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The Busy Physician's Guide to Genetics, Genomics and Personalized Medicine

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I dedicate this book to my wife, Michele and to my children, Gabriella and Isabel for their inspiration, sustaining love and support. I also dedicate this book to my father and maternal grandmother, who passed away during the course of writing, and to my mother, who each in their own way shaped the person I am today.

Kevin Sweet

I dedicate this book to my children, Matt and Kathryn. My desire to be their role model continues to inspire and motivate me in everything I do.

Ron Michaelis

Finally, we would both like to dedicate this book to Dr. Jack Tarleton. Jack has been a great friend, mentor and role model for us both. We greatly appreciate the role he has played in our development as professionals, and wish him continued success in all his endeavors.

Foreword

Senior Vice President for Research in the Office of Health Sciences; Vice Dean for Research in the College of Medicine; Executive Director of the Center for Personalized Health Care, The Ohio State University; Board Member, Personalized Medicine Coalition

Congratulations on completing this important work that contributes significantly to the dissemination of foundation principles in genetics and genomics education. In a widely read article[1] published in 2009, Keyan Salari, a Stanford scholar, argues that rapid advances in the scientific discovery of human genetics and genomics expose a huge gap in the education of clinicians to fully understand the potential as well as limitations of genetics and genomics in medicine practices. This book will help close this gap.

The ability to understand and translate genetics and genomics into clinical practices are a key to developing and implementing personalized medicine. Salari argues that physicians have long used personalized histories like family history, diet, sleep and exercise in their evaluation of a patient to design preventative health and treatment strategies; using this self-reported information with targeted genetic/genomic tests to create personalized medicine has not been well understood or adopted by most clinicians. Individuals now have choices to acquire this information, including that provided by direct-to-consumer genetic testing companies like 23andMe and Navigenics, which challenges our health care system to respond to these personal genetic data and the attendant questions accompanying these data.

In addition to these commercial platforms, direct sequencing of the human genome is approaching the price point where large communities of individuals will choose to have this done. This additional large amount of data will further test an uncomfortable physician workforce to expand consultations with medical geneticists and genetic/genomic counselors to interpret and act on these data. Already, personalized genetic information is being used to improve outcomes in the area of pharmacogenomics and in the treatment of several diseases, including breast cancer. As personal genetic information becomes an increasingly integral component of

[1]Salari K, 2009 The Dawning Era of Personalized Medicine Exposes a Gap in Medical Education. PLoS Med 6(8): e1000138. doi:10.1371/journal.pmed.1000138

the patient medical record, it is becoming more urgent that practicing physicians as well as medical students be educated to use and interpret this information appropriately and responsibly.

In 2008, during the first Personalized Health Care National Conference hosted by The Ohio State University's Center for Personalized Health Care, Kevin shared with me his vision of writing a book. This idea was sparked after one of the guest speakers mentioned rapid technological advancements in genomics would soon overwhelm the 800,000 practicing physicians in the U.S. without sufficient targeted educational interventions in genetics/genomics. As evident in this book, Kevin and Ron accomplish the mission of educating not only practicing physicians and medical students, but also the general public about genetics and diseases and genetic test options, providing them with tools to help them better manage and become more actively involved in their own healthcare decisions.

The Ohio State University Medical Center has embraced the transformation of healthcare delivery through personalized medicine. We strive to change the current reactive mode of care delivery to proactive, P4™ (predictive, preventive, personalized and participatory) Health Care. P4 Health Care utilizes advances in genomics and molecular diagnostics discoveries and provides ***predictive*** information that is necessary to tailor ***personalized*** disease management approaches for each individual, based on genetic, environmental, behavioral and cultural factors. Therapeutics and health management tools are being developed to help ***prevent*** disease instead of merely treating the symptoms. P4 Medicine also promotes health maintenance and wellness, and engages consumers to actively own and ***participate*** in their healthcare decisions.

As we move to develop and implement P4 medicine at Ohio State, we are very fortunate to have a scholar and educator like Kevin whose passion and enthusiasm for genetics research and education are the driving force leading to the germination and completion of this important work. Kevin has made tremendous strides in the field of clinical genetics and genomics and it is truly my pleasure to write the foreword for his book.

I wish Kevin and his co-author, Dr. Ron Michaelis continued successes in translating the science of genomics discovery to a wide range of audiences so that the vision of personalized medicine can be achieved within the next 10–15 years. The future of medicine becoming predictive, preventive, personalized, and participatory is exciting and exhilarating. Kevin and Ron's book begins to pave the road to this future.

Clay B. Marsh, M.D.

Preface

We wrote this book for several reasons. First, we truly believe that we have entered the age of genetics, genomics and personalized medicine, and despite the difficulties that have been encountered in the early stages of the field's development, these revolutionary advances will ultimately improve health care in all fields of medicine. Surveys of practicing physicians consistently report, however, that many practitioners do not feel they know enough about genetics and genomics to apply these personalized medicine principles to their practice. If personalized medicine is ever to live up to its considerable potential, it is essential to provide health care practitioners with the resources they need to educate (or refresh) themselves regarding the foundational molecular biological principles that underlie personalized medicine, and allow them to critically appraise the new information that they will receive from different sources in the near future. We felt we could provide a reference that would review the foundations of personalized medicine, help physicians appreciate both the potential and the limitations of these tests, describe the clinically useful advances that have been made in the field so far, and in the process help health care practitioners better understand how to evaluate the potential clinical usefulness of the tests that will be developed in the future.

Second, we feel that we are at a time when there is a lot of confusion (among physicians and lay people alike) regarding the benefits and limitations of the personalized medicine tests that are available today. Many discoveries get publicized well before they have been developed into clinically useful tests, and some of the tests that commercial companies now advertise provide little to no actionable information. In addition, genetic testing services are advertised directly to consumers, and this has led to an increase in both informed patients and patients who are misinformed regarding the benefits and limitations of personalized medicine testing. Physicians must know what tests are and are not available at the present time, as well as what the benefits and limitations of the currently available tests are, in order to make the proper recommendations in situations in which personalized medicine testing is available.

We hope this book helps you be the best physician you can be.

We would like to gratefully acknowledge the following people for their help and support during the course of writing this book: Kirk Mykytyn, Ph.D., Kandamurugu Manickam, M.D., Amy Curry Sturm, M.S., CGC and Amanda Toland, Ph.D. We also thank the reviewers for their very helpful comments.

Kevin Sweet
Ron Michaelis

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Introduction

It is far more important to know what person the disease has than to know what disease the person has.

—Hippocrates

You Want to Provide Your Patients with the Best Care Possible…

We all know that health care providers want to provide their patients with the safest and most effective treatments possible. Unfortunately, in all fields of medicine a significant percentage of patients either do not improve or suffer adverse effects from their prescribed treatment. Doctors prescribe as wisely as they can, but they often have limited, anecdotal evidence to document their own patients' experiences, and limited time to keep up with the vast and ever-changing body of literature in their field. When deciding how to treat a patient, they often have no choice but to begin with a standard first-line treatment, pursue an iterative trial-and-error strategy and react to the events that unfold.

Personalized medicine involves the capacity to use new molecular biological principles and techniques to identify genetic susceptibilities to common diseases before symptoms appear, and better tailor medical treatments to the individual characteristics of each patient. Personalized medicine is based upon the principles of genetics and genomics, which expands genetics to include studies of DNA, RNA, proteins and other molecules that interact with DNA. In the coming years, personalized medicine tests will be developed that incorporate not only DNA sequence information, but information from RNA and protein tests. The most clinically useful tests will also incorporate clinical data, personal information and family history into their predictive algorithms. These tests will strengthen your ability to actively promote your patients' health and well-being over their entire lifespan.

In order for personalized medicine to be truly personal, however, patients must also become active participants in their own health care. The patient should be made aware of the fact that the vast majority of common disorders are multifactorial

disorders, usually resulting from a combination of genetic and nongenetic factors. The physician must be able to understand genetic risks in the context of the patient's care. As these genetic risks are not modifiable and can sometimes be distressing, these risks must be delivered in a sensitive and compassionate manner in the context of genetic counseling. The patient needs to understand what is at stake and what their genetic risk factors mean not only to their own health but also in the context of their family. In addition, he/she must be able to help the patient understand the importance of the nongenetic factors, and motivate the patient to modify his/her exposure to the critical nongenetic factors if possible.

…And This Book Can Help

Unfortunately, many practicing physicians feel that they do not have a strong background in genetics and genomics. A recent review in the *Journal of the American Medical Association* (*JAMA*)[2] noted that:

> The most important and consistent finding from our literature review is that the primary care workforce, which will be required to be on the front lines of the integration of genomics into the regular practice of medicine, feels woefully underprepared to do so.

This book is intended to enable you to put these principles of personalized medicine into your practice, regardless of how long it has been since you had your education in genetics. For those who feel the need to refresh their basic education in genetics, this book provides you with a thorough review of the principles of genetics that underlie personalized medicine. This includes the basic molecular biology you need to know in order to understand the genetic variability that underlies personalized medicine, the fundamental principles of inheritance that determine genetic risk, and some guidance on how to use family history to better estimate the patient's susceptibility to disease.

The importance of family history is often overlooked, in part because family history can take time to collect. To help make the collection and implementation of this information easier, we list several web-based programs that make it easy to input family history and draw a pedigree. You can share these websites with your patients, as a means of enabling them to arrive at your office with the relevant family history information diagrammed as an annotated pedigree that will allow for your review and analysis.

After reviewing the necessary foundational material, we provide a wide-ranging review, not only of the genetic tests that are available for patients today, but of the discoveries that will give rise to the next wave of personalized medicine tests. We hope that, after finishing this book, each reader will feel confident that he/she understands what can be done today to improve the level of patient care, and can critically appraise the new scientific information that will be available in increasing abundance in the near future.

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[2]Scheuner, et al., 2008. JAMA 299(11):1320–1334.

A Great Deal of Work Remains, but the Principle Has Clearly Been Proven

Medical journal editorials frequently emphasize the limited progress that has been made in personalized medicine, and the limited predictive utility of the newer personalized medicine tests. These criticisms are largely valid at the present time; even the most staunch advocates of personalized medicine admit that very few basic research discoveries have been translated into tests with true clinical utility. The human DNA sequence has turned out to be even more variable than most scientists thought it would be, and the sheer number of gene variants that influence the activity of proteins, and therefore influence risk for disease or response to treatments, has exceeded most people's estimates. In addition, recent research has revealed that the activity of our genes is regulated by genomic factors other than the sequence of the DNA, including interfering RNAs and epigenetic factors such as the methylation of DNA. At the present time there have been many useful discoveries made regarding the effects of DNA sequence variations on one's risk for diseases or response to treatments. As genomic researchers uncover more of the factors that influence the activity of our proteins, however, personalized medicine tests will expand to include assessments of RNA, proteins and chemical modifications of the DNA.

It is also clear, however, that properly designed personalized medicine testing can improve diagnostic accuracy as well as the safety and efficacy of treatments. Several of the personalized medicine tests that are currently available are already personalizing diagnoses and treatments in fields like oncology and cardiology, and informing medication dosing recommendations in many fields of medicine. In addition, researchers are providing new discoveries every day, from the foundational molecular biology to "translational research," which emphasizes the best way to translate molecular biological discoveries into clinically useful tests.

The pace of this research will only increase in the future. The cost of these procedures is declining rapidly, and as it does, researchers will collect ever-increasing amounts of data. In addition, as personalized medicine testing becomes increasingly cost-effective, it will also become more widespread, further accelerating the pace of clinical research.

There are no insurmountable obstacles to the further progress of personalized medicine. The fact that the best predictive algorithms will often require collecting data on thousands of contributory gene variants can easily be accommodated by microarray-based SNP analyses, which enable the analyst to test hundreds of thousands of gene variants in one assay, or whole-genome sequencing, which provides information on an individual's entire complement of genes. In addition, a number of dietary, environmental and lifestyle risk factors that contribute to many diseases are already known, and future research will undoubtedly uncover many more.

Some personalized medicine tests have now become well established and have good clinical utility. Some of the personalized medicine tests that are currently available, however, are limited in their usefulness, because pressure to commercially exploit new discoveries has caused companies to bring what they could to the market

quickly, to establish their presence in the market, rather than to wait until the testing evolved to a form with better clinical utility. For example, with respect to pharmacogenomic tests, it has been easier to determine the genetic variants that affect the pharmacokinetics of drugs than variants that affect their pharmacodynamics, because one merely needs to measure the levels of the drug in the blood to determine the effects of the individual's genetic status, rather than some aspect of the drug response that requires more invasive measurement techniques. Consequently, most of the pharmacogenetic tests that are well-developed enough to be marketed focus on pharmacokinetically relevant gene variants. In addition, even tests that include pharmacokinetically and pharmacodynamically relevant gene variants rarely combine this genetic information with family history, clinical data or diet, environment and lifestyle data.

We have come to recognize that most common diseases are multifactorial diseases, and that genetic factors only constitute a portion of the factors that influence the individual's risk for any given disorder. Because nongenetic factors influence the individual's risk for many diseases and response to many drugs, there will always be a limit to the predictive value of tests that use only genomic information. Genetic and genomic tests should not be seen as replacements for conventional predictors such as family history, age and clinical data, but rather as additional weapons in the arsenal. The most clinically useful tests will combine genetic/genomic information with family, personal and clinical data to maximize predictive power.

The Necessary Infrastructure Is Evolving

In the last few years, the institutional, educational and legal infrastructure that is necessary to support personalized medicine has begun to evolve. A number of medical schools have developed genetic and genomic medicine training programs. In addition, the federal government and several states have initiated programs to help educate practicing physicians. The Genetic Nursing Credentialing Commission offers a program whereby practical nurses and registered nurses can be certified as specialists in genetics. A number of medical centers have developed Centers devoted to the practice of personalized medicine, and several hospitals have adopted policies which use personalized medicine tests to guide treatment decisions from the beginning of the patient's care.

Major changes in the health care system are not possible without the involvement of the federal government, and the new federal administration has made it clear that it appreciates the ability of personalized medicine to improve efficiency and reduce the cost of health care and new drug development. The Genomics and Personalized Medicine Act was introduced to Congress in March, 2007, by then-senator Barack Obama. Now that Mr. Obama is President, he has included in the American Recovery and Reinvestment Act of 2009 a plan to spend $19 billion to upgrade the nation's medical information technology and create electronic health records, in part to enable the more effective and efficient use of genetic testing data to reduce the cost of health care. This dovetails with the Department of Health and

Human Services' Personal Health Care Initiative (PHCI), which began in March 2007. The PHCI is intended to encourage better communication between basic researchers and clinical researchers, improve the information technology in the health care industry, and protect individuals from misuse of their genetic information. Lastly, the director of the National Institutes of Health (NIH), Dr. Francis Collins, who was instrumental in overseeing the completion of the Human Genome Project, now plans to emphasize five "themes," including health care reform and translating genomic research into medicine, as his platform.

We are increasingly recognizing the need for better communication between basic researchers and clinicians, and programs are slowly developing to integrate the different subdomains of several fields. For example, the National Cancer Institute's (NCI) Biomedical Informatics Grid initiative, which began in 2004, is building a network of communication between research laboratories, clinical laboratories, academic centers and private corporations that will maintain an integrated cycle of discovery, application and feedback that will make the process of going from discovery to clinical application more effective and efficient. In addition, the Centers for Disease Control and Prevention (CDC) is developing a process for evaluating the analytic validity, clinical validity, clinical utility and ethical, social and legal implications of genetic tests.

Major changes in the health care system are also not possible without the cooperation of the health insurance industry. This, too, is moving forward as it becomes obvious that genetic medicine can reduce health care costs throughout the individual's lifespan. Better understanding of the genetic basis for disease risk can help some people tailor their diet, environment and lifestyle to reduce their preventable risk of diseases for which their genetic susceptibility is greatest, avoiding the cost of treatment. Further, by informing decisions about the choice and dose of medications, genetic tests can reduce the costs associated with ineffective treatments and adverse side effects.

The American Association of Health Plans, as well as individual insurers such as Aetna, United Health and Kaiser Permanente, have already recognized that personalized medicine can sharply reduce the cost of health care for many individuals. Some insurers are now paying for pre-symptomatic genetic tests that can predict risks and guide treatment decisions before the patient begins to exhibit symptoms of the disorder. In addition, the CDC is working with the insurance industry to help resolve issues related to approval of and payment for tests.

Finally, we predict that public interest will contribute to the development of personalized medicine to a considerably greater degree than public interest usually contributes to the development of medical fields. Aided by the popularity of forensic television shows, public acceptance of genetic testing is growing. Having one's genome screened has even become fashionable in some well-to-do circles, and as the cost of genome screening or sequencing drops, many others will become interested as well. Some people are sharing the results of their genomic scans on social network websites, or signing up for involvement in online research studies at commercial genomic companies. As the number of people who decide to have genetic/genomic analyses and share their information increases, the accumulating data will give rise to new discoveries and developments.