throughput genotyping, as discussed in this issue by Peltonen and McKusick (*5*). Another new benefit is that much of the hard work of positional cloning has been replaced by cloning by computer. Thus, gene sequences, and even polymorphisms can be identified by searching appropriate computer databases.

Identifying QTLs is one thing, but understanding their effects will take much more time. Functional genomics and proteomics (*6*), where the focus is on gene products, their structure and expression, can be generally viewed as bottom-up strategies. But there are other levels of analysis at which we can understand how genes work. A top-down approach highlights the behavior of the whole organism. For example, we can ask how the effects of specific genes unfold in behavioral development and how they interact and correlate with experience. This top-down, behavioral genomic level of analysis (*7*) will complement the current functional approaches in the human species. Furthermore, genome sequences of other organisms will be especially important because of the great similarity of genes and gene organization between, for example, mouse and man (*8*).

Ultimately, the human genome sequence will revolutionize psychology and psychiatry. The most important impact will be on understanding the neurobiological basis of individual differences and achieving a better grasp of the etiology of diseases. The latter, in turn, should lead to the discovery of new and more specific drug treatments. The use of genomics as a path to drug discovery holds considerable potential (*9*). It is also probable that DNA testing will be used to predict which patients will respond to different drugs or be susceptible to particular side effects (*10*). However, there are two built-in limitations to this DNA revolution. The first is that all behavior involves gene-environment interplay. The second is the unsolved question of the distribution of effect sizes of QTLs; some may involve effects so small or so complicated that they will never be detected.

The probabilistic rather than deterministic influence of genes on behavior means that some of the ethical specters raised by the advent of behavioral genomics probably have little substance. For example, it has sometimes been suggested that geneticization is likely to increase the stigma of mental disorders. To the contrary, far from increasing the stigma, advances in genetics have the opposite effect. As a case in point, it is now perfectly acceptable for an ex-president of the United States and his family to acknowledge that he has Alzheimer's disease, a disorder for which much progress has been made in understanding its basis at a molecular level. In the recent past this might have been called "going senile" and would have been seen as somehow morally reprehensible. We predict that this is the start of a trend and that identifying genes involved in behavioral disorders will do much to improve public perception and tolerance of behavioral disorders.

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FUTURE DIRECTIONS: POLICY ISSUES

Political Issues in the Genome Era

James M. Jeffords and Tom Daschle

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Regulating use of genetic information. President Clinton signing an executive order prohibiting civilian federal agencies and departments from using genetic information in any hiring.

The sequencing of the human genome heralds a new age in medicine, with enormous benefits for the general public. For example, it will allow scientists to identify all of the genes contributing to a given disease state, leading to a more accurate diagnosis and precise classification of disease severity. In addition, healthy patients can know the diseases for which they are at risk, giving them the opportunity to make beneficial lifestyle changes or to take preventive medications to protect their health. Understanding the genetic bases of heritable diseases also will allow researchers to develop therapeutics at the molecular level, resulting in better treatments with fewer side effects.

Despite the potential benefits, many ethical, legal, and social concerns exist. The U.S. Congress recognized this early in the development of the publicly funded human genome project and so set aside approximately 5% of the budget, starting in 1990, to fund the ELSI program (Ethical, Legal, and Social Implications of Human Genetics Research) (*1*). Initially, the ELSI program focused efforts on four areas: Privacy and fair use of genetic information, clinical integration of genetic technologies, issues surrounding research ethics, and public and professional education. Later these goals were expanded to include studies of the societal impact of knowing the complete human genome sequence, the interpretation of genetic variations among individuals, integration of genetic technologies into clinical and nonclinical settings, and the implications of genetic technologies for religious, philosophical, ethical, and socioeconomic concerns.

One of the most difficult issues is determining the proper balance between privacy concerns and fair use of genetic information. The growing number and use of genetic tests has many worried about discrimination due to inappropriate access to, and use of, private genetic information. A Gallup poll by the Institute for Health Freedom released this past September revealed that 86% of U.S. adults 18 years of age or older believe that physicians should obtain permission before doing any genetic testing beyond routine testing (*2*). Similarly, 93% of adults believe that their permission should be granted before researchers use their genetic information. Francis Collins, Director of the National Human Genome Research Institute (NHGRI), has written, "It is estimated that all of us carry dozens of glitches in our DNA—so establishing principles of fair use of this information is important for all of us" (*3*). Without adequate safeguards, the genetic revolution could mean one step forward for science and two steps back-

Senator James M. Jeffords (R–Vermont) is the Chair of the Health, Education, Labor, and Pensions Committee. Senator Tom Daschle (D–South Dakota) is the Democratic Leader of the United States Senate.

wards for civil rights. Misuse of genetic information could create a new underclass: the genetically less fortunate.

Many Americans are concerned about potential genetic discrimination by their employers. In 1998 the National Center for Genome Resources (NCGR) surveyed 1000 American adults, and found that the majority (85%) believed that employers should not have access to a patient's genetic information, and 63% indicated they "probably" or "definitely" would not undergo genetic testing if they knew that insurers or employers could discover the results (*4*). However, members of the business community report that employment discrimination based on genetic information is currently very rare. The American Management Association surveyed 2133 employers this year, and of all those surveyed, only 7 indicated that they used genetic testing, either for testing job applicants or employees (*5*).

However, it is important that this situation not become more prevalent, and even a perception of genetic discrimination can seriously impede future progress. Craig Venter put it succinctly: "...there are more barriers to achieving that era [of personalized and preventive medicine] than the scientific ones that have now been overcome. A key barrier is the fear that is pervasive in our society that genetic information will be used to deny health insurance or a job.... Without the enactment of legislation, I fear that this new era will be delayed" (*6*).

In the United States, federal laws such as the Americans with Disabilities Act and the Rehabilitation Act provide some protections against genetic discrimination in the workplace, but the scope of that coverage has not been tested in the courts (*7*). Former President Clinton recently signed an executive order barring genetic discrimination against employees in federal executive departments and agencies (*8*). Just this past November, the Society for Human Resource Management (SHRM) issued a policy position that stated, in part, "For this reason, the SHRM would oppose employment policies that permit employment decisions to be made based on an individual's genetic information" (*9*).

U.S. federal law does provide some protection against discrimination in health insurance. Specifically, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) bars a group health plan, or an issuer of a group health plan, from using genetic information as a basis for implementing rules of eligibility for the plan or for setting premiums (*10*). But it does not cover people who buy insurance as individuals, nor limit collection and disclosure of genetic information by insurers.

Most protections, whether in terms of employment or health insurance discrimination, are at the state level. At present, 37 U.S. states have laws regarding genetic discrimination and health insurance; 24 states have laws regarding genetic discrimination and employment. Although this patchwork of state laws affords some protections, it also contains loopholes. For example, definitions vary from state to state. One state may protect only DNA and RNA; another may extend protection to family history data and other medical information that could offer genetic clues. In addition, because of federal law preemptions, state laws do not protect the nearly one-in-three Americans who get their health insurance through their employer.

Ethical ambiguities are not limited to how genetic information will be made available and applied, but extend to the research methods used to gather the data in the first place. For example, in large community studies, obtaining informed consent from every community member is often impractical. Furthermore, studying groups of people within relatively small gene pools may have an unintentional stigmatizing effect. Policies protecting confidentiality in research are crucial both to guard individual privacy and to promote advancement of the science. Some organizations have published guidelines in this area. For example, general recommendations to protect privacy in genetic research have been published by members of the Privacy Workshop Planning Subcommittee of the National Action Plan on Breast Cancer (*11*).

Genetic information has begun to be catalogued and maintained in many different forms, such as pathology specimens, blood bank donations, newborn screening samples, and research collections. In addition, the U.S. Armed Forces require all members to donate a sample of their DNA for future casualty identification. Many countries including the United States maintain forensic DNA banks for use in criminal courts as well as commercial DNA banks. Outside the United States, there have been efforts to create national genetic databases. For example, in December 1999, Iceland's parliament passed a bill allowing Decode Genetics, a biotechnology company, to combine all Icelanders' genetic, medical, and genealogical information into one database to be sold to researchers. Critics of this research have expressed concerns over the "ownership rights" of genetic information, especially when a profit is to be made from the information (*12*). Estonian scientists are trying to create a similar genetic database and also to address concerns regarding access (*13*). Their goal is to include the genetic information, as well as other health and lifestyle data, on more than 70% of the Estonian citizens. If established, the participants will receive access to their own genetic profiles in exchange for their contribution.

One of the most challenging areas of policy development involves genetic testing in the reproductive sciences. Research advances

Senator Jeffords:
As chairman of the U.S. Senate Committee on Health, Education, Labor, and Pensions, Senator Jeffords held a hearing on Genetic Information in the Workplace during the 106th Congress and a hearing on Genetic Information and Health Care during the 105th Congress. During the 106th Congress, Senator Jeffords joined with Senators Snowe and Frist in cosponsoring the Genetic Information Nondiscrimination in Health Insurance Act. The bill is designed to protect American consumers from discrimination by health insurance companies based on predictive genetic information or the use of genetic services. It prohibits the use of this information by health insurers to set eligibility requirements or premium rates. It clearly specifies the very limited conditions under which a company may request genetic information from individuals. Furthermore, it calls for the establishment of safeguards within the insurance companies to protect the confidentiality of the individual's genetic information. On 29 June 2000, the Senate adopted the measure as an amendment to the Labor/Health and Human Services Appropriations bill. It was subsequently removed by the Conference Committee. This bill will be reintroduced during the 107th Congress. Senator Jeffords' Committee will also continue its examination of issues surrounding the use of genetic information and workplace discrimination.

Senator Daschle:
I believe that Congress must pass strong federal laws against genetic discrimination. I believe that the United States should develop legislation that conforms to the Universal Declaration of the Human Genome and Human Rights: "No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity."

Thus, I believe that employment and health insurance discrimination on the basis of predictive genetic information should be firmly prohibited. Further, I believe that limits must be placed on the collection and disclosure of individuals' genetic information. In crafting these protections, lawmakers should actively solicit opinions from others, including—at a minimum—scientists, geneticists, ethicists, consumers, employee and employer groups, and insurers.

in this area have been remarkable, but are fraught with controversy. Couples considering pregnancy now have many options for genetic screening. In fact, those undergoing in vitro fertilization may now opt to have their embryos genetically screened before implantation (*14*). This can be helpful to couples whose offspring are known to be at risk for an inherited disease. Although some view this technology as a wonderful breakthrough, critics argue that it borders on eugenics.

In our lifetime, we have watched with amazement the progress of this field from the initial discovery of the structure of DNA in 1953 by Watson and Crick (*15*), to the present-day sequencing of the human genome. Increased understanding of the human genome may ultimately result in the eradication of common diseases, but in the meantime we need to be on guard against potential misuse of genetic information. This is an emerging technology, and we should proceed with caution. The science is expanding at a breathtaking pace, and the overwhelming amount of new information puts governments under increasing pressure to pass legislation.

Eventually every country must decide what genetic information should be protected, who will have access to it, and how it may be used. In addition, governments must ensure that the public realizes practical gains from their investment in genetic technology, because much of the research is made possible by taxpayer-supported federal enterprises in partnership with academic and industrial institutions. Further, for this partnership to continue, the public must understand the new technologies so that unfounded fears will not develop and slow progress. Ultimately, the greatest difficulty will be for policy-makers to strike a balance between timely promotion and use of the best genetic research and careful protection of people from genetic discrimination.

Editor's note: The authors have chosen to express their individual views about future directions for legislation in the United States separately. *See page 1250.*

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FUTURE DIRECTIONS: SEQUENCE INTERPRETATION

Functional Annotation of Mouse Genome Sequences

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With the reports of the DNA sequence of the human genome and progress in sequencing the mouse genome, the first phase of the Human Genome Project is complete (*1–3*). Analysis of these DNA sequences will reveal the inventory of genes used for building these organisms, as well as many regulatory elements that compose the "instruction manual" for converting the genetic "parts list" into organismal form and function. Research attention is now beginning to shift from problems of gene structure and genome organization to questions of protein function and interactions, developmental and physiological pathways, and systems biology.

Various computational methods are being used to deduce functions for genes. Analyses of the genome sequences of species such as *Haemophilus influenzae*, *Helicobacter pylori*, *Caenorhabditis elegans*, and *Drosophila melanogaster*, and humans illustrate the power of these methods (*1*, *2*). However, many fundamental aspects of biological functions are not directly evident in DNA sequences. It is not unusual to discover a gene sequence about which little functional information can be deduced. For example, sequence analysis leads to no prediction of function for as many as 30% of the genes in the human genome, and the inferred functions of most of the remaining genes have yet to be proven (*1*, *2*). Because of the striking sequence similarities between humans and mice (*1*), discoveries in one species lead to strong inferences in the other.

Laboratory mice and related species can make important contributions to functional genomics and identification of new models of human disease. Many spontaneous mutants have contributed profoundly to biomedical research and our understanding of disease etiology and pathogenesis. The ability to make crosses between genetically defined strains, to work with large sample sizes, to engineer mutations in specific genes, and to generate mice with induced mutations facilitates identification of genetic variants of biomedical interest. By including known single-gene mutants in surveys of mutagenized mice (also known as "sensitized surveys"), induced mutations that modulate the mutant phenotype can be identified, as was done with great success in the discovery of naturally occurring variants that suppress disease traits in *Apc* and *Cftr* mutant mice (*4*). These mouse models reveal new drug targets for adenomatous polyposis coli and cystic fibrosis, as well as provide ways to evaluate potential therapeutics, predict treatment effects, and prioritize treatments for clinical trials.

Remarkably, despite more than 100 years of research in mouse genetics, fewer than 5000 out of an expected total of 30,000 genes have functions attributed to them through direct experimental studies. Recent progress in mouse genetics and genomics has provided proof-of-principle for large-scale studies to produce compre-

[1]The members of the IMMC are listed in (*21*).

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