Clinical Genomics – Changing the scene of clinical diagnostics and patient care

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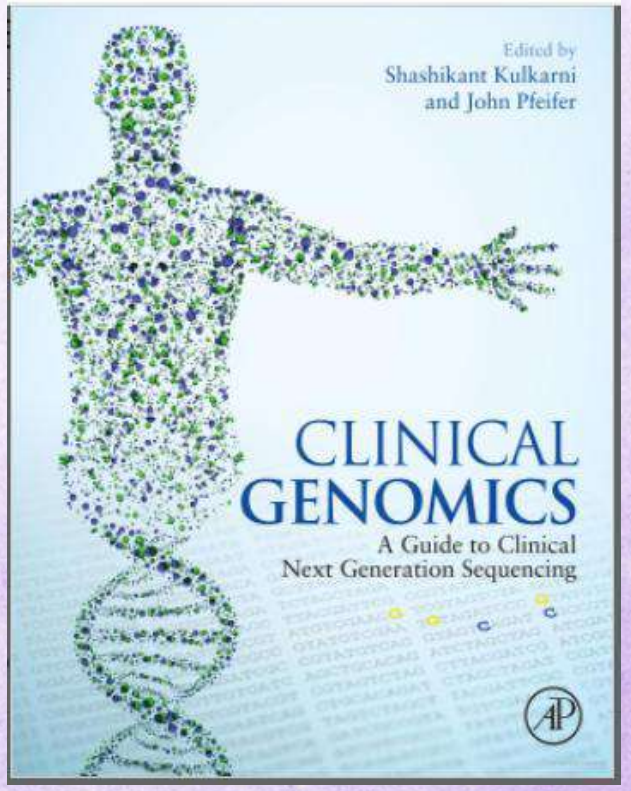
Definition: Clinical Genomics

Clinico-genomic medicine is an emerging medical discipline that involves ***using genomic information about an individual as part of their clinical care***

(e.g. for diagnostic or therapeutic decision-making)

and dealing with the ***health outcomes and policy implications*** of that clinical use



"The study of clinical outcomes using genomic data"

The “Human Genome Project”

- International Human Genome Sequencing Consortium : **1990**
- Launched in the United States of America
- Six countries : USA, UK, Japan, France, Germany and China
- Twenty universities and research centers of government-sponsored sequencing centers (Tax Payers money)
- Time taken : **2001 first draft / 2003 final draft published- 13 years**
- Amount Taken : 2.7 billion dollars (FY 1991)

The Human Genome Project : 13 years!!

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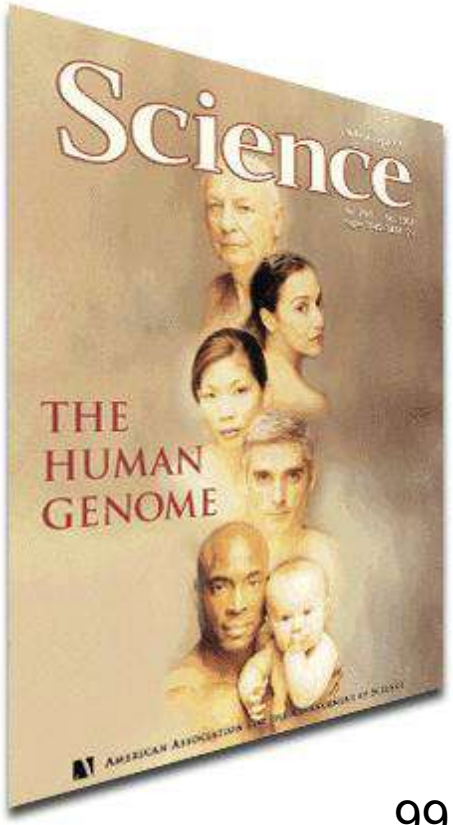
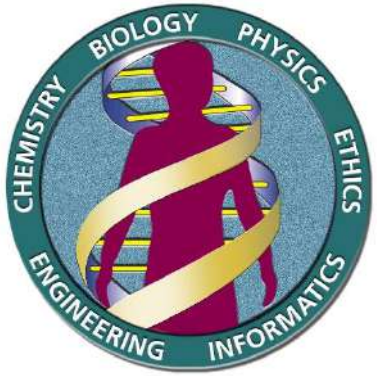
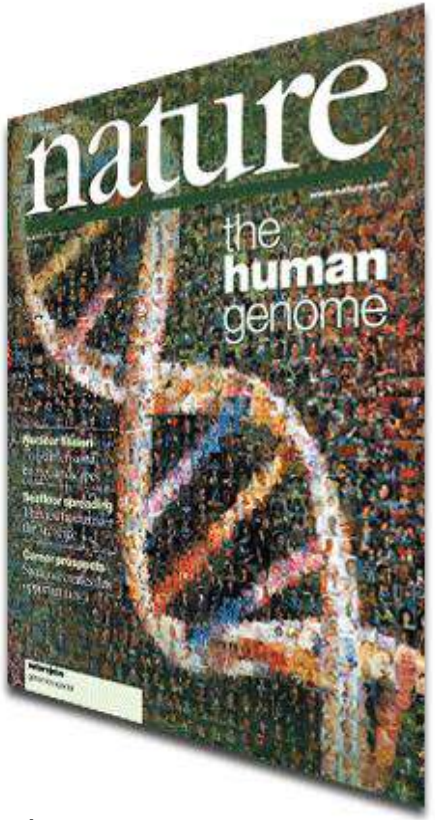




3 billion base pairs (ATGC)

20,000 protein-coding genes



99.9% inter-individual identity (yet 4 millions differences)
99% identical to chimpanzee genome (yet 6% different genes)

Pause for a thought : 3 billion = No. of seconds in around 95 years!!

Work in Progress??

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Science

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SPECIAL ISSUE RESEARCH ARTICLE | HUMAN GENOMICS

The complete sequence of a human genome

SERGEY NURK, SERGEY KOREN, ARANG RHIE, MIKKO RAUTIAINEN, ANDREY V. BZIKADZE, ALLA MIKHEENKO, MITCHELL R. VOLLGER, NICOLAS ALTEMOSE, LEV URALSKY, [...] ADAM M. PHILLIPPY +91 authors Authors Info & Affiliations

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CURRENT ISSUE

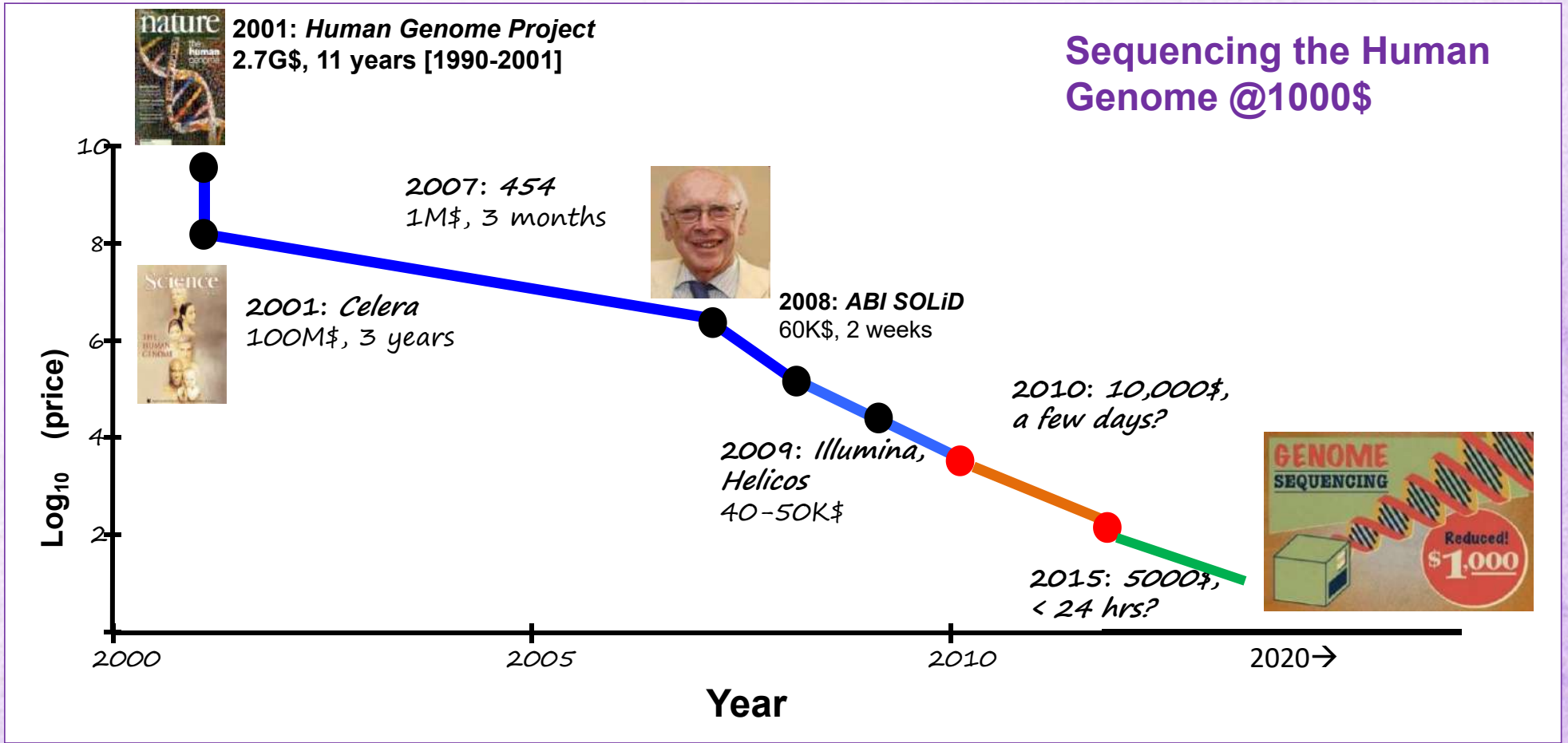
The genome full version is composed of :

- 3.055 billion base pairs
- 19,969 genes encoding proteins.
- Of these genes, the researchers identified about 2,000 new ones.
- They also spotted **2 million additional genetic variants**, 622 were present in key genes

https://www.science.org/doi/10.1126/science.abj6987

Paradigm Shift : Post Human Genome Era

Innovations in **chemistry, optics, fluidics, computational hardware, bioinformatic solutions** has its impact on the cost and time taken to sequence the genome



Pre and Post HGP: A Revolution!!

Then…1977 onwards

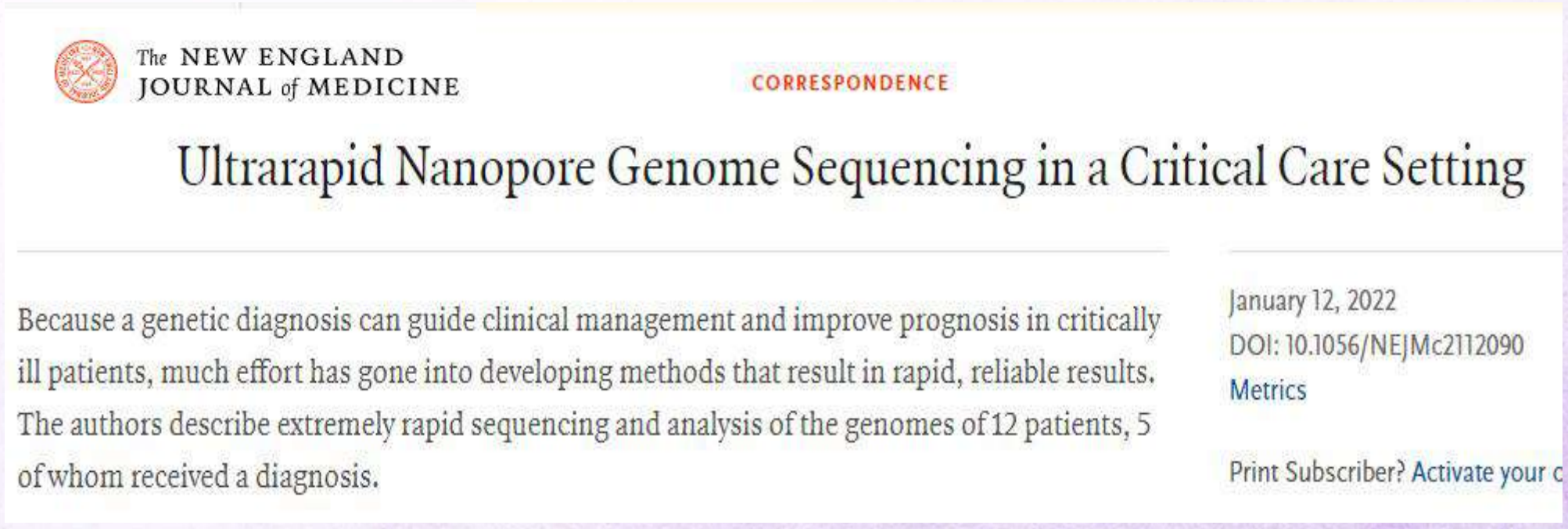
- 1.2 M bases/day/instrument
- $ 1-2 M for 1Gb raw data
- **1 human genome= 13 years**

Now…since 2004

- 2500 M bases/day/instrument
- $ 50 for 1Gb raw data
- **1 human genome= few hours**

NGS = Modern /high-throughput/ massively parallel/ rapid DNA sequencing technology

Guinness World Record for fastest DNA sequencing technique



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Ultrarapid Nanopore Genome Sequencing in a Critical Care Setting

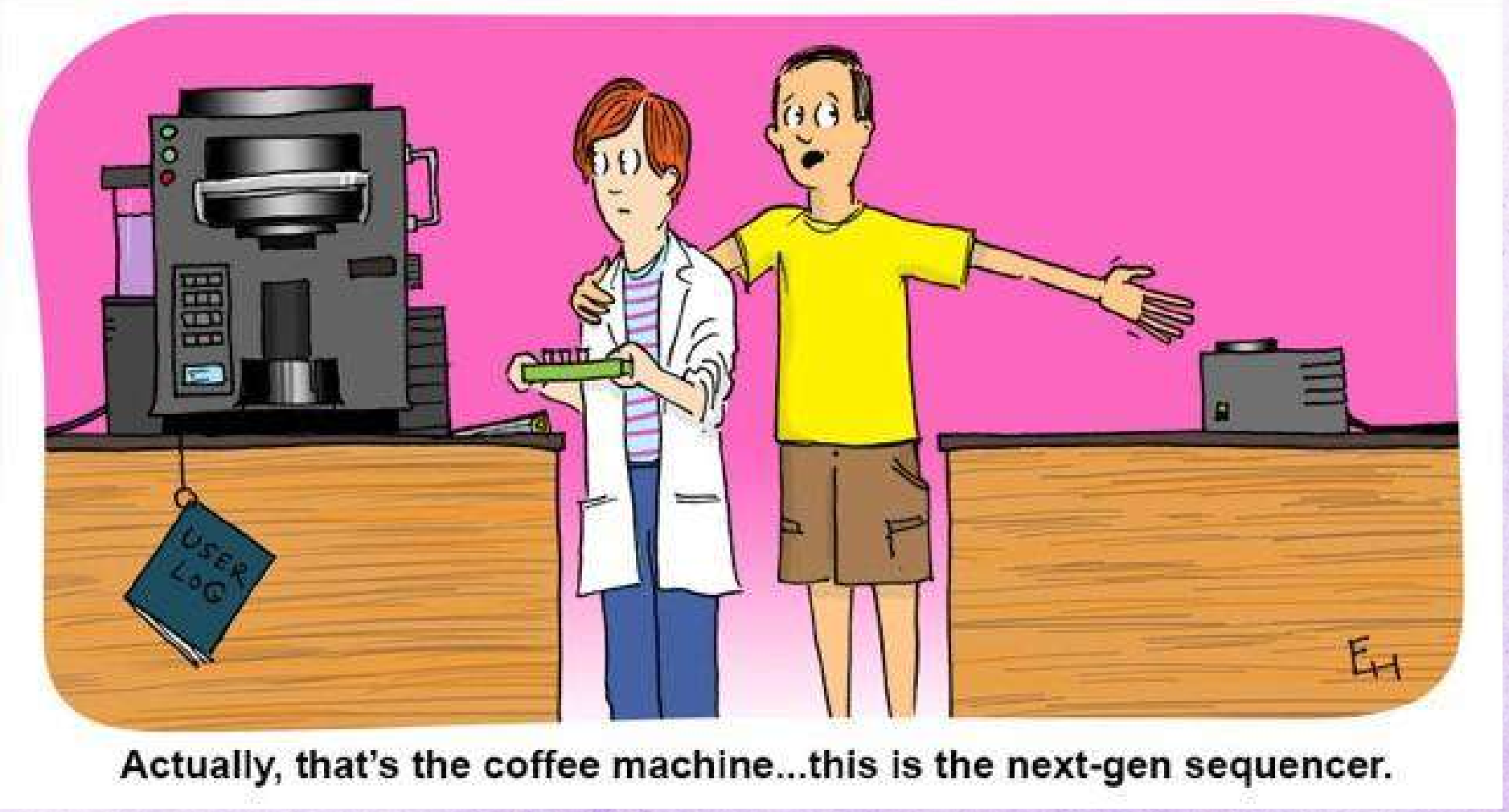
Because a genetic diagnosis can guide clinical management and improve prognosis in critically ill patients, much effort has gone into developing methods that result in rapid, reliable results. The authors describe extremely rapid sequencing and analysis of the genomes of 12 patients, 5 of whom received a diagnosis.

January 12, 2022
DOI: 10.1056/NEJMc2112090
Metrics

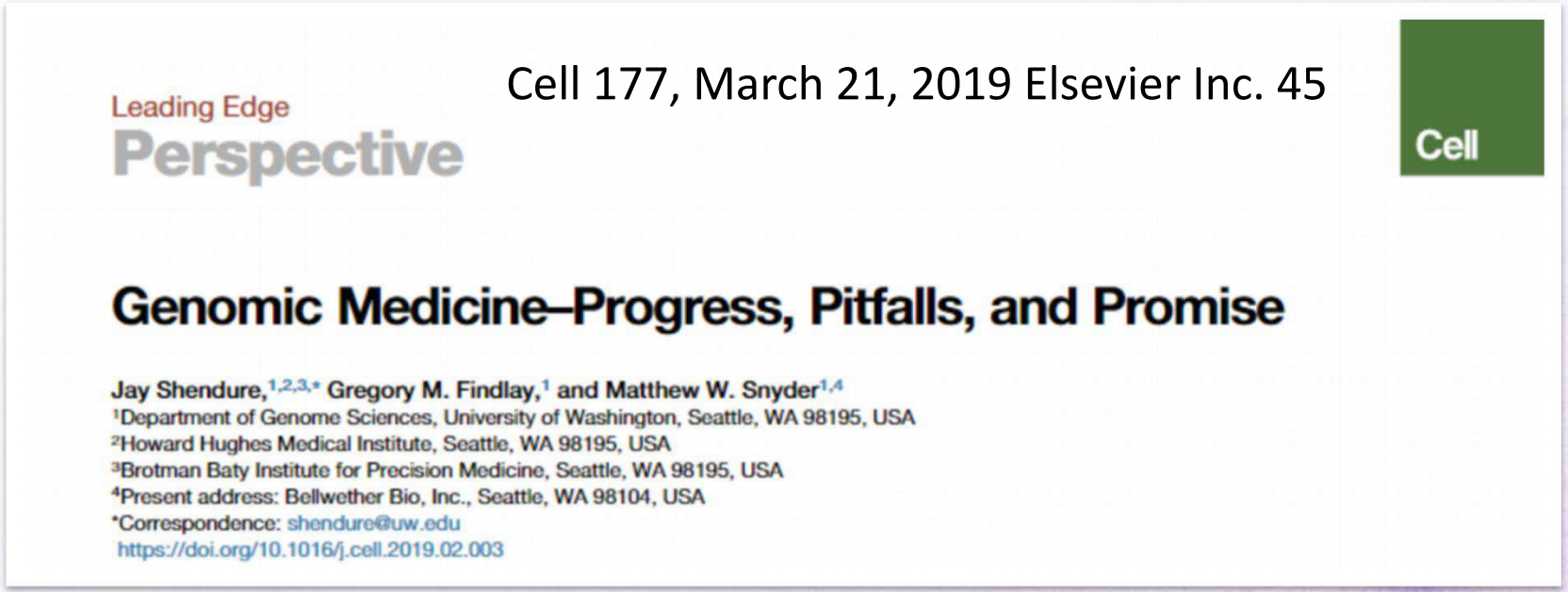
Print Subscriber? Activate your c

- Sequencing the genomes of 12 patients and managing to get a genetic diagnosis for **five of them in about eight hours.**
- One case took only **5hrs & 2m** to sequence and 7hr & 18m to diagnose

Near future…


USER LOG
Actually, that's the coffee machine...this is the next-gen sequencer.

Cell 177, March 21, 2019 Elsevier Inc. 45



Leading Edge

Perspective

Cell

Genomic Medicine–Progress, Pitfalls, and Promise

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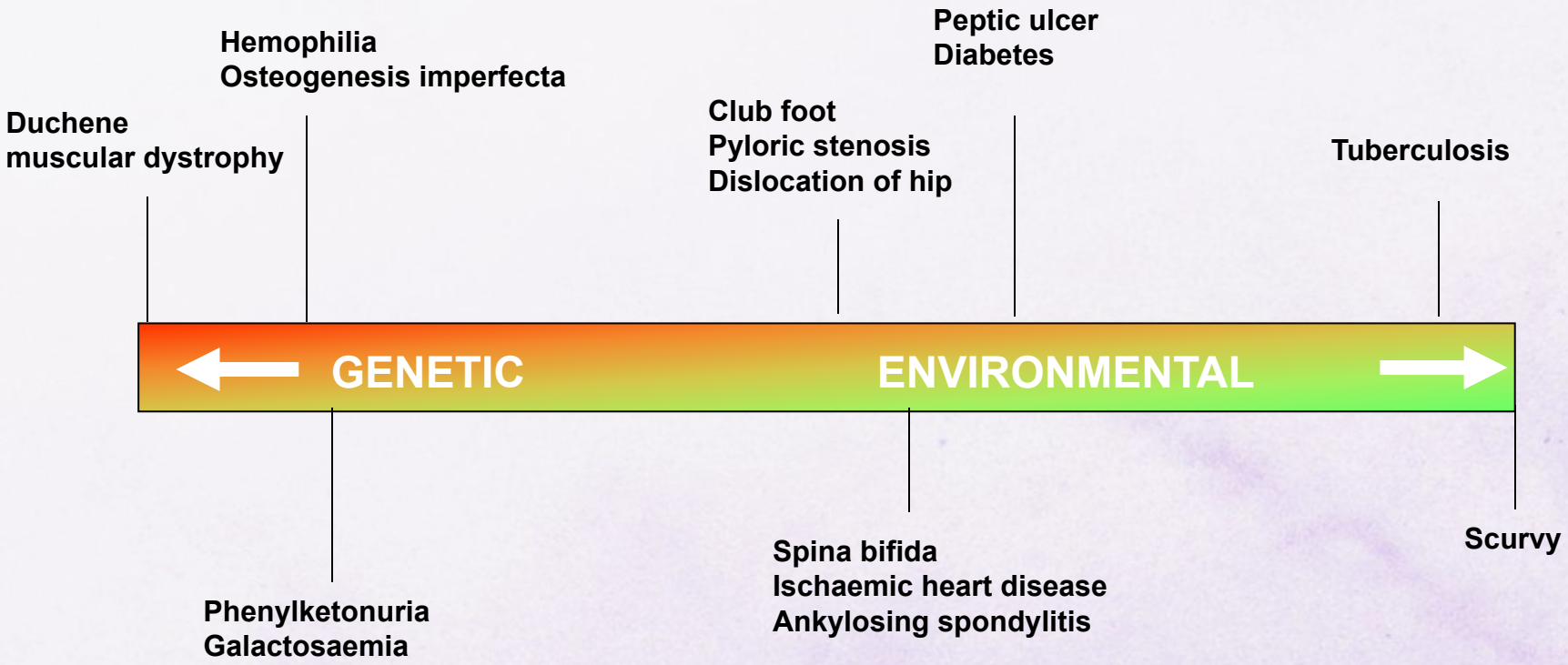
https://doi.org/10.1016/j.cell.2019.02.003

- "THE human genome" emphasizes the nearly **perfect similarity of individual humans** to one another (~ 99.9%) but downplays the **millions of differences (~ 0.1%)** that make each of us genetically unique.
  - **Application of the field of human genetics lies not with our similarities but our differences→** disentangling how our genotypic differences underlie our phenotypic differences.

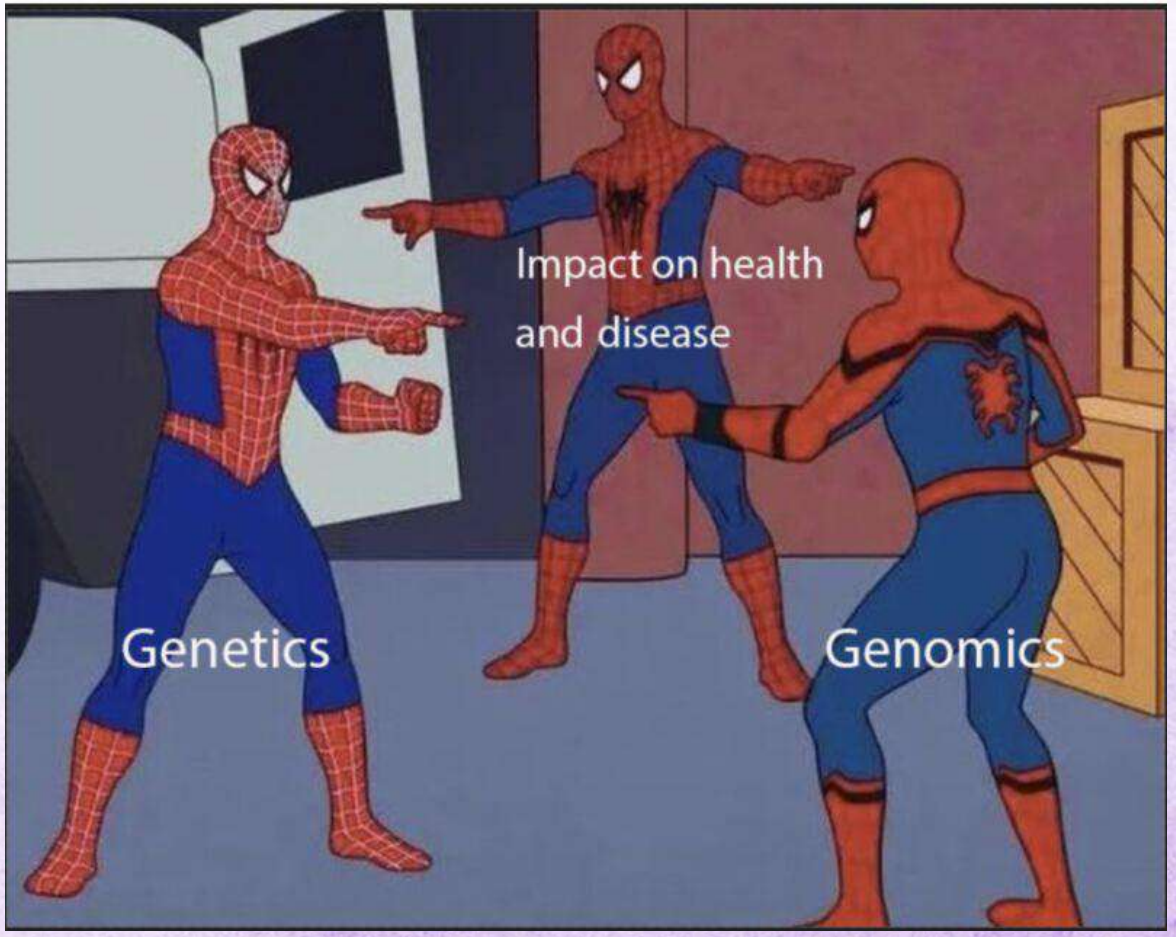
The contributions of genetic and environmental factors to human diseases



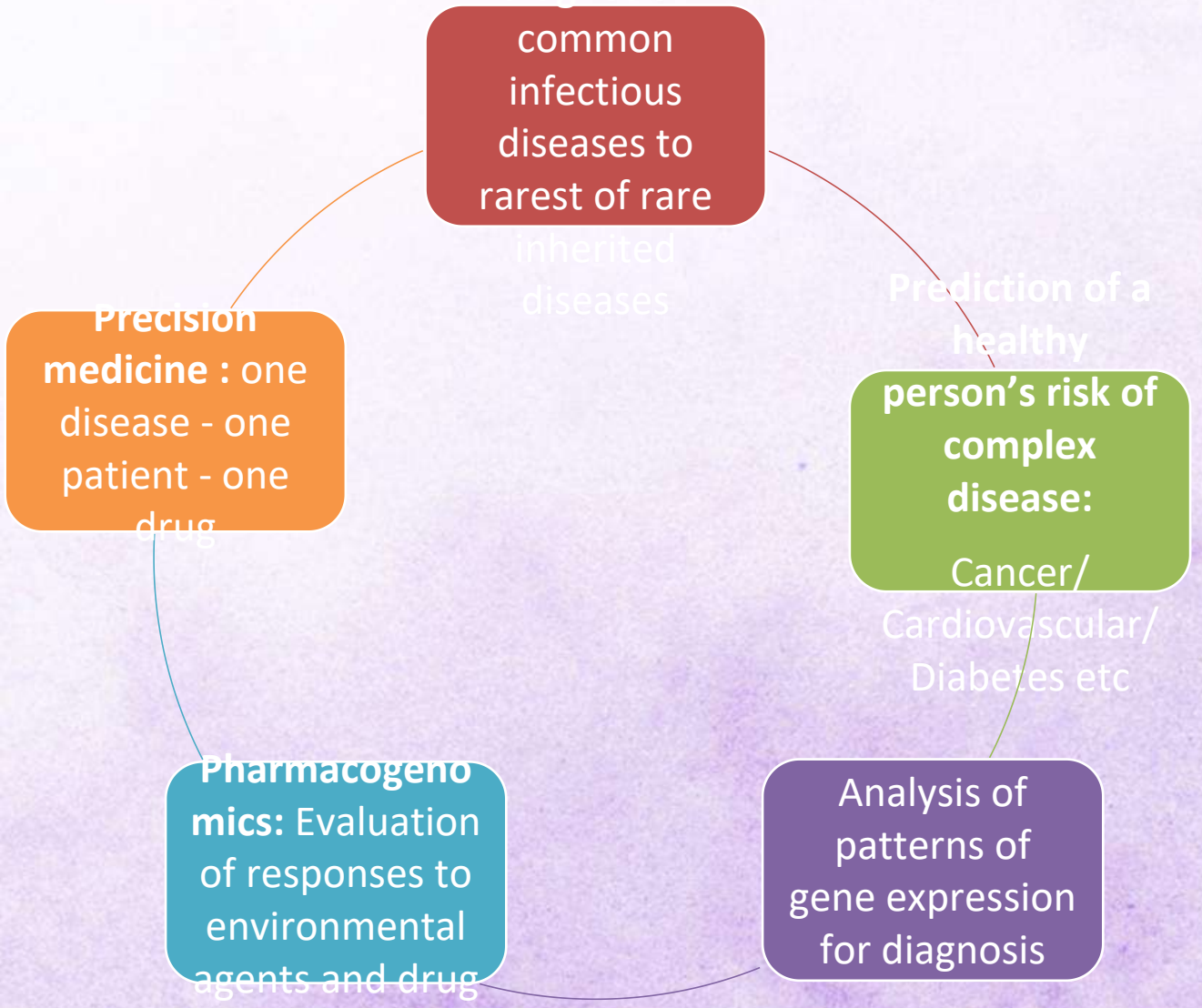
Rare
Genetics simple
Unifactorial
High recurrence rate

Common
Genetics complex
Multifactorial
Low recurrence rate

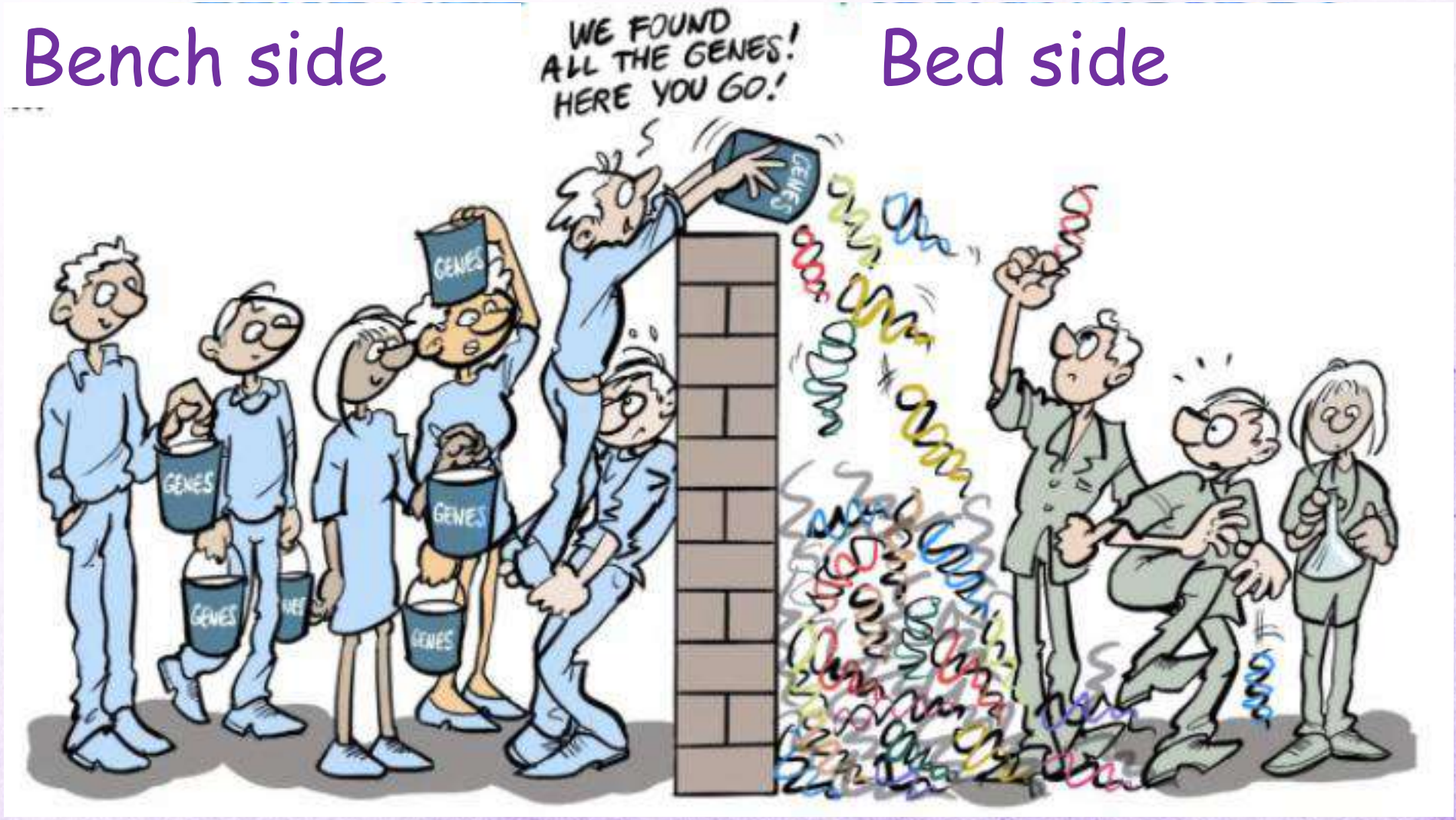
High time we understand the impact of genetics and genomics in health care



Application of genomics into clinical practice



Molecular Diagnosis : All segments



Credits to: Tom van Dun from https://infocomics.nl and @BRAINSCAPES1

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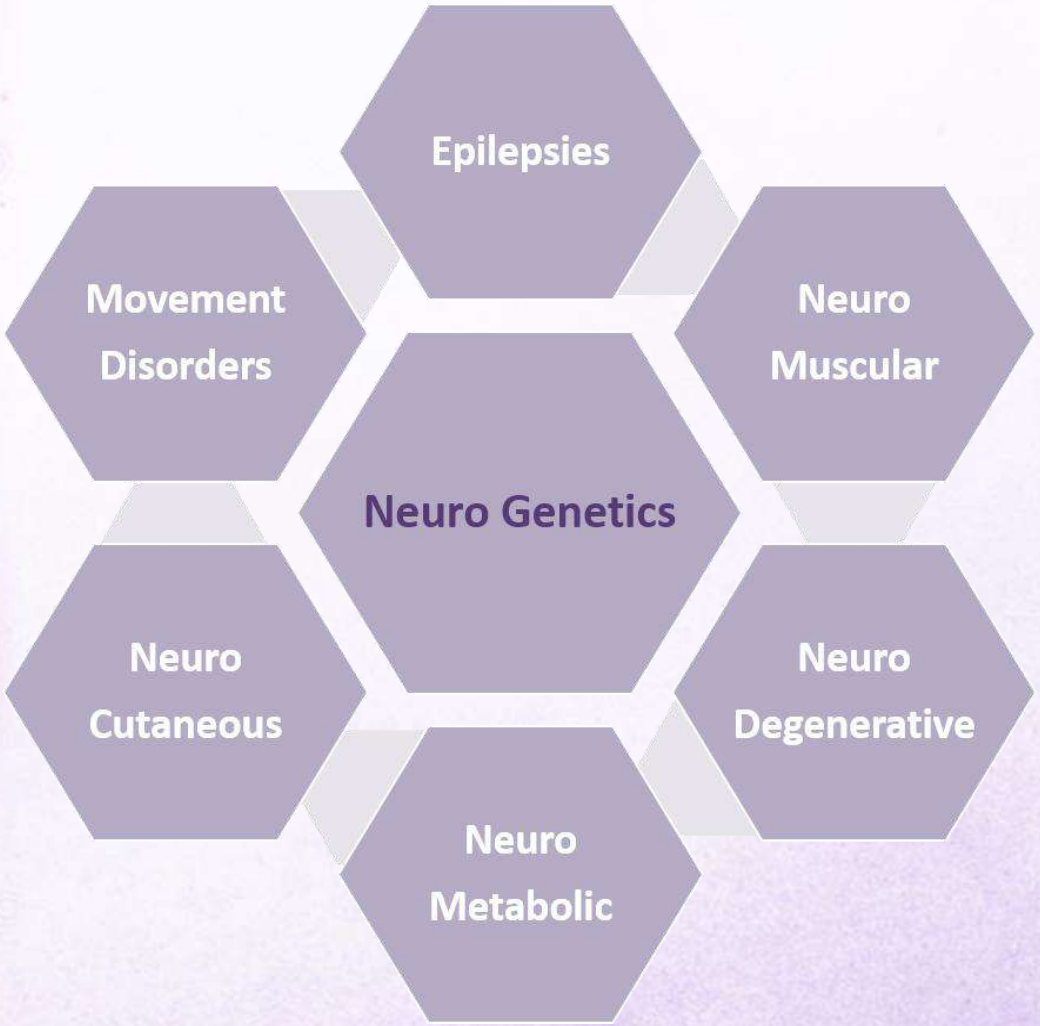

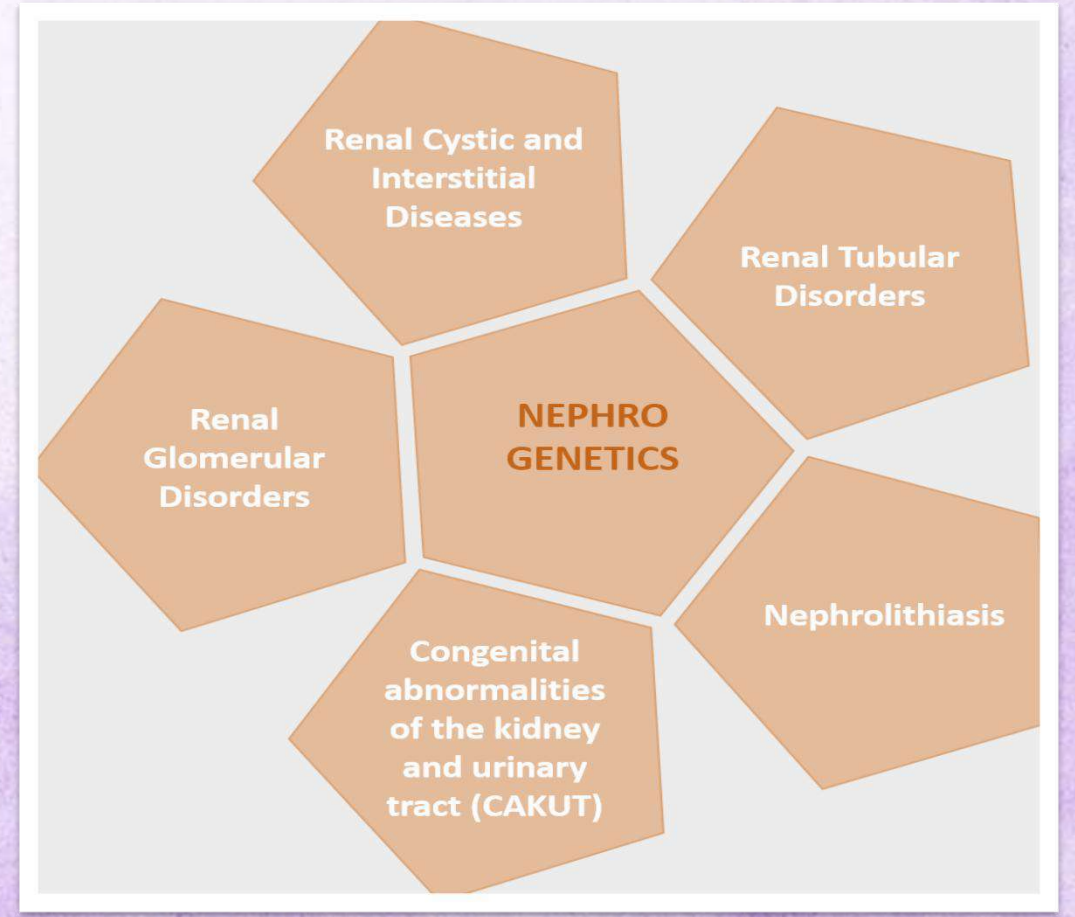

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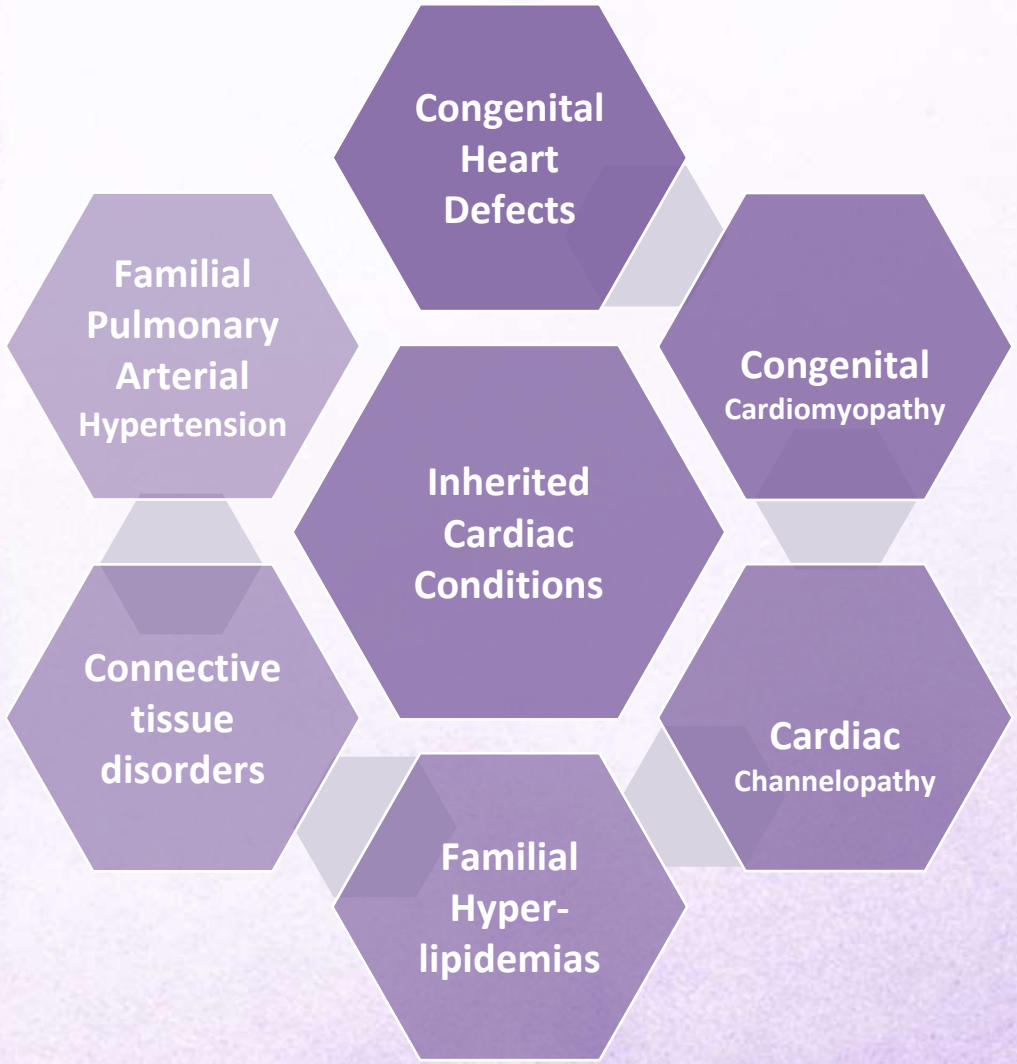


New Born Screening

Carrier testing

Pre-natal Diagnosis

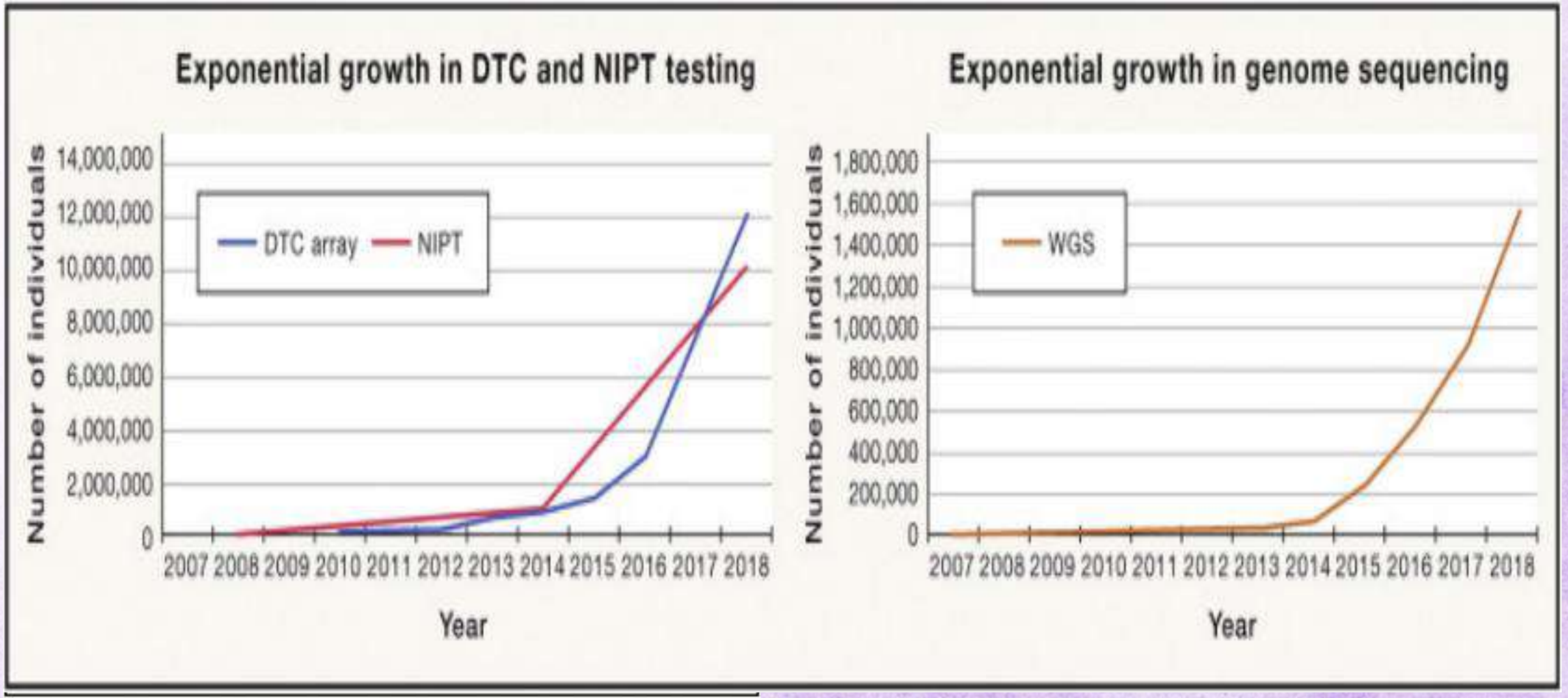
Reproductive Genetic Testing

NIPT

PGS + IVF

Pre-implantation Genetic Diagnosis

High clinical impact of genomic medicine in four areas: common inherited diseases / rare inherited diseases/ reproductive health/cancer



Genomic *Medicine throughout the Human Life Cycle*

Is molecular diagnosis a MUST ??

For many genetic disorders diagnosis depends on :

- **Clinical features:** DMD, congenital malformation syndromes
- **Biochemical:** Enzyme analysis in LSD
- **Hematological:** HbF/A2 in Thalassemia or FVIII assay in Hemophilia
- **Imaging :** CT/MRI for Neurodegenerative BD
- **Combination:** Clinical + Inv: GSD type I

DNA based tests ***may not be required for the diagnosis*** →
but it plays an important role in Carrier Detection and PND

Implication of Molecular Diagnostics & process of decision making using genetic reports

Individual

- Prognosis/ Life expectancy
- Functioning capacity
- Social acceptance

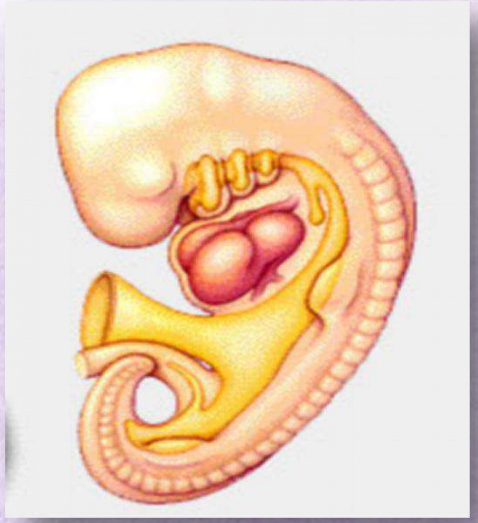
Family

- Interventions/ successfully treat complications/ early acceptance
- Financial and educational aid/ support groups
- Risk of recurrence
- Prenatal diagnosis
- Carrier identification

“NO DIAGNOSIS” IS BETTER THAN A “WRONG DIAGNOSIS”

Prevention of genetic disorders→ levels

- Tertiary prevention : Post natal→ NBS
- Secondary prevention : at embryo/ fetal stage → Prenatal diagnosis (PND)
- Primary prevention : Preimplantation stage embryo → Pre-implantation genetic diagnosis (PGD)
- Primary prevention (? Better) : Premarital / pre-conceptional carrier screening



Planning health care policies by government

HEALTH

Turkey to require SMA disease screening before marriage

SMA disease also to be included in genetic screenings for newborns, says Health Minister Fahrettin Koca

Therapies in SMA: HOPE or HYPE??

Nusinersen

FDA approved injection which increases expression levels of SMN protein using an anti sense oligonucleotide to alter splicing of the *SMN2* transcript.

Risdiplam

FDA approved oral drug which alters *SMN2* splicing in order to increase functional SMN protein.

Zolgensma

FDA approved gene therapy that utilizes an adeno-associated virus serotype-9 vector to increase low functional SMN protein levels.

Growth of Genomics in Clinical Diagnostics

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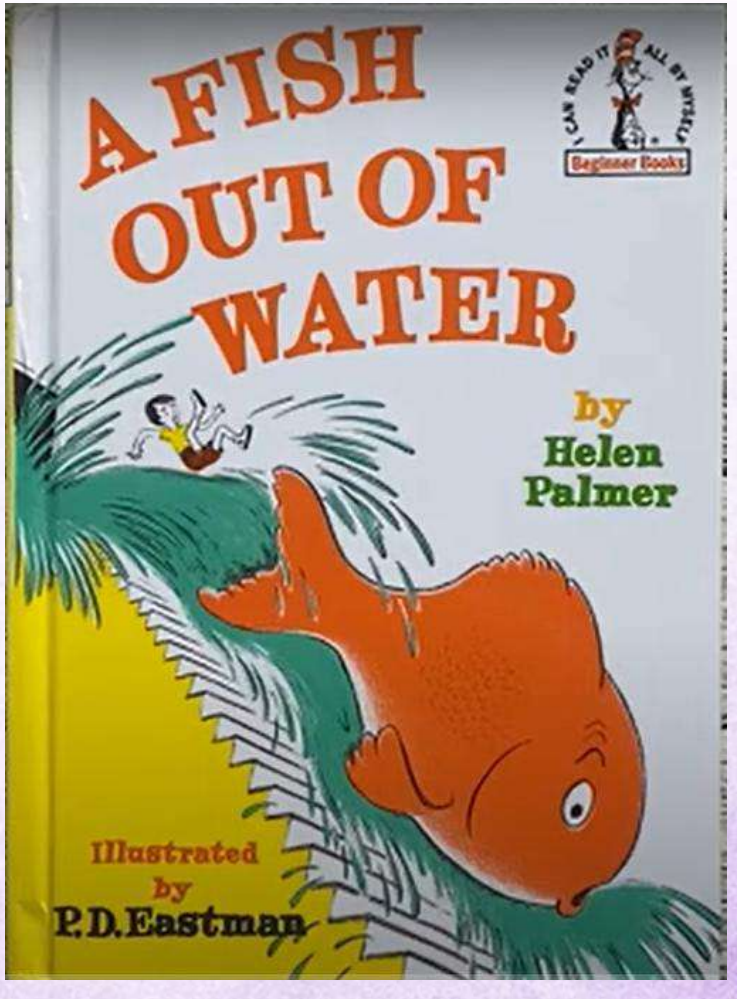

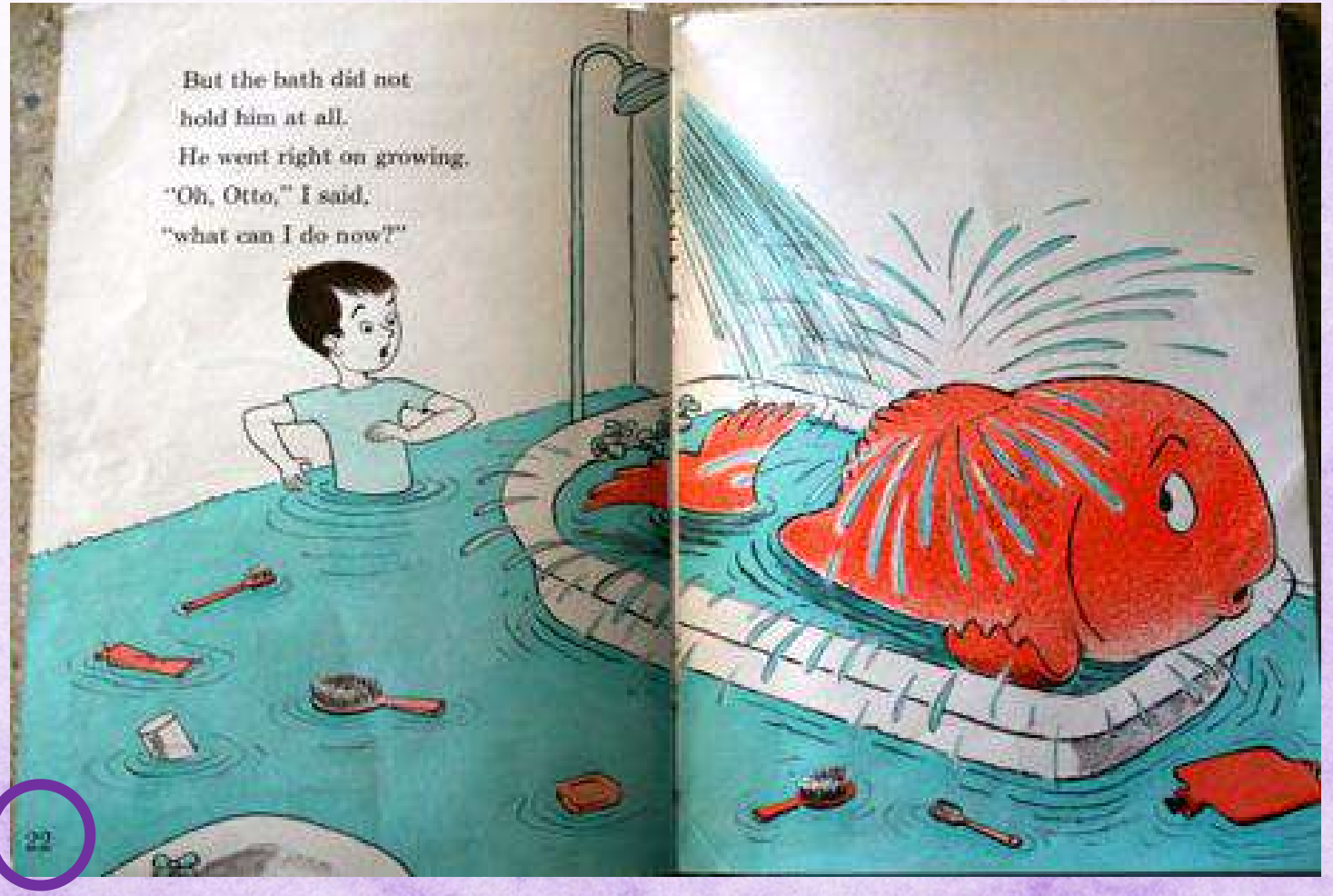

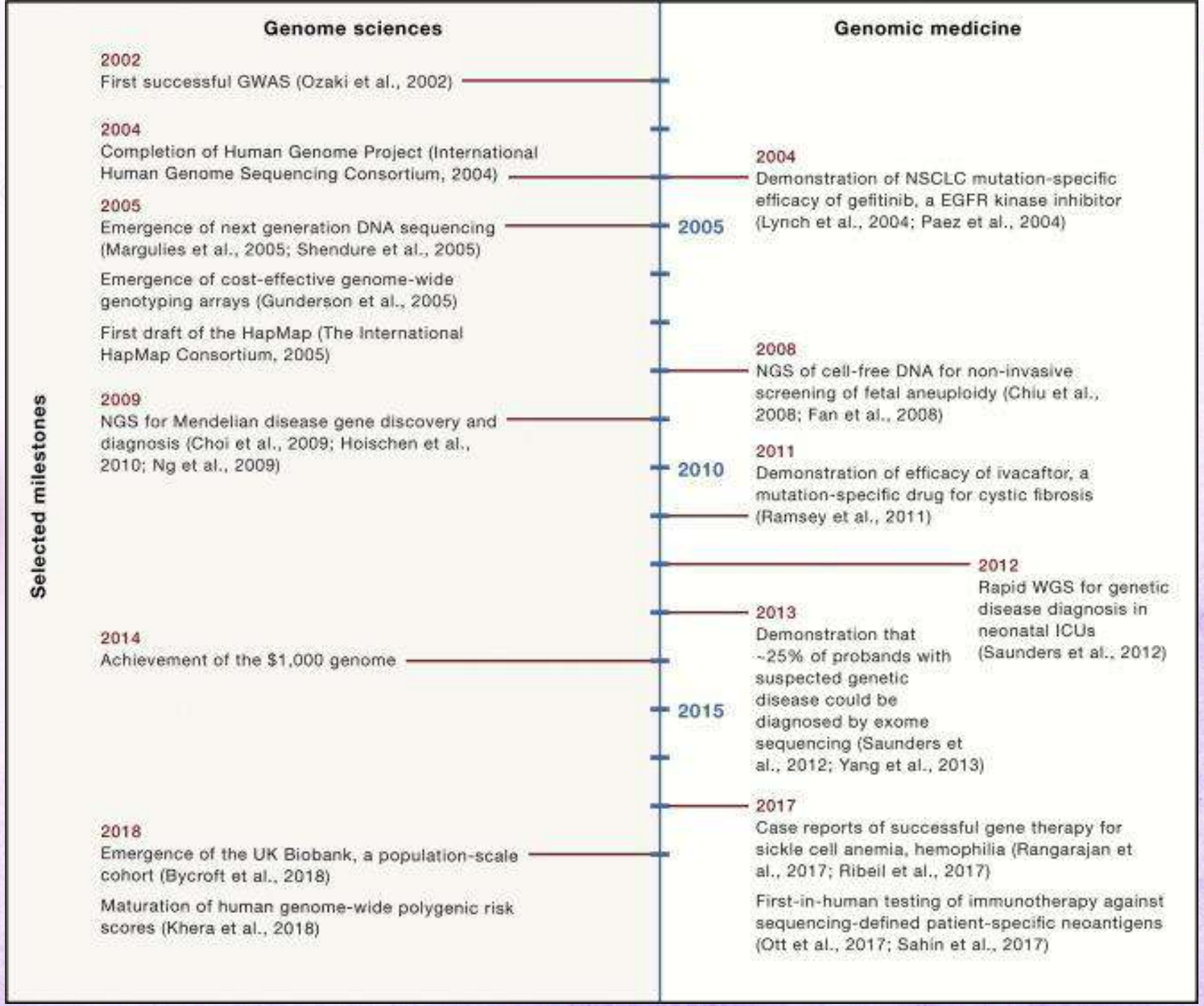

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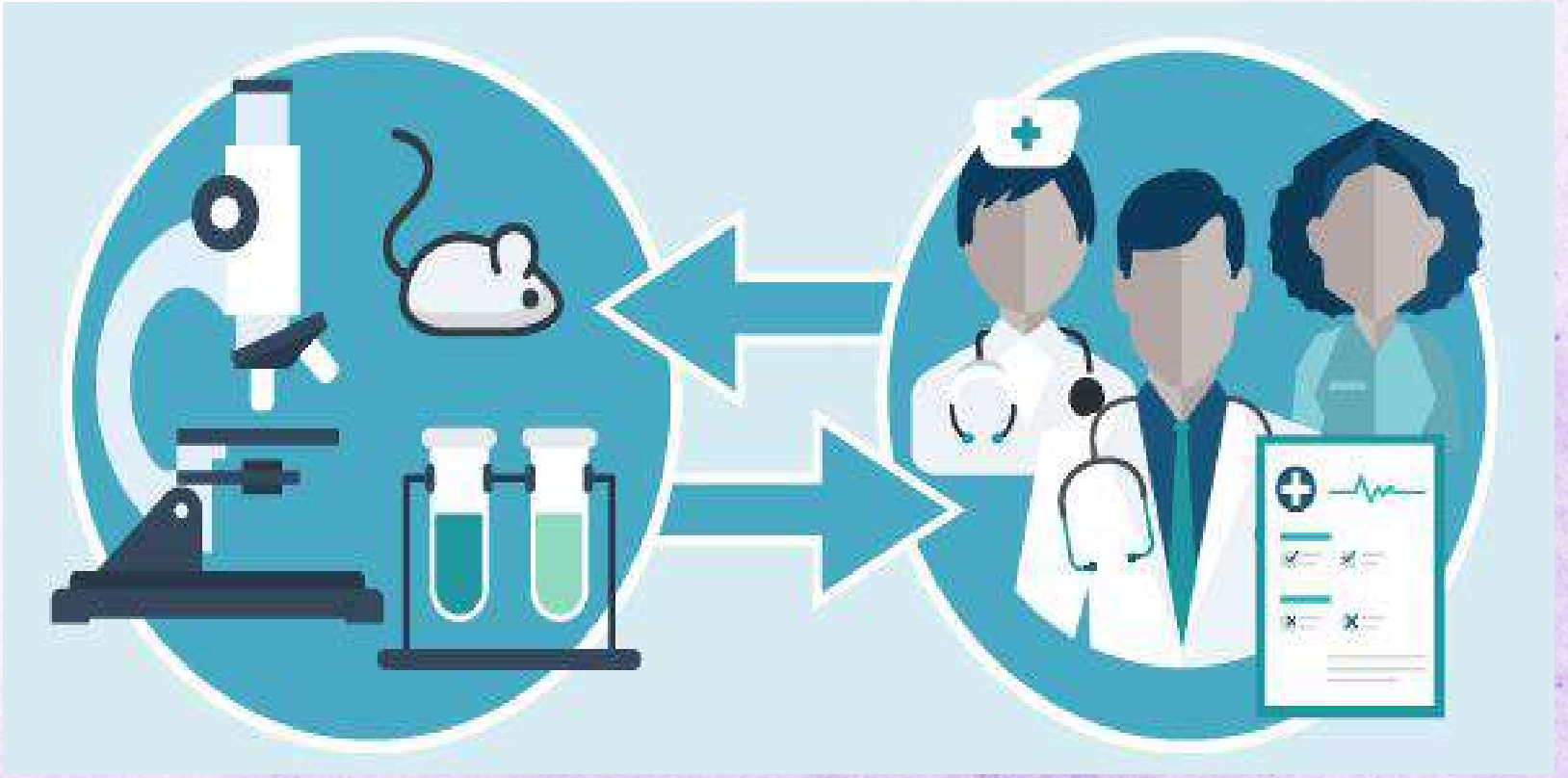
Milestones for Genome Sciences and Genomic Medicine

Benchside-to-bedside→
translating science from the lab to the clinic



https://thl.fi/en/web/thlfi-en/research-and-development/research-and-projects/p6-genomics-to-healthcare

https://www.docwirenews.com/docwire-pick//

Challenges facing clinical practice in genomics era

- How can we better train the current/ next generation of clinicians to practice genomic medicine
- How can increasingly complex genetic knowledge be made readily accessible to all practitioners when they need it

- What kind of tests are available for genetic disorders?
- Which test should be prescribed in which disorder?
- What would be the interpretation of reports?
- What does a negative report mean?
- What would be the further management after getting reports? Does it change??

Early (pre-symptomatic stage) diagnosis and better management?

Case review:

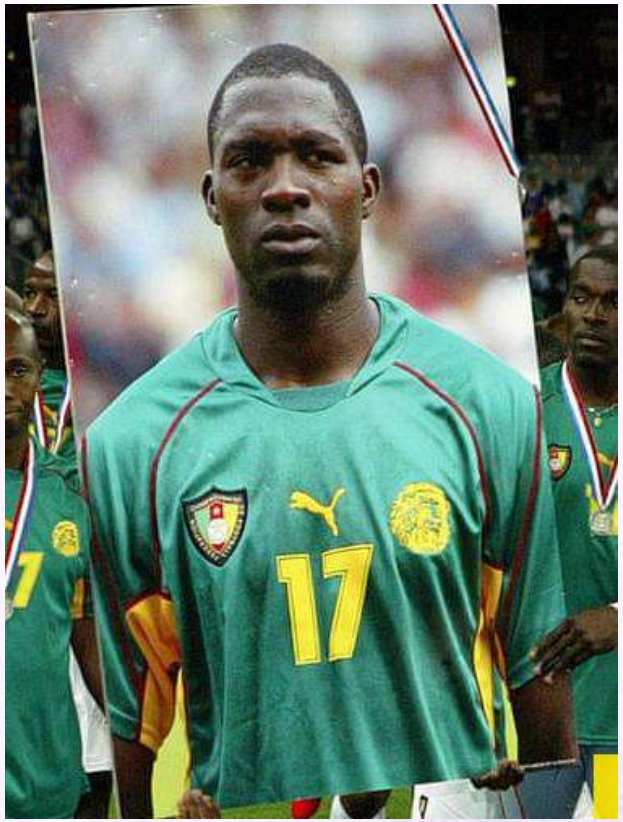
Mr. ABC / 50yrs/ family history of his father who had a heart attack at age 59 years
His physical exam (including ECG and treadmill test) were fine
His cholesterol was 'a little high'
Recommended reduced-fat diet and lipid lowering drug

- Mr. ABC has heard about a new DNA test that provided an **individual genetic profile and personalized recommendations** for supplements to prevent CAD
- **Should he get the test?**

Targeted lifestyle changes such as diet, exercise and stop smoking

- Screening at earlier ages, more frequently and with more intensive methods than might be used of average risk individuals
- Use of chemoprevention approaches : Aspirin
- Referral to a specialist for **assessment of genetic risk factors??**

Complex disorders : Predictive risk scores



https://www.theguardian.com/science/2018/aug/08/more-young-footballers-dying-of-heart-problems-than-thought-fa-study-finds

REVIEW

MAYO CLINIC

Check for updates

Acute Myocardial Infarction in Young Individuals

Rajiv Gulati, MD, PhD; Atta Behfar, MD, PhD; Jagat Narula, MD, PhD; Ardaas Kanwar; Amir Lerman, MD; Leslie Cooper, MD; and Mandeep Singh, MD, MPH

https://www.sciencedirect.com/science/article/pii/B9780128219720000083

Risk factors for MIYA

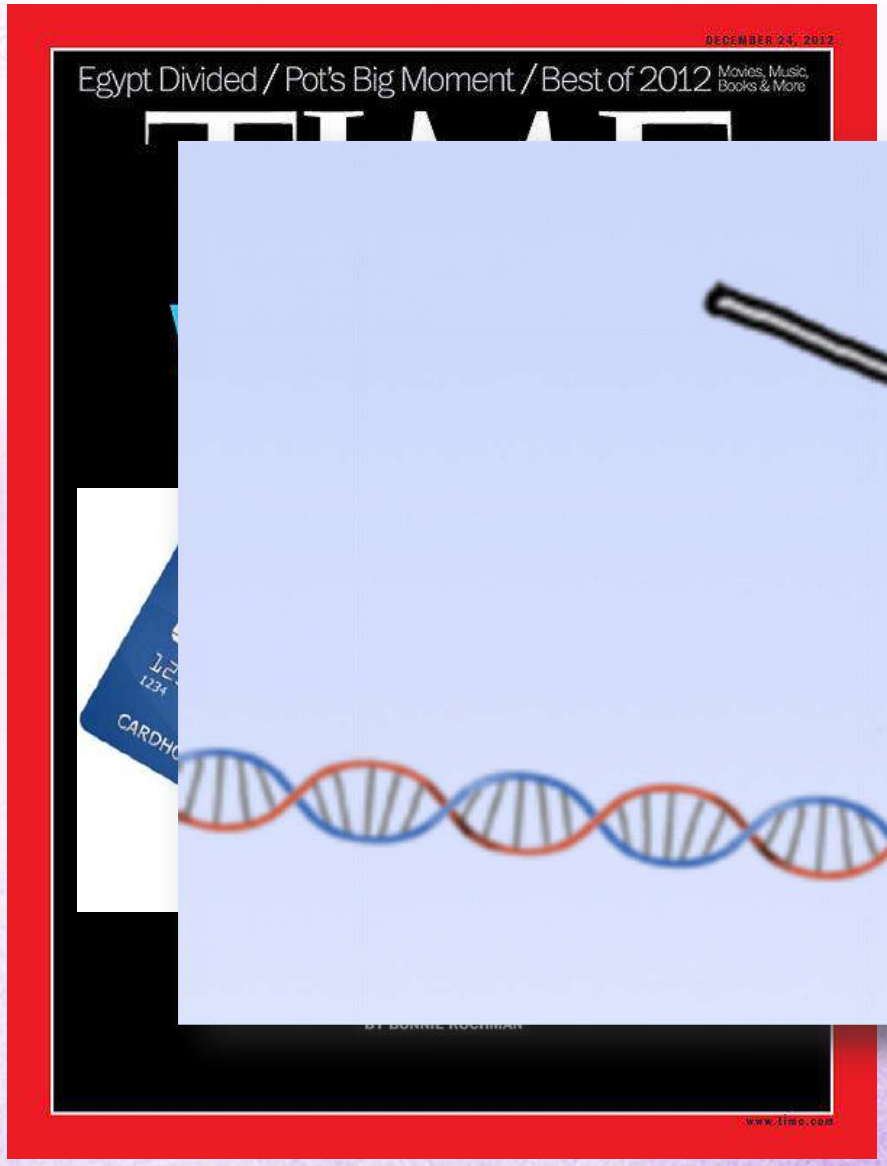
The cut off age of 45 has been used in most studies to define young patients with CHD or MI

Normal coronary arteries
Coronary artery spasm
Cocaine and amphetamine abuse
Alcohol (39)
Hypercoagulable states
Antiphospholipid syndrome
Nephrotic syndrome
Embolic phenomena
Endocarditis
Paradoxical embolism (40)

Abnormal coronary arteries
Accelerated atherosclerosis
Smoking
Diabetes
Familial hypercholesterolaemia
Combined hyperlipidaemia
Type II remnant dyslipidaemia
Anomalous coronary arteries
Myocardial bridging
Spontaneous coronary artery dissection
Peripartum
Immunosuppression
Hypertension (22)
Coronary artery aneurysms
Kawasaki's disease

- Antiplatelet agents: aspirin and clopidogrel
- Warfarin : hypercoaguable state and continued lifelong
- Statins are invariably prescribed in all patients with MI
- Statins also stabilise plaques in patients with atheromatous CHD
- Niacin and omega 3 fatty acids: hypertriglyceridaemia and low HDL concentrations.
- B-complex vitamins: hyperhomocysteinaemia

What do clinical geneticists do ?



My journey of genetic testing -

- 2008
- Marfan Syndrome
- Cost of Test
- Sample Collection
- Sample Logistics
- Report Arrival
- Reproductive decision
- Total Time: 1 year

- 2020
- Suspected Marfan Syndrome
- Cost of Test
- Sample Logistics
- Report Arrival
- MS ruled out- Contractural arachnodactyly
- Total Time: 1.5 months

To summarize….

Implementation of NGS into clinical application requires that clinicians be sufficiently versed –

- Ordering tests (what /when /where) and receiving results
- Familiarize with the contents of the report
- Understand the
  - Clinical Validity (whether the results are of clinical significance)
  - Clinical Utility (whether the knowledge of the result is likely to benefit the patient)
- Be aware of the medico–legal as well as ethical considerations [ELSI]
- Pre-test & post-test counseling and written informed consent is a very important part of Genetic Testing

To conclude…

- Genomic medicine is profoundly changing patient care.
- Routine genome sequencing will enable a high number of patients to benefit from more personalised diagnostics and personalised therapeutic care.
- This includes rare diseases and cancer but also more common diseases (e.g. metabolic, cardiovascular, neurological diseases).

- https://www.youtube.com/watch?v=KiQgrK3tge8

Welcome to the era of clinical genomics!!