Entering the Age of the New Genetics with Eyes Wide Open

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A concerted international effort currently is being made to localize human genes and to identify their role in specific diseases. This will enable physicians to test for a broader range of genetic characteristics and to manipulate human somatic and germ-line cells. With this new age of genetics comes a host of ethical issues and questions.

Introduction

Richard is 2 years old and his uncle just died from Huntington's disease. His parents read in *Reader's Digest* that a simple blood test could determine if he, too, will develop Huntington's disease.

Malia, 35, is 10 weeks pregnant. She is requesting "genetic testing" on her fetus because she and her husband want to have "the perfect family."

Susie is 21 and from Cleveland; she has been dating your patient Kimo. They recently visited her family on the Mainland, including a few cousins with cystic fibrosis and now Kimo is concerned that Susie may be a carrier. Today she presents at your office asking to be screened for the cystic fibrosis gene.

Any one of these patients may present at the physician's office with questions concerning medical genetics. Questions which hitherto had been prefaced with *if* and *when* have now burst forth as the issues for the here and now. Ready or not, primary care physicians will move to the frontlines of this genetic revolution as they manage their patients' requests and needs for genetic services.

Genetic Testing

Genetic screening is generally used in two arenas: 1) testing of presymptomatic individuals for medical treatment, and 2) testing of couples for reproductive decision making. Ideally, in the former case, people learn they have a genetic disorder and then receive effective treatment through conventional medical or genetic therapy. And in the latter, couples can decide whether they will risk conception, terminate a pregnancy, or prepare for the birth of an affected child.

Why Test if There is No Cure?

Almost everyone agrees that presymptomatic testing is appropriate when an intervention is efficacious when started before symptoms appear.[1] But is testing beneficial when no cure for the disease is available?

For example, Huntington's chorea is an autosomal-dominant disease that usually cannot be clinically diagnosed until the fourth or fifth decade of life. But it can be genetically diagnosed in an asymptomatic individual. Unfortunately, no cure exists for this mentally and physically debilitating condition yet. Individuals have approached their physicians requesting testing for themselves or their offspring hoping that they are not at risk. Usually they are unaware of the emotional and social harm stemming from a positive test result.

Some studies suggest that as many as one in 10 patients who test positive for the Huntington's disease mutation never make a full emotional recovery.[2] Even with professional counseling, a few have had to be hospitalized for severe depression and some have even committed suicide.

Individuals who test positive may be stigmatized. In the past, large screening efforts were made for sickle cell traits, Tay-Sachs disease, and Alpha$_1$-antitrypsin deficiency which led to adverse psychological consequences for parents of affected children. They felt afraid, worried, and anxious.[3] Carriers of the sickle cell trait were stigmatized as being undesirable marriage partners and were socially ostracized.[4] Additionally, children who test positive may become scapegoats who are abused because they remind their parents of their own unacceptable traits.[5]

Similarly, Dr Bruce Ponder, who has been seeking the genetic marker for breast cancer at Cambridge University, worries that patients who test positive for cancer might actually increase their cancer mortality. Positive test results, by triggering depression, may actually worsen a patient's chances of survival.[2] Emotional stress, disturbed sleep patterns, and decreased appetite may all contribute to a diminished immune response and hasten disease progression.

On the other hand, a large study conducted in Canada suggested that knowledge of disease status can actually improve the quality of life. After they requested testing for Huntington's disease and learned of their risk, many patients reported improved well-being, less anxiety, less depression, and general improvement in their psychological status than when they were living with uncertainty.[6]

Clearly, for some people living with ambiguity is worse than bad news. For these individuals a case can be made for testing even if there is no cure. For others, ignorance is preferable to knowledge of impending disease. Those who request testing will need counseling and education regarding how the test result might affect them.

Primary care physicians are familiar with patients requesting a variety of diagnostic tests and medical therapies. They know

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their patients well, and they are skilled at helping them understand the risks and benefits of medical services. When necessary, they do not hesitate to discourage certain patient requests believing that more harm than good would result. These patient-care skills, coupled with an understanding of the new genetics, will allow the primary care physician to assume the lead advisory role with regard to genetic testing.

Will Genetic Testing Enforce Fatalistic Attitudes?

Some critics have condemned the overemphasis, particularly in the media, on genetic causes of behavior and disease. They speak of the *geneticization of society* and argue that over-expenditure of resources on genetic research will be at the expense of basic social needs, such as food, shelter, and routine prenatal care.[7] *Over-genetization* can adversely affect individuals and frustrate the physicians who work with them.

Both genetic predispositions and environmental influences bear on a patient's health. Yet some fatalistic patients blame their lack of health on everything except their poor life-style choices. Armed with knowledge of genetic markers for diseases like alcoholism and obesity, these patients will deny responsibility for their conditions all the more and may stubbornly refuse to participate in their health care.

If patients test negative for breast cancer, would they conclude that they no longer need routine breast examinations? If a patient were determined to be susceptible to coronary heart disease because of his or her genes, might this cause him or her to ignore dietary and exercise advice? To the extent that genes are seen as more important than the environment, our actions may be viewed as genetically determined, rather than as a result of free will. For example, some criminals have attempted to use the *XYY defense* arguing that their genetic composition predisposed them to criminal activities beyond their control. The XYY defense generally has been rejected in court.[8]

The focus on *genetic disease* should not pull society away from personal responsibility. Fortunately, most patients understand how life-style choices affect their health. When reporting results of genetic screening to their patients, physicians must reinforce the notion that genetic predisposition is but one determinant of disease and emphasize suggestions for minimizing disease expression.

Will Defective Genes Invite Discrimination?

Predictive genetic testing reveals asymptomatic conditions that can manifest themselves later in life or can remain unveiled. This information is not only of interest to patients and their physicians but also to their prospective employers and insurers. A recent article described 41 cases of discrimination against otherwise healthy people based solely on their genetic risk. In most cases, the victims were refused health or life insurance. Some were refused jobs; others were banned from adopting children.[2] According to a 1991 survey conducted by the Congressional Office of Technology Assessment, only 12 of 330 *Fortune 500* companies reported they were conducting genetic monitoring or screening. Roughly half of these executives thought genetic monitoring or screening would be acceptable, either for the benefit of the employee or the employer.[9]

The Americans with Disabilities Act (ADA) ensures that handicapped individuals are not discriminated against in the job market. Applicants are considered qualified if they are able to meet all the program's requirements in spite of their handicap. Additionally, the employer could be required to provide reasonable accommodations to make employment possible. However, the Equal Employment Opportunity Commission, the federal agency for enforcing the ADA, has stated that "physical or mental impairment" does not include "characteristic predisposition to illness or disease."[10] This narrow construct could mean healthy people can be denied opportunities based on conditions to which they are predisposed, while the symptomatic are protected from discrimination. This is unfair and irrational.

Consider insurance companies. Currently insurers may be satisfied with gleaning information from genetic tests already performed and will undoubtedly be gathering this information from applicants through questionnaires or medical records. Already children with genetic disorders may lose their health insurance when they become adults; this potential loss has often prompted geneticists to avoid seeking a definitive diagnosis.[7] Thus far, state insurance commissions in the United States have placed genetic information in the same category as other types of medical information that insurers could legally require as a condition of insurance.[7] However, legislation has been introduced in several states to allow people to keep genetic information, including family histories, from insurers.[6] Such legislation would help protect people from discrimination, but may overburden insurance companies, especially life insurance companies, in their underwriting practices. Insurers have argued that if they cannot access an applicant's genetic profile they will be at an unfair disadvantage—some individuals, on learning that they could develop a serious condition, will buy large amounts of insurance.[10]

Patients with genetic predispositions to disease must have the right to pursue happiness through financial stability and productivity. Employers and insurance companies have the right to make a profit. In the new genetics, a victory for society should not be at the expense of any of these players. Insurance companies should provide coverage for those with genetic risks, with such policyholders paying modestly higher premiums for their coverage. Employers should hire these people and when reasonable they should accommodate their predispositions. For example, if current or prospective employees test positive for $Alpha_1$-antitrypsin deficiency, reasonable accommodations ought to be made for them to avoid contact with noxious inhalants.

Should Carriers of Serious Genetic Disorders Burden Society with Their Offspring?

In a 1990 general population survey, 39% of the respondents believed that "every woman who is pregnant should be tested to determine if the baby has any serious genetic defects." Twenty-two percent thought that, regardless of what they would want for themselves, "a woman should have an abortion if the baby has a serious genetic defect." Nearly 10% believed a poor woman should be required by law to have an abortion rather than have the government pay for the child's care.[11]

As health care becomes increasingly rationed, taxpayers could resent having to pay for the support of disabled children if their births could have been prevented. If a woman undergoes a prenatal diagnosis and then decides to carry to term a baby with a serious, incurable, and costly problem she may be socially scorned. She could, of course, refuse prenatal diagnosis, but she would still be considered irresponsible for doing so. But many genetic tests contain only crude predictive value. A positive result often cannot predict the extent of potential penetrance and expression of a defective gene in an individual. A society that coerces women into having abortions based on the results of

genetic tests will force "throwing out many healthy babies along with the bathwater." Private insurance companies in the United States have already tried to withhold reimbursement for medical care of children with cystic fibrosis who were diagnosed before birth and whose parents refused to abort. Thus far, state insurance commissioners have prevented this type of discrimination.[11]

Can a culture that places such high value on a woman's right to choose abortion even consider limiting her right to choose life?

What is Normal?

People are special because they possess unique genetic characteristics expressed as strengths and weaknesses. Individuals and societies pencil the fine line between what is distinctive and extraordinary and what is peculiar and unacceptable. Prenatal genetic screening allows parents to make decisions for selective abortion. Some insist that parents should have full autonomy to terminate pregnancies for babies that seem inferior. Others argue that babies should be protected from those who would reject them because they do not meet an arbitrary standard.

The vast majority of Americans believe couples should have the right to abort a seriously defective fetus. About 80% would terminate a pregnancy if they were told their fetus had Down's syndrome. A survey of parents of children with cystic fibrosis showed that 20% would abort for cystic fibrosis, 17% would abort for incurable disorders starting at age 40, and 7% for those starting at age 60.[12] Greater than one in 10 would abort for obesity and another 2% to 3% would terminate a pregnancy if their fetus were diagnosed to have treatable diseases like cleft palate or nearsightedness. Some parents even feel that the sex of a child is relevant. A recent study of American genetic counselors concluded that a large percentage would perform prenatal testing for the sole purpose of sex selection.[13]

How would limits be placed on selective abortion? In an agricultural society, genes with potential for physical deftness rather than intellectual prowess would be valued. For the academic, the opposite might hold. For some couples, reproductive decisions can center on cosmetic issues and pregnancies could be terminated because of straight-hair genes or lack of height. Ideas such as *normal* and *disabled* are rooted in shifting societal values; even if restrictions for abortions after prenatal diagnosis were legalized, the determination of these boundaries would be formidable.

This analysis may seem out of place in a society that permits abortion on demand. And it would be pointless were it not for the impact of physician counsel on patient decisions. In a recent study, the parents whose doctors approved of an abortion for cystic fibrosis were nearly twice as likely to abort for cystic fibrosis than those parents with disapproving doctors.[14] Well-informed, compassionate, and insightful physicians ought to assist patients in their own understanding of what normalcy is and guide them to make appropriate decisions.

Who Should Offer Genetic Services?

Many believe that genetic specialists should be the ones offering counseling and screening services.[2] Geneticists are concerned that most physicians are not familiar with genetic concepts and lack the tools to serve as effective counselors. They demand a minimum of graduate-level training as a prerequisite. A recent study found that many primary care physicians, especially those who are not exposed regularly to genetics, are not familiar enough to serve as competent counselors.[15]

Although it is reasonable to assume that geneticists are more familiar with all the nuances in their field, it is equally true that primary care physicians are more informed about their patients' individual and family needs and desires. These physicians can familiarize themselves with pertinent issues regarding the new genetics. But not every genetics counselor can come to know patients and their families with the intimacy their personal physicians can. Patients look to their primary care doctors to interpret many other laboratory tests and to give appropriate advice. Well-informed physicians who understand the limits, benefits, and risks of genetic testing should play the central role as advocates and advisors for their patients.

Genetic Therapy

The goal of genetic manipulation is twofold: First, to repair or replace defective genes in somatic or germ-line cells; and second, to improve the genetic makeup of the sperm, egg, or early products of conception to improve the attributes of descendants. The former is considered correction; the latter, enhancement.

Gene therapy involves the manipulation of somatic or germ-line cells to alter their genetic composition. Germ-line engineering produces genetic changes that become permanently encoded in the sex cells of the person, while somatic cell alteration affects only the individual and should not produce inheritable changes.

Somatic-Cell Therapy

Somatic-cell gene therapy is a treatment of existing gene pathology. Many clinical protocols are presently underway to offer therapy for individuals with adenosine deaminase deficiency and certain types of cancer. On the horizon are treatments for other diseases including Lesch-Nyhan syndrome, herpes simplex, melanoma, familial cholesterolemia, and many types of malignancies. Previously, no effective cures had been available for most of these conditions.

Somatic-cell gene therapy cannot abolish genetic disease. In fact, should it become widely successful, it will increase the number of gene carriers with homozygous disease who will face the certainty of passing problem genes to their children.[16] This in turn will lead to a logarithmic increase in the need for somatic-cell therapy in future generations. Therefore, somatic-cell therapy alone is not beneficial in the long run.

Germ-Cell Therapy

Germ-line engineering of the human genome may become technically feasible within a decade. Specific techniques for the genomic alteration of germ cells has been demonstrated in animal models.[17] Germ-line changes generally would be expected to affect the genetic make-up of all tissues and cells in the developing offspring and all subsequent generations with grave implications for both the individual and for society at large.[18]

Potential justification for germ-line alterations include the correction of genetic defects not otherwise amenable to somatic-cell treatment, permanent stabilization of genetic material in offspring of high-risk mating, or the elimination of the need for repeated prenatal diagnosis and selective abortion in genetically at-risk families.[17] According to one view, a trial of genetic therapy would be justified only if the following conditions held: 1) the risk of treatment were no greater than the risk of being born with the given condition or of being destroyed

prior to implantation (the non-treatment options); 2) no other treatment were available that offered a superior risk/benefit ratio; 3) the purely research components of the trial did not pose substantial risk; and 4) consent had been obtained from an appropriate guardian.[18]

Dr Marc Lappe, professor of health policy and economics, argues that since changes in the germ-line potentially affect others in addition to the recipient of the altered germinal tissue (ie, the offspring and future descendants), such experimentation raises novel questions of traditional research ethics. Foremost among these is the adequacy and acceptability of proxy consent. Germ-line interventions may subject at least one or probably two generations of future persons to experimentation before the phenotypic effects of the germinal change can be said to test out.[17] Medicine is not an exact science. Many times patients are treated with well-researched FDA-approved drugs and develop serious side effects. Germ-line manipulation must surely be at least as problematic. Germ-line research presupposes direct experimentation on and destruction of embryos. The acceptability of this pivots on the acceptability of killing genetically altered but defective embryos or allowing their creation in the first place.[17]

Criteria to safeguard the direct genetic manipulation of the pre-embryo have been proposed. They include: 1) a specific correction of a defective gene will be made, 2) the procedure will not introduce any genetic errors or new genetic material that could have unpredictable effects in subsequent generations, and 3) such procedures include a check to ensure that the procedure has been carried out as intended, before allowing the pregnancy to proceed.[16]

In our fast-food and microwave society, quick processes tend to be over-esteemed. Nature already has a way of ridding the genetic pool of inferior genes via spontaneous abortion and natural selection. We cannot be assured that scientists in their laboratories will be able to better this process.

Enhancement of Normal Individuals

Germ line interventions can promote desirable genes or decrease deleterious ones to produce an improved genetic profile.[17] For many, this eugenic goal stirs memories of the forced genetic and ethnic cleansing attempted by Germany and the Soviet Union and the legislated sterilization of the disabled in the United States.

Enhancement is one side of eugenics. Instead of removing *bad* genes, it hopes to improve on *normal* ones. As knowledge of the structure and function of the human genome expands, social pressures will mount not only to repair defects and disorders, but also to intervene at improving or perfecting the structure and function of the genome. Enhancing a child's genes, one might argue, is analogous to giving a child a private education, a trip to Europe, or plastic surgery. If parents have the right to give their children these other benefits, do they not also have the right to give them enhanced genes?[9] Is the ability to pay determinative, and would this not serve to widen the gap between the haves and the have nots?

And as genetic enhancement becomes more frequently used, the cost of services may actually drop making the technology available for almost everyone. What then would our brave new world look like?

Conclusion

Ready or not, we are entering the age of the new genetics. Professional perspectives vary. Generally, geneticists are concerned about improving the gene pool, lawyers are interested in setting legal precedence, sociologists look beyond individuals to consider society as a whole, and entrepreneurs drool over the prospects of this new industry. Who, if not doctors, will lead us into this new era and advocate for and protect individual patients and their families?

Some physicians will remain largely ignorant or disinterested in these issues. Others will opt to refer their patients for genetic services, thus missing the opportunity to tailor-make plans for patients best known to them. Still others will become well-versed in the new genetics. They will recommend appropriate genetic services and expertly counsel their patients who trust them. They will also guide their patients in their decisions regarding screening and therapeutic options in the same manner they have guided their patients before the age of gene sampling, selection and cure.

Are primary care physicians prepared to lead? First, they must draw on the resources of the geneticists to understand the science; then they must look to the philosophers to appreciate fully the bioethics. Legal issues, societal concerns, and financial matters must also be appreciated. These are the caring and responsible physicians who will set the cadence and direction of our march into the new genetics.

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