GENOMICS AND NEUROLOGY

AN ETHICAL VIEW

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Jessica Blasko's review of genomic neurology clearly illustrates one of the most immediate consequences of the completion of the Human Genome Project (HGP). The HGP has resulted in a steady stream of new information and an exponential growth in the understanding of disease and its genetic basis. As Blasko notes, this increase in our ability to understand the influence of genetics on disease has far outpaced our ability to implement this information clinically. Indeed, many current ethical issues in genomic medicine stem from our ability to know but not to cure. For this reason, many of the ethical issues that arise in the context of genomic neurology will be similar to those raised by the impact of genomics on other areas of medicine.

Still, one could get the impression that there is something different about the potential impact genomic advances will have on the field of neurology. Perhaps it is the hypothesis that half of our genes are encoded in the brain; or maybe it is because we now know the brain has much more plasticity (the likely key to eventual cures in the area of neurology) than was long believed. Perhaps it is the hope that science will someday be able to prevent the devastating effects that degenerative neurological disorders have on our rational and autonomous capacities, which—though not a condition of our inherent and inalienable human dignity—are closely associated with what it means to be a human person.

The ethical issues raised by genomic medicine also seem to take on added complexity when they are considered in the context of neurology. In this article, I will examine some of the shared ethical issues of the "postgenome era" of medicine in light of the stirring potential and added complexity offered by genomic neurology and the guidance provided by the moral tradition in which the Catholic health ministry is rooted.

GENETIC TESTING AND NEUROLOGY

The steady flow of information arising from the HGP has resulted in a nearly ubiquitous trend in the postgenome era of medicine. The trend, unfolding within many subspecialties of medicine, is an increase in our ability to test for genetic disorders, or, more often, to screen for susceptibility to certain diseases with a genetic component. As already noted, therapeutic interventions, either curative or preventive, are lacking for many of the conditions for which genetic testing is available.

Clearly, this trend is occurring in the field of neurology, just as it is in other areas of medicine. As with many types of cancers, many neurological disorders—for example, most forms of Alzheimer's disease (AD)—are likely the result of a complex interaction of genes modifying other genes, as well as environmental factors acting on those genes. Just as in oncology, then, so must one resist the temptation in neurology toward genetic reductionism and the tendency to view genetic testing as the ubiquitous solution for all that ails us.[1]

Beyond the temptation toward genetic reductionism, another ethical challenge in the context of genetic testing and neurology concerns whether and when genetic testing for disorders for which there is no therapeutic intervention ought to be performed. This question is one that has been dealt with in the context of prenatal diagnosis for some time. In that context, an option sometimes offered to the parents, when there is no treatment for the pathological condition diagnosed, is termination of the pregnancy. While this option is contrary to the norm of respect for human dignity as understood within the Catholic moral tradition, there are morally valuable reasons to have prenatal testing when one does not intend to terminate the pregnancy.[2]

Likewise, there can also be good reasons in the context of neurology to have a genetic test for an untreatable condition, including:

- Psychological relief from uncertainty
- Improved personal planning (including reproductive decisions)
- Avoidance of harm arising from lifestyle changes
- Advanced care planning
- Preventive treatment of associated co-morbidities[3]

Whether these considerations justify genetic testing for diseases without a therapeutic intervention will need to be determined on a case-by-case basis in light of the disease in question and the circumstances of the individual patient.

COMPLEXITIES OF NEUROLOGICAL TESTING

Several factors give an added dimension of complexity to the question of when genetic testing in the context of neurology is appropriate. First, not all families and individuals will yield a positive test for some genetic conditions—for example, domi-

nant spinocerebellar ataxia—although those families may in fact have some form of the condition.[4] Thus the fact that a person receives a negative test result does not necessarily mean that he or she is free of that disease. A second difficulty lies in identifying appropriate candidates for testing in the first place. For example, patients with early-onset dystonia are better candidates for genetic testing than those patients with late-onset dystonia. And, third, there are certain genetic markers for which two different patients could both test positive, with one acquiring the disease while the other does not.

An inherent complexity of genetic testing is that the presence of a genetic risk factor is not a guarantee that the individual will actually acquire the disease. As Blasko points out, "In predictive genomic testing based on risk factors, one challenge is that each risk factor is just one of several factors likely contributing to the more common [neurological] diseases." These limitations also arise from gaps in our current state of knowledge, which may be due either to limitations in our understanding of the role of certain genetic mutations in the disease mechanism or to an incomplete genetic map of a particular disease. Nonetheless, physicians have an obligation rooted in beneficence to ensure that patients are appropriate candidates for a particular genetic test before recommending it.

Although significant, these limitations do not necessarily obviate the moral validity of genetic testing for neurological diseases. Rather, the implication of these limitations from an ethical perspective is twofold. First, when considering whether genetic testing is appropriate for a particular patient, one must distinguish between diagnostic testing to confirm a symptom-based diagnosis and presymptomatic screening (predictive testing). Genetic testing is often appropriate as part of the diagnostic workup of symptomatic patients, intended as it is to confirm more efficiently and with greater certitude the presence of a particular neurological condition, such as Huntington's disease or multiple sclerosis.

However, additional issues need to be considered when the screening is presymptomatic. Distinguishing between causal genetic mutations and genetic susceptibility is critical when considering presymptomatic screening. Presymptomatic tests for a single predictive genotype may not be appropriate for diseases with a multifactorial etiology.[5] For example, predictive testing for early-onset AD is not considered appropriate, except in families with autosomal dominant inheritance.[6] And the Ethics Committee of the American Geriatrics Society holds that genetic testing for late-onset AD should not become the standard of care.[7]

Testing, Informed Consent, and Counseling

The second implication of these limitations, when viewed from an ethical perspective, is that the informed consent process for genetic testing must be absolutely thorough and pristine. Physicians have an obligation, rooted in respect for human dignity, respect for autonomy, and the norms governing informed consent, to ensure that the patient *understands* the rationale for the testing in his or her particular case. The discussion with the patient should also include the ramifications of a positive or negative result concerning his or her prognosis, as well as its implications for family members (who may not themselves be consenting to the test).

Informed consent for genetic testing is generally—and should always be—obtained through the process of genetic counseling. The counseling process takes place over a series of pretest meetings with specially trained counselors and allows time for comprehension and deliberation.

The benefits of genetic counseling go beyond ensuring that truly informed consent is obtained; they extend into the posttest context. Genetic counseling ensures that the test results are accurately interpreted and understood. Genetic counseling in the posttest context also helps ensure that appropriate follow-up medical services—as well as necessary psychological, emotional, and social support—are available and coordinated. Subsequently, employers and society in general have an obligation rooted in respect for human dignity, the common good, and justice to ensure that any benefits coverage for genetic testing is accompanied by coverage for genetic counseling.

Not everyone is an appropriate candidate for gene testing.

Pre- and posttest counseling takes on even greater importance when the patient is a minor child or an adult suffering from a devastating neurological disease.

Human Subjects Research

Although, as Blasko informs us, animal models can be useful for elucidating the genes and proteins involved in human neurological pathogenesis, human subjects research (HSR) and randomized clinical trials will eventually be necessary in order to safely bring any therapeutic discoveries

to market. Obtaining informed consent from participants in HSR is inherently more complex than obtaining it for standard clinical treatments. This increased complexity arises from several factors.

While all informed consent is the culmination of a process rather than simply a signature on a form, informed consent for clinical trials is a *continuous process* occurring throughout the entirety of the trial.[8] Moreover, clinical trial protocols and informed consent forms are often very complex and not easy for even well-educated participants to understand. Because participation is usually sought in the context of a therapeutic relationship between physician and patient, potential participants may be apt to rely more on the recommendation of a physician than on their own assessment of the burdens and benefits. In some instances, patients might even feel intimidated by the expertise of the health care professional seeking their participation. Finally, some patients may be motivated by a misperceived therapeutic benefit—that is, they may assume that the trial is being conducted for *their* benefit, when it is actually being done for subsequent patients and for the common good.[9]

"Human subject research," called HSR, raises ethical questions.

Again, these issues take on an added complexity in the context of neurology.

Protecting Vulnerable Populations

Issues concerning informed consent are further complicated when an HSR participant has a degenerative neurological condition, such as AD. As a result of memory loss, which occurs even in early stages of AD, patients might comprehend information and quickly forget it, or even fail to remember that they consented to participate in a trial. Patients with AD also eventually lose the ability to communicate as the disease progresses. This decrease in the ability to communicate can make it difficult for physicians, researchers, and surrogate decision makers to detect side effects and associated burdens that the patient may be experiencing as a result of the experimental treatment.[10] It is not always clear how the changing preferences of patients who are losing decision-making capacity due to dementia should be honored.

The issue of proxy consent for participation in HSR trials on behalf of those with dementia raises several contentious issues. For example, a proxy's attitude may influence him or her to make decisions that are not truly in the patient's best interest. A loving adult child might give proxy consent as a last hope of (even minimal) therapeutic benefit, especially if the burdens to the participant go undetected. On the other hand, a bad relationship could result in a negative attitude, leading to indifference on behalf of the surrogate or proxy.[11]

Another contentious issue related to proxy consent concerns the concept of "maximal potential risk."[12] What threshold of potential risk should be permitted when a proxy is giving consent? Should proxy consent even be allowed in higher-risk research, especially when there can be no therapeutic value in it for the patient? Furthermore, is it ethical even to allow proxy consent when there may be intermediate treatments that can provide some symptomatic relief or slow the progression of the disease—when those intermediate interventions will not be part of the study?[13]

Stem Cell Research and Neurology

The ethical issues related to HSR in the context of neurology are not limited to challenges involved in obtaining ongoing consent in one or two populations. Indeed, one can hardly think of a hope for alleviating neurological disorders these days without also thinking of stem cell research. This association may not be without reason. As Blasko informs us, in the next 25 years or so, stem cell research may give us the ability to respond clinically to neurological disorders. Of course, here the relevant ethical distinction is between human embryonic and adult stem cell research.

From the Catholic moral perspective, there is nothing inherently immoral about genomic research in and of itself, nor is there anything necessarily wrong with adult stem cell research (so long as it is done in accord with the customary moral norms governing medical research). Rather, "the church respects and supports scientific research when it has a genuinely humanist orientation, avoiding any form of instrumentalization or destruction of the human being and keeping itself free from the slavery of political and economic interests."[14] In other words, the church does not view genomic science as "playing God" in the sense of usurping God's authority, though it can become so when misguided by hubris.

Rather, the church views genomics and other scientific engagements—when guided by and consistent with authentic human values—as a form of participation through the use of reason in God's ongoing act of creation. In short, conducting scientific research in service of the common good is one way human beings give life to what it means to image God.

The Catholic Church objects to *embryonic* stem cell research not because it is scientific or because it is manipulative of the human genome, but because it entails the destruction of human life—life that the church considers to be deserving of moral respect and protection. The question of whether the human embryo is a person deserving full moral respect—or, on the other hand, is simply human genetic material that may be used for the benefit of postnatal sentient human persons—has been at the heart of the public and scientific debate regarding embryonic stem cell research.

However, the significance bestowed upon this question could be considered misplaced from a Catholic moral perspective. The church's teaching is not predicated on the human embryo being a human *person*, but, rather, on the fact that the embryo is human *life*.[15] Moreover, this teaching is also predicated on the fact that science itself is not capable of answering the broader philosophical and theological question of when personhood properly begins. As Norman Ford describes the teaching, "for practical and moral purposes, the Church teaches that the fruit of human generation, from fertilization onwards, should be treated as a personal being, but at the same time stopped short of making an express philosophical commitment to the personal status of the zygote."[16]

The "Slippery Slope"

There is another, more practical reason that the debate about personhood can be considered misplaced. Regardless of whether one is willing to give personal status to individual embryos, treating even early embryonic human life as merely an instrument for the benefit of others ultimately leads to its commercialization, further eroding respect for life,[17] and to the very narrow precipice of a slippery slope. Imagine that in the next 25 years there are breakthrough embryonic stem cell treatments for Parkinson's disease, AD, spinal cord injuries, and stroke. Now imagine that these treatments require the destruction of a different human embryo for the production of stem cells each time one of them is used. After a while, the supply of "spare" embryos from the cryopreservation tanks of fertility clinics is quickly exhausted, while the demand for embryos inevitably increases.

The next viable source of three-to-five-day-old embryos would be "therapeutic cloning"—the creation of human embryos, through somatic cell nuclear transfer, for nonreproductive purposes, which some countries already allow. In this scenario, unless technological advances reduce the number of ova needed for the isolation of stem cells, large numbers of them would be required. The commodification of human ova would very likely involve exploitation of women, especially those who are economically vulnerable. Moreover, if treatments should be discovered for some diseases using stem cells from cloned three-to-five-day-old embryos, would society be able to resist using the cells, tissues, and even organs from more developed clones, perhaps at the fetal stage of development, to cure other devastating diseases?

While "slippery slope" arguments rely less on logic and more on emotions evoked by hypothetical contingencies, the use of embryos in the service of "political and economic interests" would seem to have serious potential consequences for the acculturated moral attitudes of society towards human life itself.

Still, there is another slippery slope of which one must be wary, regardless of whether breakthroughs in the treatment of neurological disorders come from embryonic or adult stem cell research. As Blasko suggests, science may one day be able to introduce new genes, or modify existing ones, to make proteins that our brains need for improved functioning. If this ability becomes a reality, then so too will the potential for misusing the technology for enhancement purposes, rather than for strictly therapeutic purposes.

> Treating even embryonic human life as an instrument erodes respect for life.

Although it is unlikely that research would be undertaken with this specific end in mind, new enhancement interventions would likely appear as "off-label" applications of legitimate therapeutic interventions.[18] This is not strictly a hypothetical proposition. The issue has already arisen regarding human growth hormone.[19] There are generally five types of potential genetic enhancements, of which several directly involve the brain and neurology in some fashion:

- An increase in physical size
- A decrease in the need for sleep
- "Prolongevity" (extending life)
- A suppression of aggressive behavior
- An improvement in memory and general cognitive ability[20]

From an ethical perspective, the potential for neurological therapies and enhancements using genomic technologies lends an added dimension of complexity to existing questions regarding the just distribution of access to health care services and resources. For example, what portion of our

health care resources should be dedicated to stem cell and other forms of genomic research for new therapies when 46 million Americans lack access to basic preventative medical care on any given day? Moreover, will society ensure that the benefits of genomic research are distributed fairly and justly, or will advances in genomic technology only exacerbate an already unjust system of distributing access to health care and health care resources?

In the context of neurology, genomics, and stem cell research, these issues tend to be overshadowed by the debate regarding the moral status of early embryonic human life. However, in the future, we may also be faced with the challenge of ensuring the fair, equitable, and just distribution of the very traits and capacities associated with what it means to be a human person. ■

NOTES

1. For an ethical analysis of genetic testing in the context of oncology, see Carol Bayley, "Cancer and Genetic Medicine: An Ethical View," *Health Progress*, vol. 86, no. 5, September-October 2005, pp. 35-37.
2. Carol Tauer, "Obstetrics and Pediatrics: An Ethical View," *Health Progress*, vol. 86, no. 4, July-August 2005, pp. 13-18.
3. Michael Burgess, "Beyond Consent: Ethical and Social Issues in Genetic Testing," *Nature Reviews*, vol. 2, no. 2, February 2001, pp. 147-151.
4. Regarding this and the subsequent limitations discussed in this paragraph, see Henry L. Paulson, "Diagnostic Testing in Neurogenetics: Principles, Limitations, and Ethical Considerations," *Neurologic Clinics of North America*,vol. 20, no. 3, 2002, pp. 627-643.
5. Steven Hersch, Randi Jones, Walter Koroshetz, et al., "The Neurogenetics Genie: Testing for the Huntington's Disease Mutation," *Neurology*, vol. 44, no. 8, August 1994, pp. 1,369-1,373.
6. Jill Goldman and Craig Hou, "Early-Onset Alzheimer Disease: When Is Genetic Testing Appropriate?" *Alzheimer Disease and Associated Disorders*, vol. 18, no. 2, April-June 2004, pp. 65-67.
7. Ethics Committee of the American Geriatrics Society, "Genetic Testing for Late-Onset Alzheimer's Disease," *Journal of the American Geriatrics Society*, vol. 49, no. 2, February 2001, pp. 225-226.
8. J. Cohen-Mansfield, "Consent and Refusal in Dementia Research: Conceptual and Practical Considerations," *Alzheimer Disease and Associated Disorders*, vol. 17, supplement 1, April-June 2003, pp. S17-S25.
9. Elaine Steinke, "Research Ethics, Informed Consent, and Participant Recruitment," *Clinical Nurse Specialist*, vol. 18, no. 2, March-April 2004, pp. 88-95.
10. Mary Ann Sevick, Terrance McConnell, and Melissa Muender, "Conducting Research Related to Treatment of Alzheimer's Disease," *Journal of Gerontological Nursing*, vol. 29, no. 2, February 2003, pp. 6-12.
11. Cohen-Mansfield.
12. Concerning this concept and the subsequent questions associated with it, see Stephen Post, "Full-Spectrum Proxy Consent for Research Participation When Persons with Alzheimer Disease Lose Decisional Capacities: Research Ethics and the Common Good," *Alzheimer Disease and Associated Disorders*, vol.17, supplement 1, April-June 2003, pp. S3-S11.
13. Sevick, p. 11.
14. Pope John Paul II, "Address to the Pontifical Academy for Life," *Acta Apostolicae Sedis*, vol. 95, no. 9, 2003, pp. 589-592.
15. Congregation for the Doctrine of the Faith, "Donum Vitae," *Catholic International*, vol. 12, no. 2, 2001, pp. 99-109, Part I, Section 1.
16. Norman Ford, "The Human Embryo as Person in Catholic Church Teaching," *National Catholic Bioethics Quarterly*, vol. 1, no. 2, Summer 2001, pp. 155-160.
17. See Lisa Sowle Cahill, "Stem Cells: A Bioethical Balancing Act," *America*, vol. 184, no. 10, March 26, 2001, pp. 14-19.
18. Eric Juengst, Robert Binstock, Maxwell Mehlman, et al., "Biogerontology, 'Anti-Aging Medicine' and the Challenges of Human Enhancement," *Hastings Center Report*, vol. 33, no. 4, July-August 2003, pp. 21-30.
19. Peter Conrad and Deborah Potter, "Human Growth Hormone and the Temptations of Biomedical Enhancement," *Sociology of Health & Illness*, vol. 26, no. 2, March 2004, pp. 184-215.
20. LeRoy Walters and Julie Gage Palmer, *The Ethics of Human Gene Therapy*, Oxford University Press, New York City, 1997, Chapter 4.