.* Philadelphia: Temple University Press (2001), 153–79.

28 Beeson, Bioethics in social context.

29 Unpublished data; see also Genetics and Public Policy Center, Johns Hopkins University, Human germline genetic modification: issues and options for policymakers.

30 Patrcia McCarthy Veach, Bonnie S. LeRoy and Dianne M. Bartels, *Facilitating the Genetic Counseling Process: A Practice Manual.* New York: Springer (2003).

31 McCarthy Veach, LeRoy, and Bartels, Facilitating the genetic counseling process.

32 J. Weil, Psychosocial genetic counseling in the post-nondirective era: a point of view, *Journal of Genetic Counseling* 12 (2003), 199–211; McCarthy Veach, LeRoy and Bartels, Facilitating the genetic counseling process.

33 Issac Rabino, Gene therapy: ethical issues, *Theoretical Medicine* 24 (2003), 31–58.

34 Unpublished data; see also Genetics and Public Policy Center, Johns Hopkins University, Human germline genetic modification: Issues and options for policymakers.

35 A.L. Kalfoglou, T. Doksum, B. Berhardt, *et al.*, Opinions about new reproductive genetic technologies: Hopes and fears for our genetic future, *Fertility and Sterility* 83 (2005), 1612–21.

36 Genetics and Public Policy Center, Johns Hopkins University, Human germline genetic modification: issues and options for policymakers.