Clinical Whole Genome Sequencing
The Final Frontier

July 2017

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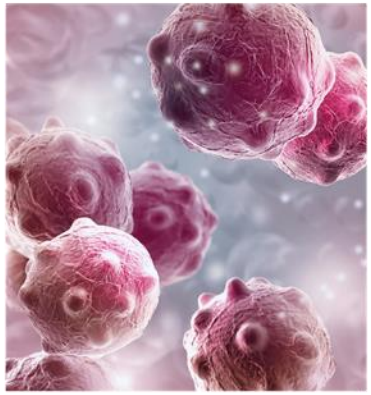
Our Mission

To improve human health by unlocking the power of the genome



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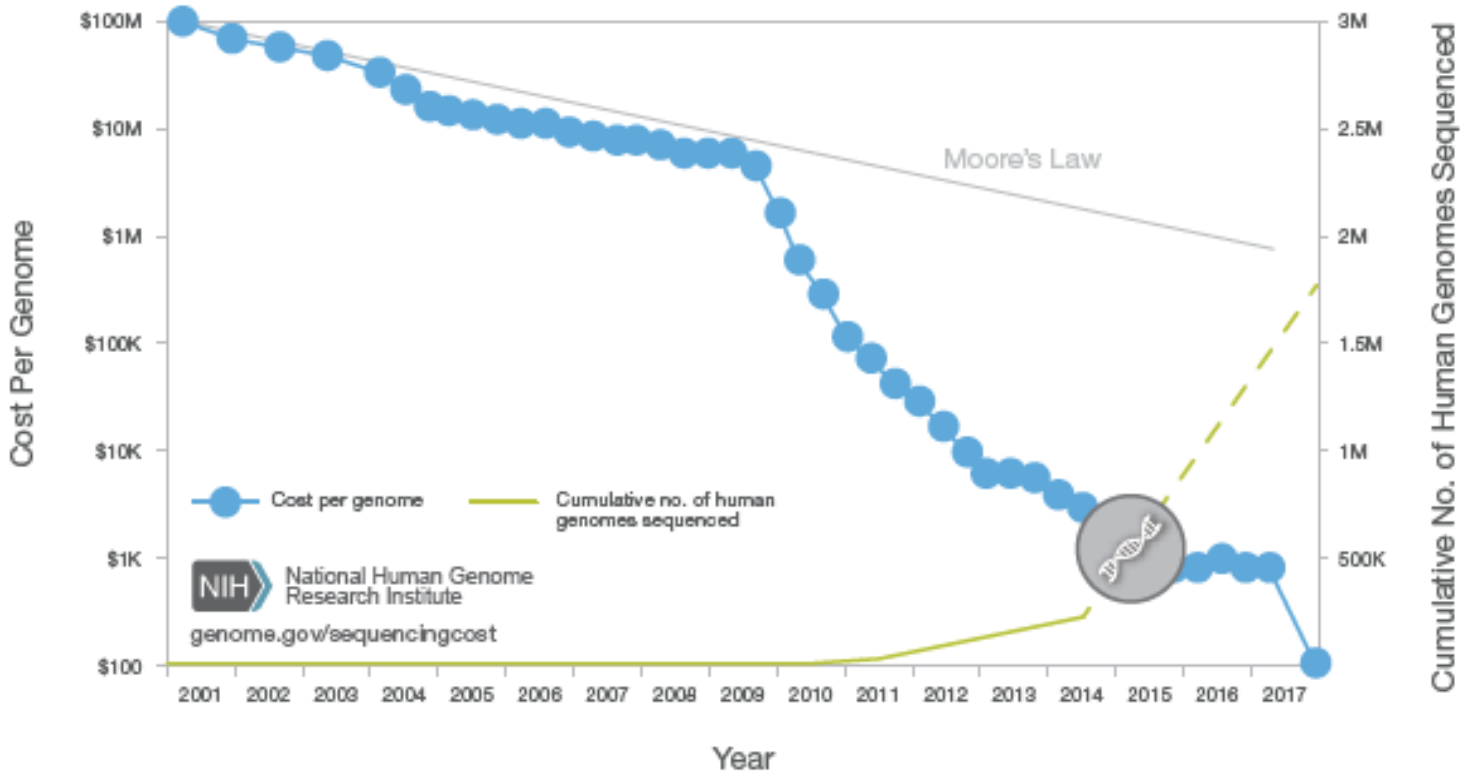
Sequencing Costs Continue to Fall



The Unprecedented Drop in the Cost of Genome Sequencing—The cost of genome sequencing has declined at a rate that outpaces Moore's Law. This opens up new markets for which sequencing costs were previously thought to be too expensive.

Reproduced from "Roadmap for Bringing Personalized Medicine to British Columbians," 2015.

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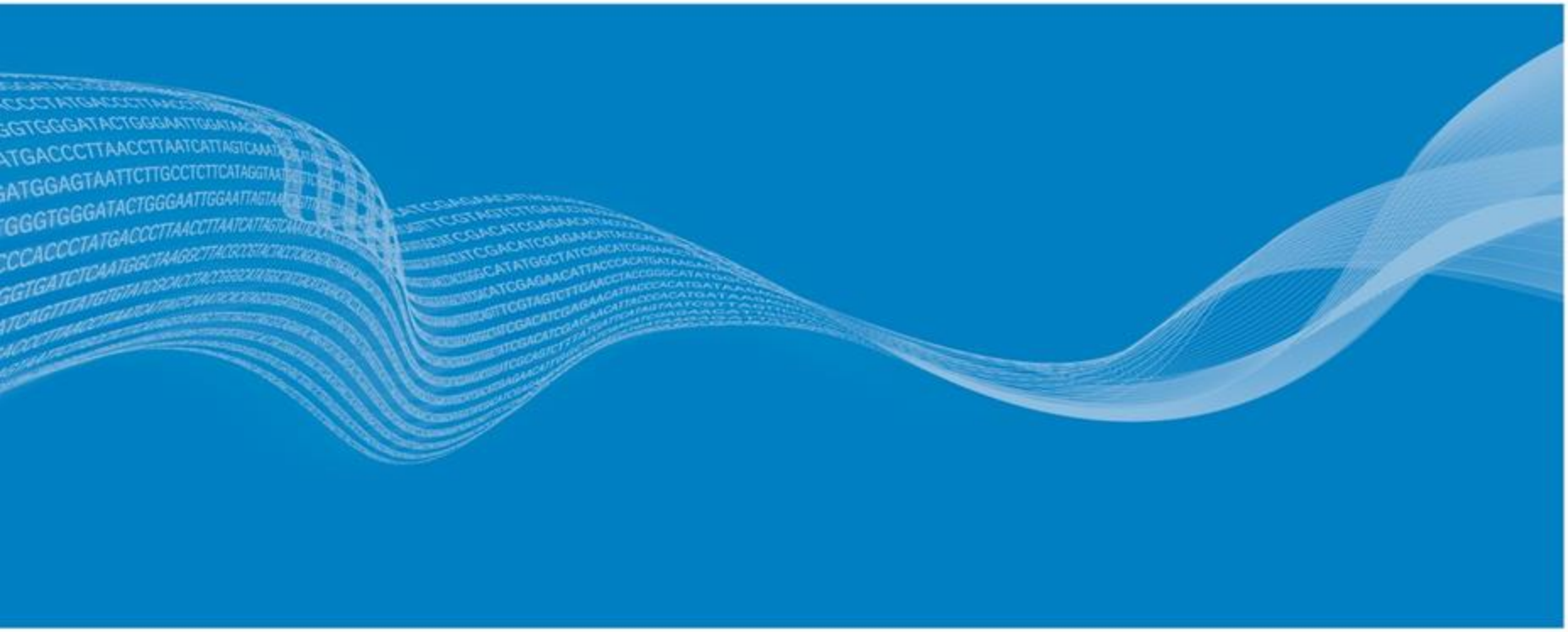
Diagnostic Need



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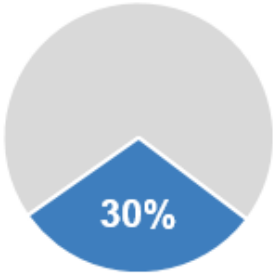
Rare Undiagnosed Disease – Defined

Acute Care Market

% of NICU Admissions



- 50% of rare diseases touch children
- 30% of children affected by RUGD die by age 5
- 4.5% of children annually present with a genetic condition

- **300 million individuals globally estimated to live with rare and undiagnosed diseases (RUGD)**
  - 30 Million U.S.
  - 30 Million U.K.
- **There are are ~7,000 different rare diseases and disorders**
  - 80% % of all RUGD patients are affected by ~350 rare diseases
- **The Definition of Rare Disease**
  - In US a rare disease is defined as occurring less frequently than 1 in 200,000
  - In UK/Europe rare disease defined as occurring less frequently than 1 in 50,000
  - In Australia, a rare disease is defined as a condition, syndrome or disorder that affects 1 in 10 000 people or less (TGA).

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Why Whole Genome Sequencing (WGS)?

Clinical WGS will transform patient lives

RUGD patients 34-71% of pediatric hospital admissions

Average pathway to diagnosis for patient with RUGD to receive a proper diagnosis includes:

- **8x physicians (4x primary care and 4x specialists)**
- **5-7 Year Diagnostic "Odyssey"**
- **Average cost of diagnostic tests $15-25K per patient**

Already strong evidence that cWGS can markedly increase diagnostic yields in this population

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Diagnostic Yield

Assay type	Sanger sequencing	NGS-based gene panels[5]	Exome sequencing[2,3,4]	Genome sequencing[1]
Detection rates	3-5%	5–10%	~20–40%	~34-60%

Sequence all exonic, intronic and intergenic regions in one test

Replace iterative testing model with one test approach

1. Gilissen C, Hehir-Kwa JY, Thung, DT et al. Genome sequencing identifies major causes off severe intellectual disability. Nature 2014; 511:344-7.
2. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. N Engl J Med 2013; 365:1502-11.
3. Wright CF, Fitzgerald TW, Jones WD et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet 2015;385:1305-14.
4. https://www.nextgxdx.com/order-guides/exome-sequencing
5. https://www.genomeweb.com/sequencing/hereditary-cancer-panels-increase-dx-yield-vus-rate-high-clinical-guidelines-mis

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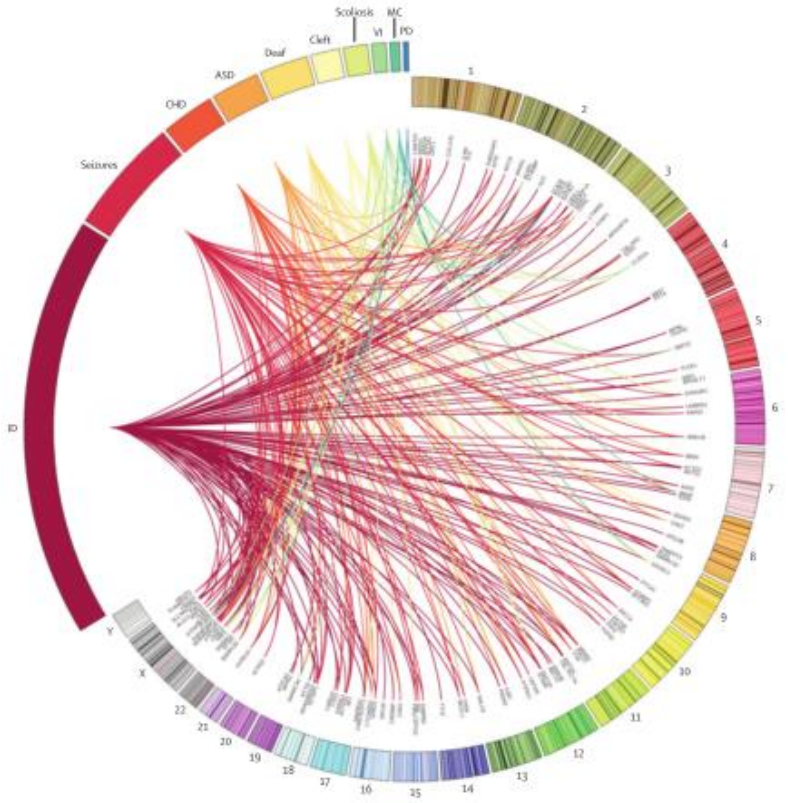
Sequencing Broadens the Scope

Of genetic elements impacting certain phenotypes



1128 genes in the Developmental Disorders Genotype-to-Phenotype database

Growing on average by 20 genes per month

1. Wright CF, Fitzgerald TW, Jones WD et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *Lancet* 2015;385:1305-14.

Informatics

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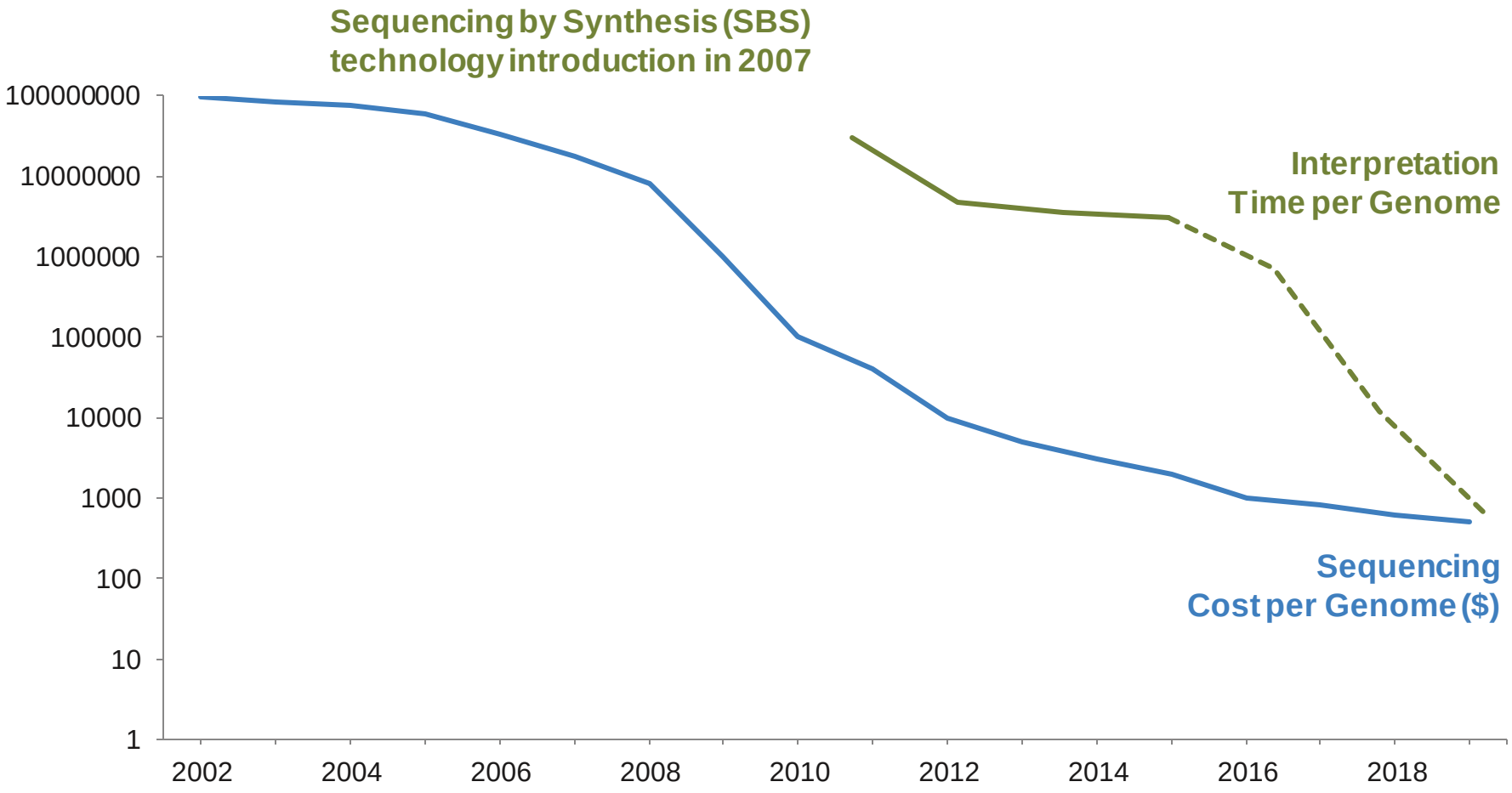
Genome Interpretation in 2017 Resembles Genome Sequencing Back in 2007



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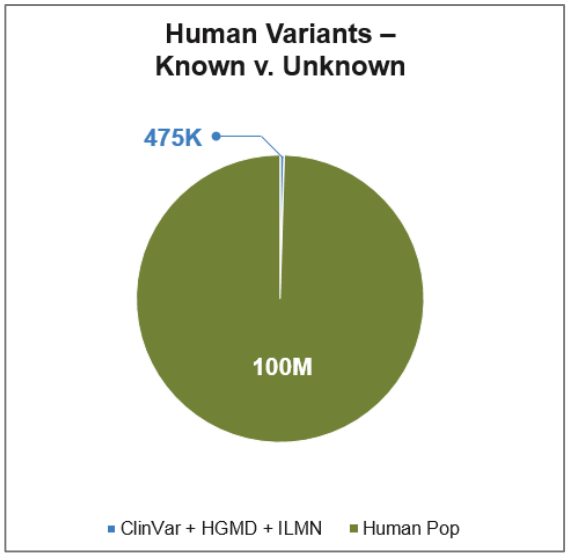
Challenge: Millions of Variants, Few Known

Each patient genome contains 4 million variants; 99.9% are of unknown function

This model no longer scales: no one can keep up with the explosive growth of scientific and genomic knowledge.



Whole Genome (Start Here)
4,000,000 variants

Automated Interpretation

Human Review 15 minutes

The Answer
1-2 variants

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Approaches to 'Solving' Interpretation

Data Sharing Initiatives

GenomeBridge

Global Alliance for Genomics & Health

Three Outstanding Barriers to Sharing Genomic Data

- **Patient privacy:** Individual patient genetic and clinical information is identifying and cannot be shared.
- **Data ownership:** Institutions don't want to donate to a central repository and lose control of their data.
- **Standardization:** Differences in platforms, pipelines, and clinical and genetic data representation makes normalization challenging.

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Genetic Health Vision

Within 10 years, clinical whole genome sequencing (cWGS) will **replace CMA and WES** as the first line test for rare disease, intellectual disability, developmental delay, and multiple congenital abnormalities in **both critical care and pediatrics settings**.