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As anyone who has ever assembled a piece of furniture can attest to, instruction manuals are only useful if you can read them. Similarly, knowing what makes each of us unique by sourcing the information contained in our genomes requires the ability to read the order of As, Cs, Gs and Ts that constitute our DNA. This feat is made possible by DNA sequencing technologies. In this *Nature Milestones in Genomic Sequencing*, we chart the history of these extraordinary technologies and their continuously expanding applications over the past two decades.

Since its emergence, genomic sequencing has become one of the most influential tools in biomedical research. The potential of sequencing technologies was quickly recognized, with half of the 1980 Nobel Prize in Chemistry being awarded to Walter Gilbert and Frederick Sanger “for their contributions concerning the determination of base sequences in nucleic acids”, a mere 3 years after the development of Maxam–Gilbert sequencing and Sanger sequencing in 1977. In the late 1980s, automated Sanger sequencing machines could sequence approximately 1,000 bases per day. With continuous methodological advances and computational developments occurring in parallel, the 1990s saw DNA sequencing applied to large bacterial genomes and the first unicellular and multicellular eukaryotic genomes.

Sanger sequencing dominated the research landscape until the early twenty-first century and led to exceptional achievements, including the completion of a high-quality, reference sequence of the human genome under the auspices of the Human Genome Project (HGP), which is where we have chosen to start our milestones (MILESTONE 1). The field took off in earnest with the development and commercialization of high-throughput, massively parallel or next-generation sequencing, which democratized sequencing by offering individual laboratories access to the technology. In this *Nature Milestones in Genomic Sequencing* timeline, we want to highlight methodological and computational advances and projects that have propelled the field forwards, culminating in an entire, virtually gap-free human chromosome, assembled telomere to telomere (MILESTONE 17). We also shine a light on research areas revolutionized by the application of sequencing technologies over the past 20 years.

Science is a team effort. We appreciate that each milestone that we have selected stands on a mountain of preceding work and that the histories of technological advances, applications and discoveries are interwoven. We apologize in advance for any missed contributions and extend our gratitude to all the researchers who have advised on this project or agreed to be interviewed. Finally, we would like to acknowledge financial support from Illumina. As always, responsibility for the editorial content remains with Springer Nature.

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