

มุมมองอนาคตของการแพทย์จีโนมิกส์ A Futuristic Perspective on Genomics Medicine

ศ.นพ.วรศักดิ์ โชติเลอศักดิ์

คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย



ประวัติการทำงาน:

- ผู้อำนวยการศูนย์เชี่ยวชาญเฉพาะทางด้านเวชพันธุศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รองคณบดีฝ่ายวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- นายกสมาคมมนุษยพันธุศาสตร์ และอุปนายกสมาคมพันธุศาสตร์แห่งประเทศไทย

Future Perspective on Genomics Medicine

Vorasuk Shotelersuk, MD, FABMG

“Insanity is doing the **same** thing over and over again and expecting **different** results.”

Albert Einstein

$$E=mc^2$$

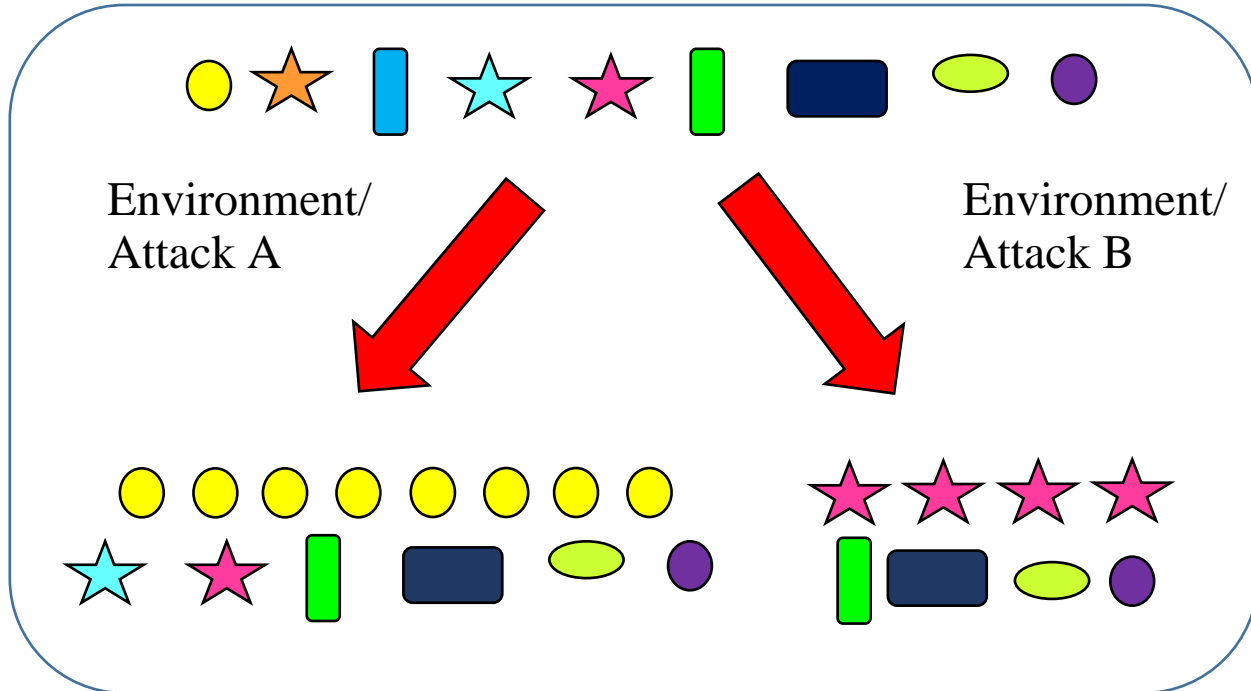


“For living-related issues, doing the **same** thing would direct to extinction.”

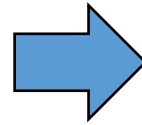
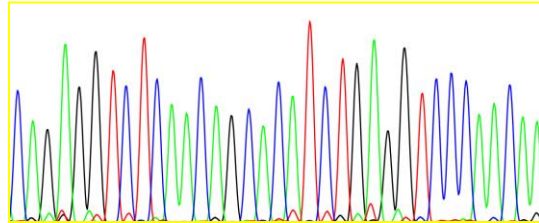
Vorasuk Shotelersuk

Challenge: Future is uncertain
Solution: Diversity

- Among members of a species (esp, human)
- Among species

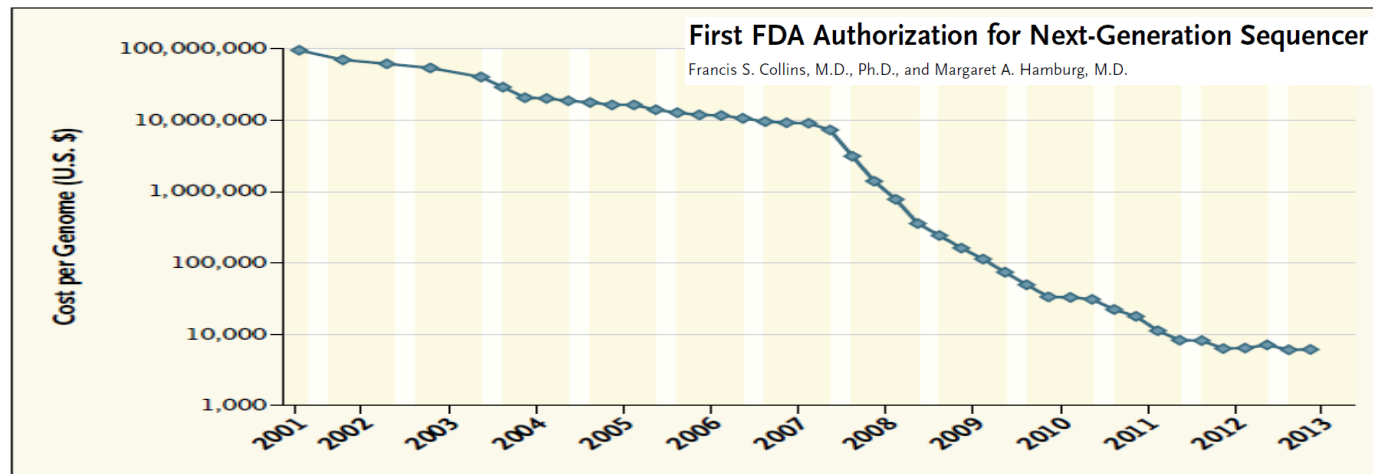


to read the origin of diversity: DNA Sequencing Technologies



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ATATTAACGGDATAGATCTGGAATATTAACGGDATAGATCTGGAATATTAACGGDATAGATCTGG#  
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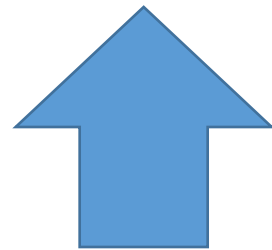
Million times faster
(1 million years -> 1 year)



Million times Cheaper

Personalized medicine

Although the incidence of SE is low, but is it gonna be me?
Which COVID Vaccine?



Population-Average Medicine

COVID vaccine reduces morbidity and mortality,
But has serious side effects (SE)

Goal

Personalized medicine

(After knowing population average,
where exactly this person lies)

Tool

Genomic medicine

(using genomic technology)

Tools

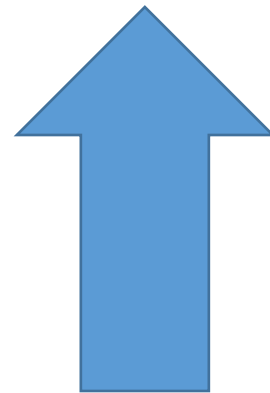
Precision medicine

(using genomic, behavior, environmental factors)

Scientists think
their time is exceptional.

Personalized Medicine

Read
(+ **Understand**)



Write
(+ **Target**)

Population-Average Medicine

Read

Understand

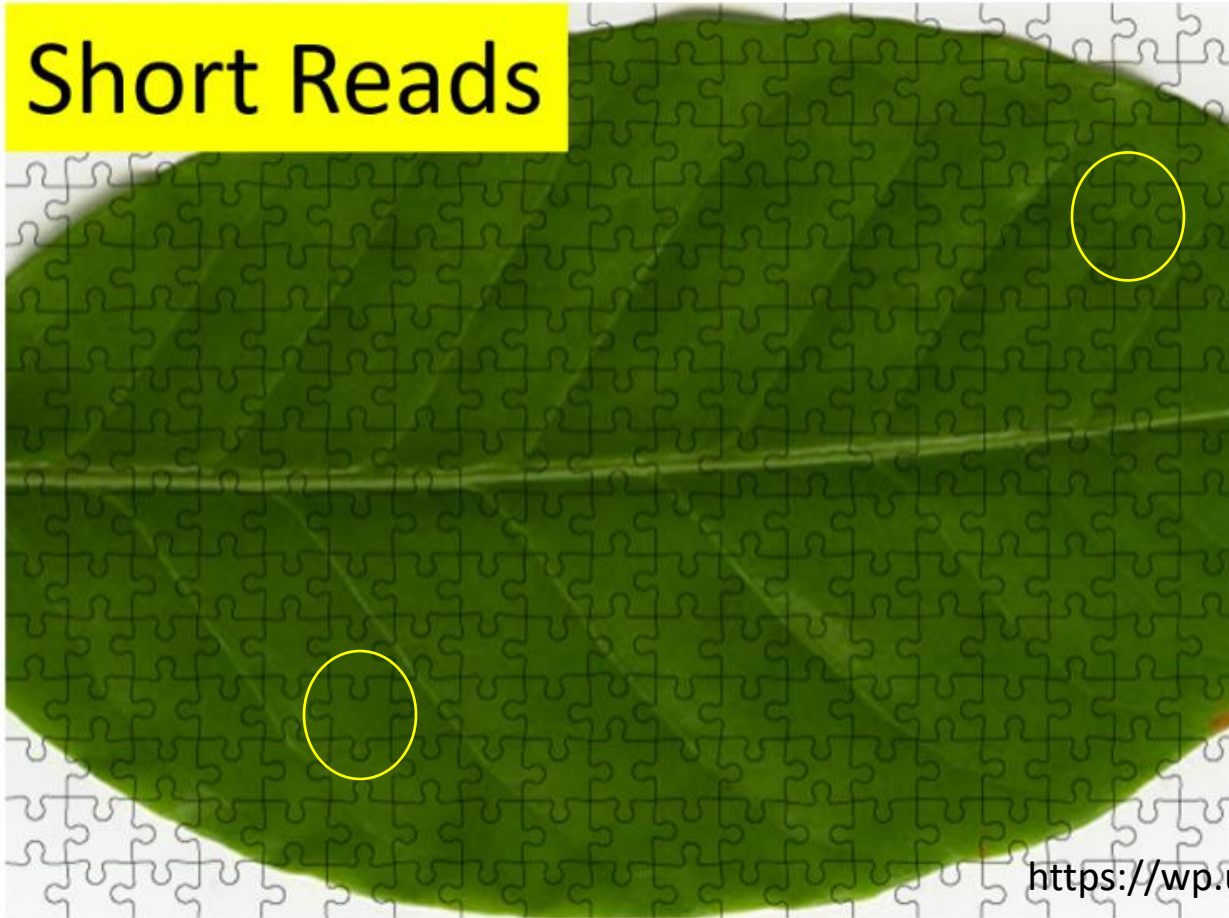
Write

Target

Tools

Applications

Short Reads



<https://wp.unil.ch/gtf/>

92% complete
Before 2021

Long Reads



100% complete

HUMAN GENOME

Nurk, BioRxiv May 2021



Short-read



Long-read



NAC2022
17th NSTDA Annual Conference
การประชุมวิชาการประจำปี สวทช. ครั้งที่ ๑๗



10x
GENOMICS
Linked-read
Single-cell



Ultralong-read



WANG Jian: BGI's 20th Anniversary (2000)

- From KM/GTP

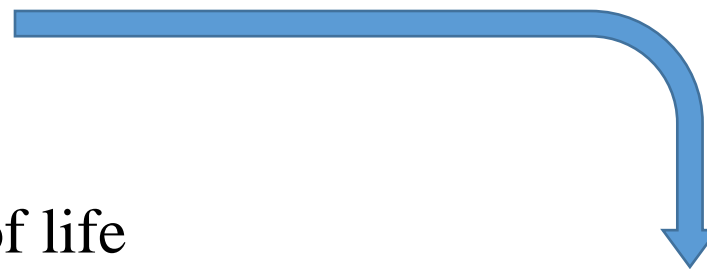


T10 (10Tb/day): NB sequencing:
birth defects, cancer, cardiovascular

- to EZY and 8B99



Exa, Zetta, Yotta: internet of life



8 billion people; live to 99+ years old

1. **Single gene – germline:** Rare Dx, Genetic Dx
2. **Single gene – somatic:** Cancer
3. **Single gene – environment:** PGx
4. **Polygenic – germline or somatic:** NCD
5. **Polygenic – environment:** Infectious diseases

2008 - 2019



REPORT

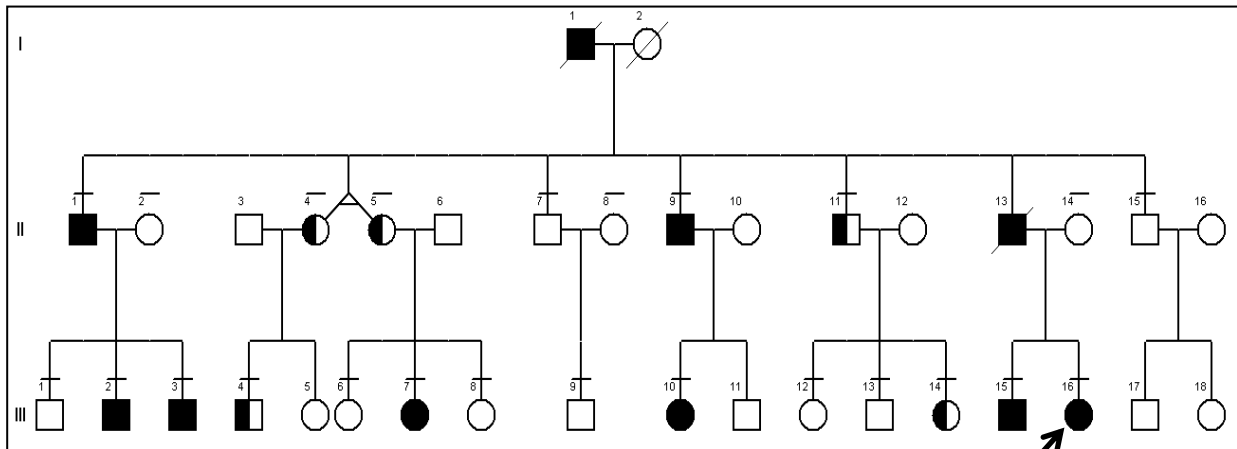
TTTCA repeat insertions in an intron of *YEATS2* in benign adult familial myoclonic epilepsy type 4

Patra Yeetong,¹ Monnat Pongpanich,^{2,3} Chalurmpon Srichomthong,^{4,5} Adjima Assawapitaksakul,^{4,5} Varote Shotelersuk,^{4,5} Nithiput Tantirukdham,¹ Chaipat Chunharas,⁶ Kanya Suphapeetiporn^{4,5} and Vorasuk Shotelersuk^{4,5}

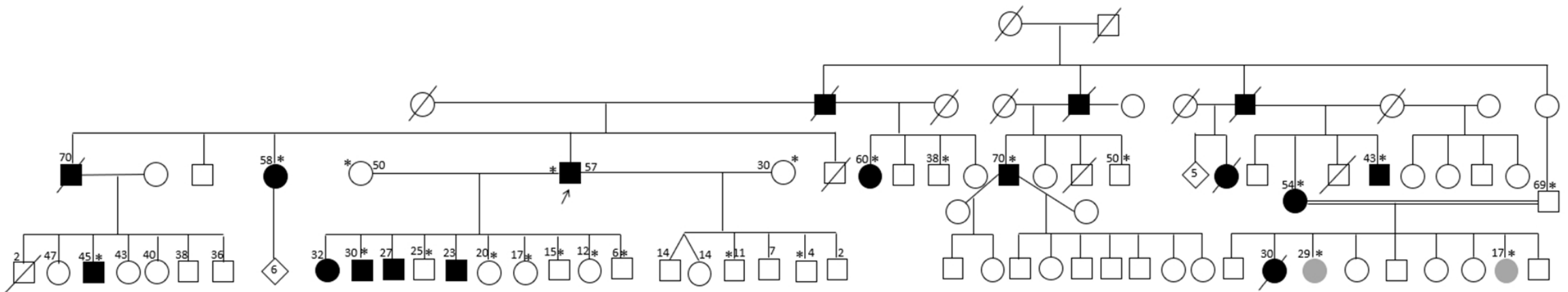
20(TTTTA)



500(TTTTA)-500(TTTC A)



African family (Mali)

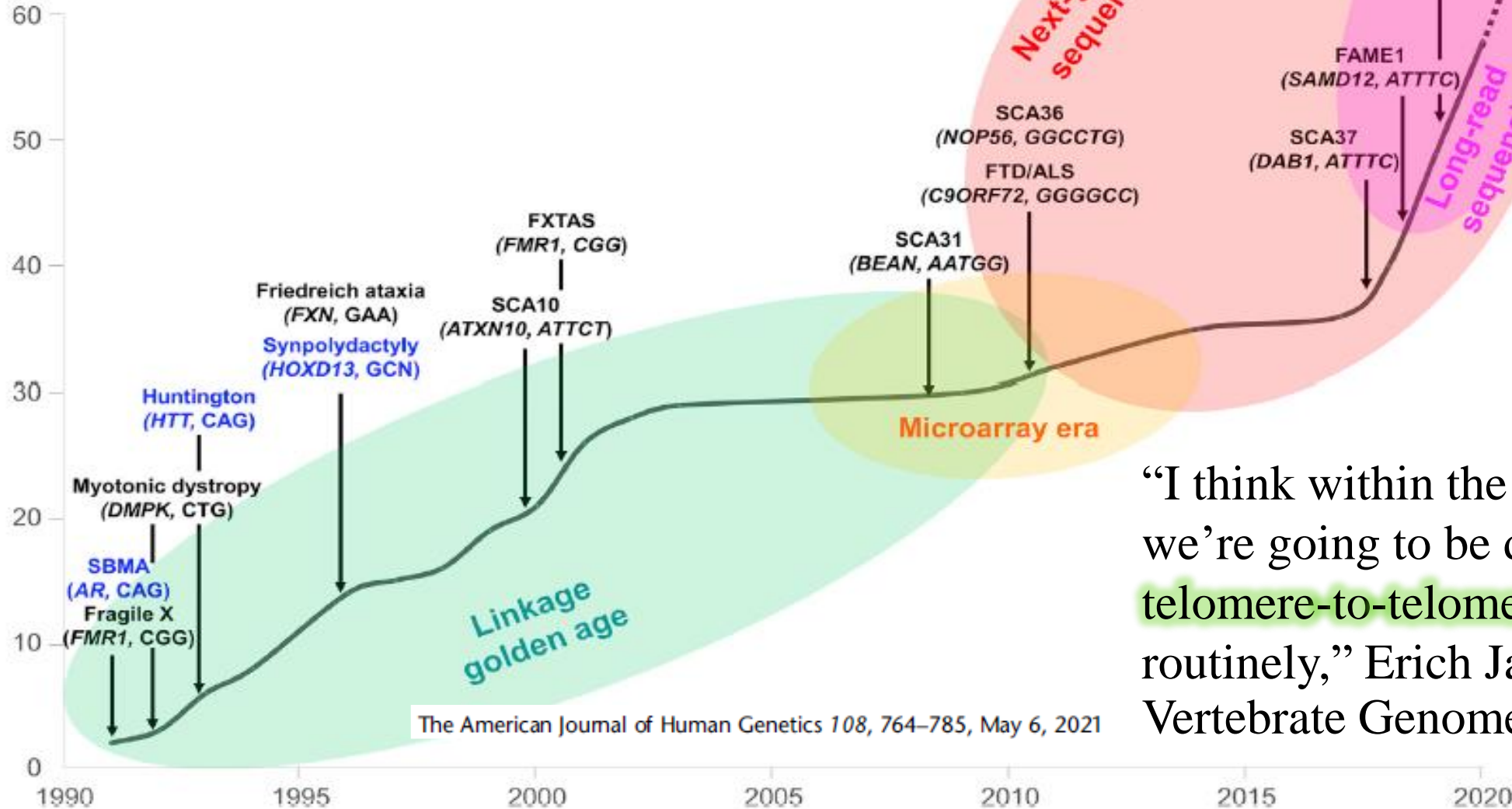


75

Known Unknown Unknown Unknown



Number of identified disorders



The American Journal of Human Genetics 108, 764–785, May 6, 2021

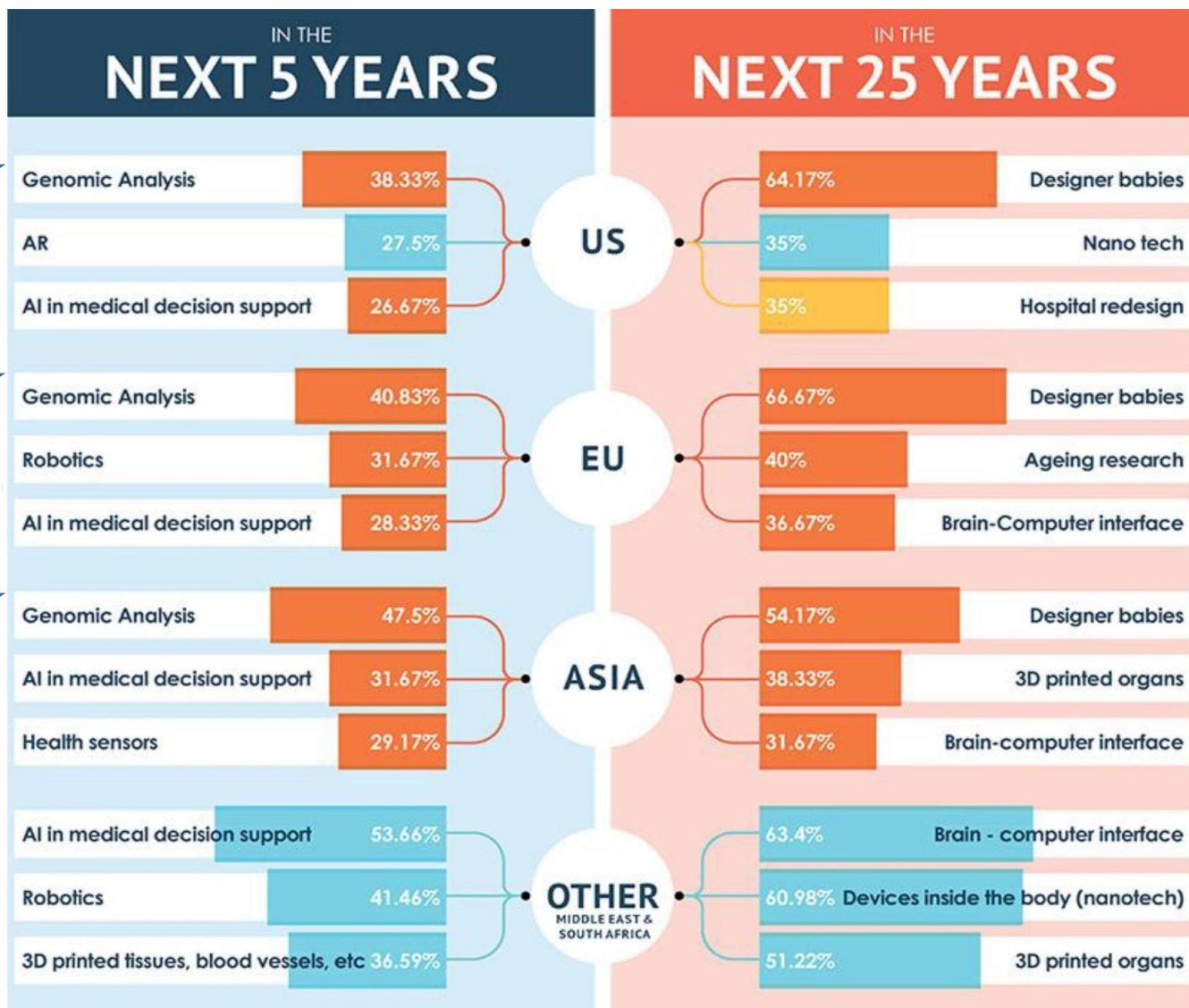
“I think within the next 10 years, we’re going to be doing telomere-to-telomere genomes routinely,” Erich Jarvis, chair of the Vertebrate Genomes Project

Read

Understand

Write

Target



3 Bbp Genome:
5 Mbp different

What are the impacts of this genetic variant?

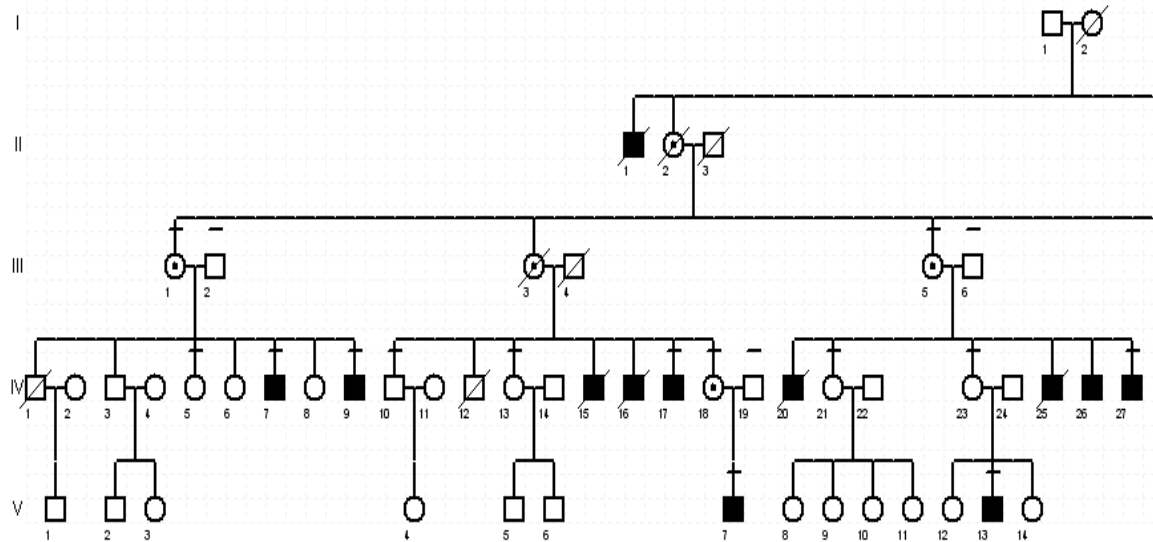
Combined variants?

Non-coding?

Structural variants, CNV?

<https://thefutureishere.economist.com/healthcare/>

X-linked osteogenesis imperfecta



nature COMMUNICATIONS

ARTICLE
 Received 1 Dec 2015 | Accepted 12 May 2016 | Published 6 Jul 2016
 DOI: 10.1038/ncomms17920 OPEN

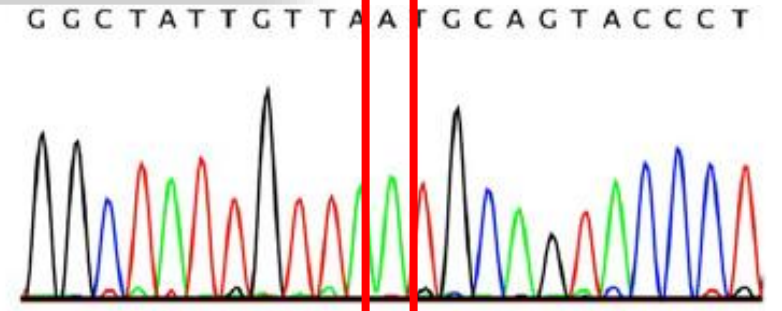
MBTPS2 mutations cause defective regulated intramembrane proteolysis in X-linked osteogenesis imperfecta

Uschi Lindert^{1*}, Wayne A. Cabral^{2*}, Surasawadee Ausavarat^{3,4,*}, Siraprapa Tongkobpetch^{3,4}, Katja Ludin⁵, Aileen M. Barnes², Patra Yeetong^{3,4,†}, Maryann Weis⁶, Birgit Krabichler⁷, Chalurmon Srichomthong^{3,4}, Elena N. Makareva⁸, Andreas R. Janecke^{7,9}, Sergey Leikin⁸, Benno Röthlisberger⁵, Marianne Rohrbach¹, Ingo Kennerknecht¹⁰, David R. Eyre⁶, Kanya Suphapeetiporn^{3,4,*}, Cecilia Giunta¹¹, Joan C. Marin^{2,*} & Vorasuk Shotelersuk^{3,4}

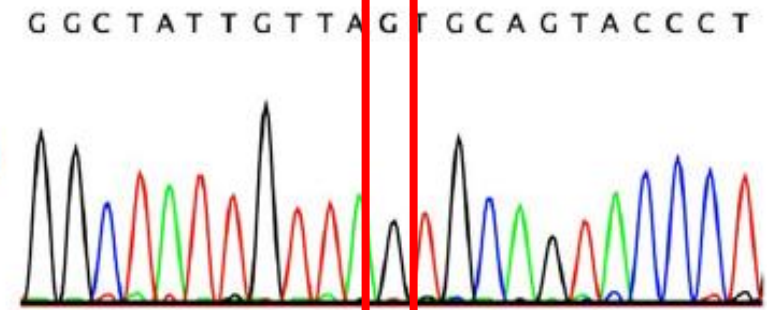


5 Yr

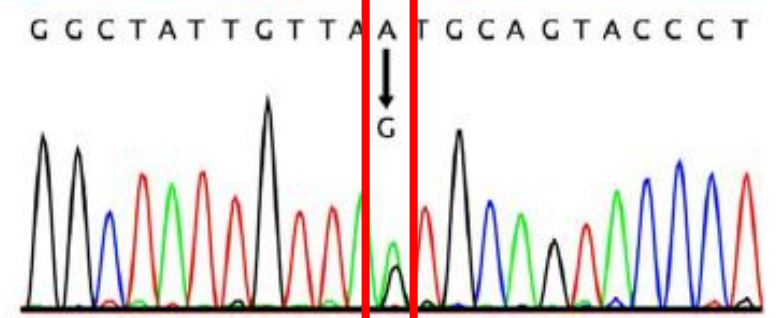
Father



P1/I (N459S)



Mother



A roadmap to increase diversity in genomic studies

NATURE MEDICINE | VOL 28 | FEBRUARY 2022

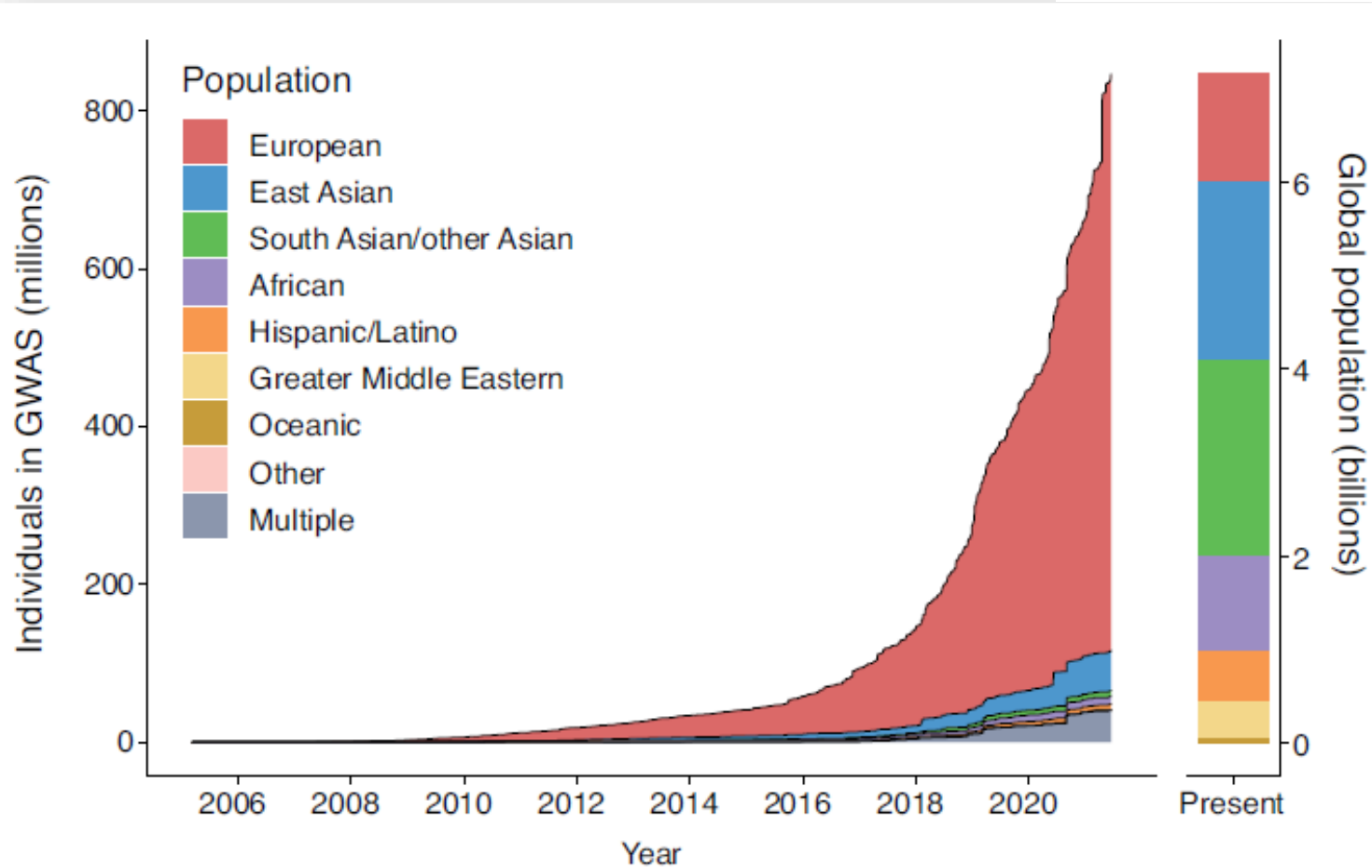


Fig. 1 | The proportion of samples from individuals cumulatively reported by the GWAS Catalog¹ as of 8 July 2021.



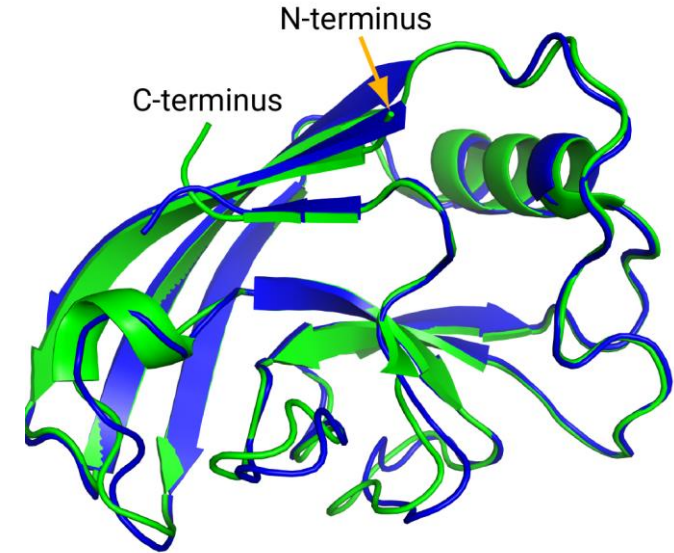
The Thai reference exome (T-REx) variant database

Vorasuk Shotelersuk^{1,2}  | Duangdao Wichadakul³ | Chumpol Ngamphiw⁴ |
Chalurmpon Srichomthong^{1,2} | Chureerat Phokaew^{1,2} | Alisa Wilantho⁴ |
Sujiraporn Pakchuen⁴ | Vorthunju Nakhonsri^{4,5} | Philip James Shaw⁶ |
Rujipat Wasitthankasem⁴ | Jittima Piriyaongsa⁴ | Pongsakorn Wangkumhang⁴ |
Adjima Assawapitaksakul^{1,2} | Wanna Chetruengchai^{1,2} | Keswadee Lapphra⁷ |
Athiphat Khuninthong⁴ | Pattarapong Makarawate⁸ | Kanya Suphapeetiporn^{1,2}  |
Surakameth Mahasirimongkol⁹ | Nusara Satproedprai⁹  | Thantrira Porntaveetus¹⁰ |
Prapaporn Pisitkun¹¹ | Verayuth Praphanphoj¹² | Piranit Kantaputra¹³  |
Wichitra Tassaneeyakul¹⁴ | Sissades Tongsimma⁴

Meaning (effect, impact)

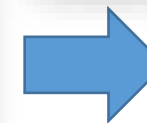
Structure dictates function.

- AlphaFold2 (predicting 3D structure from its aa sequence)
Nature July 2021; doi10.1038
- Cryo EM (atomic resolution) (Mahidol U)

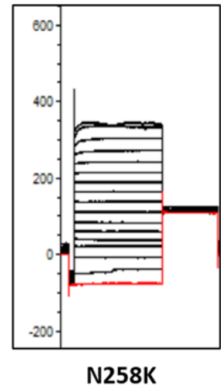
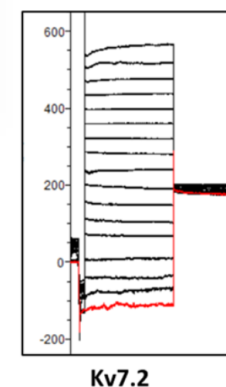


Function:

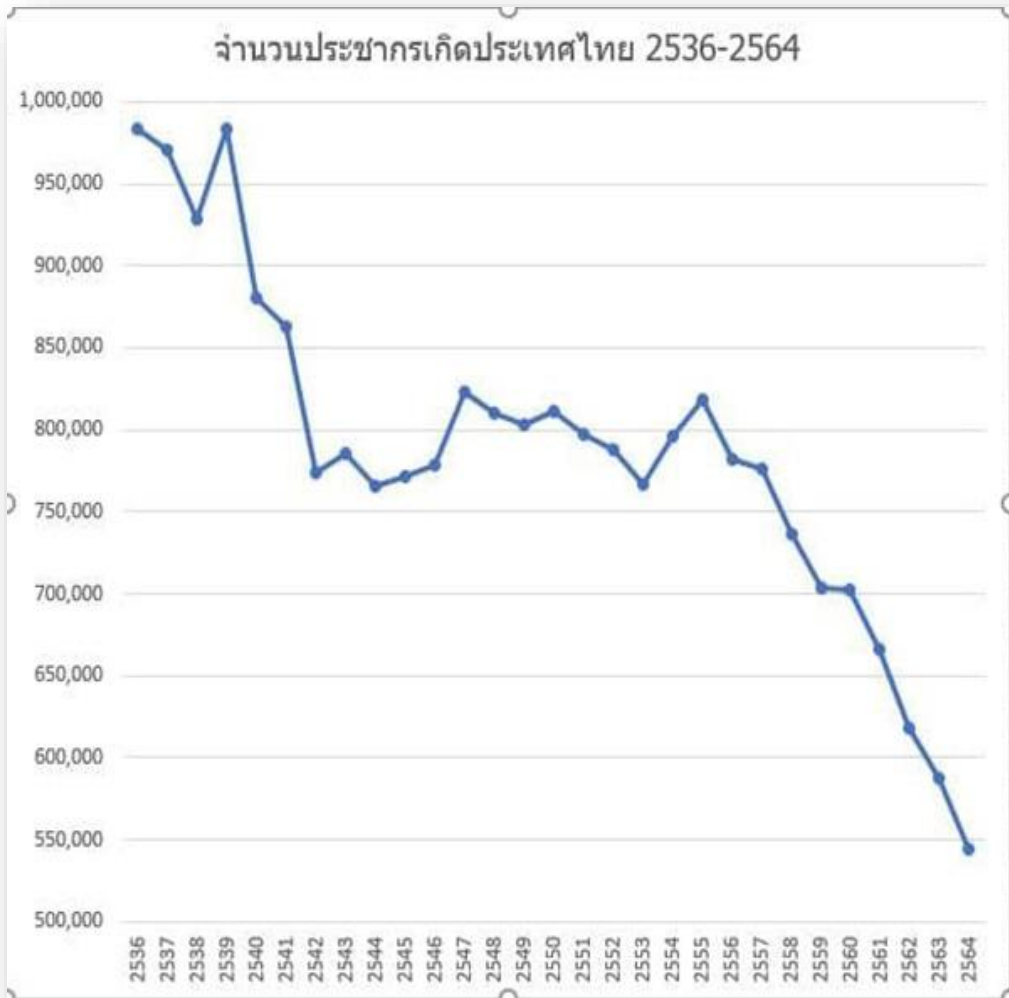
- expression level
- patch clamp, enzyme assay, etc
- animal model



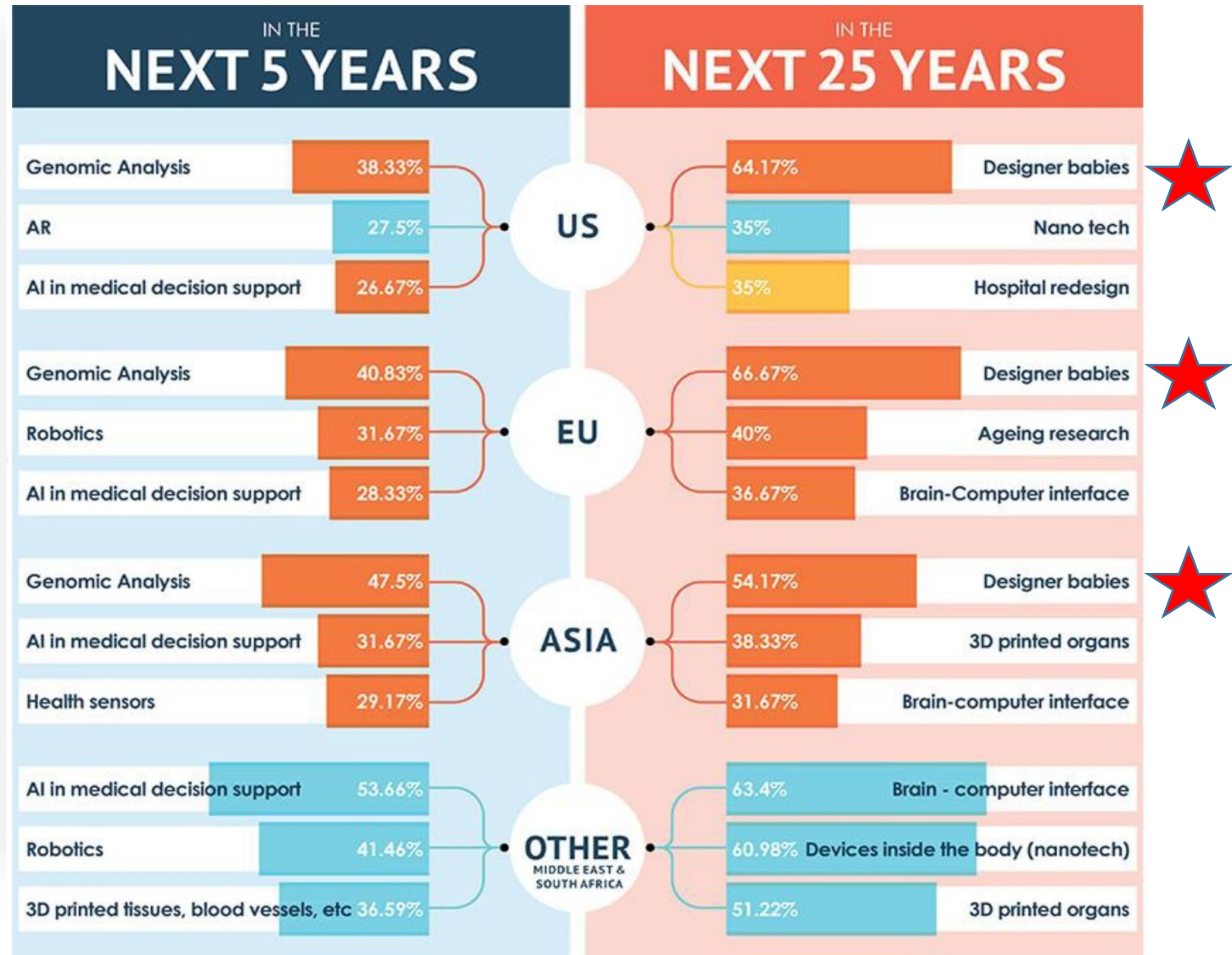
2 Yr



Designer babies: Germline genome editing (technical VS ELSI)



ดร.ธัญวัต สมใจทวีพร สถาบันการจัดการปัญญาภิวัฒน์



<https://thefutureishere.economist.com/healthcare/>

Exome sequencing as the first-tier investigation

SHORT REPORT

11 hospitals

CLINICAL GENETICS WILEY

Clinical Genetics. 2021;100:100-105.

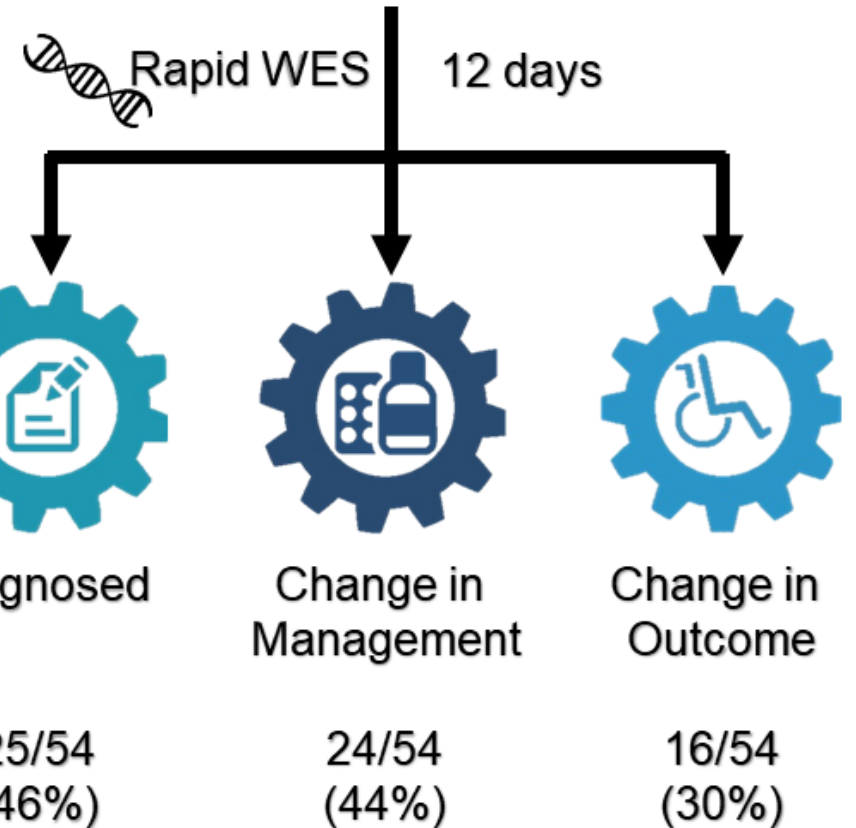
Rapid exome sequencing as the first-tier investigation for diagnosis of acutely and severely ill children and adults in Thailand

Wuttichart Kamolvisit^{1,2} | Prasit Phowthongkum^{2,3} | Ponghatai Boonsimma^{1,2} |
Chulaluck Kuptanon^{4,5} | Kitiwan Rojnueangnit⁶ |
Duangrurdee Wattanasirichaigoon⁷  | Mongkol Chanvanichtrakool⁸ |
Chutima Phuaksaman⁹ | Pattara Wiromrat¹⁰ | Chalurmpon Srichomthong^{1,2} |
Chupong Ittiwut^{1,2} | Chureerat Phokaew^{1,2} | Rungnapa Ittiwut^{1,2} |
Adjima Assawapitaksakul^{1,2} | Wanna Chetruengchai^{1,2} | Ayalida Buasong^{1,2} |
Kanya Suphapeetiporn^{1,2} | Vorasuk Shotelersuk^{1,2} 

1st in LMIC, in adults, as a network

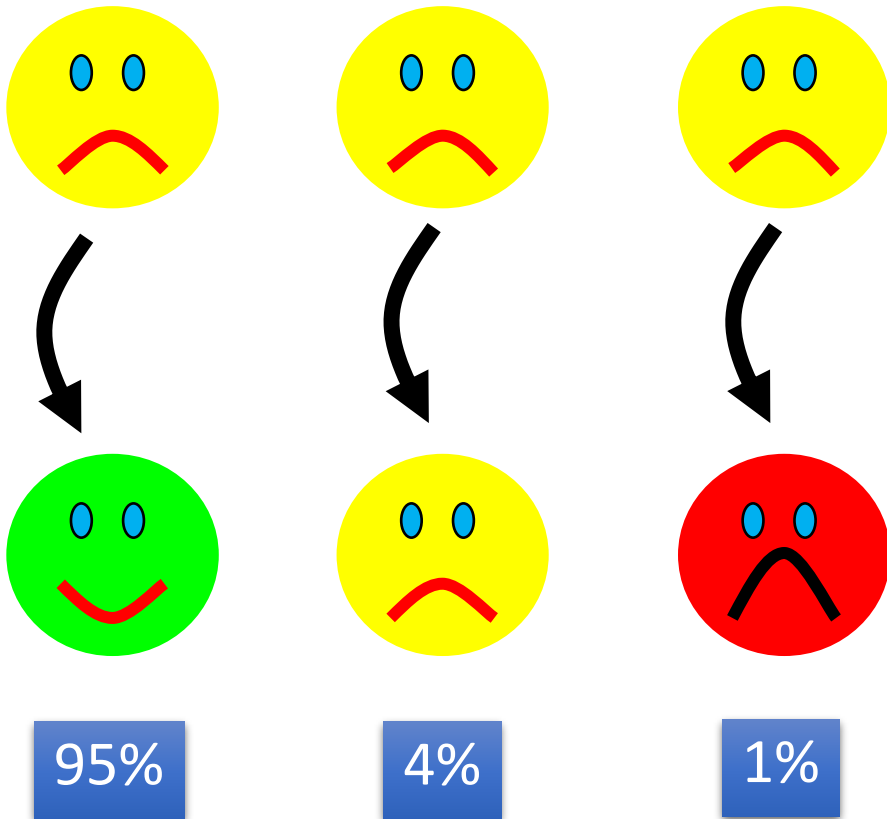


[54 critically ill Thai patients]



Pharmacogenomics

Diversity -> Uniqueness

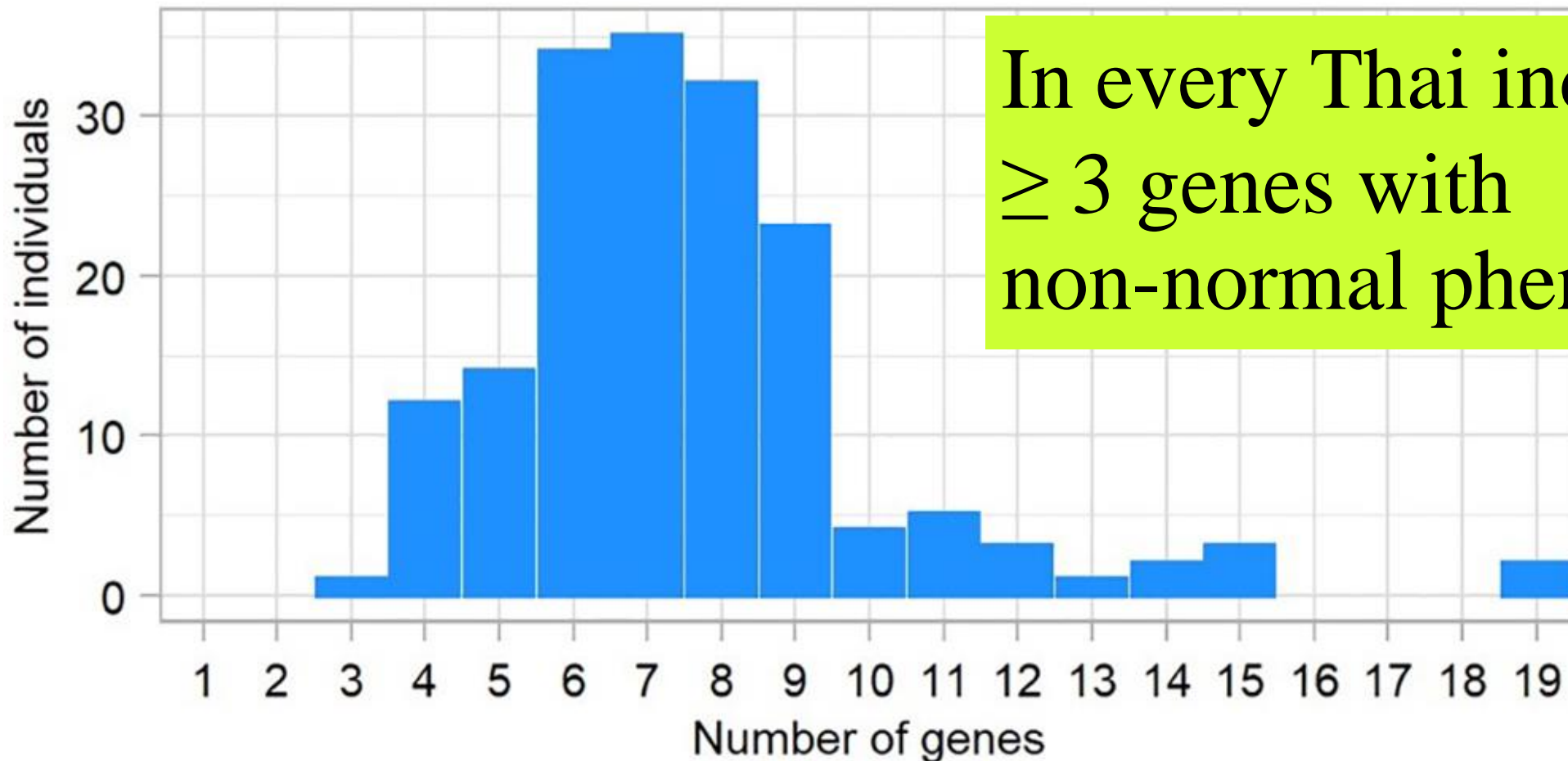


Genotypic and phenotypic landscapes of 51 pharmacogenes derived from whole-genome sequencing in a Thai population

Natnicha Wankaew¹, Pajaree Chariyavilaskul^{2,3}, Monpat Chamnanphon^{2,4}, Adjima Assawapitaksakul^{5,6}, Wanna Chetruengchai^{5,6}, Monnat Pongpanich^{7,8*}, Vorasuk Shotelersuk^{5,6}



PLOS One. Feb 2022



In every Thai individual, ≥ 3 genes with non-normal phenotype.

Read

Understand

Write

Target

Scenarios

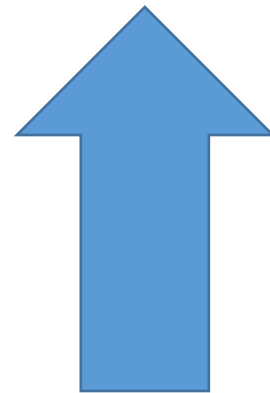
1. Couples
2. Fetus
3. Newborn
4. Child to Elderly

Genetic Diseases,
Pharmacogenomics,
Cancer
Actionable NCDs

NB Screening → NB Sequencing

Personalized Medicine

Read
(+ **Understand**)



Write
(+ **Target**)

Population-Average Medicine

Read

Understand

Write

Target

Diagnosis

Treatment

Principles

1. Pathogenesis-based
2. Genome editing

Rx: Pathogenesis-based: Great, but time consuming

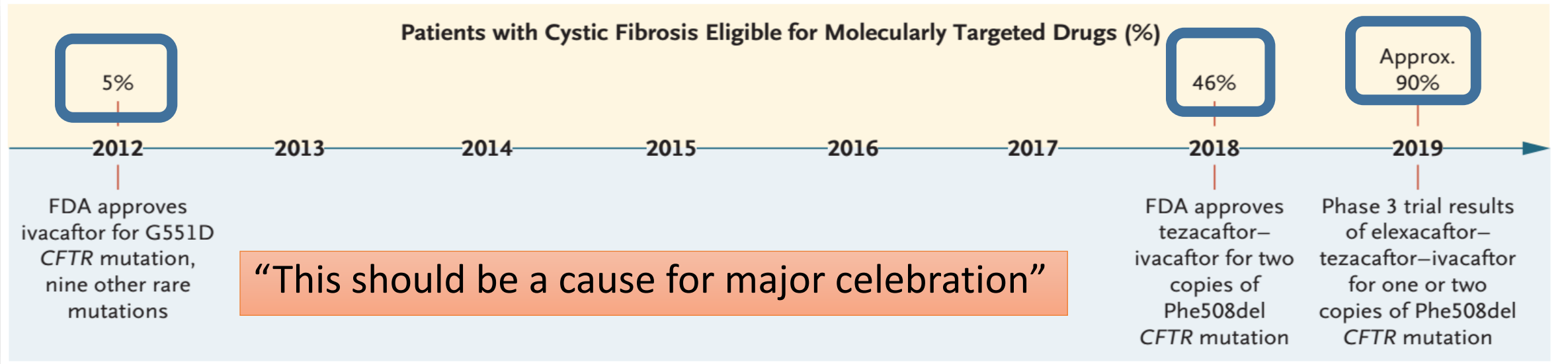


October 31, 2019

Realizing the Dream of Molecularly Targeted Therapies for Cystic Fibrosis

Francis S. Collins, M.D., Ph.D.

- 1989: The gene for CF was found.
- The first 10 years: deep understanding of CFTR function.
- 1 -> 2 -> 3 drugs (correctors + potentiators)



Read

Understand

Write

Target

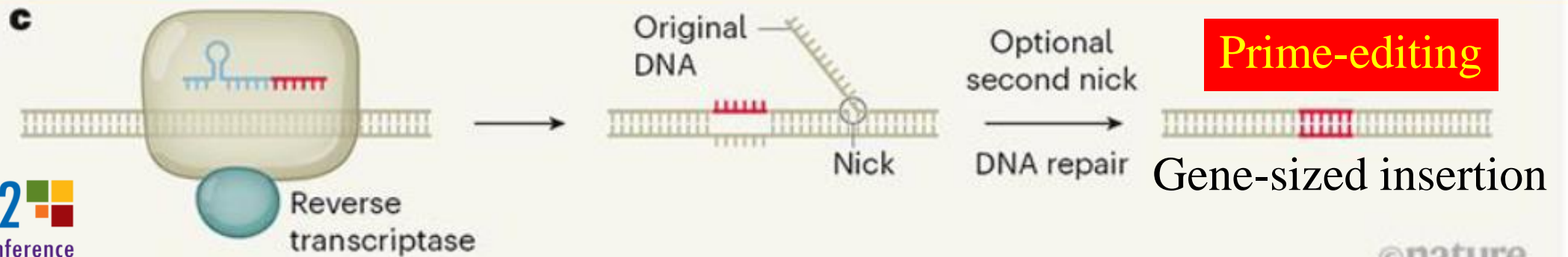
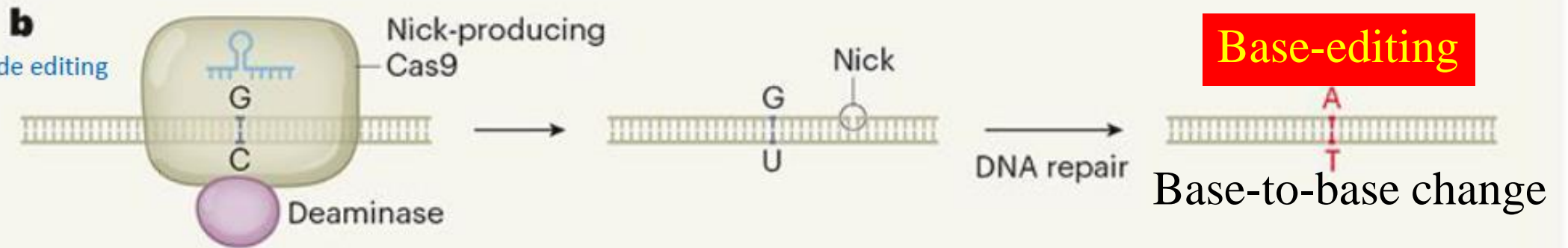
Tools: Precise genome manipulation

Destroy



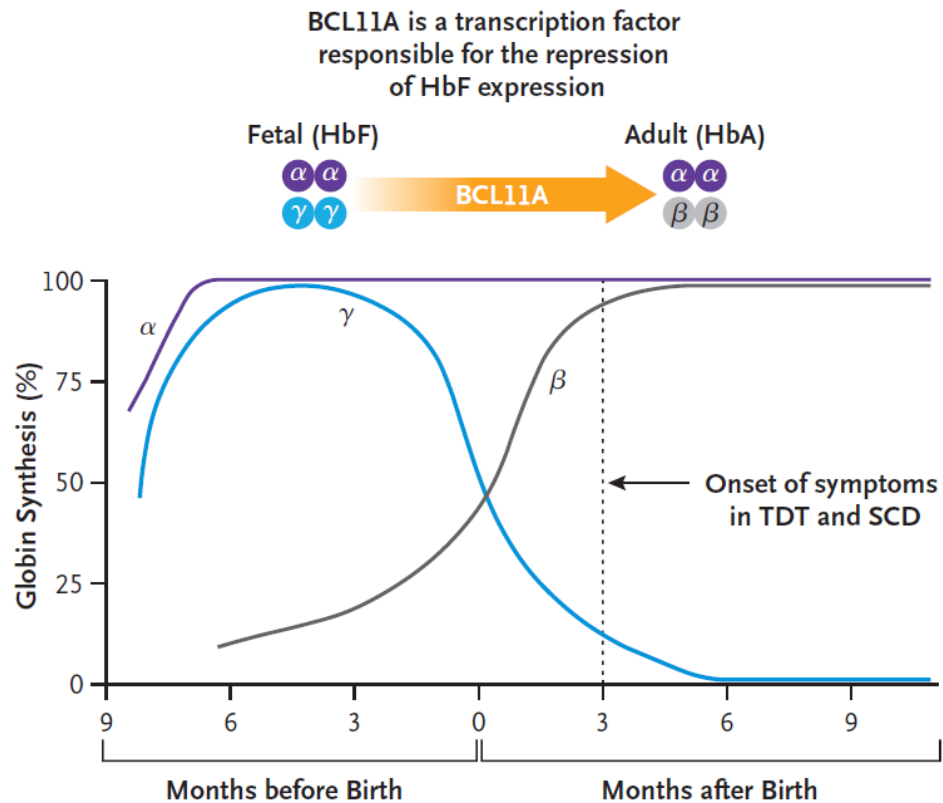
Repair

Single nucleotide editing

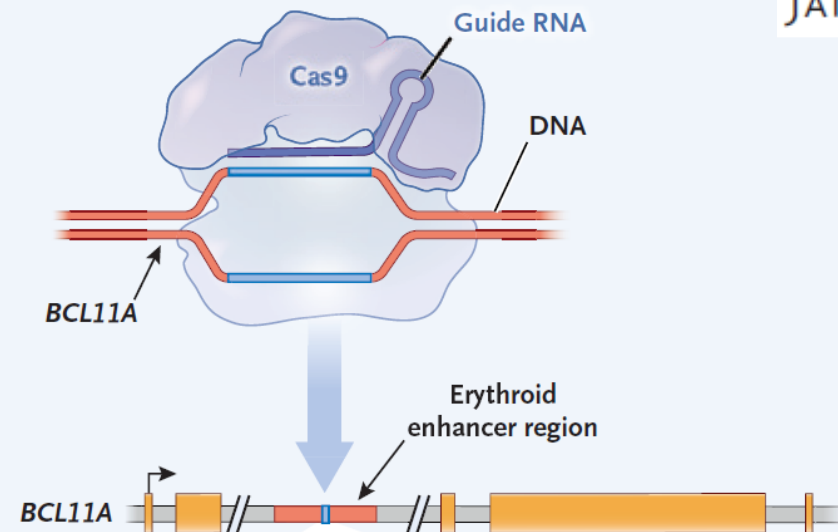


CRISPR-Cas9: destroy > repair

A Transition from Fetal to Adult Hemoglobin



B Targeting of Editing Site



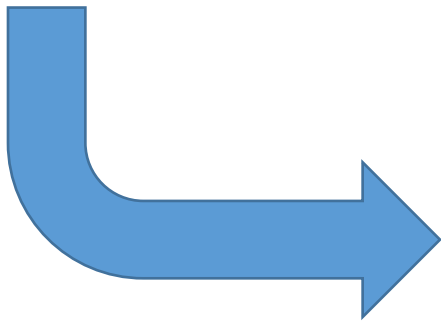
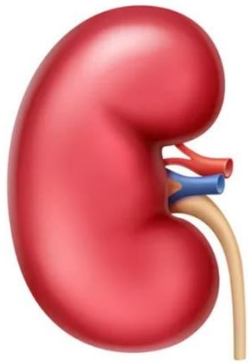
N ENGL J MED 384;3
 JANUARY 21, 2021

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β -Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace,

Xenotransplantation

Sep 2021:
genetically modified pig kidney
to a deceased recipient



World first pig heart transplant into a human

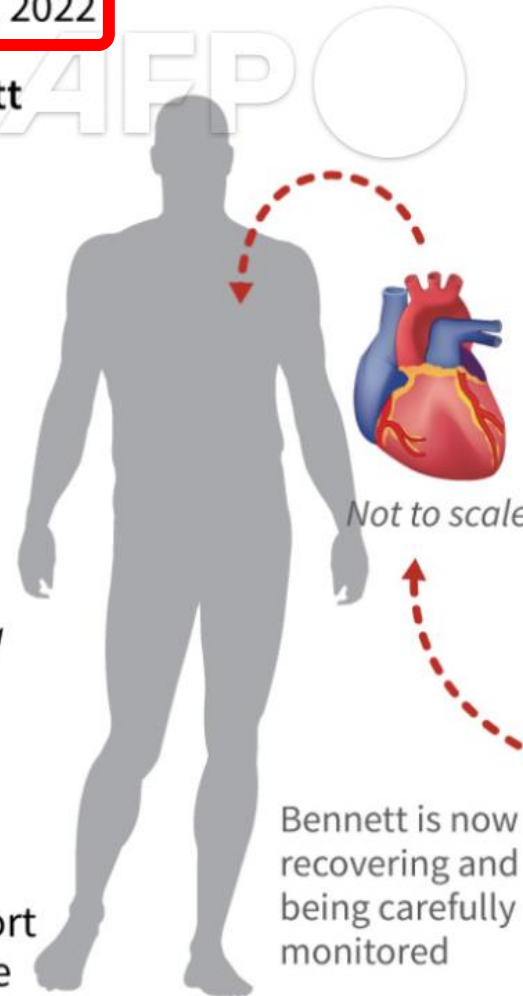
“Historic” procedure at the University of Maryland Medical School
on **January 7, 2022**

David Bennett
57-years-old

Ineligible
for
human
transplant

*Decision
commonly
taken when
patient has
poor underlying
health*

Use of a pig
heart was
considered a
last-ditch effort
to save his life



Bennett is now
recovering and
being carefully
monitored

Genetically modified pig
10 genes edited

- ▶ 3 genes that would have led to rejection by humans knocked out
- ▶ 1 gene switched off to prevent excessive growth
- ▶ 6 genes added to allow human acceptance

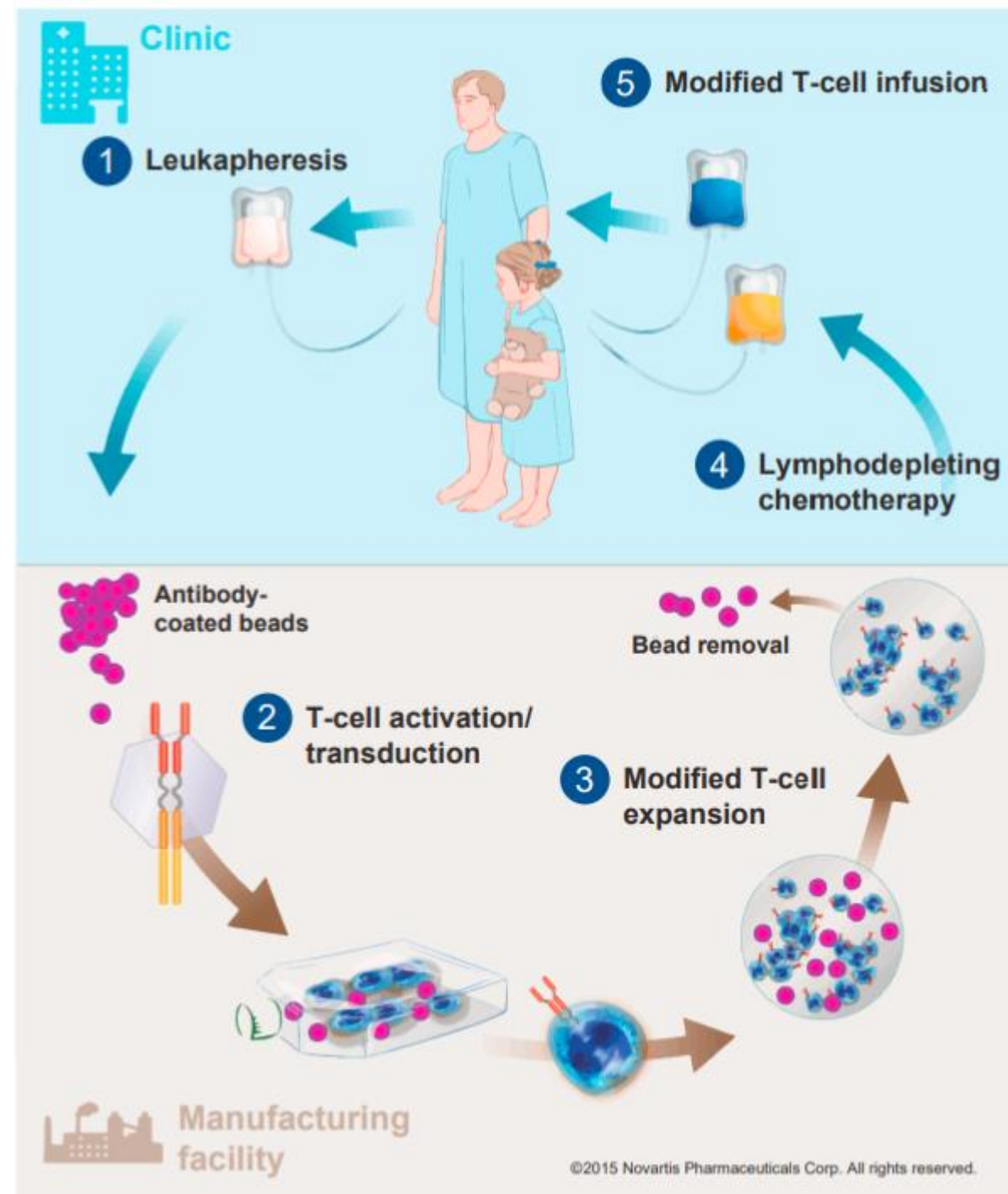
CRISPR-Cas9

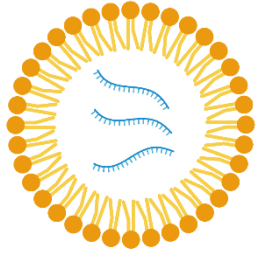
*Editing by Virginia-based
biotech firm Revivicor*

Source: University of Maryland School of Medicine

How to get the tools to the right cells?

- *In vivo*:
accessible e.g. retina, liver
- *Ex vivo* (Hematopoietic stem cells CD34+, CAR-T cells, etc)

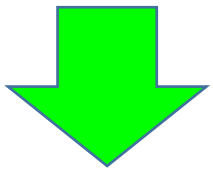




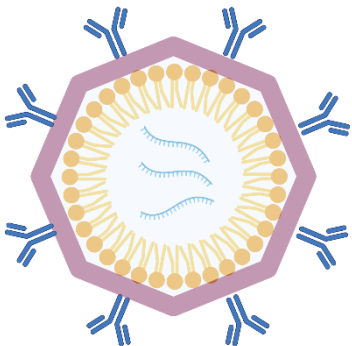
mRNA vaccine
(short-lived)
(GMP production: the same)



Vaccine (Weissman)



Targeted gene Rx
1. Changing compositions of LNP
2. Cell-specific antibodies



eg CAR-T cells (*in vivo*):
target the T cells



mRNA (Kariko)



LNP (Cullis)

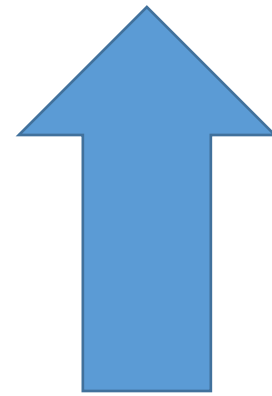
Personalized Medicine

To EZY

8B99+

(Read + Understand)

**Newborn Sequencing
+ annual analysis
(preventive medicine)**

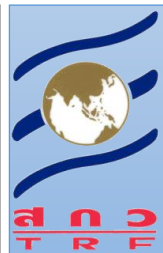


(Write + Target)

**Tissue-specific
gene therapy +
Xenotransplant**

Population-Average Medicine

From KM/GTP



Center of Excellence for Medical Genomics, MDCU
Excellence Center for Genomics and Precision Medicine, KCMH





สวทช.
NSTDA

Bioeconomy
Circular economy
Green economy

ขอบคุณครับ

