HUMAN GENOMICS

PALLE DUUN ROHDE

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Genomic Medicine

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THE COURSE TEAM

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Ass Prof
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THE AIM
OF THIS COURSE

The course provides students with a comprehensive understanding of **human genetics and genomics**, emphasizing their applications in **personalized medicine**.

LEARNING OBJECTIVES

KNOWLEDGE

- Explain organisation of the human genome
- Explain different types of genetic variation
- Understand the relationship between genotype and phenotype
- Understand which forces affect alleles in a population
- Explain how genetic variation regulates and affect disease with monogenic and polygenic aetiology
- Describe genetic and proteomic biomarkers in diagnostics, biomarker discovery and validation in a personalised medicine context

SKILLS

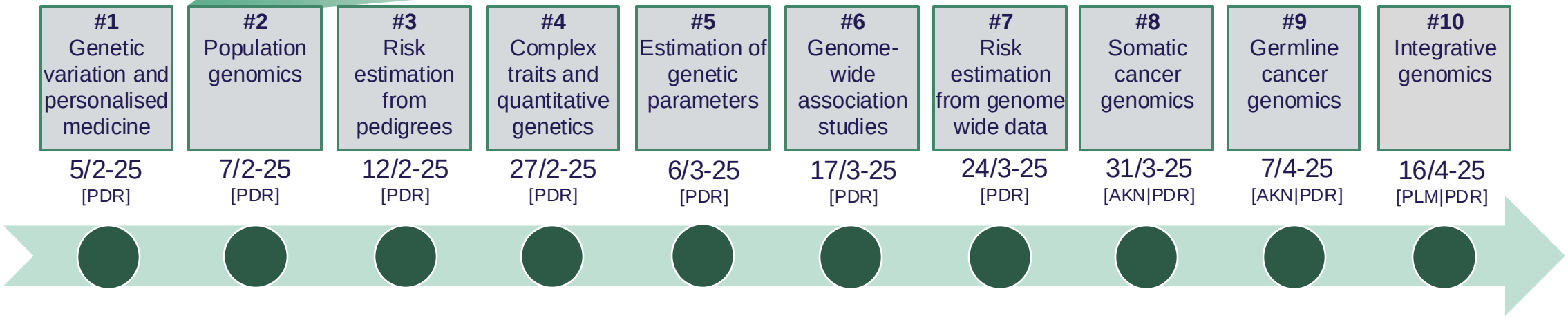
- Apply advanced molecular methods in genetics
- Evaluate a choice of method or technology to detect and analyse genetic variation
- Choose appropriate databases, algorithms, statistics and parameters in a bioinformatics analysis
- Use bioinformatical and analytical strategies to solve problems in personalised medicine
- Understand the genetic architecture of monogenic and complex traits

COMPETENCES

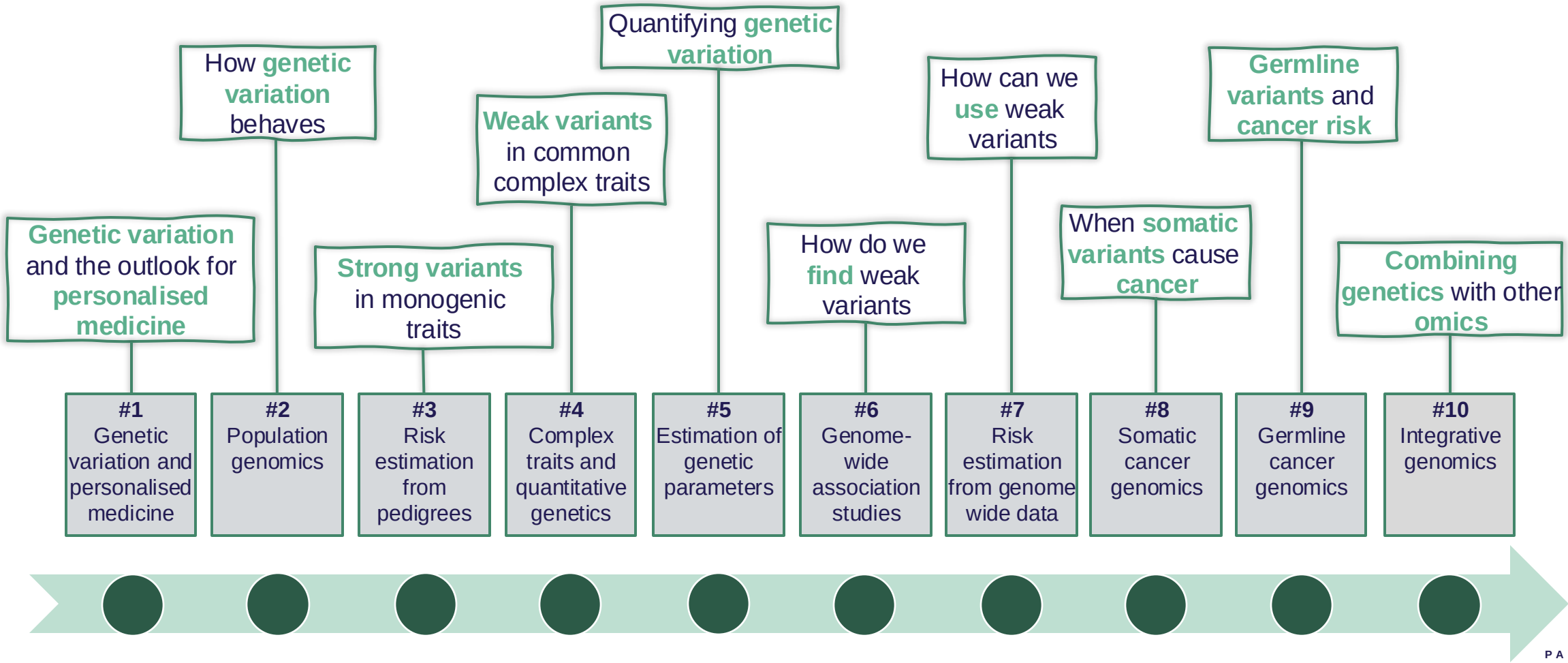
- Assess and evaluate the suitable technologies and methods for detection of genetic variants in polygenic vs monogenic diseases
- Perform simple genetic analyses
- Evaluation of scientific articles at the highest international level

COURSE PLAN

08:15 – 08:30	Recap
08:30 – 08:50	Lecture 1 [*Introduction to population genetics*
08:50 – 09:30	Break + Exercises 1 [*1-4*]
09:30 – 09:50	Lecture 2 [*Hardy-Weinberg*]
09:50 – 10:30	Break + Exercises 2 [5-7]
10:30 – 10:50	Lecture 3 [*Modulation of genetic variation*]
10:50 – 11:45	Break + Exercises 3 [8 + *computer exercise*]
11:45 – 12:00	Padlet evaluation



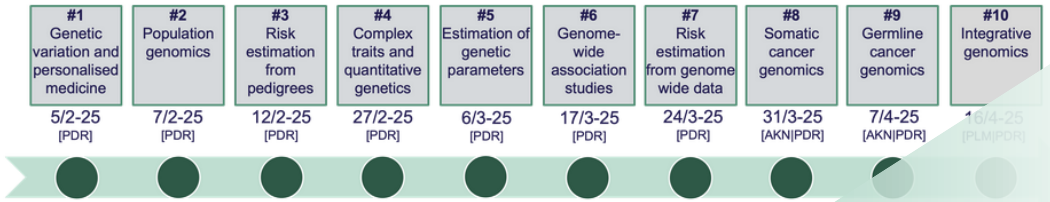
WHY THIS COURSE PLAN



COURSE MATERIAL IN MOODLE

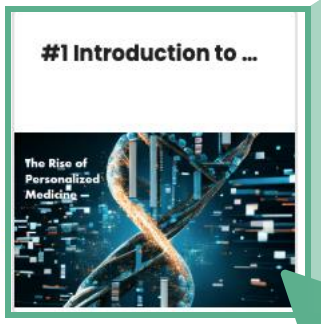
Welcome to the new module, ***Human Genomics.*** This module aims to provide you with insight into what shapes the human phenome, and how genetics and genomics can be applied to advance our understanding of human traits, health, and disease, including their application in personalized medicine.

Below is a brief overview of the module's content:



By the end of this module, you will have a comprehensive understanding of human genomics and its transformative role in biology and medicine. This course is designed to equip you with both theoretical knowledge and practical skills, preparing you for further research or careers in genomics-related fields.

All the material needed for this module will be made available for you below with external links for computer exercises. We will use the programming software R for many of the exercises, thus, please download R (HERE) and R studio(AND HERE) before the first session.



Preparation prior to the lecture and exercises

1) Review the following figures in **Medical Genetics (sixth edition)** by Jorde, Carey and Bamshad. The book is available via AUB. Use this link, and log in under "*Log in via your institution*", and search after Aalborg University.

You should review them to an extent where you are able to explain the figures. All figures are part of the curriculum in the "*Advanced Biochemistry and Genetics*" course at 4th semester and represents ***essential terms*** that we will be building upon in this course.

- Figure 2-20, page 21 (mitosis)
- Figure 2-21, page 23 (meiosis, production of gametes)
- Figure 2-22, page 24 (crossover) + Figure 8.2, page 147
- Figure 3-3, page 27 (missense and nonsense mutations)
- Figure 3-4, page 27 (frameshift mutations)
- Figure 3-5, page 28 (splice site mutation)
- Figure 3-6, page 29 (GOF and LOF)
- Figure 3-10, page 32 (compound heterozygous)
- Figure 4-3, page 58 (pedigree symbols)
- Figure 4-6 page 59 (autosomal dominant disorder)
- Figure 4-8 page 60 (autosomal recessive disorder)
- Figure 5-8 page 82 (X-linked recessive trait)
- Figure 6-8 page 103 (meiotic nondisjunction)

2) Read "NNF white paper on precision medicine in cardiometabolic disease" [download here], and the scientific version published in 2023 in Lancet Diabetes and Endocrinology [download here].

3) Download (here) **and install R-studio** (and R here)

Learning outcome

After session 1 (reading the curriculum, participating in the lecture and the following exercises) you are expected to:

- Explain organisation of the human genome.
- Explain different types of genetic variation.
- Understand the relationship between genotype and phenotype

Exercises in class

We will do two rounds of exercises in class. You do not have to look at the exercises beforehand. You will work in groups to solve the exercises. We will go through them afterwards in class. The exercises are available at **this link** [*will be available before the session starts*].

Lecture notes

Lecture notes are available at **this link** [*will be available before the session starts*].

THE EXAM

- Individual, oral examination.
- Duration: 20 min including assessment.
- Preparation time: 20 min with aids.
- Internal censor. Course coordinator will be responsible for the exam.
- Grading: Passed/Not passed.
- Re-examination is oral.

WHAT IS GOOD TEACHING?

LETS GET STARTED

INTRODUCTION TO

ILLUSTRATION BY GREG CLARKE

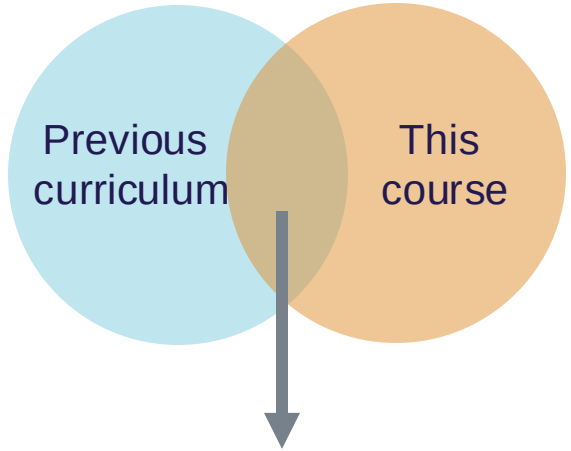
PERSONALISED MEDICINE

4. Semester batchelor curriculum

- The centrale dogma
- Codons and open reading frame
- Genotype, haplotype, locus, allelle
- DNA variants
  - coding, intronic, splice-site
  - synonymous and nonsynonymous
  - missense, frameshift, nonsense, stop-gain, stop-loss
  - GOF and LOF
- Monogenic disease, punnett square
- Pedigree symbols and inheritance patterns
- Penetrance-expressivity
- Ploidy and non-disjunction
- PCR-Array-Exome-Genome sequencing

Where to start ?

Modul: Videregående biokemi og genetik MS (M 4.2)



Refresh key concepts

OUTLINE

08:15 – 08:30	Welcome (15 min)
08:30 – 08:55	Exercises 1 (25 min) [*figure recap*]
08:55 – 09:20	Lecture - *What is personalised medicine?* (25 min)
09:20 – 09.35	Break
09:35 – 10:05	Exercises 2 (30 min) [*1-6*]
10:05 – 10:20	Plenum (15 min) [*solutions*]
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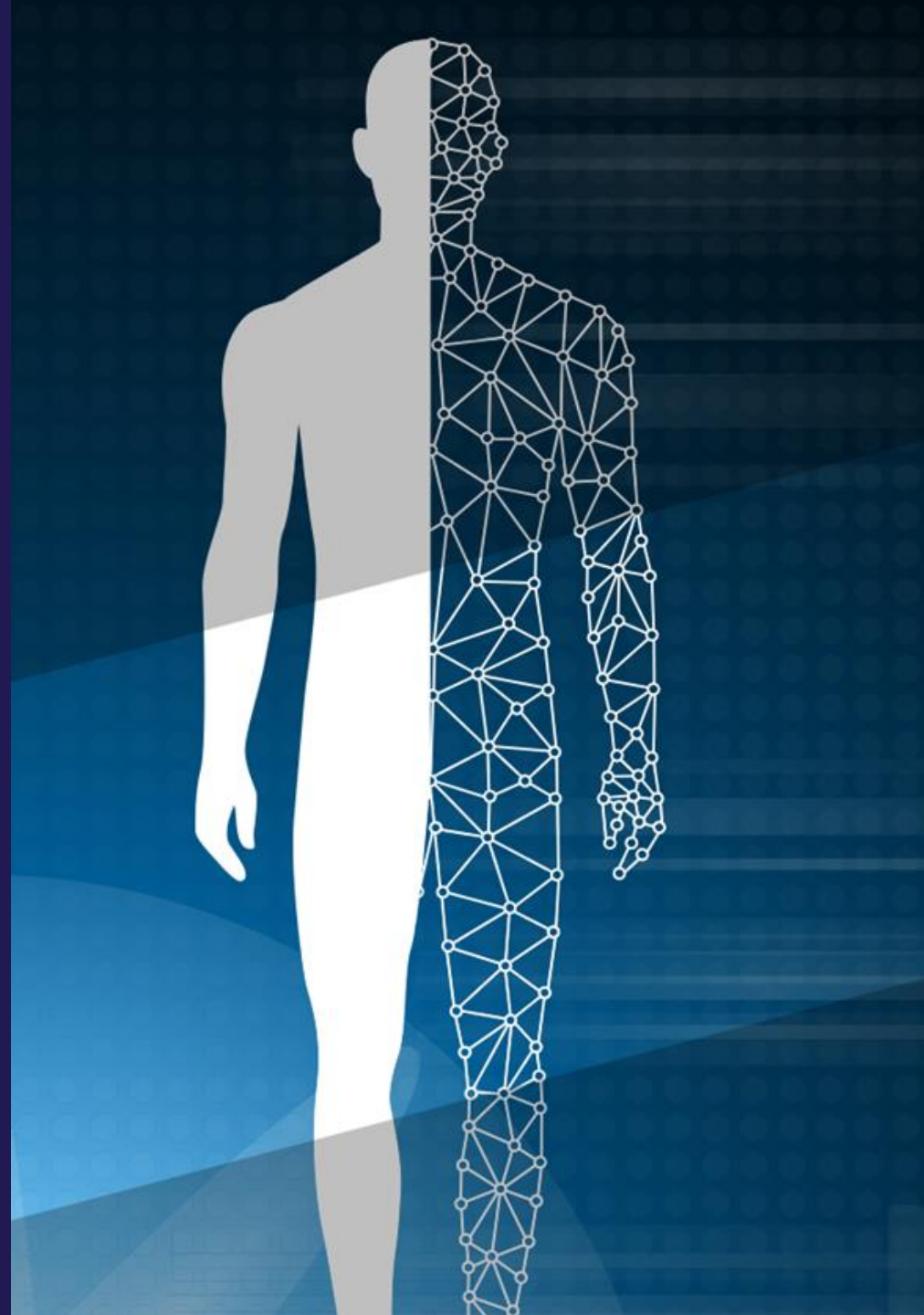
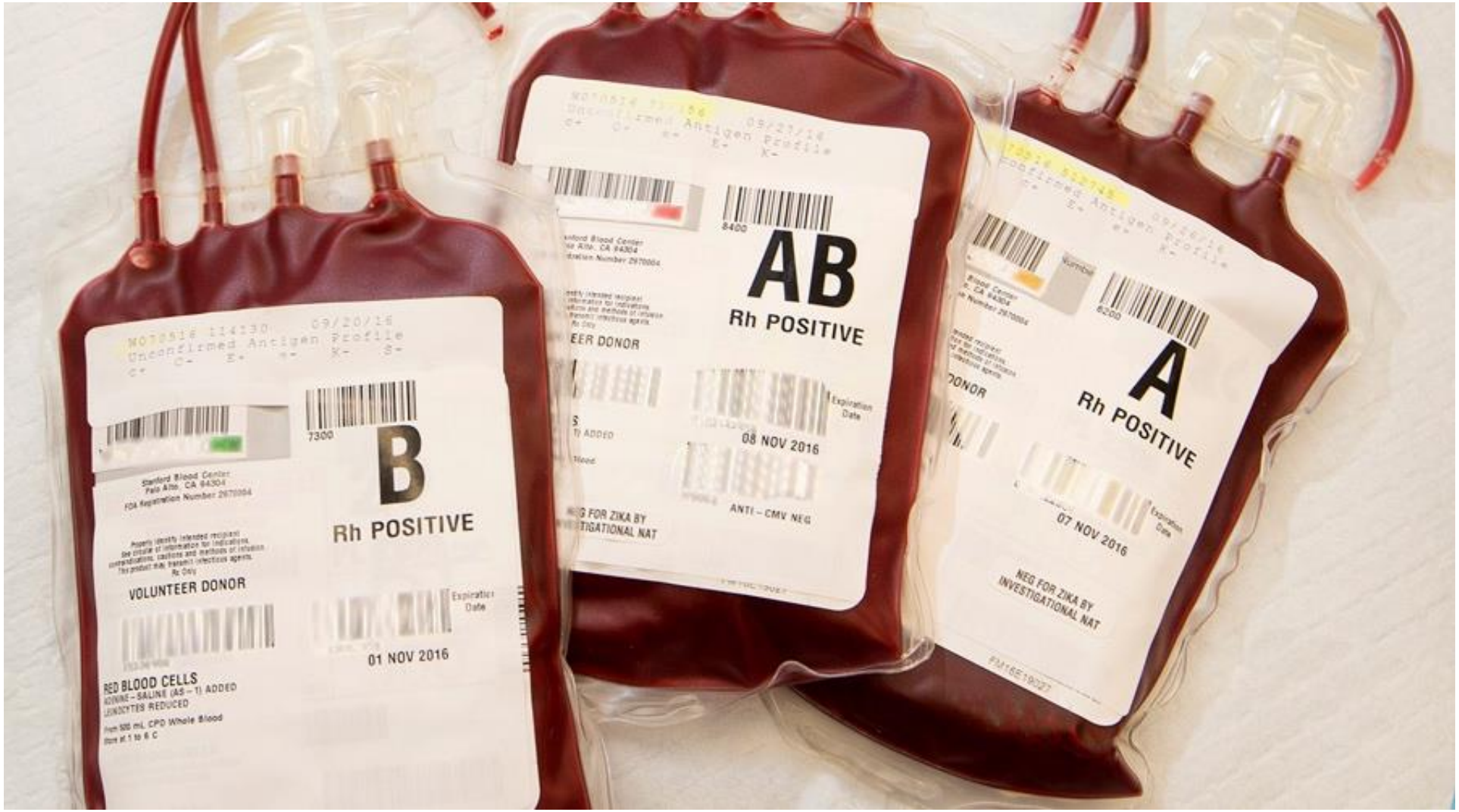
PERSONALISED MEDICINE

- What is Personalised Medicine?
- Why do we need it?
- Why so much focus on genetics?
- How is it presented to society?



What do you think, when someone says *personalised medicine ?*

- **can you think of an example?**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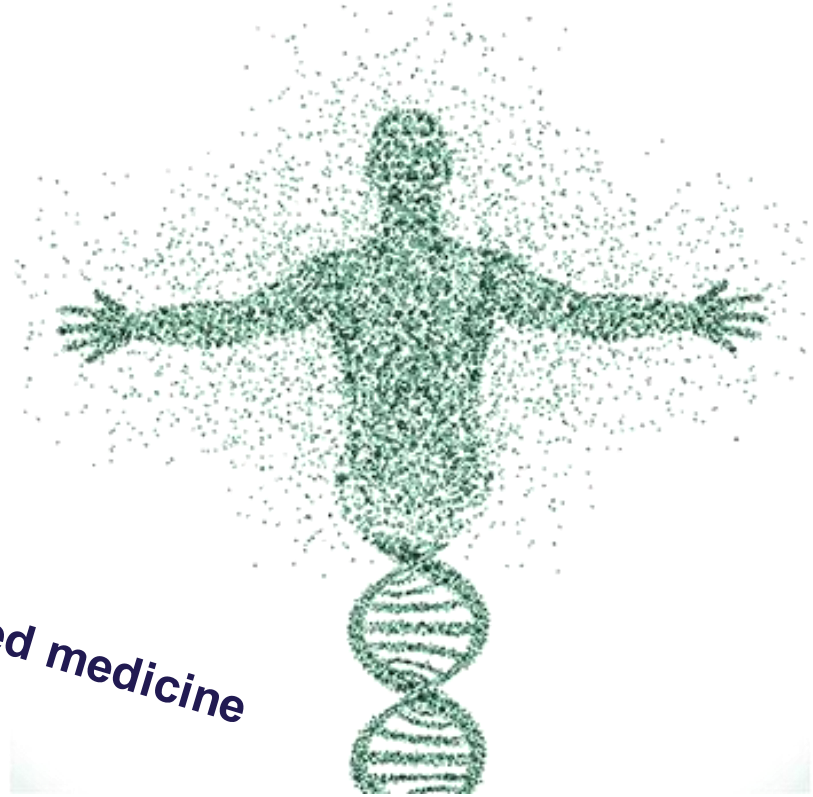
… PM is not new

WHAT IS PERSONALISED MEDICINE?

Evidence based medicine

Personalised medicine

Precision medicine



Genomic medicine

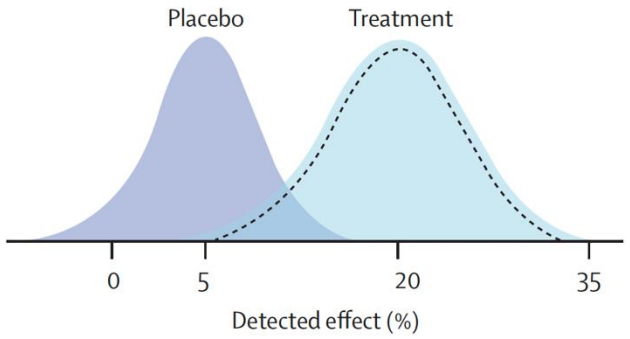
Individualised medicine

IMPLEMENTATION OF PRECISION MEDICINE

EPPOS [evidence-based precision personalised objective subjective]

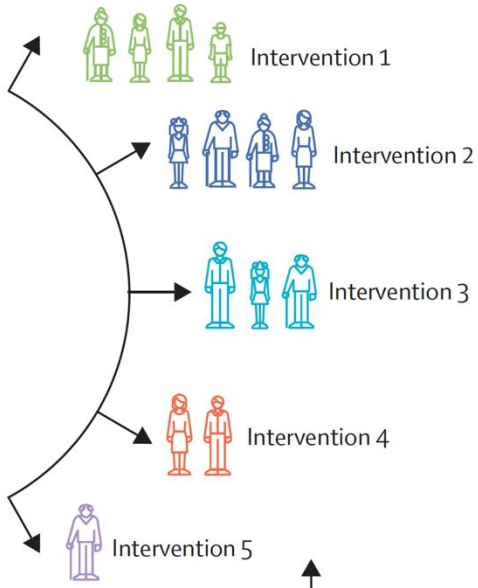
Evidence-based Medicine

(1) Contemporary evidence-based medicine
Estimate average risk or response using epidemiological and clinical trial cohorts



Precision Medicine

(2) Probability scoring and stratification
Maximise response and minimise risk using subclassification

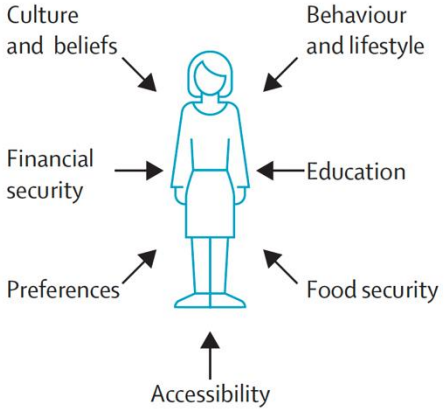


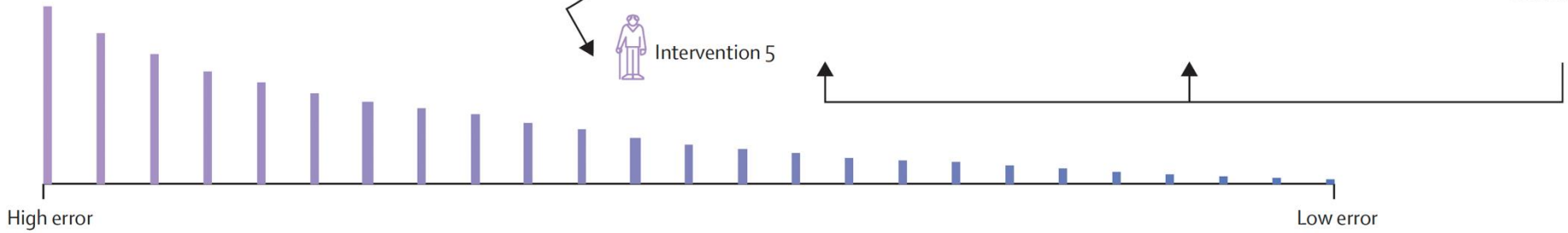
Personalised Medicine

(3) Personalisation (objective)
Monitor response to optimise dose, timing, and delivery

Individualised Medicine

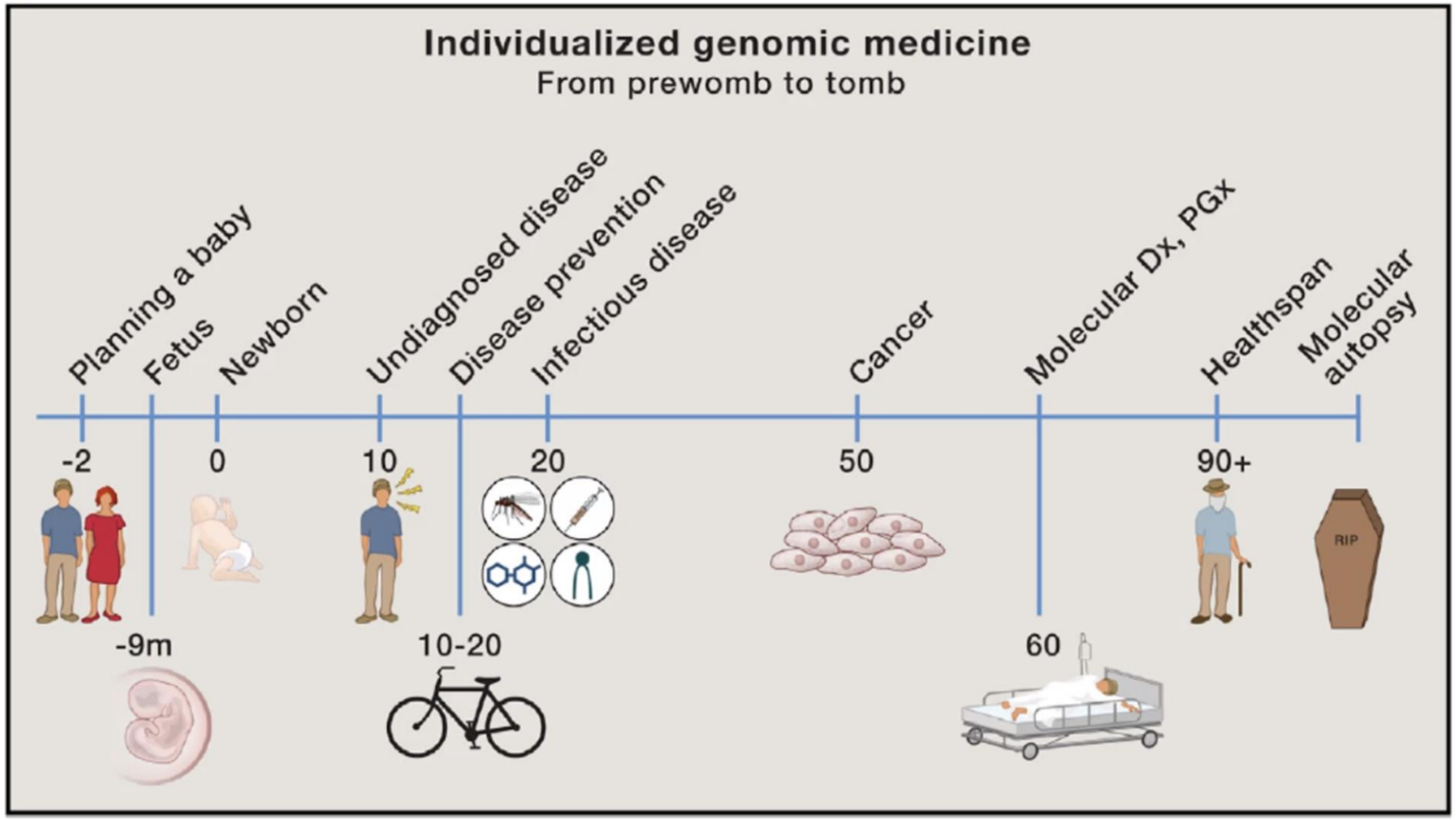
(4) Personalisation (subjective)
Adapt intervention to fit the person's needs, capabilities, and preferences





The Novo Nordisk Foundation, Precision medicine for cardiometabolic disease 2022

Franks et al, 2023, Lancet Diabetes Endocrinol; 11: 822–35



Eric J. Topol. Cell 2014

WHAT IS PERSONALISED MEDICINE?

Tailoring medical decisions and interventions to the individual patient based on genomic data.

Move away from a *one-size-fits-all* policy to customising treatments for each patient.

Diagnostics, prognosis, treatment

WHY PERSONALISED MEDICINE?

Because people are different

→ different disease risk

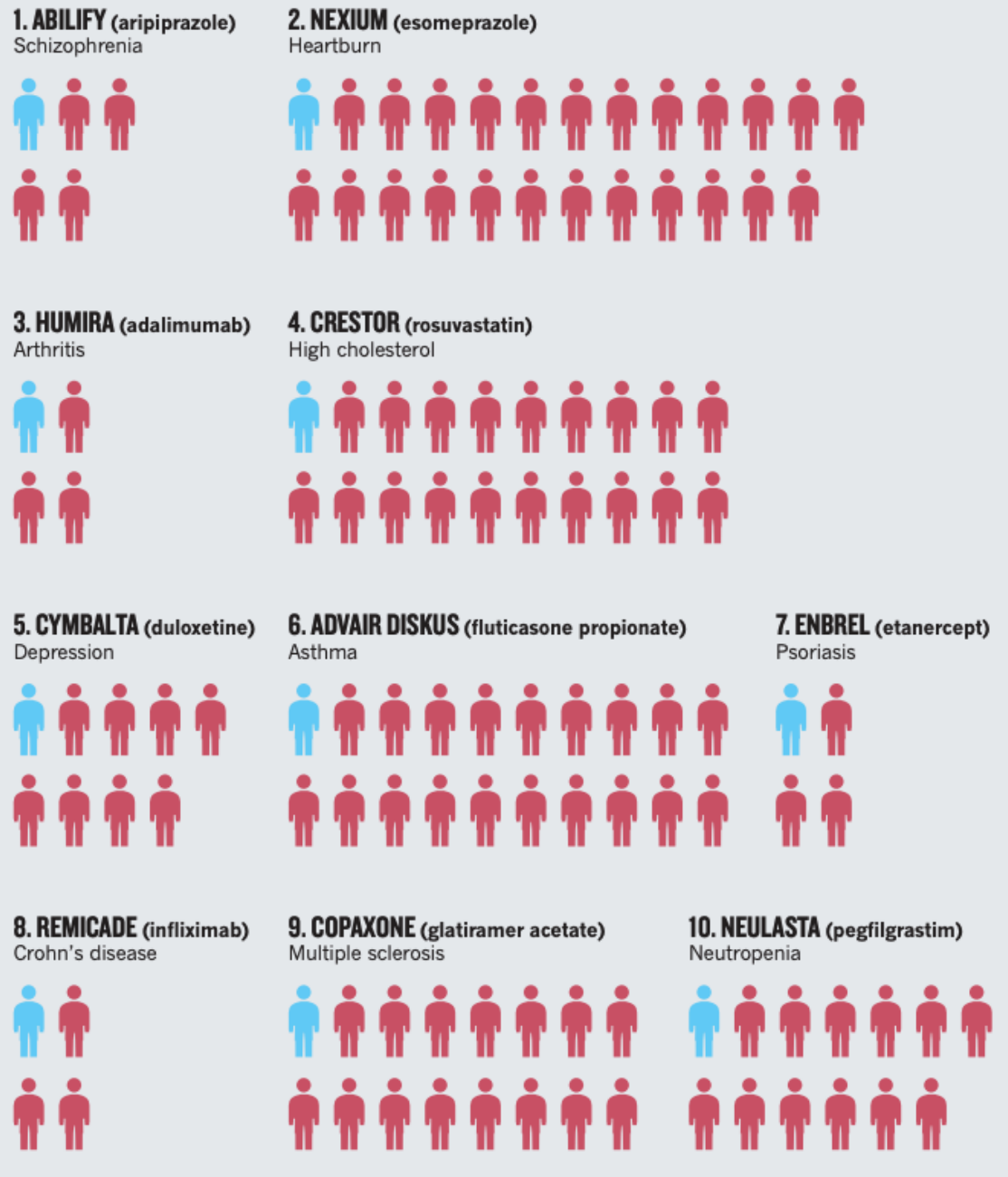
→ respond differently to medication

→ different side effects

Diagnostics, prognosis, treatment

IMPRECISION MEDICINE

The top ten highest-grossing drugs in the US **help between 1 in 25 and 1 in 4** of the people who take them.

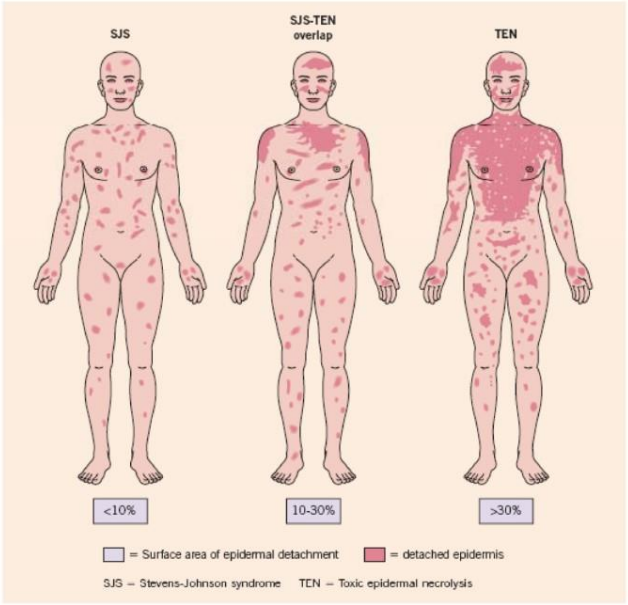


Schork, N. Personalized medicine: Time for one-person trials. Nature 520, 609–611 (2015).

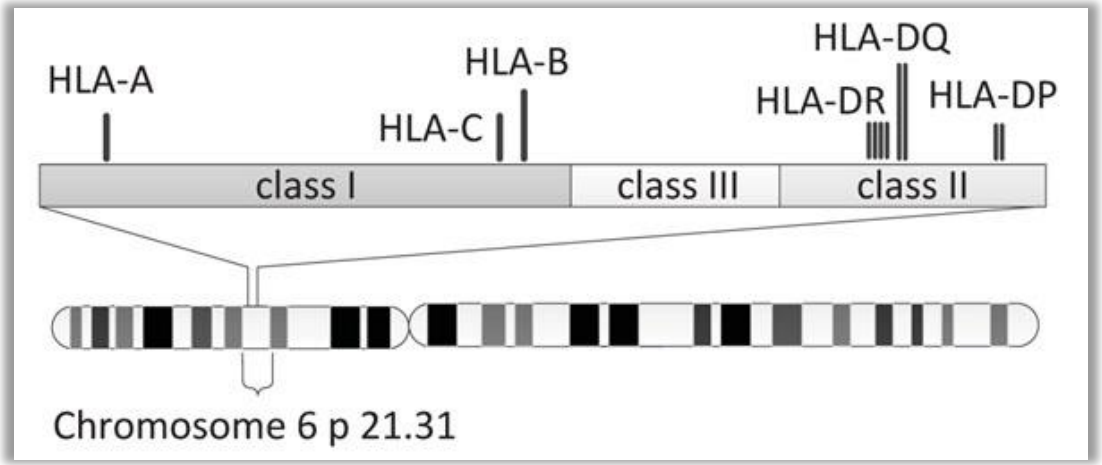
ADVERSE DRUG REACTIONS

Some medications are directly harmful for certain individuals

Carbamazepine-induced [used to treat Epilepsy and nerve-pain in diabetes] Stevens-Johnson syndrome in patients with specific genotypes in the MHC region.

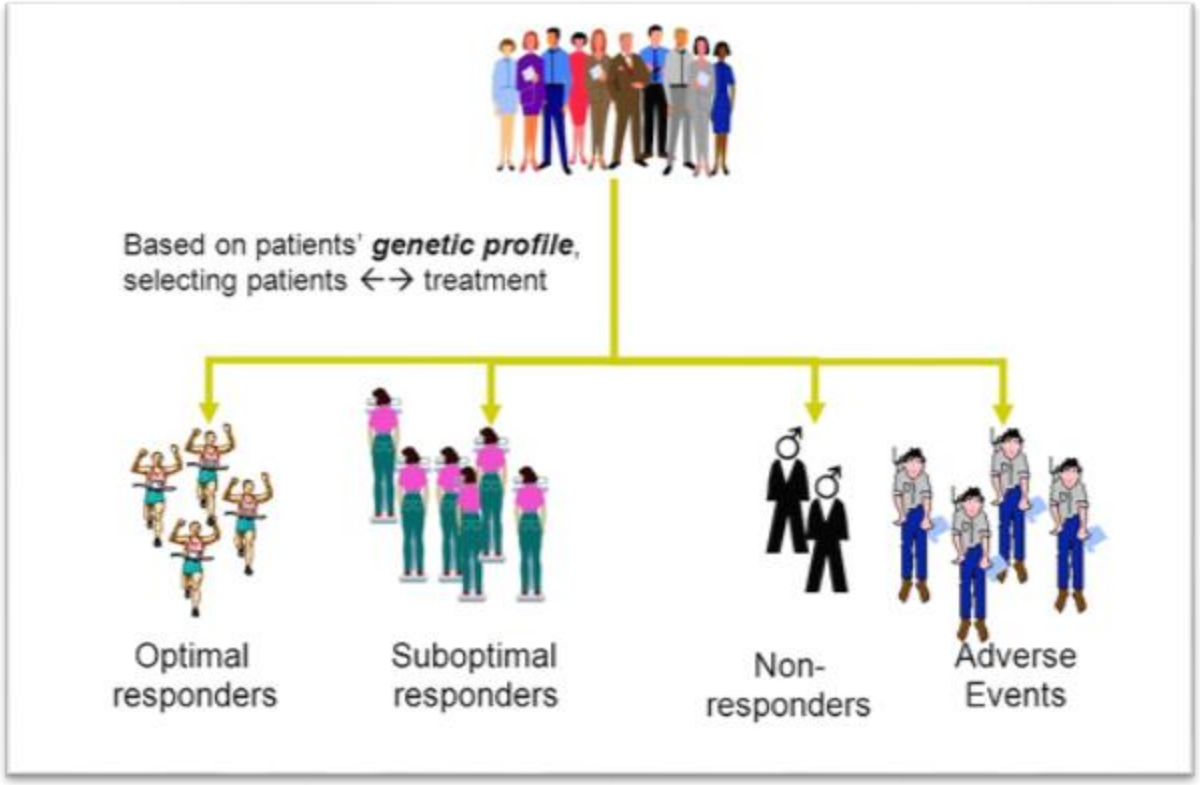


*HLA-B*1502 in Chinese*
*HLA-A*3101 in Caucasians*



YOUR TURN

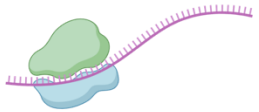
When you see this
Is this Evidence – Precision – Personalised or Individualised medicine ?

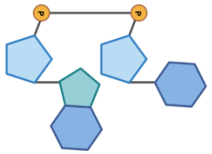


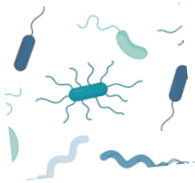
YOUR TURN

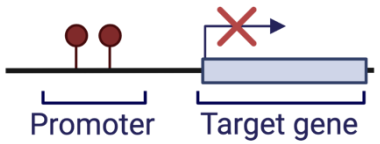
Which of these *omics* technologies can be used in personalised medicine?

Genes	Genomics
Transcripts	Transcriptomics
Protein	Proteomics
Metabolites	Metabolomics
E.g., gut bacteria	Microbiomics
DNA methylation	Methylomics









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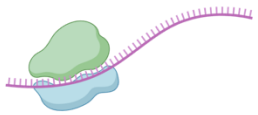
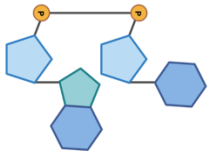
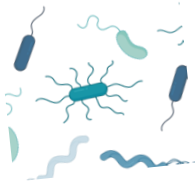
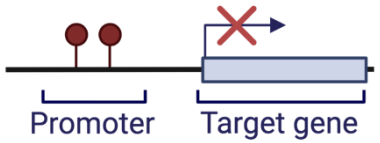








BECAUSE …

1) DNA is the *Blueprint* – identical from cradle-to-grave
2) Driven by *technological development* – price per base
3) One way causation [sickle cell disease]

Better understanding of human sequence variation

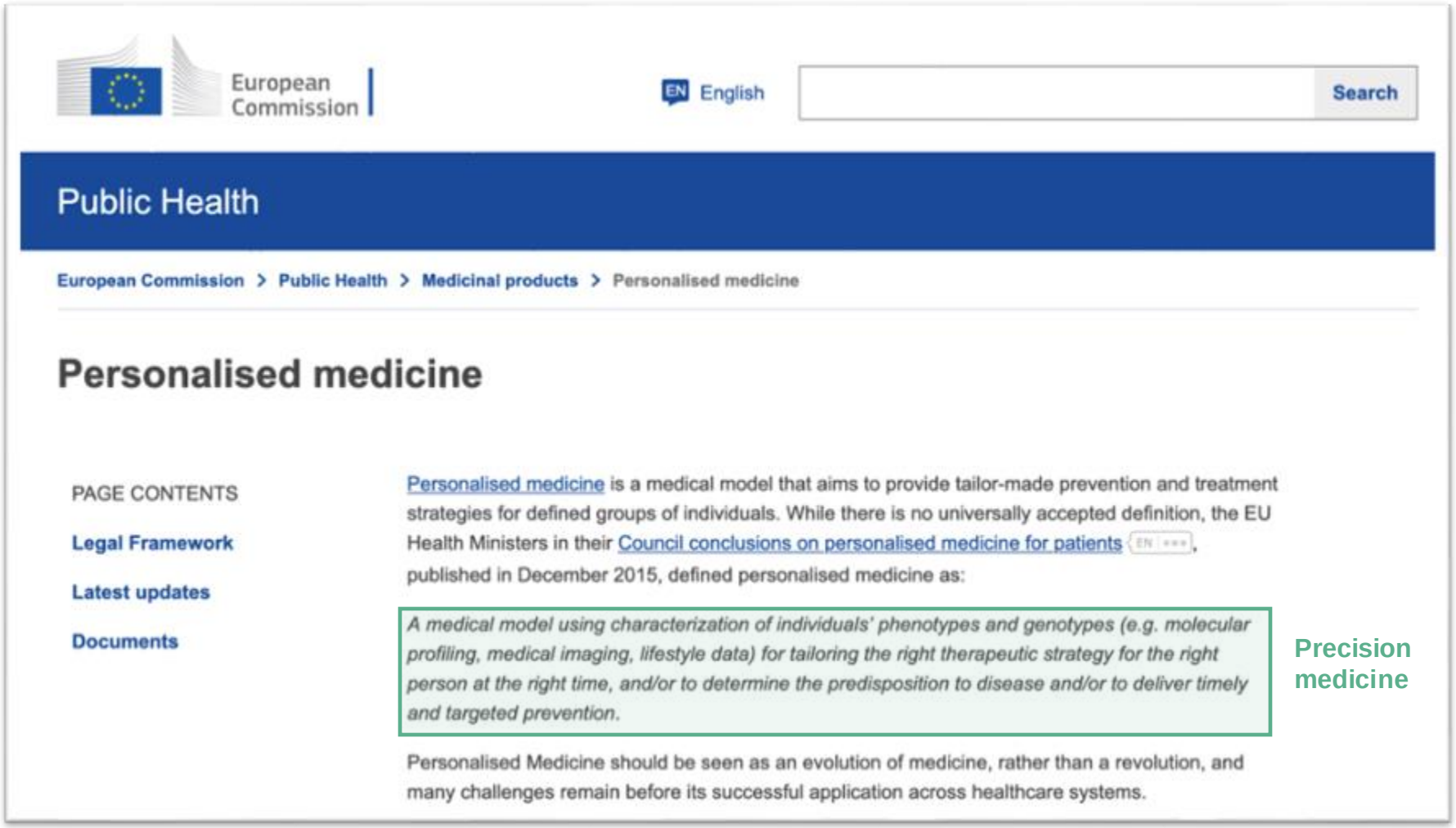
Advances in genotyping and sequencing technologies

biobank uk
Enabling scientific discoveries that improve human health

Sample collections of adequate size

Large-scale human studies linking genetic variation with disease suceptibility

YOUR TURN



(1) Take a look at EUs definition on Personalised medicine https://ec.europa.eu/health/medicinal-products/personalised-medicine_en

(2) How does this agree with our definition Evidence – Precision – Personalised or Individualised ?

How is personalised medicine presented to the society

”Delivering the right treatments,

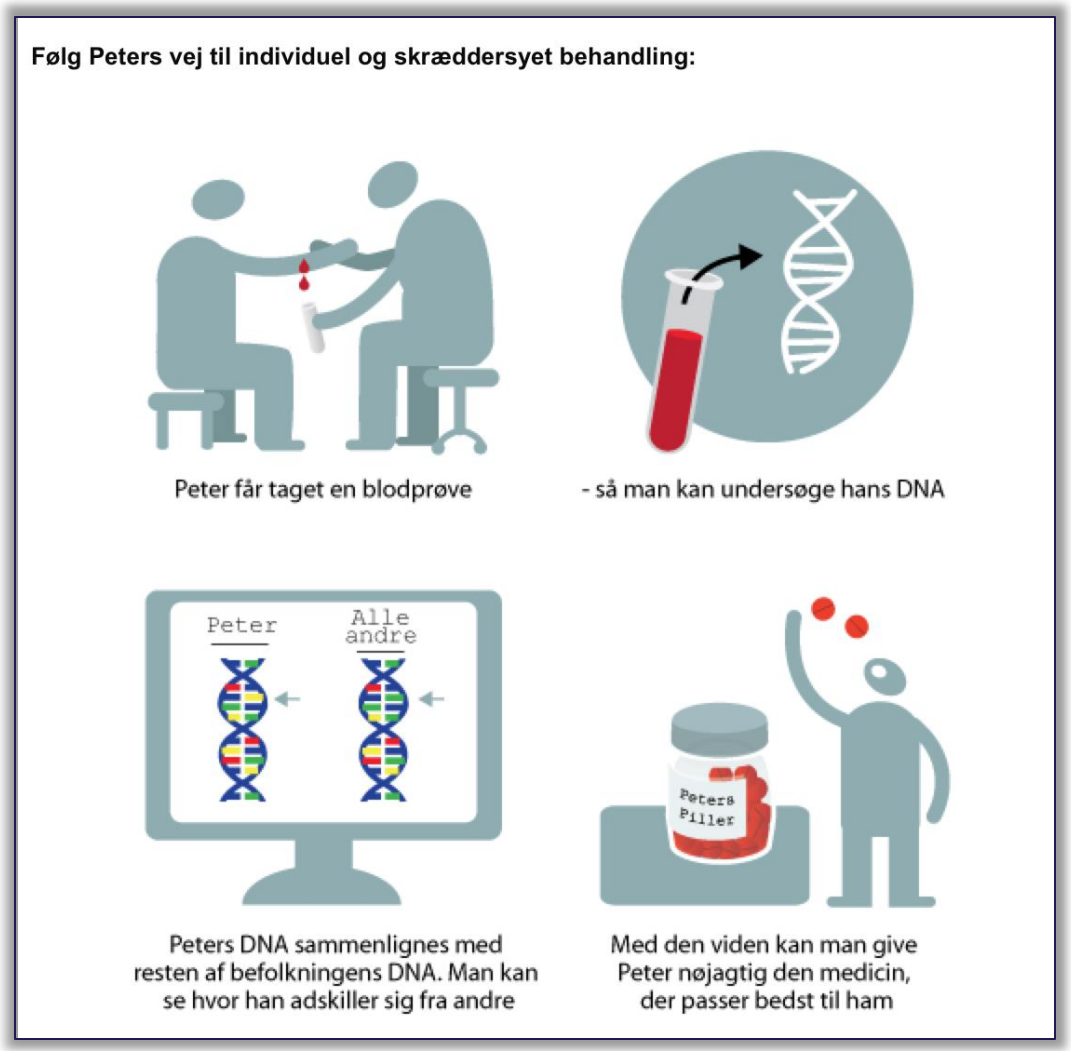
at the right time, every time

to the right person"

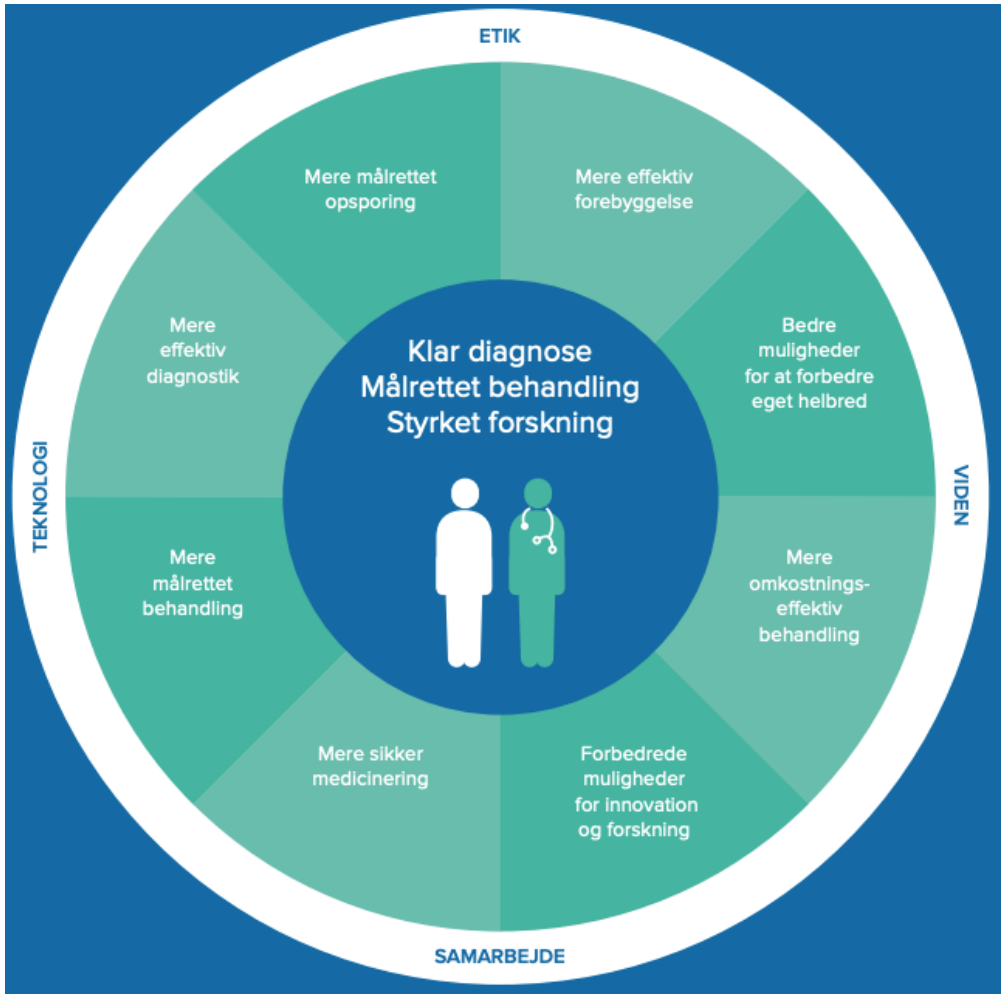
”Sagen er ret enkel: Er vi i stand til at give patienterne den rigtige behandling fra starten af, bliver de også hurtigere raske. Og når patienterne bliver hurtigere raske, kommer de hurtigere tilbage på arbejdsmarkedet. Det er bedst for borgerne, det er bedst for samfundet. Det er en win-win.

Bent Hansen,
Formand, Danske Regioner

Danish society spent >100 mio kr over three years to establish Nationalt Genom Center



https://www.regioner.dk/sundhed/medicin/personlig-medicin

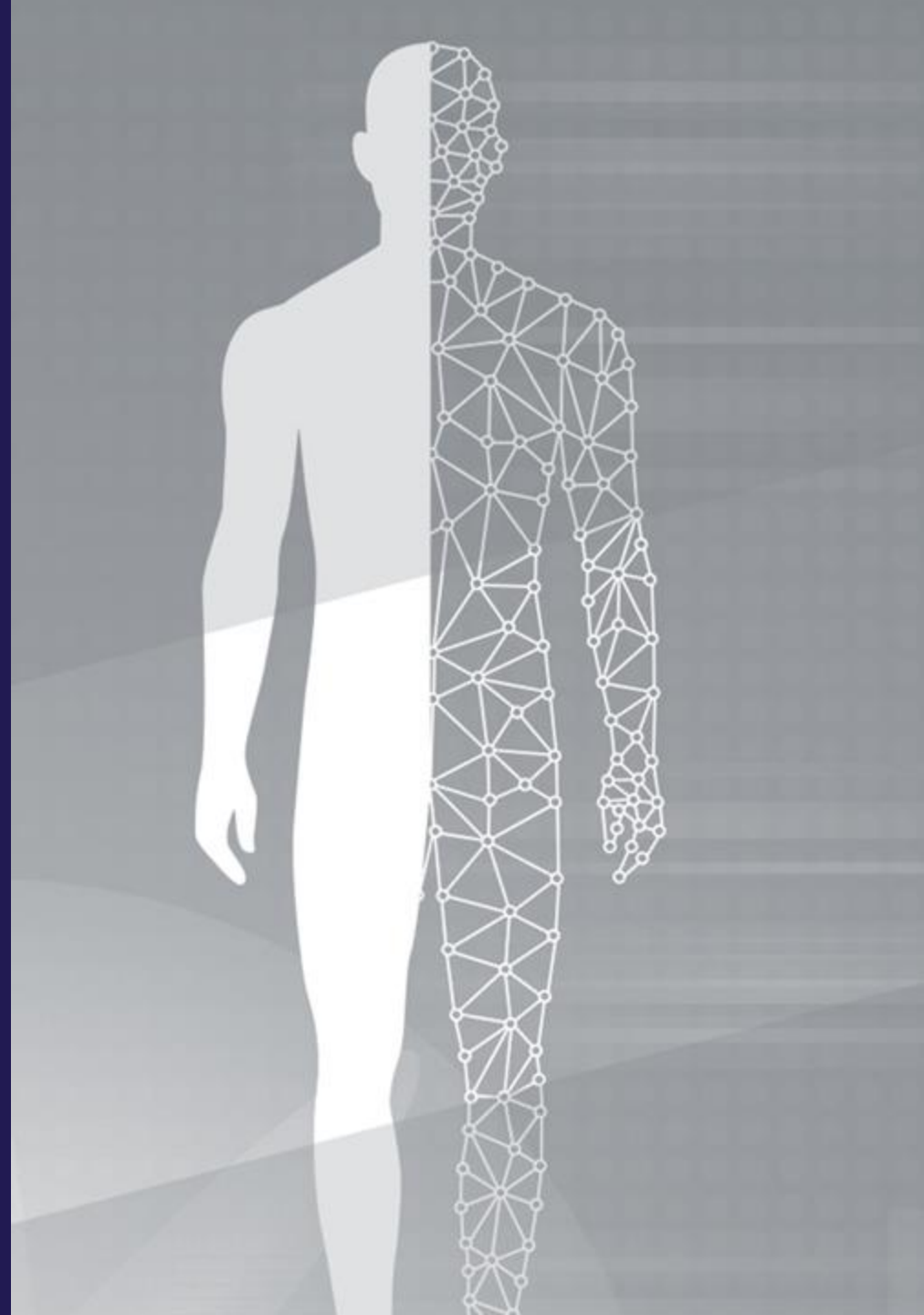


National handleplan 2021

SUMMARY

PERSONALISED MEDICINE

- ☑ What is Personalised Medicine?
- ☑ Why do we need it?
- ☑ Why so much focus on genetics?
- ☑ How is it presented to society?




BREAK

OUTLINE

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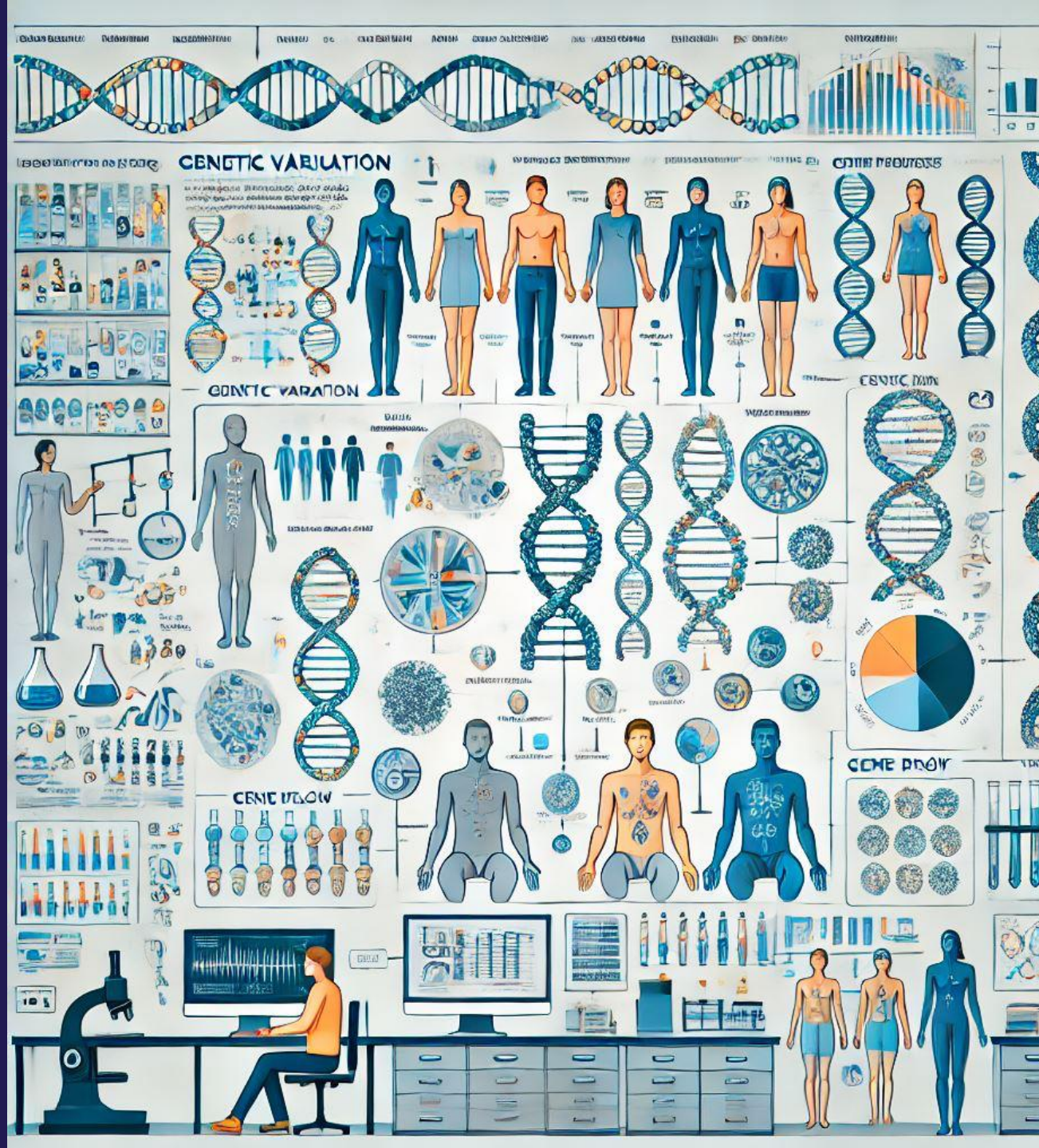
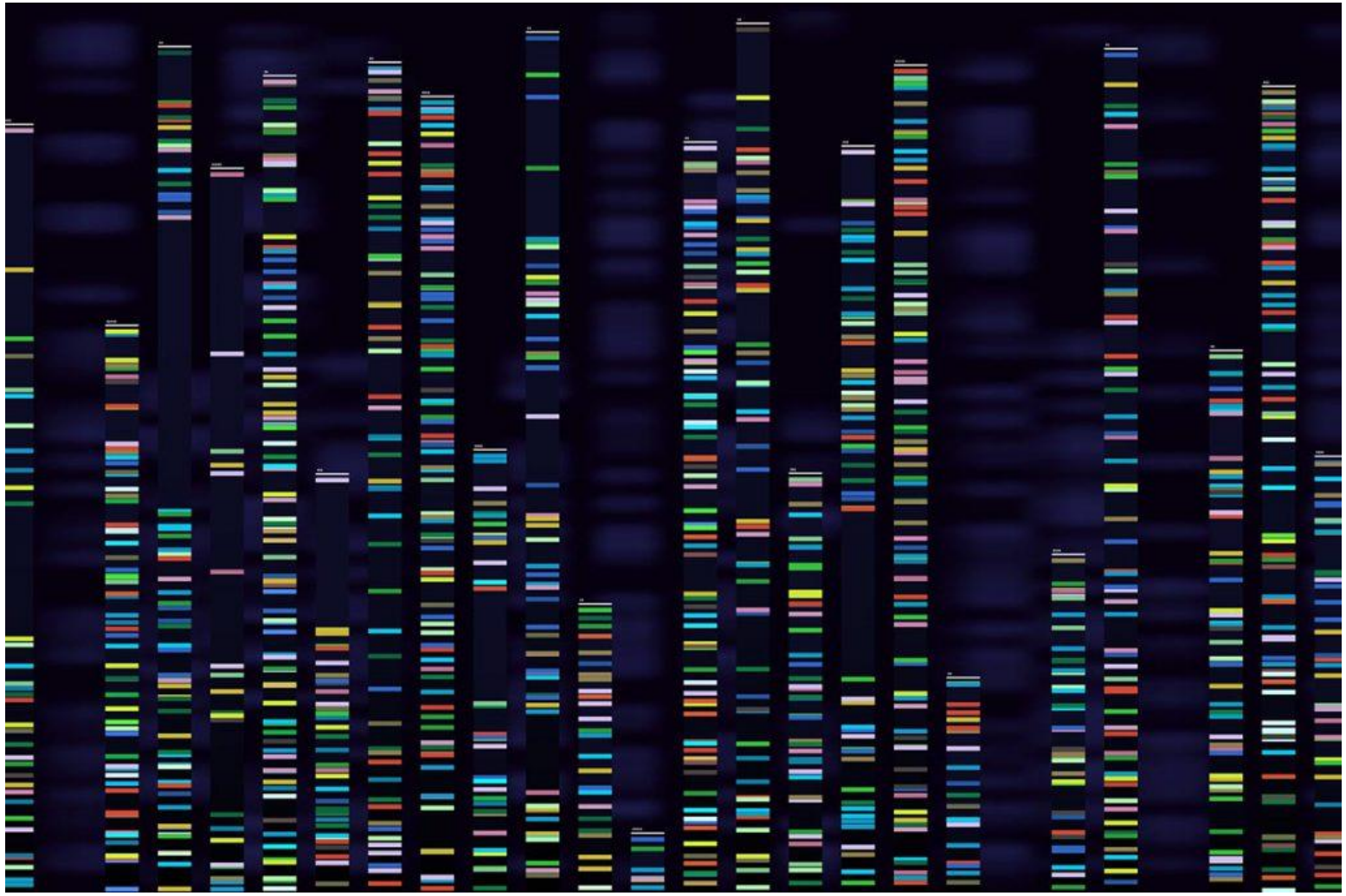
GENETIC VARIATION

- Different types of variation
- The genetic architecture plot
- The journey from monogenic diseases to complex diseases

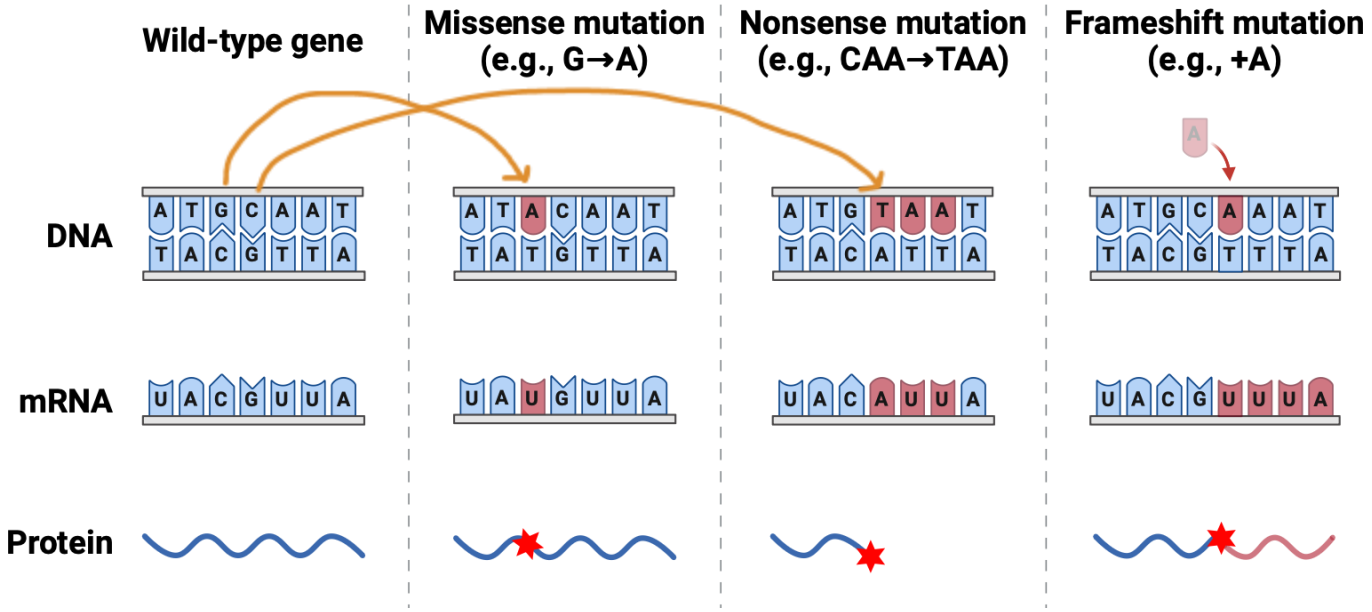


YOUR TURN

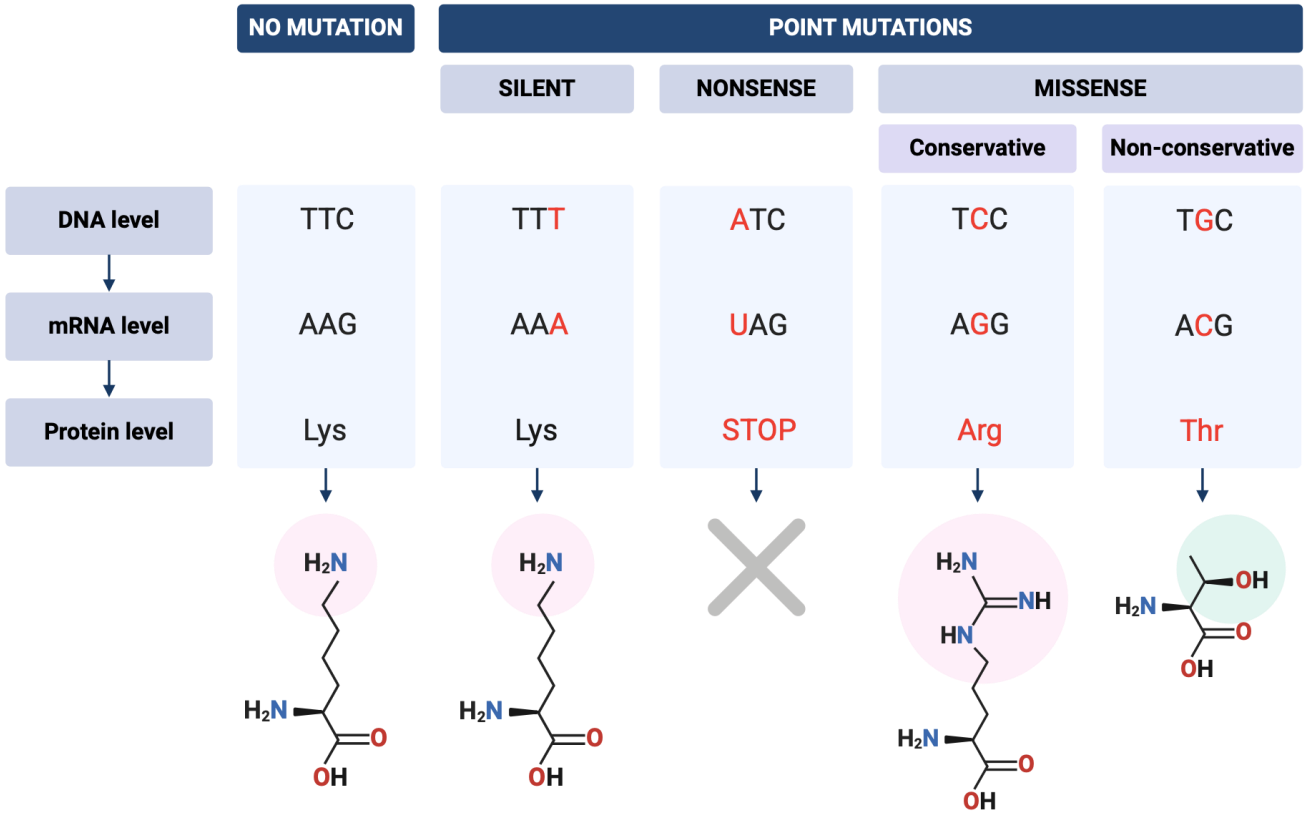
What generates genetic variation?



MUTATIONS GENERATE GENETIC VARIATION

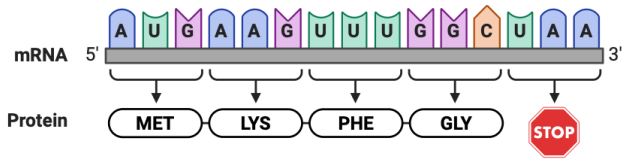


MUTATIONS GENERATE GENETIC VARIATION

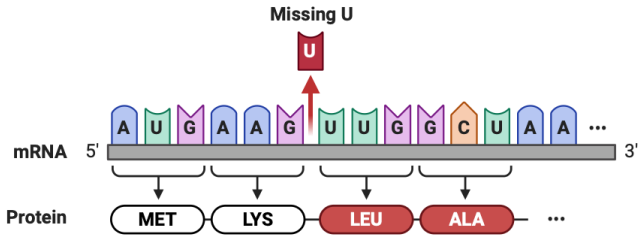


MUTATIONS GENERATE GENETIC VARIATION

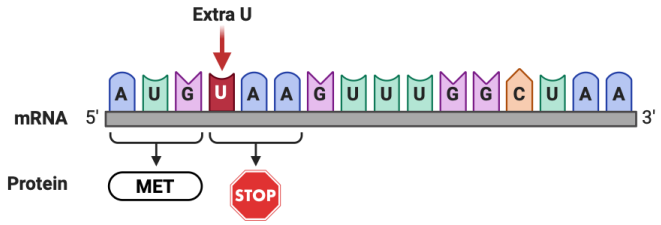
Wild type
mRNA sequence without any mutation



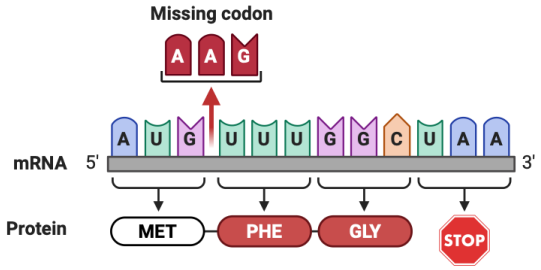
Base-pair deletion
Frameshift causing extensive missenseMissing U



Base-pair insertion
Frameshift causing immediate nonsense



Three-nucleotide insertion/deletion
Extra/missing amino acids



GENETIC DIVERISTY

Human evolution is driven by several different (evolutionary) factors

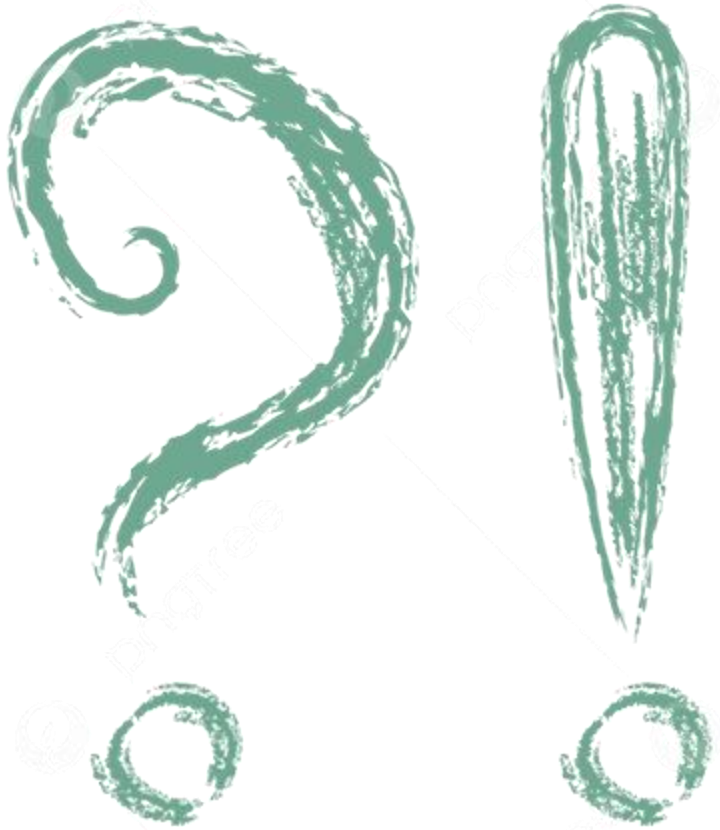
- Genetic mutations
- Migration
- Natural selection
- Genetic drift

The product is genetic diversity within a population.

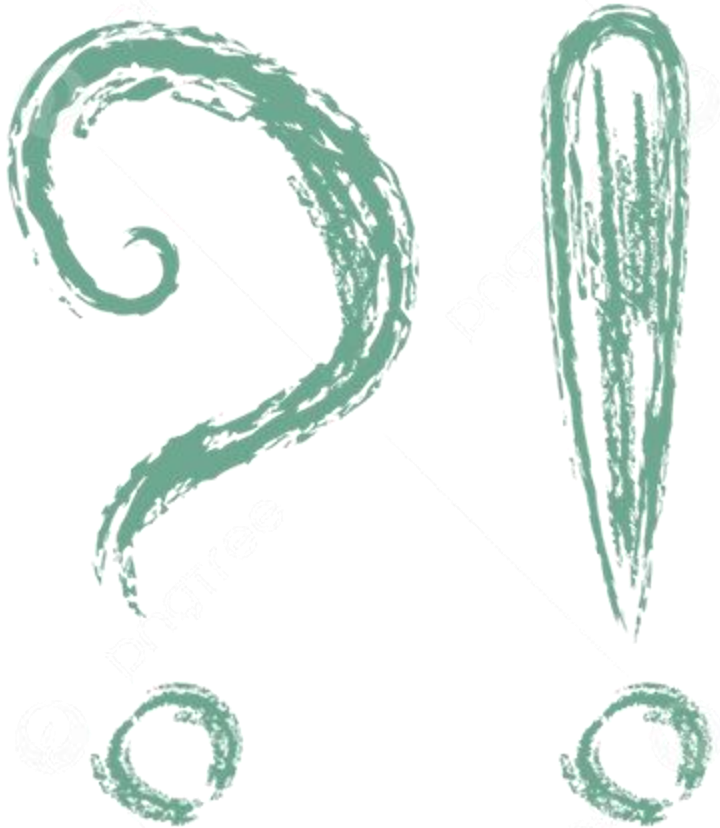
Understanding the genetic diversity and how it has arisen is a necessary precursor to understand the genetics of complex traits.

GENETIC TERMINOLOGY 1/2

- The **genome** refers to the complete set of genetic information found in a cell and includes 22 pairs of autosomal chromosomes plus XX or XY.
- The human genome of made up of >20,000 **genes**, and the location of a gene is refered to as a **locus**.
- Genetic variation at a locus is referred to as **allelic variation**, where the different forms are known as **alleles**.
- Underlying genetic variation are **changes in DNA sequence**.



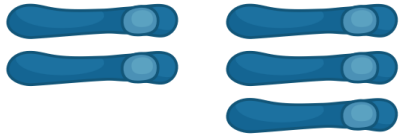
GENETIC TERMINOLOGY 2/2



- Traditionally, the term **mutation** has been used in two ways;
  - an event that produces a change in the base sequence
  - the outcome of the process, the altered DNA sequence.
- The great majority of mutations are neutral on the phenotype, thus more neutral terms are now preferred:
  - **DNA variant** or **genetic variant**
- In population genomics, a DNA variant is classified as common (>5%), low frequent (0.5-5%), or rare (<0.5%).
  - Single Nucleotide Polymophisms (**SNPs**, DNA variant freq of >1%)
  - Single Nucleotide Variants (**SNVs**)

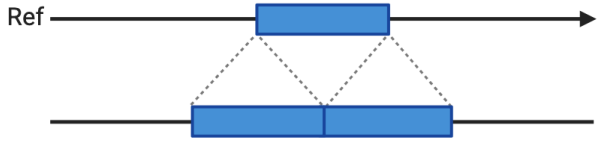
SIZES OF GENETIC VARIATION

Chromosome abnormality



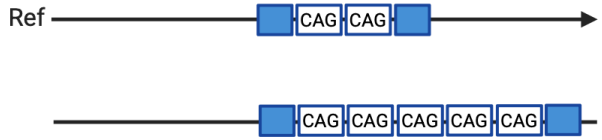
~Chromosome size

Copy number variants



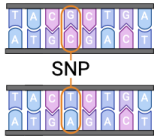
1000 - chromosome

Tandem repeats



2-5 | 15-100 base pairs

Single nucleotide polymorphism (SNP)



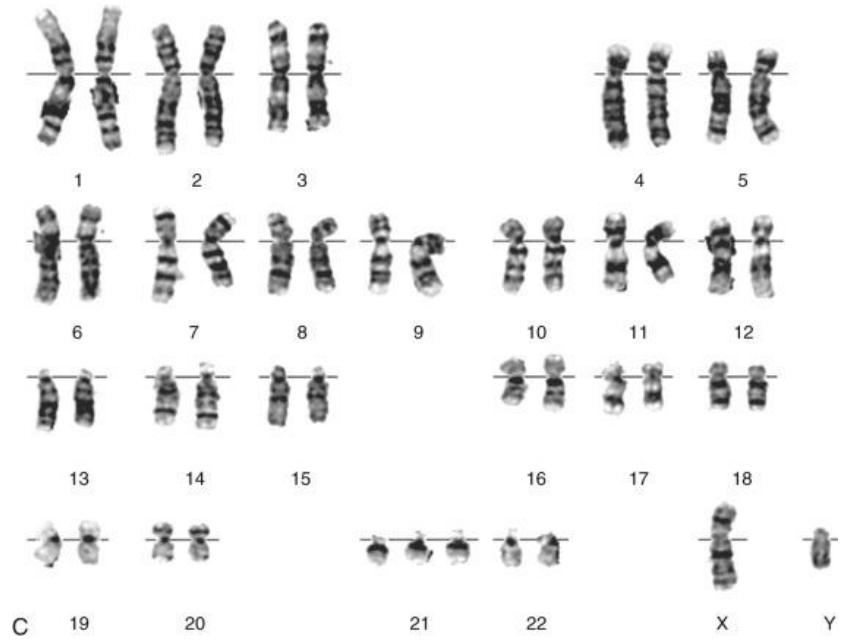
1 base pair

Size of the genetic variant

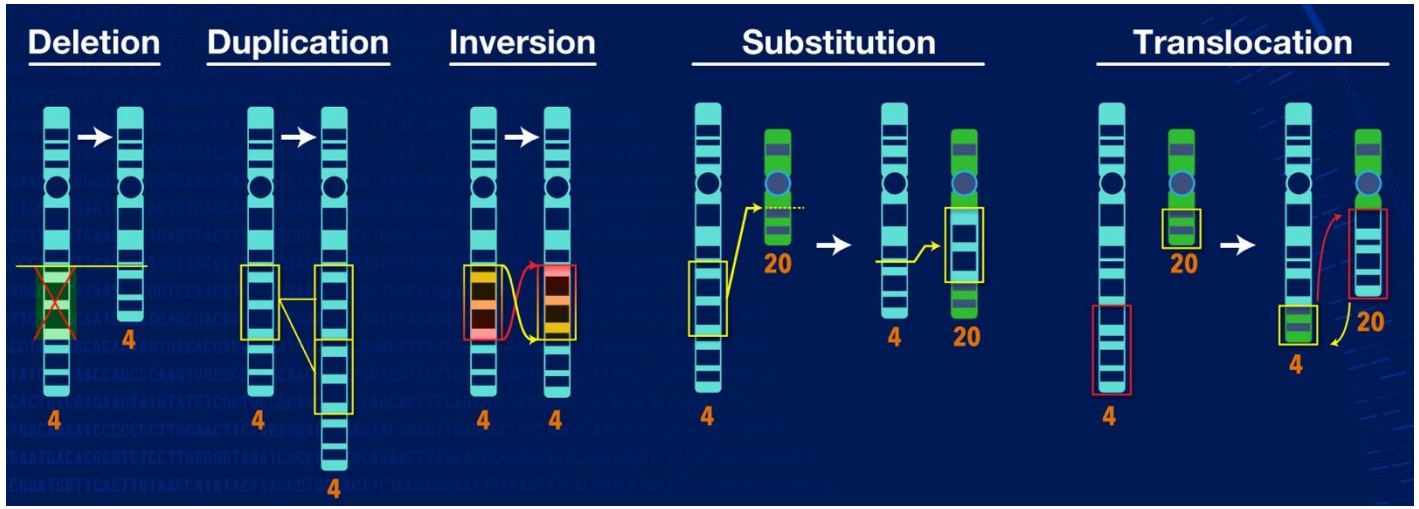
GENETIC VARIATION

CHROMOSOME ABNORMALITIES

Chromosome abnormalities can be numerical or structural.



Trisomi 21



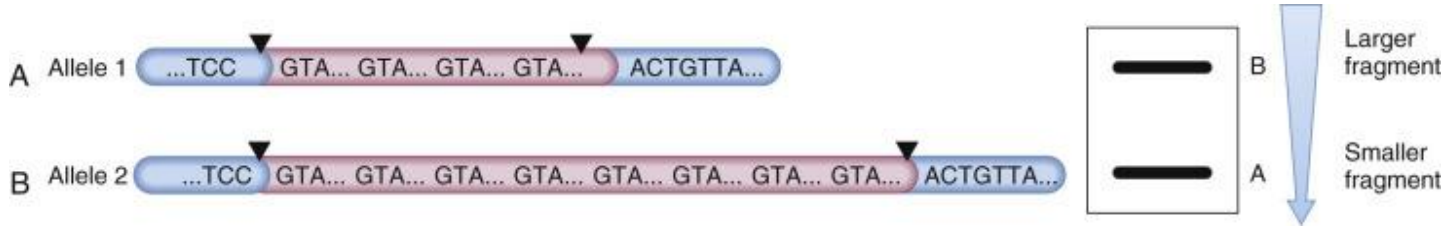
GENETIC VARIATION

TANDEM REPEATS

Advantage: many many alleles exists

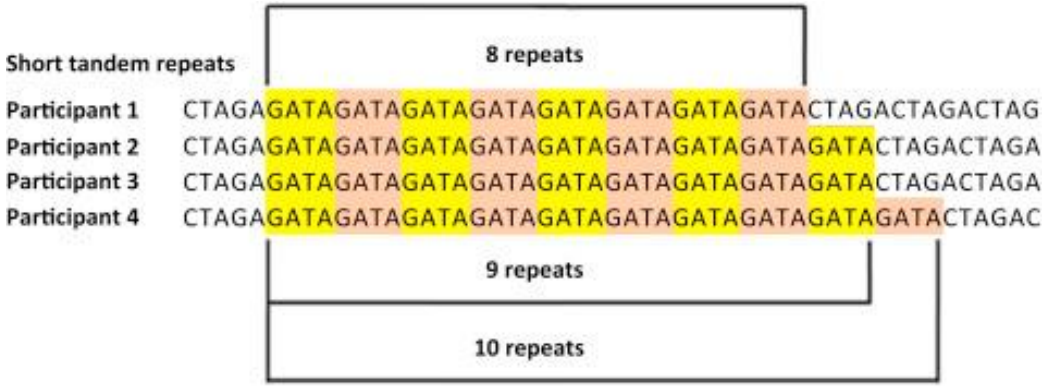
Micro satellites (2-5 bp) - STRs

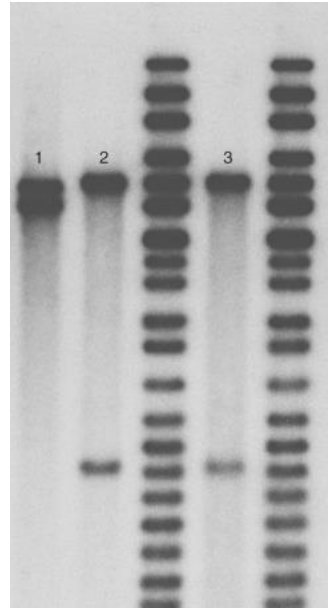
Mini satellites (15-100 bp) - VNTR



Forensic DNA analysis

United States, 13 autosomal Short Tandem Repeat (STR) loci are now accepted as the system used for forensic purposes.



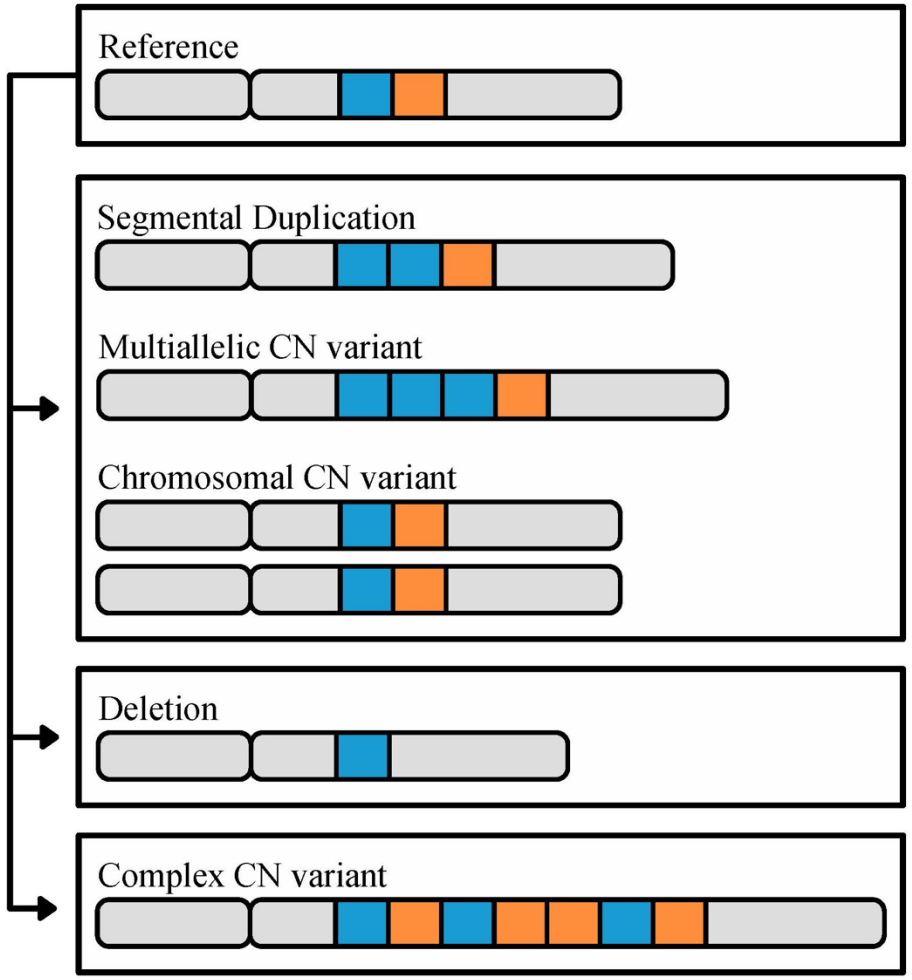


Herrera, R. J., and Garcia-Bertrand, R. Ancestral DNA, Human Origins, and Migrations

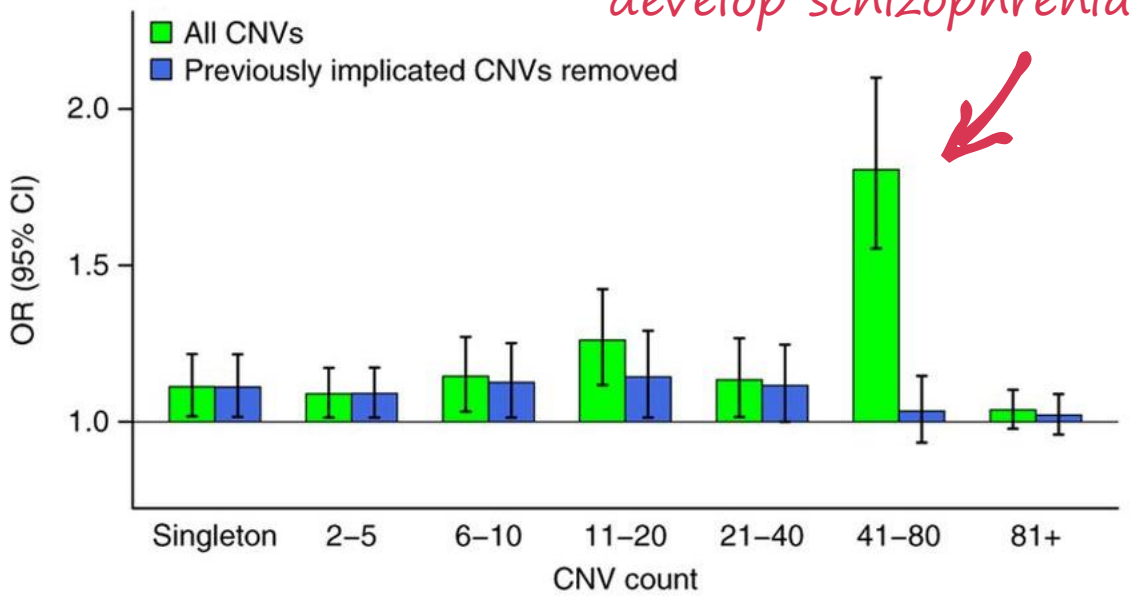
GENETIC VARIATION

COPY NUMBER VARIANTS (CNV)

50 bp - kromosom



1.8x more likely to develop schizophrenia

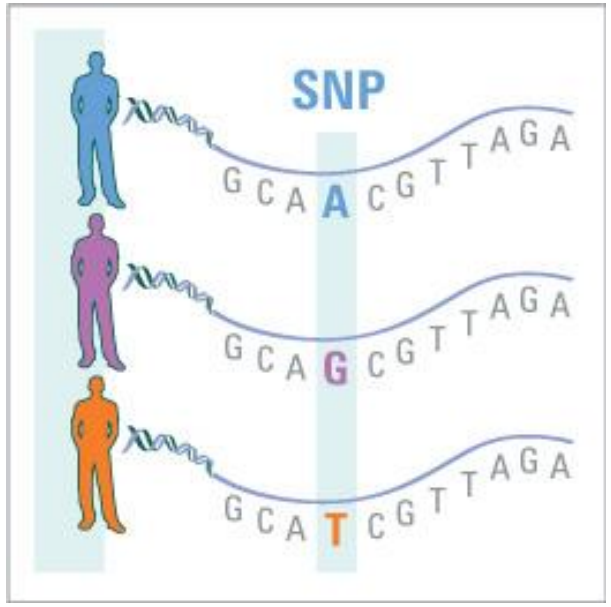


GENETIC VARIATION

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

A common change in a single base pair; ~1/1000 bp

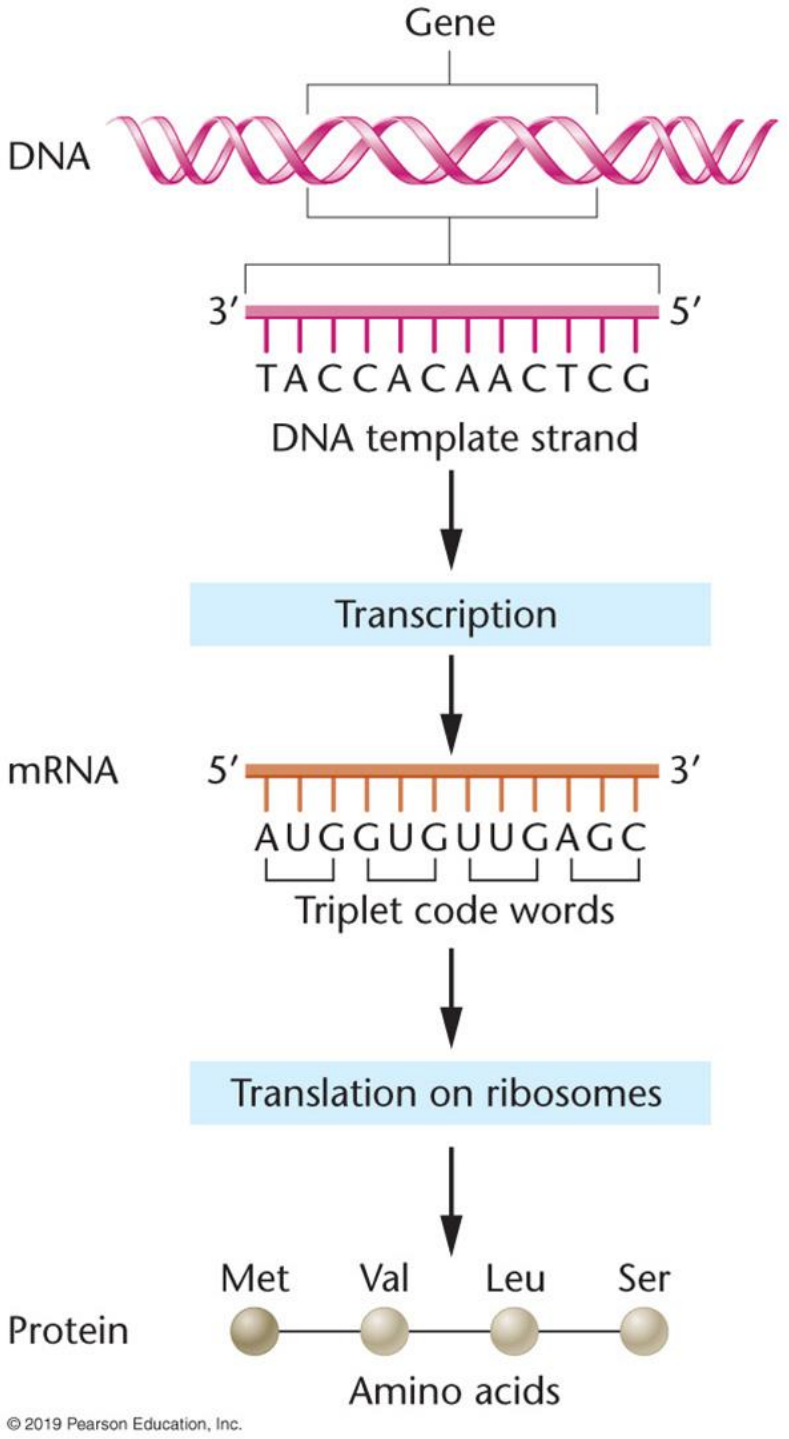
Accounts for ~90% of all variation in the human genome



All (known) SNPs has a unique identifier

(independent of alleles)

rsXXX – Ref-SNP cluster ID number

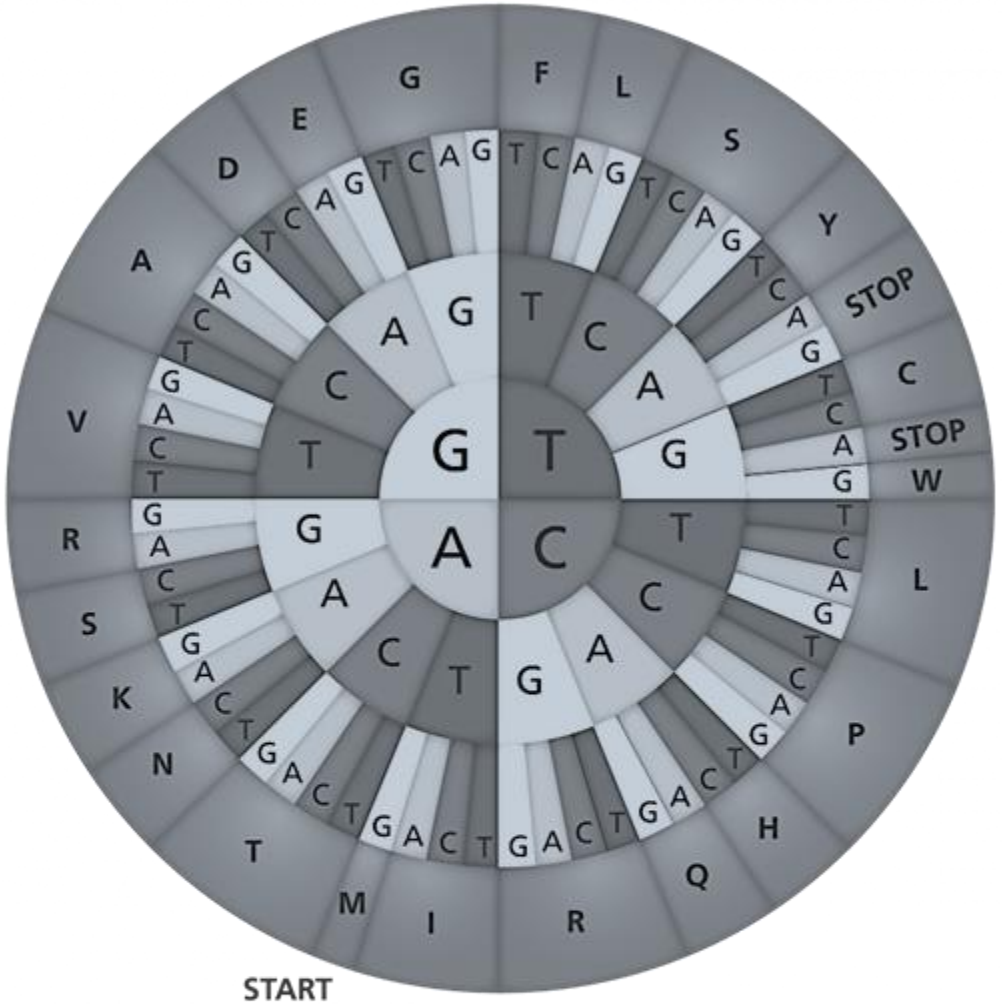


GENETIC VARIATION

Genetic variation arise as a consequence of changes in the DNA sequence

Can change the order of amino acides

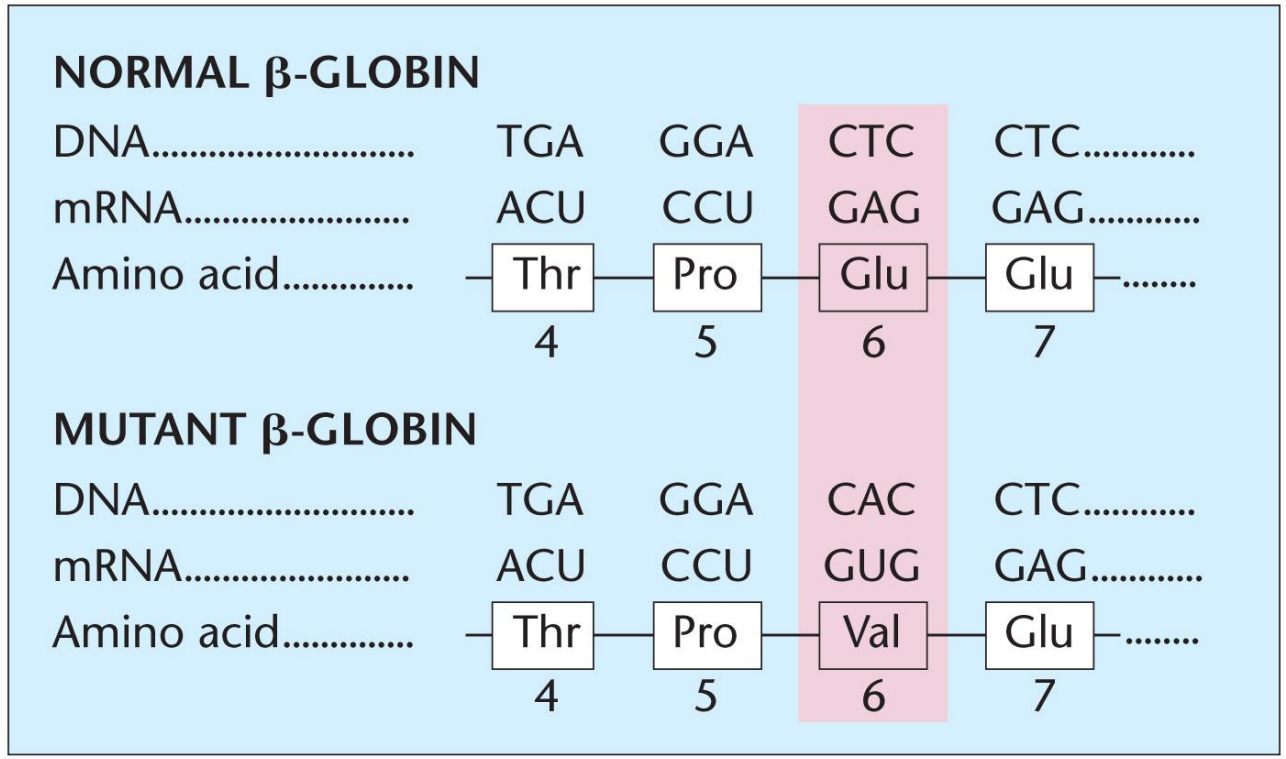
The structure of the protein is changed

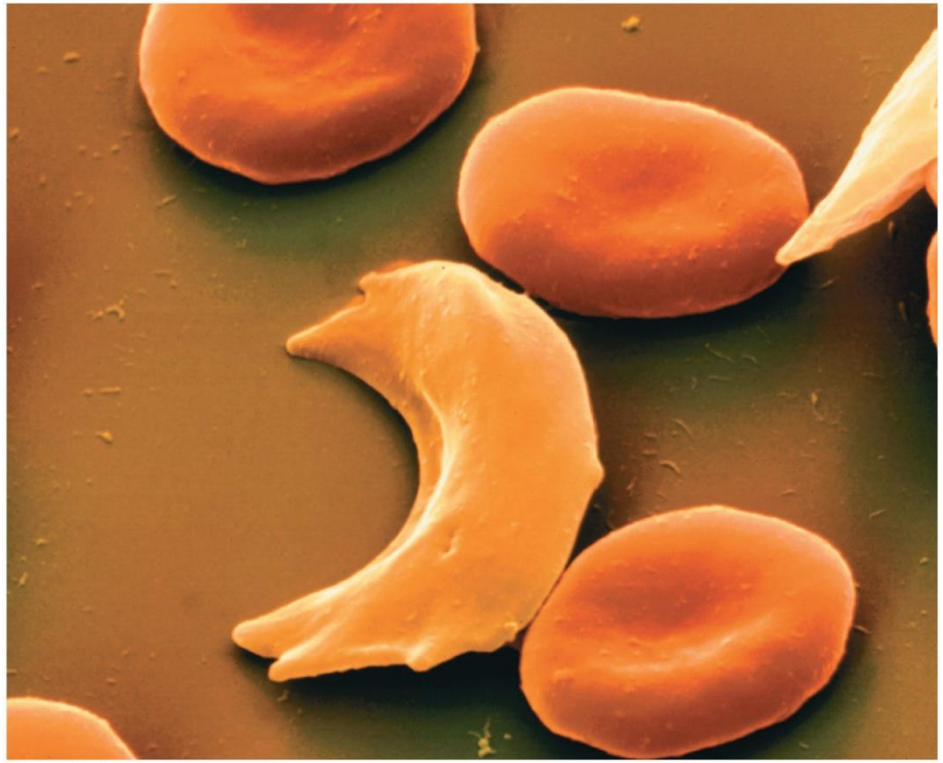


Amino acid code

A – Alanine	G – Glycine	M – Methionine	S – Serine
C – Cysteine	H – Histidine	N – Asparagine	T – Threonine
D – Aspartic acid	I – Isoleucine	P – Proline	V – Valine
E – Glutamic acid	K – Lysine	Q – Glutamine	W – Tryptophan
F – Phenylalanine	L – Leucine	R – Arginine	Y – Tyrosine

GENOTYPE TO PHENOTYPE





SIZES OF GENETIC VARIATION

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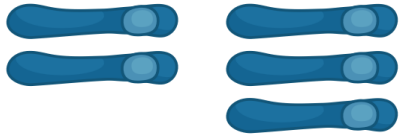
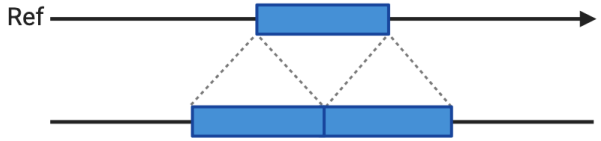


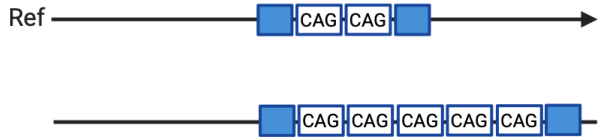
~Chromosome size

Copy number variants



1000 - chromosome

Tandem repeats



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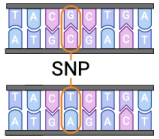
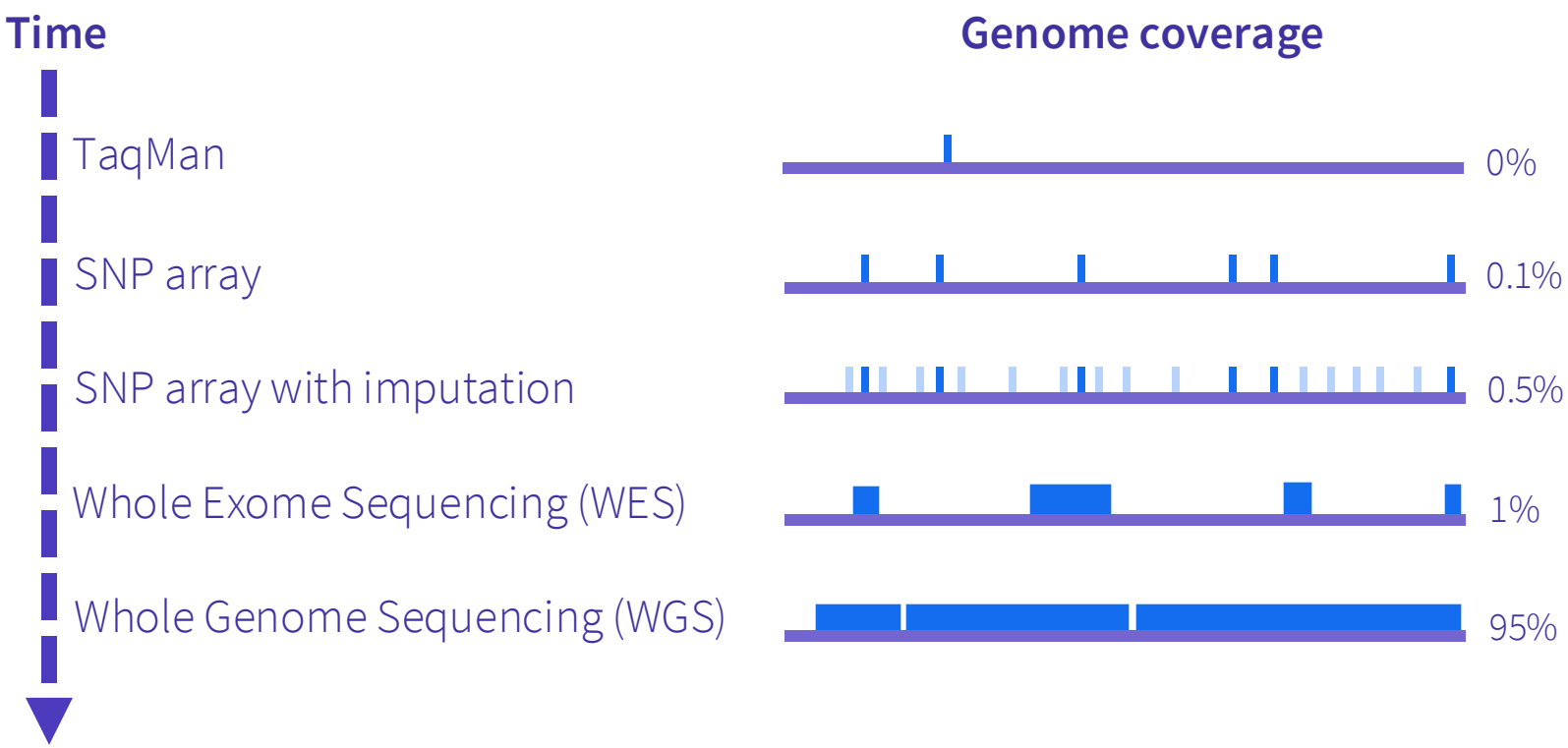


1 base pair

Size of the genetic variant

GENOMIC COVERAGE

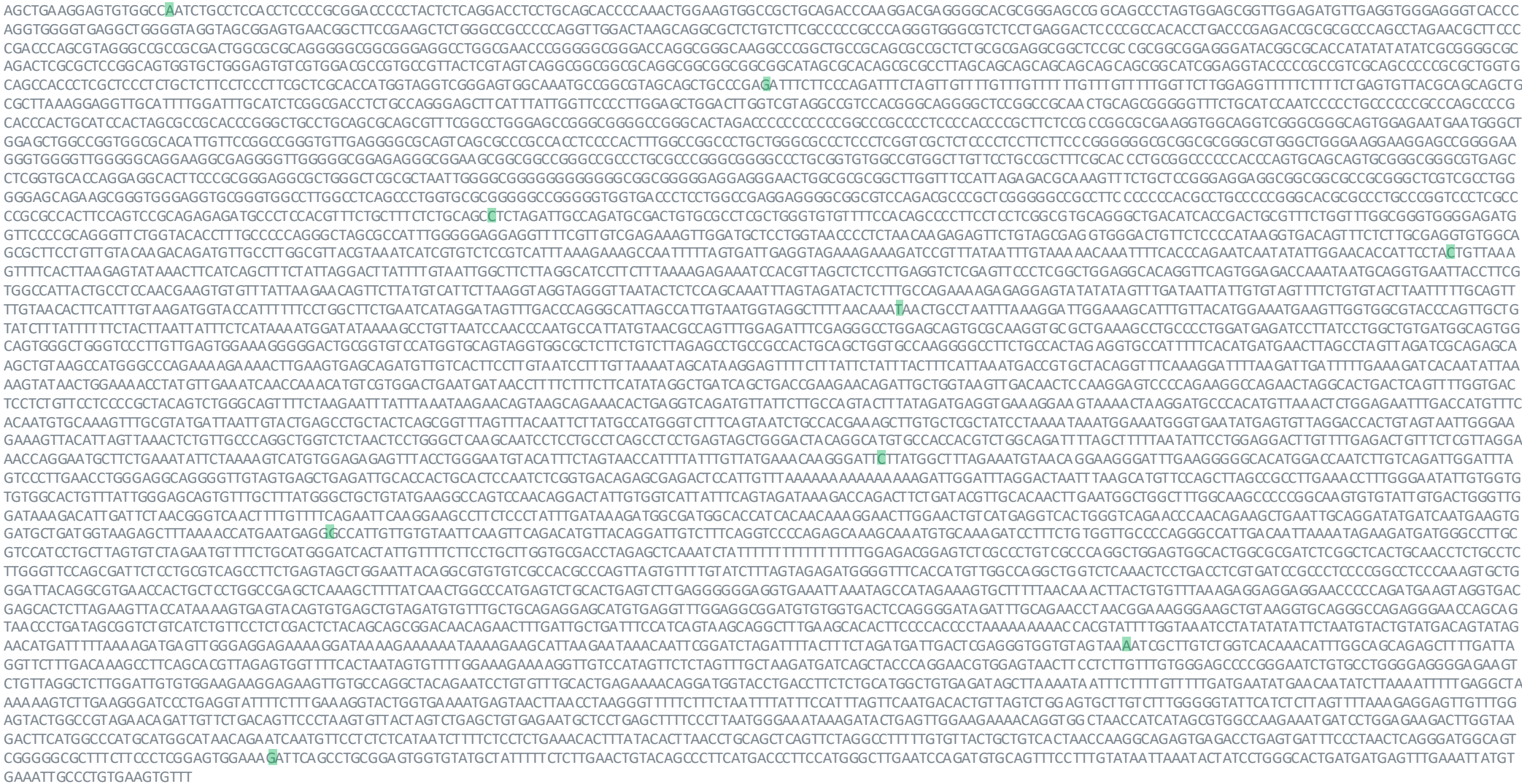


Adapted from Uitterlinden A. (2016) An Introduction to Genome-Wide Association Studies: GWAS for Dummies. Seminars in Reproductive Medicine, 34(4): 196-204.

GENOTYPING VS SEQUENCING

GENOTYPING VS SEQUENCING

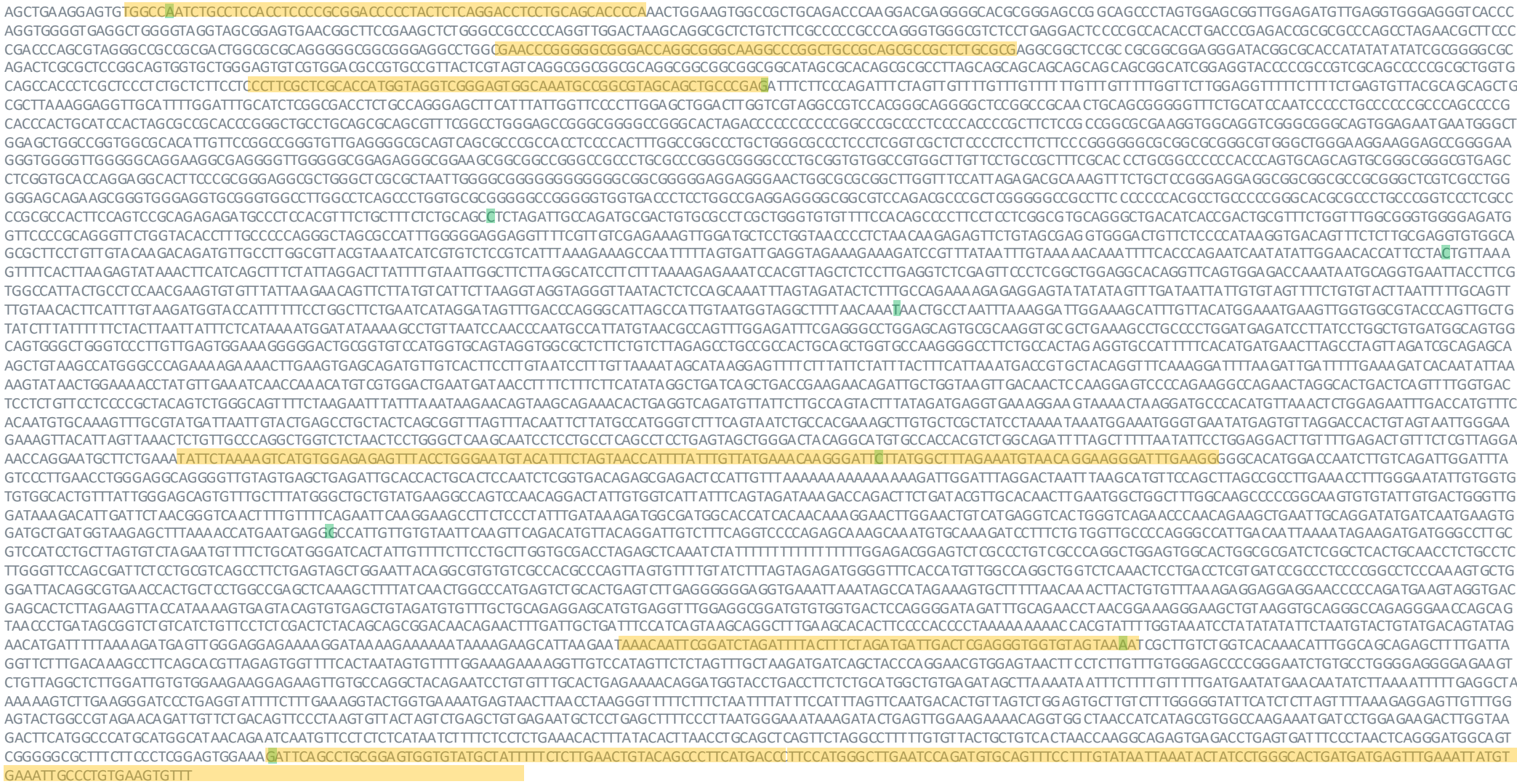
Genotyping



GENOTYPING VS SEQUENCING

Genotyping

WES

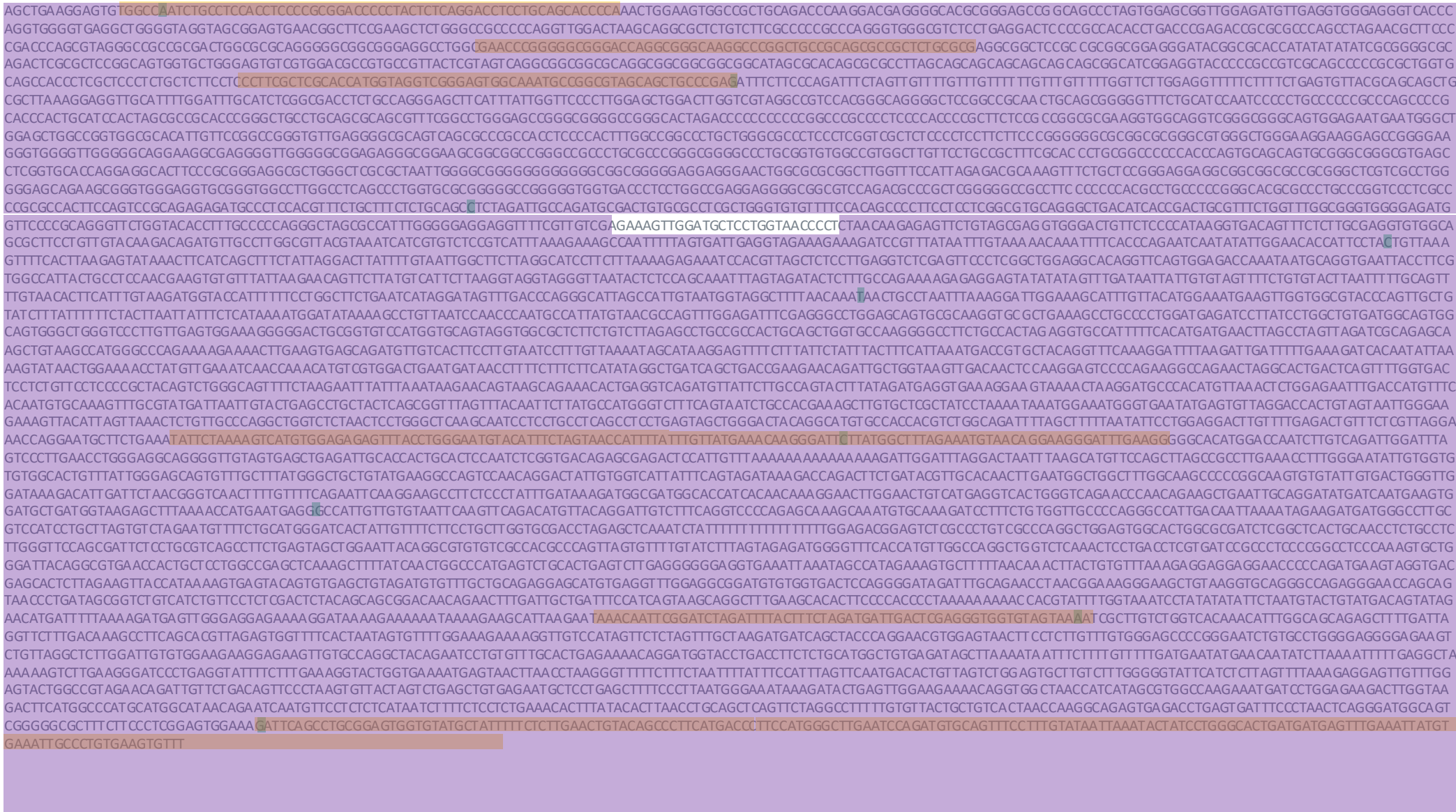


GENOTYPING VS SEQUENCING

Genotyping

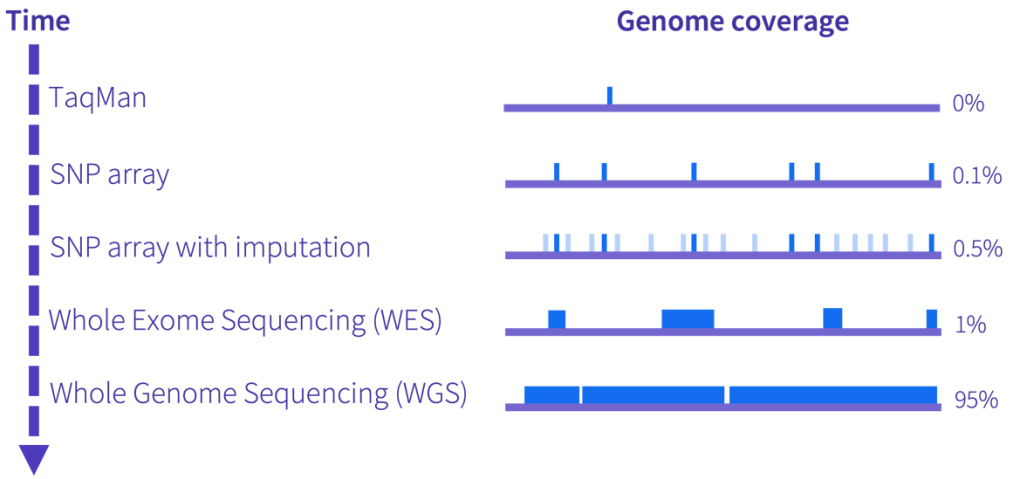
WES

WGS



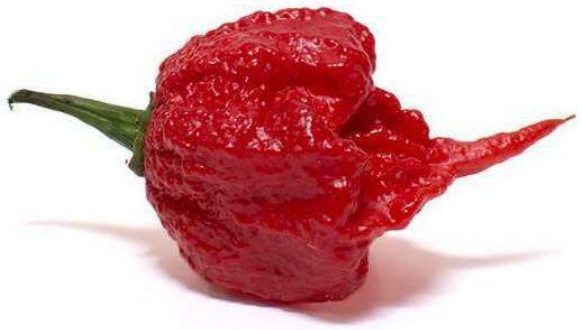
WHICH TECHNOLOGY?

The choice of technology fir detecting single nucleotide polymorphisms (SNPs) depends upon the application.



GENETIC VARIATION IS LIKE CHILI

Carolina reaper



Strong effect on phenotype

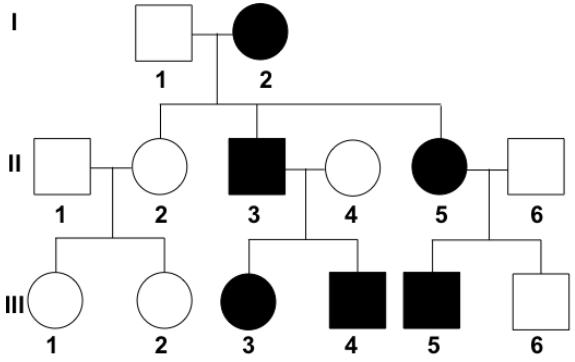
Habanero Lemon

Moderate effect on phenotype

Bell pepper

Weak effect on phenotype
(or none at all)

GENETIC VARIATION IS LIKE CHILI

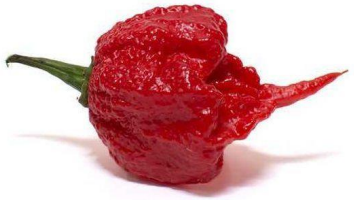


Mutation

Each genetic variant is both necessary and sufficient

+

Each genetic variant is neither necessary nor sufficient



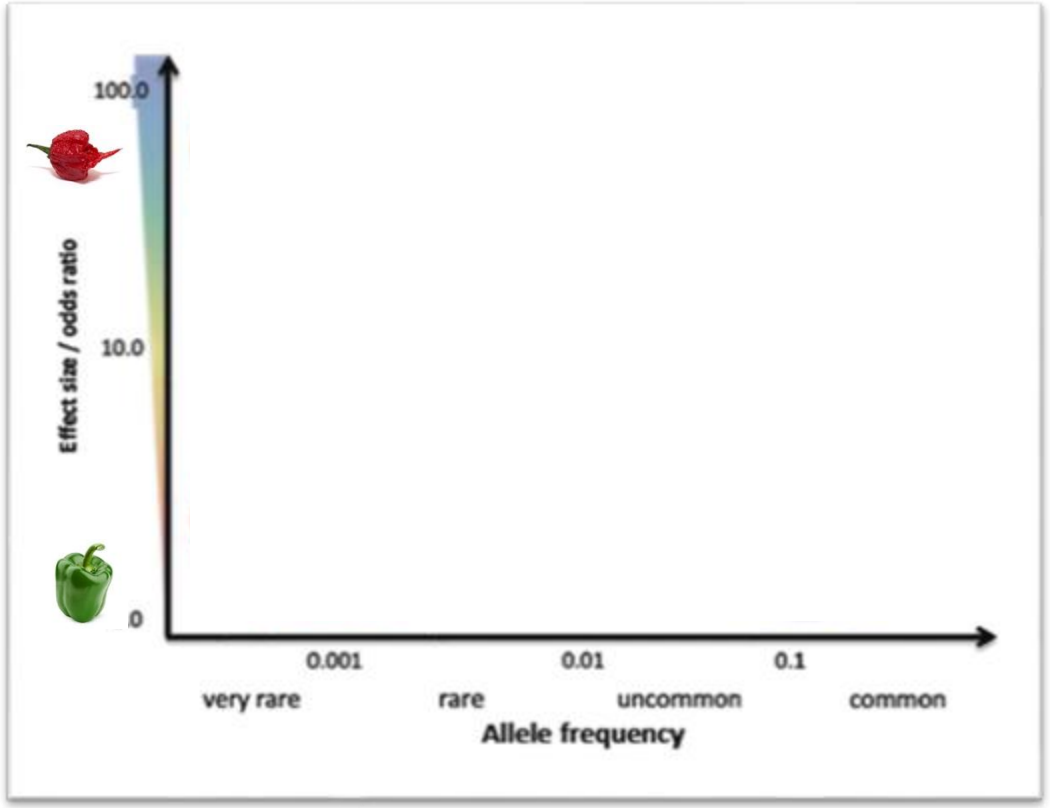
ARCHITECTURE PLOT

All genetic variants have a spot in the architecture plot (for a certain phenotype)

YOUR TURN

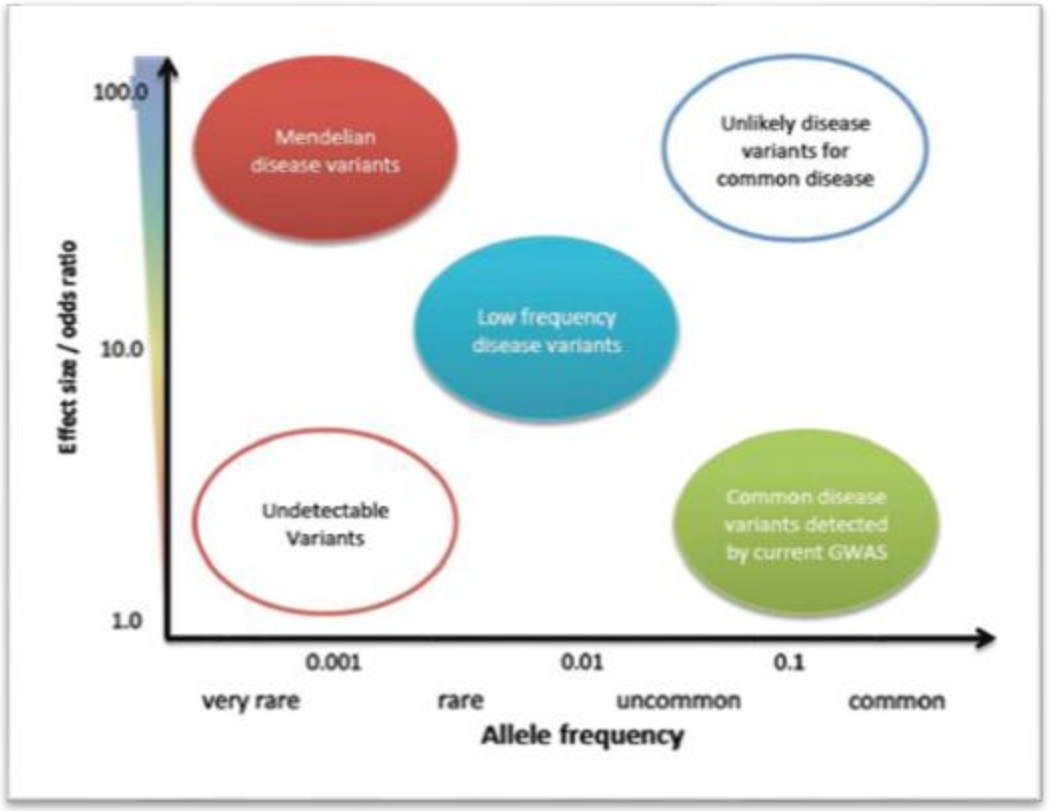
Where are variants causing monogenic disease?

Where are the variants causing complex disease?



Monogenic and **complex diseases** have different genetic architectures

IN THIS COURSE WE LOOK AT THE FULL SPECTRUM

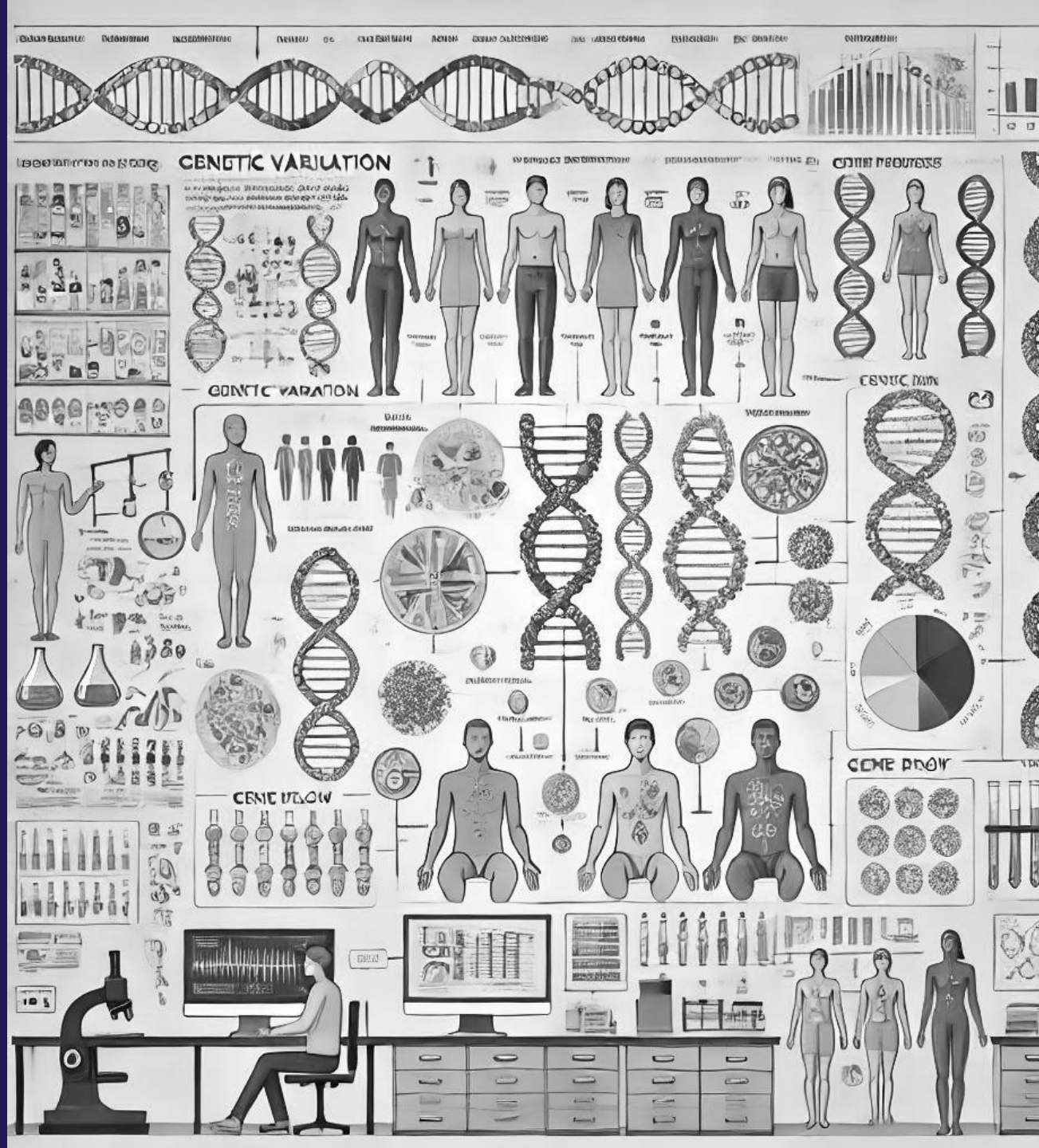


Monogenic and **complex diseases** have different genetic architectures

SUMMARY

GENETIC VARIATION

- Different types of variation
- The genetic architecture plot
- The journey from monogenic diseases to complex diseases




BREAK

OUTLINE

08:15 – 08:30	Welcome (15 min)
08:30 – 08:55	Exercises 1 (25 min) [*figure recap*]
08:55 – 09:20	Lecture - *What is personalised medicine?* (25 min)
09:20 – 09.35	Break
09:35 – 10:05	Exercises 2 (30 min) [*1-6*]
10:05 – 10:20	Plenum (15 min) [*solutions*]
10:20 – 10:45	Lecture - *Genetic variation* (25 min)
10:45 – 11:00	Break
11:00 – 11:30	Exercises 3 (30 min) [*7-9 + R intro*]
11:30 – 11:45	Plenum (15 min) [*solutions*]
11.45 – 12:00	eBoard evaluation + Crossword

SUMMARY

- 10 sessions - read the readme - prepare before class **– this is important**

- Personalised medicine is not new
- We need it because people are different – different response and side effects
- Evidence-Precision-Personalised-Individualised
- Strong focus on genetics because of blueprint and causality (and price per base)

- All genetic variants have a place in the architecture plot
- This course will look at ***all*** variants – strong and weak

OUTLINE

08:15 – 08:30	**Welcome (15 min)**
08:30 – 08:55	**Exercises 1 (25 min)** [In pairs *figure recap*]
08:55 – 09:20	**What is personalised medicine? (25 min)**
09:20 – 09.35	Break
09:35 – 10:05	**Exercises 2 (30 min)** [*1-6*]
10:05 – 10:20	**Plenum (15 min)** [*solutions*]
10:20 – 10:45	**Genetic variation (25 min)**
10:45 – 11:00	Break
11:00 – 11:30	**Exercises 3 (30 min)** [*7-9 + R intro*]
11:30 – 11:45	**Plenum (15 min)** [*solutions*]
11.45 – 12:00	**eBoard evaluation + Crossword**

eBOARD EVALUATION

LINK

GENOMICS CROSSWORD

https://crosswordlabs.com/embed/pm-genomics-brushup

Hint: Use “-” to indicate a space

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