The Human as an Experimental System in Molecular Genetics

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There are compelling reasons for choosing to develop the human as the highest-order experimental system in genetics: an obvious social context that stirs interest, wide medical observation of the population that permits identification of an abundance of genetic defects, and our ability to perceive in the human subtle or complex variations that may not be observable in other species. Various lines of genetic inquiry that are based on research in other systems—cytogenetic analysis, biochemical studies, mapping of defective loci by linkage analysis in affected families, and in vitro techniques such as the creation of transgenic organisms—complement and enrich each other. New phenomena that would not have been predicted from investigations in other organisms have been found in humans, such as the discovery of the "giant" Duchenne muscular dystrophy gene and the identification of recessive cancer genes. Genetic research is yielding insights into human biology that are raising new possibilities for therapy and prevention of disease, as well as challenges to society in the form of ethical decisions about the appropriate application of genetic information.

THE HUMAN SPECIES HOLDS A SPECIAL FASCINATION FOR scientific investigation. As a consequence, skilled investigators have been drawn to direct study of the human, independently of specific experimental problems or advantages. Earlier researchers had selected *Drosophila* for its favored genetic traits and because of its short generation time, ease of culture and other experimentally useful characteristics. Additional, crucially important experimental advantages are embedded in the enormous background of knowledge that has accrued from decades of detailed study and that continues to be expanded by the current cohort of skilled investigators. Techniques that have been developed in *Drosophila* are now being applied to the study of human genetics. However, the human system has extrinsic advantages that are committed to the human as the system of choice for study of many fundamental problems in molecular biology and genetics.

Funding is one of the requisite tools of research. The human system has fared well in this competition, because a primary motive of society in the funding of research is the hope of discoveries that will ease the human condition. Proposals to clarify mechanisms of specific diseases have had a high priority. The human social context has created a critical mass of knowledge and of investigators

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A Complex Surveillance System Exists for Human Populations

No other species is observed so closely for variation as *Homo sapiens*. Physicians examine hundreds of millions of individuals, sometimes detecting even the most subtle variations. Geneticists are complemented by clinicians and researchers in hematology, oncology, immunology, cardiology, and neurology. Each group has made significant contributions toward the identification of genetic defects that may be associated with complex conditions such as leukemia, arthritis, hematologic disorders, vascular disease, and psychiatric and neurological anomalies. Because this screening takes place on such a large scale, examples of even quite rare events are often documented. As a consequence, the catalog of human genetic variants now describes more than 4000 distinct Mendelian conditions (*1*); by comparison, only 700 genetic loci have been identified in the mouse (*2*).

The human system, therefore, comes equipped with an astonishingly broad array of characterized mutant phenotypes; thousands of human genes have been identified by virtue of the phenotype they confer when inherited in mutant form. The mutations range from straightforward deficiencies in enzymes that are important in basic metabolic pathways to subtle alterations that affect our psychology. The number of individual subjects examined in detail by phenotypic experts, the physicians, is far greater than for any other system.

Clinical surveillance uncovers rare metabolic mutations. The clinical description of a patient may identify a genetic variation, but rarely determines the etiology of the defect. Further characterization depends on a judicious choice of appropriate testing methods. For example, molecular and biochemical study of human heritable metabolic diseases has been a highly productive means of identifying genes. In this arena, the human has an advantage over the mouse as an experimental system, since metabolic disorders frequently bring the patient, of his or her own volition, to the physician. Table 1 details some of the disorders for which biochemical analysis has provided insight into the deleterious mutation and a logical strategy for cloning the normal gene.

For each genetic anomaly listed, identification of a defective protein or enzyme, or of a compound produced in excess or accumulated in postmortem tissue in affected individuals, permitted investigators to accurately predict the nature of the genetic deficiency. A wide spectrum of molecular approaches was then applied for successfully cloning the putative gene as Table 1 shows; cloning strategies are outlined in Fig. 1. Automation and other improvements in procedures for sequencing and synthesizing amino acids and nucleic

acids have greatly simplified these alternatives (*3*). Once a gene is cloned, its chromosomal "home" can be readily identified by somatic cell hybridization. We estimate that more than 200 heritable genetic defects have been isolated and mapped by this approach.

Because multiple examples even of rare mutations are often available, a cloned gene provides access to a number of distinct mutations that may occur at the same locus. A variety of different mutations observable in a specific gene can provide valuable information on normal gene function and regulation, and insights into the natural history of the disorder in the population.

For example, the large number of mutations that have been examined at the hemoglobin loci in thalassemia patients have specified a wide spectrum of mutational lesions capable of reducing gene activity (*4*). Many of these have been analyzed, providing insights into messenger RNA metabolism as well as the specific molecular mechanism underlying the disease state for each patient. Examples of defects in transcription initiation, loss of proper splice sites, and emergence of new, improper splice sites have documented the belief that "anything that can go wrong, will go wrong" in human genetic systems.

Furthermore, mutational variants at the low-density lipoprotein (LDL) receptor locus (*LDLR*) yielded insights into the mechanism of receptor-mediated endocytosis (*5*). Variants were identified through an extensive population survey that detected many families who were segregating hypercholesterolemia. Mutant alleles that specifically block transport of the LDL receptor molecule to the membrane, or prevent association of the receptor with coated pits, or interfere with binding to the ligand, were each characterized; in turn, each mutation so identified served to characterize a specific step in lipid metabolism.

Nevertheless, for many inborn errors of metabolism the enzyme deficiency is unknown, and significant research opportunities remain. For example, the nature of the defect (or defects) resulting in X-linked Menkes' syndrome (*6*) and the autosomal-recessive Wilson's disease (*7*), both related to defective copper metabolism, is yet unresolved.

Medical observation uncovers rare but significant cytogenetic events. High-resolution cytogenetic studies often provide vital clues to the chromosomal location of an inherited defect or a somatic mutation. Again, even though the diseases and the presence of cytogenetic abnormalities may be rare (with a combined incidence in the population of about 0.05%), the large size of the population surveyed permits us to observe association between specific cytogenetic events and disease phenotypes frequently enough to make correlations. Several examples are listed in Table 2.

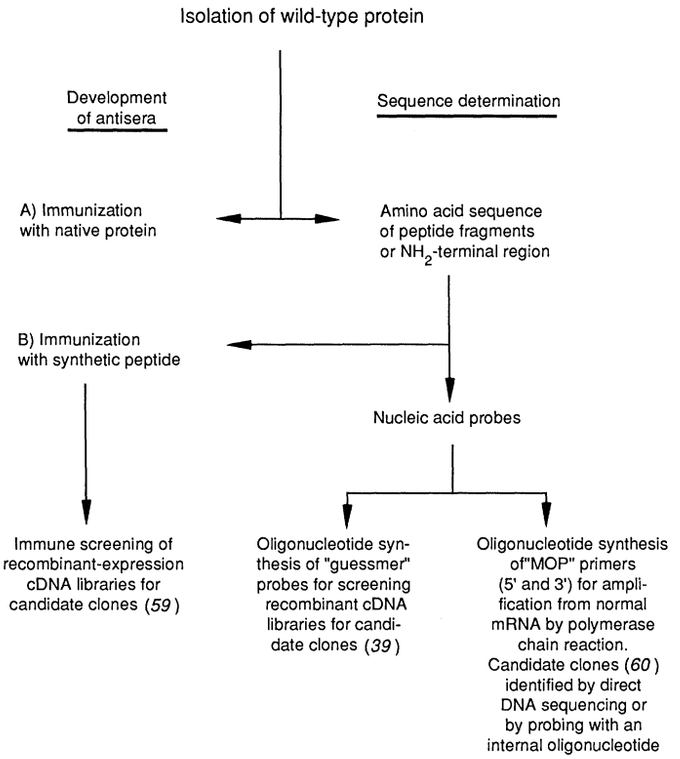

Fig. 1. Common strategies for isolation of disease genes.

Because of this surveillance system, a few individuals have been detected who are phenotypically males but have two X chromosomes. Analysis has revealed that a small portion of the Y chromosome has been translocated to the X, and has recently led to the identification of a putative testis-determining factor gene (*8*).

When chromosomal translocations are associated with specific tumor types, specific oncogenes can be implicated, as they have been in Burkitt lymphoma and chronic myeloid leukemia (CML). In these cases the translocation breakpoints are near the known location of an oncogene that was originally identified by its ability to cause cellular transformation to malignancy. In Burkitt lymphoma, both implicated genes involved in the translocation were cloned

Table 1. Mendelian disorders in which identified biochemical abnormalities have led to gene cloning. Abbreviations: HPRT, hypoxanthine-guanine phosphoribosyltransferase; ASA, arginosuccinase synthetase; PH, phenylalanine hydroxylase; LDL, low-density lipoprotein.

Disorder	Biochemical and genetic abnormality	Deficiency	Method for cloning gene
Lesch-Nyhan syndrome	X-linked hyperuricemia	HPRT	1. Overexpression: Isolation of cDNA from cells in which the gene is amplified (*33*) 2. Isolation of genomic fragment after nuclear DNA gene transfer (*34*)
Citrullinemia	Autosomal recessive; serum hyperammonemia and elevated serum/urinary citrulline	ASA	Overexpression: isolation of cDNA from cells with abnormal gene regulation (*35*)
Phenylketonuria	Autosomal recessive; elevated serum/urinary phenylalanine	PH	Antibody enrichment of polysomes containing PH mRNA (*36*)
Type IIa hypercholesterolemia	Autosomal dominant; hypercholesterolemia and elevated plasma LDL	LDL receptor	Antibody identification of a cDNA in a prokaryotic expression vector (*37*)
Tay-Sachs	Autosomal recessive; excess GM_2 ganglioside in postmortem brain tissue of children	Hexosaminidase A, α subunit	Antibody identification of a cDNA in a prokaryotic expression vector (*38*)
Hemophilia A	X-linked deficiency in intrinsic clotting pathway	Factor VIII	Synthetic oligonucleotide screening of genomic libraries (*39*)

prior to their being associated with the disease (*9*); in CML, the *abl* oncogene facilitated identification of its junction partner, *bcr*, which was previously unknown (*10*). Apparently, translocation causes juxtaposition of new regulatory regions, displaces normal regulatory elements, and alters the expression of genes involved in regulation of cell growth and differentiation. The ability to compare the location of translocation breakpoints with the known locations of oncogenes greatly enhances our ability to identify specific genes that are activated by a translocation; the large number of loci already mapped in the human genome facilitates such comparisons. This approach is complemented by the application of pulsed-field gel analysis (*11*), which can detect translocation junction fragments over long stretches of DNA. These methods may prove particularly useful for identifying the gene (or genes) involved in acute promyelocytic leukemia, where >95 percent of patients show a (15;17) translocation (*12*), and in acquired hematopoietic defects commonly associated with three deletions in chromosome 5 (*13*).

One form of X-linked mental retardation, which affects approximately 1 in 2000 males, is associated with another type of chromosomal abnormality, a fragile site at Xq27; it is the object of intensive cloning efforts (*14*). This kind of aberration, in which gaps or breaks occur more frequently when cells from affected individuals or carriers are grown in vitro, was first observed in the human system. The location of other fragile sites on human chromosomes, in some cases, appears to coincide with the location of proto-oncogenes (*15*).

Chromosomal deletions associated with such heritable diseases as Duchenne muscular dystrophy (DMD) and retinoblastoma (RB) have provided critical information leading to cloning of the gene involved (*16, 17*). The large size of the DMD gene (2000 kb) could not have been predicted beforehand. In both DMD and RB, cytogenetic alterations in patients' cells were the first clue to the molecular basis of the disease. Subsequently, they helped significantly in the identification of the genes; the deletions enabled investigators to sort quickly through libraries of cloned DNA segments for sequences specific to the region of interest, and even to enrich for them (*18*). The availability of region-specific clones then allowed the investigators to identify new deletions that had escaped cytogenetic detection because of their very small size. Cloned DNA sequences corresponding to the segment missing in the smallest deletions became excellent probes for investigating complementary DNA libraries derived from tissues where the putative genes were likely to be expressed. The large number of independent mutations harbored by the population as a whole at the loci for DMD and RB played an important role in these stepwise protocols.

Deletions within chromosome 13 found in surveys of patient populations not only provided the basis for the mapping of the gene for retinoblastoma to chromosome 13 but also opened the door for the significant and unexpected discovery of a new class of oncogenes, the "recessive oncogenes." The association of deletions with the disease suggested that hemizygosity for a mutant allele might be important in the disease; studies with DNA markers confirmed that indeed, loss of a chromosome 13 homolog was associated with tumorigenesis (*19*). This observation strongly supported the idea that a recessive, mutant allele of the retinoblastoma gene was located on the homolog that was retained and its phenotype revealed by loss of the normal allele.

Subsequently, chromosome loss or deletion has been characterized in a number of tumor types, both inherited and sporadic (*20*). Loss of a characteristic chromosome has recently served as a key to the mapping of the loci for two important inherited tumor types, acoustic neurofibromatosis (*21*), and multiple endocrine neoplasia, type I (*22*).

A substantial number of disorders that includes Prader-Willi syndrome (*23*), Miller-Dieker syndrome (*24*), and the myeloid and acute promyelocytic leukemias mentioned earlier (*10, 12*) have been associated with specific cytogenetic abnormalities, thus localizing important genes and giving molecular biologists a starting point for eventual identification of the molecular defect. It is possible to predict that the application of cytogenetic studies to diagnosis of birth defects will contribute to the localization and, ultimately, identification of human developmental genes as well.

Table 2. Diseases in which observation of cytogenetic abnormality has led to cloning of the implicated genes.

Disease	Cytogenetic findings	Genes implicated
Burkitt lymphoma	Translocation (8;14)	*myc*; μ heavy-chain enhancer (*9*)
Chronic myeloid leukemia (CML)	Translocation (9q;22q)	*abl*; *bcr* (*10*)
Duchenne muscular dystrophy	Deletion Xp21	Dystrophin (*34*)
Retinoblastoma	Deletion 13q14	*Rb* (*35*)

Mapping and Identification of Genes

Often the gene in which a human mutation occurs has no biochemical or cytogenetic correlate and is recognized only by its phenotypic effect on people who inherit the mutant allele. The biochemical and cytogenetic approaches outlined above are not applicable then. However, classical linkage analysis in families segregating the disease can still permit localization and identification of a gene whose product is unknown.

The logic underlying this approach is simple in concept and has been used in many other systems but its implementation in human systems is intricate. The basic premise of linkage analysis is that the defective gene must be located at some specific place on a specific chromosome. By correlating the inheritance of specific chromosomal regions (defined by DNA markers) with inheritance of the putative gene (defined by its phenotypic effect on family members) one can map the mutation to a specific region of a particular chromosome. The disease locus will show co-inheritance, or genetic linkage, with a DNA marker segment in its immediate vicinity on the chromosome. The linked marker may in turn serve to diagnose the inheritance of the mutant gene by family members in whom the phenotypic effect is not yet apparent.

The linkage approach depends completely, however, on our having genetic markers that will allow us to trace the inheritance of each part of every chromosome. A system of markers to cover the entire genome, based on direct detection of common variations in DNA sequence within the population, was considered several years ago (*25*); restriction enzymes would detect the variations in DNA sequence and DNA probes would define the fragments derived from specific genetic loci. The method is applicable both to arbitrary fragments of human DNA and to DNA segments associated with cloned genes. Large-scale screening is required to identify the combinations of DNA probes and restriction enzymes that detect common population variants in DNA sequence. The importance of identifying human genes that cause disease has stimulated development of hundreds of genetic markers in recent years, making the linkage approach now generally feasible. A growing number of mutations associated with human disease have been localized to specific chromosomal regions by linkage to DNA markers in affected families; Table 3 is a partial list.

Table 3. Chromosomal localization of defective genes by linkage analysis in affected families.

Disease	Chromosomal location
Chronic granulomatous disease*	Xp21 (*40*)
Huntington's chorea	4p16 (*41*)
Cystic fibrosis	7q21–22 (*42*)
Familial adenomatous polyposis	5q21–22 (*20*)
Polycystic kidney disease	16p13 (*43*)
Multiple endocrine neoplasia, type IIA	10q4 (*44*)
Type 1 neurofibromatosis	17cen-q21 (*45*)

*Cytochrome oxidase deficiency has been identified as the CGD defect.

For each of the disorders listed, major efforts are now under way to identify and clone the gene that harbors the mutation. Once localized to a particular chromosomal region, the gene must be more precisely mapped to a segment that contains only 1 to 3 million base pairs of DNA; a chromosomal segment of this size will contain only a few genes that are likely to be expressed in specific tissues affected by the disease in question. Chromosomal landmarks such as translocation breakpoints or small deletions can help to implicate a "candidate" gene within such a region, as described above. Biological assays for the candidate gene based on its activity would be helpful at this point, but usually none are available; direct sequencing may be the only way to correlate the disease phenotype with specific mutations that are capable of altering the product of a candidate gene.

Sometimes, DNA sequence variants associated with the locus of a candidate gene can be detected by probes based on cloned DNA segments from the gene itself. Genetic markers constructed this way allow investigators to confirm or eliminate candidate genes by testing them for linkage to specific diseases. For example, reason once suggested that familial polyposis, a genetic disorder characterized by large numbers of adenomatous colonic polyps that can become malignant, might be a consequence of inherited mutations in one of the *ras* oncogenes, either Kirsten or Harvey, because mutant K-*ras* genes in tumor cells are characteristic of human carcinoma of the colon. However, variant DNA sequences in the vicinity of each of these candidate oncogenes were shown to be unlinked to the polyposis locus in families segregating the disease (*26*); linkage tests subsequently located the gene on chromosome 5 in a region that had been implicated by a rare deletion (*27*). Linkage tests with candidate genes for cystic fibrosis (*28*) and mytonic dystrophy (*29*) are being undertaken now, since the regions containing these two defects have been narrowed sufficiently that candidates can be identified. Even failure to find linkage is valuable, because quick elimination of suspected genes from candidacy frees investigators to pursue other leads.

Similarly, familial hypercholesterolemia (FH) often results from inheritance of a mutant *LDLR*. However, lesions in other genes involved in LDL metabolism, for example apolipoprotein B, could presumably confer a similar phenotype. The question of genetic etiology can be resolved for individual FH pedigrees by linkage studies with genetic markers that are associated with the LDL receptor and the apolipoprotein B genes (*30*). As more human genes are identified and cloned, and speculation arises as to what phenotype a mutant gene might confer on its host, it seems likely that this approach will become even more effective.

In vitro techniques complement genetic studies. Human cells grow well in culture. In consequence, the intrinsic interest in human molecular biology has led to development of cell lines derived from various human tissues, on a scale well exceeding that for any other organism. To provide investigators free access to genetically valuable human cell lines, a Human Genetic Mutant Cell Repository has been established by the National Institute of General Medical Sciences (NIGMS). The 1986/87 catalog of the repository lists almost 4000 human cell lines carrying a wide variety of mutations, ranging from metabolic variants to translocations.

Moreoever, human genes can be cloned readily in *Escherichia coli*; again, the number of cloned human genes greatly exceeds the total for any other organism. The American Type Culture Collection (ATCC) now carries over 1000 human DNA clones and is adding more than 300 new ones every year. These in vitro resources allow investigators flexibility to pursue basic questions in human biology, untrammeled by problems of experimentation with the intact organism.

Advantages and Disadvantages of the Human System: A Challenging Mixture

The human system at times clearly lacks the intrinsic advantages one might hope for in an experimental organism. From a geneticist's point of view, the generation time is overlong and social proscription prevents the investigator from carrying out controlled crosses. This inability to construct strains of known genotype denies access to one of the most powerful approaches geneticists have always used to critically test hypotheses. Can we overcome these liabilities of the human experimental system and recover the power of classical genetics?

Recent advances in DNA technology—specifically, the development of many markers for the genome—offer some relief by making it possible to define inherited genotypes much more accurately than before. Genotypes in the offspring of natural human matings can now be determined in enhanced detail, so that individuals of a specific genotype can be examined to test hypotheses. The large set of linkage markers now available is a strong advantage, having grown out of the need to answer specific questions in the human system.

The need to protect individual rights and to obtain informed consent from the participant places serious constraints on the range of experimental possibilities, although recent concern for the rights of laboratory animals is narrowing this experimental gap. On the

Table 4. Human disease equivalents derived from genetic alterations in the mouse. HGH, human growth hormone; MBP, myelin basic protein; HPRT, hypoxanthine guanine phosphoribosyl transferase; MDX, X-linked muscular dystrophy.

Genetic alteration	Method	Phenotype
Introduction of HGH into GH-deficient mice	Nuclear microinjection of HGH minigene	Growth deficiency corrected (*46*)
Introduction of mouse MBP gene into MBP-deficient mice	Nuclear microinjection of MBP nuclear gene	Shiverer phenotype corrected (*47*)
Introduction of mutant collagen gene into wild-type mice	Nuclear microinjection of mutant minigene	Osteogenesis imperfecta (*48*)
Introduction of activated human *ras* and c-*myc*	Nuclear microinjection of inducible minigene	Induction of malignancy (*48*)
Inactivation of mouse HPRT gene	Insertion of retrovirus into HPRT locus in embryonic stem cells	HPRT deficiency in F_3 generation (*49*)
Mutation at locus for MDX	Male mutagenesis followed by identification of female carriers	MDX phenotype and genotype (*50, 51*)

positive side, human subjects are long-lived relative to the experimental lifetime of the investigator; he or she need not establish a strain or maintain a colony in order to complete a study. Furthermore, clinical research centers provide an avenue for direct experimentation in humans; the rapid progress stemming from in vitro technologies will increase the demand for direct testing of hypotheses in the intact human organism.

It is important to bear in mind that the human is not the only system available for testing hypotheses that have been formulated in the human. Construction of individuals of a specific genotype (the construction of transgenotes through in vitro gene implantation, for example) will be banned from the human system for the foreseeable future. For many purposes, however, all mammals are virtually identical; gene regulation during early development should be the same in mouse and human and pig. When information is available about human genes responsible for aberrant phenotypes, one can transfer genetically altered homologous genes to another mammalian species, the mouse for example, to test hypotheses related to human disease. Examples of such models have already been reported and the related technologies required to establish them are summarized in Table 4. The field is rapidly advancing, aided by the capacity to carry out legitimate recombination in embryonic stem cells of mice (*31*) and possibly to engineer mouse mutants. The challenge with the human, then, is to evaluate the experimental context carefully and to make choices on animal systems that are appropriate to the needs and questions at issue for man.

The genetics of complex diseases. Complex, common diseases subtend an area of genetics almost unique to the human. Many such disorders are reflected in relatively subtle phenotypes—psychiatric diseases, for example—that would not be recognized easily in other genetic systems. The human sensitivity to complex variations presents an opportunity for research into interactions between genotype and environment, research that may reveal genetic bases for behavioral traits of fundamental interest. For example, the study of genes that confer predisposition to schizophrenia may shed light on mechanisms of psychological homeostasis. Providing discrete windows into complex metabolic and biochemical systems has been the traditional contribution of those who analyze mutation; for complex disorders, we take advantage of detailed and large-scale human surveys to identify intriguing variants.

The apparent familiality of cardiovascular disease suggests that significant genetic components participate in a wide range of phenotypes, from hypertension to premature atherosclerosis. Genetic analysis promises eventual identification of the individual genes involved, with the concomitant expectation that clear relationships between individual alleles and specific environmental components subsequently can be identified. If we can clarify the genetics, the environmental components may become recognizable on their own. In the case of cardiovascular disease, the phenotypic associations between clinical disease and lipid profiles or apolipoprotein concentrations in blood have come from epidemiological studies whose large scale and expense reflect our special concern with human disease. Without biochemical correlates to study as genetic traits, however, it would be much harder to investigate the genetics underlying the familial nature of cardiovascular diseases.

Genetic diagnosis. A particularly rewarding characteristic of human genetic research is that new findings frequently can be translated directly into clinical interventions. Notable in this category are the ability to determine preclinically, or even prenatally, genotypes of individuals at risk for a disease, or to discriminate among individuals for forensic purposes (*32*).

Information derived from molecular approaches to human heritable disease is already being applied to the prevention of severe genetic disease, the identification of patients at high risk for neoplasia and atherosclerosis, and the detection of carriers for common recessive traits. As the methods rapidly improve in speed, simplicity and cost, many are becoming "standard of practice"; a selective summary of DNA tests that are being applied with increasing frequency is given in Table 5. These successes are a direct outgrowth of the study of humans as a genetic system.

The challenge for DNA-based diagnostics will expand greatly as the genetic components of common, complex diseases emerge in detail. In general, disorders such as cardiovascular disease, cancer, and diabetes become manifest only in adult life. An individual likely will benefit from knowing, well in advance of symptoms, whether he or she is at special risk because of genetic predisposition to an adult-onset disease whose medical management may forestall major complications of the disorder.

Progress in our ability to diagnose before the development of symptoms will have to be matched with programs of therapeutic intervention; retinoblastoma and adult polycystic kidney disease provide cases in point. Finally, and particularly for adult-onset neurodegenerative disorders like Huntington's chorea, for which no therapeutic option presently exists, the predominant benefits will for the moment be related to halting disease in subsequent generations, at the psychological expense of those who are identified as presymptomatic heterozygotes.

Ethical challenges. Challenges to ethics and values will come with our increased ability to diagnose the presence of predisposing genes for common disorders well in advance of symptoms. One of the earliest is likely to arise from the problem of insurability of individuals found to be carrying a predisposing allele. Insurance companies will want access to such information and may mandate testing for the presence of the predisposition. Is an unlucky draw in the genetic lottery an appropriate basis for deciding insurability? Many think not, while others maintain that persons who do not carry predisposition to a given illness should not be required to pay higher insurance rates to support those who do. It is important to bear in mind that predisposition does not automatically result in the development of the disease. The dialogue will intensify as more and more predisposing alleles are characterized and we begin to discover that most of us are predisposed to *something*. This issue may well add fuel to the debate over national health insurance.

Table 5. Determination of disease risk by DNA-based methods.

Disease	DNA method	Heterozygotes identified	Prenatal diagnosis available?
Duchenne muscular dystrophy*	Linkage association and detection of deletions	Asymptomatic female carriers (*52*)	Yes (*53*)
Cystic fibrosis*	Linkage association	Asymptomatic carriers in index families (*54*)	Yes (*54*)
Lesch-Nyhan syndrome	Point mutations; deletions (*55*)	Asymptomatic female carriers	Yes (*54*) Yes (*57*)
Retinoblastoma	Linkage association (*57*)	Presymptomatic heterozygotes in index families	
Adult polycystic kidney disease*	Linkage association (*43*)	Presymptomatic heterozygotes in index families (*43*)	Yes (*35*)
Huntington's chorea	Linkage association (*41*)	Presymptomatic heterozygotes in index families (*58*)	Yes

*DNA-based detection is now standard of practice.

Sometimes, knowing that he or she harbors a strongly predisposing disease allele can severely damage a person's quality of life; we mentioned Huntington disease earlier. This dilemma is not a new one to medicine, since diagnoses of chronic disease are frequently made (for example, mental retardation, cancer, hypertension, renal failure, coronary artery disease, and multiple sclerosis).

Medical treatment and genetic counseling in the United States function on the principle of disclosure to the patient. Undoubtedly the new era of genetics will evoke difficult challenges in patient management, but they hopefully should be no worse than those that derive from lack of information.

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