Genetics and Precision Medicine

- **Precision or predictive medicine** is a model of practice in which each person's personal risk for rare and common conditions and the effectiveness of various treatments are estimated directly from his or her unique combination of genetic and environmental risk factors.

- Accordingly, a health-care provider can predict a person's risk for common diseases, select diagnostic tests to confirm the presence of disease, and prescribe the best therapeutic regimen to treat it.

- Ideally, knowledge of disease risk promotes interventions (e.g., modification of diet, choice of drug therapy) that not only can treat disease early in its course but also can delay its onset or prevent it altogether.

- The effectiveness of precision medicine depends on a number of factors.
- These include
- identifying genetic and environmental risk factors (and their interactions) that enable accurate prediction of clinically significant risk;
- demonstrating that individual risk assessment improves diagnostic accuracy and treatment outcome;
- developing technologies for cost-efficient assessment of a person's genome;
- building an infrastructure for clinicians to access risk data,
- interpret risk information, and explain risk estimates to patients; and
- developing guidelines and policies for how risk assessment information should be used in clinical and research applications.

- Not all of these aims will be achieved for every common disease. Indeed, for many complex diseases, it is likely that there will be no alternative to the conventional model of practice in the near future because so little is known about their etiology and pathophysiology.

- Nevertheless, for some common diseases and drug responses, genetic testing and, in several cases precision medicine, are already being adapted to the clinical setting.

A TECHNOLOGY-DRIVEN TRANSFORMATION

- Traditionally, the search for genetic variants that influence risk for mendelian conditions and common complex diseases has been a daunting task and has been one of the major obstacles to developing precision medicine.

- The most common approach to finding such variants involved testing whether polymorphisms in candidate genes were associated with disease risk in a small group of unrelated patients with the same phenotype (e.g., diabetes, obesity).

- This was problematic, in part because choosing the most appropriate candidate genes was difficult, small cohorts provided limited statistical power, and the process of genotyping or sequencing was labor intensive and expensive.
- This situation has changed dramatically with the development of technologies to interrogate millions of polymorphisms per person cheaply and efficiently and more recently the introduction of exome and genome sequencing.

THE IMPACT OF GENOMICS

Pharmacogenetics

- Many of the drinks (e.g., coffee, tea) and foods that we ingest each day contain thousands of complex compounds that each of us must process.
- Some of these compounds never leave the gastrointestinal tract, but most are absorbed, distributed, metabolized, and eliminated (i.e., biotransformed) to a variety of products that are used immediately, stored, or excreted.

- Exogenously synthesized compounds that are administered to achieve a specific effect on the human body (e.g., pharmaceuticals) also undergo biotransformation, and humans vary in the efficiency and speed with which they do this.
- Moreover, the response of a drug's target (e.g., enzymes, receptors) can also vary among individuals. The study of the individual genetic variants that modify human responses to pharmacological agents is called **pharmacogenetics;** the assessment of the action of many genes simultaneously is called **pharmacogenomics.**

Genetic Prediction of Serious Adverse Drug Responses

- Over the last decade, ambitious efforts have been undertaken to advance the knowledge of pharmacogenetics. This has been driven, in part, by the expectation that through the use of pharmacogenetics, we will be able to profile DNA differences among individuals and thereby predict responses to different medicines.
- For example, a genetic profile (i.e., a summary of a person's risk alleles) might predict who is more or less likely to respond to a drug or to suffer a **serious adverse drug reaction (SADR).**

- Many drugs have a response rate between 25% and 75%. For example, ACE inhibitors and beta blockers have been found to be ineffective or only partially effective in up to 70% of hypertensive patients.
- The use of such drugs in persons who are unlikely to respond increases the incidence of SADRs and adds to the burden of health-care costs. Yet, for most drugs, no tests are available to determine who will or will not respond, so these drugs are administered largely on a trial-and-error basis.

- Many drugs have adverse effects that are of clinical importance, and of the approximately 1200 drugs approved for use in the United States, about 15% are associated with a significant incidence of SADRs.
- A widely cited analysis conducted in the mid-1990s suggested that nearly 2 million people are hospitalized each year as a result of adverse drug effects, and approximately 100,000 people die from them, even when the drugs are appropriately prescribed and administered. Studies in Europe and Australia have yielded similar results.

→ identification of genetic profiles that predict a person's response to drugs is likely to increase the overall efficacy and safety of pharmaceuticals.

- Testing is currently available for a handful of alleles that predict SADRs. For example, thiopurine methyl transferase (TPMT) is an enzyme that inactivates thiopurine drugs (e.g., 6-mercaptopurine, azathioprine), which are frequently used to treat acute lymphatic leukemia and to prevent rejection of organ transplants. A mutation of the *TPMT* gene reduces enzyme activity. About one in 300 persons of European ancestry is homozygous for this mutation, and these patients can experience life-threatening bone marrow suppression upon exposure to thiopurine drugs.
- The presence of such variants can be assessed by genotyping or by enzyme assays, which are now commonly done before administering thiopurines.
- Large-scale exome sequencing studies have demonstrated that each person carries at least several alleles that alter drug metabolism compared to the general population.

Individualized Drug Therapy

- One of the major challenges of pharmacogenetics is the selection of appropriate targets (e.g., a specific enzyme, cytokine, or cell-surface receptor) that might be amenable to manipulation by a drug.

- The results of genetic studies are used to identify polymorphisms associated with varying susceptibility to disease (i.e., a potential target for a drug) or polymorphisms that modify the human response to a drug.
- For example, long QT syndrome can be caused by mutations in one of at least a dozen different genes whose protein products affect ion channel function in heart cells (e.g., sodium and calcium channels).

- Because sodium channels and calcium channels are blocked by different drugs, a person's genetic profile can be used to choose the best drug for treatment of LQT syndrome. In this case, the relationship between disease and target is well characterized.

- Polymorphisms in genes that encode angiotensinogen, angiotensin-converting enzyme (ACE), and the angiotensin II type 1 receptor have been associated with differential responses to antihypertensive agents.

- For example, the *ACE* gene contains a 190-bp sequence that can be either present (the *I* allele) or deleted (the *D* allele). Persons who are homozygous for the *D* allele are more responsive to ACE inhibitors.

- Response to antihypertensive beta blockers has been associated with polymorphisms in genes that encode subunits of the β-adrenergic receptor (Table 14-1).

- None of these variants are commonly tested prior to initiating antihypertensive therapy, but studies are under way to determine when such information, in conjunction with environmental risk factors such as smoking and diet, might facilitate the development of individualized treatment.

TABLE 14-1 Examples of Effects of Gene Polymorphisms on Drug Response

GENE	ENZYME/TARGET	DRUG	CLINICAL RESPONSE
CYP2D6	Cytochrome P4502D6	Codeine	Persons homozygous for an inactivating mutation do not metabolize codeine to morphine and thus experience no analgesic effect
CYP2C9	Cytochrome P4502C9	Warfarin	Persons heterozygous for a polymorphism need a lower dose of warfarin to maintain anticoagulation
VKORC1	Vitamin K epoxide reductase	Warfarin	Persons heterozygous for a polymorphism need a lower dose of warfarin complex, subunit 1, to maintain anticoagulation
NAT2	*N*-Acetyl transferase 2	Isoniazid	Persons homozygous for slow-acetylation polymorphisms are more susceptible to isoniazid toxicity
TPMT	Thiopurine S-methyltransferase	Azathioprine	Persons homozygous for an inactivating mutation develop severe toxicity if treated with standard doses of azathioprine
ADRB2	β-Adrenergic receptor	Albuterol	Persons homozygous for a polymorphism get worse with regular use of albuterol
KCNE2	Potassium channel, voltage-gated	Clarithromycin	Persons heterozygous for a polymorphism are more susceptible to life-threatening arrhythmias
SUR1	Sulfonylurea receptor 1	Sulfonylureas	Persons heterozygous for polymorphisms exhibit diminished sensitivity to sulfonylurea-stimulated insulin secretion
F5	Coagulation factor V (Leiden)	Oral contraceptives	Persons heterozygous for a polymorphism are at increased risk for venous thrombosis

- Many of the physiological effects of variation in drug response have been known for decades.

- A deficiency of glucose-6-phosphate dehydrogenase (G6PD), which is estimated to affect more than 200 million people worldwide, causes increased sensitivity to the antimalarial drug, primaquine, producing an acute hemolytic anemia.

- The metabolism of isoniazid (a drug commonly used to treat tuberculosis) is strongly influenced by an allele of the gene that encodes *N*-acetyltransacetylase 2 *(NAT2),* the enzyme that is used to acetylate, and thereby inactivate, isoniazid. Persons who are homozygous for this allele are known as slow inactivators and are at higher risk for developing side effects than persons who metabolize isoniazid more quickly. About half of persons of European or African ancestry are slow inactivators, but this figure is lower among East Asians.

- Succinylcholine is a drug widely used in anesthesia to induce short-term muscle paralysis. Typically, the effects of succinylcholine last only a few minutes before it is **rapidly degraded** in the plasma by circulating butyrylcholinesterase. Several alleles of the gene that encodes butyrylcholinesterase cause reduced enzyme activity. Persons who are homozygotes or compound heterozygotes for such alleles have a diminished ability to inactivate succinylcholine. This can result in prolonged paralysis and respiratory failure that requires mechanical ventilation for up to several hours.

- In each of these examples, a person who has a relatively common allele might, upon exposure to a specific chemical, experience an unanticipated pharmacological effect.

- Variants have been discovered in enzymes that produce a much broader effect on the body's response to multiple drugs. An example is debrisoquine hydroxylase, an enzyme encoded by the gene *CYP2D6.* This gene is a member of the cytochrome P450 superfamily, which encodes many different enzymes responsible for the biotransformation of compounds with widely divergent chemical structures.

- Polymorphisms of *CYP2D6* affect the metabolism of more than 25% of all pharmaceuticals, including β-adrenergic receptor antagonists, neuroleptics, and tricyclic antidepressants (Fig. 14-1).

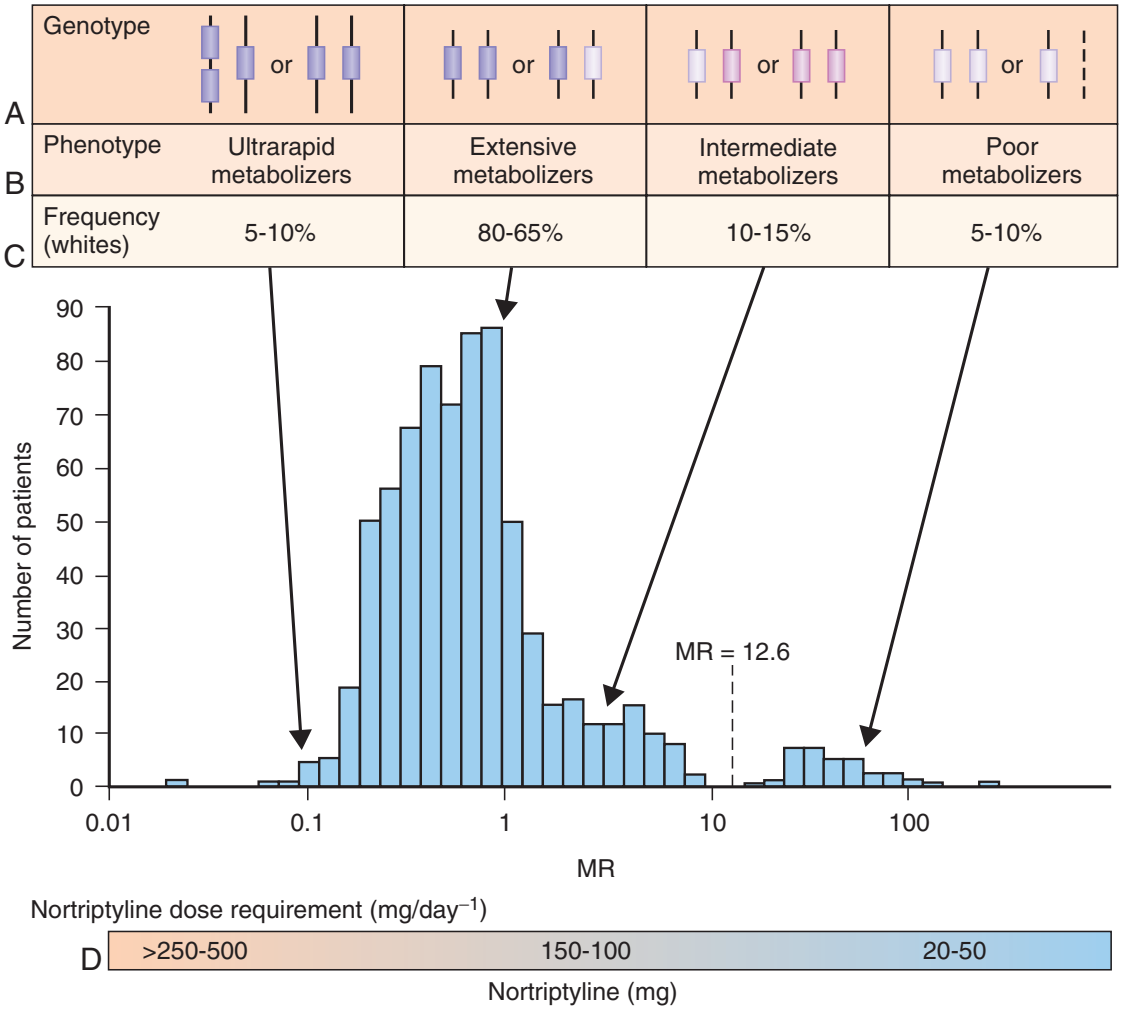

FIG 14-1 Genotype-phenotype relationships between *CYP2D6* polymorphisms and drug metabolism. **A,** Possible genotypes at the *CYP2D6* locus. Fully functional alleles of the *CYP2D6* gene are indicated by *dark purple* boxes, alleles with reduced function in *pink,* and null (i.e., inactive) *CYP2D6* alleles in *light purple.* **B,** The ability to metabolize many drugs varies depending on an individual's *CYP2D6* genotype. **C,** Distribution of phenotype frequencies assessed in a population of European Americans as determined by the urinary metabolic ratio (MR) of debrisoquine to 4-hydroxy-debrisoquine. **D,** Poor metabolizers require a smaller dose of the antidepressant drug nortriptyline, and ultrarapid metabolizers require a higher dose to achieve the same plasma concentration. (Adapted from Meyers U. Pharmacogenetics—five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet.* 2004;5:669-676.)

- Another example is variants in *CYP2C19* that diminish the rate at which the pro-drug clopidogrel, an antiplatelet drug, is metabolized to its active form.
- Clopidogrel is commonly used in the more than 2 million persons who undergo stenting of their coronary arteries, and persons with a variant in *CYP2C19* that reduces function are at substantially higher risk of stent thrombosis—which can precipitate a heart attack and death.

- All of these are examples of relatively simply genetic profiles (i.e., single polymorphisms) that affect drug response. Many drug responses are likely to be determined by much more complex profiles that are composed of multiple polymorphisms at multiple loci.

- Two common variants of *CYP2C9 (CYP2C9*2* and *CYP2C9*3),* another cytochrome P450 gene, influence the metabolism of warfarin, an anticoagulant drug. The frequencies of these alleles vary between 6% and 12% in populations of European origin, but each is found at a substantially lower frequency in sub-Saharan Africans and East Asians.
- Warfarin is widely used to prevent thrombosis, but because of variation in dose requirements, hemorrhagic complications from warfarin therapy are common. Therefore, a person's level of anticoagulation needs to be checked regularly so that warfarin is given at a dose that prevents thrombosis but avoids excessive bleeding.
- Persons with at least one copy of either *CYP2C9*2* or *CYP2C9*3* require less warfarin for effective anticoagulation than the general population. Consistent with this observation, hemorrhagic complications are, on standard dosing, more common in persons who carry the *CYP2C9*2* or the *CYP2C9*3* alleles. Thus, *CYP2C9* variants influence both warfarin metabolism and adverse outcomes associated with warfarin.
- Genetic variation in one of warfarin's pharmacologic targets, vitamin K expoxide reductase (VKORC1; see Table 14-1), also helps to predict a person's response to this drug. Genetic testing can be done on both *CYP2C9* and *VKORC1* to help to calibrate warfarin dosage.

- Pharmacogenetics and pharmacogenomics are slowly beginning to change the way that medicine is practiced, although the pace of change is likely to accelerate over the next few decades.
- A primary issue for all alleles that are associated with drug response is whether testing these alleles will affect the clinical management of patients and, if so, to what extent.

- The genetic profile of a drug response may be important if the drug is widely used in clinical practice and the response to the drug is medically important, if the drug's therapeutic and toxic effects are difficult to assess and titrate clinically, if adverse effects are difficult to predict with existing information, and if a profile provides easily interpretable results with high sensitivity and specificity.

- It is unclear how many drug–and–genetic profile combinations are likely to meet these criteria, although to date more than a hundred drugs now carry a label indicating that genetic testing should be performed prior to use.

Diagnosing and Monitoring Common Disease

- Genomic information can also be used to facilitate disease diagnosis and to monitor therapeutic responses.
- For example, a micro-array or RNA sequencing can be used to estimate the expression level of each gene (i.e., the amount of mRNA that is transcribed) in a specific tissue.
- These gene-expression profiles can be used to identify patterns of gene expression that are associated with specific conditions (e.g., increased transcription of an oncogene or reduced transcription of a tumor suppressor gene in tumor tissue).
- Such information can help to distinguish different types of cancers, different types of infections, or other phenotypes associated with disease.

- It should be appreciated that genomic information is just one of many types of data about a person and their environment that can be assessed to make predictions about disease states. This includes information about protein expression (i.e., proteome), metabolic functions (i.e., metabolome), normal body flora (i.e., microbiome), and environmental exposures (i.e., exposome).

Cancer Genomics

- Every cancer cell harbors numerous alterations in DNA sequence and copy number that affect genes or regulatory sequences, often accompanied by reversible, epigenetic, modifications. These changes perturb the expression and/or function of hundreds to thousands of genes. Collectively, these changes result in the activation or inhibition of various cellular pathways that control the characteristics of cancers such as growth or metastasis, and they determine, in part, prognosis and response to treatment.

- Cancer genomics is the study of the DNA-associated changes that accompany cancer with the overall goal of better preventing, detecting, diagnosing, and treating common cancers.
- A particularly powerful application of genomics to cancer has been the use of genome-wide gene expression analyses to provide a snapshot of gene activity within a tumor at a given point in time.
- This has facilitated the development of classification schemes based on expression profiles for many types of cancer, including leukemia, lymphoma, and cancers of the breast, lung, colon, and brain.
- This information can be used, for example, in refining prognosis, directing the application of conventional and targeted biological therapies, and identifying targets for new drug development (Fig. 14-2).

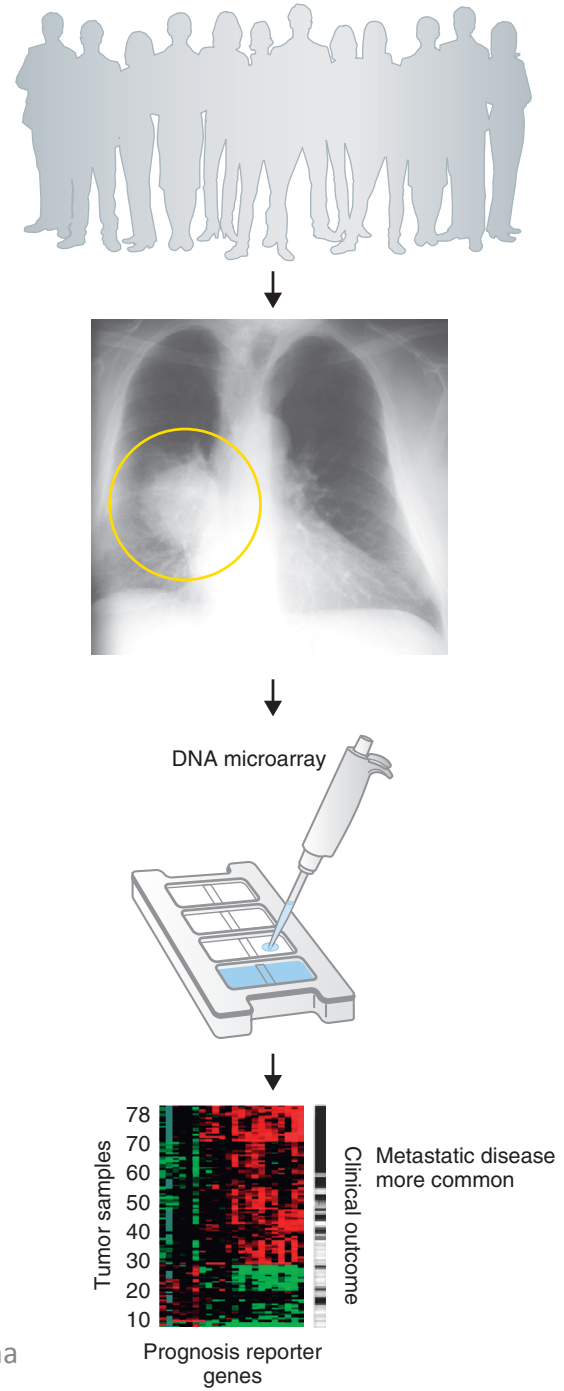

FIG 14-2 Prediction of disease outcome by gene-expression profiling. The clinical outcome of individuals with lung cancer *(circled tumor on radiograph)* is predicted by testing the expression of a set of genes known to be abnormally regulated in lung cancer cells. For each individual tumor, RNA is extracted and placed onto a microarray, and the expression of each gene is measured. *Bottom,* Each column represents the expression profile of a different tumor. Diminished expression of a gene in one lung tumor compared to other lung tumors is indicated by *green,* and increased expression is indicated by *red.* The outcome of the disease is shown at the *right,* where *white* indicates persons with metastatic disease (poor outcome) and *black* indicates no metastasis (good outcome).

- Currently, it is often difficult to predict the prognosis of cancer patients based on traditional phenotypic information such as the type of tumor (T), whether the cancer is found in nearby lymph nodes (N), and evidence of metastasis (M).
- Staging using this TNM system is currently the standard for most solid tumors, yet these stages are often not predictive of prognosis or treatment response.

- Gene-expression profiling can help to distinguish between cancers that are easily confused (e.g., Burkitt lymphoma vs. diffuse large B-cell lymphoma).
- It can also facilitate the identification of subsets of tumors of the same TNM stage that might have quite different outcomes.

- Several gene-expression profiles are currently available for assessing breast cancer prognosis, and gene-expression profiles that predict recurrence of several other types of cancer have been established. Prospective trials will determine the extent to which the use of expression profiling is of clinical benefit, but it is anticipated that its use will lead to a substantial improvement in cancer management.

- The conventional approach to cancer therapy has been to provide treatment based on the tissue or organ in which the cancer originated. However, persons with the same type of cancer often have different genetic abnormalities in their tumors, resulting in differential responses to treatment.

- For example, among young women whose breast cancer has not spread to their lymph nodes and who are treated by resection of the tumor and local radiation, only 20% to 30% will experience a recurrence.
- This subgroup of women might benefit the most from receiving adjuvant chemotherapy, and those at lower risk of recurrence (the majority) might benefit less from chemotherapy.
- Yet, because the high- and low-risk groups cannot be distinguished reliably, 85% to 95% of all women with this type of breast cancer receive adjuvant chemotherapy.
- This means that many women might undergo such treatment unnecessarily, putting them at risk for drug-related complications and increasing the overall cost of health care.

- Expression profiling has the potential to help delineate subsets of cancers that are likely to be more responsive to various therapeutic regimens and to guide the optimal selection of agents for each individual.

Common Disease

- Gene-expression profiling is being used to study the pathogenesis of common diseases and to monitor tissue-specific gene activity in order to facilitate diagnosis and monitor disease progression and treatment.

- For example, expression profiling of circulating white blood cells in patients with type 1 diabetes has revealed increased expression of a large number of proinflammatory genes.
- The expression of some of these genes is also increased in persons with rheumatoid arthritis, suggesting that some autoimmune disorders might share expression profiles.
- A screening test based on these profiles might enable earlier diagnosis and/or identify high-risk persons who could benefit from preventive care.

- Gene profiling has also been used effectively to monitor immunosuppression in individuals who have undergone organ transplantation. Studies are also under way to identify whether gene-expression profiles can predict outcome in persons infected with pathogens such as malaria, HIV-1, and tuberculosis.

Race and Genetic Assessment of Individual Ancestry

- An important and controversial issue in precision medicine is whether a person's **race—**using its historical meaning as a descriptor of Africans, Asians, Europeans, Native Americans, and Pacific Islanders—and/or **genetic ancestry** is useful for making predictions about health-related risks.

- Traditionally, it has been commonplace to use race to predict the likelihood that a person carries a particular genetic variant that influences susceptibility to disease or drug response. This practice was based partly on the observation that disparities in health are common among racial groups.
- For example, the incidence of prostate cancer is twofold higher in African American men than in European American men. Other disorders that vary in prevalence or outcome among racial groups include hypertension, end-stage renal disease, preterm birth, and type 2 diabetes.
- It remains unclear, however, whether genetic risk factors explain, even partly, these disparities. Many health-related disparities probably are influenced more strongly instead by environmental factors such as dietary differences and inequities in the provision of health-care services.
- Accordingly, the use of race to make predictions about whether a person has such risk factors is still the subject of considerable debate.

- It is important to distinguish between race and genetic ancestry.
- **Race** has traditionally been used to categorize large groups of persons and can reflect geographic origin, language, and various cultural attributes that describe a group (e.g., Native Americans or Asians).
- **Ancestry** refers to the geographic, historical, or biological origins of one's ancestors and, for any person, can be complex.
- For example, a person might have ancestors from Africa, Europe, and North America (i.e., a complex ancestry), but he or she might still self-identify as an African American.

- Race captures some biological information about ancestry, but the two concepts are not equivalent. Knowledge of a person's ancestry can provide information about his or her genetic makeup and thus can be useful for identifying genetic and environmental factors that underlie common diseases.

- Over the past several years, it has become increasingly common to use genetic markers such as single nucleotide polymorphisms (SNPs) to directly estimate the genetic ancestry of a person (Fig. 14-3). The extent to which race helps us to predict genetic differences that influence health depends partly on how well traditional classifications of race correspond with such genetic inferences of individual ancestry.

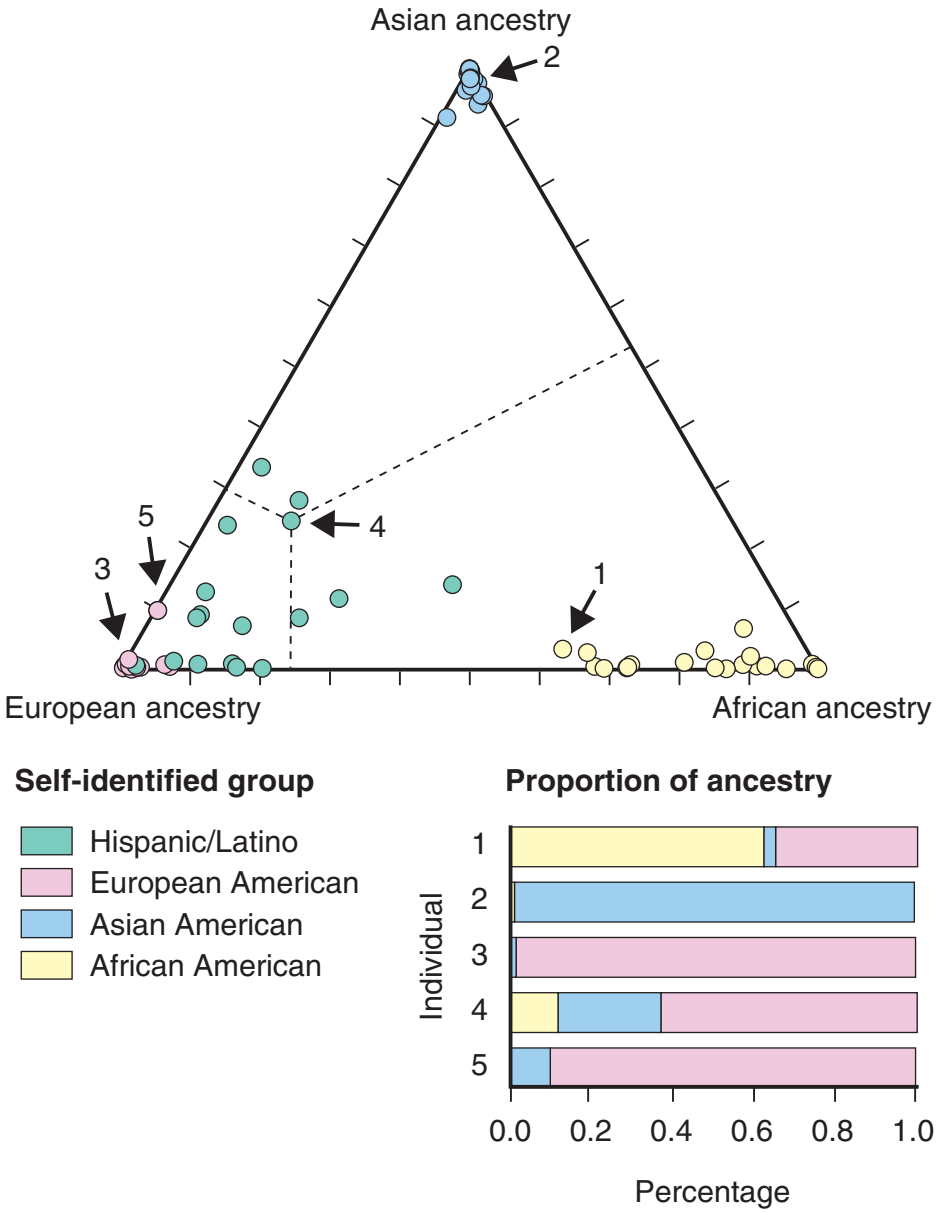

FIG 14-3 Genetically inferred ancestry fractions for persons *(colored circles)* sampled from the United States and genotyped for 6000 single nucleotide polymorphisms (SNPs). Each circle represents one person, color-coded to correspond to one of four self-identified groups. The distance of a circle to the edge of the triangle is proportional to the amount of the person's ancestry contributed by each of the three ancestral populations in the corners of the triangle (African, Asian, and European). For example, the Hispanic/Latino American labeled number 4 received about 60% of his genetic ancestry from Europe, 30% from Asia (due to Native American ancestry), and 10% from Africa. The circles representing Hispanic/Latino and African Americans are less tightly clustered because the proportion of ancestry among persons is more varied than in Asian Americans and Americans of European descent. A bar graph indicates the estimated ancestry proportions for each of the subjects labeled 1-5.

- In many circumstances, however, race is not a good predictor of ancestry. For example, populations from neighboring geographical regions typically share more recent common ancestors, and therefore their allele frequencies can be very similar.

- Consequently, persons sampled at regular intervals across some intercontinental regions (e.g., the Middle East or Central Asia) are more difficult to allocate into genetic groups that are concordant with common notions of race.

- Correspondence with geography is also less apparent for populations (e.g., Latin Americans, South Asians) that have been influenced by recent historical mixtures of multiple ancestral populations.

- In the United States, race is only a crude predictor of a person's genetic ancestry. For example, the average portion of African ancestry among self-identified African Americans is about 80%, but it ranges from 100% to 20% or even less in some persons.
- The genetic composition of self-identified European Americans also varies, with about 30% of European Americans estimated to have less than 90% European ancestry. Similarly, Hispanics from different regions of the United States have highly variable ancestries (e.g., more African ancestry in Hispanics living in the Southeast and more Native American ancestry in the Southwest). Accordingly, membership in a group does not mean that all members of the group necessarily have similar genetic ancestries.

- Although it is clear that explicit genetic information, rather than race, can be used to make more accurate inferences of ancestry, it is not yet known to what extent personal ancestry information can make useful predictions about one's risk of common disease. The consequences of using detailed ancestry information in a clinical setting are also largely unknown.
- It is possible that personal ancestry information could have adverse effects on a person's perception of risk and cultural identity. Similarly, such information could reinforce unfair stereotypes about specific populations. Further research is needed to examine the potential benefits and risks of using ancestry information in clinical practice.