article

Public health impact of genetic tests at the end of the 20th century

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Purpose: To evaluate genetics tests available for clinical, research, and public health purposes in terms of their public health impact as measured by the number of people who could potentially be tested. **Methods:** Genetic tests for the 751 inherited diseases or conditions listed in the GeneTests database as of November 2000, were classified on the basis of their use for population-based testing and the prevalence of the disease or condition being tested. The GeneTests database divides the tests into two groups: those offered for clinical use and those available for research only. **Results:** Of the 423 clinical tests, 51 had potentially greater impact on public health because of their use in statewide newborn screening programs, other population screening programs, or testing for common diseases with a prevalence over 1 in 2,000 people. Among the 328 tests performed for research purposes only, 18 met the criteria for potentially greater public health impact. **Conclusions:** Our classification scheme indicated that fewer than 10% of the genetic tests listed in the GeneTests database at the end of 2000 are highly relevant to public health. The majority of genetic tests are used in diagnosis and/or genetic counseling for rare, single-gene disorders in a limited number of people. However, as more tests are being considered for newborn screening, and associations between genes and common diseases are being discovered, the impact of genetic testing on public health is likely to increase. ***Genet Med* 2001:3(6):405–410.**

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With the Human Genome Project near completion, it is estimated that there are approximately 35,000 human genes.[1] More than 9,300 of these genes have been discovered, and for many, the gene locus, allelic variants, function, and some disease associations have been described.[2] The discovery of new genes and the rapid commercialization of genetic technology will lead to the development of an increasing number of tests that detect genetic variation. Genetic tests for more than 400 diseases and conditions are currently available in clinical practice and many more are being developed in research settings.[3]

Despite claims that genomic medicine will revolutionize clinical practice,[4] some health professionals have argued that the discovery of genes and their association with disease will have limited application to clinical medicine and public health.[5,6] The basis of this argument is that common complex diseases such as cancers and cardiovascular disease result from interactions between many low-penetrant genes and environmental factors that limit the ability to test individuals for genetic susceptibility and to tailor interventions. However, tests that detect genetic variants, such as those that predispose to familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, when used appropriately, can reduce morbidity and mortality.[7,8] Furthermore, as our understanding of gene-gene and gene-environment interactions increases, genetics will become an integral part of most, if not all, areas of medicine.

The increasing use of genetic tests necessitates establishing criteria for evaluating the benefits and risks of genetic tests and for assessing the effectiveness of each test in promoting health and preventing disease. In 1998, the Secretary's Advisory Committee on Genetic Testing (SACGT) was formed to address the medical, ethical, legal, and social issues raised by the development and use of genetic tests and to make recommendations for enhancing the oversight of genetic tests. The SACGT recommended that all new genetic tests that have moved beyond the basic research phase be reviewed to assess their benefits and risks and that the level of review be appropriate for different categories of genetic tests. To ensure that a genetic test receives the appropriate level of review, a classification scheme was proposed to divide tests into two scrutiny levels using three criteria: the analytic validity, use for population screening, and the prevalence of the disease to be tested.[9]

The purpose of our study was to evaluate the potential public health impact of genetic tests available for clinical, research, and public health purposes. We developed a clas-

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Table 1
Inherited diseases with genetic tests used in clinical practice that were classified as having more public health impact: Newborn screening

Disease	Gene(s)	Mode of inheritance[a]	Population prevalence	Incidence or birth prevalence
Biotinidase deficiency	*BTD*	AR	1.6/100,000	
Congenital adrenal hyperplasia	*CYP21A2 (CYP21)*	AR	6.7/100,000	
Congenital hypothyroidism	*FOXE1 (FKHL15), FKHL15, PAX8, TSHR*	AR	1/50,000	
Cystic fibrosis	*ABCC7 (CFTR)*	AR	1/3,900 (white); 1/17,000 (black)	
Fatty acid oxidation disorder unspecified	*ACADM, HADHB, ACADVL, ACADS*	AR	Rare	
Galactokinase deficiency	*GALK1*	AR		1/50,000–1/100,000
Galactosemia	*GALE, GALT*	AR		1/30,000
Glucose-6-phosphate dehydrogenase deficiency	*G6PD* (many variants)	XL	10% American black males	
Glutaricacidemia type I	*GCDH*	AR	Rare	
Glutaricacidemia type II	*ETFA, ETFB, ETFDH*	AR	Rare	
Hemoglobin C; sickle cell disease	*HBB*	AR	1/835 (African American)	
Hemoglobin S; sickle cell disease	*HBB*	AR	1/375 (African American); 1/100,000 (white)	
Homocystinuria	*CBS*	AR	1/200,000–1/335,000	
Maple syrup urine disease (MSUD)	*BCKDHA, BCKDHB, DBT*	AR	1/185,000	1/176 (Mennonite)
Medium chain acyl-coenzyme A dehydrogenase deficiency (MCAD)	*ACADM*	AR	1/10,000	
Propionic acidemia	*PCCA, PCCB*	AR	Rare	
Short chain acyl-coA dehydrogenase deficiency (SCAD)	*ACADS*	AR	Rare	
Very long chain acyl-coA dehydrogenase deficiency (VLCAD)	*ACADVL*	AR	Rare	
Long chain 3-hydroxyacyl coA dehydrogenase (LCHAD)	*HADHA, HADHB*	AR	1/50,000	

Note: The prevalence figures come from many sources, and although they appeared to be the best estimate available, their accuracy could not be validated.
[a]Mode of inheritance: AR, autosomal recessive; XL, X linked.

sification scheme similar to the SACGT scheme and grouped tests according to whether the test is used for population screening and the prevalence of the disease or condition being tested. We also wanted to determine whether these two criteria were sufficient for identifying tests likely to have significant public health impact or whether additional criteria should be considered. Establishing the extent of the use of genetic tests for clinical and public health purposes now before they become more common will provide a baseline for monitoring the impact of genetic tests in the future.

METHODS

We obtained the list of genetic tests used for this study from GeneTests (*www.genetests.org*).[3] GeneTests (formerly called Helix) is a Web-accessible database that lists laboratories that offer genetic testing, both within the United States and elsewhere.[10] Laboratory participation in GeneTests is voluntary. GeneTests defines a genetic test as the "analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites to detect alterations related to a heritable disorder. This determination can be accomplished by directly examining the DNA or RNA that makes up a gene (direct testing), looking at markers coinherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing)."[3] The GeneTests database includes inherited diseases or conditions ranging from diseases due to highly penetrant genes like Huntington disease to diseases where the pattern of inheritance is not as clear but there are known genetic susceptibilities, as with schizophrenia, for example. The database is organized by disease or condition and includes information on the gene(s) associated with the condition (if known), the laboratories that offer the testing, the type of test performed, and whether the test is offered for use in clinical practice or for research purposes only. At the time we prepared a database for our analysis (November 2000), 751 diseases were listed in the GeneTests database.

In addition to the information about associated gene(s) and test purpose (research or clinical), we compiled information about the prevalence of the diseases, if known, and the mode of inheritance (e.g., autosomal recessive, autosomal dominant, X-linked). Information about the mode of inheritance and disease prevalence were obtained from On-Line Mendelian Inheritance in Man (OMIM)[2] and various sources, including published studies, text books, on-line pediatric databases, and GeneClinics (*www.geneclinics.org*).[11] We also noted the intended use or settings for the tests (diagnosis, carrier screening, newborn screening, and prenatal diagnosis) and unique considerations that could affect the assessment of public health impact such as disease severity, mortality, age of onset, treatment availability, and special social concerns.

We then used two criteria to group the diseases and conditions into those for which genetic testing would have more public health impact (based on the number of people who could potentially be tested) and those for which it would have less. The first criterion was whether the test is used for population-based screening. Population-based screening is defined as testing individuals who belong to a population-defined subgroup (e.g., age, race/ethnicity) and who have no clinical signs of disease. This type of testing includes newborn screening for diseases such as phenylketonuria (PKU) and population-based carrier screening for diseases such as cystic fibrosis. Predictive testing of people who are presymptomatic but are known to be at risk because of family history, as with Huntington disease, is not considered population-based testing. The second criterion was whether the disease is common or rare. Different cut-off levels have been suggested for defining what is rare and common (SACGT used a prevalence of $<1/2{,}000$ or an incidence of $<1/10{,}000$ to define rare in its classification scheme).[9] We used a prevalence of $<1/2{,}000$ to define the rare diseases or conditions. Because we were interested in the number of people who could potentially be tested, we considered the prevalence for the disease as a whole, not just the proportion that is familial. For example, we considered the prevalence of breast cancer, not just hereditary breast cancer. Although practice guidelines specify criteria for testing based on family history and other factors, these guidelines are not always followed carefully and potential exists for more widespread testing.

When a genetic test was used for different purposes, for example, the same test was used for diagnosing disease in a person with clinical symptoms and for population-based carrier testing, the disease was classified at the higher level of potential public health impact. We also compiled a separate list of the tests that were currently listed as research, but could potentially transition into clinical use soon and would affect public health.

RESULTS

Of the 751 tests we evaluated, 423 (56%) were identified by GeneTests as being offered for use in clinical practice and 328 (44%) were identified as being available for research purposes only. Among the 423 clinical tests, we classified 51 as having more public health impact (defined by the number of people who could potentially be tested). This finding represents 12% of tests available for clinical use. The tests classified as having potentially more public health impact are divided into three groups: those used for newborn screening (19 tests), those used for other population screening (9 tests), and genetic tests for common diseases (23 tests) (Tables 1–3).

Table 4 lists the 18 diseases for which genetic testing is currently being performed for research purposes only (as of November 2000), but tests for these diseases would meet the criteria for potentially more public health impact if used in clinical practice. If all of the tests were considered regardless of their use for clinical or research purposes, 10% of the tests in

Table 2
Inherited diseases with genetic tests used in clinical practice that were classified as having more public health impact: Other population screening

Disease	Gene(s)	Mode of inheritance[a]	Population prevalence	Incidence or birth prevalence
Alkaptonuria	*HGD*	AR		4/100,000
α thalassemia	*HBA1, HBA, HBZ*	AR	Significant in Southeast Asian populations	
β thalassemia	*HBB*	AR	Carrier prevalence of 12–14% in Mediterranean populations	
Bloom syndrome	*BLM*	AR	Rare (screening for Ashkenazi)	
Canavan disease	*ASPA*	AR	15.6/100,000 (Ashkenazi)	
Down syndrome critical region	*DCR*	AL		1/800
Gaucher disease	*GBA*	AR	1/600–2,500	
Niemann-Pick disease due to sphingomylinase	*SMPD1(ASM)*	AR	1/40,000 (Ashkenazi)	
Tay-Sachs disease	*HEXA*	AR		1/3,600 (Ashkenazi)

Note: The prevalence figures come from many sources, and although they appeared to be the best estimate available, their accuracy could not be validated.
[a]Mode of inheritance: AR, autosomal recessive; AL, autosomal loci not specified.

Table 3
Inherited diseases with genetic tests used in clinical practice that were classified as having more public health impact: Common diseases (>1/2,000 prevalence)

Disease	Gene(s)	Mode of inheritance[a]	Population prevalence	Incidence or birth prevalence
Azoospermia (Y chromosome microdeletion panel)	*AZF1, AZF2, DAZ, RBMY1A1(RBM1|RBM2| YRRM1)*	YL	20% of men who seek help at infertility clinics present with nonobstructive oligospermia or azoospermia	
BRCA1 hereditary breast cancer	*BRCA1*	AD	10–20/10,000	
BRCA2 hereditary breast cancer	*BRCA2*	AD	5–10/10,000	
Congenital bilateral absence of the vas deferens	*ABCC7 (CFTR)*	AR	2% of men with obstructive azoospermia	
Coronary artery disease risk factor (*ACE*)	*ACE*	AD	CAD is leading cause of death in the United States	
Coronary artery disease risk factor (PLA1/2)	*ITGB3*	AD	As above	
Diabetes mellitus, non–insulin-dependent	*GPD2, MAPK8IP1, IB1, PPAR-gamma*	AD	6/1,000	
Factor V Leiden thrombophilia	*F5*	AD		1/1,000 symptomatic venous thrombosis
Familial adenomatous polyposis (*APC*)	*APC*	AD	6/100 (Ashkenazi)	
Familial colorectal cancer	*APC*	AD		134,000 new cases of colorectal cancer in US in 1996
Familial combined hyperlipidemia	*APOE*	AD	2/1,000	
Fragile X syndrome (*FMR1*)	*FMR1 (FRAXA)*	XL	1/1,250 (males); 1/2,500 (females)	
Hereditary hemochromatosis (*HFE*)	*HFE*	AR	3/1,000	
Hereditary nonpolyposis colon cancer	*MLH1, MSH2, MSH6, PMS1, PMS2, TGFBR2*	AL	2/1,000	
Late-onset familial Alzheimer disease	*AD5, APOE*	AD	10% of persons >70 years have significant memory loss and >50% of these have Alzheimer disease	
MTHFR thermolabile variant	*MTHFR*	AR	30–40% of French Canadians	
Multiple endocrine neoplasia type I (*MEN1*)	*MEN1*	AD		100,000 in US develop hyperparathyroidism
Nonsyndromic hereditary hearing loss and deafness (connexin 26)	*GJB2 (CX26|DFNA3| DFNB1)*	AL		1/1,000 for hearing loss with 50% being syndromic, leaving 50% for potential testing
Nonsyndromic hereditary hearing loss and deafness (mitochondrial)	*MTRNR1, MTTS1*	MT		As above
Oculopharyngeal muscular dystrophy	*PABP2*	AL		1/1,000 in some ethnic groups
Polycystic kidney disease, dominant	*PKD1, PKD2, PKD3*	AD		1/400–1/1,000
Preeclampsia	*AGT, PEE1*	AD	Affects 2–4% of pregnancies	
Prothrombin G20210A thrombophilia	*F2*	AD		1/1,000 symptomatic venous thrombosis

Note: The prevalence figures come from many sources, and although they appeared to be the best estimate available, their accuracy could not be validated.
[a]Mode of inheritance: AD, autosomal dominant; AR, autosomal recessive; XL, X linked; YL, Y linked; AL, autosomal loci not specified; MT, mitochondrial.

the GeneTest database would be classified as having potentially greater public health impact.

DISCUSSION

At the end of the 20th century, most of the genetic tests offered for use in clinical practice are for rare single-gene disorders in people who present with clinical symptoms or who have family histories of genetic diseases. A much smaller proportion of genetic tests (6%) are used for population-based screening, such as state newborn screening programs and carrier testing targeted at ethnic groups at high risk for selected diseases. A similarly small proportion of genetic tests (5%) are being used for common complex diseases such as cancer and cardiovascular conditions. A look at the diseases for which genetic tests are being developed in research settings reveals, however, that tests for additional common conditions are likely to become more prevalent.

Our study was limited in that we considered only genetic tests that are included in the GeneTests database. Although the GeneTests database is believed to be fairly complete for tests being used in clinical practice, the listing of genetic tests used for research purposes is incomplete. We limited our assessment of the impact of genetic tests on public health to criteria that were fairly objective and easy to measure: disease prevalence and use of the test for population screening. Additional

Table 4
Inherited diseases with genetic tests used in research that would be classified as having more public health impact if used clinically

Disease	Gene(s)	Mode of inheritance[a]	Population prevalence	Incidence or birth prevalence
Abdominal aortic aneurysm	*COL3A1*	AD	150/10,000 (males > 50 years)	
Alcoholism	*Unknown*		14 million Americans abuse alcohol or are alcoholics	
Bipolar disorder	*MAFD1*	AD	1–2% population	
Diabetes mellitus, MODY types 5, 4, 3, 2, 1	*TCF2 (HNF1 beta), IPF1, TCF1 (HNF1A), GCK, HNF4A*	AL	1 million+ people in US diagnosed	
Factor XI deficiency	*F11*	AR	1/190 (Ashkanazi)	
Familial hypercholesterolemia	*APOBLDLR*	AD	1/500 (heterozygotes) 1/1,000,000 (homozygotes)	
Familial hyperparathyroidism	*HRPT2, MEN1*	AD	1/1,000	
Glaucoma, dominant (adult onset)	*GLC1B, GLC1C, GLC1D, GLC1E, GLC1F*	AL	Age-dependent: 0.5% in 60s 3% in 70s 14% ≥80	
Multiple sclerosis	*MS*	AD	2,500,000 (worldwide)	
Neural tube defect	*Unknown*			1/1,000
Noonan syndrome	*NS1*	AD		1/1,000 worldwide
Oculocutaneous albinism	*TYR, OCA2(P), TYRP1*	AR	1/20,000 in most populations, giving a heterozygote frequency of 1/70	1/10,000 in African Americans, 1/227–240 in some Amerindian populations
Otosclerosis	*OTSC1*	AD	1/330 (Caucasians); 1/3,300 (African Americans)	
Parkinson disease	*SNCA (PARK1)*	AD	10–35/10,000	
Premature ovarian failure	*DIAPH2 (POF1)*	AD or XL	1% of women <40 years	
Prostate cancer	*HPC1, HPCX, PCAP (HPC2)*	AL or XL		100,000+ cases in US per year
Psoriasis	*PSORS1, PSORS2, PSORS3*	AD	1–2% of population	
Schizophrenia	*SCZD1-7*	AL	1% of the population develops schizophrenia during their lifetime	

Note: The prevalence figures come from many sources, and although they appeared to be the best estimate available, their accuracy could not be validated.
[a]Mode of inheritance: AD, autosomal dominant; AR, autosomal recessive; XL, X linked; AL, autosomal loci not specified.

criteria could be considered, including disease severity, mortality, age of onset, treatment availability, efficacy, cost of diagnosis and treatment, accuracy of the test, and numerous ethical, and legal and social issues. These important criteria should be considered when new tests are being developed and approved for clinical use.

We based our assessment of public health impact primarily on the number of people who could potentially be tested, and the majority of tests we evaluated were easy to classify. However, our evaluation of genetic tests for a few diseases raised some important issues. Some of the diseases we reviewed have complex gene-disease relations, and our assessment did not account for the clinical validity of the tests or testing process. Clinical validity measures how accurately the test identifies or predicts the disease or clinical condition. Identifying a genetic mutation is not sufficient to diagnose or predict disease. The expression or penetrance of gene mutations varies. Although many of the genetic tests we evaluated were for highly penetrant gene mutations that lead to unique clinical syndromes, in a few diseases such as hemochromatosis and hereditary breast cancer, no consensus exists about clinical validity in many settings.

Another important consideration is the intended use or setting for a genetic test. Some of the tests we evaluated were used for different purposes. For example, genetic testing for Bloom syndrome in symptomatic people would be considered as having less public health impact than carrier testing for this condition among people of Jewish heritage. Similarly, testing for medium chain acyl-coenzyme A dehydrogenase deficiency (MCAD) would have more public health impact when used for newborn screening than it would when used for diagnosing clinical symptoms. Another aspect of intended use is the specific gene being tested. We found instances where one genetic test could be used for multiple conditions. For example, hyper-

lipidemia type III is rare, but testing is based on ApoE genotyping as is testing for late-onset familial Alzheimer disease.

Determining whether a disease was rare or common was difficult for many of the diseases we evaluated. Prevalence and incidence data are limited for the majority of diseases and conditions for which genetic testing is being offered today. In many instances, we had to infer that a disease was rare on the basis of the few cases reported in the literature. Although we used a cut-off level of $<1/2{,}000$ to define a rare disease, we could have used the same definition of a rare disease as both the National Institutes of Health, Office of Rare Diseases,[12] and the National Organization of Rare Diseases.[13] They define rare as a disease that affects fewer than 200,000 people in the United States. That translates to a prevalence of approximately 1/1,350 people, given the current U.S. population. Using this lower cut-off level to define rare diseases would not have changed the results of this study.

Although the majority of rare diseases we evaluated did not have substantial public health impact by our criteria, some rare conditions are associated with unique medical, ethical, legal, and social issues. Examples include acute intermittent porphyria, which has a higher prevalence in psychiatric populations; and Huntington disease, where the test is predictive, the condition is uniformly fatal, and no treatment is available. These diseases affect a very small percentage of the population, but potential risks (including social, economic, psychological, and medical harms) associated with genetic testing warrant careful monitoring.

Pharmacogenomic tests also warrant consideration. These tests determine individual response to pharmacologic agents. Few pharmacogenomic tests are used in clinical practice today, but many are being developed.[14] Although the adverse drug reactions that are being tested for are rare, the important public health issue is how many people have the disease or condition being treated and could potentially be tested. Pharmacogenomic testing is being developed to treat common conditions such asthma[15] and to identify people at risk due to common exposures such oral contraceptives.[16] These genetic tests have the potential to affect many people.

In summary, our assessment of genetic tests offered at the end of 2000 showed that only a small percentage of genetic tests are highly relevant to public health. The majority of genetic tests are used in diagnosis and/or genetic counseling for rare, single-gene disorders in a limited number of people. Although individually inherited disorders are rare, in aggregate, they represent approximately 5% of the total disease burden in the population.[17] As more genetic tests are considered for newborn screening, and associations between genes, the environment, and common diseases are discovered, the number of people who could potentially be tested will certainly increase. The two-criteria classification scheme used in our study represents a basic and simple model for test assessment. To develop a paradigm for review and approval of new genetic tests for clinical and public health applications, critical issues such as clinical validity and utility, intended use, factors affecting disease prevalence, and genetic variations influencing individual response to medicines or environmental exposure need to be considered. In response to these and other issues, the Centers for Disease Control and Prevention has initiated activities to make information about genetic tests more available to medical professionals and the public, establish standard methods for collecting data to evaluate genetic tests, and monitor the impact of genetic testing on individuals, families, and society.[18]

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References

1. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;409:860–921.
2. Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD), and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2000 *http://www3.ncbi.nlm.nih.gov/OMIM/*.
3. GeneTests, 2001. *http://www.genetests.org/*.
4. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA* 2001;285:540–544.
5. Holtzman NA, Marteau TM. Will genetics revolutionize medicine? *N Engl J Med* 2000;343:141–144.
6. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet* 2001;357:709–712.
7. Rabelo R, Foulkes W, Gordon PH, Wong N, Yuan ZQ, MacNamara E, Chong G, Pinsky L, Lasko D. Role of molecular diagnostic testing in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer families. *Dis Colon Rectum* 2001;44:437–446.
8. Renonene-Sinisalo L, Aarnio M, Mecklin JP, Jarvinene HJ. Surveillance improves survival of colorectal cancer in patients with hereditary nonpolyposis colorectal cancer. *Cancer Detect Prev* 2000;24:137–142.
9. Department of Health, and Human Services, Secretary's Advisory Committee on Genetic Testing. Request for public comment on a proposed classification methodology for determining level of review for genetic tests. *Federal Register* 2000;65: 76643–76645.
10. Tarczy-Hornoch P, Covington ML, Edwards J, Shannon P, Fuller S, Pagon RA. Creation and maintenance of helix, a Web based database of medical genetics laboratories, to serve the needs of the genetics community. *Proc AMIA Symp* 1998;:341–345.
11. GeneClinics, 2001. *http://www.geneclinics.org/index.html*.
12. National Institutes of Health, Office of Rare Diseases, 2001. *http://rarediseases.info.nih.gov/ord/diseases.html*.
13. National Organization of Rare Diseases, 2001. *http://www.rarediseases.org/*.
14. Mancinelli L, Cronin M, Sadee W. Pharmacogenomics. The promise of personalized medicine. *AAPS Pharmsci* 2000;2 (1) article 4.
15. Liggett SB. The pharmacogenetics of β_2-adrenergic receptors: Relevance to asthma. *J Allergy Clin Immunol* 2000;105:S487–S492.
16. Vandenbroucke JP, van der Meer FJJM, Helmerhorst FM, Rosendaal FR. Factor V Leiden. Should we screen oral contraceptive users and pregnant women? *BMJ* 1996; 313:1127–1130.
17. Rimoin DL, Connor JM, Pyeritz RE, editors. Principles and practices of medical genetics, 3rd ed. London: Churchill Livingstone, 1997:31.
18. Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention, 2001. *http://www.cdc.gov/genetics/default.htm*.