

Section 1: Next-Generation Sequencing

These two readings introduce and review the birth of next-generation sequencing (NGS). The first is an original research study introducing the first successful use of NGS technology, and the second is a review paper that describes the progression of NGS technology from its inception to its modern forms and applications.

Wheeler et al. describes the successful NGS sequencing of an individual, Dr. James D. Watson. It details the key specifics of the process (7.4-fold redundancy, runtime of 2 months, scaleable, 100-fold cheaper than Sanger sequencing (~\$1 million), *in vitro* cell-free system, etc). Additionally, Wheeler et al. examine the genome they sequenced, identifying small-scale indels and copy number variants, as well as novel genes. To highlight clinical applications, the authors compared genomic polymorphisms with the HGMD compendium of human disease alleles, and reported 10 carrier alleles for highly penetrant, Mendelian genetic disorders. The authors could not confirm homozygosity due to low sequence coverage. They note the inability to efficiently detect single-base indels, but claim that mate-pair read technology will later allow the method to capture a wider range of such variants. The authors conclude with the claim that this technology amounts to a milestone on the path to apply genome information to personalized medicine.

Goodwin et al. begins by describing recent progress in NGS. This includes the drastic decreases in sequencing costs and increases in genomic discoveries. At the same time, it addresses some problems associated with NGS, including short read lengths, higher error rates, and the increased cost of long-read NGS. It covers the basics of the technology behind both short-read and long-read models, and then describes biological applications. Specifically, Goodwin et al. argue that NGS can identify genotype-phenotype correlations, regulatory mechanisms, structural variants, transcription patterns, and other properties of biological relevance. The authors then note novel sequencing solutions and developments in the “NGS arms race”, and the challenges of analyzing the vast amount of data available. They then close with tempered excitement for the research progress that has and continues to be made using NGS.

- Wheeler DA et al. "The complete genome of an individual by massively parallel DNA sequencing," *Nature*. 452:872-876 (2008).
- Goodwin S. et al. "Coming of age: ten years of next-generation sequencing technologies" *Nature Reviews Genetics*. 17 (2016).