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1998 ASHG PRESIDENTIAL ADDRESS
Making Genomic Medicine a Reality

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First, I want to express my deep appreciation for the honor of serving as president of our Society and for the opportunity to share some thoughts with you today. For the theme of my address, I propose to ask how genetic advances will impact the practice of medicine over the next decade or two—and what we, as members of the American Society of Human Genetics, should be doing to influence these developments. I will focus on dilemmas that I perceive in prenatal genetics, on population-based genotyping to bring significant changes to the practice of adult medicine (considering both single-gene disorders and more-complex traits), and on the potential to make greater use of family-based genotyping for autosomal dominant disorders. I will advocate using our genetic knowledge to advance the practice of medicine, and I will take the liberty of being a bit provocative and speculative. Some of you may disagree with certain of my perspectives, but healthy disagreement may stimulate new intellectual contributions and dialogue and might even provoke us to develop new technologies that will move our discipline forward.

I would like to begin with a bit of historical perspective. In 1931, after 3 decades of seminal observations, Sir Archibald Garrod wrote that "diathesis is nothing else but chemical individuality," which he explained in remarkably prescient molecular and chromosomal terms as follows: "[T]he factors which confer upon us our predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure, and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang" (Garrod 1931).

In more recent years, many of our colleagues have emphasized the theme of genetic individuality and its relevance to the practice of medicine. For instance, many of you will remember Charles Scriver's elegant lectures since the 1970s, which conveyed the potential for using genetic screening for disease intervention in the adult population, through the image of the artist Folon depicting "the man in the red hat" in a crowd (Scriver 1979). Are we ready to translate Garrod's concept of chemical individuality as depicted by the man in the red hat into a genotype-based practice of medicine?

It is instructive to look back at some of the major advances of the last 25 or more years that are related to our field. The advent of testing and treatment for phenylketonuria (PKU) epitomizes what we would hope to achieve again and again throughout the practice of adult as well as pediatric medicine. Improved methods of chromosome analysis, including banded karyotypes and FISH, have greatly advanced our diagnostic capacity. Prenatal diagnosis, particularly for cytogenetic abnormalities, and maternal serum–screening programs have become mainstays of obstetrical care. Population-based heterozygote testing for conditions such as Tay-Sachs disease and β-thalassemia has dramatically reduced the prevalence of these conditions in many parts of the world. The use of folic acid for prevention of neural-tube defects is an important therapeutic advance. Genetic diagnosis and risk counseling have become substantial medical disciplines in their own right. Other advances have included cloning disease genes and mutation detection for almost all the common single-gene disorders, delineation of novel genetic concepts such as expanding triplet repeats, and many more developments that have made the recent meetings of our Society so extraordinarily stimulating. The already substantial output of the Human Genome Project is changing our discipline. Protein-replacement therapies for hemophilias, adenosine deaminase deficiency, and Gaucher disease are significant therapeutic advances, and exciting new data for iduronidase were presented this morning. Although only indirectly related to human genetic research, the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors deserves mention because of their impressive potential for preventing coronary atherosclerosis, an extremely common genetically influenced disease. Finally, I would mention forensic DNA testing as a direct outgrowth of research in our

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discipline that yields many benefits to society, such as more-accurate identification of criminals and protection of the falsely accused. Each of us could add to this list, but it is important to note that there have also been major disappointments, particularly the lack of effective therapies for the many disorders that we can diagnose so precisely.

Leaving the past and turning to the present and future, I will begin with dilemmas that we face in reproductive and prenatal genetics. I would describe certain disorders that appear most challenging as "seemingly insurmountable"—insurmountable in the sense that I find it difficult to envision curative therapeutic advances. In this group I include disorders that are difficult or impossible to anticipate prior to conception and that are accompanied by a developmental injury likely to be irreversible by the time of birth. This group includes the majority of cytogenetic disorders, such as trisomies and de novo deletion syndromes. For example, my laboratory has contributed to the identification of the gene for Angelman syndrome, but it troubles me that this discovery is unlikely to have much immediate effect on the prevalence of or disability associated with the condition. Also seemingly insurmountable are hundreds of rarer recessive disorders for which population-based heterozygote testing may not be feasible (e.g., Meckel syndrome) and de novo dominant mutations (e.g., thanatophoric dysplasia and osteogenesis imperfecta type II). Ask yourself how many of the elegant mutation studies of malformation disorders that you are hearing described at this meeting will dramatically impact the prevalence or burden of the disorder anytime soon. This group of cytogenetic and single-gene disorders includes a wide spectrum with some severe and some milder phenotypes. Some of the conditions may be amenable eventually to prenatal or postnatal treatment of varying effectiveness. But, returning to our meeting 20 years hence, we may well find that definitive intervention for the cytogenetic and single-gene developmental disorders that we know today is little changed.

Looking forward, I feel assured that diagnostic advances with newer cytogenetic technologies will allow for the identification of novel disorders, particularly terminal deletions, smaller interstitial deletions and duplications, and more-subtle rearrangements. In addition, it is at least possible that sampling fetal cells in the maternal circulation could dramatically alter the prenatal-diagnosis landscape. Some of our most persistent challenges, however, are dilemmas of reproductive avoidance. The first two dilemmas confront individual families and societies as a whole. They are not dilemmas of genetics or current technology but ones of ethics, social mores, and religious beliefs. Once aware of genetic risks, couples must first decide whether they wish to use prenatal testing, in the form of either carrier testing or fetal testing. If fetal test results snatch the hope for a normal, healthy child from the family, they then face the second dilemma of two grim options: termination of the pregnancy or birth of a disabled infant.

There is another dilemma that I see for us as geneticists. Should we continue current approaches, or should prenatal diagnosis be offered to all families as an option for those seeking maximal screening? Prenatal diagnosis could be expanded not only by offering testing to all families but also by testing for a much wider group of disorders. The technology is in place—and much of the methodology has been in place for many years—to accomplish prenatal diagnosis for virtually all cytogenetic disorders and numerous other single-gene abnormalities. I believe that we—society at large and the medical practitioners—would make use of prenatal diagnosis for virtually all pregnancies and test for a very wide range of disorders, if curative therapies were available but effective only if implemented during the second trimester. Why do we choose not to offer the option of prenatal diagnosis for all pregnancies? I do not accept that this is a matter of cost or even a matter of maternal and fetal risk, given current technology. The willingness to invest huge sums in treatments that offer the hope or the certainty of major benefits, such as bone-marrow transplantation for advanced cancer or enzyme replacement for Gaucher disease, demonstrates that, at least in the United States (and probably in many other Western societies), there would be a readiness to bear the costs of universal prenatal diagnosis, if cures for the disorders in question were available. Rather, I believe it is societal ambivalence and differences of opinion regarding abortion, as the only alternative for avoidance of many disorders, that restrain the use of prenatal diagnosis. Interestingly, there are intense efforts to enhance maternal-serum screening, and this emphasis has considerable merit but seems ambivalent—ambivalent in the sense that we would not emphasize a strategy that detects only a fraction of cases but, rather, would insist on a plan to detect 100% of cases if a cure were available. If prenatal detection were focused on curative intervention rather than selective abortion, I suspect that the emphasis would be on universal prenatal sampling and on automation and high-throughput methods to detect as many disorders as possible

In expanded reproductive screening, it is certainly feasible to envision much broader programs for identifying affected fetuses or couples at risk. Population-based carrier testing for cystic fibrosis (CF) is one example, but intense debate has surrounded this option. I have long advocated more widespread offering of CF-carrier testing, and I emphasize "offering" in a very nondirective fashion. More recently, the recommendations are increasingly toward offering testing. If we imagine various high-throughput technologies, we could consider testing

for Duchenne muscular dystrophy, fragile X syndrome, perhaps spinal muscular atrophy, cytogenetic microdeletions, and various ethnic-specific risks. There are often choices between carrier screening for parents and testing fetuses. Each has disease-specific advantages and disadvantages. Preconception testing of parents for recessive carrier status or women for Duchenne muscular dystrophy or fragile X syndrome offers a broader range of reproductive options. However, fetal testing is the only option for most microdeletions, offers advantages in testing males for X-linked disorders, and can be considered for recessive disorders in various screening strategies. We already see reports of pilot programs screening for fragile X syndrome and other disorders, and expanded ethnic mutation testing is common in the Ashkenazic population. There can be substantial difficulties, such as the prediction of the phenotypic effect in the case of female fetuses with fragile X, but more widespread testing is being evaluated and may become more or less attractive, depending on factors such as prenatal or postnatal therapeutic advances.

So, what actions might be appropriate under the circumstances? First, there is the possibility that some young inventive mind in this audience might be able to develop a strategy to solve these dilemmas for many disorders, by reducing the frequency of nondisjunction or preventing the conception or implantation of affected embryos. A miraculous way to suppress nondisjunction or cure cytogenetically abnormal fetuses would be far preferable to selective termination of pregnancy, but such advances currently seem out of reach. Universal preimplantation diagnosis would be a theoretical but ridiculously impractical option. Second, we should not abandon efforts to develop postnatal treatments, even if such may be only palliative and feasible for only a few disorders. Third, I believe it is worthwhile to acknowledge the seemingly insurmountable factor, confront these dilemmas, promote societal understanding of the problems, and avoid offering false hope that all genetic disease is necessarily treatable in the foreseeable future. Finally, we should *consider and debate* offering expanded preconception carrier testing and prenatal diagnosis for all pregnancies to those families that desire maximal screening. If ambivalence about selective termination of pregnancy is a pivotal variable, as I suggest, then logic might dictate offering expanded services to families seeking maximal prenatal assessment—and remaining nondirective toward and supportive of families, whether they decline or seek such services. I would suggest that we vigorously investigate the societal, technological, and economic aspects of offering universal expanded strategies for reproductive avoidance to families seeking such services. Of all the challenges that I will discuss, I believe that finding better solutions to these dilemmas of reproductive avoidance is the most difficult. So I conclude with a paradoxical message: We desperately need better options than selective termination of pregnancy, but, until we have them, maybe we should make the only options we have more widely available.

Now, I will leave reproductive questions and take up what I have termed "genomic medicine" in the title of my presentation, "Making Genomic Medicine a Reality." I would define genomic medicine as the routine use of genotypic analysis, usually in the form of DNA testing, to enhance the quality of medical care. On the one hand, we can envision a revolution of individualized, genotype-based medicine harking back to the insights of Garrod (1931) and the urgings of Charles Scriver (1979). On the other hand, genomic medicine might prove a disappointment and remain confined to a minor role. In addition, there are very appropriate and substantial fears of predictive testing in the absence of definitive intervention.

I am going to assume that certain advances are assured. The Human Genome Project will be completed in the near future, and this will identify all human genes. We had a report just this week that perhaps half of all human genes are now identified (GeneMap '98; also see Deloukas et al. 1998). I think we can also assume that disease-related mutations and polymorphisms will continue to be identified at a rapid pace. It is also likely that we will have new technology, such as DNA chips (Southern 1996), that will allow for the economical collection of nearly unlimited amounts of genotypic information on a routine basis.

The widespread use of genotyping in the practice of medicine would not involve new principles. Newborn screening for PKU is a model that we can and should carry to the adult population. We have evolved principles for determining which newborn-screening tests are appropriate, depending primarily on the availability of therapeutic intervention, and this requirement for effective intervention should be applied to adult screening. We also see numerous examples in adult medicine that provide precedent for population-based screening to achieve therapeutic benefits. These include testing for hypertension, glaucoma, and cholesterol, as well as routine mammography and measurement of prostate-specific antigen. While some might argue that certain forms of screening are for disease rather than predisposition, the distinction between predisposition and disease is often not as clear as might be imagined. Is hypertension a disease or predisposition to a stroke? Is hypercholesterolemia a disease or predisposition to myocardial infarction? Is a germ-line mutation for hereditary nonpolyposis colon cancer (HNPCC) a predisposition to disease or an early stage of colon cancer? Although most of us would answer that an HNPCC mutation is a predisposition, the distinction is not always clear. Some

forms of well-accepted screening in the adult population—such as screening for cholesterol, hypertension, and glaucoma—are analogous to many potential forms of genotypic screening.

In the context of population-based genotyping, the difference between ancient mutations and recent mutations is relevant. Ancient mutations can confer the same genetic risks on thousands or millions of individuals in the population, while recent mutations will affect one or a few individuals. Obvious examples of ancient mutations include the sickle cell–anemia mutation, the α_1-antitrypsin Z allele, apolipoprotein E (apo E) polymorphisms, factor V Leiden, some BRCA1 mutations, premutations for triplet repeats, and innumerable recessive alleles. It is easier to screen for ancient mutations, since we can search for specific known alleles. There typically are substantial differences in the frequency of ancient mutations in different ethnic groups. The circumstances are somewhat different for recent mutations, which are often found with deleterious dominant or X-linked conditions that have an impact on reproductive fitness. Examples would include Duchenne muscular dystrophy, Marfan syndrome, and neurofibromatosis. Laboratory testing is more difficult because of the different mutation in each family, although it is increasingly possible, with newer technologies, to screen genes for any mutation, on a routine basis. Typically, there are minimal differences between ethnic groups, in the frequency of these more recent and short-lived mutations. There are disorders in which a combination of ancient and recent mutations contributes to the incidence, with both particular alleles in specific ethnic populations and still extensive heterogeneity among families, as exemplified by BRCA1 and BRCA2. Of course, there is also the fascinating example of achondroplasia, in which de novo mutations are extremely common but the same mutation recurs. The potential value of population-based genotyping in the practice of medicine will be influenced by the extent to which ancient mutations contribute to risk factors for common adult diseases. The greater the role of ancient mutations, the greater the potential to screen for at-risk genotypes and develop specific interventions. Using newborn screening as a model, we should attempt to identify instances where population-based genotyping will enhance the practice of adult medicine and bring significant benefits to the population.

One potential application of genomic medicine relates to "pharmacogenomics," a term that is used loosely to describe a number of different concepts and strategies. First, we are all familiar with traditional pharmacogenetics, or those genotypic variations that alter responses to drugs. G6PD deficiency, malignant hyperthermia, butyrylcholinesterase deficiency, and the debrisoquine hydroxylase polymorphism are examples (Daly 1995). Universal genotyping for a much-expanded panel of pharmacogenetic traits could significantly improve the risk-benefit ratio for many medications, and we might strive to realize this attractive promise over the coming decade. There is evidence for genotypic susceptibility to aminoglycoside-induced deafness (Fischel-Ghodsian et al. 1997) and to death from 6-mercaptopurine administration (Daly 1995); genotyping could reduce or eliminate these risks. An extension of pharmacogenetics is the potential to resurrect drugs abandoned because of side effects or to improve the possibilities, through extensive pharmacogenetic testing, for new drugs dependent on the avoidance of untoward reactions. A further variation on the pharmacogenomic theme is to use extensive genotyping, perhaps including a large group of single-nucleotide polymorphisms (SNPs), to identify responder subgroups. Yet another application is the development of novel pharmaceuticals for specific genotypes, based on new insights derived from a genetic dissection of pathogenesis. We already have diverse therapies—hematin for porphyria, hormone replacement for congenital adrenal hyperplasia, phenylacetate for sickle-cell anemia, and factor replacement for hemophilia—in which some level of understanding of pathogenesis allows the development of a specific intervention. There might be good reason to believe that specific therapeutics may one day be developed for triplet-repeat neurodegenerative disorders or other single-gene conditions, but even more important is the possibility that genotype-specific therapeutics will be applicable to more-common disorders such as asthma, schizophrenia, or hypertension. Perhaps an understanding of the role of the presenilins or apo E in the pathogenesis of Alzheimer disease will lead to the development of novel drugs that could prevent development of disease *without regard to genotype*. Finally, the pharmaceutical industry sometimes uses the term "pharmacogenomics" to refer to the strategy of using information from the Human Genome Project to identify new drug targets.

In conclusion, there is a broad range of pharmacogenomic concepts and strategies, many of which might justify universal genotyping to provide higher-quality medical care. As we consider the possibility of population-based DNA testing for pharmacogenetic traits, the benefits are attractive, since effective intervention is often simply avoidance of offending drugs. The risk of discrimination is minimal, and the disadvantages are primarily the costs of such a program and the modest number of individuals benefiting, but these disadvantages might be ameliorated by efficiencies of multiplex testing.

Turning from pharmacogenomic perspectives to specific diseases, we might ask, further, whether DNA screening for the adult population as part of routine primary care will be justified soon—and whether there are genotypes and disorders that are attractive candidates at present. I will comment briefly on α_1-antitrypsin

deficiency, hemochromatosis, factor V Leiden, and apo E in this context. The α_1-antitrypsin ZZ genotype confers a high risk of emphysema and has a frequency of ~1/5,000 in the U.S. Caucasian population, with a higher incidence in some European populations (Cox 1995). Smoking is a crucial variable in survival, and counseling for smoking cessation or avoidance is a potentially important intervention. Recombinant-protein therapy is under evaluation, and gene therapy is a possibility for the future. Do the potential benefits justify population-based testing? There is a dramatic reduction in morbidity and mortality if smoking is avoided. The age for 50% survival is ~40 years for ZZ smokers, compared with >60 years for ZZ nonsmokers (Larsson 1978). One could argue either that the current absence of population-based screening for α_1-antitrypsin is a missed opportunity for genomic medicine or that the current lack of screening provides evidence that genomic medicine will not be embraced by the medical establishment. Alternatively, perhaps the current intervention is not adequate, so that the case for ZZ screening is not compelling. The answer likely hinges on the effectiveness of intervention, a recurring theme in evaluating the potential for genomic medicine. If further research indicated that 90% of ZZ individuals would avoid smoking if they knew their genotype and risks early in life, or if a pharmacological or gene-therapy cure were available, the justification for screening programs would become compelling. Perhaps it is unrealistic to hope for dramatic behavior modification, although a Swedish study found that only 10% of 18-year-olds detected as ZZ through newborn screening smoked, compared with 21% of controls (Sveger et al. 1995).

I would like to turn to hemochromatosis, which I have long seen as an extraordinary opportunity for population-based screening to save lives. Even before cloning the gene, we could anticipate the existence of a few common mutations based on linkage-disequilibrium data, and an effective treatment was well established. Hemochromatosis is an autosomal recessive disorder that causes life-threatening damage to the liver, heart, pancreas, and other organs (Bothwell et al. 1995). The frequency of homozygotes for susceptibility is remarkably high, with 1/200–500 Caucasians at risk. Men are more often symptomatic in approximately a 5:1 ratio, and alcohol intake is a risk factor. The treatment is avoidance of iron supplements and removal of blood—and, thus, iron—by phlebotomy, if iron overload develops. The available data suggest that outcome is excellent if treatment is implemented early. The penetrance for a homozygous susceptibility genotype in hemochromatosis is uncertain, but a much higher frequency is found when populations are screened for serum iron elevations than when symptomatic probands are diagnosed. The gene for hemochromatosis, designated "*HFE,*" was cloned in 1996 (Feder et al. 1996). Two mutations, C282Y and H63D, are particularly common, and various DNA studies have found two mutant alleles in 70%–95%—or even 100%—of symptomatic probands (Burke et al. 1998). Thus, there is the potential to dramatically reduce or eliminate morbidity and mortality from hemochromatosis, through population-based genotyping. Individuals with at-risk genotypes could be monitored, and phlebotomy initiated, if iron overload occurs.

A consensus conference convened March 3, 1997, by the Centers for Disease Control and Prevention and the National Human Genome Research Institute specifically addressed the question of population-based screening by DNA analysis (Burke et al. 1998). A prestigious group recommended against population-based screening for hemochromatosis at this time and identified concerns regarding prevalence, penetrance, optimal care, stigmatization, and discrimination. It was recommended that there be a high priority for population-based research. Despite this recommendation, I believe there is still room for considerable concern regarding the proper course of action. Even prior to cloning of the gene, population screening by serum iron was recommended by the College of American Pathologists (Witte et al. 1996). I am troubled by the consensus recommendation against screening, and I believe there may be considerably greater benefits to proceeding with screening rather than delaying, recognizing the uncertainties. On the basis of reports of the incidence of symptomatic probands (Bothwell et al. 1995; Burke et al. 1998), there is the potential to save 250–1,000 lives/year in the United States, or more, if underdiagnosis of symptomatic individuals is significant; these numbers compare to ~200 new phenylketonurics diagnosed per year. The situation is reminiscent of the early days of PKU treatment. If we had delayed dietary therapy for PKU until we had all the answers, many more children would have suffered irreversible brain damage. I fail to see a significant threat of stigmatization or discrimination for a disorder for which there is agreement that effective treatment is available. We are the most informed consumers in this area, and I suspect that most of us would decline apo E testing for Alzheimer disease (which I will discuss in a moment) but would welcome hemochromatosis testing. If it would be good for us, why not for the rest of the population? Would a patient diagnosed in the terminal untreatable phase of this disease 2–3 years hence have a legitimate retrospective complaint that screening was not performed in earlier years? Screening for hemochromatosis may be primarily a question of how rapidly to proceed, rather than deep disagreement, but I believe that population-based screening will become routine soon, perhaps due more to changes in perception than to new data.

If we consider factor V Leiden, we learn that this

mutation causes resistance of factor V to degradation by activated protein C. Heterozygosity for the mutation is remarkably frequent, with 6% of the population being a representative number. One study found a 2.7-fold relative risk for venous thrombosis overall and as high as a 7-fold increased risk for primary disease in older men (Ridker et al. 1995). What remains to be determined is whether there is an effective intervention that should be offered on a routine basis to individuals with this genotype. Another interesting question might be whether the genotype represents a risk factor for thrombosis with birth control pills, in which case screening prior to administration would be relevant. It is reasonable to imagine that existing or novel drug therapies might be indicated on a prophylactic basis for individuals with factor V Leiden, under at least certain circumstances. Factor V Leiden represents a very interesting example where the uncertain benefits relative to burdens, such as undue anxiety, make it difficult to argue for routine genotyping at present, although this could change. Factor V Leiden exemplifies the many complexities that we will face in determining whether genotypes of modest effect or penetrance are suitable for screening.

Apo E genotyping poses a thought-provoking situation. The 2/2 genotype is associated with type III hyperlipoproteinemia. Heterozygosity for the 4 allele is associated with increased risk and/or earlier onset of Alzheimer disease. Importantly, 35%–50% of Alzheimer patients do not have the 4 allele. The risk is higher for Alzheimer disease in 4/4 homozygotes. There is certainly general agreement at present that genotyping for apo E is not appropriate as a presymptomatic assessment for risk of Alzheimer disease (ACMG/ASHG Working Group on ApoE and Alzheimer Testing 1995). However, if novel pharmacotherapies or other interventions were developed that reduced, delayed, or eliminated this risk, a case might evolve in favor of population-based genotyping. On the other hand, one might imagine new interventions that were relevant to the occurrence of Alzheimer disease generally raising questions of population-based therapeutics *without regard to genotype*, perhaps more reminiscent of the use of folate supplementation for prevention of neural-tube defects.

Although everyone may not be convinced quite yet, it is likely that primary-care medicine will soon incorporate age-related panels for genetic screening focused on those disorders for which there is compelling therapeutic intervention. We might envision a young-adult screening panel—and perhaps a childhood or adolescent panel—for those disorders where earlier intervention was shown to be essential. These panels would probably evolve rather rapidly over the next 2 decades, and testing might be repeated at intervals, because the panel used in 2005 will be quite outmoded compared with that available in 2010. The single most important variable in pursuing this strategy is the need for effective intervention for those individuals identified as having specific genotypes. This requirement substantially reduces concerns that individuals will suffer discrimination or undue anxiety based on genotype. When intervention is beneficial but not completely effective, it will be more difficult to balance the risks and benefits of screening. It is likely and appropriate that societies will incorporate legal prohibitions against discrimination based on genotype, which would help in maximizing the benefit and minimizing the risk of these strategies. There may be an important threshold effect for population-based DNA testing. Perhaps this strategy awaits a single compelling application to justify implementation, as was the case for PKU and newborn screening; hemochromatosis may prove to be the icebreaker for population-based screening in adults. If this were to occur, the cost of adding tests would be significantly reduced as the processes for consent, sample collection, and reporting could serve for multiple tests. Multiplexing disease-specific genotyping with pharmacogenetic testing might be an attractive early option. The understanding and consent for such strategies could become as routine as those for measuring blood pressure or cholesterol in today's medical care. We can anticipate great challenges in the education of medical providers and the public, but the education process is likely to parallel rather than precede implementation. Perhaps the education experiences will be similar to that for maternal-serum screening, with a generous mix of deficiencies and successes but eventual achievement of understanding comparable to that for any other aspect of complex modern medicine. Any screening panel for reproductive risks unrelated to the health of the individual should presumably be maintained as a separate process, with the informed-consent requirements for reproductive screening being substantially different from those for general health screening.

Next I will consider how complex traits might fit into this futuristic genomic medicine. Let me begin by distinguishing two types of complexity with relevance to genotype-based diagnosis and treatment (fig. 1). One instance involves phenotypes in which multiple loci contribute to increased genetic susceptibility in individual

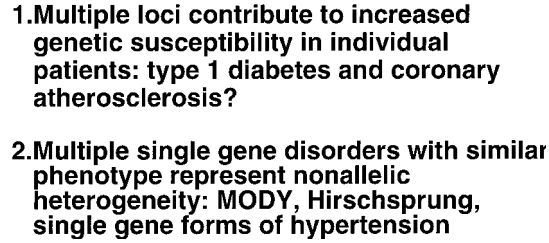

Figure 1 Two types of complexity within complex traits

patients, what I might call "truly complex traits." Type 1 diabetes mellitus and most cases of coronary atherosclerosis are likely to fit such a model. This can be contrasted with complexity involving multiple single-gene disorders giving rise to a single phenotype, essentially representing examples of locus heterogeneity. In the latter case, a single major locus is the determining factor in any one patient or family. Research on complex traits often will not be able to distinguish prospectively those instances where multiple loci contribute to disease in a single individual from instances of phenotypically similar single-gene disorders. The distinction may be only a retrospective one, and both types of complexity will often exist within a single disorder. It is worthwhile to emphasize the perspective that there is no boundary between single-gene disorders and complex traits. Virtually all single-gene disorders are subject to modifier effects by the remainder of the genotype. This is particularly true for dominant mutations and genotypes with low penetrance. Figure 2 depicts this continuum, including a single-gene example with small modifier effects, a case determined by a major-gene effect with more substantial modifiers, and a more complex trait with many genes contributing modest effects. Nongenetic factors modify—or, here, rain down on—all of these underlying genotypes. In many cases, this should be thought of as a continuum of individual subjects within a single disorder—with a proportion of cases having single-gene, major-gene, or complex genetic effects—rather than as a continuum of different disorders. We can imagine virtually any number of genes contributing to a phenotype, with the impact of any one locus ranging from minimal to major, so that there are virtually infinite combinatorial possibilities for genetic contribution to susceptibility to any disease process.

If we ask about recent dramatic progress in the etiology of complex traits, our attention is likely to be drawn to maturity-onset diabetes of the young (MODY), Hirschsprung disease, and some single-gene forms of hypertension. Heterozygous mutations at any of at least four loci are now known to cause MODY, including glucokinase and three different hepatocyte nuclear-transcription factors (Vionnet et al. 1992; Yamagata et al. 1996*a,* 1996*b;* Horikawa et al. 1997). In the case of Hirschsprung disease, heterozygous mutations have been identified for at least five or six genes, including the *RET* oncogene and those for glial-cell line–derived neurotrophic-factor receptor (*GDNF*)–α, Sox 10, endothelin-B receptor, endothelin 3, and neurturin (Attie et al. 1995; Edery et al. 1996; Hofstra et al. 1997; Doray et al. 1998; Kuhlbrodt et al. 1998; Tanaka et al. 1998). The *RET* oncogene is the major player. Although the genetics of Hirschsprung disease is somewhat complex, with modifier effects and possible digenic inheritance, MODY—and, to some extent, Hirschsprung disease—seem to me to be complex primarily in the same way that Sanfilippo diseases A–D, with four different enzyme defects, are complex—that is, they represent examples of locus heterogeneity for single-gene disorders. These examples alert us to the possibility that heterogeneity of single-gene or major-gene effects may be more extensive within complex traits than we anticipate—or, at least, that progress in dissecting genetic factors may come more readily in such cases.

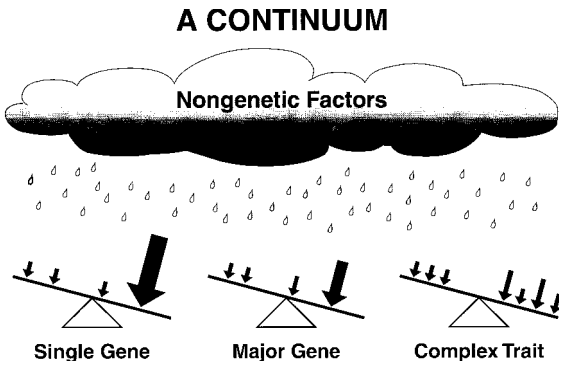

Figure 2 A continuum of genetic complexity. This continuum can be considered among disorders ranging from single gene, to major gene, to complex trait but can also be considered in the context of individual subjects within a single phenotype such as Hirschsprung disease, hypertension, or coronary atherosclerosis.

Similarly, there are now numerous single-gene disorders identified as causing hypertension, including glucocorticoid-remediable aldosteronism caused by unequal crossing-over affecting the aldosterone synthase locus; apparent mineralocorticoid excess caused by mutations of 11 β-hydroxysteroid dehydrogenase; and pseudohyperaldosteronism caused by activating mutations in either of two subunits for a renal sodium channel (Lifton 1996). The case of unequal crossing-over putting the aldosterone synthase–coding region under control of the ACTH-inducible 11β-hydroxylase promoter is particularly satisfying, since a genotype-specific therapy based on corticosteroid administration is highly beneficial. Perhaps the sodium-channel loci are intriguing as candidates for harboring milder polymorphic alleles that could predispose to more-common forms of hypertension. Angiotensinogen polymorphisms are also strongly implicated as a risk factor for hypertension. The evolving data on hypertension demonstrate that there are likely to be individuals in the population who essentially have a single-gene disorder—along with many others, presumably the majority, who have a complex trait with multiple loci contributing to their increased susceptibility—and a continuum where any number of loci may contribute to varying degrees for any one individual. It is attractive to consider the possibility that there are still a few major common alleles to be identified in hyper-

tension and that the condition involves more locus heterogeneity—with major-gene effects in more patients and families—than we anticipate. Perhaps this is not beyond hope, given major ethnic differences in risk.

In attempting to derive some additional perspective regarding complex traits, I found it useful to refer to the report of a meeting, entitled "The Genetic Architecture of Complex Traits," that I had the opportunity to attend at the end of 1997. The executive summary begins with the following: "Most genetic traits of interest in populations of humans and other organisms are determined by many factors, including genetic and environmental components, which interact in often unpredictable ways. For such complex traits, the whole is not only greater than the sum of its parts, it may be different from the sum of its parts. Thus complex traits have a genetic architecture that consists of the genetic and environmental factors that contribute to the trait, as well as their magnitude and their interactions."

As I listened to researcher after researcher emphasize the enormous complexity of the problem, I think that one of the "communications" from the meeting summed it up the best for me, as follows: "The analysis of complex traits does not lend itself to quick and easy solutions"—and perhaps I might add "and thus applications to the practice of medicine may be slow to evolve."

In a more optimistic perspective, one more-recent proposal is to move aggressively to identify thousands of SNPs and to focus on the use of association studies to identify common variants affecting disease risks (Lander 1996; Risch and Merikangas 1996; Collins et al. 1997). SNPs may themselves be risk factors or might identify nearby disease polymorphisms by virtue of linkage disequilibrium. An emphasis on coding regions or cSNPs that involve amino acid polymorphisms is envisioned. The data for many such polymorphisms are probably already embedded in private and public databases of redundant cDNA sequencing, waiting to be unearthed. This approach now has a substantial momentum and is likely to identify numerous polymorphisms of disease relevance. If many of the variants identified have very modest phenotypic effects, they may be more useful for dissecting pathogenesis and developing general therapeutic approaches than for genotype-based diagnosis and intervention.

Along these lines, exciting data are being generated, and I would particularly note the recent report of the sequencing of 9.7 kb of the lipoprotein lipase gene (Clark et al. 1998; Nickerson et al. 1998). Sequencing of this region from 71 individuals, or 142 chromosomes, identified 88 variable sites, or 1/500 bp. This included 79 SNPs, of which 4 changed amino acids in the coding sequence. Nine insertion/deletion variants were identified. On the one hand, this is exactly the type of data we seek, but, on the other hand, the interpretation of this extraordinary complexity is extremely challenging. For today's perspective, perhaps the most relevant fact is that one of the amino acid polymorphisms was already implicated as a risk factor in coronary atherosclerosis.

Given some of these possibilities regarding complex traits, I will offer a few speculations. First, it is likely to be proportionally more difficult to unravel genotype-phenotype correlations with increasing numbers of loci contributing to the phenotype in a single patient, and genotype-based medicine may be slow to evolve for the disorders with more-complex genetic etiology. On the other hand, it seems likely that a modest or even substantial number of additional common disease–related polymorphisms involving amino acid substitutions ("coding SNPs" in today's jargon) comparable to factor V Leiden and apo E will be identified in the population over the coming decade or two. Variants of this type would seem to hold the greatest promise for the short term. It would be favorable in terms of the potential for research progress and therapeutic intervention if many of the common disorders in the adult population involved a single locus contributing a major portion of the genetic risk in a single patient or family, even if different loci were pivotal in different patients. The greater the role of a major gene in an individual patient, the better the prospects for genotypic diagnosis, understanding the pathogenesis, and rational intervention. To the extent that individual patients are affected by complex traits in which many loci contribute to the susceptibility to disease, efforts to develop therapeutic intervention might best be focused on some final common component of pathogenesis, and efficacy may be similar for a broad range of genotypes.

Given the relative importance of heart disease and cancer in the adult population, I would like to briefly consider these two conditions in the context of genomic medicine. Focusing more specifically on coronary atherosclerosis, we now know of innumerable loci that can affect risks, including the LDL receptor; apolipoproteins A–I, B, E, and others; lipoprotein(a); lipoprotein lipase; loci affecting homocysteine levels; and others. There are almost certainly numerous additional important loci whose contribution to risk is yet to be defined. Considering these data, we might think that a genotyping panel would be extremely valuable in complementing LDL and HDL cholesterol values for the assessment of atherosclerotic risk. However, nongenetic factors are also very important, and extensive genotyping is certainly not widely utilized and may be difficult to justify. We know that a modest proportion of patients have their risk determined primarily by a single locus, as in the case of familial hypercholesterolemia, but it seems likely that genetic risk is determined by multiple loci for the majority of individuals with coronary atherosclerosis. For families with a single major locus, aggressive efforts to

establish the diagnosis at a gene-specific and mutation level and to offer testing to extended families is a potentially important strategy, particularly if there is evidence for genotype-specific intervention. On the other hand, we must consider the possibility that genotype-based medicine will not be the way of the future, regarding coronary atherosclerosis. Brown and Goldstein, in an editorial entitled "Heart Attacks: Gone with the Century?" (1996), suggest that noninvasive screening methods to detect coronary atherosclerosis in its earliest stages, combined with aggressive use of the statin class of HMG-CoA reductase inhibitors, might dramatically reduce the incidence of myocardial infarction in the next century. In preparing for today's presentation, I conferred with Dr. Goldstein, and he continues to envision this scenario, with uncertain emphasis on genotype-specific intervention. It is difficult to predict the extent to which diagnosis and management of coronary atherosclerosis risks will involve genotype-based or genotype-independent medicine, but some combination of the two is likely to prevail. A genetic-based further dissection of the pathogenesis of and risk factors for atherosclerosis, particularly the endothelial and inflammatory components that are currently poorly defined, is sure to be important. Although we, as geneticists, would find it intellectually far more satisfying to evolve toward a genotype-based prevention, the widespread use of statins or other novel interventions based on coronary imaging, rather than genotyping, may prove to be the most pragmatic course.

Turning to genomic medicine and cancer, I would like to narrow the discussion to colon cancer, to highlight a few perspectives. You are aware of the remarkable molecular data demonstrating mutations in the *APC* locus causing polyposis of the colon and mutations in mismatch-repair genes causing HNPCC, as exemplified by the work of Bert Vogelstein, this year's Allan Award recipient. I asked Dr. Vogelstein what he perceived to be the current and future impact of genotype-based medicine in the field of colon cancer. He felt that "the impact was already dramatic in the case of familial polyposis and HNPCC," with numerous lives undoubtedly saved by family evaluations and appropriate screening for pathology (B. Vogelstein, personal communication). There are exciting new data suggesting that chemoprevention for colon cancer may be a significant strategy to delay or preclude the need for colectomy.

Turning for a moment to polyposis of the colon, we learn an interesting lesson regarding the milder phenotypic spectrum associated with allelic heterogeneity. We start with the evidence that classical polyposis families represent only a small proportion of all cases of colon cancer. This is followed by reports of families with attenuated disease with smaller numbers of polyps but still increased risk of colon cancer. These kinds of observations might lead us to suspect that the genetic contribution to many cancers and to adult diseases in general may yet prove greater than is generally appreciated. The occurrence of the I1307K allele at the *APC* locus is particularly fascinating and instructive (Laken et al. 1997). In this instance, a single nucleotide mutation generates an eight-base tract of adenine nucleotides in the coding region. This allele, then, is hypermutable, with increased occurrence of frameshift mutations. The mutation is found in 6%–8% of individuals of Ashkenazic descent. The allele is associated with an increased risk of colorectal cancer and perhaps other tumors, but the penetrance is quite low, with only a 1.5–2.0 odds ratio for various tumors. Although this allele is conceptually fascinating, the low penetrance makes its clinical importance uncertain, and it would seem to be a questionable candidate for population-based screening, depending once again on the potential for intervention.

In the case of HNPCC, there is an immediate opportunity for improving the practice of family-based genomic medicine. The incidence of HNPCC is ~1/200–1,000, in various studies, and related genotypes are estimated to cause ~3% of colorectal cancer (Kinzler and Vogelstein 1998). In the case of HNPCC, there is a very high penetrance, with one study reporting a lifetime risk for colorectal cancer of 74% in males and 30% in females, an impressive sex difference (Dunlop et al. 1997). The risk of uterine endometrial cancer is very high, at 42%. Heterozygous, germ-line, and loss-of-function mutations at any of four loci involved in mismatch repair (*MSH2, MLH1, PMS2,* and *PMS1*) can cause HNPCC. There is strong evidence that screening for polyps and the option of colectomy provide very meaningful intervention. The lifetime penetrance for various cancers is a 91% total risk for males and 69% for females (Dunlop et al. 1997). Interestingly, these data were generated in Scotland by studying 156 relatives of only six probands, to identify 67 gene carriers; this is 11 gene carriers found for each proband. In families with a history of colon cancer or in individuals presenting with newly diagnosed colon cancer, it would be extremely desirable to identify those individuals with germline mutations involving the mismatch-repair genes. The vast majority of individuals with HNPCC have inherited rather than de novo mutations, as is also true for many other forms of genetic cancer predisposition, including BRCA1 and BRCA2. This means that diagnosis of a single index case can often lead to the identification of innumerable at-risk relatives for whom careful family evaluations could prevent many cancer deaths. Once again, the availability and quality of intervention are major determinants of the attractiveness of such family-based screening. In general, intervention for the cancer genetic syndromes varies from extremely valuable but certainly not simple, for HNPCC, to complex for

BRCA1 and BRCA2, to very problematic for Li-Fraumeni syndrome. At present, the majority of individuals with HNPCC-related cancers probably are not having their germ-line mutation recognized, and much more effective programs in this regard could save many lives. If HNPCC represents 3% of colorectal cancer and there are ~60,000 deaths from this condition in the United States each year, ~1,800 lives could be saved per year if we could eliminate deaths from colorectal cancer in HNPCC families. Perhaps the biggest challenge is to educate family members about the great benefits of screening and to convince them that the benefits outweigh the burdens of testing.

The use of family-based rather than population-based screening for identification of at-risk genotypes is relevant to many autosomal dominant disorders, when most cases represent inherited rather than de novo mutations. Any family-based strategies depend on the level of interest within at-risk families, which in turn depends on our ability to develop definitive interventions that are so clearly beneficial that they overcome the understandable skepticism and fears regarding testing.

This leads me to the possibility that reproductive options may deserve greater consideration for these dominant disorders. Many disorders—such as HNPCC, BRCA1/BRCA2, MODY, triplet-repeat neurodegenerative disorders, and familial hypercholesterolemia—could be considered in this context. In many cases, the potential for therapeutic advances for these disorders is intriguing but uncertain. With regard to the many disorders where the majority of cases represent inherited mutations, it seems safe to assume that couples would prefer to bear children spared of these mutations, particularly if therapeutic advances are slow to evolve. The incidence of many of these disorders theoretically could be dramatically reduced in the population, through reproductive avoidance. Although most couples would welcome a simple method to preferentially conceive children free of the disease genotype, few are ready to consider conventional prenatal diagnosis and selective termination of pregnancy, in this clinical setting. Perhaps preimplantation diagnosis could play a much greater role. In view of the fact that the risk of disease would be eliminated for future generations within a family, the burden, inefficiencies, and cost of preimplantation diagnosis might be acceptable, to avoid the risk of serious and poorly treatable disorders for generations. Thus, another challenge for young investigators is to greatly enhance current methods for preimplantation diagnosis. One *substantial* obstacle in avoiding these dominant disorders through reproductive options is the need for young, reproductive-aged family members at risk to put aside their fears and learn about the disorder within a family. In a more futuristic vein, it is interesting to speculate whether disorders of this type might be avoided through some completely novel strategy such as sorting of sperm on the basis of single-nucleotide differences. This would permit reducing the incidence of a disorder by half, in each generation. Perhaps this fantasy is beyond the reach of even the brightest young investigators in our midst. In the reproductive strategies for this group of disorders, there are many important issues. These include age-related penetrance, with many years of good health leading us to think less about reproductive prevention; the uncertainties of present and future therapeutic interventions; and, perhaps most important, the need for reproductive-aged family members to become intimately involved in assessing their genetic risks. If a disorder is more serious and resistant to alternative therapies, the impetus to consider reproductive avoidance is greater, so that such an option may be much more relevant to a disorder such as Li-Fraumeni syndrome, where treatment is very difficult, than for familial hypercholesterolemia, where drug therapy is of great benefit. I would again propose the challenge to develop novel technologies to allow families in this circumstance to preferentially bear children free of serious deleterious mutations.

As I move toward the end of my presentation, I would like to return to my opening questions: How will genetic advances impact the practice of medicine over the next decade or two? One way genetics will impact the practice of medicine is through new advances in our discipline. I think it is quite predictable that there will be major technical improvements in detecting cytogenetic abnormalities, and I would propose that some of these improvements may be of the magnitude that we observed with the development of banded karyotypes. Many of our patients with mental retardation and birth defects may have cytogenetic abnormalities detectable by new technologies. I think we can also predict with confidence that there will continue to be major advances in the identification of disease genes and mutations, with major benefits for diagnosis and counseling. It would seem that we are completing the first of what may be 2 or 3 decades of a research boom in this arena. Although we have identified disease genes for the vast majority of more-common, single-gene disorders, similar developments for rarer disorders should occur at a faster and faster pace. We should also expect the discovery of many more disease-related coding SNPs. I anticipate incremental advances in disease-specific therapies, such as the example of glucocorticoid-remediable aldosteronism, which I mentioned, or implantable pacemakers for genetic disorders causing arrhythmias and sudden death. In the next few years, I anticipate the identification of single-gene or major-gene effects contributing to psychiatric illness, perhaps starting with schizophrenia or manic depression. I speculate that we will see remarkable pharmacological advances, with drugs for Alzheimer disease

and drugs for neurodegenerative triplet-repeat disorders, and improvements in drugs for atherosclerosis. I anticipate that genetic dissection of pathogenesis will be a major factor in developing these novel therapies. I anticipate the development of drugs that have true effectiveness for weight control, on the basis of genetic insight into the pathogenesis of obesity. These drugs would have major relevance to diseases such as hypertension and type II diabetes. The use of chemoprevention to reduce cancer risks is also a very promising and relatively new area for further study, although it seems unlikely that such strategies would completely eliminate the risk of some of the more penetrant genetic predispositions to cancer. Of course, there will be the unanticipated breakthroughs, and we might ask ourselves what the next equivalent of PCR in human genetics will be. Will we see breakthroughs that have a dramatic and generalizable relevance to therapeutic intervention as opposed to diagnosis?

There is also the question of whether somatic gene therapy might eventually live up to its promise. On this issue I will enroll as a somewhat chastened, but persistent, optimist. Continuing efforts provide some evidence for improvements in nonviral delivery systems, adeno-associated viral vectors, newer generations of adenoviral vectors, and lentiviral vectors. The ability to produce extracellular proteins such as clotting factors, erythropoietin, and other hormones seems imminent, through delivery to skeletal muscle, hepatocytes, or other sites. The potential for persistent expression in hepatocytes could provide correction of numerous inborn errors of metabolism and treatment of other disorders. The potential to correct genetic defects in bone-marrow stem cells, by one or another strategy, continues to hold great promise for the treatment of globally important disorders such as sickle-cell anemia and β-thalassemia. I believe that we should continue to press for advances in somatic gene therapy, in the hope that the benefits we might have envisioned for the current decade will come to fruition in the next decade or two.

Another way for genetics to impact the practice of medicine is for us to draw certain lessons from available data. As we consider the potential for genomic medicine, it is obvious that genes of major effect and genotypes causing serious burden or high penetrance, such as HNPCC, are of much greater potential importance than alleles with smaller effects, such as for the I1307K mutation at the polyposis locus. Within "complex traits," circumstances where a single locus has a major effect appear much more tractable for applications of genomic medicine than when multiple loci determine susceptibility in a single individual. The availability of intervention is the most crucial variable. We are paralyzed by its absence in the case of apo E genotypes and Alzheimer disease, but we have more to offer in the case of phlebotomy and hemochromatosis. Some therapies will be very genotype specific, such as phenylacetate for sickle-cell anemia or enzyme replacement for Gaucher disease, while others may be broadly applicable in the population, benefiting people of widely different genotypes, as may be the case for folic acid supplementation, antioxidants, or statin drugs. The more widely applicable interventions raise the rather frightening specter of large portions of the population taking numerous medications on a lifelong basis, something we would need to consider carefully, case by case. In some instances it may be quite appropriate to consider population-based testing, as perhaps in the case of α_1-antitrypsin, hemochromatosis, or pharmacogenetic traits, while family-based testing may be more appropriate in disorders such as HNPCC. We should keep in mind that genotypic information collected in one generation may dramatically alter considerations for future generations. Increasingly, children will be born into families in which they grow up to learn that their parents have particular genotypes of disease relevance. This may be acceptable if we have restricted ourselves to collecting genotypic information that allows meaningful therapeutic intervention. In some cases, we may encounter milder alleles at loci initially discovered on the basis of severe phenotypes, as I mentioned for polyposis and speculated on in the context of sodium-channel genes and hypertension. Attempts to educate medical providers and the public are likely to be successful at the time when new programs are implemented, as has been experienced to date with new genetic services.

Let us now return to my other question: What should we be doing to influence these developments? I have suggested that we should explore expanded reproductive screening and prenatal diagnosis for the group of disorders I characterize as seemingly insurmountable, focusing on couples seeking maximal prenatal screening. I think that we should work to make population-based screening for treatable adult diseases a reality, and I have emphasized how we could be saving lives taken by hemochromatosis. I have advocated identifying probands and using family-based screening for treatable dominant disorders, as exemplified by how we could be saving lives taken by HNPCC.

In conclusion, I want to lay out some challenges or recommendations for us as a Society. We cannot be oblivious to the risks of genetic testing or to the fears it engenders. I have focused excessively on opportunities and have given insufficient time to the risks, harms, and burdens of these approaches, and we do need to recognize these risks, but we should not let these concerns prevent us from vigorously exploring the benefits of genetic testing. Some inconveniences, emotional burdens, and financial costs can be accepted if the benefits are real and substantial, as we have experienced for newborn

screening. Both the scientific and the lay press are *emphasizing the risks,* as exemplified by a recent headline citing the advice of a British committee properly cautioning against the risks of genetic testing for mental disorders (Dickson 1998). We need comparable emphasis on the potential benefits. To make the benefits of genomic medicine clearly outweigh the risks, we must develop more and better therapeutic interventions. Although a research society such as ours is dedicated, in part, to the pursuit of knowledge for its own sake, and although we can take great pride in the molecular definition of genetic disease that is being developed, I believe we should make every effort to maximize the benefits to society, largely through improved disease prevention and therapeutic intervention. We must develop new technologies and approaches to solve difficult problems. We should encourage young investigators to take on the most difficult challenges, some of which I have mentioned. Are we ready to use the insights of chemical individuality, as recognized by Garrod (1931), to practice a new form of genotype-based medicine? The membership of our Society encompasses broad expertise in human genetics, and it is our responsibility to provide the leadership to maximize the benefits of human genetic knowledge for society.

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Electronic-Database Information

GeneMap '98, http://www.ncbi.nlm.nih.gov/GeneMap

Genetic Architecture of Complex Traits, http://www.sfbr.org/nigms/Report.html

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