June 26, 2010, marked the 10th anniversary of the completion of the draft sequence of the human genome, an achievement that was the pinnacle of the Human Genome Project, started approximately 11 years earlier and officially completed in 2003. The Human Genome Project offered the first systematic glimpses into the sequence of a haploid genome. It facilitated immensely the identification of the genes and mutations responsible for single gene disorders. However, an individual extent of the DNA sequence variations (DSVs) in the human genome remained largely unknown until the publication of Craig Venter’s diploid genome in 2007. By revealing the extent and complexity of variations in the human genome, the findings ushered in new insights into the remarkable genetic diversity of our species. Particularly intriguing was the finding that approximately 45% of Venter’s genes were polymorphic and that his genome contained approximately 4 million DSVs, including greater than 3 million single-nucleotide polymorphisms (SNPs), approximately 10,000 nonsynonymous (ns) SNPs, and several hundred thousand structural variations (SVs). Some SVs involved several million DNA base pairs (bps) and multiple genes, resulting in copy number variations (CNVs). Because of their size, often involving large DNA segments, the SVs accounted for three-fourths of the variant nucleotides.

The success in sequencing the human genome was achieved using the ingenious DNA sequencing method developed by Frederick Sanger and Walter Gilbert. However, this technique (for which Sanger and Gilbert were awarded the Nobel Prize in Chemistry in 1980) was relatively costly and time-consuming and, therefore, not practical for routine whole-genome sequencing. Thus, clinical application of the information content of the DSVs had to await the development of more efficient DNA sequencing methods. The introduction of the array-based 454 pyrosequencing technology in 2005 ushered in the era of Next-Generation or massively parallel DNA sequencing. This technique has increased the output and reduced the cost of DNA sequencing by several orders of magnitude. DNA sequencing technology has continued to advance at lightening speed, affording the opportunity to sequence the entire human genome in weeks and targeted genomic regions of interest in days. Today, the entire human genome can be sequenced in a relatively short period of time for less than $5000. Analysis of the massive output of the newer DNA sequencers, which had been a bottleneck, is also evolving rapidly, and robust bioinformatics programs are now routinely applied to decipher the terabytes of digital DNA sequence data. Thanks to this explosion of technology, several individual genomes have been sequenced, including James Watson’s genome and the genomes of an African man, a Korean man, and a Han Chinese man, among others.

The findings show that the genomes of different individuals differ in 1% to 3% of their DNA sequence, which comprises approximately 3.2 billion base pairs, corroborating the enormous genetic diversity of humankind. The technology is also being increasingly applied for disease gene discovery. Thus, it is probably not premature to suggest that in the not-too-distant future, whole-genome or whole-exome sequencing will be readily available for the extraction of biological and medical information.

This explosion of advances in technology and informatics will have many major reverberations. First, it will dramatically enhance our understanding of the molecular basis of disease. Nobel laureates Michael Brown and Joseph Goldstein described a physician-scientist as “a broad-based investigator who discovers fundamental biological mechanisms and applies these insights directly to the cure of disease.” The most profound and lasting effect of whole-genome/whole-exome sequencing is likely to be the provision of fundamental insights into the molecular basis of human disorders, thereby opening the opportunity for the cure of human disease. It is because of these considerations that the editors of Circulation Research assign high priority to manuscripts that describe novel molecular genetic mechanisms of human diseases and encourage their submission to the journal.

Besides advancing our understanding of disease mechanisms, another consequence of whole-genome sequencing will be to facilitate the early identification of individuals who are at risk of cardiovascular disease, thereby providing an opportunity to intervene to prevent the evolving phenotype. Phenotypic diagnosis obviously depends on the expression of the phenotype, which is typically time-dependent. This limitation is compounded by the fact that the phenotype, even when expressed, is often not detected or recognized until the development of clinical symptoms or a tragic event, such as sudden cardiac death (SCD). A typical example is coronary atherosclerosis: patients with significant coronary or carotid atherosclerosis are often asymptomatic and thus are not diagnosed until they develop acute coronary syndromes or stroke. The potential impact of early genetic diagnosis is illustrated by loss-of-function mutations in PCSK9, which lower plasma low-density lipoprotein cholesterol levels and reduce the risk of coronary heart disease dramatically over a 15-year period. Similarly, in the case of single-gene disor-
ders, such as familial cardiomyopathies, a significant number of family members express the phenotype but are asymptomatic and not aware of the problem. A classic illustration is human hypertrophic cardiomyopathy, which often manifests as SCD in young competitive athletes. Whole-genome sequencing is likely to enable preclinical identification of both individuals at risk and healthy individuals, which would represent a major step forward.

The advances in genetics will also impact diagnosis. The current practice of medicine is based on the phenotypic characteristics of the disease, which are highly variable and neither completely sensitive nor specific. Clinical phenotyping often does not enable accurate distinction between a specific disease and other conditions that mimic it (phenocopies), because of the phenotypic overlaps. For example, more than a dozen phenocopy conditions clinically mimic genetic cardiomyopathies. Genetic diagnosis is expected to complement the current approach of phenotype-based diagnosis, leading to accurate differentiation of the phenocopy conditions from the disease that they mimic. This, in turn, would have considerable practical implications, as the respective treatments differ.

Another major consequence of the genetics revolution will be the advent of pharmacogenetics. William Osler, the father of modern medicine, advocated individualized therapy, emphasizing that no two patients are identical in their diseases and responses to treatment. Today, we are fortunate to be able to harness genetic information to individualize therapy using pharmacogenetics, an approach that is expected to reduce the risk of adverse effects and maximize the benefits of treatment. Pharmacogenetics should help physicians deal with the problem of drug toxicity, which occurs in a fraction of those who are taking the drug and is a major impediment to successful drug use. The examples are numerous. One is the individual differences in the response to warfarin therapy, which can vary by 10-fold among patients and is partially determined by SNPs in genes encoding the cytochrome P450 isofrom 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1). Similarly, the response to the platelet inhibitor clopidogrel is, in part, determined by SNPs in CYP2C19. At the other end of spectrum, ie, drug toxicity, a notable example is the susceptibility to skeletal myopathy conferred by SNPs in the solute carrier organic anion transporter 1B1 gene (SLCO1B1). The encoded protein regulates hepatic uptake of many drugs, including statins. The loss-of-function variants of SLCO1B1 impair hepatic uptake of statins, which leads to increased plasma levels of these drugs and increased risk of skeletal myopathy. With the availability of the whole-genome sequence and increasing knowledge of the functional significance of DSVs, pharmacogenetics is likely to have a major impact on the practice of medicine.

Finally, the advances in whole-genome sequencing call for massive new efforts to elucidate the genetic–phenotypic interrelations. The human genome is a very complex structure regulated at multiple levels, the most basic being variations in its nucleotide sequence. The complexity is multifarious, involving not only enormous diversity in its sequence but also extensive alternative splicing of the coding genes and noncoding RNAs, including microRNAs. The significance of CNVs in cardiovascular diseases is only beginning to be explored. Similarly, the biological significance of alternative splicing, which involves ~94% of the coding genes in the genome, remains largely unexplored. Moreover, the human genome encodes at least 677 microRNAs, the vast majority of which have functions that are yet to be defined (http://www.microrna.org/microrna/home.do). The clinical phenotypes are even more complex because they result from intertwined, stochastic, complicated, and often nonlinear interactions among DSVs (including copy number variants), epigenetic factors, microRNAs, and posttranslational modifications of proteins, as well as environmental factors. The time is ripe for studies that shed light on the bewildering genetic and phenotypic complexity of human diseases.

In summary, the landscape of medicine is likely to be enriched by the incorporation of sequencing information. With the advent of technologies that enable rapid assessment of "personal genomes," a new epoch in biomedical science has been ushered in. Molecular genetic studies are elucidating the fundamental mechanisms that govern human diseases, which, in turn, provides the opportunity to identify new diagnostic and prognostic markers and preventive or therapeutic targets. Whole-genome sequencing is expected to lead to the identification of a handful of DSVs in each genome that have large effects on the phenotype. These advances have the potential to enable physicians to accurately target specific therapies and intervene early to prevent the evolving phenotype. Whole-genome sequencing will also be used to maximize the benefits of therapy and minimize drug toxicity.

In this exciting time of rapid progress, the editors are committed to making Circulation Research the premier journal for publication of human molecular genetic studies that provide mechanistic insights in cardiovascular disease. We encourage submission of high-quality manuscripts in the areas of human molecular genetics, particularly robust discoveries based on the whole-genome and whole-exome deep-sequencing approaches. We reiterate our interest in molecular mechanistic studies aimed at delineating the mechanisms that link genetic mutations to human phenotype. In addition, we encourage submission of manuscripts reporting epigenetic studies that delineate expression and variability of human phenotypes and studies that delineate clinical and phenotypic consequences of noncoding RNAs and alternative gene splicing. Large-scale population genetic studies, including pharmacogenetics studies, will also be viewed with interest.

Our desire to make Circulation Research a “home” for the best work in cardiovascular genetics is reflected in a number of recent changes in the journal. We have expanded our key

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<tr>
<td>CNV copy number variation</td>
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<tr>
<td>DSV DNA sequence variation</td>
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<tr>
<td>SNP single-nucleotide polymorphism</td>
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<tr>
<td>SCD sudden cardiac death</td>
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<td>SV structural variation</td>
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words to include terms commonly used in genetics articles, such as GWAS and CNVs. We have invited a number of experts in genetics to join the new Editorial Board, and five of the Associate/Consulting Editors have specific expertise in this discipline (Christine Seidman, Hugh Watkins Silvia Piori, Elizabeth McNally, and A. J. Marian). We have commissioned a number of invited Reviews focusing on such topics as cardiovascular genomics and genome-wide association studies, epigenetics, inherited arrhythmogenic syndromes, cardiomyopathies, and the genetic basis of various cardiovascular disorders.

As indicated in our editorial manifesto, the mission of the journal is to advance our understanding of the mechanism of human diseases. We believe that an important strategy to accomplish this mission is to emphasize translational and first-in-human investigations that offer mechanistic insights. Accordingly, the editors welcome the opportunity to publish state-of-the-art molecular genetic studies of human cardiovascular diseases that illuminate the pathogenesis and pathophysiology of a disorder. As in all areas of research, the main aspects that will determine priority include novelty, robustness of the data, and depth of mechanistic insights.

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