Genomics: the coming revolution in medicine

Sequencing the human genome is not an end in itself, says **Francis Collins**. It is just the start of a revolution in genomics and genetics that will change the face of medicine in the 21st century

For nearly 100 years the medical community has been aware of heredity's powerful role in human health and disease. Yet a wide chasm filled with scientific uncertainties has stood between that understanding of the principles of human genetics and medicine's ultimate aim of alleviating human suffering. A bridge is now on the horizon. Equipped with our new-found knowledge of the genetic Book of Life – the human genome – the world's leading scientists are laying the foundation for a genomics revolution that will change the face of medicine in the 21st century.

This is one revolution that should take no one by surprise. In contrast to most other ambitious scientific undertakings, the Human Genome Project (HGP) has been international since its inception. Although the US invested the largest amount in HGP, many nations – including the UK, France, China, Germany and Japan – have made critical contributions.

HGP leaders also agreed at the outset to release all mapping and sequencing data into the public domain immediately, making the information freely available to the worldwide scientific and pharmaceutical communities without restrictions on access or use.

Furthermore, in a highly unusual step for a basic science enterprise, the US HGP set aside 3-5% of its budget for research on the ethical, legal and social implications of this exponential increase in knowledge about humans' genetic make-up. In the past, analysis of the ethical, legal and social consequences of a scientific revolution were often not addressed until after a crisis had arisen.

Taking full advantage of this multidisciplinary, multi-institutional, international approach, the HGP has attained historic milestones, while consistently running ahead of schedule and under budget. HGP scientists are currently on target to finish the sequence of all 3 billion base pairs of human DNA by April 2003 – more than two years ahead of schedule and coinciding with the 50th anniversary of James Watson and Francis Crick's seminal publication of the double-helix structure of DNA.

However, now is not the time for leaders in the scientific, economic and political arenas to rest upon the HGP's monumental achievements. Obtaining the sequence of the human genome is not an end in itself, merely the end of the beginning – and the start of the next exciting chapter in genomics and genetics.

Already the availability of genetic and physical maps produced by the HGP has dramatically accelerated the successful identification of genes involved in relatively rare, single-gene disorders. The next challenge is to apply information about the human genome sequence and its variants to identify genes that play a significant role in common human diseases, such as cancer, diabetes, heart disease and schizophrenia.

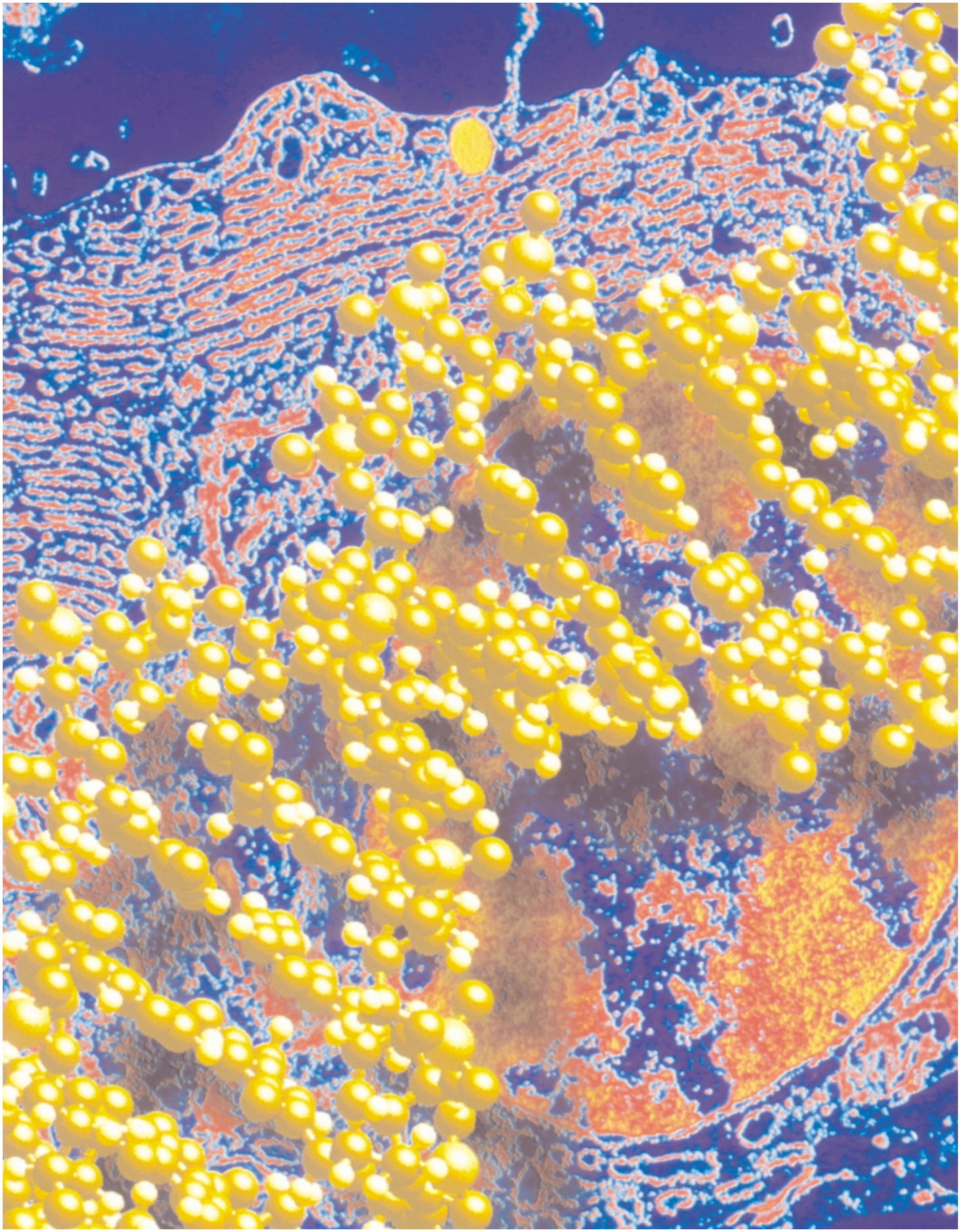
Although humans around the globe are 99.9% identical in their genetic make-up, the 0.1% difference is thought to hold key clues to individual differences in susceptibility to disease. Taking aim at that critical 0.1%, a five-nation coalition recently launched a highly ambitious, $100 million public-private venture, called the International HapMap Project, to construct a catalogue of human genetic variations and how they are organized along chromosomes.

Among those playing a pivotal role in that endeavour is The SNP Consortium (TSC), a collaborative genomics effort of major pharmaceutical companies, the Wellcome Trust and academic centres. TSC was the major force behind the creation of an existing public database (dbSNP) which describes 2.8 million genetic variants called single nucleotide polymorphisms (SNPs).

Following the lead of the Human Genome Project, the HapMap team has enlisted the help of ethical, legal and social experts to maintain and strengthen the delicate threads of societal trust, which are likely to come under strain as genetic and genomic research begin to intersect with the daily lives of people worldwide.

When completed, the HapMap will serve as a tool for researchers trying to discover the genetic variations associated with common diseases, as well as variations associated with differences in drug metabolism and with hallmarks of good health, such as longevity.

The development of new technologies and strategies for the large-scale, high-throughput generation of biological data at relatively low cost has been crucial to the success of genomics research in the past 15 years. However, there is still an urgent need to improve and add to our existing tool kit of technologies for performing high-throughput analysis of the human



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genome, along with the wide array of proteins produced by these genes. Indeed, one of my institution's most audacious goals for the next decade is to establish technologies that will allow us to sequence a person's entire genome for $1,000 or less.

Bear in mind that it will do people little good to learn about the genetic variations that predispose them to illness if medicine can offer no assistance in averting or treating such suffering. Identification of a gene or collection of genes that contributes to disease represents the initial step in a multipronged process of moving basic genetic and genomic knowledge into the medical mainstream (see diagram, right).

Typically, the first practical payoffs of a genetic discovery are new or improved diagnostic tests. By 2010 it is expected that validated, predictive genetic tests will be available for as many as a dozen common conditions. These tests will enable individuals who wish to learn more about their personal disease susceptibilities to take preventive steps to reduce the risk of their developing a condition.

Such steps could take the form of close medical surveillance such as more frequent mammography or colonoscopy screening, lifestyle modifications such as changing diet, avoiding environmental triggers or increasing exercise, or preventive drug therapy similar to the current use of cholesterol-lowering agents in people at risk of coronary artery disease.

Beyond diagnosis and screening

Gene-based tests will by no means be limited to diagnosing disease or screening for disease susceptibility. The discovery of genes for drug responsiveness is likely to lead to predictive tests to determine whether a person is likely to have a good or bad reaction to a specific pharmaceutical agent.

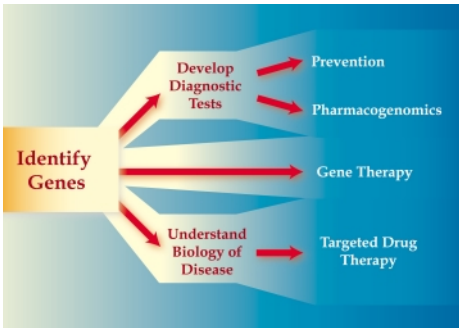
The expectation is that many such gene-drug correlations will be found over the next decades, fuelling the growth of a rapidly emerging field known as pharmacogenomics and eventually enabling doctors to tailor their prescribing practices to each person's genetic profile. In short, medicine's current "one size fits all" approach to managing patients will become a thing of the past.

One much-publicized application of genetic knowledge – gene therapy – burst on to the scene in the early 1990s, generating hope among patients that it could provide quick solutions to a long list of medical problems.

However, this strategy, which uses genetically engineered viruses or other vectors to insert a "healthy" copy of the gene into an affected person's cells, has suffered a series of disappointments over the past few years. These included the death of a young man in a US medical trial in 1999 and the development of vector-induced cancer in a child in a French trial in 2002.

Still, it remains likely – after researchers have spent more time at the bench answering basic science questions more thoroughly and developing safer, more effective vectors – that gene therapy will re-emerge to play a significant role in the treatment of some diseases.

Although grabbing fewer headlines than gene therapy, an equally promising or even more promising therapeutic approach is grounded in using new-found genetic and genomic knowledge to gain a better understanding of the underlying biology of disease.



Genetics leads to a range of treatment strategies

Identification of each genetic variant conferring disease risk will point towards a critical pathway for that illness, often immediately suggesting targets for pharmaceutical therapy. Many of these pathways will come as a surprise, given our limited understanding of the molecular basis of most common diseases.

In response to the dominant role that genomics is likely to play in future drug development, the pharmaceutical industry is already gearing up to put in place efficient, high-volume methods of developing and designing the small-molecule drugs needed to target biological pathways.

At the same time, basic scientists are contemplating ways of using small-molecule compounds as probes in their efforts to chart more precisely the complex pathways affected by different genetic variations and gene mutations.

This area of activity is just one of several examples that highlight the potential for increased interactions between academic scientists and the private sector in the genome era.

Such efforts are already starting to pay off, as indicated by the development in 2000 of the targeted drug STI-571, or Gleevec, which has produced dramatic responses in people suffering from otherwise untreatable chronic myelogenous leukaemia.

Gleevec was discovered using information about an abnormal protein produced because of a genomic rearrangement found to occur in leukaemic cells.

Given the large amount of genetic and genomic information already collected about various types of cancer, it is likely that within the next two decades all cancer patients will have their malignancies genetically "fingerprinted" and their therapies will be individually targeted to those fingerprints.

In fact, by 2020 the impact of genetics and genomics on medicine is likely to be far more sweeping than any of us can envisage today. Among the developments we can expect are the introduction of new gene-based designer drugs for diabetes, high blood pressure, mental illness and many other conditions that currently take such a high toll on individual lives, as well as economic productivity.

We can also expect that the pharmacogenomics approach for predicting drug responsiveness will be standard practice for many common drugs and disorders. More predictive genetic tests for disease susceptibility will become available, to be used not only for people with a strong family history of a disorder but also for healthy people who are seeking to enhance their chances of staying well.

Despite these exciting projections, there will be tensions. Antitechnology movements, already active in the US and elsewhere, are likely to gain momentum as the focus of genetics turns even more intensely towards human applications. Efforts at public education need to start now to explain the potential benefits of genetic medicine and to be honest about the risks.

The public also remains deeply concerned about the possibility that genetic information will be misused in a discriminatory manner – an issue that must be dealt with effectively by governments worldwide. Even the most exciting clinical breakthroughs generated by genomic science will come to nought if they are met with a societal backlash.

As is the case with most other hi-tech medical advances, access to health care is a major issue. It is clear that millions of people in both industrial and developing nations will be deprived of new genetics and genomics advances unless many medical care systems change in significant ways.

Some observers also discount the importance of genomics to the developing world. However, a better understanding of the genetic factors that influence susceptibility and/or response to various infectious diseases, including malaria, tuberculosis and AIDS, could have a great impact on health in the developing world.

Furthermore, genomics holds the promise of reducing the research and development costs of vaccines and pharmaceutical agents, which should help make such products more available throughout the world. The continued vigorous support of science is critical to realizing this promise of a revolution in medical practice.

But science alone is no match for all these daunting global challenges. Sustained partnerships must be developed between leaders in the field of genetics and their counterparts in all realms of society – from public policy to international economics, from corporate decision-making to elementary education.

The World Economic Forum provides a strategic opportunity for such partnerships to be formed and strengthened. GA

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