The journey of exome sequencing from disease mutations discovery to clinical genomics

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The history of medicine has been punctuated with landmark developments that made lasting imprints on healthcare delivery. Our ability to deconvolute the phenotype, the very core of clinical medicine, to precise changes in DNA or the “coding software of life”, made possible by the advent of next-generation sequencing technology can be described in a no less loaded term than revolutionary, and we are just beginning! While this technology is capable of sequencing entire genomes, its deployment to a full genomic scale has been largely shaped by the humbling fact that we know very little about the function of large swathes of DNA. It is very much the “let’s tackle what we understand first” that keeps exome sequencing, with its focus on the coding genome, thriving in an era of a shrinking cost gap between it and whole genome sequencing. Exome sequencing has quickly penetrated clinical medicine and established its utility in a wide range of applications that cover the entire spectrum of diseases, from the ultrarare to the very common. In this special issue, we are proud to share with our readers an assortment of review articles from leaders in the field with topics carefully chosen to provide a balanced coverage of the different facets of exome sequencing implementation. We open this special issue with a highly thoughtful perspective from Jim Lupski who reflects on what exome sequencing has done thus far to serve the medical and human genetics communities at large. The review by Gilissen et al. provides a fitting

introduction to the series of reviews by discussing the currently available bioinformatics tools used in variant calling and interpretation. After all, interpreting exome sequencing is all about sifting through many variants to extract what is needed for the specific test indication! We then present the review by Alkuraya on the use of exome sequencing for decoding Mendelian diseases, the very context in which exome sequencing first came into practice. This is followed by the review of Neale and co-authors who elegantly discuss the use of exome sequencing to identify relevant variants in the context of complex diseases, an increasingly popular application of this technology. The review by Park and co-authors provides a much needed coverage of state-of-the-art exome sequencing in cancer, a strikingly different application compared to that in the germline. We then conclude with two excellent reviews on the clinical application of exome sequencing, one from a clinician’s vantage point by Miller and O’Donnell-Luria, and the other by Hegde and co-authors from a clinical laboratory standpoint with a focus on the current state-of-affairs of regulating clinical exome testing.

We hope this lineup of high-quality reviews will meet the expectation of our readers regardless of their backgrounds. We are fully cognizant of the incredible speed with which this field is evolving so we expedited the publication of these reviews to keep them timely. We have good reasons to believe that we will not need to wait another decade to reminisce over this special issue, so catch it while it is still relevant!

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