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## Welcome to the Genomic Era

Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries, but his cup of joy is full when the results of his studies immediately find practical applications.

— Louis Pasteur

This issue of the *Journal* includes the last installment in a monthly series on genomic medicine that began in November 2002.<sup>1-11</sup> The series has focused on the ways in which the rapidly appearing tools of genomics have already begun to change the practice of medicine. In this issue, for instance, Burke explores how genomics has started to improve our understanding of the biology of health and disease in ways that were never before possible.<sup>11</sup> Although the series demonstrates that genomics has indeed begun to change the practice of medicine, it catalogues only the birth of the genomic era and thus no more captures in detail the ultimate effect of genomic medicine than does the examination of a newborn foretell what the mature adult will be like.

If the genomic era can be said to have a precise birth date, it was in the midst of the appearance of the series, on April 14, 2003. That was when the international effort known as the Human Genome Project put a close to the pregenomic era with its

announcement (available at <http://www.genome.gov/11006929>) that it had achieved the last of the project's original goals, the complete sequencing of the human genome. The extent and pace of progress in genomics are suggested by the fact that this achievement occurred 11 days shy of the 50th anniversary of the publication of Watson and Crick's seminal description of the DNA double helix. If science, technology, and medicine have consistently demonstrated anything, it is that they proceed at an ever-quicken pace. That we have gone in the past 50 years from the first description of the structure of our DNA to its complete sequencing gives some indication of how much the impact of genomic medicine on the health care of today's neonates will increase by the time they turn 50 years of age.

However, it is not solely the next 50 years that will witness important advances in genomic medicine. Many such advances have already occurred, including some during the interval since the launch of the Genomic Medicine series. Indeed, one need look no further than the pages of the *Journal* to see potent additional examples of what has occurred during these past few months: the use of genomics for the rapid identification of newly discovered pathogens such as that involved in the severe acute respiratory

syndrome (SARS)<sup>12,13</sup>; the use of gene-expression profiling to assess prognosis and guide therapy, as in breast cancer<sup>14</sup>; the use of genotyping to stratify patients according to the risk of a disease, such as the long-QT syndrome<sup>15</sup> or myocardial infarction<sup>16</sup>; the use of genotyping to shed light on the response to certain drugs, such as antiepileptic agents<sup>17</sup>; and the use of genomic approaches in the design and implementation of new drug therapies, such as imatinib for the hypereosinophilic syndrome,<sup>18</sup> and to improve our understanding of the role of specific genes in the causation of common conditions, such as obesity.<sup>19,20</sup> During this same brief period, other notable genomics-based advances in our understanding of biology and of health have included the first comprehensive analysis of human chromosome 7,<sup>21</sup> clarification of the male-specific region of the human Y chromosome,<sup>22</sup> and the identification of the gene responsible for progeria.<sup>23</sup>

In recent months we have seen not only the promise of the genomic era with respect to medicine, but also its pitfalls. An example of the latter has been the revelation that confusion and misinformation have occasionally accompanied the counseling of persons who undergo screening for mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) — the gene responsible for cystic fibrosis. Different mutations in *CFTR* have different effects, leading to a range of phenotypes. Proper interpretation of screening results demands an understanding of the clinical implications of specific genotypes. For example, the relatively common 5T variant leads to the phenotype of classic cystic fibrosis only when it is accompanied by the R117H mutation on the same chromosome arm. However, there have been anecdotal reports of persons who were told that the presence of the 5T variant alone was indicative of a serious risk of cystic fibrosis. There is reason to believe that such problems are not intrinsic to genomic medicine and merely reflect the temporary difficulties of integrating virtually any new form of technology into health care. But this example certainly points out the urgency with which genetic literacy must be achieved among all health care providers. In the genomic age, *primum non nocere* remains a useful aim.

Genomics provides powerful means of discovering hereditary factors in disease. But even in the genomic era, it is not genes alone but the interplay of genetic and environmental factors that determines phenotype (i.e., health or disease). This point is not new, but it bears repeating. For example, a mutation in *CHE1* may be innocuous until a person

carrying it is exposed to succinylcholine chloride anesthesia, when it leads to prolonged apnea. Conversely, substantial mutations in phenylalanine hydroxylase inevitably result in the sequelae of classic phenylketonuria, including profound mental retardation, unless the affected newborn is placed on a special diet, in which case essentially normal intellectual development can be expected. Recent reports further expand our knowledge of the complex interactions between genes and the environment. For instance, one such study suggests that common variations in the serotonin-transporter gene influence the likelihood of depression after exposure to stress.<sup>24</sup>

Since it remains difficult to alter genes in humans (for both technical and ethical reasons), for the next couple of decades we will generally use personalized modifications of the environment, and not of genes, to translate genomics-based knowledge into improvements in health for most of our patients. Clinicians will much more frequently suggest to patients with hereditary hemochromatosis that they avoid iron supplementation than that they consider gene therapy. Women who carry mutations in *BRCA2* will profit more from taking tamoxifen than from manipulations of their genotype.

With the end of the pregenomic era in sight, more than 600 experts recently collaborated to produce a vision for the future of genomic research and its applications to biology, health, and society.<sup>25</sup> According to that vision, for instance, within a decade or two, it will be possible to sequence anyone's entire genome for a laboratory cost of less than \$1,000. If this proves true, one can imagine how not only research, but also clinical care, may change dramatically. However, as is true for so much of the application of genomics, ethical, legal, and social issues complicate this optimistic picture. Unless complex issues regarding the patenting and licensing of gene-based knowledge and techniques are dealt with more successfully than they are today, the "\$1,000 genome" will remain a wish, not a reality. Even if the intellectual-property discussions are complex, the math is simple. Assuming that roughly half of the approximately 30,000 human genes are patented, if each patent holder were to charge only \$1 per test to license his or her gene, the \$1,000 genome would become the \$16,000 genome, a very different economic, and thus clinical, reality.

Another social issue, with particular relevance in the United States, is the understandable concern of many patients that obtaining genetic information

important to their health care is not worth the risk of discrimination stemming from the use of such information by potential insurers or employers. Although more than 40 states limit employers' and insurers' access to or use of genetic information, many people believe that only the passage of legislation mandating uniform national protection against the misuse of such information will lead to full use of genetic testing. Congressional leaders from both major parties and the current administration have supported such federal legislation, and passage of such legislation is currently closer to reality than ever before. However, until it is enacted and signed into law, the fear of discrimination will remain.

Other social issues require our attention if genomic medicine is to benefit our patients. How should genetic tests be regulated? What, if any, are the appropriate uses of direct-to-consumer marketing of genetic tests? The Internet has recently had a proliferation of genetic-testing sites that feature claims grounded in greed and pseudoscience, rather than in data or reality. How will health care providers and the public distinguish between these and responsible testing services, whether they are available through the Internet or in the hospital?

It would be easy to assume that for the foreseeable future the benefits of genomic medicine will accrue only to people in developed countries. However, even in resource-poor regions of the world, genomic approaches can offer dramatic benefits to health, as the publication within the past year of the genomes for *Plasmodium falciparum*<sup>26</sup> and *Anopheles gambiae*<sup>27</sup> exemplifies. Nonetheless, another important social issue is the challenge of harnessing this unprecedented opportunity so that genomic medicine benefits all.

While recognizing such challenges, we look forward with curiosity and real hope to the advances of the next 50 years — the first 50 years of the genomic era. As evidenced by the Genomic Medicine series, today's researchers and clinicians have already started to use the power of genomics to improve health, and we anticipate that this is but a hint of the progress to come.

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