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News & Highlights

Genomic Sequencing Costs Set to Head Down Again

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The race is on again in DNA sequencing. In what has been described as "the year of the big shake-up" [1], a wave of new competitors entered the market in 2022, challenging industry leader Illumina (San Diego, CA, USA). New systems from both Illumina and emerging rivals are now poised to push costs down—closing in on the oft-cited goal of 100 USD per genome. The prospect of more economical sequencing is big news because the spectacular cost reductions that helped fuel the genomics revolution in previous decades have stalled in recent years (Fig. 1). Lower costs will make sequencing affordable for a broader array of users and applications in fields such as biology, biotechnology, and medicine.

Sequencing is used to determine the order of the four nucleic acid bases (adenosine, thymine, cytosine, and guanine) that make up a DNA molecule. Those sequences hold a key to understanding a wide range of biological phenomena, from heritable diseases to evolutionary origins to viral pandemics, making sequencing an indispensable tool in fields across biology, biotechnology, and

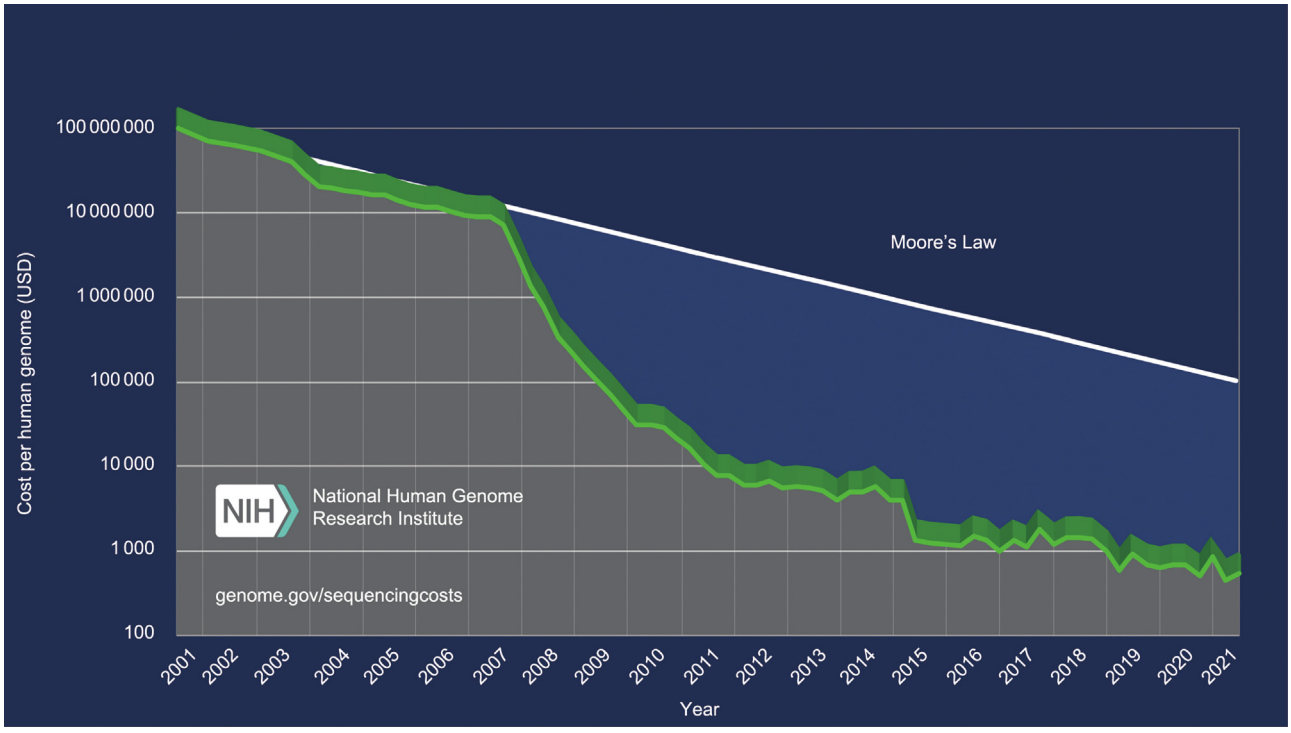

Fig. 1. Sequencing costs have fallen precipitously over the last two decades, especially after the commercialization of massively parallel "NGS" in the mid-2000s. From 2006 to 2015, costs dropped from 10 million USD to around 1000 USD per genome. That is a 10 000-fold reduction in less than ten years—far faster than Moore's Law (Moore's Law posits a two-fold doubling of computer chip density roughly every two years). Progress has slowed markedly in recent years, however, as sequencing costs plateaued in the 500 to 600 USD-per-genome range. Credit: National Human Genome Research Institute (public domain).

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medicine [2]. The first generation of automated sequencers was introduced in the late 1980s and improved rapidly during the 1990s through the early 2000s, spurred by initiatives such as the Human Genome Project and the US National Human Genome Research Institute Genome Technology Program [3].

The technology took another leap with the advent of massively parallel, "next-generation sequencing" (NGS) in the mid-2000s. In contrast to first-generation sequencers (also known as Sanger sequencers), which can read at most a few hundred short DNA fragments at a time, NGS platforms can sequence billions of fragments simultaneously, providing a huge jump in throughput [4]. It took years to produce the first draft of a human genome using Sanger sequencers; modern NGS machines can now sequence an entire human genome in a day [5].

While the specific techniques employed by various manufacturers differ, Illumina and most other NGS vendors use some version of short-read sequencing by synthesis [4]. In this process, long DNA strands extracted from biological sources (e.g., a blood sample) are chopped into myriad small pieces (typically 150 to a few hundred bases each), which are anchored to a substrate (plastic beads or a glass slide) and then copied (amplified) to create clusters of many identical segments. These clustered fragments serve as templates for the synthesis of new, complementary DNA strands. Bases are added one by one with the help of enzymes and chemical reagents, and a variety of methods are used to detect the bases as they are added. One common approach is to label the bases with fluorescent tags that light up when the bases are incorporated. A camera records the fluorescent signals, which are then analyzed by software to deduce the sequences and reassemble the fragments into a whole genome. All of this is done in bulk. Billions of fragments comprising multiple genomes can be loaded into reaction vessels (called flow cells) and processed en masse, harnessing economies of scale to drive costs down.

The first widely used commercial NGS sequencer was introduced by 454 Life Sciences (Branford, CT, USA; no longer in business) in 2005 [6]. Other companies, including Solexa, soon followed with their own NGS platforms. Illumina entered the sequencing market in 2007 when it spent 650 million USD to acquire Solexa [7], whose innovations are at the core of what has become known as Illumina sequencing [8]. Illumina refined and improved the technology over the years, making it faster, cheaper, and easier to use. During a period of fierce competition in which Illumina bested a series of other vendors including 454 Life Sciences, Life Technologies (Carlsbad, CA, USA), Ion Torrent (now owned by Thermo Fisher Scientific of Waltham, MA, USA), and Complete Genomics (San Jose, CA, USA), sequencing costs plunged from 10 million USD per human genome in 2006 to close to 1000 USD by 2015 (Fig. 1) [3,9,10]. By the mid-2010s, Illumina dominated the sequencer market, with a share that at one point exceeded 90% [11]. At roughly the same time, after a decade of breathtaking advances, costs began leveling off and have remained around 500 to 600 USD per human genome in recent years.

Notably, such USD-per-genome figures apply only to the cost of operating the sequencer—essentially the expense of chemical reagents consumed during a sequencing run. They do not include the many other costs of sequencing: the purchase price of the machine; the preparation of DNA samples prior to sequencing; the computational analysis of data produced by the sequencer; and the clinical interpretation of the results. That final stage, interpretation, is often the most expensive part, since it involves human experts attempting to figure out, for example, the medical implications of genetic variations [1,9]. Equally important, commonly quoted cost-per-genome numbers are based on best-case high-throughput scenarios in which large sequencers are run at full capacity, processing dozens of genomes at once. Sequencing smaller batches—by using smaller sequencers or running large sequencers at partial capacity—can cost significantly more.

Those caveats notwithstanding, cost-per-genome still offers a convenient benchmark for gauging progress and comparing sequencers under similar conditions. And the fact that that benchmark has been static for so long has become a problem for the industry. Sequencing is still too expensive for many potential applications, particularly for users with modest budgets or less-than-industrial-scale requirements. Examples include the sequencing of individual patient genomes to diagnose genetic diseases; small genome sequencing (e.g., sequencing a virus such as SARS-CoV-2, which has roughly 30 000 bases compared to the human genome's 3 billion); and sequencing by smaller labs and facilities. "There is a large pent-up demand for more affordable sequencing at smaller scales," said Brian Krueger, founder of the laboratory diagnostics consultancy BaseX Scientific (Chapel Hill, NC, USA), who previously set up and ran large sequencing centers at Duke University (Durham, NC, USA), Columbia University (New York, NY, USA), and life sciences company Labcorp (Burlington, NC, USA). "The current costs are holding many applications back."

Many analysts attribute the slowdown in cost reductions to slackening competition in recent years. Illumina's NGS systems have become the de facto industry standard for workaday sequencing, generating an estimated 90% of the world's total sequence data and accounting for roughly 80% of all current sequencer sales [11,12]. (The remaining 20% of sales is divided up among smaller NGS vendors; suppliers of so-called "third-generation" sequencers, which provide the longer-read capabilities required by some applications but cannot compete with NGS systems on cost or throughput; and a few remaining sellers of first-generation systems.)

Now, a number of Illumina's patents have expired or soon will [1,12]. In addition, a years-long patent infringement battle between Illumina and Chinese genomics company BGI Group (Shenzhen, China) was finally settled in 2022, allowing BGI subsidiary MGI Tech Co. (Shenzhen, China) to sell its sequencers in the United States for the first time [13]. And several of Illumina's key acquisitions have been blocked in recent years by antitrust regulators in the United States and Europe [12,14,15].

These developments set the stage for the market "shake-up" of 2022. "We are finally seeing competition in the sequencing market again after several years of Illumina's virtual monopoly," said Shawn Baker, head of the genomics business consultancy SanDiegOmics (San Diego, CA, USA) and former product manager at Illumina. "That is great news for consumers, who will benefit from more choices and better economics."

In March 2022, sequencing start-up Element Biosciences (San Diego, CA, USA) unveiled its Aviti System, a compact benchtop unit designed to economize mid-range sequencing. According to Element, the Aviti can match the per-genome cost (560 USD) of high-throughput Illumina NovaSeq 6000 systems while sequencing as few as three genomes at a time (versus dozens for the NovaSeq) [16]. More recently, the company announced a new option on the Aviti System that it says will further drop the cost of whole genome sequencing to 200 USD [17].

In May 2022, Ultima Genomics (Newark, CA, USA), a heavily funded start-up with 600 million USD in venture capital, made headlines when it claimed to have developed novel technology that achieves the long-sought goal of a 100 USD per genome [18]. Like Illumina's flagship NovaSeq systems, Ultima's UG 100 is designed for high-volume sequencing, but it puts a new spin on sequencer architecture, using a silicon wafer, like those used to make computer chips, in place of the flow cells employed by Illumina and most competing systems. Ultima contends that the wafer, which rotates like a compact disc, allows for more efficient

distribution of reagents and easier imaging, sharply reducing materials and costs.

In August 2022, MGI began offering its line of DNBSEQ sequencers for the first time in the United States [19]. The sequencers, sold through Complete Genomics, which BGI acquired in 2013, come in a range of models—from benchtop systems to large sequencers—that go head-to-head with Illumina's entire product line on throughput and cost-per-genome [20].

Illumina made news of its own in September 2022, announcing the biggest update to its product line in years: new high-throughput additions to its NovaSeq family (Fig. 2) [21]. According to Illumina, the new NovaSeq X and NovaSeq X Plus systems, slated for commercial availability in 2023, bring a slew of innovations to the sequencing market, including new reagents that allow "up to 2 times higher speed and up to 3 times greater accuracy" [9,22,23]; faster, higher-resolution optics [24]; and denser flow cells. The result, Illumina says, is big improvements in both throughput and costs. The company claims that the high-end NovaSeq X Plus will be able to sequence 20 000 whole human genomes per year while slicing costs to 200 USD per genome [25]. By comparison, Illumina's current top-of-the-line machine, the NovaSeq 6000, can crank through 7500 genomes per year at 560 USD each. An additional advantage of the new reagents is that they ship at ambient temperatures and do not require special cooling, a boon for customers in developing countries and other locations where the lack of reliable cold chains (temperature-controlled supply chains) has hindered access to sequencing in the past [26].

Experts caution that these vendor claims have yet to be borne out in practice. Many of the new products are not available yet; others have only just begun shipping. "We really will not know if they can deliver on their cost targets until customers have gotten their hands on the systems and put them to work," said Keith Robison, a principal scientist at biotechnology company Ginkgo Bioworks (Boston, MA, USA) who tracks the sequencing industry in his *Omics! Omics!* blog. Many details of some new products are still vague, making it difficult to gauge the veracity, for example, of Ultima's promised 100 USD per genome [9,27]. As for Element's 200 USD-per-genome claim, Baker said that number may only be achievable in a narrow range of medium-throughput scenarios that might not match the needs of many customers. Baker has similar doubts about another new entrant, Singular Genomics (La Jolla, CA, USA), whose G4 system was announced in late 2021 but is only now starting to ship. While Singular says the G4's speed (less than 24 h per run) and flexibility will allow medium-sized labs and sequencing centers to juggle a changing mix of individual samples more easily, "the jury is still out on how much the market values this kind of flexibility," Baker said.

Fig. 2. Illumina's NovaSeq products are the workhorses of high-throughput sequencing in many of the world's genome centers. Illumina says its new NovaSeq X (a), announced in 2022 and set to ship in the second half of 2023, raises the bar dramatically, providing 2.5-times the throughput of the current top-of-the-line NovaSeq 6000 system (b), at less than half the cost-per-genome. Credit: Courtesy of Illumina, Inc.

Though uncertainties remain, there is general agreement that lower costs will make sequencing technology more accessible to smaller institutions and developing nations, and—importantly—more widely available for an array of promising applications [28], such as:

- Non-invasive prenatal genetic testing: Fetal DNA in the maternal bloodstream can be sequenced to identify genetic abnormalities and ensure prompt treatment of affected newborns [9];
- Cancer diagnosis and monitoring (using an approach known as "liquid biopsies"): Tumors and other malignancies have characteristic genetic markers, which circulate in the blood and can be picked up by sequencing, enabling early cancer detection and improved monitoring of treatment impacts [1,29];
- Broader population studies: More affordable sequencing will enable the creation of larger genomic databases, providing new insights into human genetic diversity, evolution, and disease [18];
- Personalized medicine: Routine sequencing of individuals will help physicians and genetic counselors tailor healthcare to each person's unique genetic profile [18]; and
- Genomic surveillance: Sequencing can be used to monitor ecosystems, the food supply, wastewater, and other environments for emerging pathogens, new genetic variants, and other changes in biomes and microbiomes [30].

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