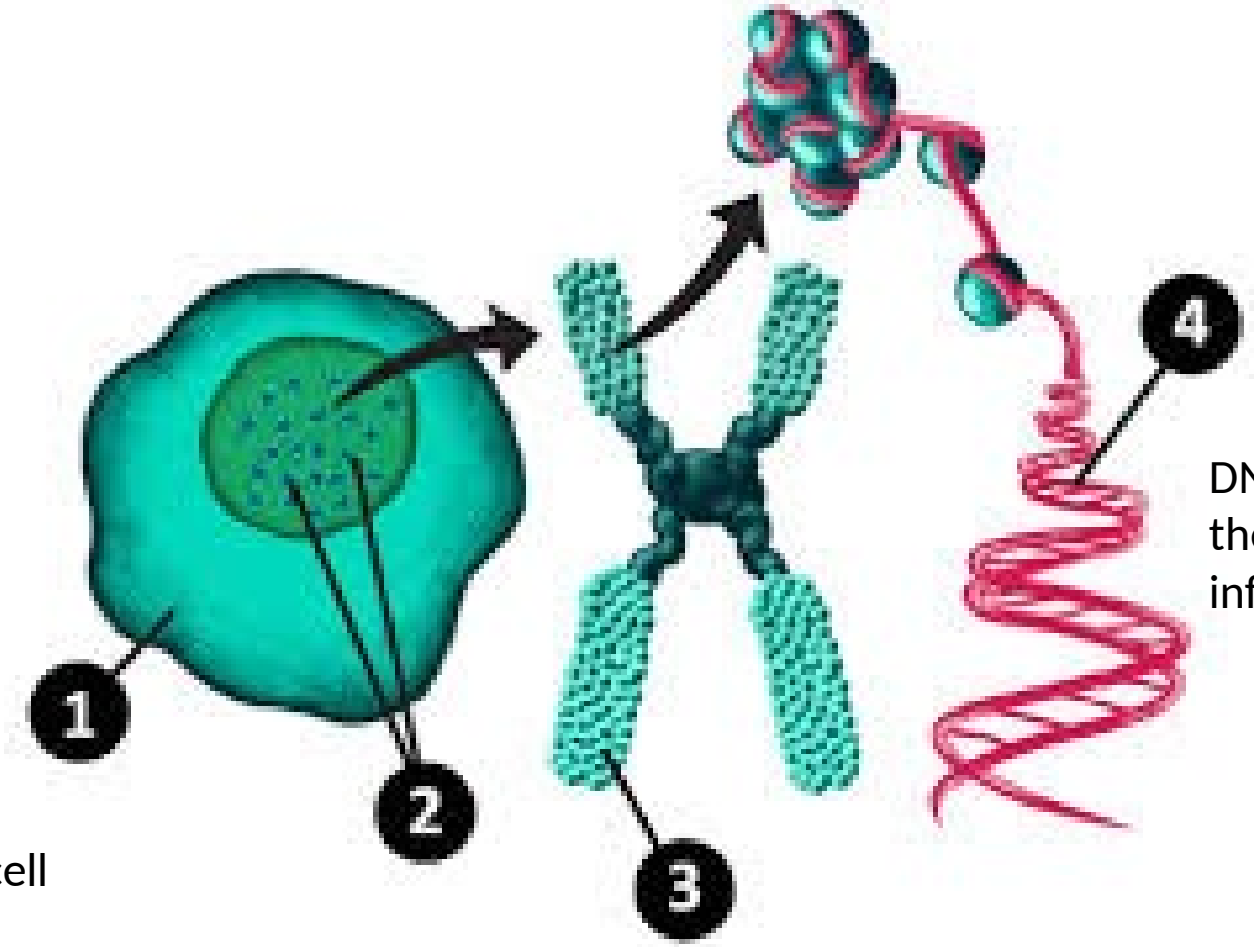
Visions of the future of clinical genetics

Helena Kääriäinen
Clinical geneticist
National Institute for Health and Welfare
Helsinki, Finland
Consultant in Blueprint Genetics Laboratory

What is gene, what is genome?

- A gene is the basic unit of inheritance. It is a stretch of DNA that the cell reads to create a protein with a certain specific role.
- A genome contains an individual's entire genetic material: all the genes as well as other DNA elements including those involved in regulating the genes.

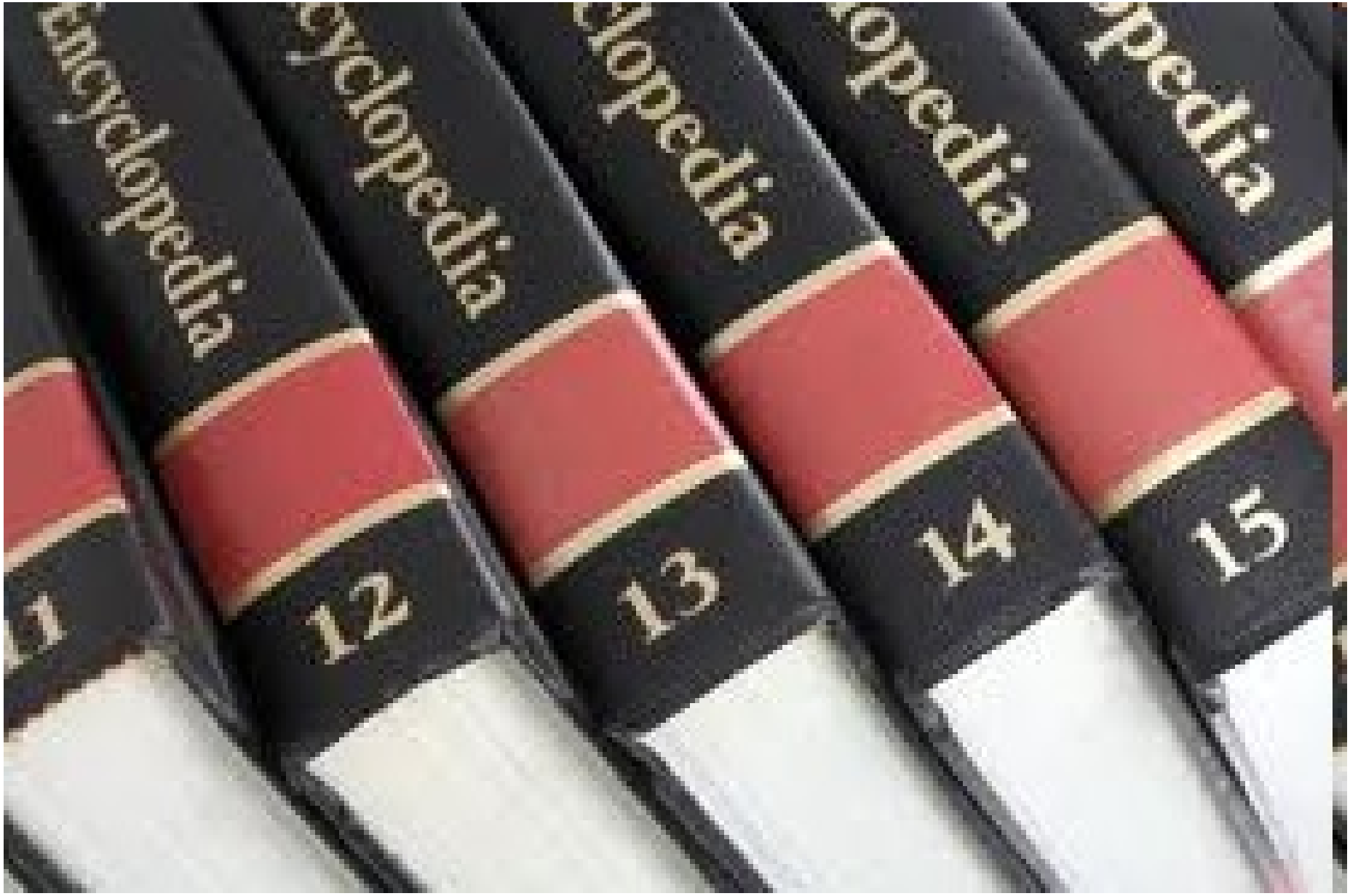


DNA that contains the genetic information

cell

nucleus

chromosome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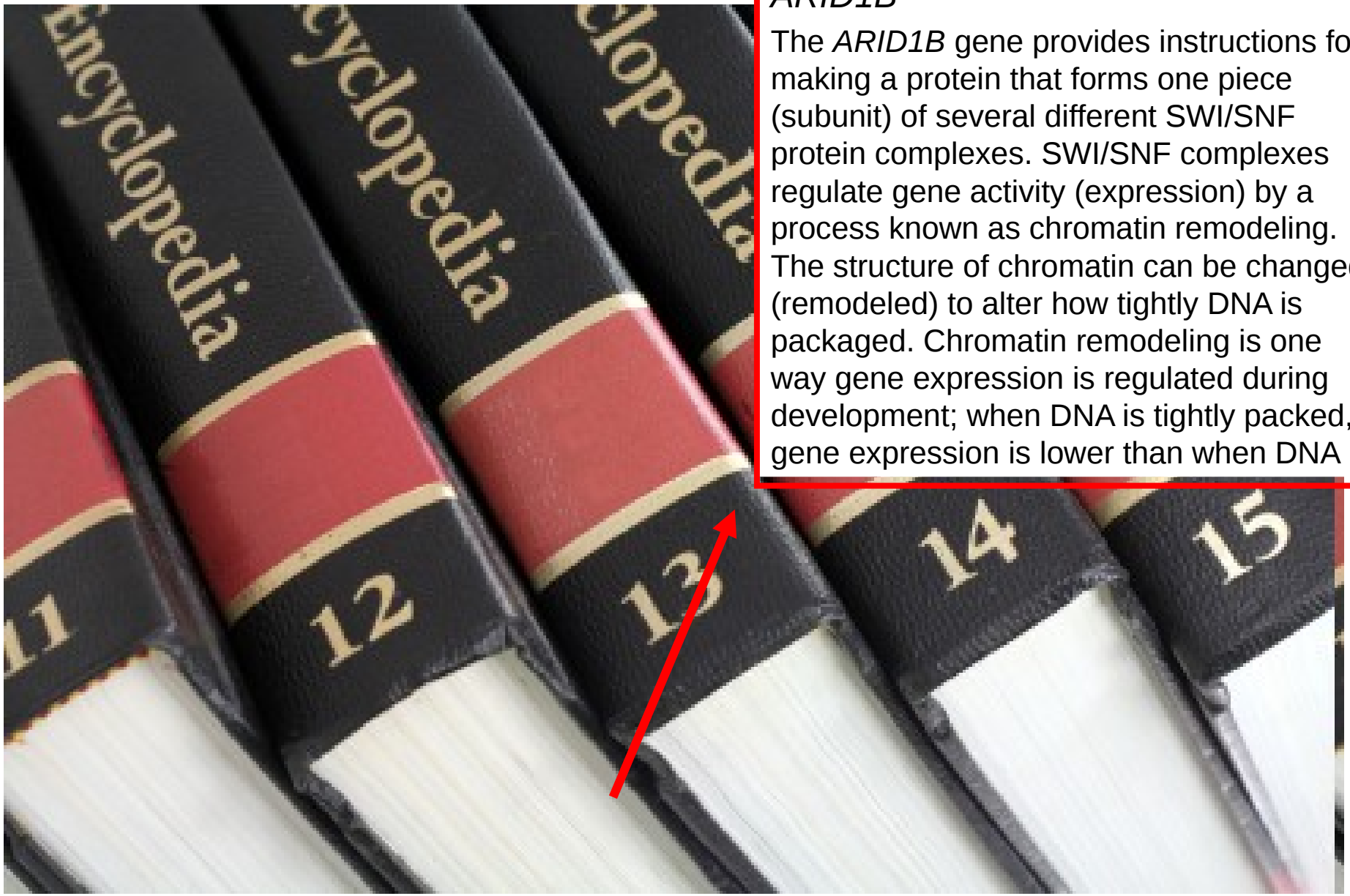
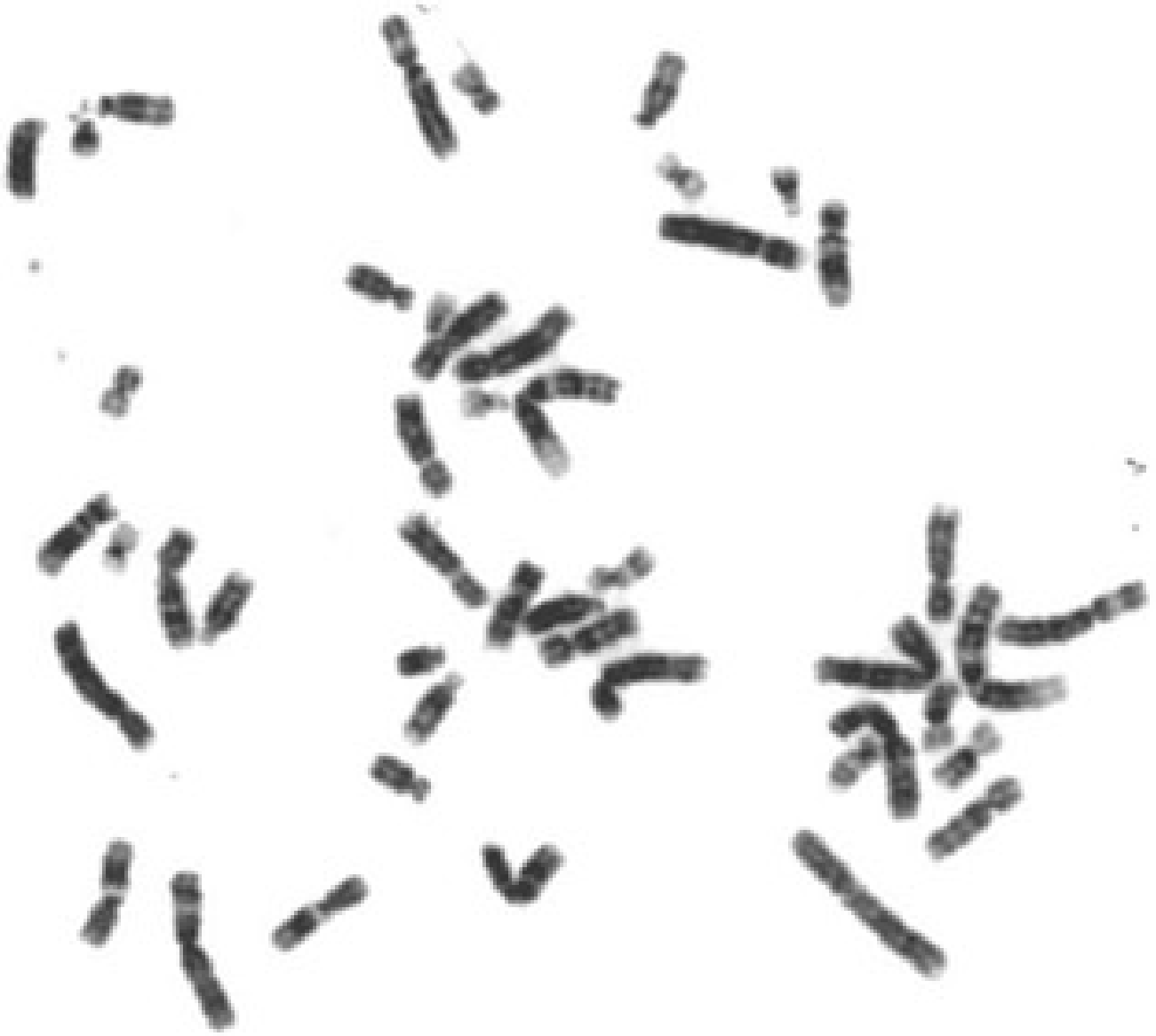
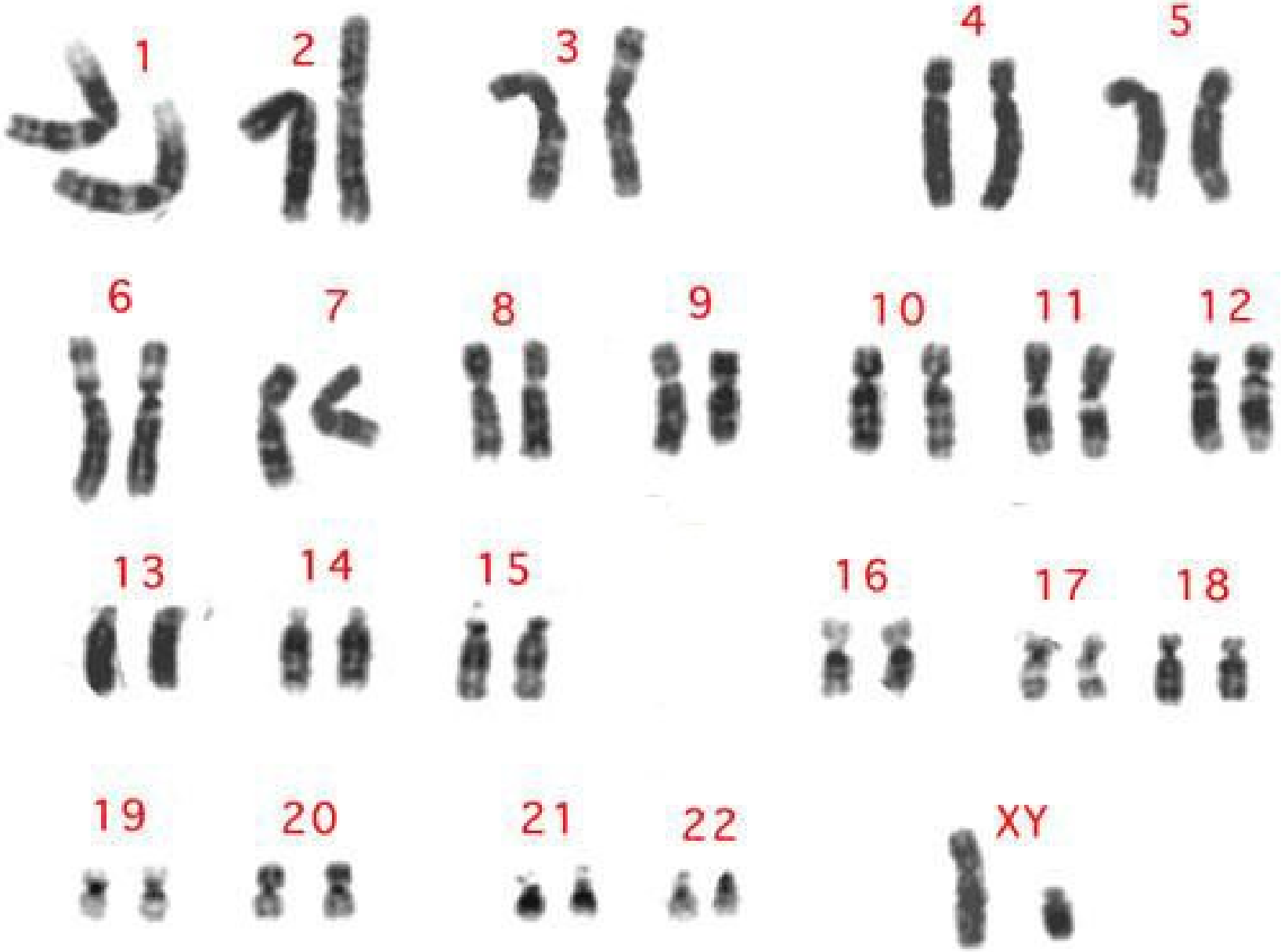


ARID1B

The *ARID1B* gene provides instructions for making a protein that forms one piece (subunit) of several different SWI/SNF protein complexes. SWI/SNF complexes regulate gene activity (expression) by a process known as chromatin remodeling. The structure of chromatin can be changed (remodeled) to alter how tightly DNA is packaged. Chromatin remodeling is one way gene expression is regulated during development; when DNA is tightly packed, gene expression is lower than when DNA

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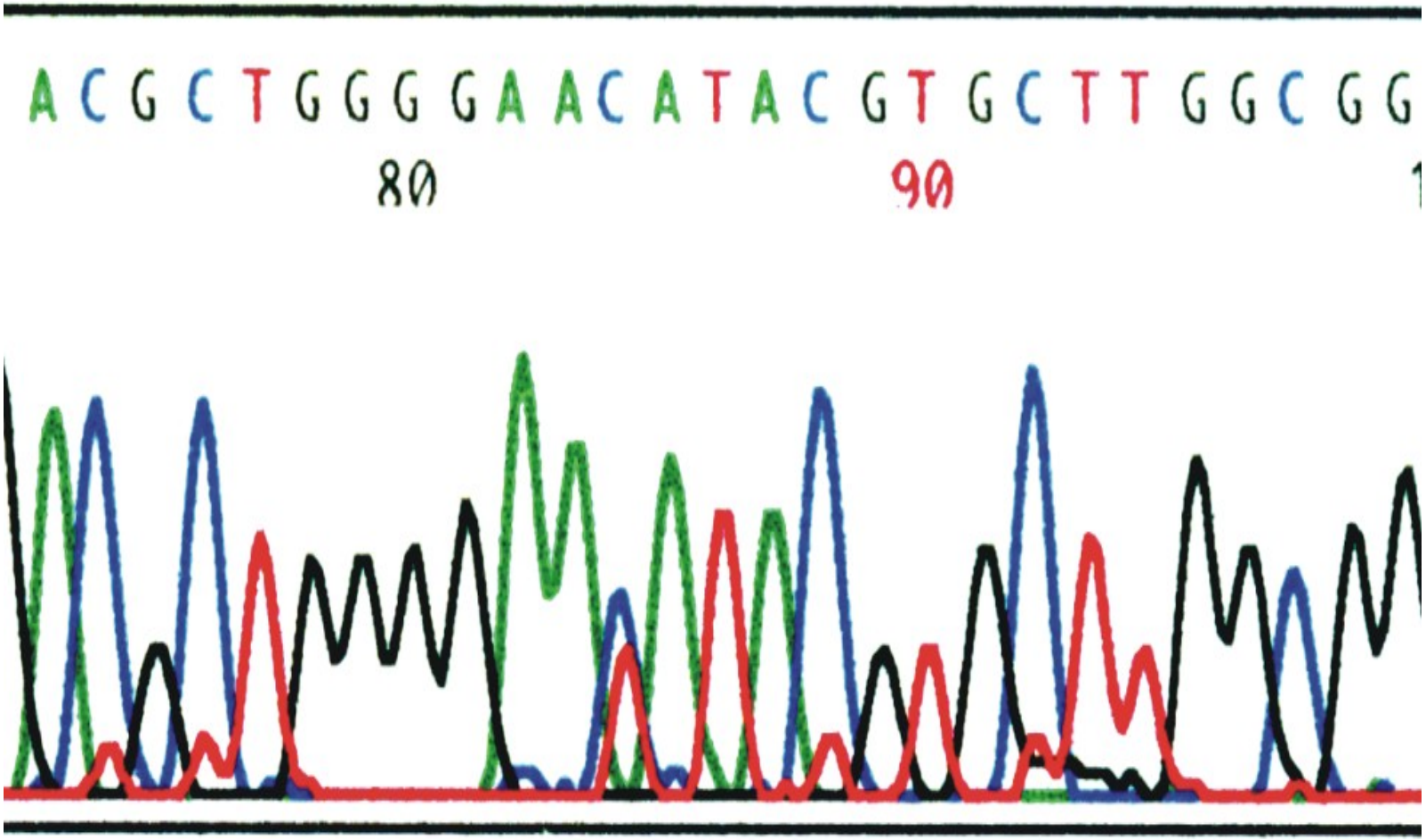


In this presentation

- I will start from the present role of a genetics clinic:
  - diagnostics of rare diseases
  - genetic counselling of index families and their relatives
- Then I will try to forecast the futures roles for clinical geneticists.

Ideally, a genetic diagnosis of a rare condition changes everything

- The natural history and prognosis of the disease comes clear and can be explained to the patient
- The possible specific care can be started
- The mode of inheritance, including risk of the disease for near relatives is solved
- It will be easy to find specific patient organisations and peer support
- It becomes possible to participate in clinical trials

How do we reach a genetic diagnosis for a rare disease?

- Yesterday: the clinician observed all possible symptoms and findings and, with the help of books, publications, databases and diagnostic tools, a clinical diagnosis was made and then confirmed by a specific gene test.

How do we reach a genetic diagnosis for a rare disease?

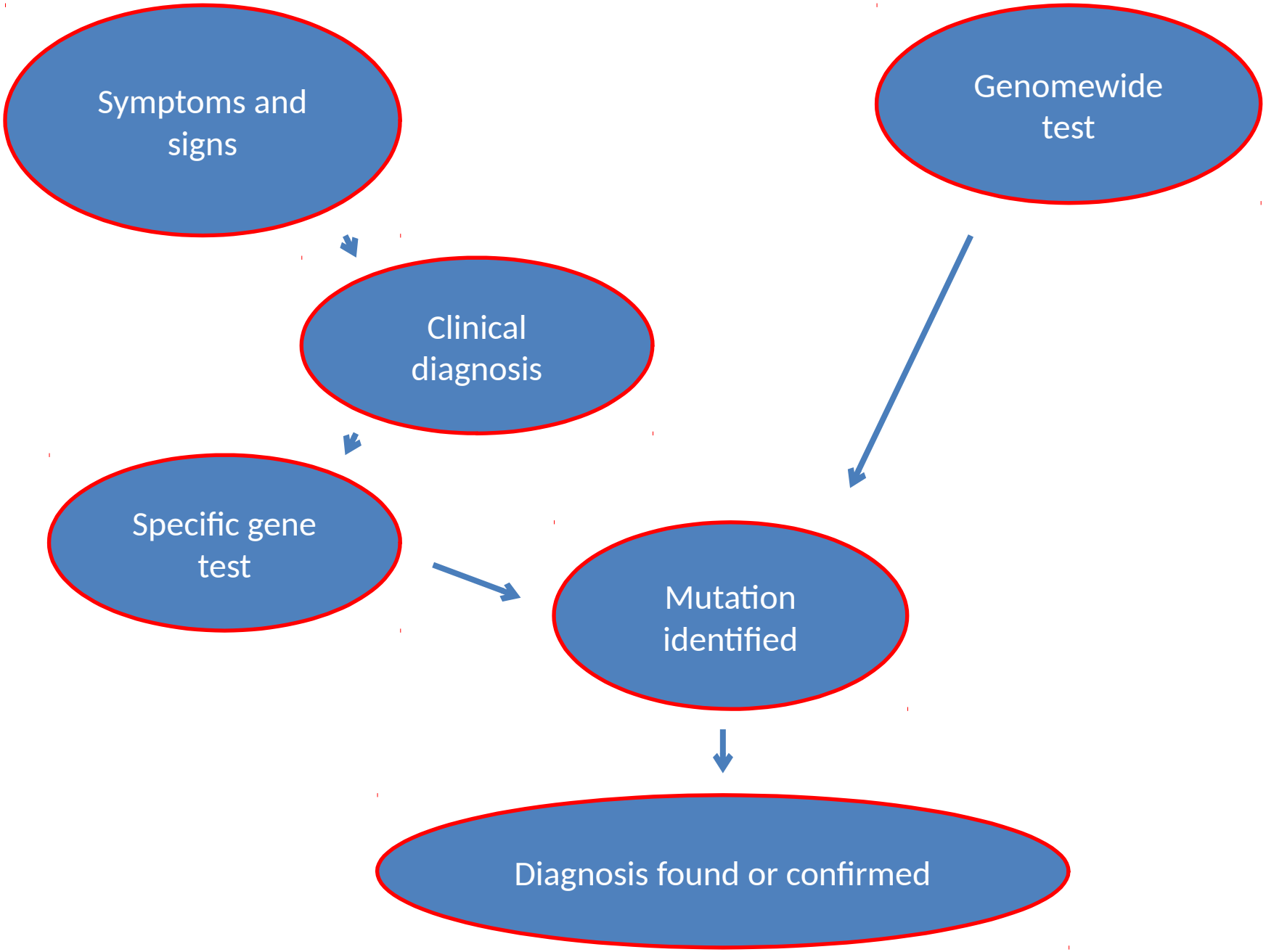
- Today: the clinician lists main symptoms and findings and chooses a gene panel test with some tens or hundreds of possible genes.

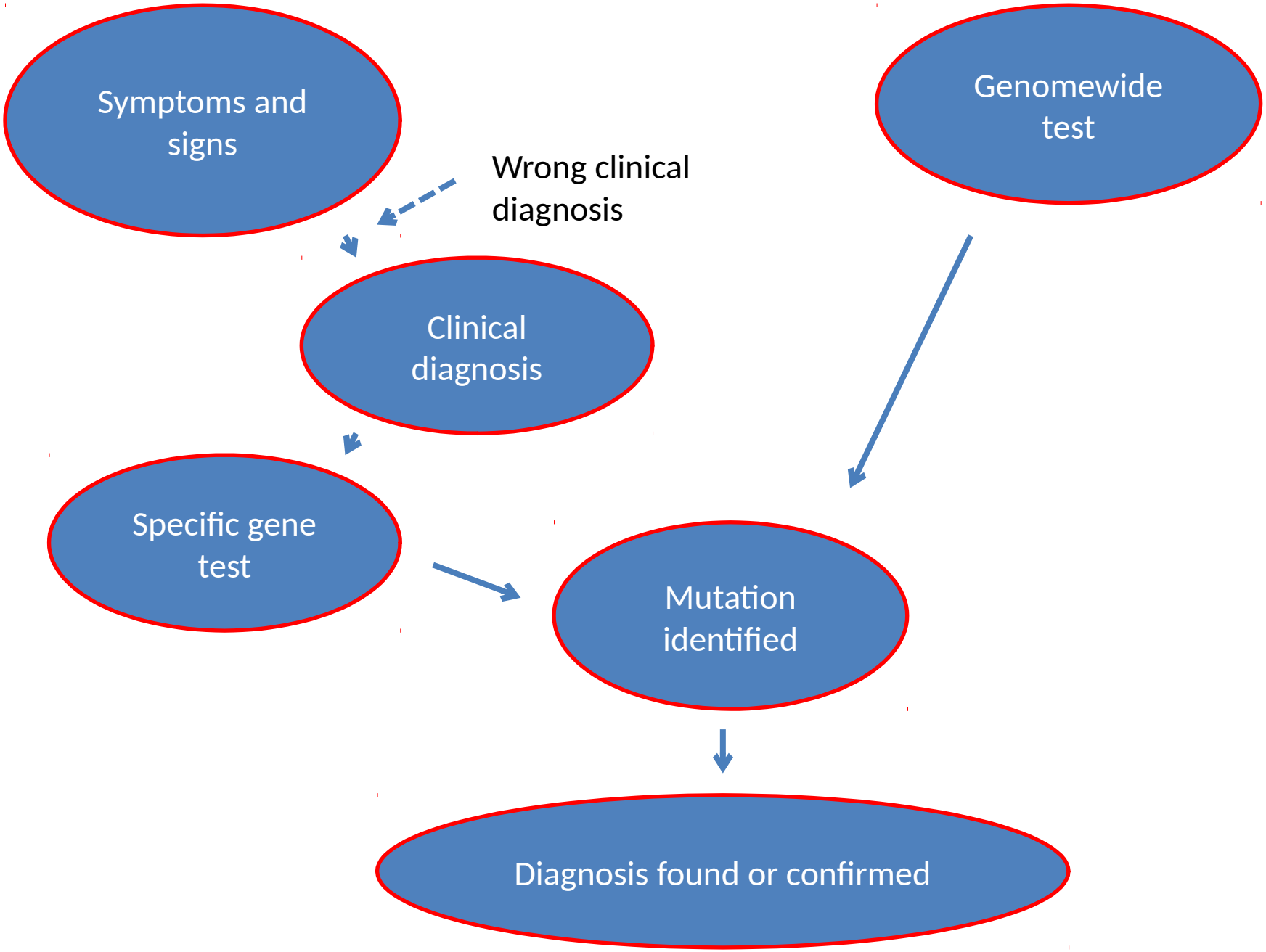
How do we reach a genetic diagnosis for a rare disease?

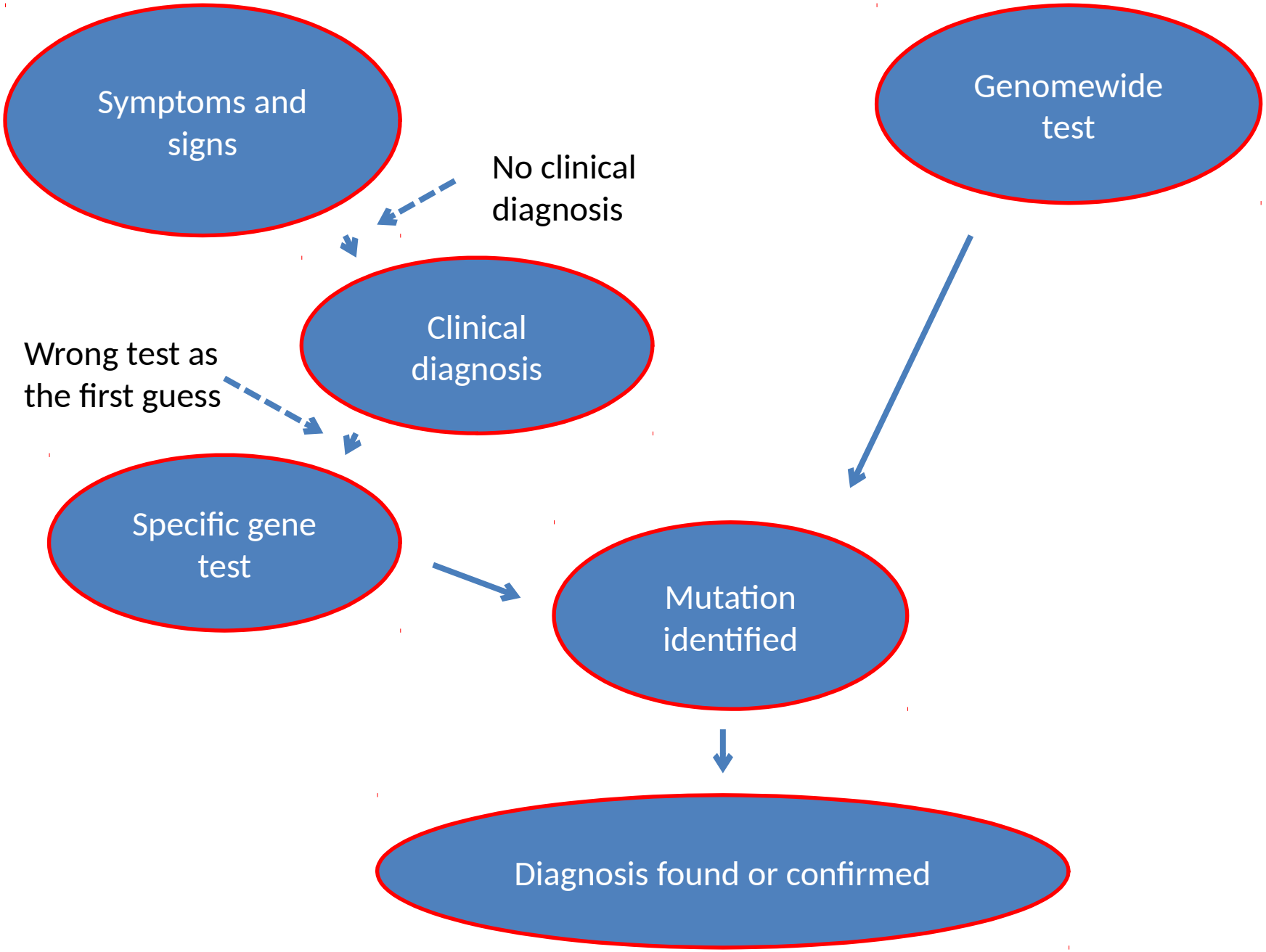
- Tomorrow: a genomewide test is performed, most striking mutations and variants are noted and, with the help of bioinformatic tools, a specific variant guides the clinician to make the correct diagnosis.

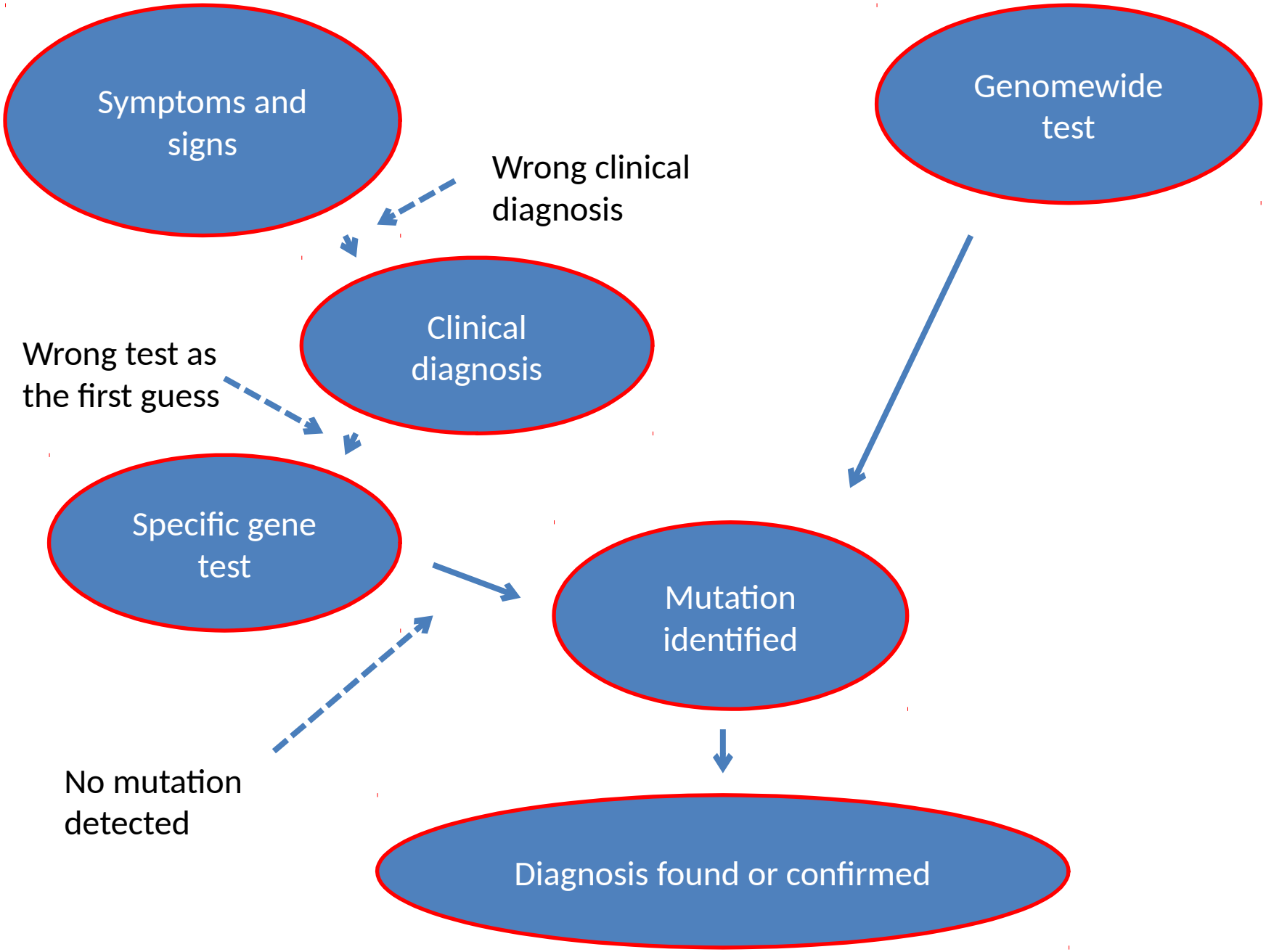
Are we living in yesterday, today or tomorrow?

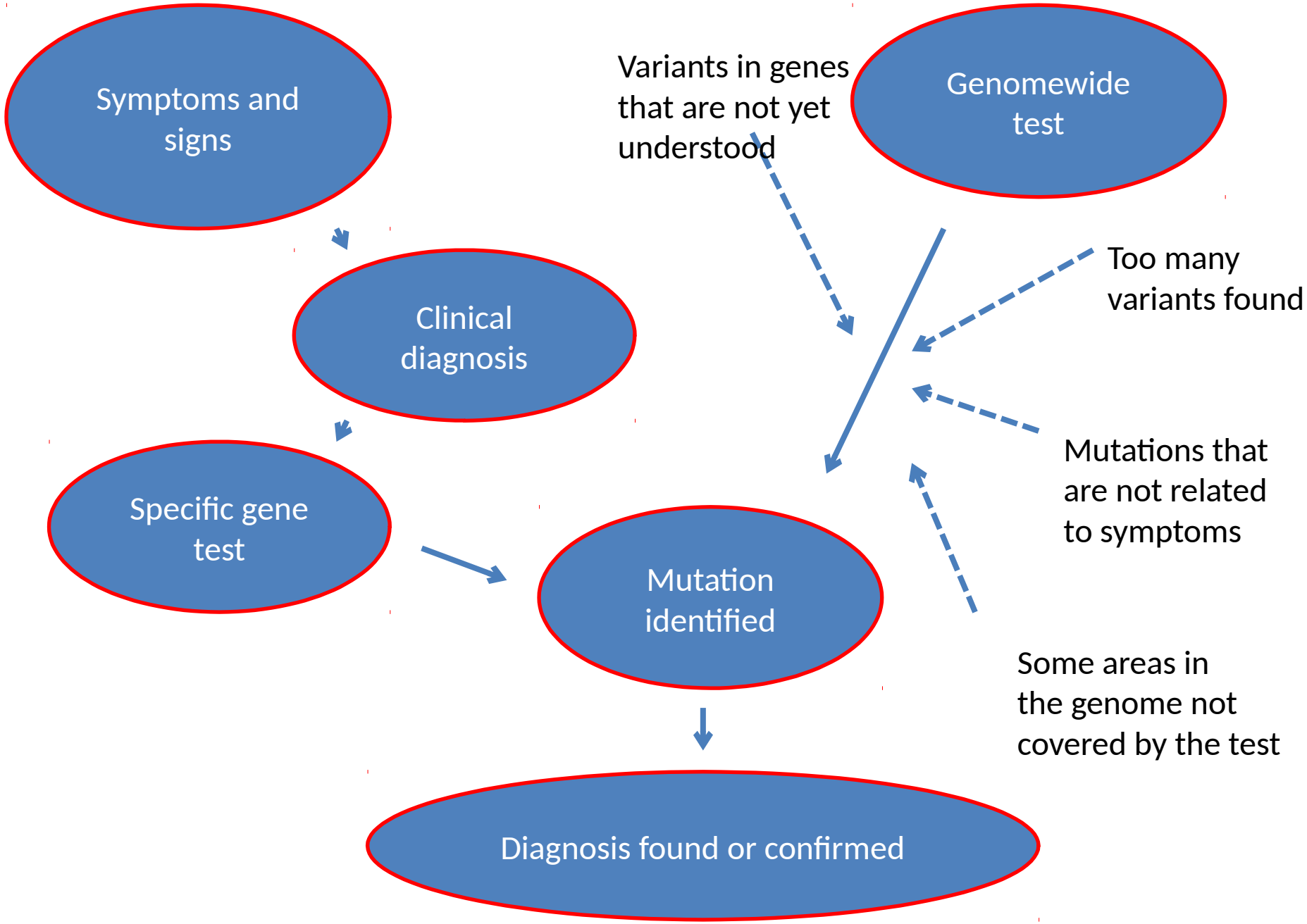
- Yesterday: the clinician observed all possible symptoms and findings and, with the help of books, publications, databases and diagnostic tools, a clinical diagnosis is made and then confirmed by a specific gene test.
- Today: the clinician lists main symptoms andfindings and chooses a gene panel test with some tens or hundreds of possible genes.
- Tomorrow: a genomewide test is performed, most striking mutations and variants are noted and, with the help of bioinformatic tools, the variant guides the clinician to make the correct diagnosis.

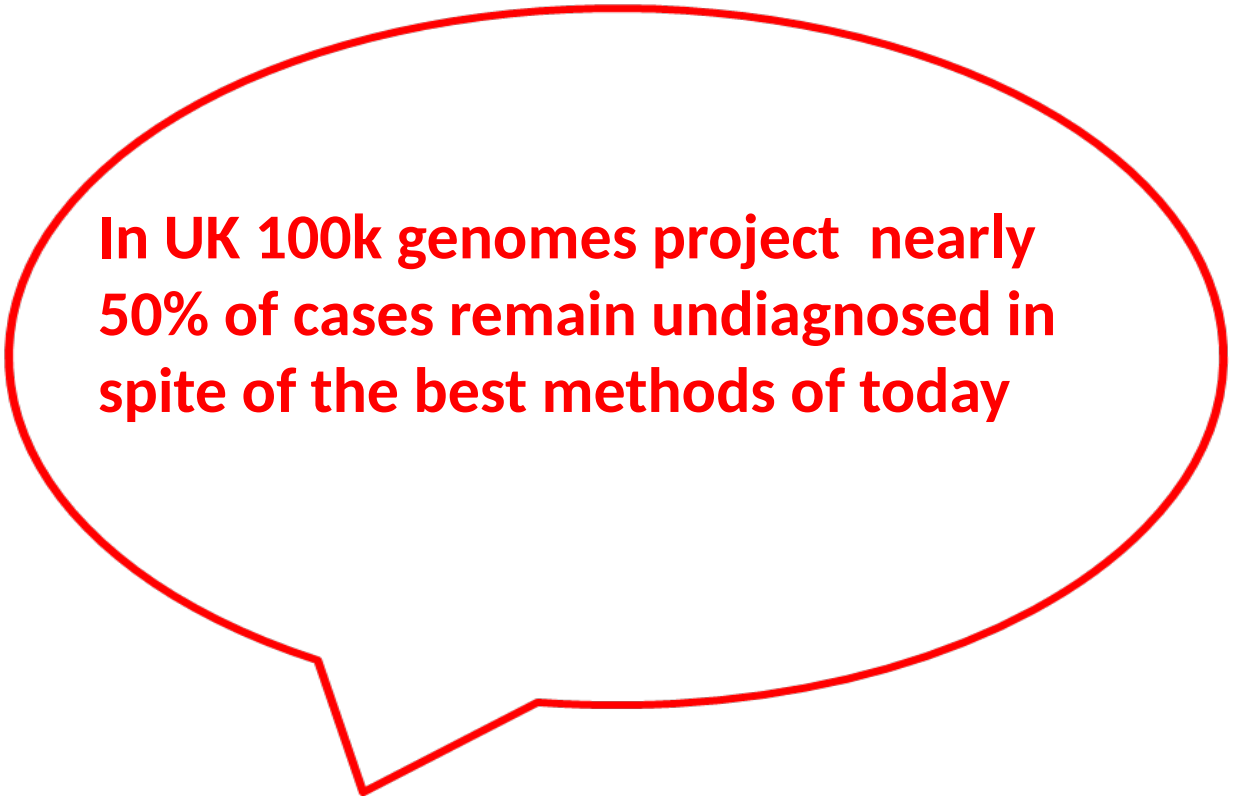

Symptoms and signs
Genomewide test
Clinical diagnosis
Specific gene test
Mutation identified
Diagnosis found or confirmed


Symptoms and signs
Wrong clinical diagnosis
Genomewide test
Clinical diagnosis
Specific gene test
Mutation identified
Diagnosis found or confirmed


Symptoms and signs
No clinical diagnosis
Genomewide test
Clinical diagnosis
Wrong test as the first guess
Specific gene test
Mutation identified
Diagnosis found or confirmed


Symptoms and signs
Wrong clinical diagnosis
Genomewide test
Clinical diagnosis
Wrong test as the first guess
Specific gene test
Mutation identified
No mutation detected
Diagnosis found or confirmed


Symptoms and signs
Clinical diagnosis
Specific gene test
Mutation identified
Diagnosis found or confirmed
Variants in genes that are not yet understood
Genomewide test
Too many variants found
Mutations that are not related to symptoms
Some areas in the genome not covered by the test


In UK 100k genomes project nearly 50% of cases remain undiagnosed in spite of the best methods of today

- But the genomic diagnostics take place in laboratories, maybe in other countries.
- What is the role of a clinical geneticists here?

- *De novo* missense mutations in *PPP2R5D* have been recently shown to cause intellectual disability as well as other clinical features including autism spectrum disorder, macrocephaly, hypotonia, seizures, and dysmorphic features (PMIDs 26168268, 25972378, 26576547). Most of the reported *de novo* mutations (p.(Glu197Lys), p.(Glu198Lys), p.(Glu200Lys), p.(Pro201Arg), and p.(Trp207Arg)) occur in the highly-conserved acidic loop of the B56δ subunit, which is essential for holoenzyme formation. Functional studies indicate that these mutations in the acidic loop, which faces the A and C subunits, disrupt binding of the B56δ subunit to the A or C subunits, and therefore impairs B56δ-dependent dephosphorylation dynamics (PMID 26168268).

New skills are needed???:

- Clinical geneticists, together with laboratory geneticists, have to comprehend what effects a certain gene/variant might have and in which tissue?
- They also have to be able to explain, with the correct amount of uncertainty, the meaning of the results to other clinicians and to the patients.

Genetic counselling

- At present, most clinical geneticists meet a patient/a family in a counselling session.
- Depending on the case, also near relatives are invited to counselling.
- Most patients are very satisfied with this type of service.
- This suits well rare, severe diseases, but will not be possible if everybody gets his/her genomic results for personalized health care or health improvement.

So what about the future?

- Clinical geneticsts will continue to have roles in diagnostics of rare diseases and in genetic counselling.
- But what else?


BIOPANKKI
BOREALIS
Itä-Suomen
BIOPANKKI
KESKI-SUOMEN
BIOPANKKI
Tampereen
Biopankki
AURIA
BIOPANKKI
HELSINGIN BIOPANKKI
HELSINGFORS BIOBANK
HELSINKI BIOBANK
FHRB
Biopankki
Suomen
Terveystalon
Biopankki
Veripalvelun
BIOPANKKI
THL BIOPANKKI
Alueelliset biopankit
Valtakunnalliset biopankit

Diagnosis for symptomatic patients or before the symptoms?

- If a genome wide test would be performed to everybody, we might find diseases, predispositions or risks before any symptoms.
- We could start a new approach: personalized prevention instead or parallel to the general health education.
- Here the role of clinical geneticists is mainly in planning the programs and education.

Medication for personalized prevention?

- If a healthy individual is found to have a mutation that causes long Q-T or familial hypercholesterolemia, medication could be started and that might prevent symptoms and early death.
- Which specialty should take care of these patients and their families?
  - Cardiology, internal medicine, primary health care?

Follow-up for early diagnostics?

- If healthy individual is found to have a mutation that causes predisposition to colon cancer (Lynch syndrome), who should counsel the patient and the family?
- To day we can detect monogenic cancer risks but in the future also polygenic risk scores for specific cancers.
  - Task could be devided between genetics clinics, gastroenterology, primary health care?

Life-style changes?

- In case of high polygenic risk score for diabetes type 2, people should have normal weight, do physical excercising and avoid smoking. But shouldn't we all?

- There is evidence that intensive personal health education helps in prevention of diabetes type 2.
  - Primary health care, specialized nurses, "personal trainers"?

Screening for family planning?

- For instance, in Israel, after the tradition of Tay-Sachs screening for some 40 years, nationwide screening for young couples for common mutations of some tens of recessive diseases is offered.
- If public health care does not implement these posibilities, then the wealthy and well-educated will use them anyway which will add to the unequalities of health.
  - Special screening organization, nurses, midwifes?

Direct to consumer?

- What is the role of clinical genetics in this business?

DNA Genetic Testing & Analysis

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Clinical geneticists may be asked to deal with

- Diagnostics and counselling of rare diseases
- Genomic results from clinics and biobanks, both monogenic unsolicited findings and polygenic risk scores?
- Direct-to-consumer results?
- Population screening projects?
- Research projects focusing genetic/genomic issues?
- Creating (in native language) information (”leaflets”) on the growing number of rare diseases.
- Education for all health care and the population

Can there ever be enough clinical geneticists?

- If many new tasks are added, part of the present work has to be ommitted.

- In my opinion, everything that is not related to rare diseases has to be dealt with by other speciaties.

Genetics Clinic of the Future (GCOF)

This multidiciplinary project outlined visions for future health care where a genomic test wolud happen as a (nearly) first step in the health care process.

The project concluded

- Clinical geneticists will have important role in counselling patients and families with rare diseases, as well as feeding data to the databases which serve diagnostics of RD.
- However, their main task will be to support the other health care in implementing genetics into the clinic.