

Lee-Jun C. Wong *Editor*

Next Generation Sequencing

Translation to Clinical Diagnostics

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Preface

The recent development of high-throughput next-generation sequencing (NGS) technology has transformed the way DNA-based molecular diagnostic testing is performed in clinical laboratories. NGS allows parallel sequencing analyses of multiple genes effectively at any desirable depth of coverage. It is often difficult for clinicians to fully understand and utilize NGS-based tests effectively due to the sophisticated instrumentation, the enormous amount of data generated, the complex analytical tools involving sequence alignment, and the bioinformatics for variant annotation. While professional interpretation can address these issues, the purpose of this book is to help physicians to better understand the science behind and clinical utility of NGS to maximize benefit for their patients.

In Part I, DNA sequencing principles, the underlying chemistries, and the development of NGS technology are described. This is followed by an overview of the methods used in the traditional molecular diagnosis of human genetic diseases. Part II details the instrumentations, bioinformatics, and computational techniques involved in NGS. This section of the book includes a comparison of the different methods used for target gene enrichment and the various sequencing platforms, as well as the algorithms and bioinformatics used for sequence analysis, variant annotation, and interpretation of the final results. Part III describes specific applications of NGS to the molecular diagnosis of clinically defined diseases (e.g., congenital disorders of glycosylation), genetically heterogeneous disorders involving many different genes leading to the same or similar clinical phenotypes (e.g., retinitis pigmentosa), diseases associated with a particular region or a whole chromosome (e.g., X-linked intellectual disability), and dual genome mitochondrial respiratory chain disorders involving nuclear and mitochondrial DNA. The utility of NGS for noninvasive prenatal diagnosis is also described. Part IV discusses the College of American Pathologists (CAP) / Clinical Laboratory Improvement Amendments (CLIA) guidelines for establishing a clinically based test using novel technology and compliance issues for laboratories offering NGS-based testing.

I am indebted to the contributing authors who have made this book entitled *Next-Generation Sequencing: Translation to Clinical Diagnostics* possible. I particularly appreciate the patience of the authors who submitted their chapters on time.

Houston, TX, USA

Lee-Jun C. Wong

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Part I

Overview

Chapter 1

History of DNA Sequencing Technologies

Lisa D. White

Abstract DNA sequencing technologies have a relatively short history – with the first published report in 1973 – a mere 39 years. But what a history! In 1973, Walter Gilbert and Allan Maxam published the 24 base pair sequence of the *lac* operator using chemical sequencing techniques Gilbert and Maxam (Proc Nat Acad Sci USA 70(12):3581–3584, 1973). Through innovation and automation, we are now able in 2012 to sequence the entire human genome (three billion base pairs) in a little more than a week. This chapter will review this short but amazing story of brute force, automation, and innovation from its infancy to the present. Suffice it to say that advances and technological leaps are continuing apace and this chapter will be outdated by the time you are reading it.

1 The Early Days of Sequencing

The 1953, landmark publication suggesting the structure of DNA by Watson and Crick [1] began what has become one of the most successful modern endeavors carried out by humans. The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to Francis Harry Compton Crick, James Dewey Watson, and Maurice Hugh Frederick Wilkins “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material”[2].

After the 1962 Nobel recognition for the discovery of the structure of DNA, it was only a short 18 years later that the Nobel Prize in Chemistry 1980 was divided, one half awarded to Paul Berg “for his fundamental studies of the biochemistry of

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