GENOMIC AND PRECISION MEDICINE

PRIMARY CARE

THIRD EDITION

Edited by
SEAN P. DAVID
Series Editors
GEOFFREY S. GINSBURG
HUNTINGTON F. WILLARD

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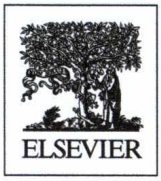

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Preface

From the time of completion of the Second Edition of "Genomic and Personalized Medicine" until today, the broad field of genomic medicine has advanced from a period of rapid discovery from genome-wide association studies to—according to the National Human Genome Research Institute's Eric Green, M.D.—enhancing the understanding of the biology of many diseases and has entered into a phase of advancing the science of medicine with an ultimate endpoint of improving the effectiveness of health care. Although many evidence gaps remain, such as the need to demonstrate clinical validity and clinical utility for most disease associated genetic variants and pharmacogenomics, the potential of "precision medicine" to vastly improve the efficacy of treatments for cancer, neurological diseases, preventive medicine, and reducing health disparities was deemed substantial enough for President Obama to launch the "Precision Medicine Initiative" in his 2015 State-of-the-Union Address. However, as the field of medicine stands poised to advance genomic medicine on many fronts, ensuring that the entire population of patients can benefit from innovations in an evidence-based fashion will rely on partnerships between primary care physicians and clinical genetics professionals. The present text addresses a continuum of domains of genomic medicine that are germane to the primary care of patients and the scope of primary care grounded in family history taking and appropriate referrals, such as the continuing education of all health professionals, what genetic and genomic testing and precision treatments are presently available, and what is on the horizon for a wide range of conditions and population health challenges. It is our hope that primary care providers will, as a result of using this text, develop transdisciplinary thinking and begin to share a common language and sense of partnerships with clinical genetics professionals as we continue to forge this new frontier together for the ultimate goal of improved health, healthcare and more evidence-based, personalized, and patient-centered medicine for the 21st century.

The present, "Primary Care" volume is one of a series of texts tailored to clinicians from a range of medical specialties and academic disciplines. As genomic medicine transitions from a research aspiration to an integral component of personalized health care, the role of primary care physicians and allied health professionals is becoming paramount in the goal of leveraging genomic knowledge to better care for diverse populations. We, therefore, have sought to cover a sample of topics that are essential for building a foundation of general knowledge that we hope will guide primary care clinicians, educators, and

healthcare institutions in advancing translation into practice. The range of topics are not comprehensive, but do provide entry-level content for a range of major health concerns that are equally useful for students, residents, attending physicians, other primary care health professionals, healthcare organizations, and policy makers.

The preface to the previous volume asserted that "We stand at the dawn of a profound change in science and medicine's predictive nature and in our understanding of the biological underpinnings of health and disease" but noted "grand challenges" to implementation of precision medicine from the potential to exaggerate health disparities to the need for educating the healthcare workforce and developing frameworks for aligning appropriate delivery models with good evidence and appropriate economic incentives. We have attempted to address many of these grand challenges, which align with the National Human Genome Research Institute's Grand Challenges II (genomics to health) and III (genomics to society) in forward-thinking chapters spanning multiple domains including:

- The role of primary care clinicians in genomic medicine and frameworks for integration with primary care redesign and clinical implementation science
- Genetic screening and diagnostic testing for rare diseases from preconception to neonates and throughout the life span
- Family history and its application to health risk assessment and predictive genetic testing
- Educational strategies for genomic medicine in primary care
- Policy, ethical, and societal considerations
- Current precision medicine treatments and future directions in research for common diseases (cancer, cardiovascular disease, hypertension, diabetes and metabolic syndrome, and autism spectrum disorder)

These topics represent only a fraction of the many diseases and thousands of type of genetic tests and clinical scenarios that are rapidly expanding in number. As Francis Collins envisioned in 2003, with increasing knowledge about the role of genetics in disease risk prediction, "many primary care physicians will become practitioners of genomic medicine, having to explain complex statistical risk information to healthy individuals who are seeking to enhance their chances of staying well. This will require substantial advances in the understanding of genetics by a wide range of clinicians." This prediction was prescient given the burgeoning research output of genetic studies and the availability of direct-to-consumer genetic testing and diminishing costs of next generation sequencing. We hope this text provides utility to all of us who practice primary care and prevention as vital stakeholders poised to learn together to build a more patient-centered, evidence-based, and personalized healthcare experience for all patients.

Sean P. David,
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Contents

14. Diabetes

Miriam S. Udler and Jose C. Florez

15. Metabolic Syndrome

Matthew B. Lanktree and Robert A. Hegele

16. Autism Spectrum Disorder

Akanksha Saxena and Maria Chahrour

17. Viral Hepatitis

Thomas Tu, Keyur Patel and Nicholas A. Shackel

Chapter 1

Genomic Medicine in Primary Care

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Chapter Outline

The last two decades has seen unprecedented genomic discovery and major clinical advances in the management of common diseases including cardiovascular disease and cancer [1]. In the fast-paced practice environment with limited time to stay current with new medical literature, many primary care physicians may not highly prioritize continuing education about genomic medicine in particular. Moreover, many primary care physicians express little confidence in their ability to make clinical decisions when genetic or genomic information is involved. This challenge is not unique to primary care; as new medical discoveries often outpace an individual specialist practitioner's ability to master it as well. Even so, primary care physicians now have better resources to help them incorporate new medical knowledge, including genomic medicine, into practice [1]. Emphasis on generalist practice principles, especially the value of maintaining a broad knowledge base, spurs many to stay current with new literature while prioritizing what is most important to their patients' health. This may manifest as reliance on clinical practice guidelines in addition to cultivation of networks of trusted colleagues (through both informal "curbside" and formal consultations). With the rise of genomic medicine, these networks will increasingly include geneticists, genetic counselors, informaticists, and pharmacists.

Knowledge learned through such patient-centered interactions contributes to innovation in systems design that streamlines management of complex medical information. Such clinical decision support systems are increasingly being

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introduced into electronic health records across North America, and provide just-in-time alerts to front-line clinicians for many issues; including, adverse drug interactions or overdue health maintenance interventions. Efforts are already underway within leading health systems to incorporate genomic data into the electronic records in a similar fashion, in order to create systems to help manage large quantities of genomic information [2]. Since it is also important to prepare the future primary care physician workforce for this innovation, primary care residencies may also include more focus on genomics education and training [3].

The potential benefits of genomic medicine are many and include improved disease-risk assessment as well as precise selection of drug therapy. Potential detriments include provider and patient anxiety, the unnecessary and expensive tests and procedures that might follow from a genomic result, and many scenarios where current scientific understanding fails to ascertain actionable results [4]. Further, despite rapid advances in understanding the genetic architecture of many diseases, translational research that demonstrates outcome improvement from this knowledge has lagged. The full risk–benefit ratio is thus unknown for almost all genomic tests, particularly for long-term clinical outcomes. Since primary care practice fosters a culture of evidence-based medicine that seeks to maximize health benefits and minimize unnecessary harms to patients, primary care physicians may be reluctant to integrate genomics into clinical practice. While certain genomic tests have been better studied than others—for example, variants in the *BRCA1/2* genes which have proven implications for the risk assessment and management of hereditary breast and ovarian cancer, and pharmacogenetic considerations for efficacy and safety on the labels of more than 130 medications including clopidogrel, warfarin, and citalopram [5]—developing an evidence base for most genomic tests comparable to what is known about *BRCA* testing, for example, will require decades of research in large populations. Pending such research; however, primary care physicians may still make clinical decisions to benefit individual patients despite an underdeveloped evidence base.

Upon the completion of the Human Genome Project in 2003 and on the 50th anniversary of Watson and Crick's landmark discovery of the double-helical nature of DNA [6], then National Human Genome Research Institute Director Francis Collins, M.D., Ph.D. (now Director for the National Institutes of Health) envisioned a blueprint for research in the genomic era and a series of Grand Challenges (Table 1.1) to guide the translation of genomic knowledge to enhance understanding of biological mechanisms of disease (Grand Challenge I), genomics to health (Grand Challenge II), and genomics to society (Grand Challenge III). Rapid advances in Grand Challenge I rapidly ensued over the following decade. From 2005 to 2012, the number of genome-wide association studies (GWAS) increased exponentially with 1,350 publications in 2012 [7]. More than 150 GWAS markers have been associated with common diseases including cancer, type 2 diabetes mellitus, dyslipidemia, multiple sclerosis, nicotine dependence, and psoriasis, there are also dozens of GWAS hits associated