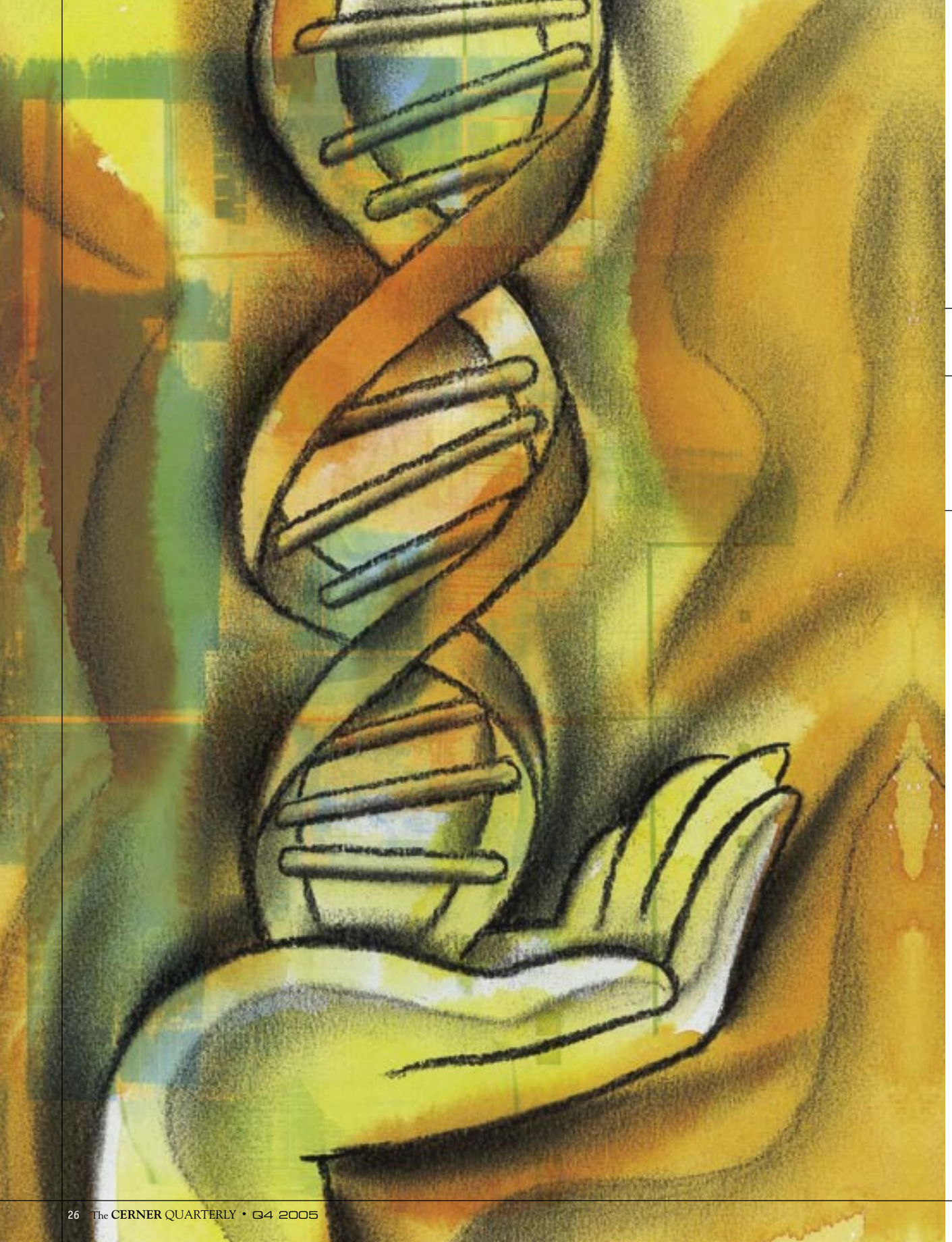

Personalized Medicine in the Postgenome Era

By **William Neaves, Ph.D.**
President and CEO
Stowers Institute for Medical Research

At the beginning of the new millennium, the first published sequences of insect[1], plant[2], and human genomes[3,4] changed forever how we think about ourselves in relation to other species. Human beings have no more than 25,000 distinct genes[5], far fewer than many plants such as rice[6] or wheat[7]. We share 10 percent of these genes with the fruit fly, and nearly 200 genes implicated in the etiology of human disease have been found in the fly genome. These include genes associated with numerous forms of cancer as well as Alzheimer's disease, Parkinson's disease, cystic fibrosis and muscular dystrophy[8].

Prior to the sequencing of the Drosophila genome, few would have expected a nephrologist to seek insights into human disease from an animal without kidneys. In fact, several human genes involved in renal disease have counterparts in the fly genome[8]. These genes code for proteins that play crucial roles in the transport of fluid and electrolytes across epithelia. Like all living organisms, flies must excrete metabolic byproducts to maintain homeostasis, but they rely on Malpighian tubules rather than kidneys to move ions across membranes. Both flies and human beings use similar molecular machinery to accomplish the same task.

If some were surprised by the direct relevance of fly genetics to human disease, physicians confronted even more unlikely revelations when the first sequenced plant genome was published in December 2000. The lowly mustard weed was found to have more than 100 homologues of human genes that are involved in diseases such as xeroderma pigmentosum, hyperinsulinism, Wilson's disease, ataxia telangiectasia, cystic fibrosis and breast cancer[2].

Perhaps the most significant similarities between the genomes of mustard weeds and humans reside in the family of

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DNA repair genes. These are the genes involved in diseases such as xeroderma pigmentosum and ataxia telangiectasia. Upon reflection, this makes sense. As different as plants and humans are, they both must engage in the maintenance and repair of an information-encoding system based on the integrity and fidelity of sequences of DNA bases over extended periods of time. This is why the mustard weed genome contains homologues of many DNA repair genes that are defective in human diseases such as hereditary breast cancer, non-polyposis colon cancer and xeroderma pigmentosum[2].

Suddenly, scientists who study plant genetics are publishing papers that cannot be ignored by the medical profession. This is a portent of things to come in the postgenome era. Physicians must prepare for an exponential increase in the mass of medically relevant new information that patients will expect their doctors to master. And patients' expectations grow every day as they rely on the Internet to educate themselves about the latest medical advances. Physicians in the postgenome era risk burial in an avalanche of new information relevant to the health and sickness of their patients. Only innovations in information technology can save them from knowing less than their patients about the newest developments in biomedical science.

As the postgenome era begins, privately endowed medical research institutes, universities and hospitals are adding their efforts to those funded by the $30 billion annual budget of the National Institutes of Health. Pouring forth from this collective endeavor is a tidal wave of new information that can drown physicians. Every week brings the publication of breakthroughs in the understanding of the genetic causes of disease and the rate at which these breakthroughs are coming increases each month. The burgeoning productivity of this research fuels the revolution in biomedicine and illustrates the overwhelming task faced by physicians who must assimilate and use this new knowledge to improve patient care.

So how should physicians cope with the flood of relevant information? First, physicians in training and physicians in practice must learn to understand, appreciate, and use the best tools information technology can offer. The platform of this toolkit is a mental prosthesis. Many of us need visual prostheses such as eyeglasses or contact lenses to improve our ability to see. Eventually, many of us will need auditory prostheses such as hearing aids to improve our ability to hear. Already, we need mental prostheses to improve our ability to acquire, organize and interpret information.

Physicians cannot survive without a mental prosthesis. The massive amount of information that must be retrieved each day and used to make decisions is far beyond the capacity of human memory. It can only be accomplished with the help of a portable computer connected to an interactive network and equipped with data-mining software that exercises logic in locating and assembling information specific to the individual physician's professional requirements. These devices will serve as mental prostheses.

For those who deliver healthcare in the 21st century, the challenge will be bringing all the relevant information together at the same time and place so that an informed decision can be made about what is best for the patient. Just as medical education had to be transformed in the early 20th century to enable physicians to practice scientific medicine, 21st-century training will have to change to allow them to practice informatic medicine. Physicians must prepare for lifelong, everyday, just-in-time acquisition of knowledge from afar, and they will need new and better information management tools.

The "low-hanging fruit" for physicians in the postgenome era are diseases in which single-gene mutations play a decisive pathogenic role. Many recent examples represent subsets of a larger disease category. Each traditional disease category and each distinctive constellation of symptoms may be divided into many different subsets involving one or more genes. Clearly, some subsets and some entire categories of disease will involve more complex causes. Some will involve tens or even hundreds of different genes. In all cases, interactions among genes, as well as those between genes and the environment, must be considered.

Although much low-hanging fruit will be harvested in the next decade, many multigenic diseases will keep biomedical scientists busy for several decades. Along the way, how we think about disease will change dramatically. If the diagnosis of disease is the first step to effective therapy, physicians will increasingly think of diseases more in terms of causes than symptoms. Knowing that someone has hypertension or muscular dystrophy or leukemia means relatively little in the new age of personalized medicine. To treat such diseases effectively, physicians need to know if the problem resides in a mutated serine-threonine kinase gene, as

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in the case of pseudohypoaldosteronism hypertension, from work by Wilson and colleagues at Yale[9]; a mutated ZNF9 gene in myotonic dystrophy, from work by Liquori and colleagues at Minnesota[10]; or a mutated tyrosine kinase gene in chronic myelogenous leukemia, from work by Drucker and colleagues at Oregon[11].

For almost a century after Rudolph Virchow described a patient with "white blood" in 1845[12], leukemia was thought to be a single disease. In much of the 20th century, leukemia was classified according to the course of the disease (acute or chronic) and the type of cell giving rise to the malignancy (lymphocytic or myelogenous). Leukemia is now known to result from a multitude of pathogenic mechanisms, many involving chromosomal translocations and gene fusions[13]. Leukemia illustrates how diseases in the postgenome era will be defined less by signs and symptoms and more by molecular pathogenesis[14]. The ability to specifically target each of the many fusion proteins that cause various forms of lymphocytic and myelogenous leukemia holds great promise for personalized treatment of patients with blood cancer.

One category of leukemia, recognized in the pregenome era as chronic myelogenous leukemia, results predominantly from a chromosomal translocation that disrupts the normal DNA sequence of the gene for a growth-promoting enzyme known as tyrosine kinase. Fusion of the c-abl gene of chromosome 9 with the bcr gene of chromosome 22 creates a novel chimeric oncogene. White blood cells carrying this chromosomal translocation produce a fusion protein, Bcr/Abl tyrosine kinase, which has tenfold greater enzymatic activity than c-Abl tyrosine kinase. The constitutively expressed and overly active enzyme causes cancerous proliferation of the affected cells[15].

The Novartis drug, Gleevec®, binds to the active site of the mutant tyrosine kinase and blocks its ability to promote abnormal cellular growth[11]. Although Gleevec can also bind normal tyrosine kinase found in white blood cells lacking the chromosomal translocation, it does no apparent harm to healthy cells and avoids the devastating side effects associated with non-specific chemotherapeutic agents traditionally used in cancer therapy. This new drug exhibits remarkable efficacy in patients with chronic myelogenous leukemia. Gleevec has quickly come to exemplify the Holy Grail of the pharmaceutical industry, "knocking out cancer cells while leaving healthy cells alone."

Gleevec offers insight into the kindof personalized therapies promised by gene-based molecular medicine. It is a dramatic departure from the "one-size-fits-all" pharmacology of the 20th century and opens the way for pharmacogenomics, one of many manifestations of the postgenome era.

Pharmacogenomics owes its existence to genetic variation among members of the human species. Among the individuals whose DNA was studied, the Celera and the public sequencing projects revealed fewer than 3 million single nucleotide differences out of nearly 3 billion base pairs in the human genome[3,4]. However, this one-base-pair difference out of every thousand in the human genome is enough to provide the theoretical basis for identifying prospectively those patients who will benefit from a therapeutic drug and those who will develop harmful side effects.

Many patients will soon be genotyped and their personal array of single nucleotide differences can be sorted into two categories—those that are found in at least 1 percent of the population (single nucleotide polymorphisms or SNPs) and those that occur less frequently (mutations). One can hardly imagine what this will mean in terms of storage and retrieval of relevant information bearing on the healthcare of individual patients. It will present enormous challenges to developers and managers of clinical databases and patient records.

The underlying concept of pharmacogenomics is not new. Karl Landsteiner introduced the concept of personalized medicine nearly a century ago with his classification of humans into four phenotypes based on blood antigens of the A, B, AB and O groups[16]. We now know that these phenotypes result from a diploid combination in each of us of three different alleles at the ABO gene locus[17]. If an individual with only A alleles at the ABO locus receives a transfusion of blood from an individual with only B alleles at the ABO locus, that recipient experiences devastating side effects such as shock, haemoglobinuria or even death. Knowing the genotype of a blood transfusion recipient permits informed selection of the therapeutic agent such as blood from a compatible donor. Similarly, knowing the SNP profile of a patient will enable a physician to avoid certain drugs in favor of those that are known to produce only desirable outcomes in people with that genotype.

For example, it has long been known that κ-opioid analgesics achieve only limited pain relief in most people. Men do not benefit from the drug, and only some women experience effective analgesia. The melanocortin-1 receptor mediates κ-opioid analgesia, and recent research has shown that only women with two mutated alleles for the receptor's gene display robust analgesia when treated with the drug[18]. Hence, genotyping the melanocortin-1 receptor identifies prospectively those female patients who will experience adequate pain relief from κ-opioid drugs such as pentazocine.

But as Gleevec illustrates, pharmacogenomics offers additional opportunities beyond the ability to deploy existing drugs more intelligently. In this age of personalized medicine, pharmaceutical companies will develop entirely new drugs to target the abnormal proteins produced by SNPs, mutations and other individual genetic variants, including chromosomal rearrangements, which alter gene sequences. Pharmaceutical companies will also focus on protein targets that turn genes on or off. There will soon emerge a new pharmacology based on drugs that target protein transcription factors to suppress expression of a disease-causing gene or to promote expression of a disease-suppressing gene.

We now know that the human body has many more proteins than genes. Although we have fewer than 25,000 protein-encoding genes in our genome, those genes are capable of producing many hundreds of thousands of distinct proteins. Add to this the potential of our personal SNPs and mutations to yield thousands more variant proteins, and one begins to appreciate the potential magnitude of the new proteomic pharmacopoeia and the database required to deploy it intelligently. Doctors must prepare for a *Physician's Desk Reference* (PDR) that will rival the *Oxford English Dictionary* (OED) in its bulk. Like the OED, the expanded PDR will only be user-friendly in an electronically searchable format.

Highly specific drugs tailored to a small subset of patients who will benefit from a new custom-designed therapy are more expensive than their predecessors. How much must a pharmacology company charge to recover its investment in highly personalized drugs and will patients and their insurers afford it? Raising this question is not intended to discourage pursuit of personalized therapies, but it does acknowledge an economic consequence of pharmacogenomics. It is no surprise that personalized healthcare based on pharmacogenomics will cost much more than the old one-size-fits-all medicine. Society must confront a very difficult question: How much of the economy can be devoted to implementing the technologies resulting from the revolution in biomedicine?

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A recent example of the financial impact of pharmacogenomics on a drug company is the Astra-Zeneca drug Iressa®. It dramatically benefits one-in-10 patients with non-small cell lung cancer and has no apparent effect on the others. Reports published in *The New England Journal of Medicine*[19] and in *Science*[20] during the spring of 2004 revealed that Iressa affects a specifically mutated form of the growth-promoting receptor that causes the cancer, and less than 10 percent of the patients with this cancer have the mutated receptor.

The stock analysts who follow Astra-Zeneca were understandably alarmed by this discovery. They realized it would make doctors more efficient in prescribing a very expensive drug. The nine-out-of-10 patients who were taking about $30,000 a year of Iressa with no benefit could now be identified (they lacked the mutant receptor) and could avoid the expense. This changed nothing about the cost to Astra-Zeneca of developing Iressa, but it showed that the population of patients for whom it might be prescribed was a small fraction of what had been anticipated. Can Astra-Zeneca recover its investment in Iressa from the one-in-10 patients for whom it can now be rationally prescribed? If not, what will the company and its stockholders conclude from Iressa's abrupt transformation into an orphan drug?

The bad news brought to Astra-Zeneca by pharmacogenomics was offset in June 2005 when an emerging pharmaceutical company, NitroMed, Inc., benefited from an unprecedented FDA recommendation of approval of a new drug for prescription to members of a single racial group[21]. The new drug, BiDil®, failed to help patients in the general population, but it decreased the risk of death from heart-failure among African Americans by 43 percent. BiDil represents a deliberate and successful attempt by a pharmaceutical company to target a drug to a large subgroup of patients whose genes make them likely to benefit from the treatment.

There are reasons to be optimistic about pharmacogenomics counterbalancing the escalating costs of new drugs that only work, but work very well, on smaller and smaller subsets of patients. Tens of billions of dollars in drug development costs, not to mention opportunities for improving health, are lost each year by pharmaceutical companies when the FDA disapproves a new drug that benefits some patients in Phase III clinical trials

William B. Neaves, Ph.D.
President and CEO
Stowers Institute for Medical Research

William B. Neaves, Ph.D., has served as president and CEO of the Stowers Institute for Medical Research in Kansas City, Mo. since June 2000.

From 1972 until joining the Stowers Institute, he served in various positions at the University of Texas Southwestern Medical Center at Dallas, including professor of cell biology; holder of the Doris and Bryan Wildenthal distinguished chair in biomedical science; dean of Southwestern Graduate School of Biological Sciences; dean of Southwestern Medical School; and executive vice president for academic affairs.

Neaves has published numerous peer-reviewed journal articles describing the results of his research funded by grants from the National Institutes of Health and the Population Council. He has also served as chair of the Liaison Committee on Medical Education, the accreditation authority for U.S. medical schools, and as a member of the boards of directors of the Sarnoff Endowment and the Damon Runyon Cancer Research Fund.

Currently, Neaves serves as a professor in the School of Medicine of the University of Missouri at Kansas City and member of the National Council of the Washington University School of Medicine.

Neaves earned an A.B. magna cum laude with highest honors in biology from Harvard College in 1966 and was awarded a Ph.D. in anatomy from Harvard University in 1970. In 1983, Neaves received the Young Andrologist Award from the American Society of Andrology for research contributions to the biology of reproduction. He was elected a Fellow of the American Association for the Advancement of Science in 1991 in recognition of his studies of cells that produce steroid hormones.

but harms others who react badly to the medication. If the patients who are susceptible to adverse reactions could be identified prospectively by molecular and genetic markers and excluded from therapy, the investment in the new drug might be saved.

The principle behind this optimistic scenario was demonstrated 20 years ago by a team led by Richard Weinshilboum at Mayo Clinic[22]. A drug that helped most children with acute lymphocytic leukemia, 6-mercaptourine, killed a small number of patients. Approximately 0.3 percent of children have a mutated enzyme that cannot metabolize the drug, and most of them will die if given it. The Mayo team found the genetic marker that identifies those who cannot tolerate 6-mercaptourine. Children with acute lymphocytic leukemia are now routinely genotyped to determine if they should not be treated with the drug.

Pharmacogenomics will enable clinical trials to yield FDA-approved drugs more efficiently. This in turn may offset the cost to the pharmaceutical industry caused by more efficient prescription of expensive drugs tailored to fit individual patients.

Clearly, much of what personalized medicine holds for the future is still speculative. But only five years into the postgenome era, one thing already seems certain: The healthcare industry must devote much more money to managing the massive amounts of patient data that pharmacogenomics portends. TCQ

Genome Glossary

Definitions are from the National Human Genome Research Institute of the National Institutes of Health, *Merriam-Webster's Collegiate Dictionary* and the National Center for Biotechnology Information.

Allele – One of the variant forms of a gene. Different alleles produce variation in inherited characteristics such as hair color or blood type.

Cell – The basic unit of any living organism. It is a small, membrane-bound, compartment filled with chemicals and a complete copy of the genome.

Chromosome – One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Different organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair.

DNA (Deoxyribonucleic acid) – The chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

Enzyme – A protein that encourages a biochemical reaction, usually speeding it up. Organisms could not function if they had no enzymes.

Etiology – A branch of medical science concerned with the causes and origins of diseases.

Gene – The functional and physical unit of heredity passed from parent to offspring. Genes are regions of DNA that contain the information for making a specific protein or RNA molecule.

Genome – All the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in the mitochondria.

Genotype – The genetic identity of an individual, including aspects that do not show as outward characteristics.

Homologue – A comparable gene or protein shared by multiple species.

Nucleotide – A component of DNA. Four nucleotides are used to assemble DNA: adenine, cytosine, guanine and thymine, commonly represented as "A," "C," "G" and "T."

Pharmacogenomics – A science that examines the inherited variations in genes that dictate drug response and explores the ways in which these variations can be used to predict whether a patient will have a favorable response to a drug, an adverse response to a drug or no response.

Proteins – A large complex molecule made up of one or more chains of amino acids. Proteins perform a wide variety of activities in the cell.

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