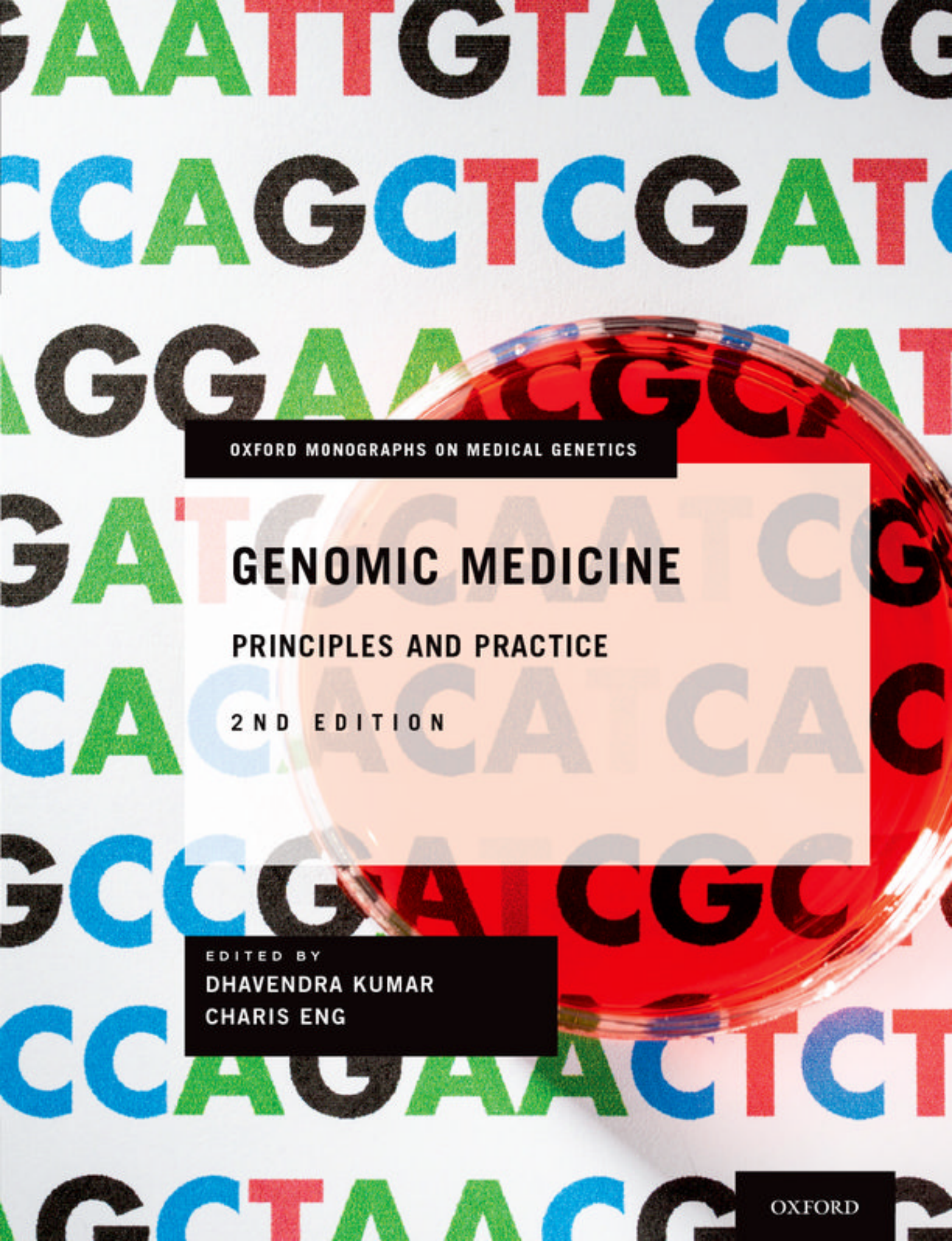
OXFORD MONOGRAPHS ON MEDICAL GENETICS
GENOMIC MEDICINE
PRINCIPLES AND PRACTICE
2ND EDITION
EDITED BY
DHAVENDRA KUMAR
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GENOMIC MEDICINE

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GENOMIC MEDICINE: PRINCIPLES AND PRACTICE

SECOND EDITION

EDITED BY

Dhavendra Kumar MD FRCP FRCPCH FACMG

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"To our Parents and Families,

To our Patients and their Families"

FOREWORD

In the foreword of the previous first edition of this book (see page ix), Dr. Francis Collins had welcomed the reader to the genome era, and has eloquently introduced the genome into the medical practice. It is my great pleasure and honor to be able to comment on the significance of the genome analyses in medicine.

It has become abundantly clear that there are two main etiological components when considering health and disease: the genomic variation, and the environmental insults. In other words, the majority of disorders result from the interaction between individual genomic composition (and history of the subsequent somatic mutations), and the environmental variables. Thus it is of paramount importance to study the genomic variation of each individual in order to begin to understand his or her disease, improve the diagnostic possibilities, and introduce intelligent treatments.

The progress in human genomic sciences continues at a remarkable pace: the HapMap Project and the 1000 Genomes Project have provided the opportunity to assess the common and rare variations in genomes from different geo-ethnic groups; the ENCODE Project has provided initial information on the functional elements of the genome; the genome-wide association studies have provided genomic signals for functional and diagnostic studies related to almost all the complex human disorders and traits with measurable heritability; the work in model organisms has provided the basis for the functional analysis of genomic variation by taking advantage of evolutionary conservation; the discovery of the pathogenic mutations of a large number of (near)-Mendelian disorders has extended the important list of rare disorders; and the exploration of *de novo* genomic variants points to genes involved in complex phenotypes and underscores the importance of the unexplored genetics of sporadic cases. All of the above advances were possible thanks to the truly extraordinary and unexpected progress in sequencing technologies, the availability of bioinformatic tools, and the collaboration of scientists worldwide.

It is extraordinary that, within only a few years after the completion of the sequencing of the first genomes, we have the capacity to determine genomic variability rapidly and within reasonable cost constraints; however, we are far from understanding the functional significance of the vast majority of variants, and we are also far from determining, monitoring, and understanding the environmental impacts of the same.

The physician who practices genetic medicine now has an "organ" or field of expertise similar (or superior?) to those of other disciplines: the genome! As the cardiologist is an expert in the cardiovascular system, the neurologist in the nervous system, the endocrinologist in the endocrine glands, and the ophthalmologist in the eye, the geneticist is becoming an expert in the genome's anatomy, variability, pathogenicity, function, inheritance, history, and evolution. The geneticist using all this information and knowledge participates as a primary actor in the diagnosis and treatment of individuals, and becomes a notable voice in the chorus for family and health planning, and a whole litany of ethical, legal, social, financial, and educational issues.

Remarkably, our knowledge of the individual genomic variations, and the access to information through the Internet and the social media, have made the physician only one aspect of the health management and have elevated the patient/consumer to a position of partnership. Medicine is becoming more participatory, and the physician less paternalistic regarding diagnostic strategies and therapeutic options. In addition, several other disciplines well versed in computational biology, information technology, and statistics participate in the diagnostic and therapeutic schemes, and their expertise is indispensable in the gathering the vast amounts of data and distilling the relevant information that guides medical decisions.

Genome sequencing has already become an important diagnostic tool. Yet, could the reading of each individual's genome solve the majority of the diagnostic problems? Undoubtedly not, even if we achieve a full functional

understanding of each nucleotide. So-called personalized medicine will need:

(a) the sequence of the genomes of key somatic cells that have become malignant, or have developed a recognizable pathological phenotype;

(b) the sequence of the genomes of billions of bacterial and other microbes that we all host in our bodies (microbiomes);

(c) the epigenetic modifications in different cell types;

(d) the repeated analysis of transcriptomes of various cell types; and

(e) the repeated analysis of other "-omics" components.

The list is not exhaustive, and the exact battery of genome-based tests will be determined on an individual basis.

The revised and rich contents of this remarkable book, edited by our outstanding colleagues, Professors Dhavendra Kumar and Charis Eng, and written by an equally outstanding roster of authors, deal with all aspects of genomic medicine. The book combines general principles and specific aspects of clinical practice, all in the light of genome analysis and the current laboratory methodologies. The genome era of medicine is well into development, and, as Shakespeare wrote in *The Tempest*: "What's past is prologue."

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June 23, 2013

FOREWORD TO THE FIRST EDITION

A scant twenty years have passed since the word "genomics" was coined by Victor McKusick, Frank Ruddle, and Tom Roderick to describe a new discipline. The suffix of the word derives from the Greek *ome* meaning all, and aptly conveyed an intention to transition the study of heredity from a focus on single genes (genetics) to the more global perspective of all of the hereditary material. A proliferation of other "omics" disciplines has subsequently erupted—including proteomics, metabolomics, transcriptomics, glycomics, microbiomics, and many more.

But genomics remains the foundation of the rest, reflecting as it does a comprehensive analysis of the DNA instruction book. The success of the Human Genome Project has now laid that instruction book wide open. As a result, the life sciences have been catapulted forward, and biology has now taken its rightful place alongside physics and chemistry as a truly digital and quantitative science.

It is the application of genomics to medicine that carries its greatest promise of benefit to humankind. Thus, the publication of this first textbook of "Genomics and Clinical Medicine" marks a milestone, a coming of age. Here in the early years of the third millennium we can see the emerging outlines of a new synthesis of the noble tradition of the healing arts with an increasingly precise way of understanding the causes of disease, based on an understanding of the human genome.

For some in the clinical medicine community, however, this textbook may come as a surprise. After all, there are still many practicing physicians who would say they see no evidence of genetics or genomics as part of their daily medical practice. Surely, however, that reveals a problem with the successful communication of rapid new developments in this field, not the facts of the matter. For in these forty-two chapters, a vast array of genomic implications for nearly every condition that affects humankind is laid out in elegant and comprehensive fashion.

The pace of progress in genomics has been astounding. Over just the last fifteen years, largely as a consequence of the tools made available through the Human Genome Project, genes have been identified for more than two thousand inherited conditions. With recent rapid advances in the understanding of human genetic variation, the specific hereditary contributions to common diseases like diabetes, heart disease, cancer, and mental illness are emerging at an unprecedented rate. The very real possibility of offering individuals who are currently healthy a personalized prediction of future risks of illness is no longer a distant dream. And given that many of the common disorders for which predictions are becoming possible are associated with proven means of reducing risk through diet, exercise, lifestyle change, medical surveillance, or pharmacotherapy, the real likelihood of widespread individualized programs of preventive medicine grows by the day. Similarly, the ability to make predictions about the possibility of a beneficial or undesirable response to drug therapy, the field of pharmacogenomics, is advancing rapidly, and will soon require health care providers to determine the genotype before writing the prescription, at least for certain drugs. Many of us predict that the complete genome sequence of an individual will become part of that person's medical record within about ten years, at a cost of $1000 or less. And the therapeutics that we use in the future will likely be heavily dependent upon an understanding of the genomic basis of illness, leading to interventions that are both more accurately targeted to the underlying problem and less likely to cause side effects.

All of these advances should be welcomed by anyone interested in the alleviation of human suffering. Yet a number of major ethical, legal and social challenges lie along the path if this vision is going to be realized. In the United States, for example, we still lack effective federal legislation to prevent discriminatory uses of predictive genetic information. Major challenges also lie ahead with regard to ensuring equitable access to new genomic technologies, especially as our medical care system seems to undervalue opportunities for preventive medicine, focusing instead on treating disease once it has already appeared. But perhaps the greatest barrier, and the one which this book admirably seeks to address, is an educational one. Most members of the public are interested in genomics, but relatively unsure

of the details. Seeking advice, they generally turn to their health care providers, but many of those professionals are poorly prepared to become practitioners of this new art. After all, most physicians have had little or no training in genetics or genomics, and will be hard pressed to quickly acquire the scientific principles, the medical knowledge, and the psychosocial skills that will be necessary for the successful introduction of genomic medicine. Busy practitioners will desperately need an authoritative source of information that includes both principles and specific applications. The introduction of this textbook, with its distinguished and authoritative list of contributors, thus arrives in the nick of time. Welcome to the genome era.

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PREFACE TO THE FIRST EDITION

Although the science of genetics is only 150 years old, genetics as inheritance has been a concept discussed since ancient times. The evolution and natural-selection theories put forward by Charles Darwin had clear overtones that are reflected in some of our present-day concepts of the genetic basis of biological life. Gregor Mendel's laws of inheritance and successive discoveries in various aspects of genetics laid the foundations of a number of disciplines covering different areas within the science of genetics. Human genetics was no exception. However, this was heavily shrouded by the dark clouds of the so-called eugenics movement (sterilization of the "unfit," etc.) of the early twentieth century, when history recorded one of the worst practical applications of modern science on fellow human beings under the pretext of scientific research.

It has taken almost sixty years to arrive at our present state in the science of genetics. The future now appears bright, opening up many opportunities on the horizon. Clinical genetics is now a recognized medical specialty among several disciplines composing the current spectrum of modern medicine. The basis of clinical genetics is grounded in the sound knowledge and understanding of medical genetics that emerged as a spinoff of "human genetics."

Fifty years after the discovery of the double-helix structure of the deoxyribonucleic acid (DNA) molecule (Watson and Crick, 1953), characterization of the complete sequence and organization of the human genome was successfully accomplished (Lander et al., 2001; Venter et al., 2001). This major scientific achievement laid the foundation of "*human genomics*"; the section of the biological sciences that studies variations, mutations, and functions of genes and controlling regions, and their implications for human variations, health, and disease. This is strengthened by developments in the other areas of genomics relating to bacteria, vectors, parasites, animals, and plants.

The identification of all human genes and their regulatory regions provides the essential framework for our understanding of the molecular basis of disease. This advance has also provided a firm foundation for the future development of genomic technologies that can be applied to modern medical science. Rapid developments in global gene analysis, gene product analysis, medical bioinformatics, and targeted molecular genetic testing are destined to change the practice of modern medicine. However, many practicing clinicians perceive developments in genomics as primarily confined to the research arena, with little clinical applicability. But DNA- and RNA-based methods of disease-susceptibility screening, molecular-based disease diagnosis and prognosis, and genomics-based therapeutic choices and prediction of treatment outcomes are some of the key areas that are likely to influence the practice of modern clinical medicine.

Undoubtedly the science of genomics holds tremendous potential for improving human health. The World Health Organization (WHO) has made several recommendations on the scope and application of genomics on global health. It is acknowledged that the information generated by genomics will provide major benefits in the prevention, diagnosis, and management of communicable and genetic diseases as well as other common medical diseases, including cardiovascular diseases, cancer, diabetes, and mental illnesses (Cardon and Bell, 2001). Together, these constitute the major global health burden, as reflected in chronic ill-health and mortality. In addition, a number of infectious diseases are associated with genomic mutations, manifesting in the form of increased susceptibility, clinical severity, favorable or unfavorable responses to anti-microbial therapy—or in conferring protection. It is possible that the protective effect of a microbial vaccine might be influenced by genomic variation.

The sequence of the entire human genome is now complete—but each person carries a distinct sequence. The variation among all humans is reflected in variation within the human genome. The genomic variation between individuals, together with environmental factors, probably determines each person's disease susceptibility, and is important in drug efficacy and side effects for that person (Holden, 2000; Chakravati, 2000). The key to genomic variation lies in finding single-nucleotide polymorphisms (SNPs) and their use in disease-association

studies (Stephens et al., 2001). The positional cloning (identifying the gene by location, followed by functional analysis) of the disease susceptibility loci will depend on the successful application of haplotype associations. In addition, these will be important in clinical studies to find individuals in whom a drug is likely to be efficacious. The use of SNPs in pharmacogenetics is currently restricted to studying genes for drug-metabolizing enzymes, such as P450s, and variations in genes that target drug receptors. The newly emerging dynamic field of *pharmacogenomics* is an exciting application of genomic variation in drug discovery and drug development.

The recent cloning of real disease-susceptibility genes for multifactorial diseases is encouraging: for example, the identification of *NOD2* as a susceptibility gene for Crohn's disease (Hugot et al., 2001; Ogura et al., 2001). This is a major development in understanding the pathophysiology of inflammatory bowel disease. Similar studies are likely to unravel the genetic mechanisms in other complex medical diseases. A comprehensive SNP map will allow the cloning of other susceptibility alleles. However, this will depend upon population sample and size, the method employed, linkage disequilibrium, or association studies, rather than on the technology used (Cardon and Bell, 2001). Some of the best genetic studies of this kind include studies of susceptibility to infectious disease; for example, of an association between chemokine receptors (CCR5) and HIV susceptibility, and between the bacterial transporter protein Nramp and resistance to macrophage-infecting bacteria such as *Mycobacterium tuberculosis*. Similarly, various alleles at the G6PDH locus determine malaria susceptibility (Tishkoff et al., 2001).

These kinds of studies, and clinical applications of the resulting outcomes, are not without ethical concerns. Some of the questions and concerns are related to "ownership" of the genes and the freedom to use collected DNA for such studies. These are complex and emotional issues, especially when we are dealing with populations who may have been exploited or are perceived to have been exploited. These issues should always be dealt with carefully under the statutory requirements and rules.

There has been a tremendous surge in various subspecialties and technologies with names ending in *-omics*. We are rapidly moving into the "omics" era. In addition to genomics, several new specialist fields with an "-omics" suffix have recently appeared; for example, pharmacogenomics, nutrigenomics, metabonomics, transcriptomics, proteomics, microbiomics, glycomics, toxicogenomics, and many more. Some of these areas are included in this book. Whatever the basis of distinction might be, the driver of all these terms is GENOMICS—the study of genomes in its entirety.

Genomics is not just about genome sequencing. Apart from full-length cDNAs and their sequences, copies of mRNAs that actually exist and code for different proteins are probably more important. The study of proteins thus derived falls within the broad field of *proteomics*, a likely outcome of functional genomics and probably a true companion to genomics. It is likely that proteomics will eventually have more practical applications in clinical medicine. This is rapidly moving ahead with the completion of the HapMap Project (Nature, 2005) and the future "functional-variant database," a natural outcome of the HapMap Project (Gibbs, 2005).

It is vital that existing gaps in our knowledge about various "omics" disciplines be filled to ensure efficient use of the valuable information emerging from research. It is also important that the gap between "genetic professionals" and the primary-care community, as well as the "public health community," be narrowed (Khoury et al., 2003). Integration of this knowledge into the medical education curriculum and the continued professional education programs is urgently required to ensure applications of genomics in the provision of health care.

During the last two decades, the practice of medical genetics or clinical genetics has found its niche within the broad purview of clinical medicine. Genetic services now constitute a small, albeit important, component of modern medical practice and public health. Currently, genetic services focus on providing information on chromosomal and single-gene diseases, with limited contributions to multifactorial/polygenic diseases. How would this then be different from genomics? Already there is tremendous enthusiasm for the recently introduced term of "genomic medicine." In a primer on genomic medicine, Guttmacher and Collins (2002) viewed "genetics as the study of single genes and their effects" and genomics as "the study not just of single genes, but of the functions and interactions of all the genes in the genome." In simple terms, there is a quantitative difference between the two fields—the study of multiple genes as opposed to one gene. Thus genetics can be seen as part of genomics. However, there is a qualitative difference between genetics and genomics in medical and health applications, ranging from the concept of *disease* in genetics to the concept of *information* in genomics (Khoury et al., 2003).

The practice of medical genetics has traditionally focused on conditions that result from specific alterations or mutations in single genes (e.g., inborn errors of metabolism, Duchenne muscular dystrophy, and Huntington's disease); in parts of, or whole, chromosomes (e.g., trisomy 21 in Down syndrome); or associated with congenital malformations and developmental disabilities. The existing model of medical genetic services for these conditions includes laboratory diagnosis and genetic counseling and management. This is supported by public health measures to ensure the delivery of genetic services and genetic screening (e.g., newborn screening or screening the high-risk population). On the other hand, the practice of genomics in medicine and public health will focus on information resulting from variations at one or multiple loci and strong interactions with environmental factors; for example, diet, drugs, infectious agents, chemicals, physical agents, and behavioral factors (Khoury et al., 2003).

What medical and public health applications could one foresee following the completion of the human genome sequence in 2003? How could these be applied and delivered to the 95% of human diseases that do not fall under the rubric of "genetic disorders"? These are some of the likely questions related to genomic medicine. Medical and public health professionals urgently need to make the changes necessary to accommodate rapid identification and characterization of the numerous genomic variants at multiple loci that increase or decrease the risks for various diseases, singly or in combination with other genes, and with various chemical, physical, infectious, pharmacological, and social factors (Khoury, 1999). This genetic and genomic information is crucial in assessing the disease susceptibility of healthy individuals, and in personalized primary- and secondary-prevention planning. Collins and McKusick (2001) stated that,

> By the year 2010, it is expected that predictive genetic tests will be available for as many as a dozen common conditions, allowing individuals who wish to know this information to learn their risks for which interventions are or will be available. Such interventions could take the form of medical surveillance, lifestyle modifications, diet, or drug therapy. Identification of persons at highest risk for colon cancer, for example, could lead to targeted efforts to provide colonoscopic screening to those individuals, with [the] likelihood of preventing many premature deaths.

Personalized medicine will not only encompass common medical diseases, but could also include a wide range of preventable diseases. Genetic testing for future disease-susceptibility using multiple genomic variants will be possible and affordable with the application of "high-throughput" microarray-based genetic testing.

A wealth of information on genomics is rapidly being acquired, with the potential for a major impact on human health. However, these data and this information are scattered throughout several scientific journals, reviews, and state-sponsored reports and bulletins. A clinician or health professional often has difficulty in accessing and assimilating this information for application in her or his medical and public health practice. More importantly, an inability to assimilate and interpret this information can lead to frustration, and therefore avoidance of potentially useful information.

In view of the above developments and the rapidly increasing gulf between the practitioners and the available literature resources, the need for a dedicated book on genomic medicine was appreciated. Writing such a book was obviously a nearly impossible task for a single author. Several leading experts in different fields of the genome science and technology therefore offered to contribute. The views and opinions reflected in their individual chapters are largely influenced by each author's experience, perception, and interpretation of the available data and information.

This book provides a wide-ranging coverage of the subject, from the historical progress to general aspects of genomics, and describes in some detail the medical and health applications. Generally, all chapters follow the same format and are written by experts in their respective fields of research and clinical expertise. Each chapter provides a detailed and comprehensive account of its subject. However, it is likely that some gaps might exist, due to the inevitable time-lag between the time of writing and appearing in print. This is due to rapid developments in each field. However, all efforts have been made to provide the reader core information on the basic principles, scientific facts, current and likely future applications, useful relevant references, and information on Internet-based resources that should be helpful in exploring the subject further.

It is hoped that this book will facilitate acquiring factual information on genomics, developing concepts about the genomic basis of human disease, and provide a practical base for any interested clinicians and health professionals to develop an understanding of applications of genomics in clinical medicine and health. It is aimed at a wide

range of scientists, clinicians, and health professionals who are engaged in research, teaching, and training in medical and health applications of genome-based science and technology.

Finally, the practice of medicine is an art based on sound scientific principles. It would be appropriate to quote Sir William Osler's remark, "If there were no individual variability, medicine would have been science, not an art." Genomics in this context provides the basis of individual variability, and the modern post-genomic clinician will need to ensure that this is applied as an art.

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PREFACE

Since the publication of Kumar and Weatherall's *Genomics and Clinical Medicine* (2008), the science of genomics has made tremendous progress (Kumar, 2008; Hamburg and Collins, 2010). The preface for the first edition (see pages.…) set out a challenging and visionary goal for authors and editors. This was successfully accomplished, as reflected in positive and constructive reviews, personal or published (Feero, Guttmacher et al., 2010). Exciting new developments in biotechnology and bioinformatics have opened horizons that were inconceivable only a few years ago. The chatter about next-generation sequencing is not restricted to post-doctoral trainees and young investigators. It is evident everywhere and is now firmly ingrained in the minds and souls of genetic and genomic researchers and healthcare professionals (Berg, Khoury et al., 2011). Indeed, even as we write this second edition of (probably) the first book on genomic medicine, many tertiary genetics centers are utilizing whole-exome sequencing for routine clinical care (Lupski, Reid et al., 2010; Green and Guyer, 2011). Unravelling the complexities of the RNA molecules has made a huge impact in molecular and experimental biology. Challenging and controversial stem cell genomic research captured the headlines and was applauded by the awarding of the 2012 Nobel Prize. This is truly the beginning of a promising phase for applied and translational genomics. The sky is the limit.

Enormous genomic data and information generated by genome-wide association studies (GWAS), deciphering the complex phenotypes by copy-number variations and single-nucleotide polymorphisms, and applying knowledge gained from genetic and genomic analysis in the so-called rare Mendelian disorders, which affect more than 18 million Americans alone, have offered fine molecular understanding of the underlying pathogenic mechanisms, as well as implementation in clinical care of molecular diagnostics, risk assessment, genetic counseling, management, and predictive testing of at-risk relatives (Chin, Andersen et al., 2011). There is a lot of enthusiasm for applying next-generation sequencing methods (alongside Sanger sequencing, given the necessity of validating of next-generation data) in new gene discoveries, unravelling novel molecular mechanisms, and identifying critical focal points in molecular pathways in designing and developing targeted molecular therapy models. Inevitably, this has led to intense debate on practical matters related to disclosure and applications of pertinent and incidental findings (Green, Berg et al., 2013).

Several major global initiatives are being pursued to curate and annotate the enormous amount of genomic data and information from new genomic technological advances. The common theme is genotype–phenotype correlation, which is vital for clinical care. Leaders in this type of multi-institutional approach include the Human Variome Project (www.humanvariomeproject.org), the GenPhen project (www.Gen2Phen.Org), and the recently launched Global Genome Alliance (http://www.ebi.ac.uk/about/news/press-releases/Global-Alliance). Successful outcomes of these projects might offer clarification and evidence that could be applied to personalizing healthcare and wellness. However, there is sufficient evidence supporting the argument for genomic applications for enhancing the diagnostic and probably the prognostic potential of genomic medicine and health (Khoury, Gwinn et al., 2007). Promising new therapeutic developments have followed, particularly the discovery and development of new drugs and the pharmacogenetic/pharmacogenomic evidence necessary for personalizing pharmacotherapy; or at least we have made a good start (Chin, Andersen et al., 2011).

So how do genomics and all the related genome technologies affect medicine and health? Do we have enough data, understanding, and robust evidence, especially of clinical outcomes, to apply and translate into practicing effective and efficient clinical medicine? It is probably safe for us to gently move into the next phase of genomic medicine and personalized healthcare.

The thoroughly revised and practically wholly new text in this second edition aims to address the above questions and dilemmas. We are pleased to present this edition under a new title, *Genomic Medicine: Principles and Practice*. Several of our colleagues and professionals in related networks might agree on this ambitious title and probably share the

view that genetics and genomics knowledge is ripe for judicious clinical practice, but determining the *practical* clinical implementation remains the challenge. Part of the challenge is bringing all clinicians some minimum of practical knowledge of genomic advances so that genomics-enabled clinical practice can be understood, embraced, and leveraged for the delivery of value-based healthcare. Our second edition seeks to reach this lofty goal. The views and opinions expressed herein reflect each individual author's content expertise and knowledge, interpretation, and determination for puutting forward their views and opinions on the future of medicine in the genome era. The editors have simply facilitated the process to present the material in the best possible and deliverable manner. Naturally, all those who worked in developing and producing the second edition of this unique genomic medicine textbook will be anxious to know how medical students, post-doctoral fellows, genome scientists, and genetic/genomic physicians would rank the new edition.

Even with the genome in our palm, we remain humbly aware that we continue to strive to be better healers, as we have for 4,600 years:

Superior doctors prevent the disease;
Mediocre doctors treat the disease before evident;
Inferior doctors treat the full-blown disease.
—Attr. Nai-Ching (first Chinese medical text), 2600 BC

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Nelson Mandela once said, "It always seems impossible until it's done." This probably applied to this mammoth book project. On a number of occasions, it did not seem possible that the book would ever come to be. Nevertheless, we are proud and very pleased to present the second edition of Kumar and Weatherall's *Genomics and Clinical Medicine* largely rewritten, extensively revised, presented in an entirely different style and format, and wrapped with a new title of "*Genomic Medicine: Principles and Practice*."

Developing and working on the second and revised edition of the Oxford genomic medicine textbook has been a rewarding and learning experience. The project had the blessings of Sir David Weatherall, who inspired and guided the original version of this book (*Genomics and Clinical Medicine,* Oxford University Press, 2008) and continued to advise and mentor us on this entirely new version from conception to completion. We are fortunate to have the support of a fresh team of dedicated experts and authors who have produced the finest possible text, presented in a number of chapters. Whilst we have retained a few selected authors and contributors from the first edition, several of our current authors are entirely new to the emerging and challenging field of genomic medicine. We will always remain indebted and grateful for their support and contribution.

A few names deserve special thanks: notably Andrew Read (Manchester, England), Stephen Pennington (Dublin, Ireland), Richard Festenstein (London), Kevin White (Chicago, Illinois), Patrick Stover (Cornell, New York), Rino Rappuoli (Novartis, Italy), Teri Monolio (National Institutes of Health, Bethesda, Maryland), Angus Clarke (Cardiff, Wales), Reed Pyeritz (Philadelphia, Pennsylvania), Michael Parker (Oxford, England), Jane Kaye (Oxford, England), Dan Arking (Baltimore, Maryland), Kenneth Mills (Belfast, Northern Ireland), Bill Cookson (London), Sarra Jamieson (Perth, Australia), Graeme Black (Manchester, England), Karen Avraham (Tel Aviv, Israel), Eugene Healy (Southampton, England), Julian Sampson (Cardiff, Wales), Ben Lim (Singapore), Neil Robertson (Cardiff, Wales), Julian Knight (Oxford, England), and Stylianos Antonorakis (Geneva, Switzerland).

Apart from having a team of world-class authors, the publishing team at the Oxford University Press (OUP) in New York worked hard and demonstrated unmatched patience for managing delays, handling few unacceptably large and poorly presented manuscripts, and applying their superb editorial and technical skills in the production of this new edition. The OUP team, led by Catherine Barnes and ground managed by Chad Zimmerman and Meredith Keller, deserve praise and gratitude for bringing this exceptional book to reality and allowing it a place in the prestigious series, *Oxford Monographs on Medical Genetics.*

All clinicians work and live for serving patients and their families—this book is dedicated to all our patients. Finally, no small or large project could be completed without the blessings and support of the family, particularly those close to our heart and soul. We are deeply indebted and grateful to our parents and families for their untiring and infinite support in the completion of this book.

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