



2001: A Base Odyssey

The era of genomics and massive parallel sequencing

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February 24, 2025

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<https://ngisweden.scilifelab.se>

2001: Draft assemblies of the human genome are published



Figure 1: The private company Celera [Venter2001] and the International Human Genome Sequencing Consortium [Lander2001] both publish a draft sequence of the euchromatic portion of the human genome.

The overture to the genomic era



A remake of the opening scene by SumoSebi, CC-BY-SA on Wikimedia Commons

Stanley Kubrick's *2001- A Space Odyssey* premieres 2 April 1968

1968: Nobel prize for the interpretation of the genetic code

Nobel Prize in Physiology or Medicine 1968



Photo from the Nobel Foundation archive.

Robert W. Holley

Prize share: 1/3



Photo from the Nobel Foundation archive.

Har Gobind Khorana

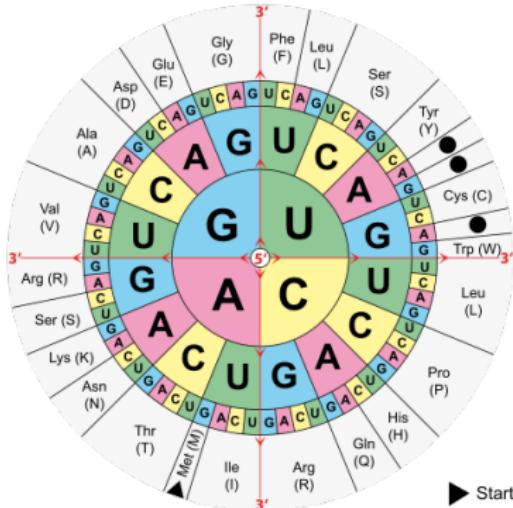
Prize share: 1/3



Photo from the Nobel Foundation archive.

Marshall W. Nirenberg

Prize share: 1/3



- The genetic code is (almost) universal^[1]
 - It was resolved entirely using synthetic sequences.

[1] <http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html/index.cgi?chapter=tgencodes>

<https://www.nobelprize.org/prizes/medicine/1968/summary/> | User:Mouagip, Wikimedia Commons, PD

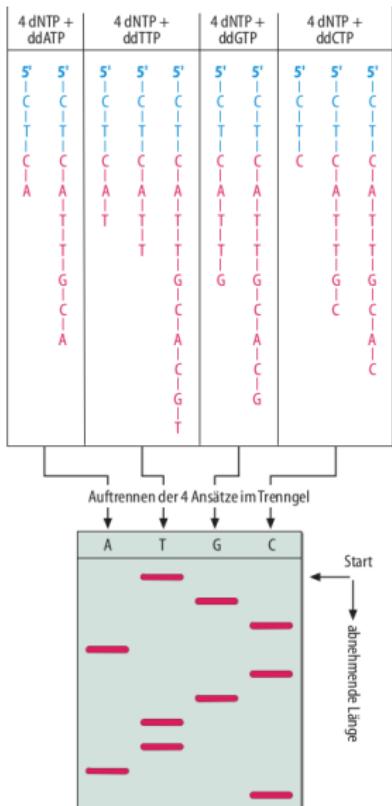
Encoded information of naturally occurring DNA unknown



- Peptides could be sequenced since the 1950s (Sanger method, Edman degradation).
- Sequencing of DNA was one of the most urgent, unresolved problems in the early 1970s.
- Frederick Sanger (Nobel laureate for sequencing Insulin 1958) started working with DNA.

F. Sanger

1977: Chain-termination sequencing by Frederick Sanger



- DNA fragments could be separated by size.
- Sanger's method creates sequence-derived length patterns.
- It relies on radioactive labeling and in-vitro amplification of DNA.

DNA sequencing with chain-terminating inhibitors

(DNA polymerase/nucleotide sequences/bacteriophage ϕ X174)

F. SANGER, S. NICKLEN, AND A. R. COULSON

Medical Research Council Laboratory of Molecular Biology, Cambridge

Figure 2: [Sanger 1977]

1980: Nobel prize for DNA sequencing

Nobel Prize in Chemistry 1980



Photo from the Nobel Foundation archive.

Paul Berg

Prize share: 1/2



Photo from the Nobel Foundation archive.

Walter Gilbert

Prize share: 1/4



Photo from the Nobel Foundation archive.

Frederick Sanger

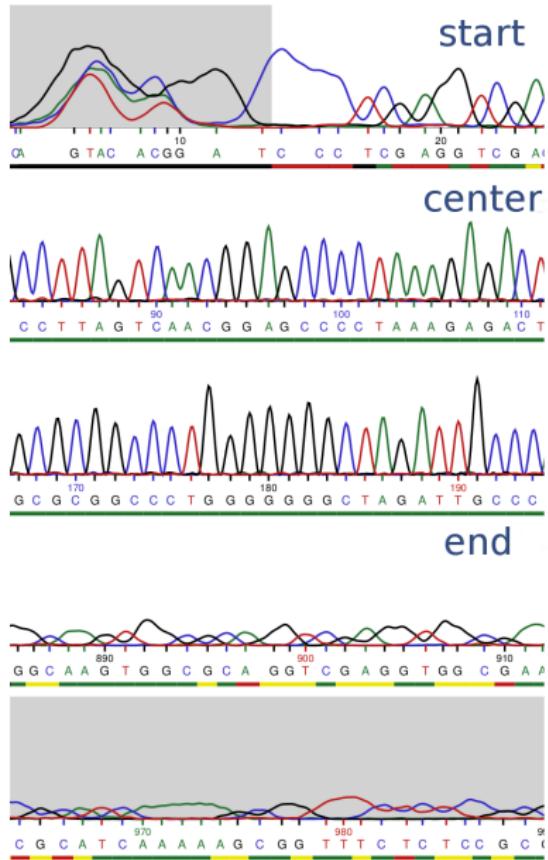
Prize share: 1/4

- Ample DNA input needed
PCR was introduced in 1989
- Four reactions per sequence
- Read length \sim 200bp



<https://www.nobelprize.org/prizes/chemistry/1980/summary/>

Advanced Sanger sequencing for the Human Genome Project



- Fluorescent chain terminators.
- Capillary electrophoresis for size separation of amplicons.
- Parallelized and automated.
- Sequencing technology of the Human Genome Project (1990-2004).

Next-generation sequencing

New high-throughput methods were developed

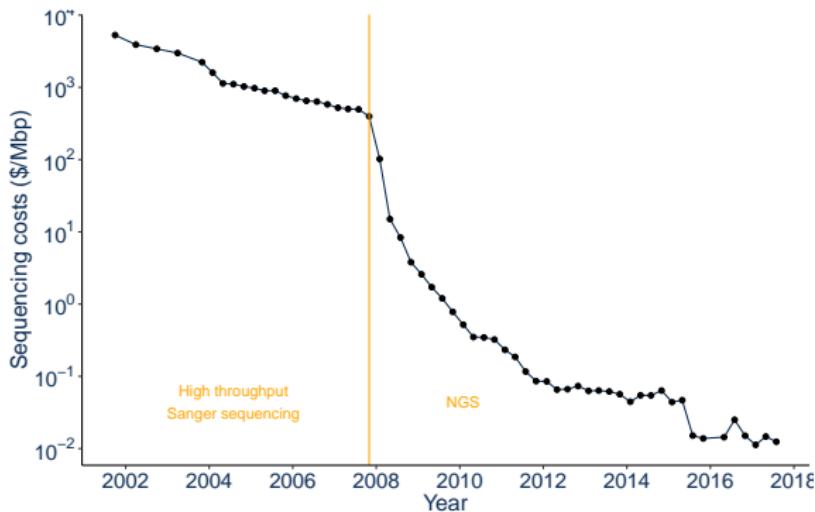


Figure 3: Sequencing costs per one million bases of raw sequence

1990-2004: Human Genome Project sequencing: US \$500 million

2025: Sequencing of a human genome: ~ US \$100-1000

National Human Genome Research Institute (NHGRI)

<https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost>

Around 2010: Sanger sequencing was outcompeted by NGS



ABI 3730xl DNA Sequencer
(Sanger Multiplex, 2013)

- ~6912 reads of 400bp
- ~2,76 Mbp / day



Illumina HiSeq 2500
(NGS / MPS, 2013)

- ~600 Million reads of 100bp
- ~60.000 Mbp / day

(depending on settings and sequencing chemistry used)

National Genomics Infrastructure

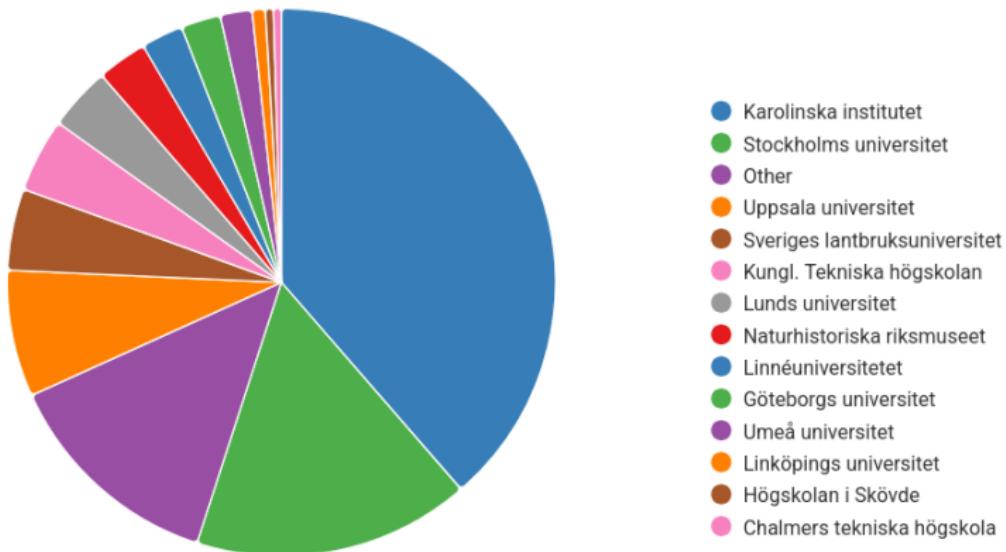
Sweden

DNA sequencing facilities provide sequencing capacity



- DNA sequencing of paramount importance for life science.
- 2013: National Genomics Infrastructure Sweden is founded.
- Our mission is to offer a state-of-the-art infrastructure available to researchers all over Sweden.

Project Affiliations in 2024



<https://ngisweden.scilifelab.se/resources/ngi-stockholm-status/>



- NGI is a sequencing facility for *research projects*
- Part of the Genomics Platform at SciLifeLab
- Distributed in 3 nodes:
 - SNP&SEQ Technology Platform, Uppsala
 - Uppsala Genome Center
 - NGI Stockholm + Eukaryotic Single Cell Genomics (ESCG), Solna

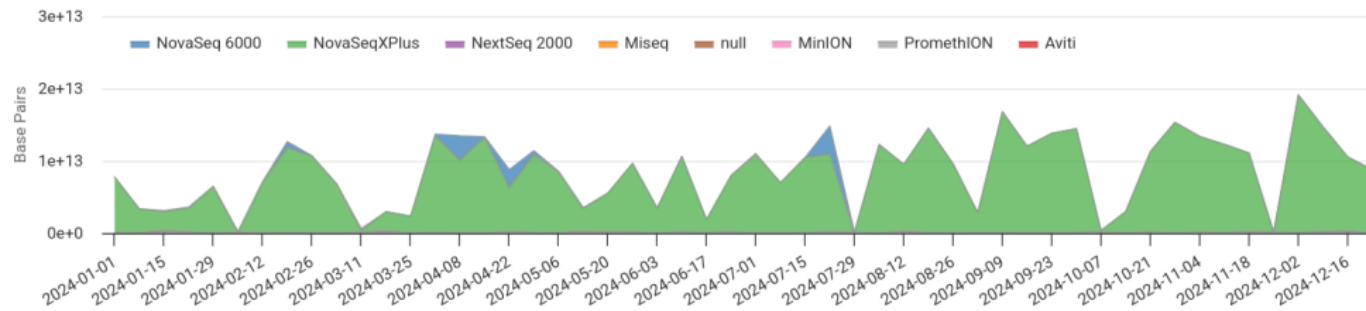
<https://ngisweden.scilifelab.se>

NGI-S employs various sequencing technologies



Sequencing Throughput

Average for 52 weeks: 1234 Gbp per day
(1 Human genome equivalent every 3.77 minutes)



- In 2024, NGI Stockholm sequenced on average 1200 Gbp/day

<https://ngisweden.scilifelab.se/resources/ngi-stockholm-status/>

Sequencing platforms

Sequencing platforms / technologies since Sanger

Next generation sequencing

- Roche 454 sequencing (Pyrosequencing)
- Ion semiconductor sequencing
- **Illumina (Solexa) sequencing**
- **PacBio HiFi Sequencing**

Third generation sequencing

- **Oxford Nanopore sequencing**
- **Element Biosciences Avidite Sequencing**
- Ultima Genomics UG 100 Sequencing
- MGI DNBSEQ Technology
- Singular Genomics G4X

Platforms in **bold** are in use at the National Genomics Infrastructure

Sequencing platforms / technologies since Sanger

Sequencing by synthesis

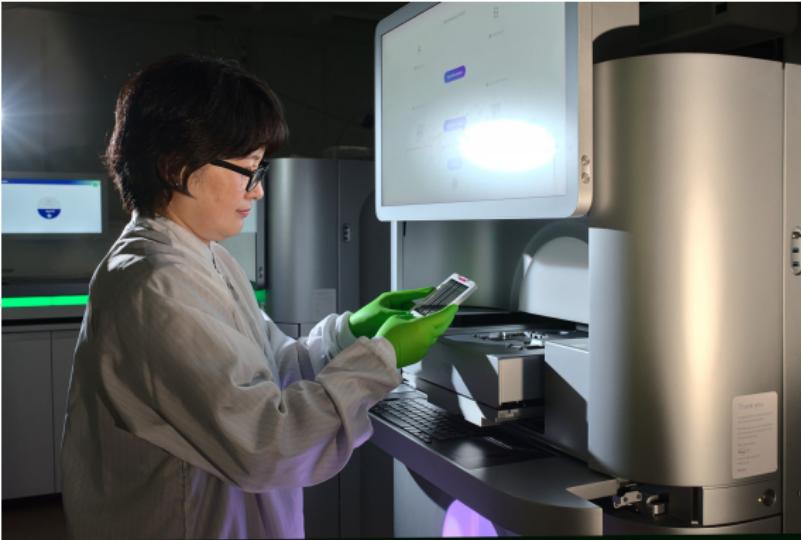
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Direct DNA/RNA sequencing

- **Oxford Nanopore sequencing**

Platforms in **bold** are in use at the National Genomics Infrastructure

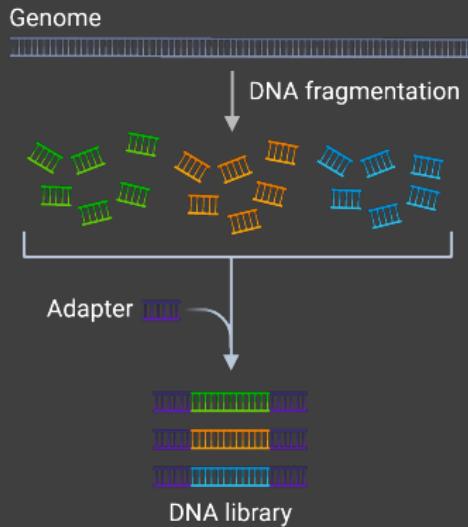
Illumina sequencing is *the* NGS sequencing platform



Illumina's sequencing by synthesis technology is NGI's bread-and-butter platform

Search engines start failing to find meaningful content

Library preparation



Direct DNA/RNA sequencing

- Oxford Nanopore sequencing

Milestones in DNA sequencing history

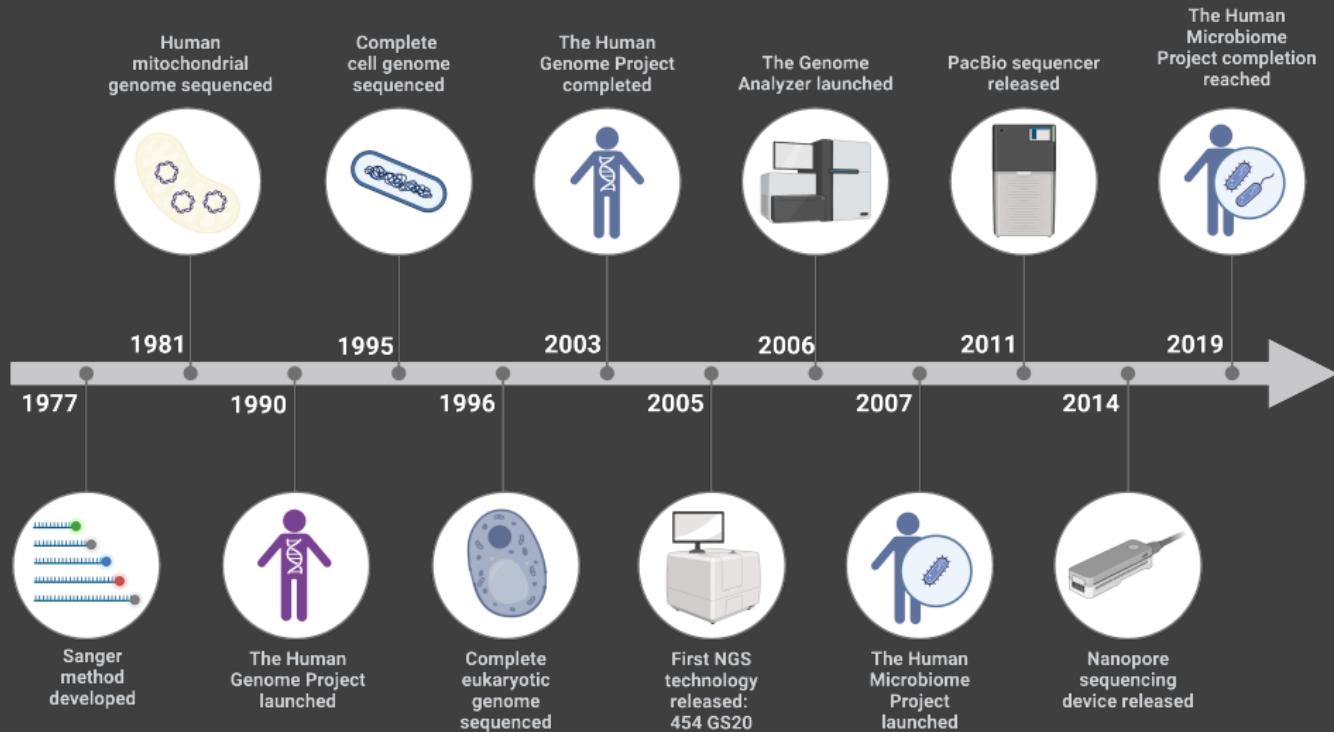


Figure by Anja Mezger

References

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