Al-Farabi Kazakh National University
Higher School of Medicine
Department of Fundamental Medicine

Pharmacogenomics

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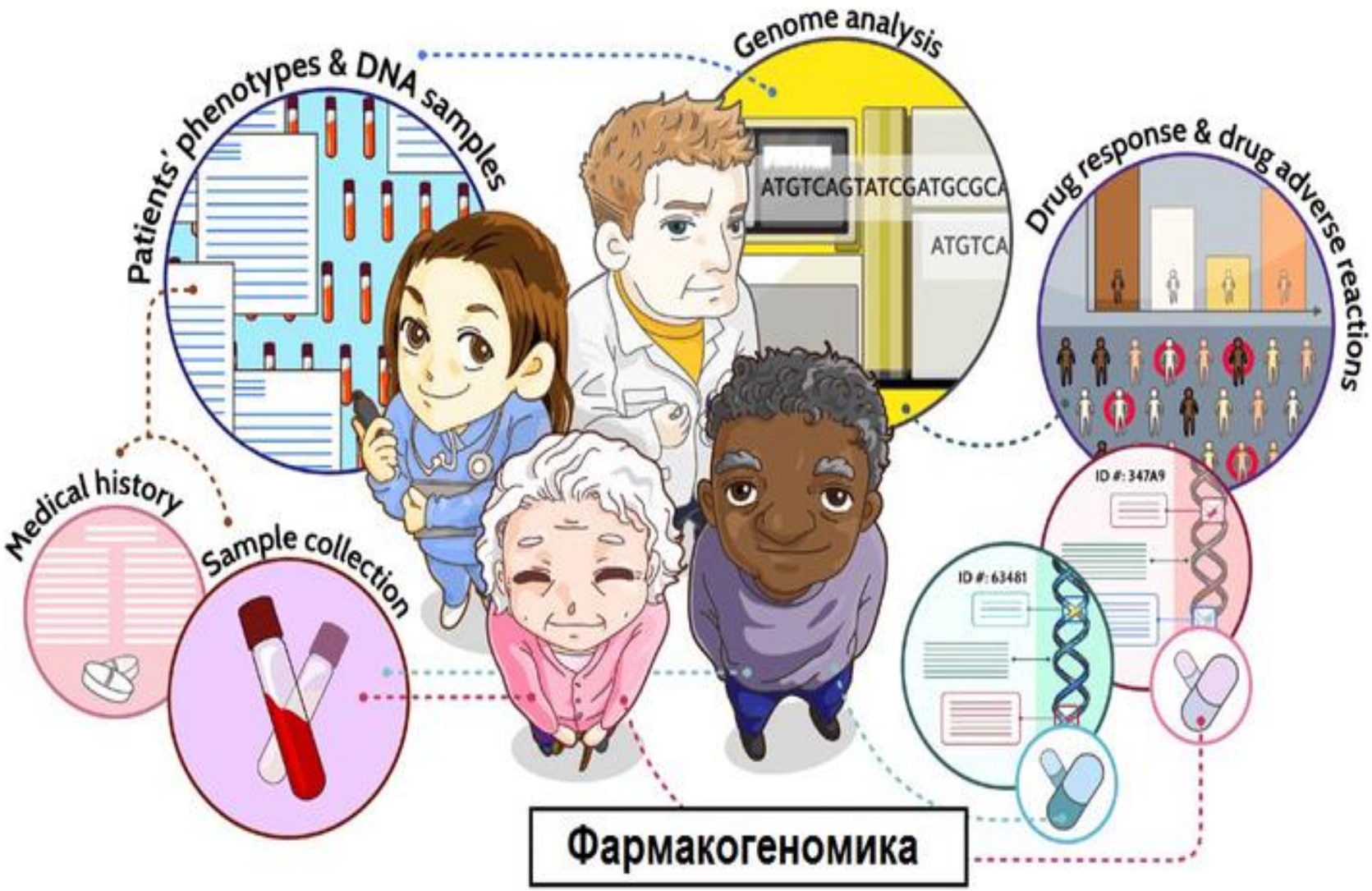
LEARNING OUTCOMES
As a result of the lesson you will be able to:

- 1. Explain the difference between the terms “pharmacogenetics” and “pharmacogenomics”.
- 2. Characterize the mechanisms of genetically based human reactions to the medical drugs, give the specific examples.
- 3. Describe the methods of pharmacogenomics.

Definitions

- **Pharmacogenomics** is the study of the role of the genome in drug response. Its name (pharmaco- + genomics) reflects its combining of pharmacology and genomics. Pharmacogenomics analyzes how the genetic makeup of an individual affects his/her response to drugs.[1]
- **Pharmacogenetics** focuses on single drug-gene interactions, while pharmacogenomics encompasses a more **genome-wide association** approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.[2][3][4]

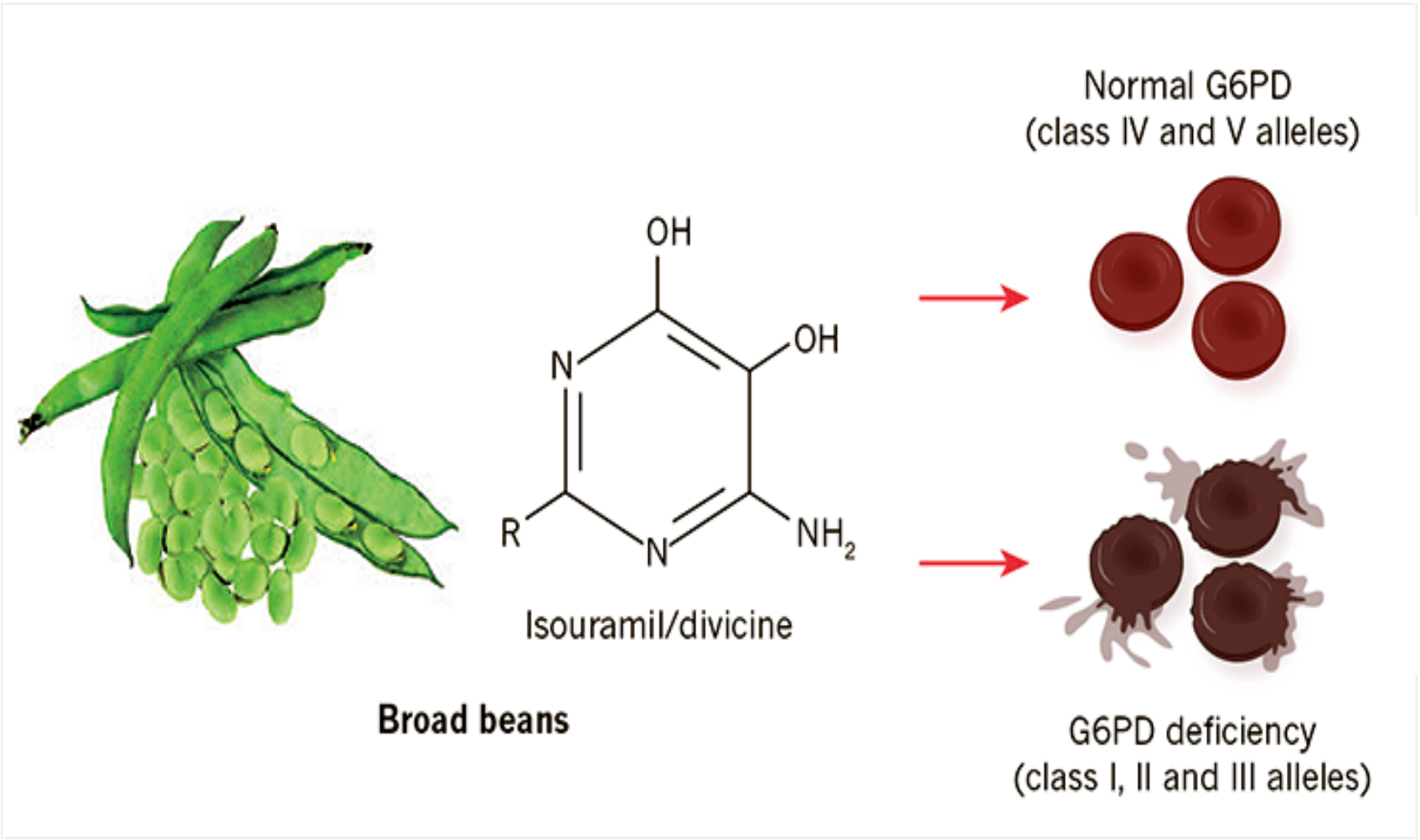


https://biomolecula.ru/articles/farmakogenomika-izuchenie-genov-na-sluzhbe-personalizirovannoi-meditsiny

History

- Pharmacogenomics was first recognized by **Pythagoras** around 510 BC when he made a connection between the dangers of fava bean ingestion with hemolytic anemia and oxidative stress. This identification was later validated and attributed to deficiency of **G6PD** in the 1950s and called **favism**.[5][6] Although the first official publication dates back to 1961,[7] circa 1950s marked the unofficial beginnings of this science. Reports of prolonged paralysis and fatal reactions linked to genetic variants in patients who lacked **butyryl-cholinesterase** (‘**pseudocholinesterase**’) following administration of succinylcholine injection during anesthesia were first reported in 1956.[8] The term pharmacogenetics was first coined in 1959 by Friedrich Vogel of Heidelberg, Germany (although some papers suggest it was 1957 or 1958).[9] In the late 1960s, twin studies supported the inference of genetic involvement in drug metabolism, with identical twins sharing remarkable similarities to drug response compared to fraternal twins.[10] The term pharmacogenomics first began appearing around the 1990s.[5]

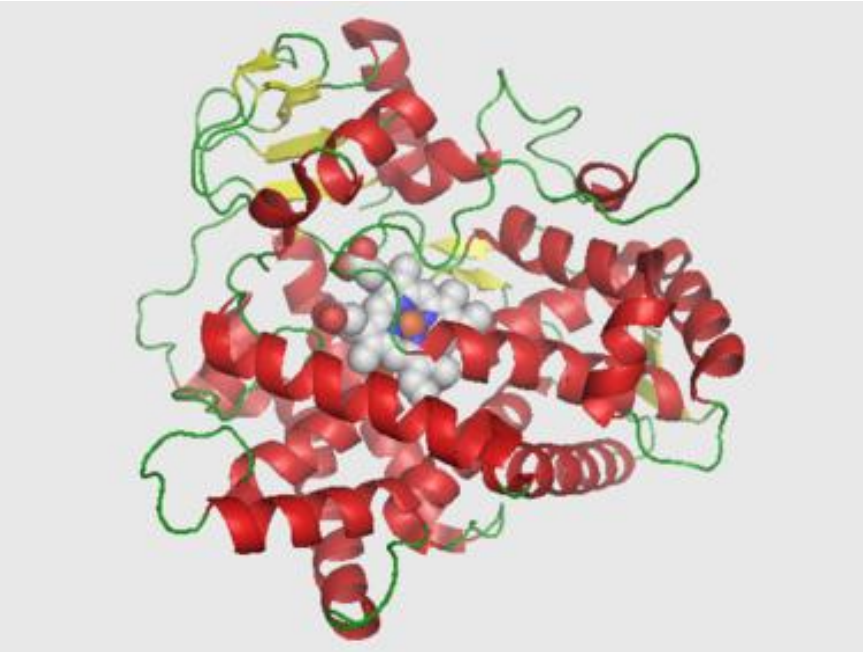
- The first FDA approval of a pharmacogenetic test was in 2005[11] (for alleles in *CYP2D6* and *CYP2C19*).



Mary V. Relling, William E. Evans. (2015). Pharmacogenomics in the clinic. Nature. 526, 343-350

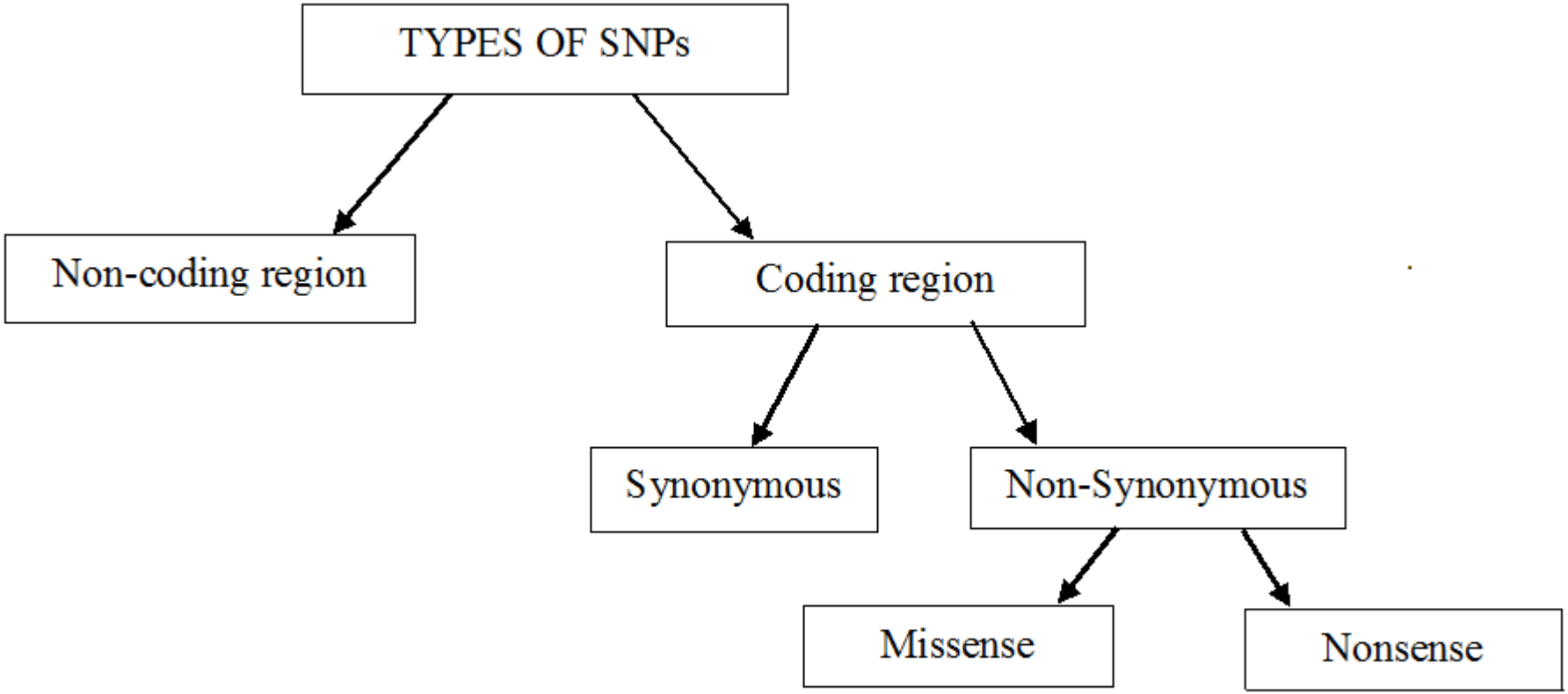
Drug-metabolizing enzymes

- **Cytochrome P450s**
- **VKORC1 (Vitamin K epOxide Reductase Complex (VKORC) subunit 1**
- **TPMT (Thiopurine methyltransferase)**

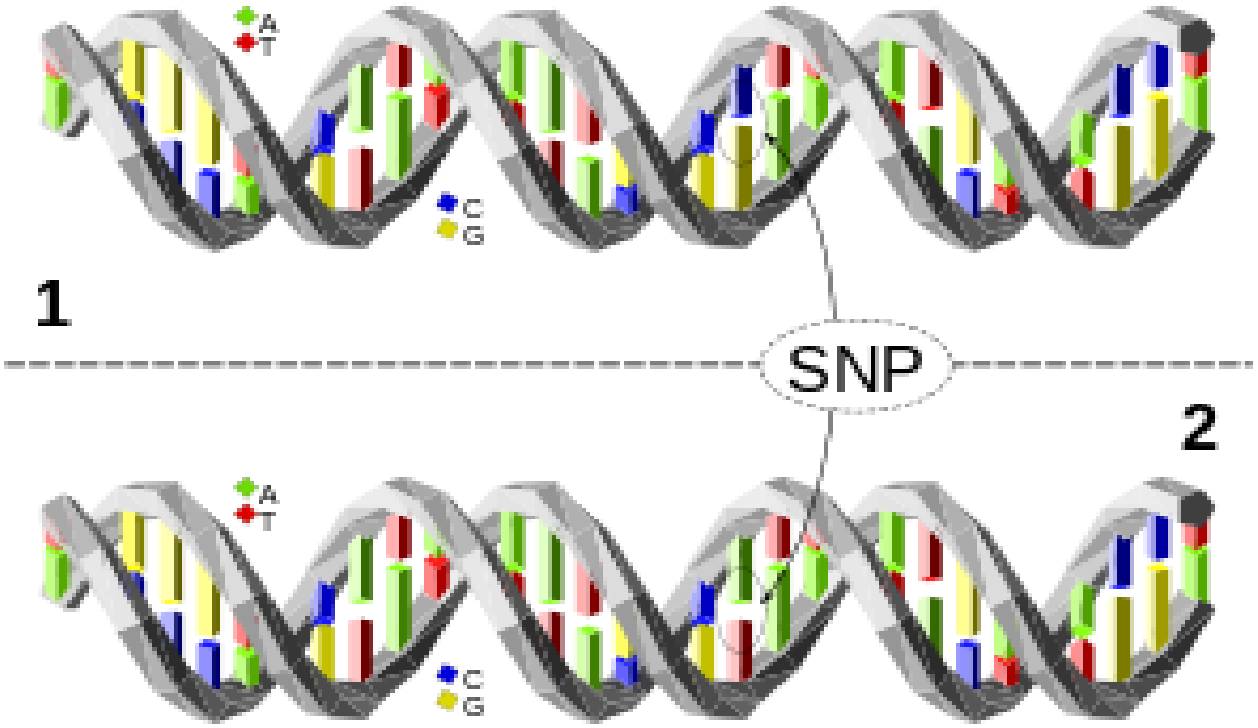


https://en.wikipedia.org/wiki/CYP2D6

Drug Metabolism of Major CYPs[12][13]		
Enzyme	Fraction of drug metabolism (%)	Example Drugs
CYP2C9	10	Tolbutamide, ibuprofen, mefenamic acid, tetrahydrocannabinol, losartan, diclofenac
CYP2C19	5	S-mephenytoin, amitriptyline, diazepam, omeprazole, proguanil, hexobarbital, propranolol, imipramine
CYP2D6	20-30	Debrisoquine, metoprolol, sparteine, propranolol, encainide, codeine, dextromethorphan, clozapine, desipramine, haloperidol, amitriptyline, imipramine
CYP3A4	40-45	Erythromycin, ethinylestradiol, nifedipine, triazolam, cyclosporine, amitriptyline, imipramine
CYP3A5	<1	Erythromycin, ethinylestradiol, nifedipine, triazolam, cyclosporine, amitriptyline, aldosterone

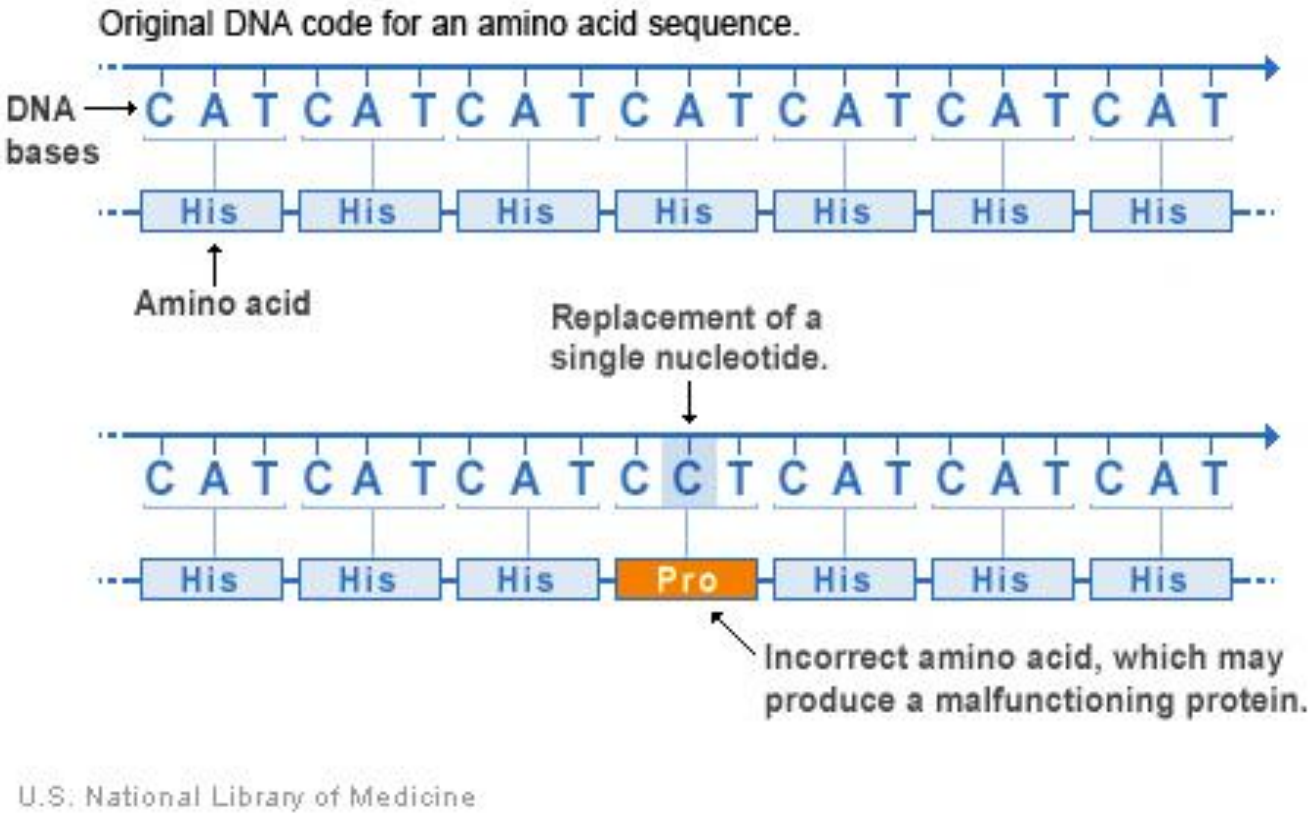


https://en.wikipedia.org/wiki/Single-nucleotide_polymorphism#/media/File:Types_of_SNP_new1.png



The upper DNA molecule differs from the lower DNA molecule at a single base-pair location (a C/A polymorphism).
https://en.wikipedia.org/wiki/Single-nucleotide_polymorphism

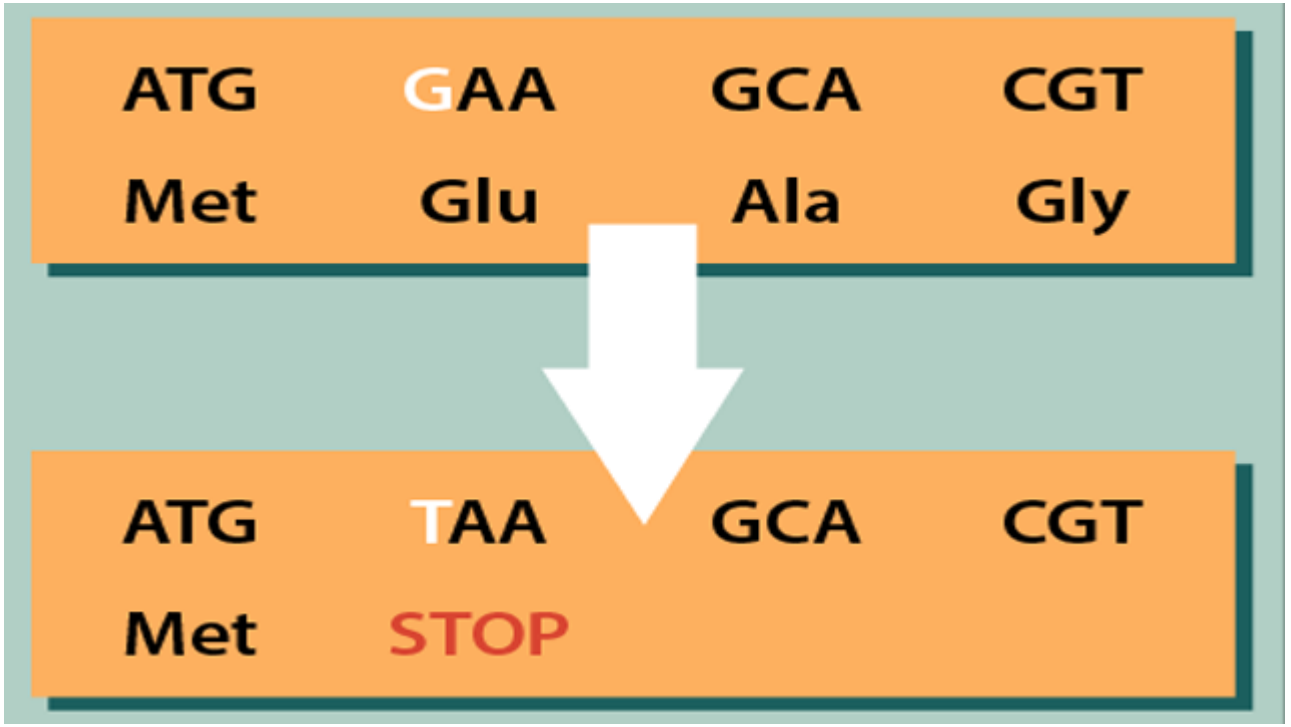
Missense mutation



U.S. National Library of Medicine

http://ghr.nlm.nih.gov/handbook/illustrations/missense

Non-sense mutation



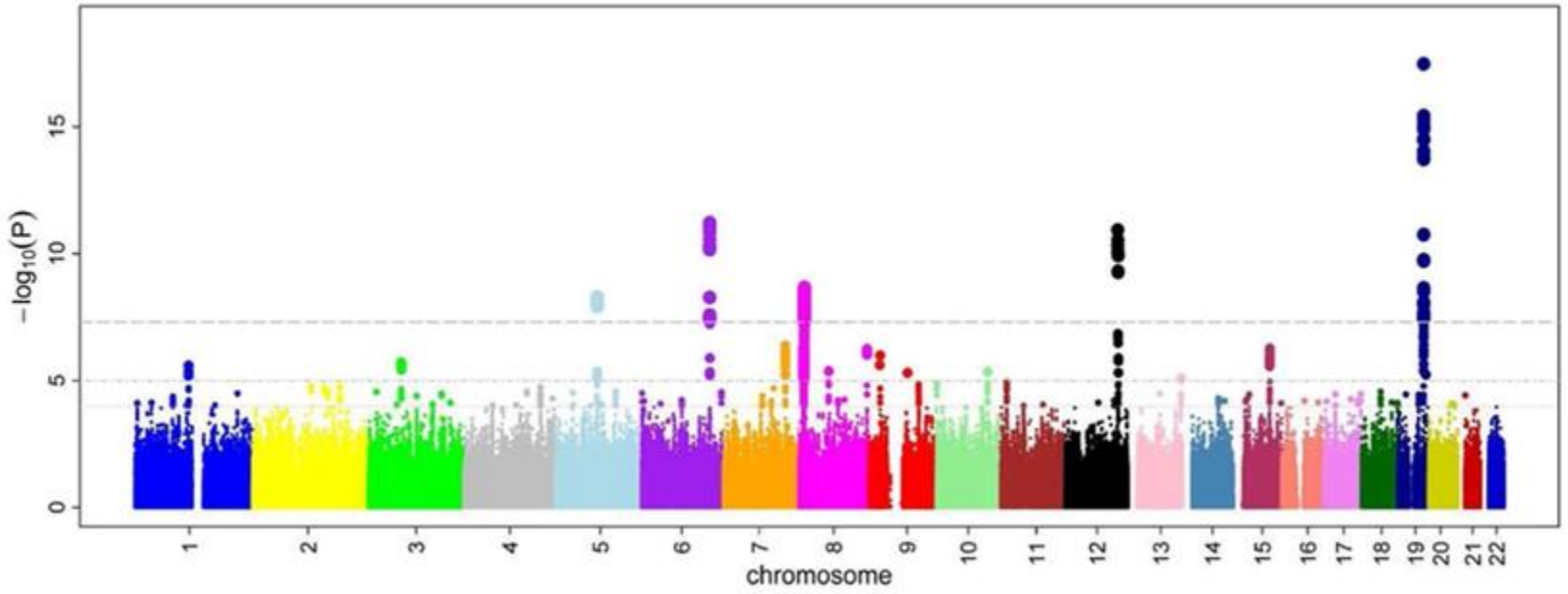
https://www.technologynetworks.com/genomics/articles/missense-nonsense-and-frameshift-mutations-a-genetic-guide-329274

Methods of pharmacogenomics

- Genome-wide association study (GWAS)
- Genome sequencing methods
- Genotyping:

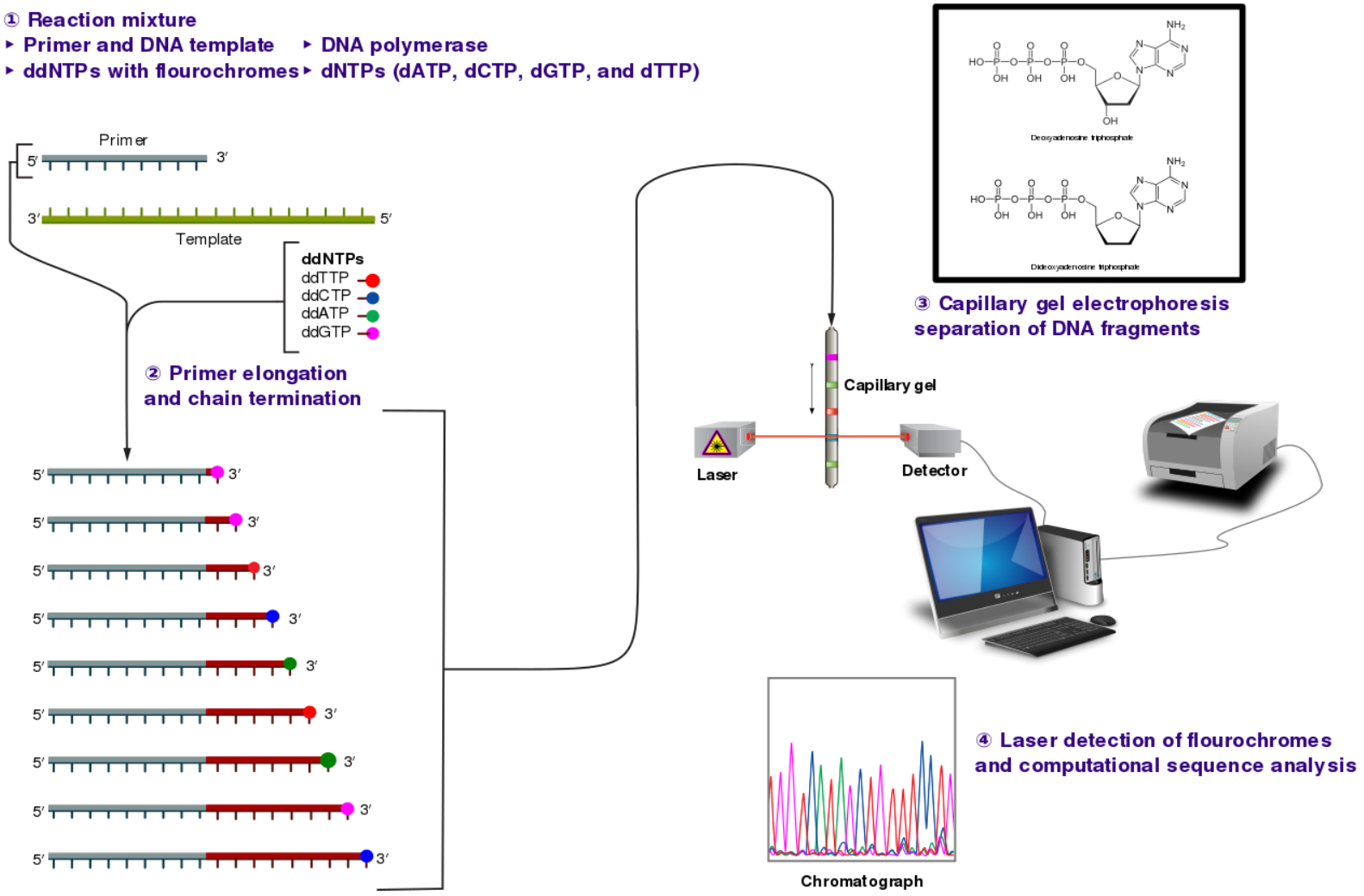
a) Restriction fragment length polymorthism (RFLP)
b) Polymerase chain reaction (PCR)
c) Amplified fragment length polymorphism (AFLP)
d) DNA microarray and etc.

Genome-wide association study (GWAS)



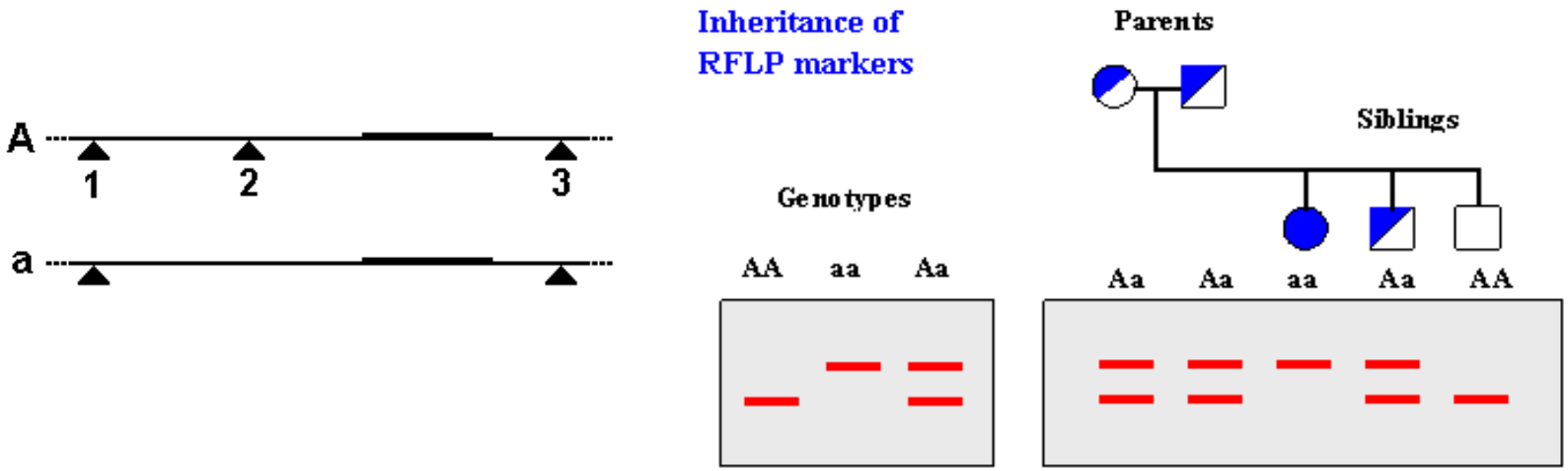
In genetics, a genome-wide association study (GWA study, or GWAS), also known as whole genome association study (WGA study, or WGAS), is an observational study of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait. [14]

The Sanger (chain-termination) method for DNA sequencing.



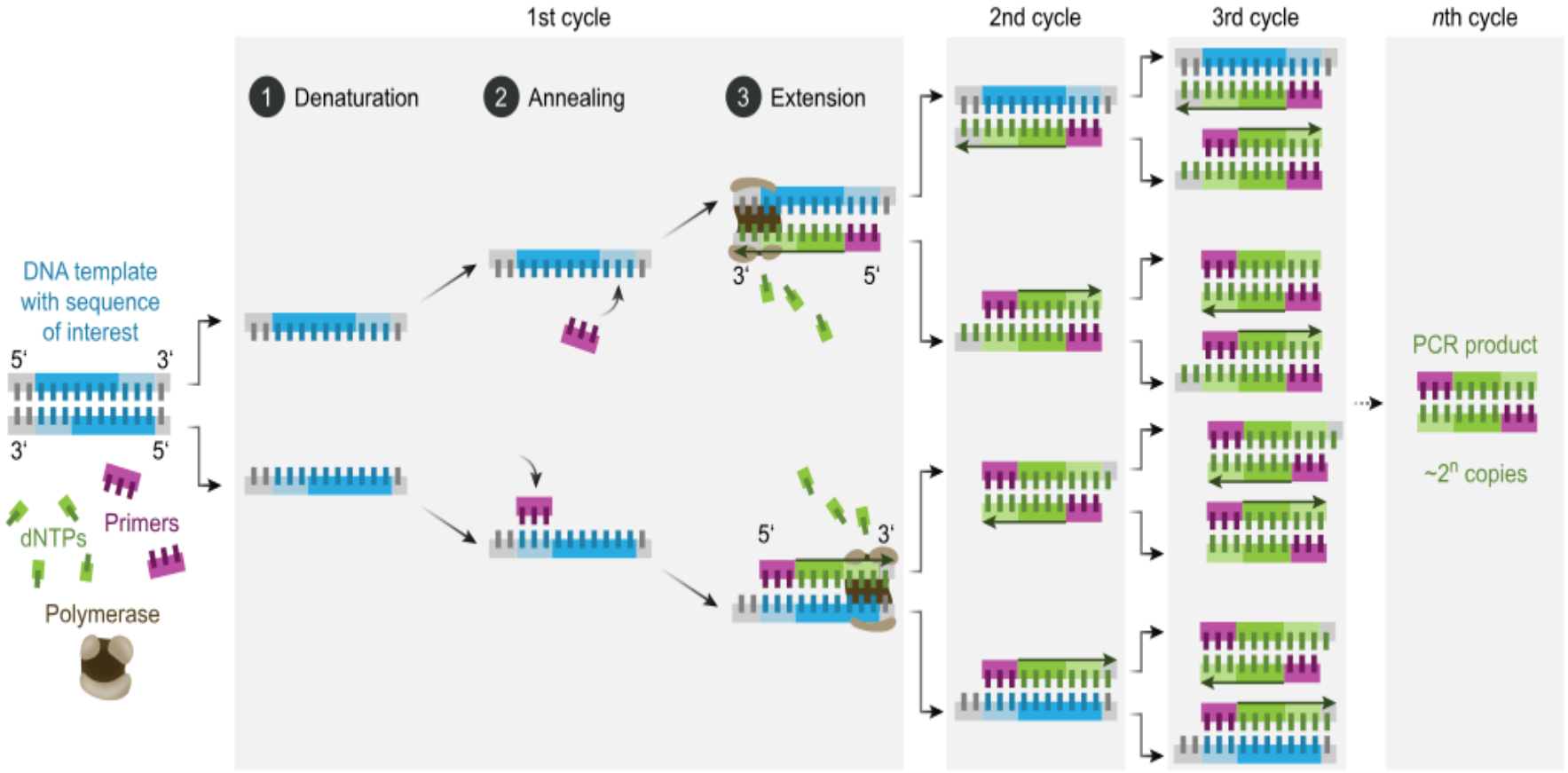
https://en.wikipedia.org/wiki/Sanger_sequencing#/media/File:Sanger-sequencing.svg

Restriction fragment length polymorphism



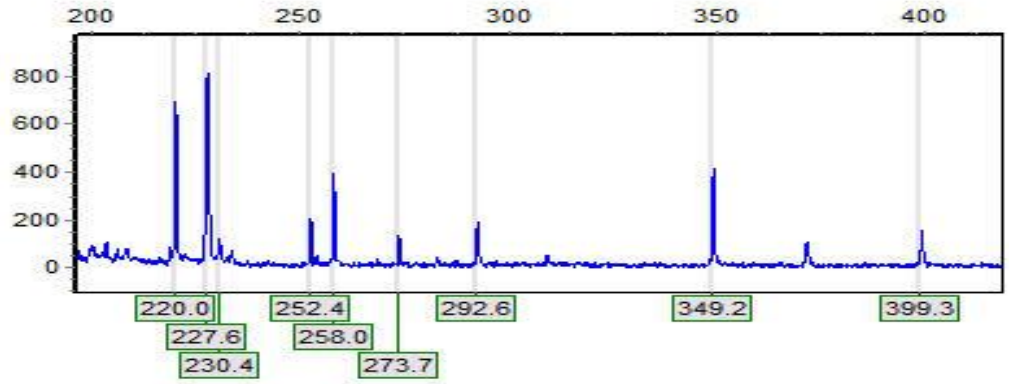
https://en.wikipedia.org/wiki/Restriction_fragment_length_polymorphism

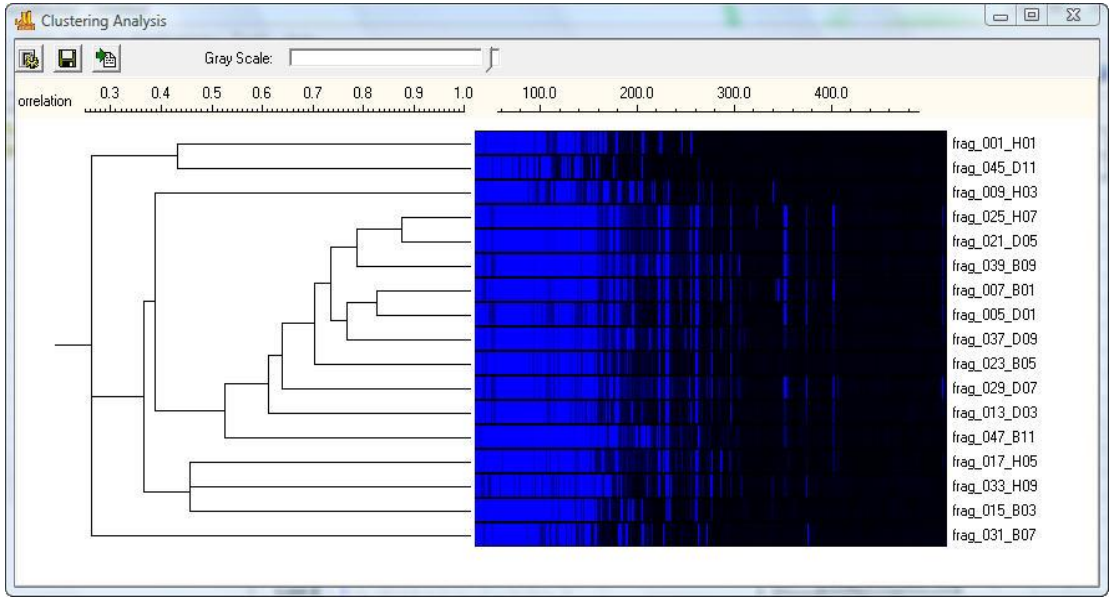
Polymerase chain reaction (PCR)



https://en.wikipedia.org/wiki/Polymerase_chain_reaction

Amplified fragment length polymorphism





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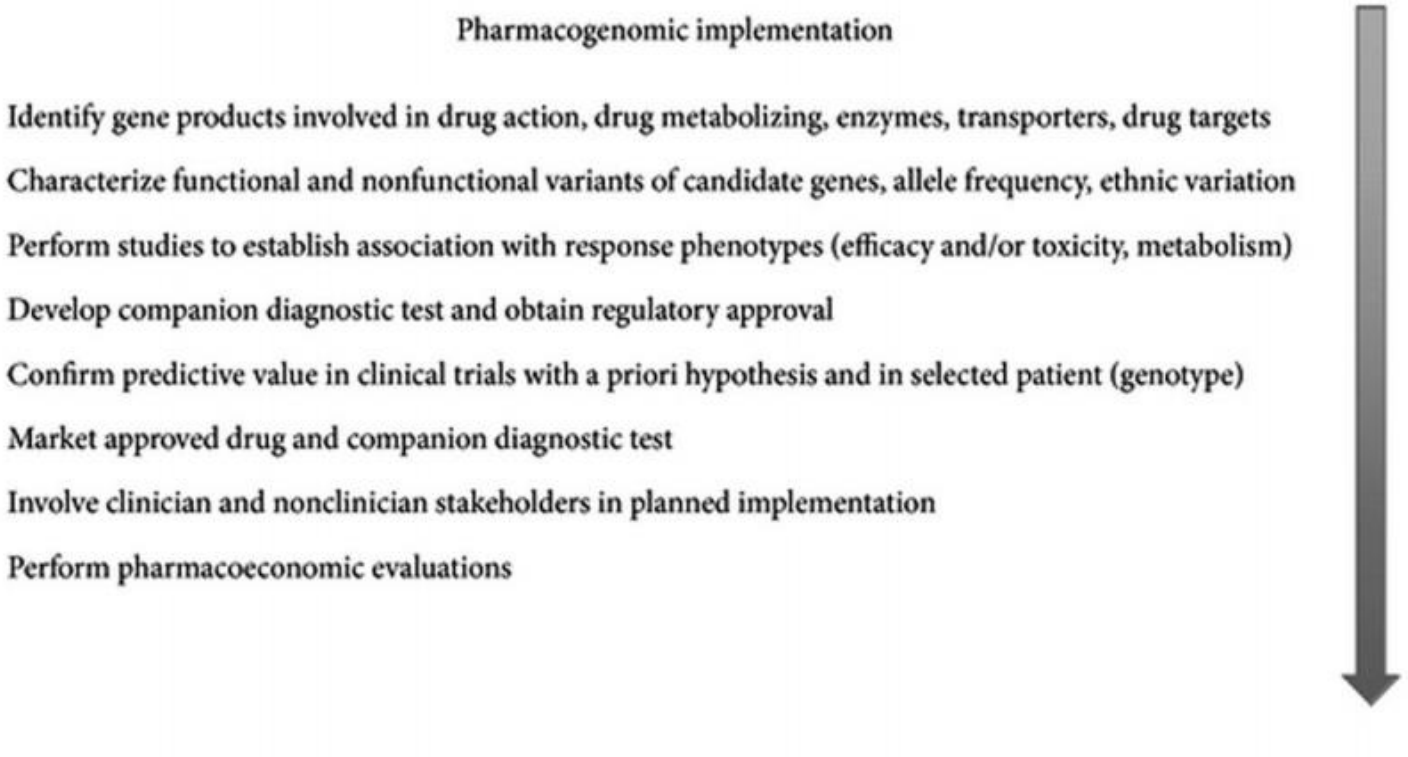

FIGURE 1: Sequence of scientific developments and implementation steps for pharmacogenomics testing in clinical practice.

Yu Liu. OMICS in Clinical Practice / 2014 by Apple Academic Press, Inc. – 456 p.

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