



HUMAN GENOMICS

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Genomic Medicine

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THE COURSE TEAM



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Ass Prof

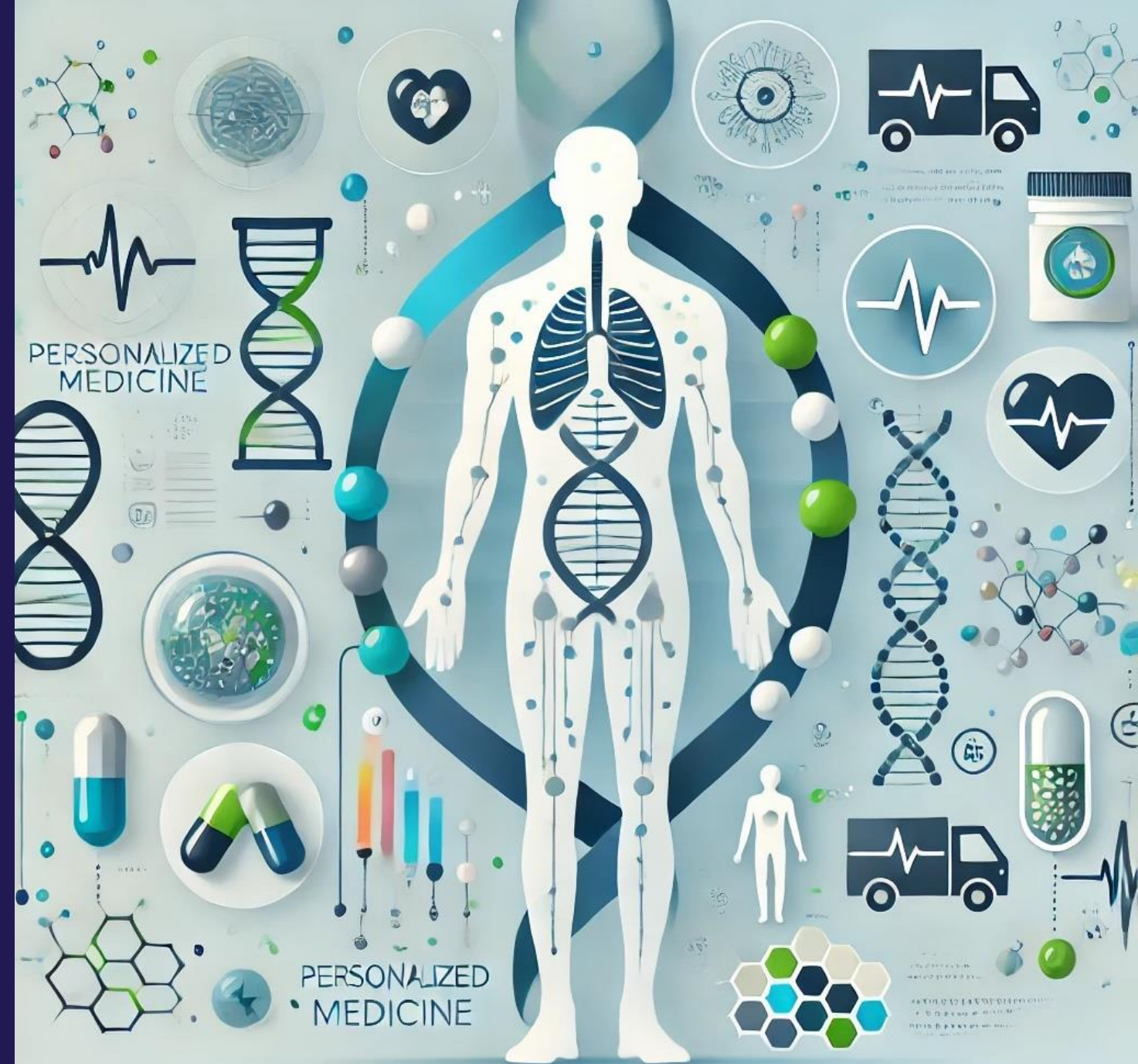
Anne

Krogh Nøhr

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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

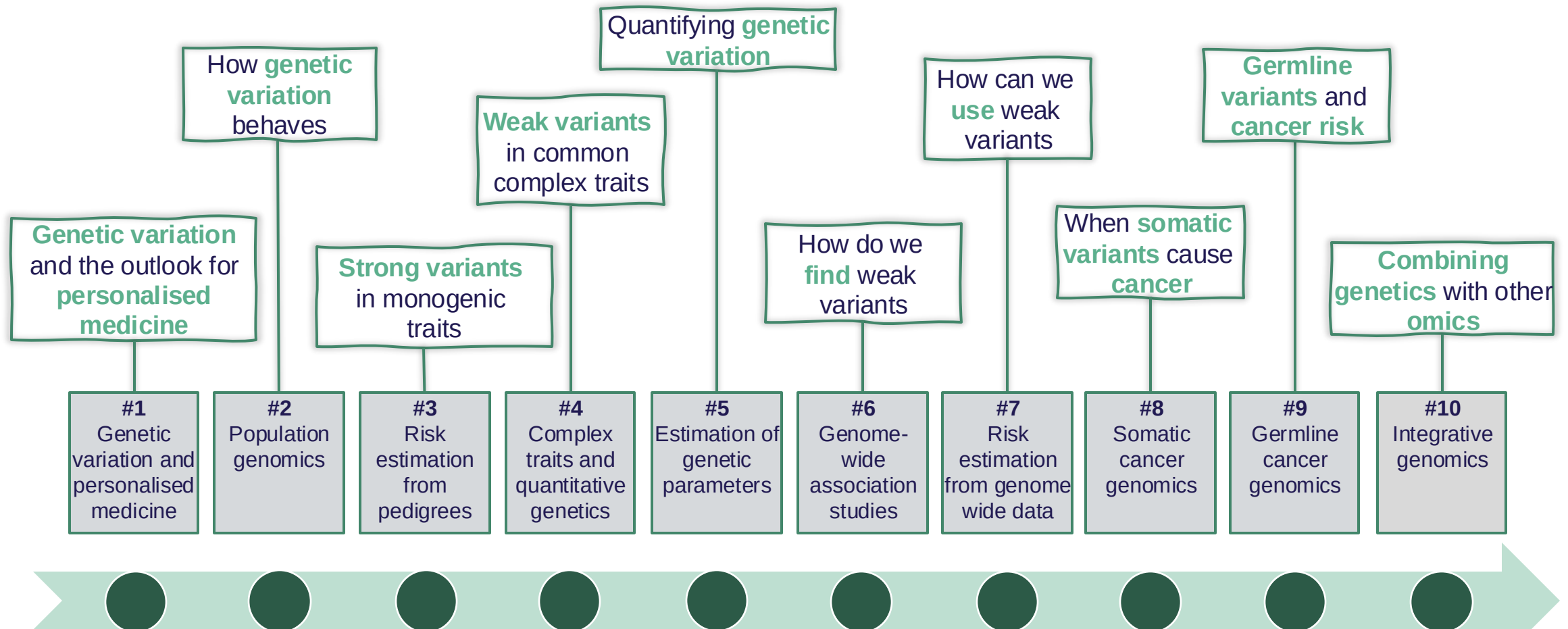
COURSE PLAN

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

#1 Genetic variation and personalised medicine	#2 Population genomics	#3 Risk estimation from pedigrees	#4 Complex traits and quantitative genetics	#5 Estimation of genetic parameters	#6 Genome- wide association studies	#7 Risk estimation from genome wide data	#8 Somatic cancer genomics	#9 Germline cancer genomics	#10 Integrative genomics
5/2-25 [PDR]	7/2-25 [PDR]	12/2-25 [PDR]	27/2-25 [PDR]	6/3-25 [PDR]	17/3-25 [PDR]	24/3-25 [PDR]	31/3-25 [AKN PDR]	7/4-25 [AKN PDR]	16/4-25 [PLM PDR]



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:

#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Genetic variation and personalised medicine	Population genomics	Risk estimation from pedigrees	Complex traits and quantitative genetics	Estimation of genetic parameters	Genome-wide association studies	Risk estimation from genome wide data	Somatic cancer genomics	Germline cancer genomics	Integrative genomics
5/2-25 [PDR]	7/2-25 [PDR]	12/2-25 [PDR]	27/2-25 [PDR]	6/3-25 [PDR]	17/3-25 [PDR]	24/3-25 [PDR]	31/3-25 [AKN][PDR]	7/4-25 [AKN][PDR]	16/4-25 [PLM][PDR]

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.

#1 Introduction to ...



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

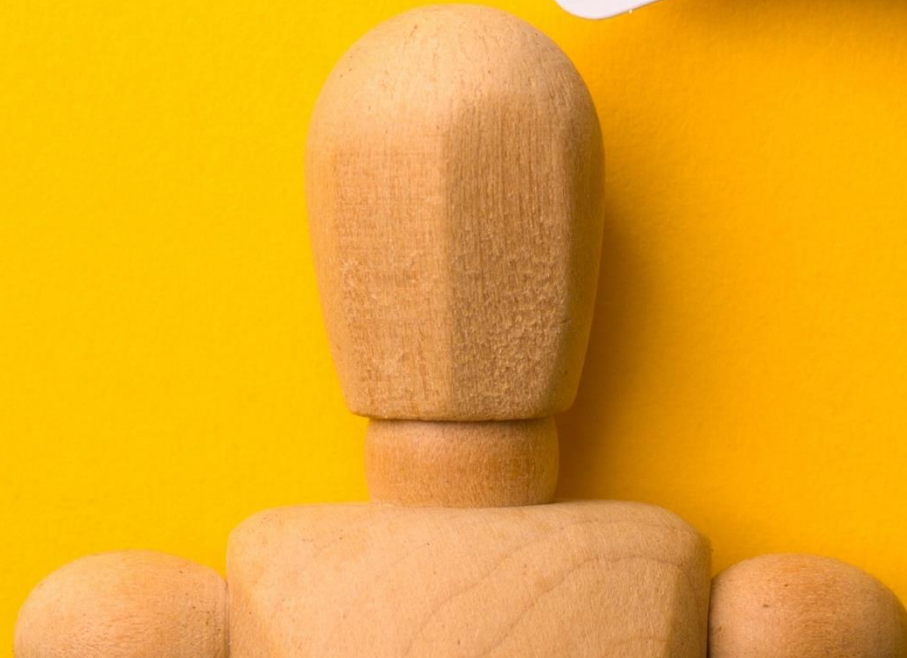
Lecture notes are available at [this link](#) [will be available before the session starts].

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



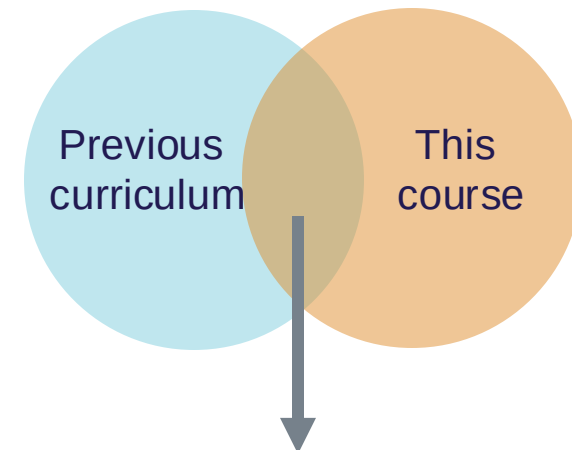
PERSONALISED MEDICINE

4. Semester batchelor curriculum

- The centrale dogma
- Codons and open reading frame
- Genotype, haplotype, locus, allele
- 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) [<i>figure recap</i>]
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11.45 – 12:00	eBoard evaluation + Crossword

OUTLINE



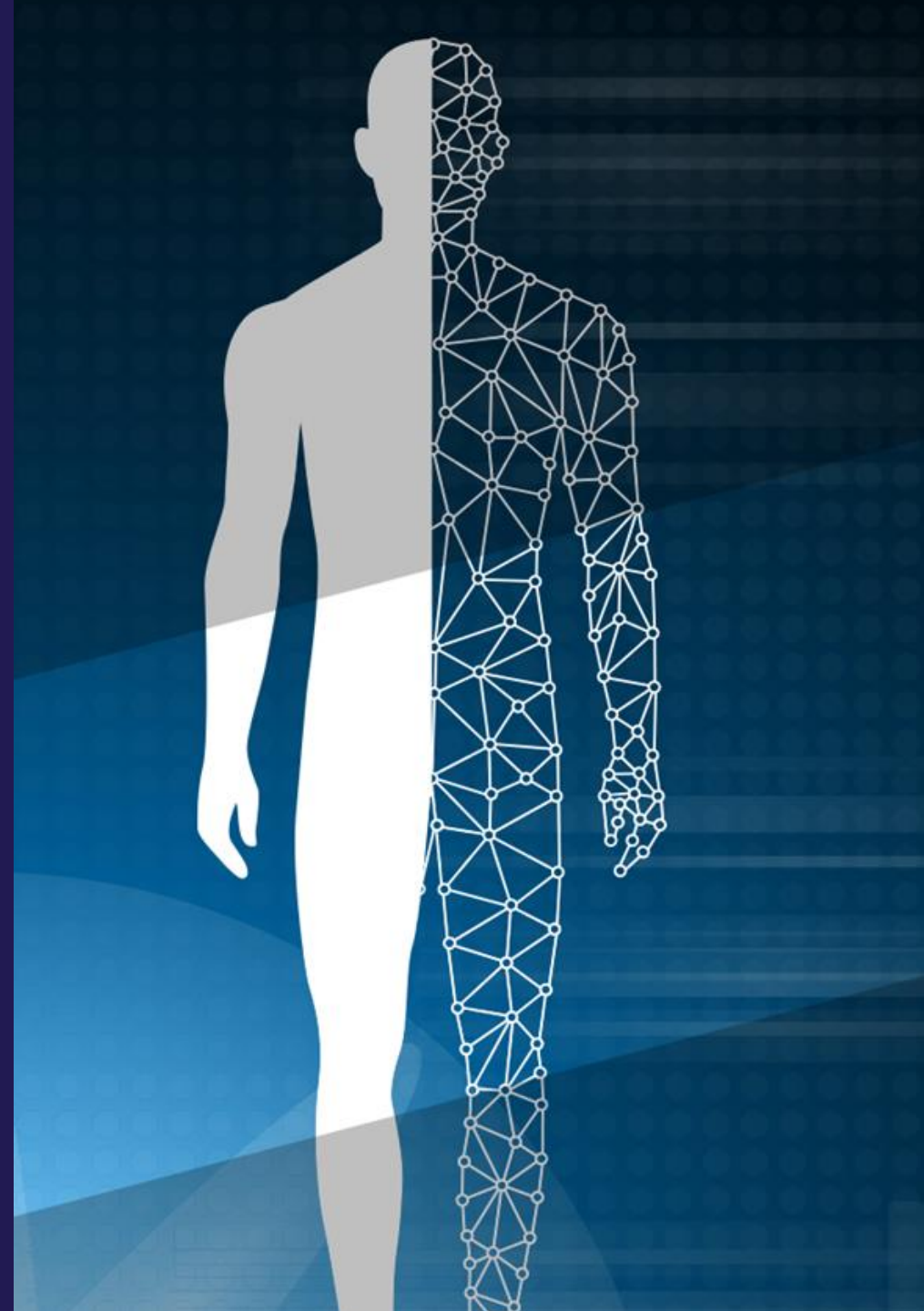
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PERSONALISED MEDICINE

- ❑ 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* ?**

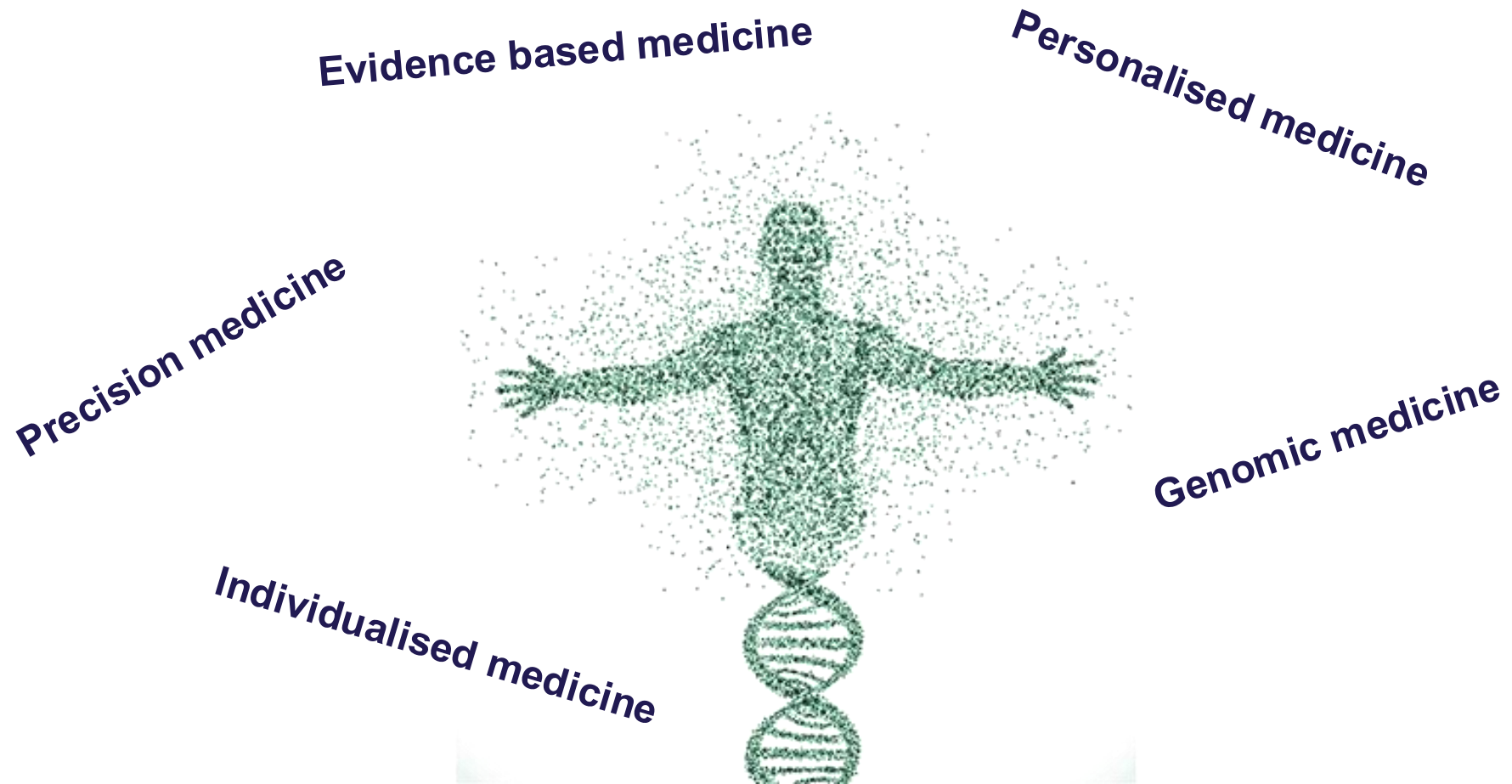
- can you think of an example?





... PM is not new

WHAT IS PERSONALISED MEDICINE?



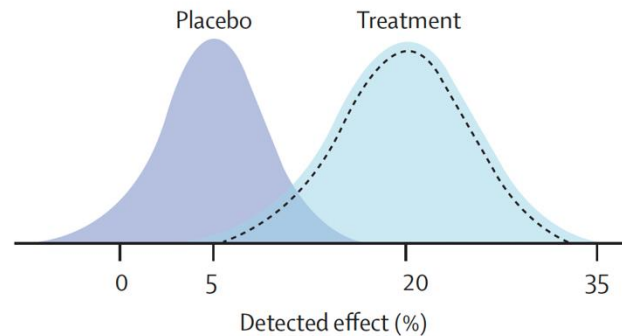
IMPLEMENTATION OF PRECISION MEDICINE

EPPOS [evidence-based precision personalised objective subjective]

Evidence-based Medicine

(1) Contemporary evidence-based medicine

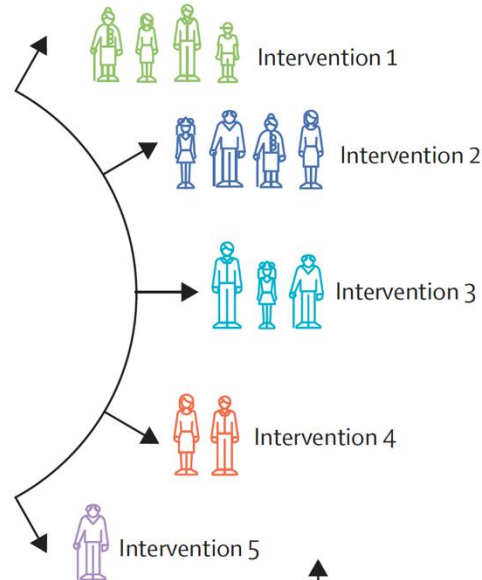
Estimate average risk or response using epidemiological and clinical trial cohorts



Precision Medicine

(2) Probability scoring and stratification

Maximise response and minimise risk using subclassification



Personalised Medicine

(3) Personalisation (objective)

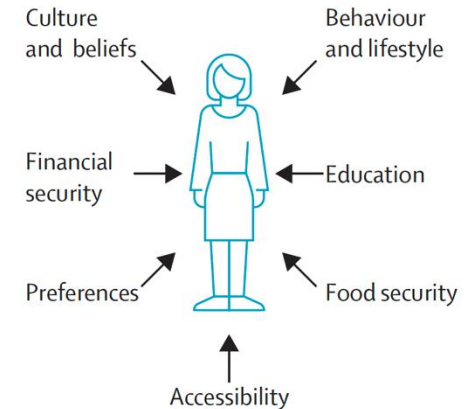
Monitor response to optimise dose, timing, and delivery

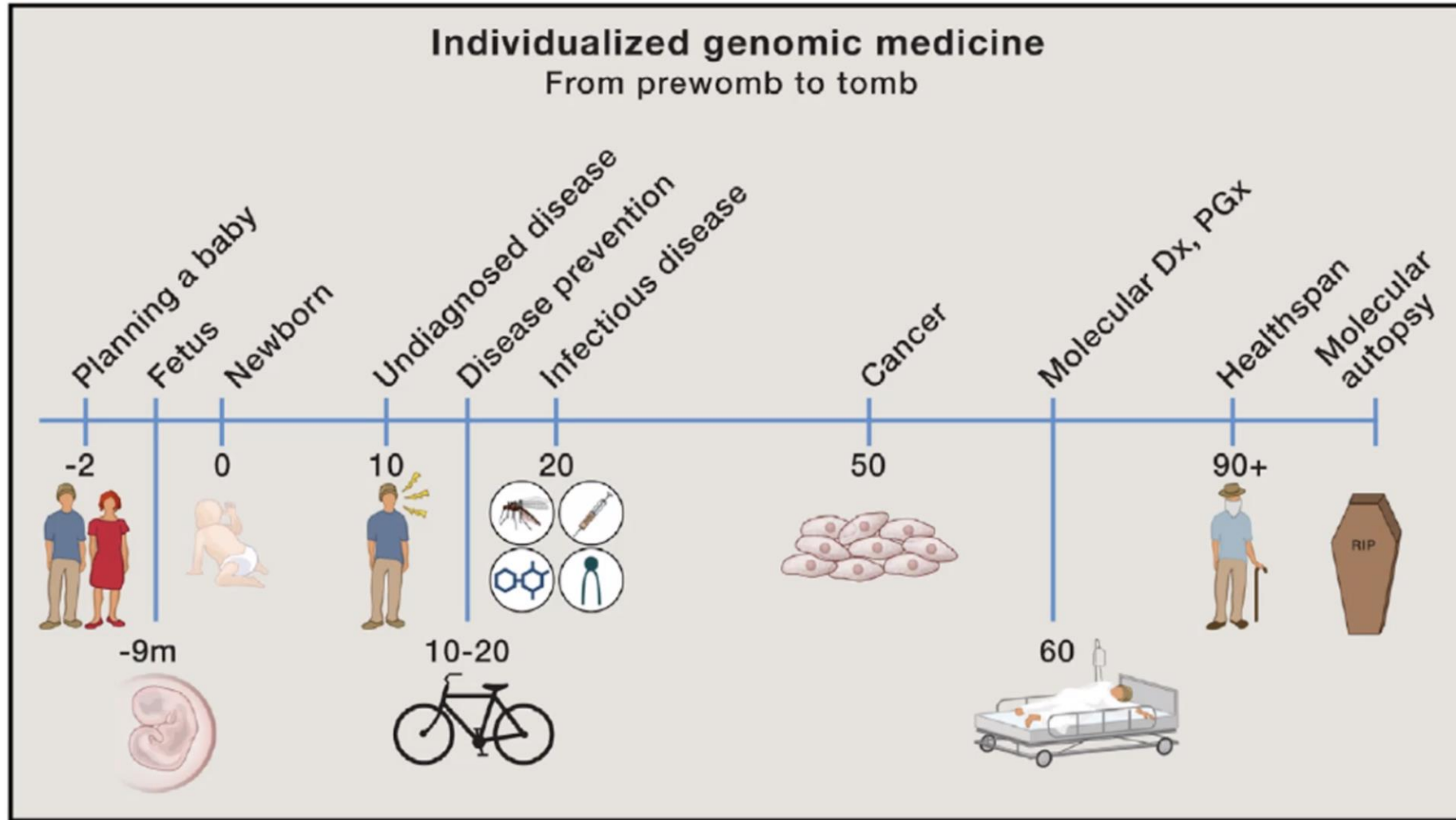


Individualised Medicine

(4) Personalisation (subjective)

Adapt intervention to fit the person's needs, capabilities, and preferences



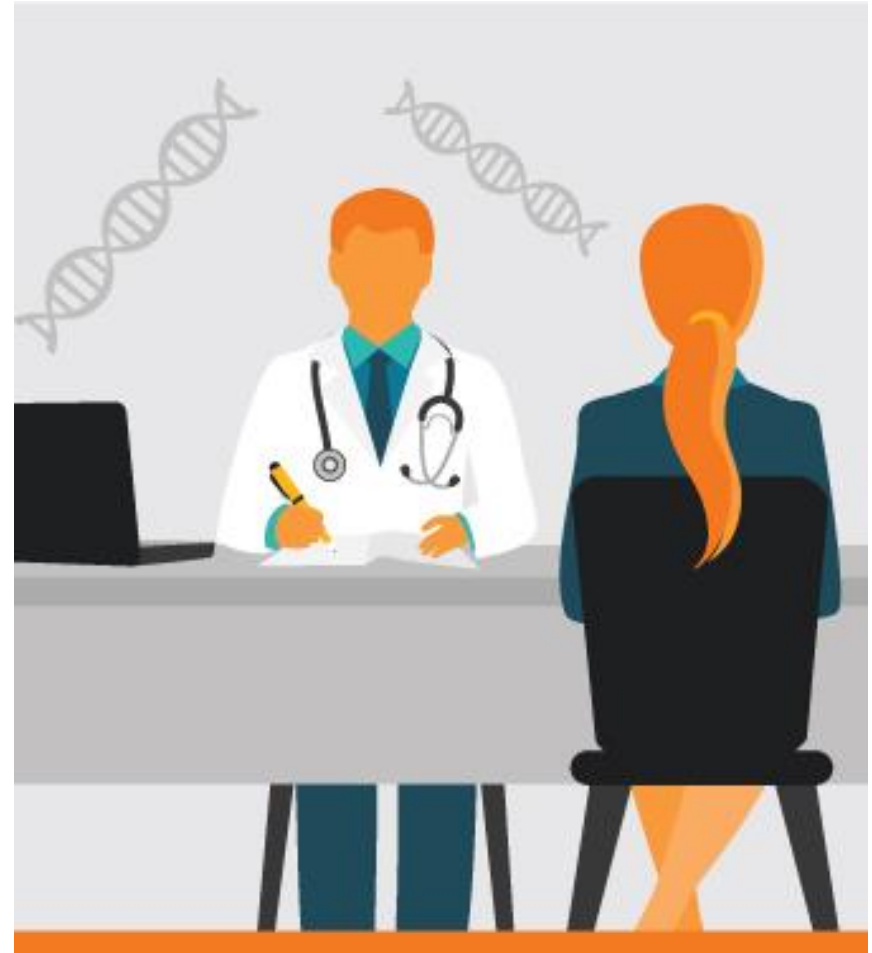


Eric J. Topol. Cell 2014

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.



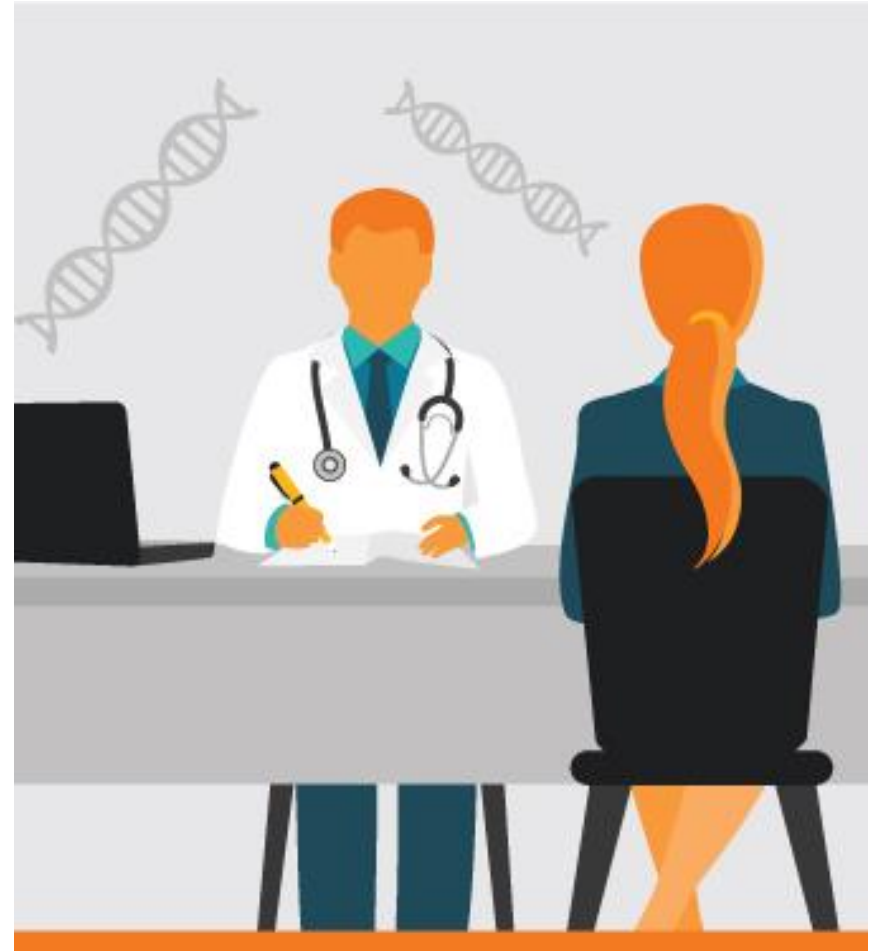
Diagnostics, prognosis, treatment

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.

1. ABILIFY (aripiprazole)
Schizophrenia



2. NEXIUM (esomeprazole)
Heartburn



3. HUMIRA (adalimumab)
Arthritis



4. CRESTOR (rosuvastatin)
High cholesterol



5. CYMBALTA (duloxetine)
Depression



6. ADVAIR DISKUS (fluticasone propionate)
Asthma



7. ENBREL (etanercept)
Psoriasis



8. REMICADE (infliximab)
Crohn's disease



9. COPAXONE (glatiramer acetate)
Multiple sclerosis



10. NEULASTA (pegfilgrastim)
Neutropenia

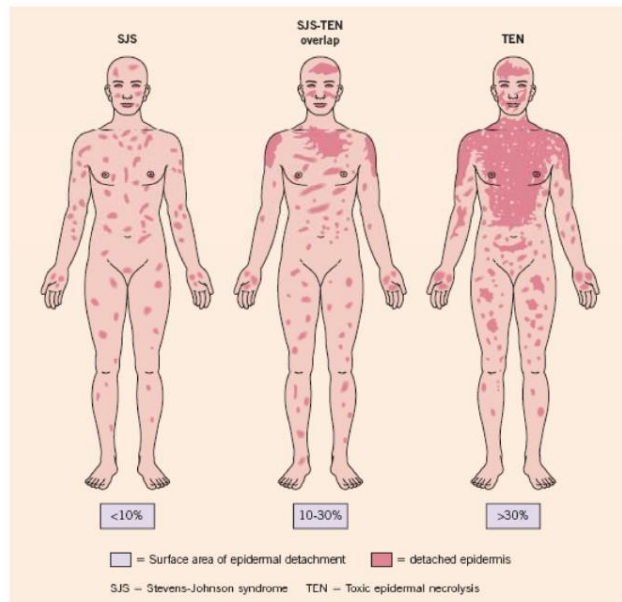


ADVERSE DRUG REACTIONS

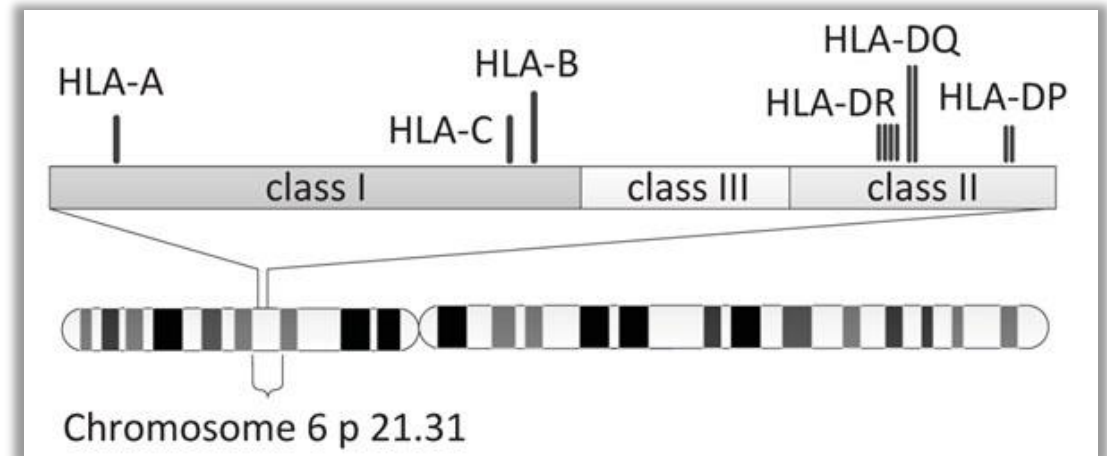


Some medications are directly harmful for certain individuals

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



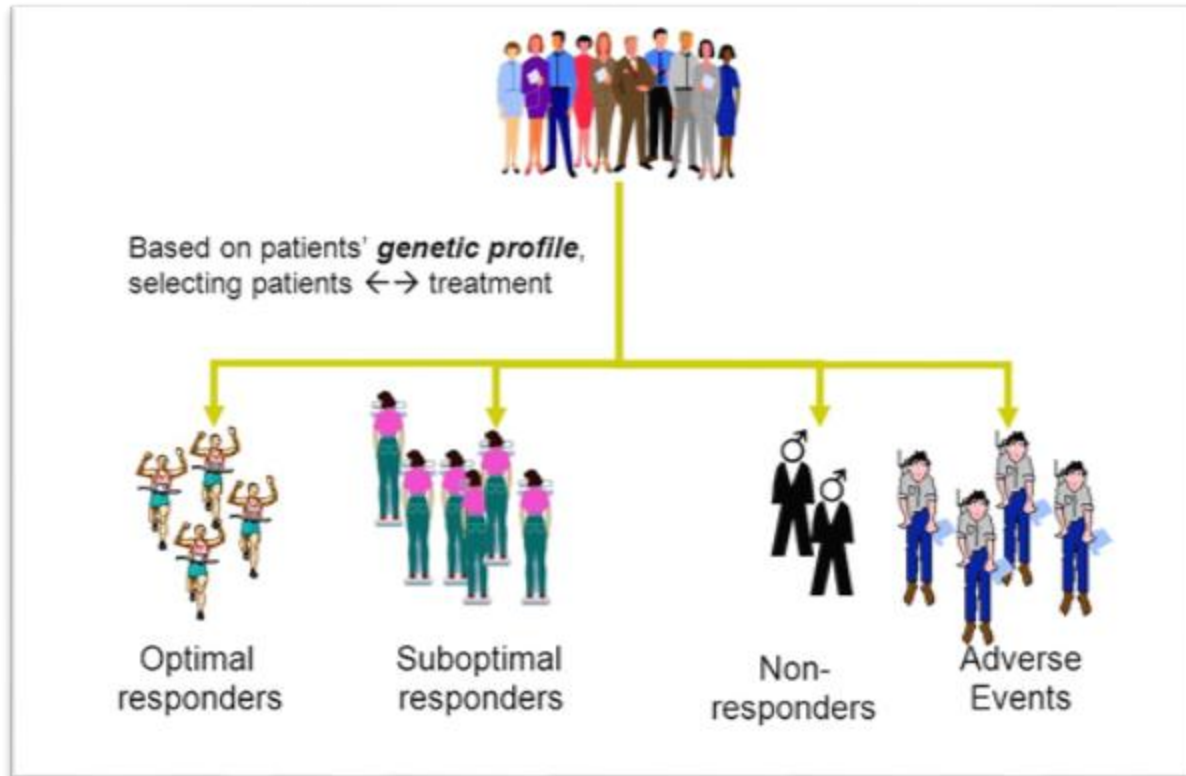
*HLA-B*1502 in Chinese*
*HLA-A*3101 in Caucasians*



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?

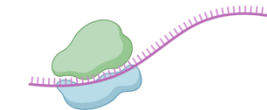
Genes

Genomics



Transcripts

Transcriptomics



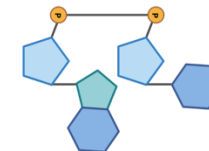
Protein

Proteomics



Metabolites

Metabolomics



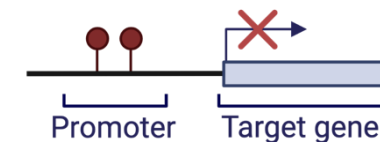
E.g., gut bacteria

Microbiomics



DNA methylation

Methylomics



YOUR TURN

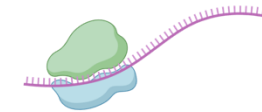
Genes

Genomics



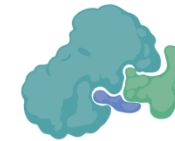
Transcripts

Transcriptomics



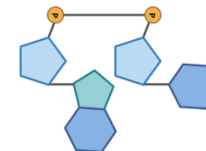
Protein

Proteomics



Metabolites

Metabolomics



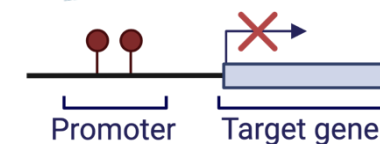
E.g., gut bacteria

Microbiomics



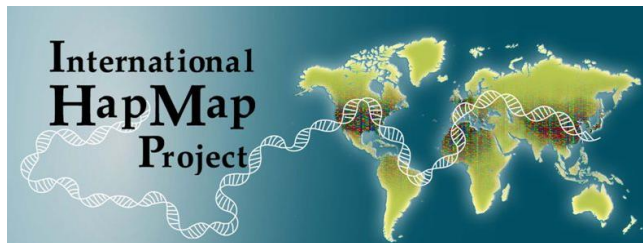
DNA methylation

Methylomics



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



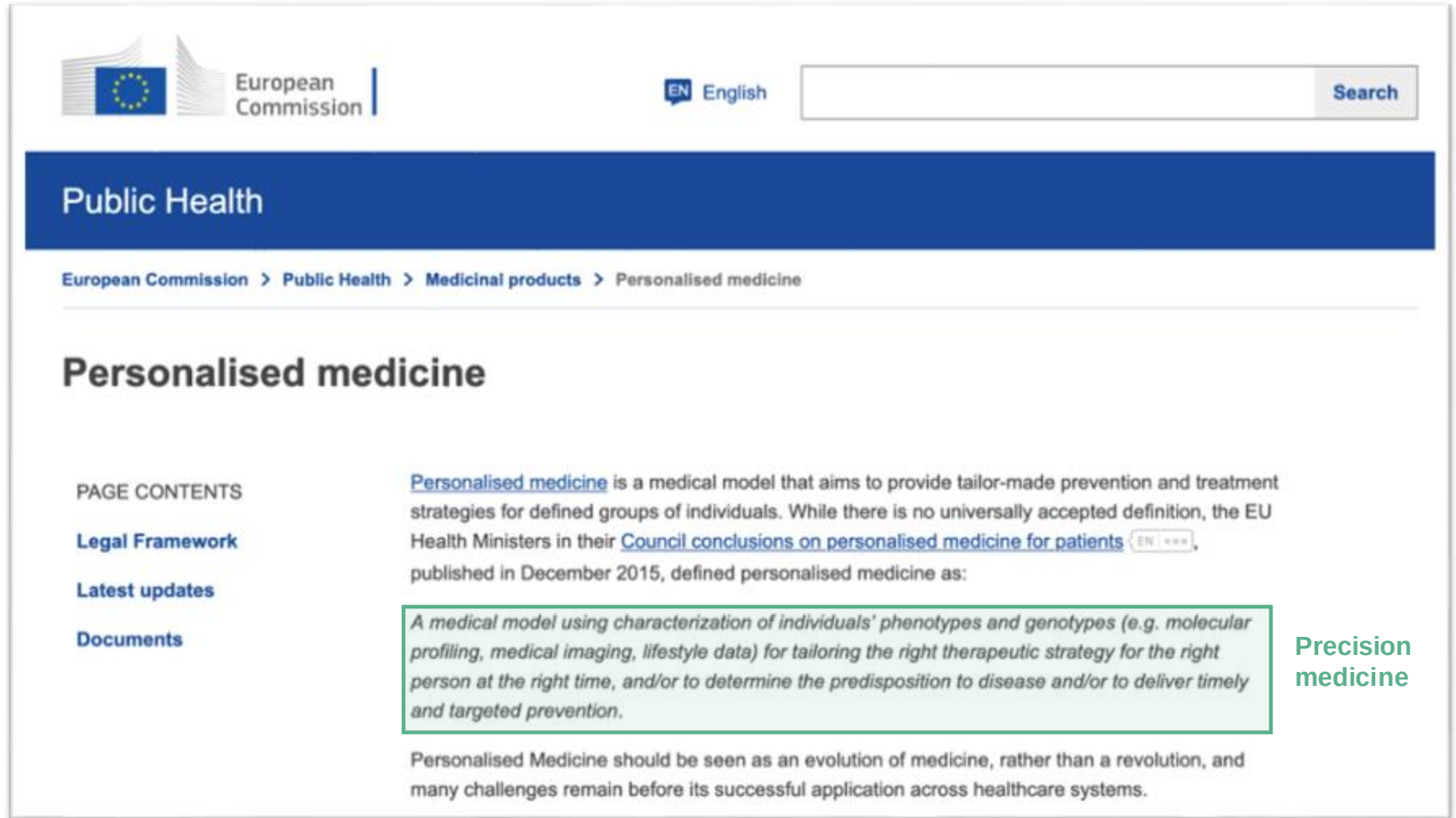
Advances in genotyping and sequencing technologies



Sample collections of adequate size

Large-scale human studies linking genetic variation with disease susceptibility

YOUR TURN



The screenshot shows the European Commission website. At the top, there is the European Commission logo and a language selector set to 'English'. A search bar is located to the right. Below the header, a blue banner reads 'Public Health'. A breadcrumb trail indicates the path: 'European Commission > Public Health > Medicinal products > Personalised medicine'. The main heading is 'Personalised medicine'. On the left, a sidebar lists 'PAGE CONTENTS' with links to 'Legal Framework', 'Latest updates', and 'Documents'. The main content area defines 'Personalised medicine' as a medical model for tailor-made prevention and treatment. A green box highlights the definition: 'A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.' To the right of this box, the text 'Precision medicine' is written in green. Below the definition, it states that Personalised Medicine is an evolution of medicine with many challenges remaining.

European Commission > Public Health > Medicinal products > Personalised medicine

Personalised medicine

PAGE CONTENTS

- Legal Framework**
- Latest updates**
- Documents**

Personalised medicine is a medical model that aims to provide tailor-made prevention and treatment strategies for defined groups of individuals. While there is no universally accepted definition, the EU Health Ministers in their [Council conclusions on personalised medicine for patients](#) EN, published in December 2015, defined personalised medicine as:

A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.

Precision medicine

Personalised Medicine should be seen as an evolution of medicine, rather than a revolution, and many challenges remain before its successful application across healthcare systems.

(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 ?

The background is a dense, abstract pattern of stylized human figures. Each figure is composed of a circular head and a rounded rectangular body. The figures are rendered in a variety of colors, including dark blue, light blue, teal, pink, red, orange, yellow, and white. They are arranged in a way that creates a sense of a large, diverse crowd. The text is centered over this pattern.

**How is personalised medicine
presented to the
society**

***”Delivering the right treatments,
at the right time, every time
to the right person”***



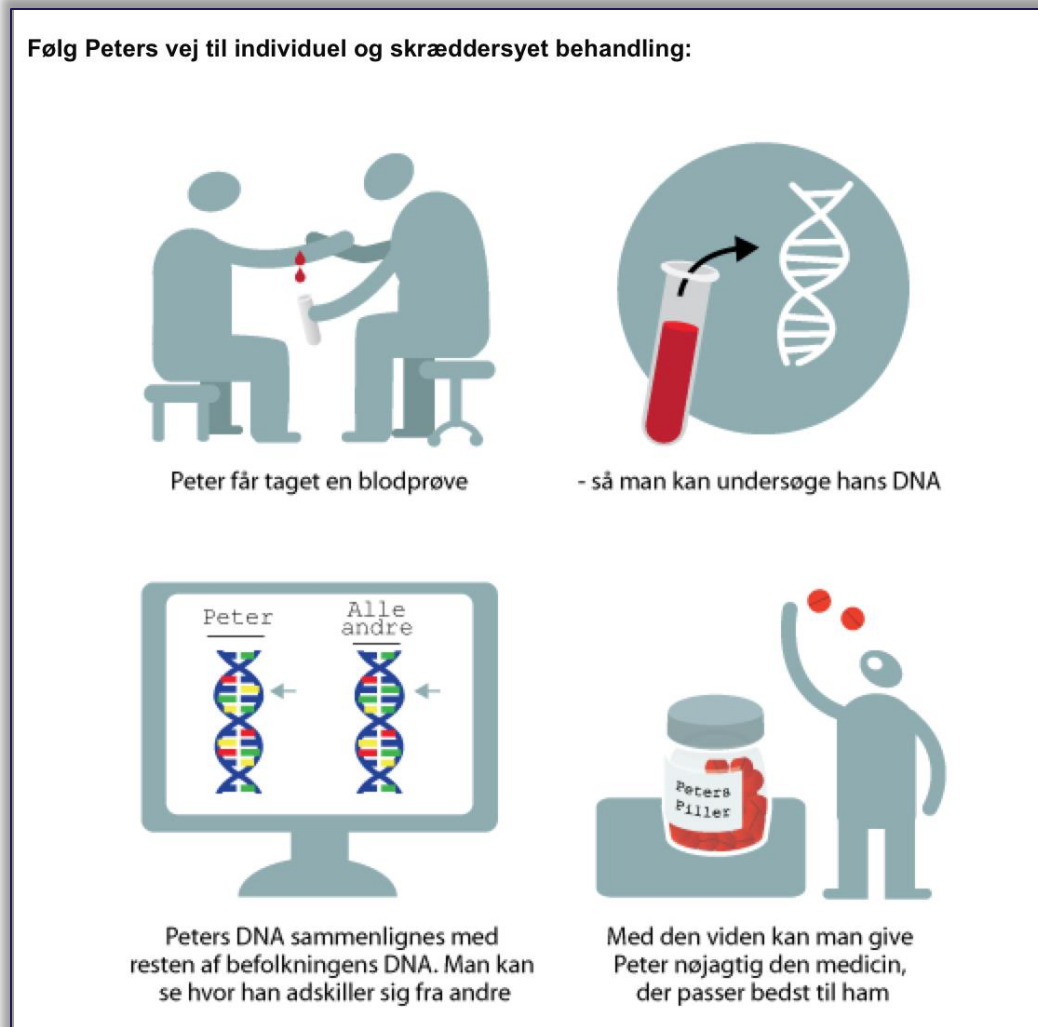
”

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>

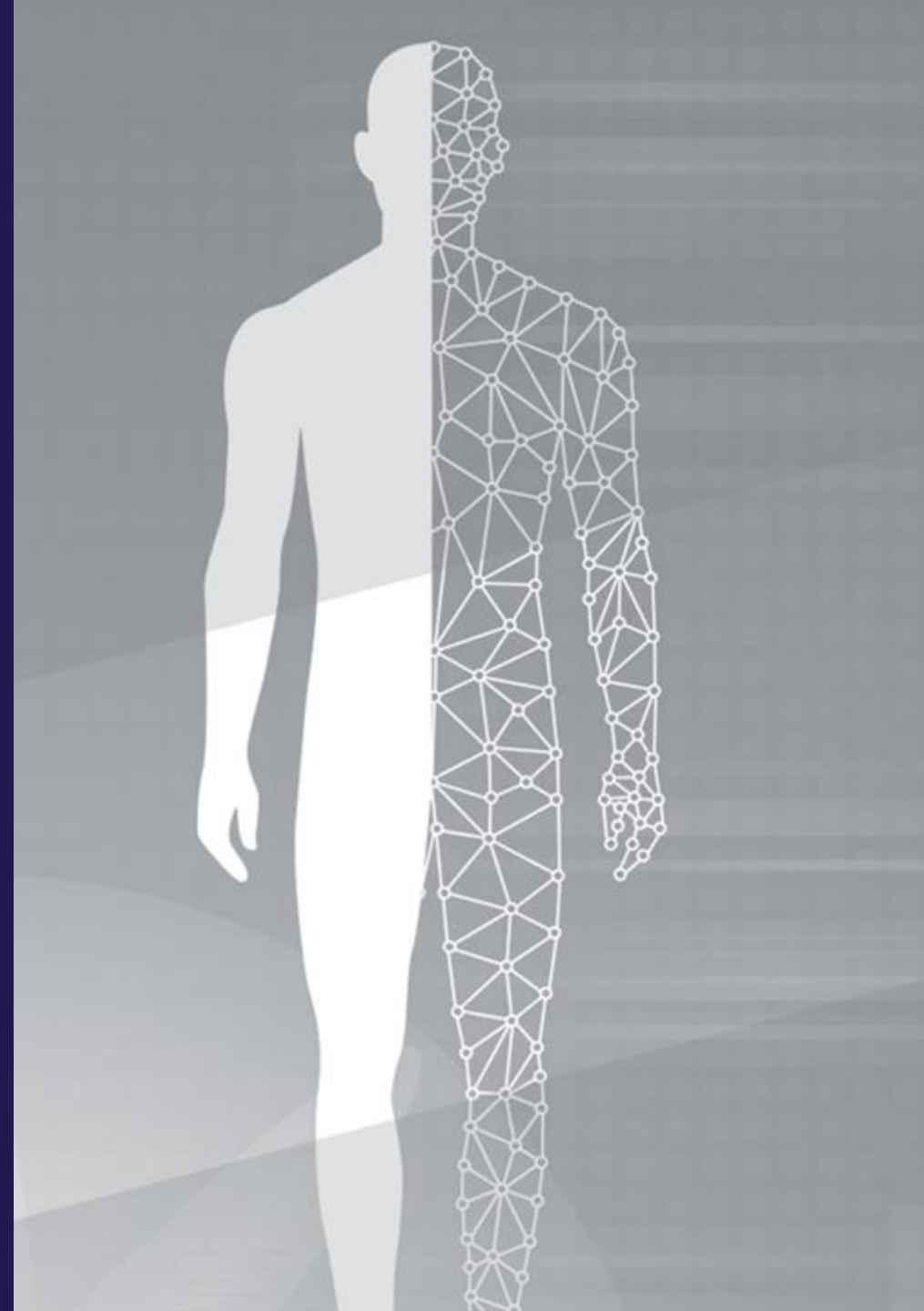


National handleplan 2021

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



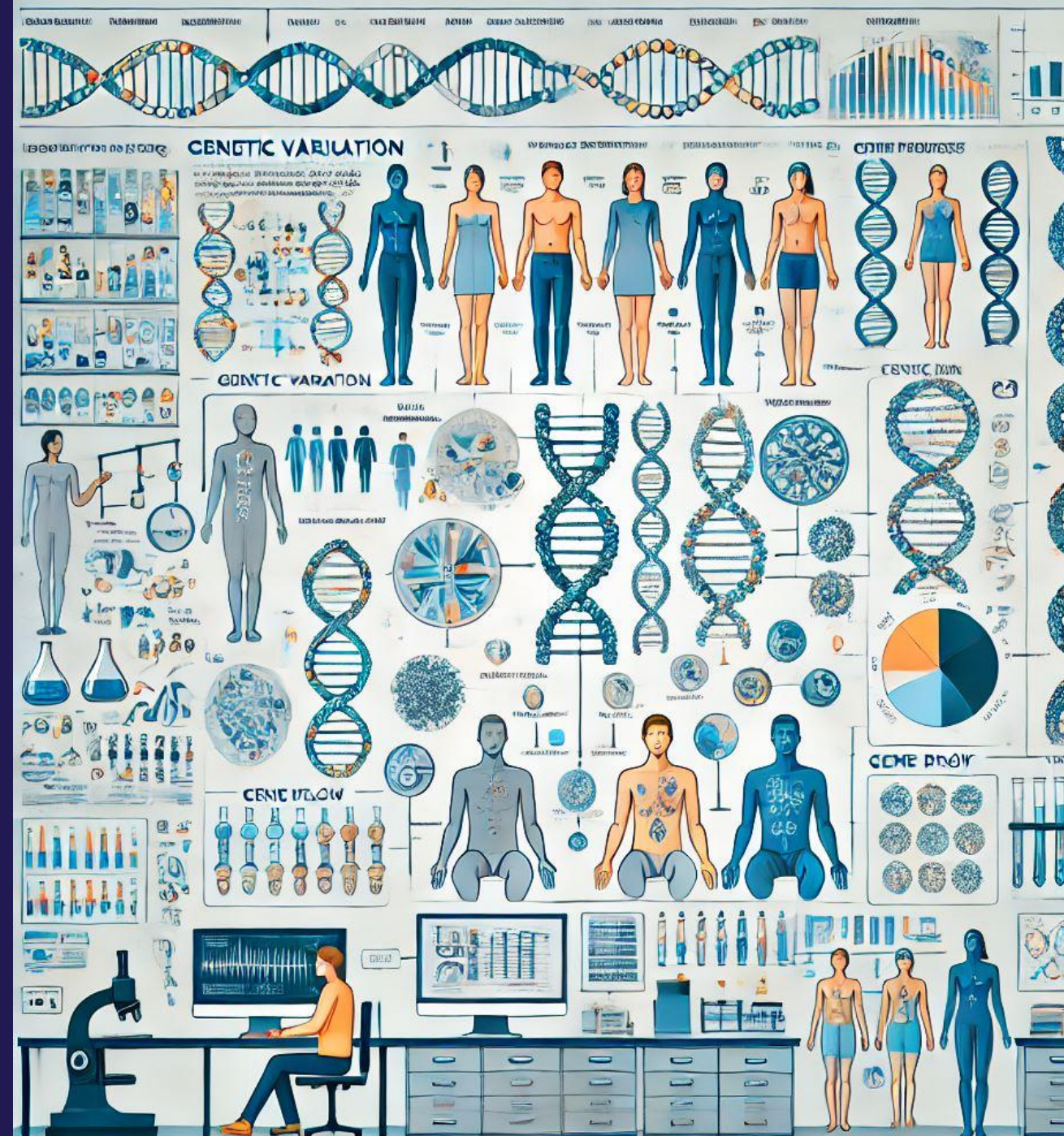
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GENETIC VARIATION

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

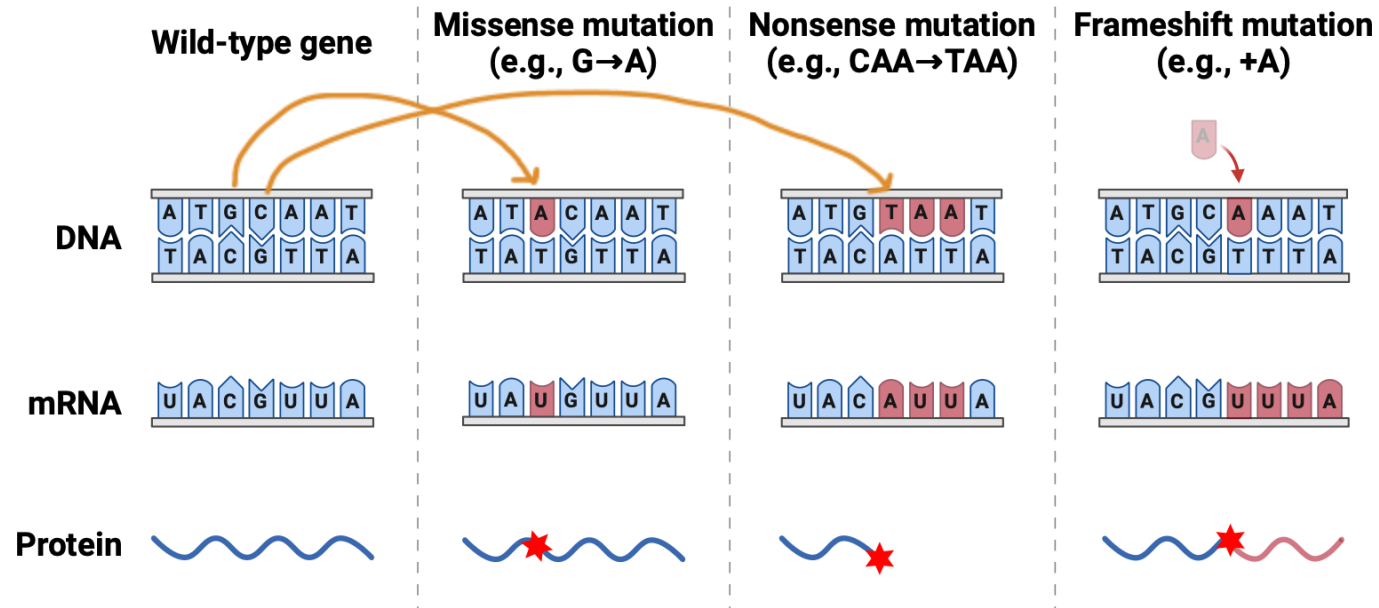


YOUR TURN

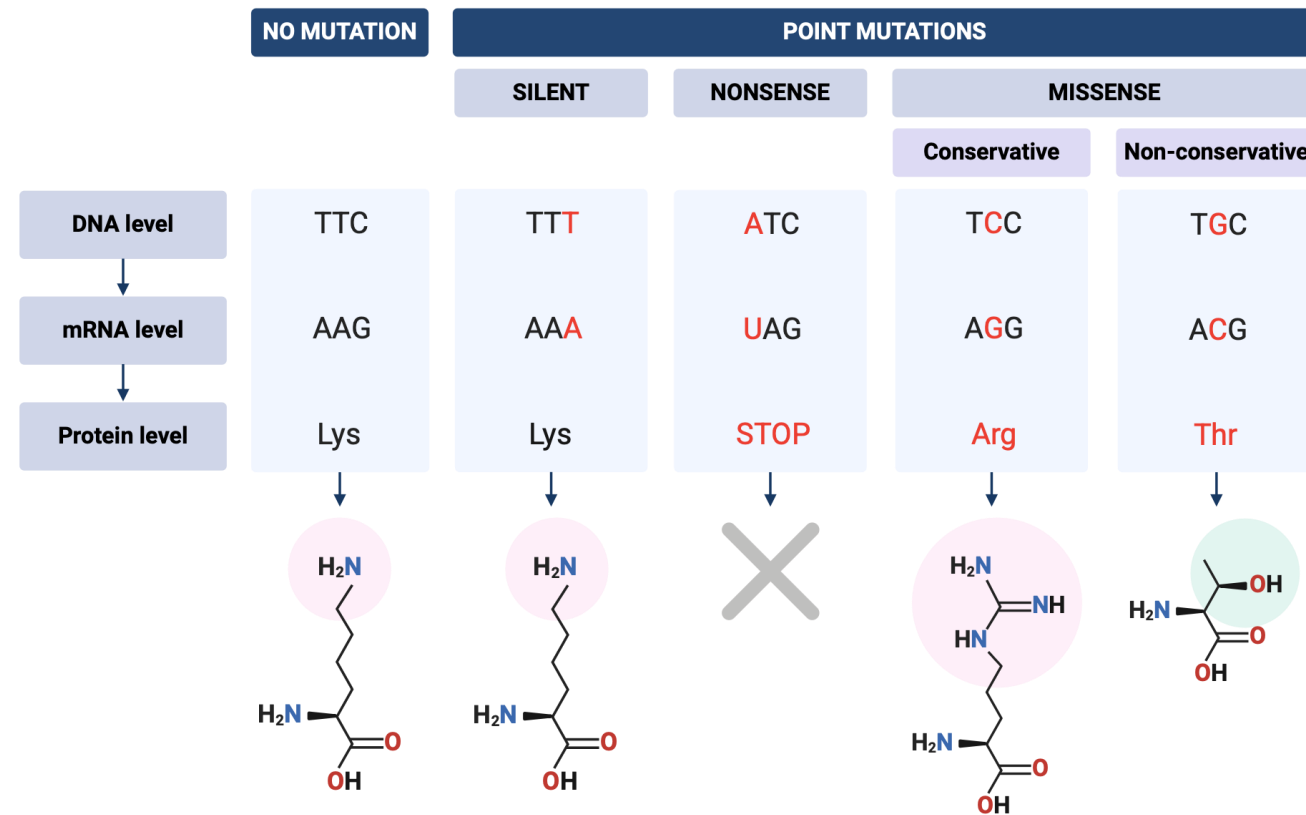
What generates genetic variation?



MUTATIONS GENERATE GENETIC VARIATION



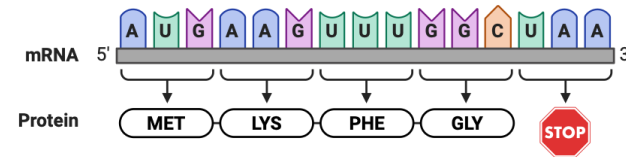
MUTATIONS GENERATE GENETIC VARIATION



MUTATIONS GENERATE GENETIC VARIATION

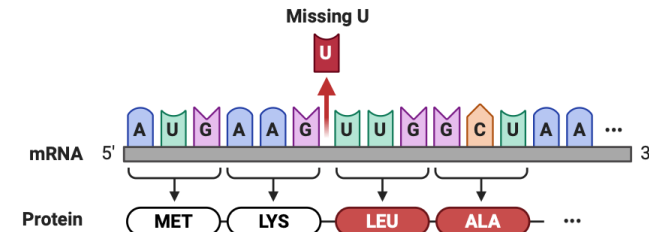
Wild type

mRNA sequence without any mutation



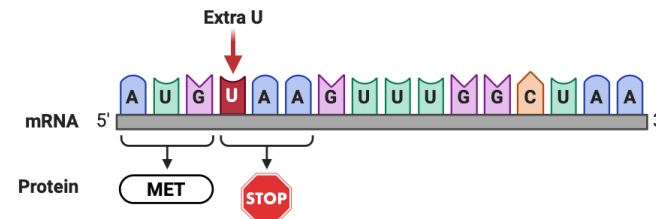
Base-pair deletion

Frameshift causing extensive missense



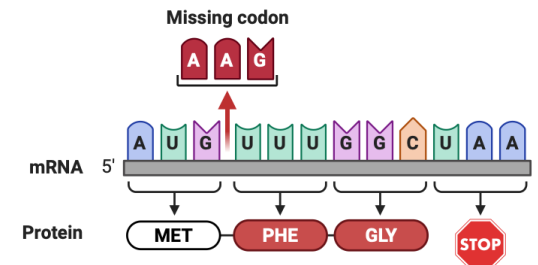
Base-pair insertion

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

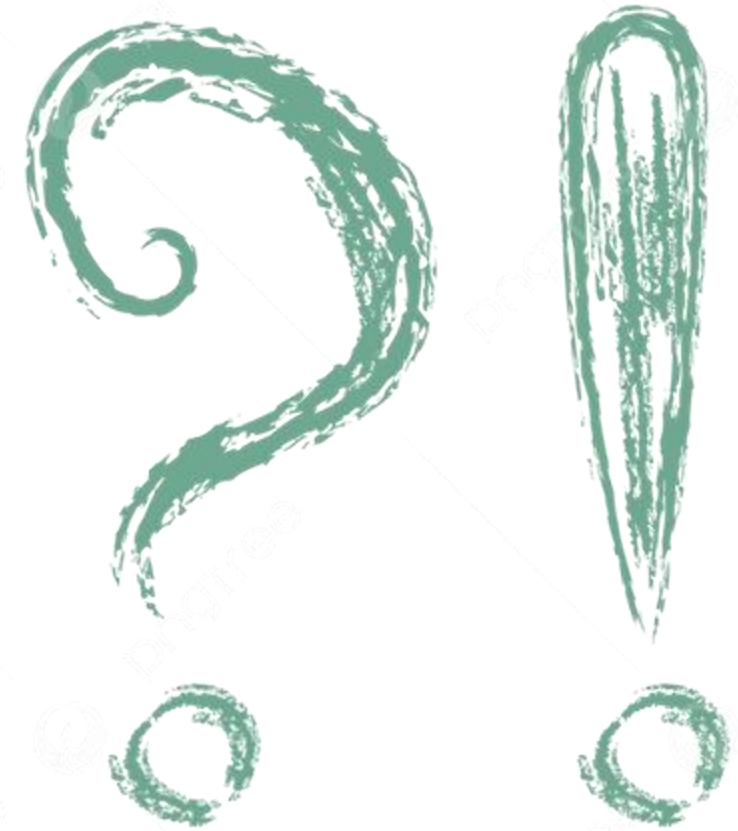
The product is genetic diversity within a population.

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



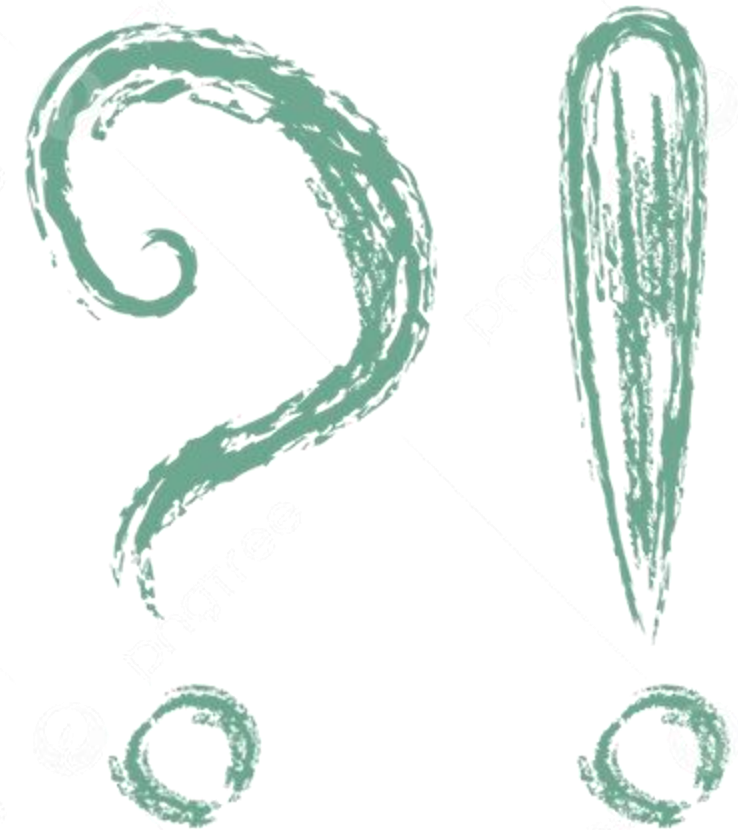
GENETIC TERMINOLOGY 1/2

- ❖ 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 is made up of >20,000 **genes**, and the location of a gene is referred 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**.



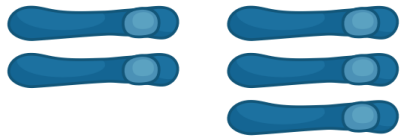
GENETIC TERMINOLOGY 2/2

- ❖ 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 Polymorphisms (**SNPs**, DNA variant freq of >1%)
 - Single Nucleotide Variants (**SNVs**)



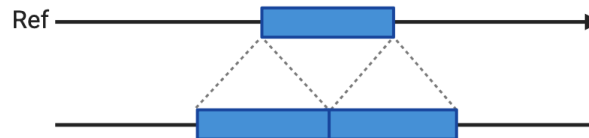
SIZES OF GENETIC VARIATION

Chromosome abnormality



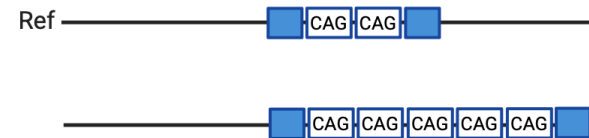
~Chromosome size

Copy number variants



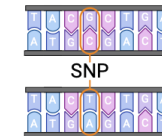
1000 - chromosome

Tandem repeats



2-5 | 15-100 base pairs

Single nucleotide polymorphism (SNP)



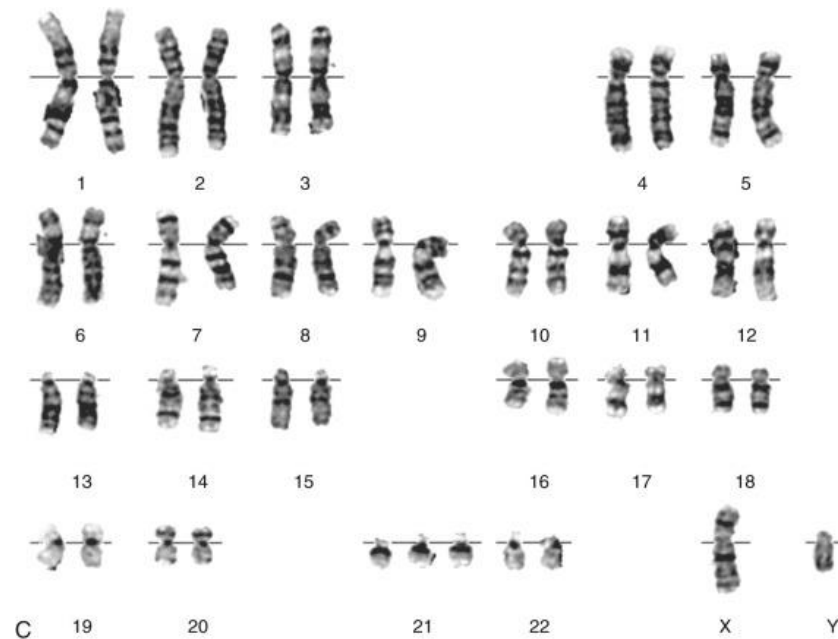
1 base pair

Size of the genetic variant

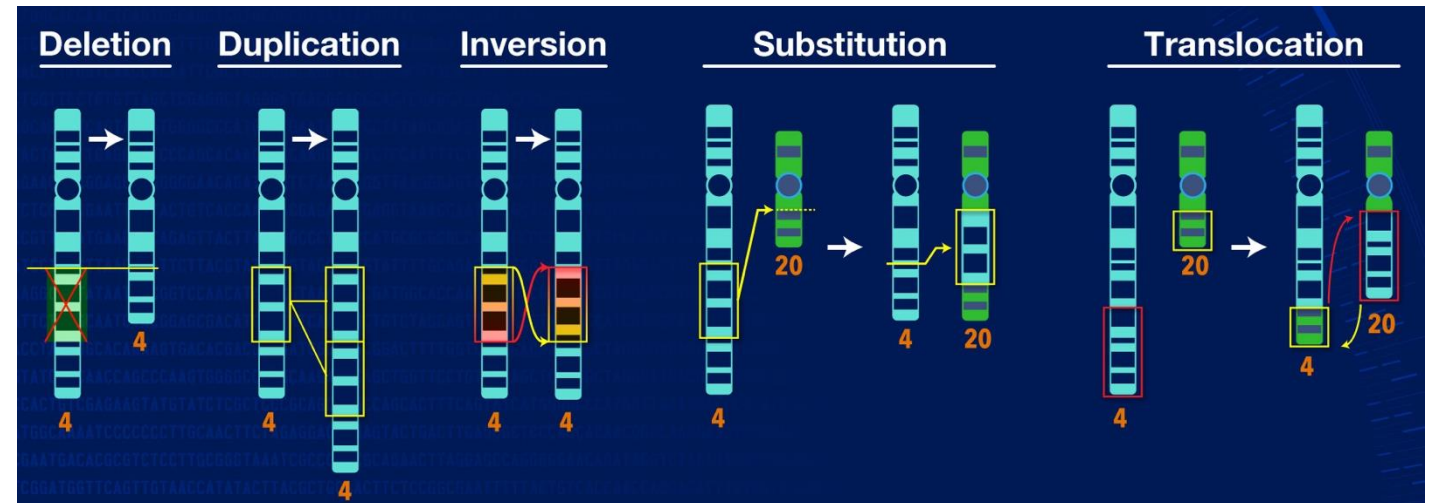
GENETIC VARIATION

CHROMOSOME ABNORMALITIES

Chromosome abnormalities can be numerical or structural.



↖ Trisomi 21



GENETIC VARIATION

TANDEM REPEATS



Advantage:
many many
alleles exists

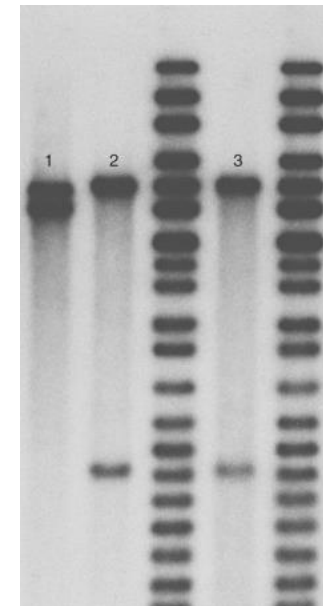
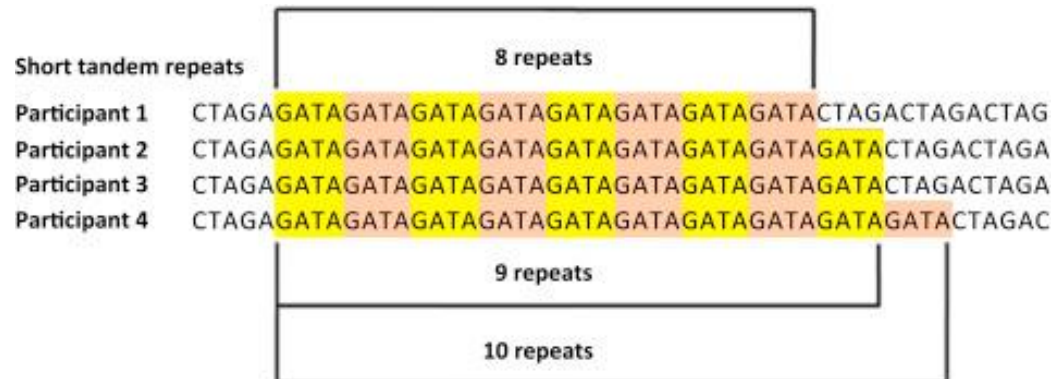
Micro satellites
(2-5 bp) - STRs

Mini satellites
(15-100 bp) -
VNTR



Forensic DNA analysis

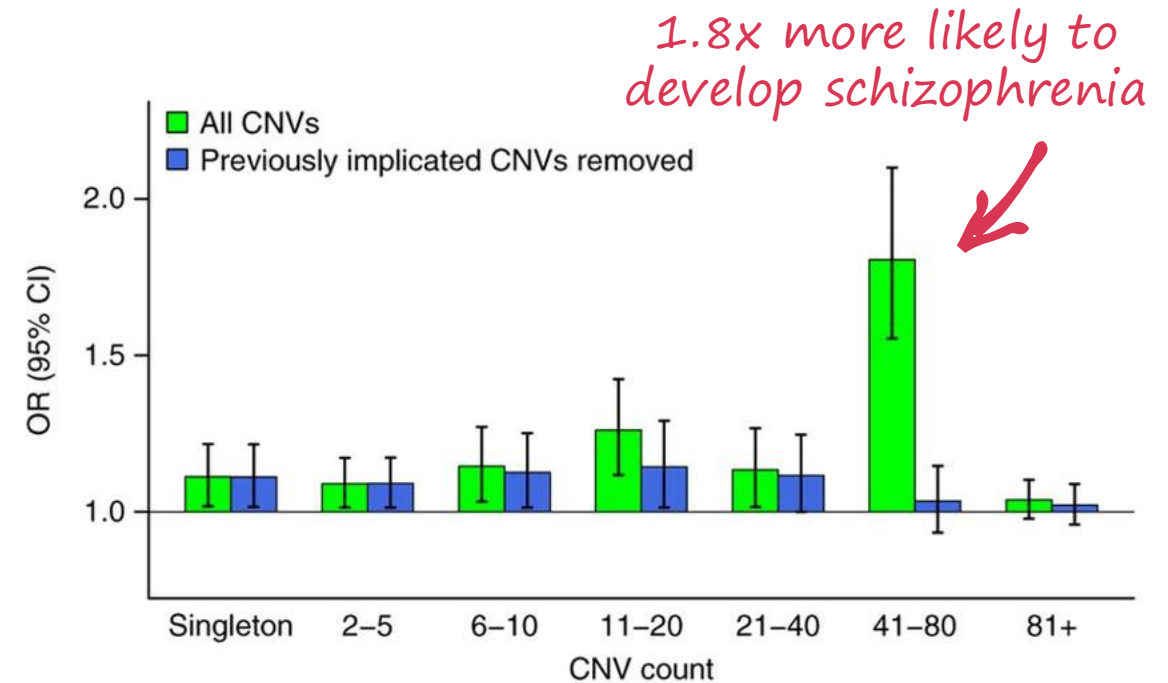
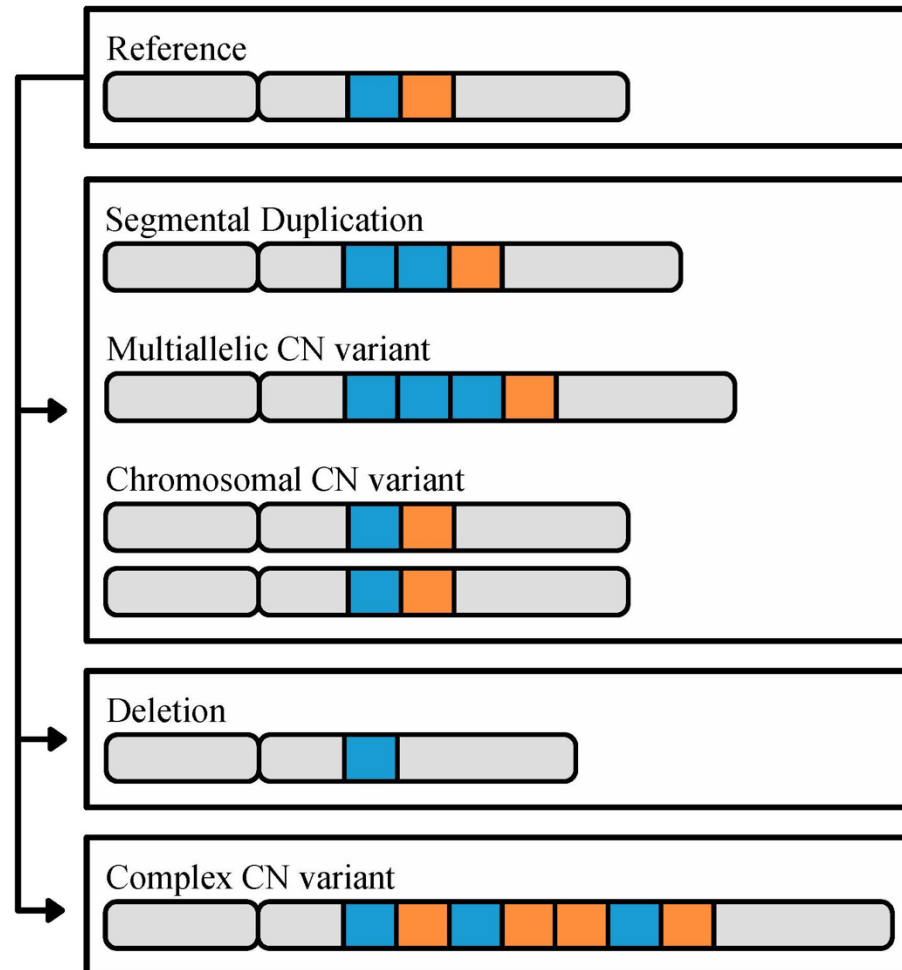
United States, 13 autosomal Short Tandem Repeat (STR) loci are now accepted as the system used for forensic purposes.



GENETIC VARIATION

COPY NUMBER VARIANTS (CNV)

→ 50 bp - kromosom

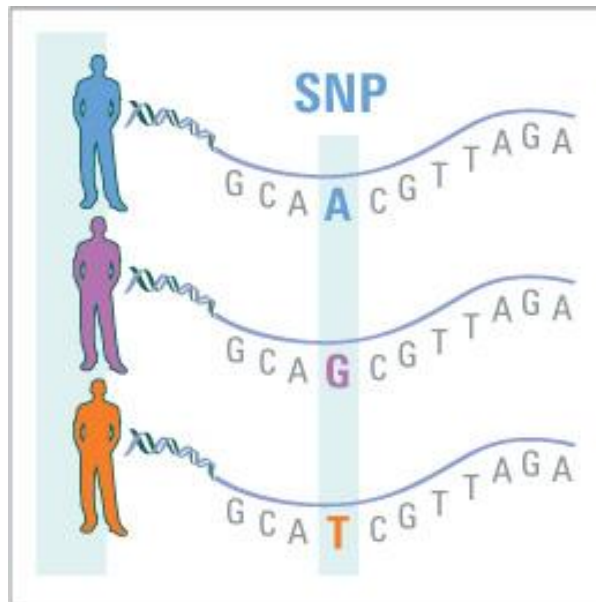


GENETIC VARIATION

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

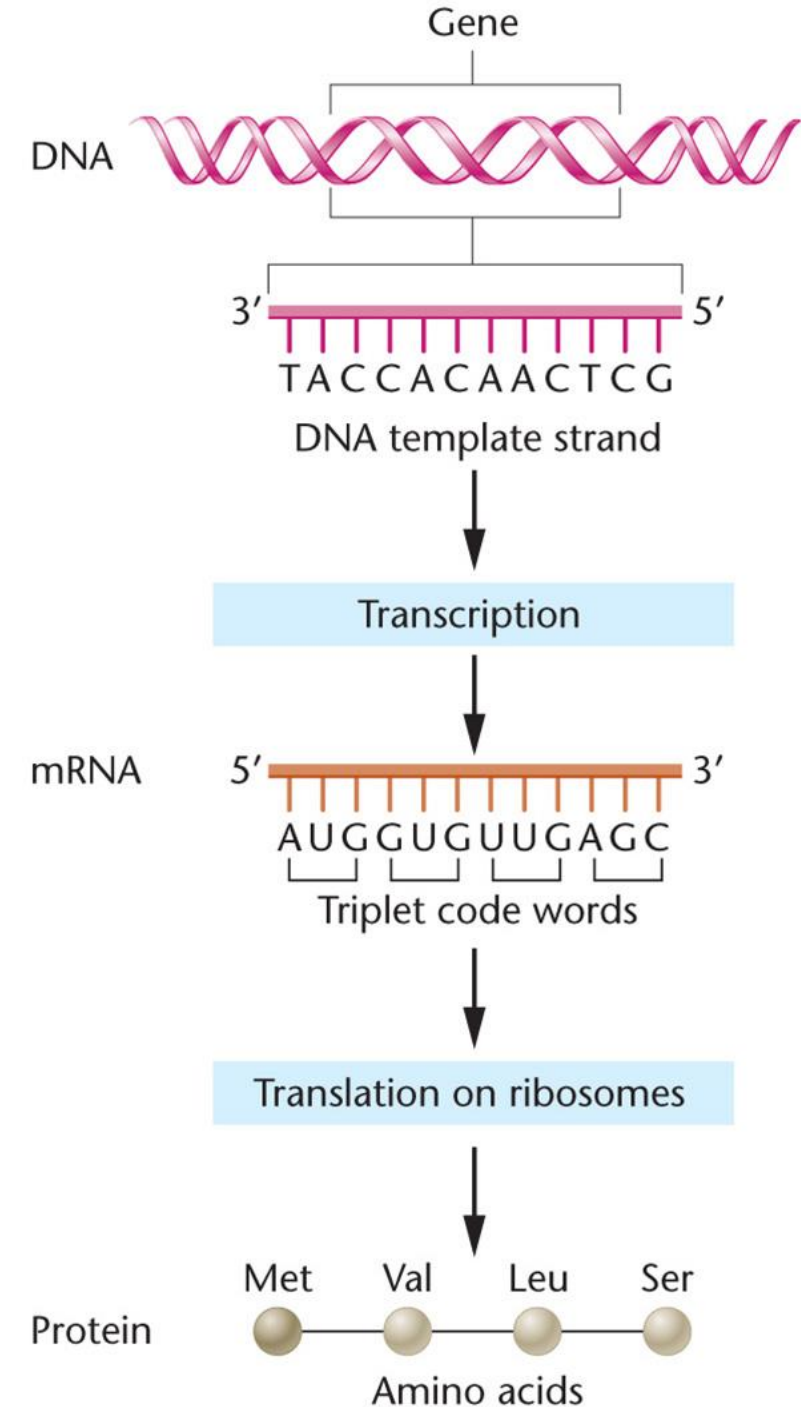
A common change in a single base pair; ~1/1000 bp

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

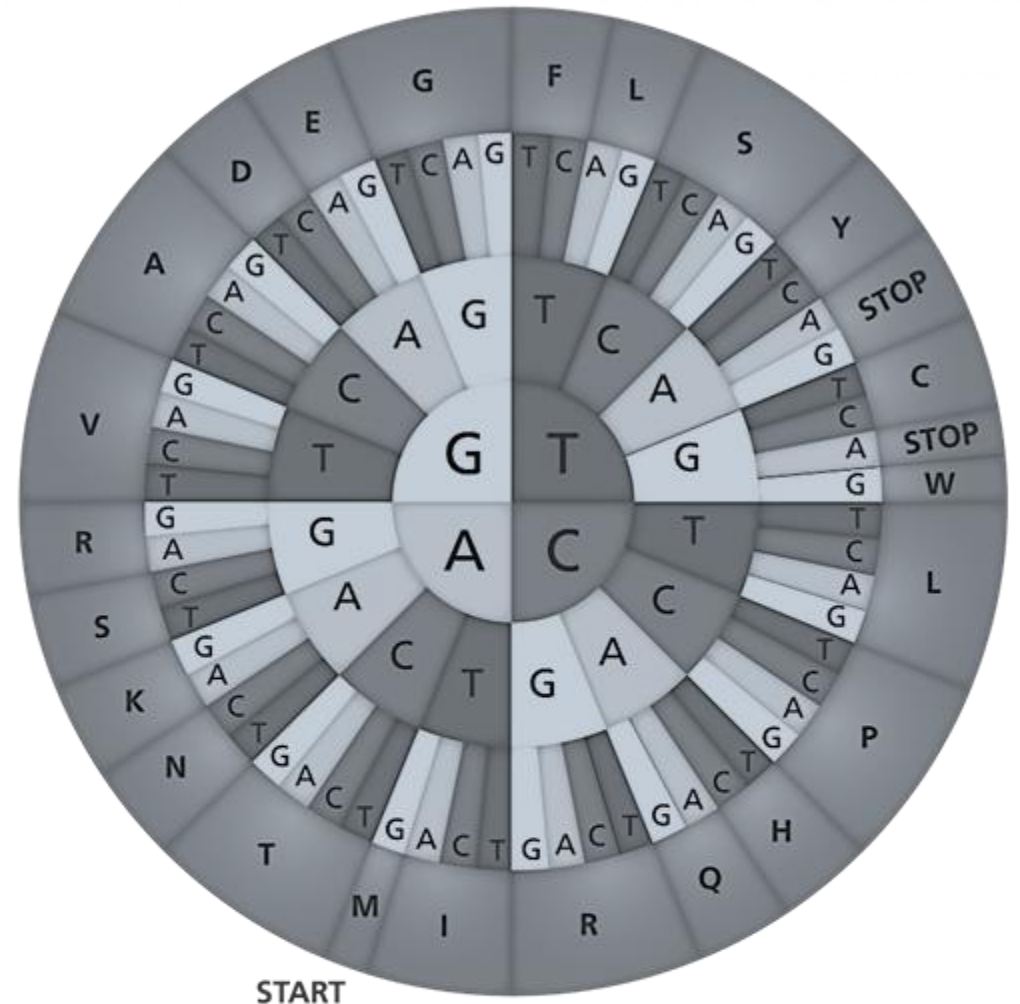
Genetic variation arise as a consequence of changes in the DNA sequence



Can change the order of amino acids



The structure of the protein is changed



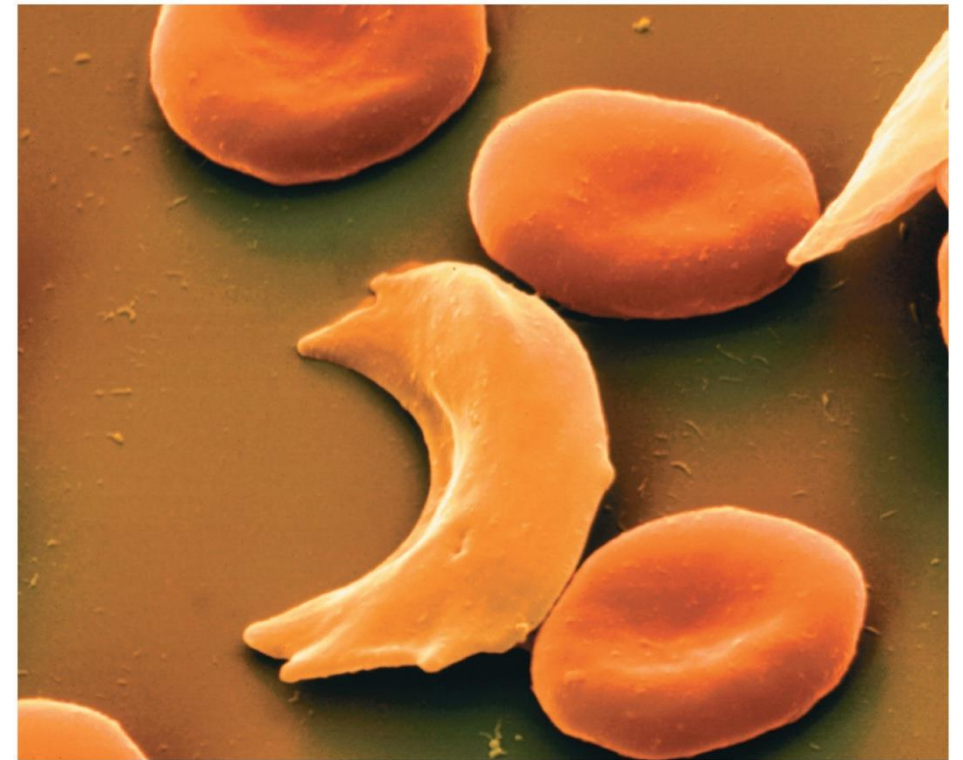
Amino acid code

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

NORMAL β-GLOBIN				
DNA.....	TGA	GGA	CTC	CTC.....
mRNA.....	ACU	CCU	GAG	GAG.....
Amino acid.....	Thr	Pro	Glu	Glu.....
	4	5	6	7
MUTANT β-GLOBIN				
DNA.....	TGA	GGA	CAC	CTC.....
mRNA.....	ACU	CCU	GUG	GAG.....
Amino acid.....	Thr	Pro	Val	Glu.....
	4	5	6	7

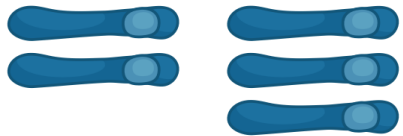
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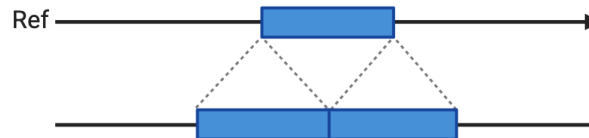
SIZES OF GENETIC VARIATION

Chromosome abnormality



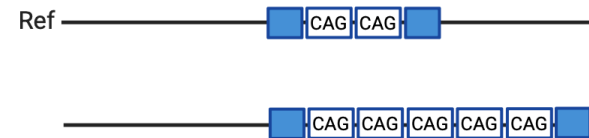
~Chromosome size

Copy number variants



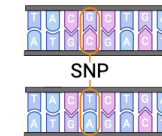
1000 - chromosome

Tandem repeats



2-5 | 15-100 base pairs

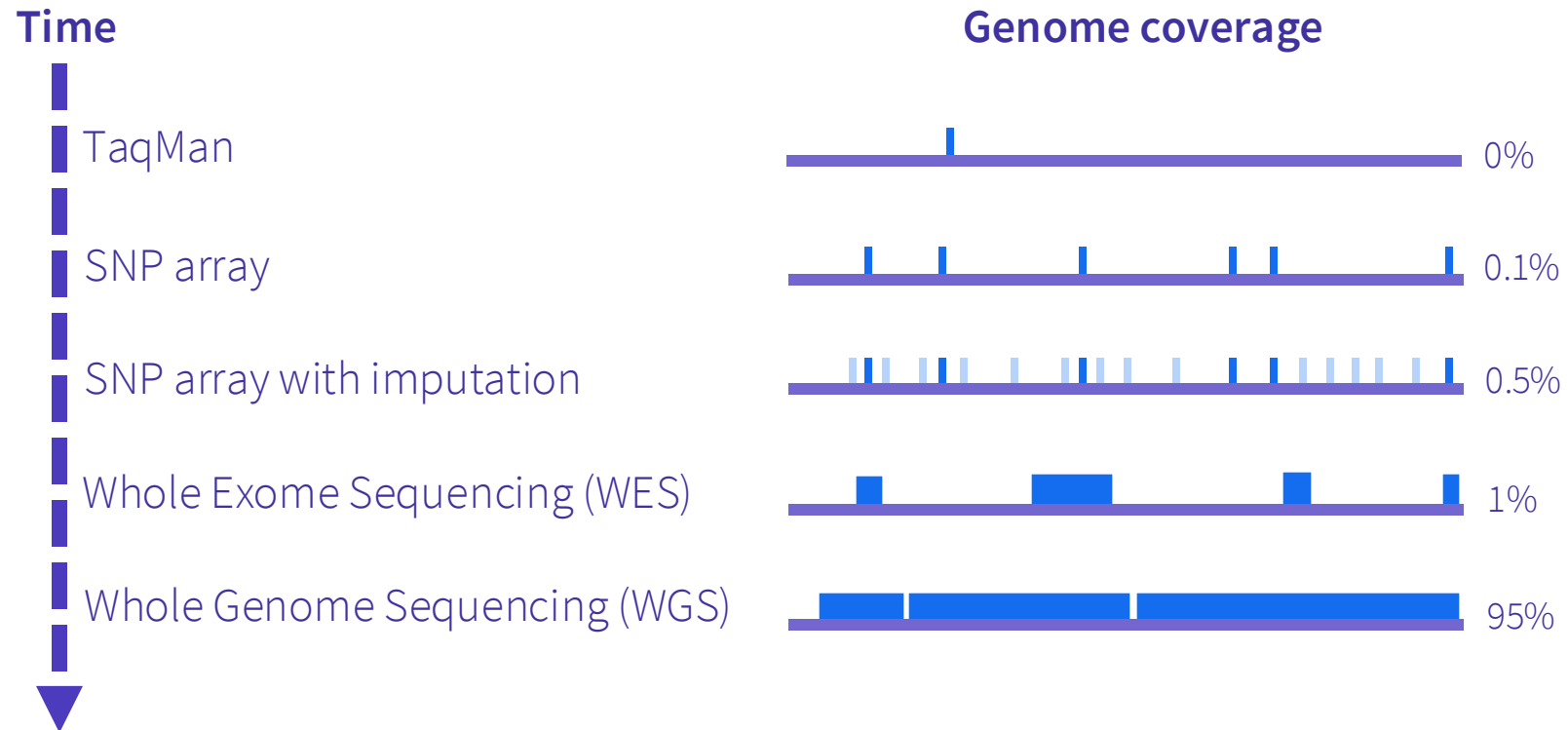
Single nucleotide polymorphism (SNP)



1 base pair

Size of the genetic variant

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

AGCTGAAGGAGTGTGGCCAATCTGCTCCACCTCCCGCGGACCCCTACTCTCAGGACCTCTGCAGCACCCCAAACCTGGAAGTGGCCGCTGCAGACCCAAAGACGAGGGGCACGCGGGAGCCG GCAGCCCTAGTGAGCGGTGGAGATGTTGAGGTGGGAGGGT CACCC
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CGGGGGCGCTTT CTT CCTCGGAGTGGAAA GATTCA GCCTGCGGA GTGGTGATGCT ATTTTT CTCTTGA ACTGTACAGCCCTTCATGACCTTCCATGGGCTTGAATCCA GATGTGCAGTTTCTTTGTATAA TTAAT ACTATCTGGGCACTGATGATGAGTTTGAATATGT
GAAATTGCCCTGTGAAGTGTTT

GENOTYPING VS SEQUENCING

Genotyping

[illegible]

GENOTYPING VS SEQUENCING

Genotyping

WES

[illegible]

GENOTYPING VS SEQUENCING

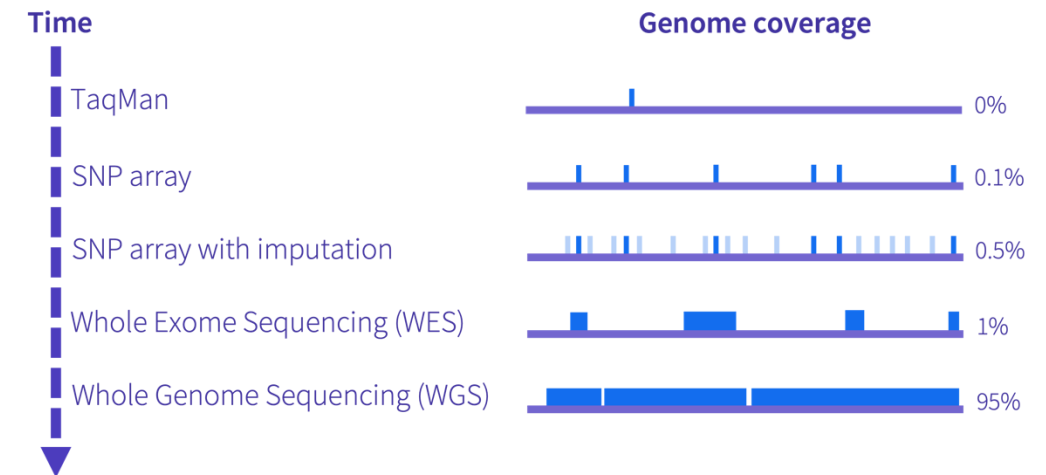
Genotyping

WES

WGS

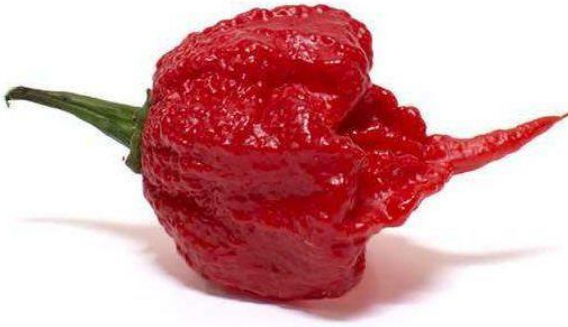
WHICH TECHNOLOGY?

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



GENETIC VARIATION IS LIKE CHILI

Carolina reaper



Strong effect on phenotype

Habanero Lemon



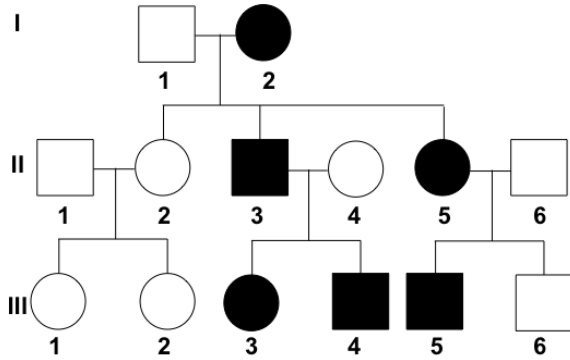
Moderate effect on phenotype

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



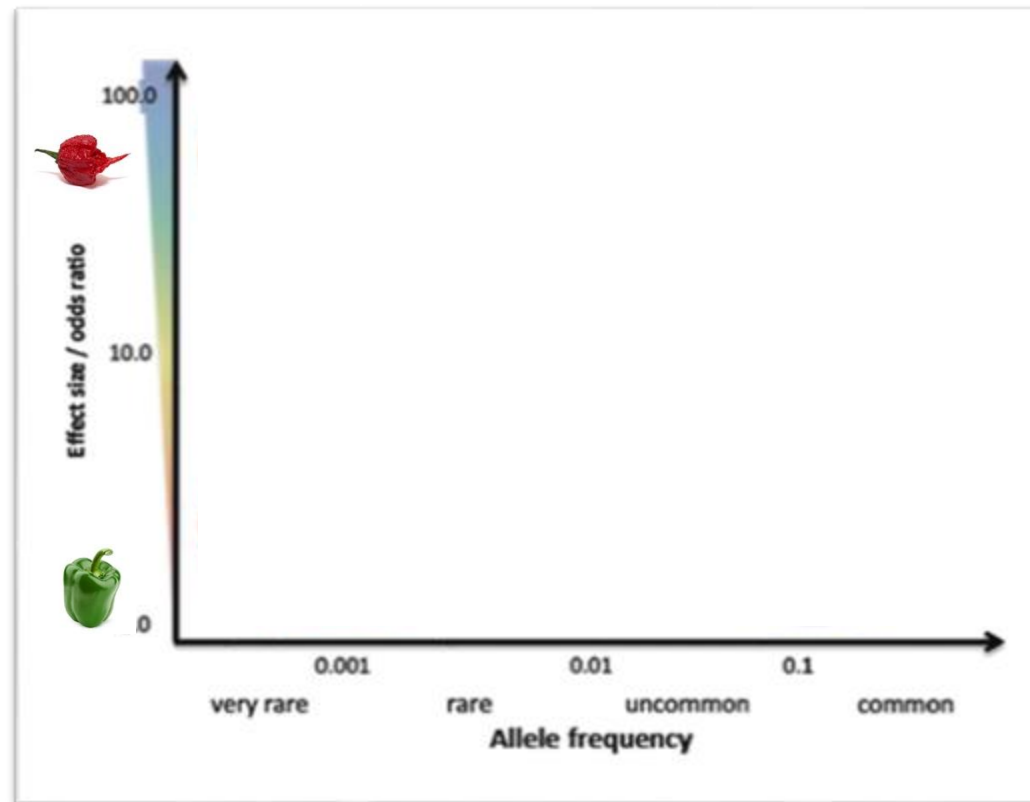
ARCHITECTURE PLOT

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

YOUR TURN

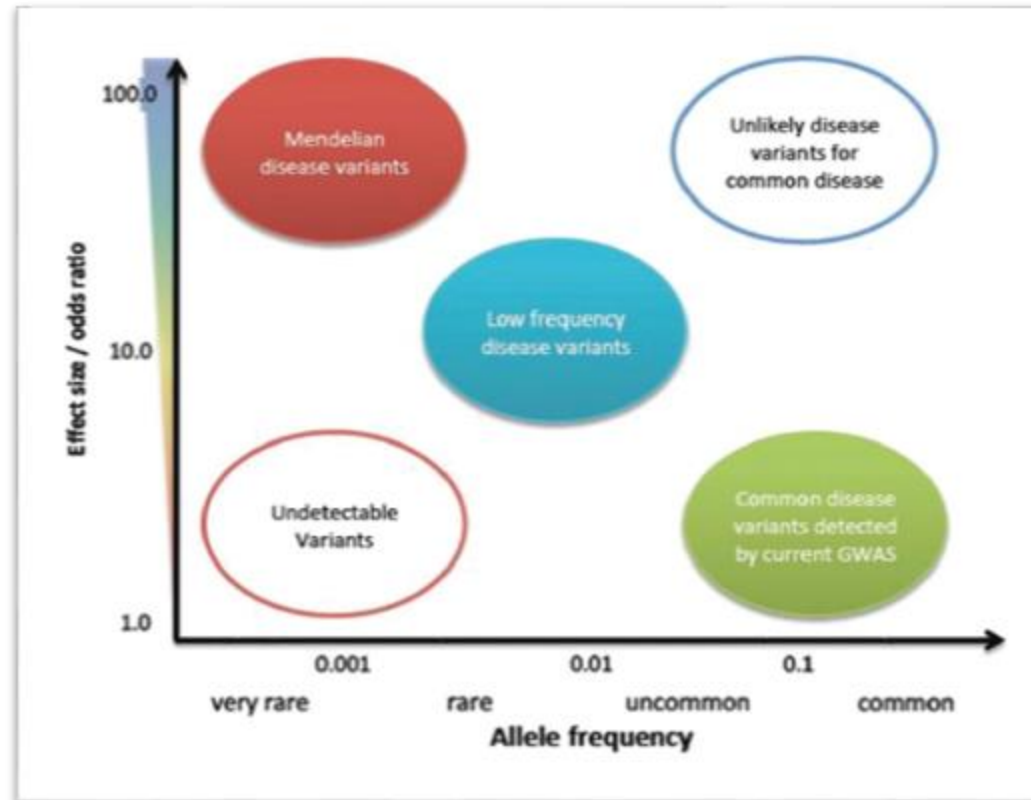
Where are variants causing monogenic disease?

Where are the variants causing complex disease?



Monogenic and complex diseases
have different genetic architectures

IN THIS COURSE WE LOOK AT THE FULL SPECTRUM

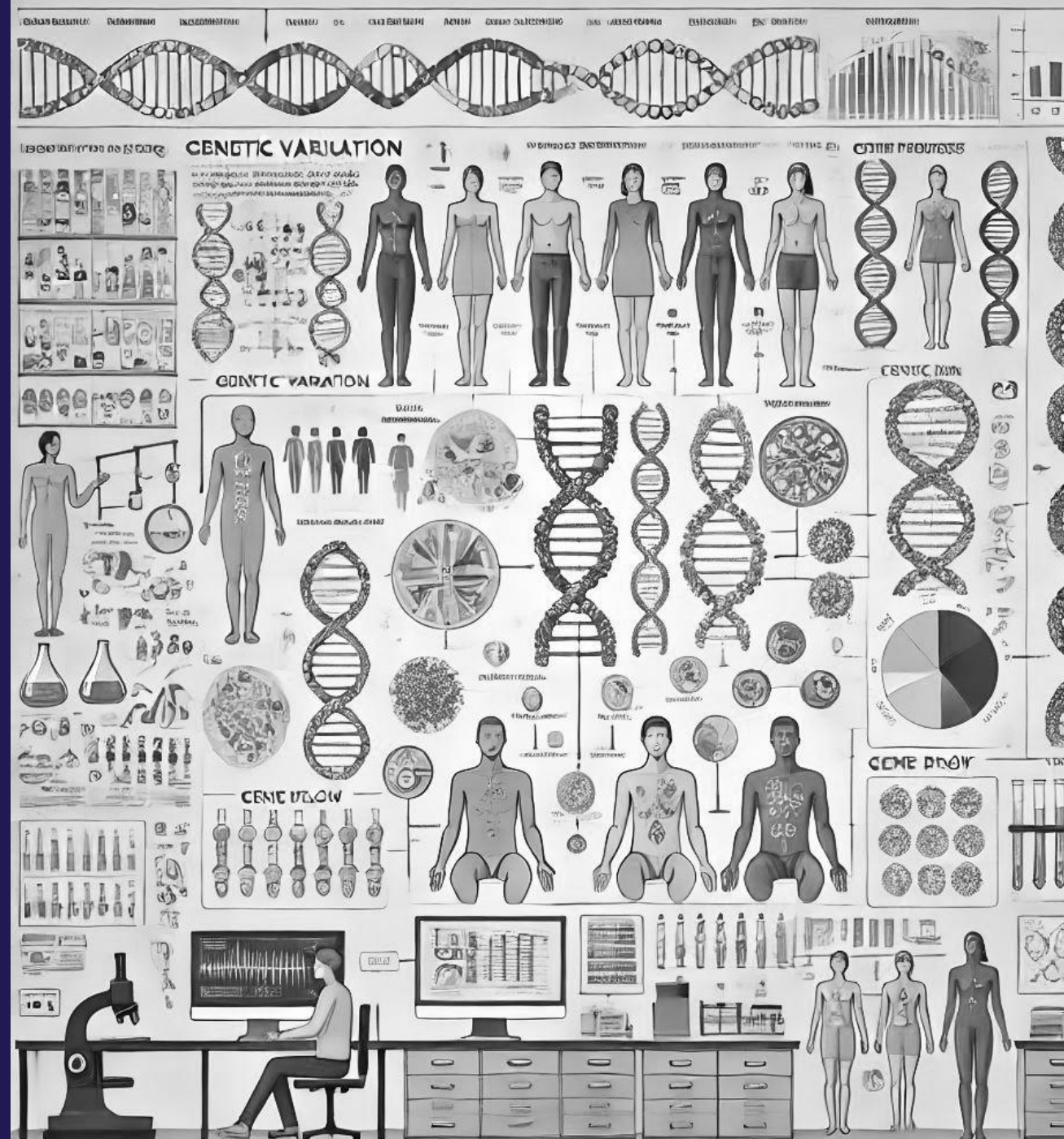


Monogenic and complex diseases
have different genetic architectures

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) [<i>figure recap</i>]
08:55 – 09:20	Lecture - <i>What is personalised medicine?</i> (25 min)
09:20 – 09:35	Break
09:35 – 10:05	Exercises 2 (30 min) [1-6]
10:05 – 10:20	Plenum (15 min) [<i>solutions</i>]
10:20 – 10:45	Lecture - <i>Genetic variation</i> (25 min)
10:45 – 11:00	Break
11:00 – 11:30	Exercises 3 (30 min) [7-9 + <i>R intro</i>]
11:30 – 11:45	Plenum (15 min) [<i>solutions</i>]
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 <i>figure recap</i>]
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) [<i>solutions</i>]
10:20 – 10:45	Genetic variation (25 min)
10:45 – 11:00	Break
11:00 – 11:30	Exercises 3 (30 min) [7-9 + <i>R intro</i>]
11:30 – 11:45	Plenum (15 min) [<i>solutions</i>]
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

