We're off to see the genome

Philip R. Reilly[1] & David C. Page[2]

We discuss some societal and legal ramifications of the human genetics revolution. Our reflections were stimulated by discussions among scientists, citizens and legal experts at a large public symposium. We outline key issues regarding oversight of genetic research on human subjects, banking of DNA data by governments and corporations, the potential impact of behavioural genetics and effects upon racial and racist thinking. We contend that, in some cases, well-intentioned but naive efforts to protect the rights of individuals and groups may hurt everyone by blocking the progress of useful research.

We recently helped organize a public symposium, "The Human Genome Project: Science, Law and Social Change in the 21st Century," that was held on the campus of the Massachusetts Institute of Technology. From the producers' perspective, two aspects of the symposium were of special note. First, the Whitehead Institute and the American Society of Law, Medicine and Ethics (the co-sponsors) were able to attract financial support from an unusually diverse group of organizations, including NIH, the Department of Energy, the Institute for Civil Society, the Alfred P. Sloan Foundation, biotechnology companies and law firms. Second, the symposium attracted more than 800 registrants, mostly from outside the ranks of the scientific and bioethics professional communities. Clergy, school teachers, lawyers, representatives of disability rights groups, high school students, journalists, physicians and nurses participated vigorously in the workshops, which gave the audience an opportunity to query and debate leading experts on the symposium's topics. Such diversity reflects broad public consensus about the importance of the issues discussed at the symposium. Listening to the discussions, one must acknowledge the mounting public concern that profound social issues will arise as we seek insights into the relationship between genotype and phenotype. It seemed that the audience viewed molecular genetics as a great and powerful Oz, while they felt more like Dorothy and her frightened but determined friends.

Both the organizers and the audience sought to move beyond the current, important debate over genetic discrimination to anticipate other bioethical quandaries that may arise in the future. Here we will highlight a few looming issues discussed at the meeting. While we lack a crystal ball, we anticipate that these topics will increasingly demand the attention of scientists and society alike as the human genetics revolution moves forward.

Review and oversight of genomic research

During the last two years, many institutions and citizens have voiced concern that genomic research is qualitatively different than other kinds of research on human subjects because it carries significant 'informational risk', that is, subjects could be harmed by inappropriate use of data. The emergence of this concern can be traced to the decade-old fear (in the United States) that clinically derived genetic information might be used to limit access to health insurance or employment. If clinical information poses such a threat, perhaps information generated in research, if disclosed, could also create such hazards. This concern stimulated proposals that research subjects remain anonymous, that researchers not disclose results to subjects and that researchers in the US obtain 'certificates of confidentiality' from the Department of Health and Human Services. Similar concerns motivated calls for more stringent rules regarding re-use of archived tissue samples. It was argued that since permission was not initially obtained to perform DNA analysis on the samples and 're-consent' was impractical, oversight bodies should carefully evaluate and monitor investigators who seek to mine such archives. These concerns assume that inappropriate disclosure is or will be a significant problem in the research setting. To the contrary, we believe that inappropriate disclosure of research findings is rare at present, and that future risks have been overstated. The human genetics research community appears committed to sustaining a culture of strict patient confidentiality.

New arguments have been made by US government bodies and interest groups that the traditional consent process, even with strict adherence, is insufficient when genome researchers study well-defined subpopulations (for example, the Apache tribe). Advocates argue that because genomic research conducted upon individuals or families belonging to such groups might yield results that could stigmatize any member of the group (whether or not he or she participated in the research), some form of 'community consent' should precede efforts to recruit research subjects. This view is supported by the 1997 NRC Report on Evaluating Human Genetic Diversity. This expanded view of consent raises the problem of how to decide if any particular human group is sufficiently discrete and well-organized to secure meaningful consent from acknowledged leaders.

In April 1998, leaders of several important Jewish organizations met with NIH officials to discuss the possibility that research on 'Jewish' genetic diseases carried an inherent risk of reinforcing anti-Semitism. Does research on 'Jewish' genetic diseases create a risk that the results will fuel prejudices? Yes. Would it be appropriate (or even possible) for researchers to seek consent from the Jewish community before seeking individual consent from a cohort of Jewish families with a strong history of (for example) colon cancer? We think not. To do so would overextend the notion of community consent. It could lead to research being blocked due to intangible (and largely undocumented) fears. In the past, concern about genetic discrimination has focused largely on the risk that a particular person or family might be denied access to insurance at reasonable rates. Concern for the discriminatory impact of genetic data on whole populations is, we think, sufficiently vague to require that those who would advocate an additional consent process produce firm evidence of harm. Of course, even if there is little evidence of harm, it is important to educate the research community about the nature

[1]*Shriver Center for Mental Retardation, 200 Trapelo Road, Waltham, Massachusetts 02452, USA.* [2]*Howard Hughes Medical Institute, Whitehead Institute, and Department of Biology, Massachusetts Institute of Technology, 9 Cambridge Center, Cambridge, Massachusetts 02142, USA.*

and gravity of these fears among the potential subject population, and to ensure that those who monitor genomic studies carefully consider relevant privacy issues.

The befuddlement that can arise when researchers and bureaucrats confront the issue of 'community consent' is evident in the National Human Genome Research Institute's current initiative to identify single nucleotide polymorphisms (SNPs). To ensure privacy and relieve SNP investigators of the need to obtain consent from research subjects, NHGRI set up a repository of DNA samples from 450 anonymous, ethnically diverse USA residents. But NHGRI went beyond individual anonymity, irreversibly severing all connections between individual samples in the repository and all information about their ethnicity and geographic origins (as well as sex, as if this could not be readily deduced from a DNA sample!). While this additional step immunized NHGRI's SNP initiative against community-consent critiques, it also stripped this large repository collection of much of its scientific usefulness. This is an example of scientific policy makers scuttling a mission rather than engaging in constructive (and difficult) dialogue when faced with a bioethical challenge.

DNA data banking

Concern over the growth of DNA banking and DNA data banking will be fueled by at least three distinct developments, each involving the widespread use of novel technologies. These are: the rapid growth of forensic DNA banking, the expansion of newborn genetic screening and the rapidly escalating interest of the pharmaceutical industry in accessing the genotypic profiles of large cohorts (millions) of individuals. In the United Kingdom, DNA forensics has grown very rapidly since its inception in the mid-1980s. As of June 1998, the UK Forensic Science Service had collected 320,000 samples for DNA analysis, and had removed 51,000 samples from the bank after suspects had been exonerated[1]. Driven by the desire to be part of the FBI's information system, every state in the US has enacted statutes directing law-enforcement officials to collect and retain tissues for DNA typing from felons convicted of any of a variety of crimes. At first, the focus was sexual felonies, such as rape, in which the odds of obtaining relevant DNA evidence are very high. But the list of crimes covered is expanding. The US appears to be following the UK's lead, where the most frequent use of DNA evidence obtained at the crime scene is now for the resolution of burglaries and auto thefts. Given arrest and conviction statistics and the scope of DNA forensic banking in the UK, one can expect the database to eventually include 30 percent of all males aged 30 or more. (About 30% of men in the UK are convicted of a felony before their 30th birthday[1].) In the US, forensic DNA databases could eventually reach a comparable size.

The social implications of DNA forensic data banking are potentially much larger than those of the century-old practice of collecting and storing fingerprints of arrested individuals. A fingerprint provides information relevant only to identification. DNA forensic banks retain whole DNA, and many state laws permit (anonymous) research on these samples. Such tissue archives will be of immense interest to those who study human behaviour, and especially to those who study criminality. Imagine, for example, the potential social consequences of an association study indicating that persons convicted of vehicular manslaughter are ten-fold more likely than those in a control group to carry an allele thought to predispose to alcohol abuse. If such correlations are found, they will influence practices (for example, sentencing and parole) in the criminal justice system. The judiciary must be educated so that it can properly manage such knowledge.

The development of powerful screening technologies will raise additional issues in newborn testing. Already, more than 10 million newborns are screened each year in the western world for between one and eight genetic disorders (depending upon the nation or state in which they are born). This public health effort, which began when Dr Robert Guthrie developed an automated bacterial inhibition assay for phenylketonuria (PKU) in 1962, will soon be significantly expanded through the use of tandem mass spectrometry (TMS) to identify infants with disorders of fatty acid metabolism, organic acidemias and other diseases. With an extremely low cost per analysed sample, TMS could easily raise the number of disorders for which all children are screened at birth to 30. DNA-based newborn screening programs, which will ask far more questions about each sample, could be deployed within a decade. Such developments would save the lives or avert serious disability in thousands of children, thus expanding the remarkable triumph of PKU screening. However, during the 36-year history of mandatory newborn screening, states have paid relatively little attention to protecting the security of the tissue sample (a dried blood spot on a filter paper disc which many programs retain for an extended period). The time is ripe for comprehensive reassessment of regulations governing newborn screening. How will we acquire, analyse and store these data? How will we use this information to help people stay well or ameliorate disease? How will we ensure that the information is not misused?

The anticipated use of DNA data banks by pharmaceutical companies is likely to pose additional problems in balancing personal privacy concerns with public health needs. The likelihood that DNA testing will yield powerful insights into predispositions to common diseases (for example, asthma, diabetes, depression, coronary artery disease and Alzheimer disease) has already caused impressive reallocations of resources in the pharmaceutical industry. This industry will have an unslakable thirst for massive amounts of clinical and genotypic data about the populations served. These data will lead to a fundamental reassessment of the efficacy of existing drugs and to new approaches to drug development. Databases composed of clinical records combined with genetic information are rapidly becoming valuable commodities. The commodification of genetic information will create pressures favouring disclosure over privacy. In the US, many states have enacted or are considering laws to forbid the use of genetic data to deny health insurance coverage. Some of these laws could inadvertently prevent reasonable access to data that could be valuable in drug development.

In the not-too-distant future it may become standard practice in technologically advanced societies to collect, analyse and store DNA samples on every citizen. It is possible that major advances

in genotype-phenotype correlations will permit DNA analysis to provide data that are critically important to preventive medicine, customized according to genotype. However, we can not yet ensure such data are not misused. In our opinion, the only effective general solution to data bank issues in the US would be a federal privacy law that applies to all medical records, but that incorporates reasonable access rules for researchers.

Behavioural genetics

Although we have barely begun to grapple with the roles of particular alleles in shaping human behaviour, the general public already fears that behavioural geneticists are conducting research that may do more harm than good, either because of misinterpretation or misuse of data. Several false starts in the 1980s involving efforts to map genes that predispose individuals to schizophrenia and bipolar disorder have fueled these fears. Many people suspect that researchers are overeager to make sensational claims and all too quiet in their retractions. Widely discussed reports of tantalizing findings on the genetics of alcoholism, shyness, thrill seeking, religiosity and intelligence, to name a few examples, have become almost monthly events.

Even modest insights that permit a correlation between genetic constitution and behaviour raise intractable social questions. How would teachers react to children labelled with a genetic predisposition to having trouble with number concepts? Would some teachers conclude that their efforts are doomed to failure, thus harming the children most in need? How would a parole board react to evidence that individuals carrying a variant neurotransmitter gene were more likely than others to be violent? Would this influence their decision to free a young man convicted of arson? We can only dimly anticipate the ultimate impact of behavioural genetics on public education and the criminal justice system. In a democratic society, adults are viewed as moral agents who are responsible for their acts. A crime is a violation of a widely agreed upon set of rules by an individual presumed to understand that he is committing the offense. In the long run, new insights provided by molecular genetics could influence society to adopt a disease model for some types of crime. Claims that a genetic condition is the underlying cause of an individual's criminal act have already appeared (albeit rarely) in the courts. As in the early days of DNA profiling, molecular biologists must be available to act as neutral parties to assist judges in weighing the admissibility of such testimony.

Genetics and racism

Racism and ethnic strife may be the most dangerous and intractable problems in the modern world. From ethnic cleansing in Bosnia to hatchet killings in Rwanda, humans seem all too eager to view their neighbours as inferior or evil. Is it possible that deeper knowledge about the human genome and its diversity could help resolve this problem? Or could such knowledge reinforce racial stereotypes and worsen the situation? Although genetic diversity within a group is much greater than genetic diversity between groups, certain DNA sequences may be far more prevalent among some racially or culturally defined groups than others. Perhaps we will identify sequence variation that indicates the race of the person from whom DNA was obtained. How would such data affect the assertion that race is an antiquated social construct that lacks a true biological basis? What would happen if research on the genetics of intelligence yielded information suggesting that 'positive' alleles were differentially distributed across racial groups?

In conclusion, the larger social issues that we have discussed may seem remote from the daily lives of most readers of *Nature Genetics*, but they are increasingly the prism through which the public views the onward rush of human genetics. Of course, it is the public who funds much of the research and provides the pool of potential research subjects. Perceived conflicts between scientific objectives and social concerns are already impacting NHGRI's basic research initiatives. We must be creative and diligent in championing the ideal that researchers and subjects are partners in a common endeavour. The challenge for scientists and society is to work together, simultaneously visualizing the great potential and discerning the real hazards of this work.

1. Remarks of Dr. David Warrett, Director of Research and DNA Services, Forensic Science Service, United Kingdom, made at a public meeting in Chicago on June 8, 1998. Meeting sponsored by the US Department of Justice National Commission on the Future of DNA Evidence.