Recent advances in sequencing technology have allowed researchers to probe the human genome at unprecedented depths. Next-generation sequencing (NGS) is rapidly transforming clinical genetics. However, significant barriers remain to the routine adoption of NGS in clinical care. Although NGS has become more affordable—an entire human genome can be sequenced for less than $2000—the bottleneck has now shifted from the laboratory to “big data” processing, analysis, and interpretation.

In this issue, Fernandez-San Jose et al.1 demonstrate the usefulness of targeted NGS sequencing in the molecular diagnosis of autosomal dominant retinitis pigmentosa (adRP), a notoriously heterogeneous group of retinal dystrophies. All 59 of their index cases had unsuccessfully been screened for RP gene mutations using a combination of traditional molecular tools. The NGS panel used in the study included 73 genes with reported pathogenic variants for retinitis pigmentosa (RP). The authors detected 17 putatively causal variants in 27% of families tested, 11 (64%) of which were novel, showing a significant benefit of NGS in adRP genetic diagnosis.

Disease variant discoveries using NGS are increasingly common. In a study of 2000 patients referred for clinical whole-exome sequencing, a molecular diagnosis was given in 504 cases (25.2%).2 Nevertheless, technical and analytical challenges abound in NGS studies. A sobering example of the complexity of sequence analysis was provided by the CLARITY Challenge,3 a contest designed to spur a convergence of methods used in NGS molecular diagnostics. Of the 30 groups engaged in the competition, only two identified the consensus candidate variants in three families tested.

In the near future, more complete variant databases, improved functional annotation, and more rigorous analysis pipelines will increase the rate of detection and causal validity of genetic disease variants. Ultimately, NGS will lead to a more complete understanding of the molecular basis of genetic disorders, and the promise of individualized medicine will be closer to being realized.

References