

Basic genetic examination

Antonin Sipek jr.¹, Antonin Sipek^{2,3,4}

1 – Institute of Biology and Medical Genetics, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic

2 – Department of Medical Genetics, Thomayer Hospital, Prague, Czech Republic

3 – Screening centre, Pronatal Sanatory, Prague, Czech Republic

4 – Department of General Biology and Genetics, Charles University, 3rd Faculty of medicine, Prague, Czech Republic



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- **History**
- **Role of clinical genetics**
- **Genetic examination**
- **Genetic consultation**
- **Primary prevention**
- **Registries**
- **Summary**

Historical milestones



J. G. Mendel – 1866:

Versuche über Pflanzenhybriden (Experiments on Plant Hybridization)



William Bateson – 1905: term *GENETICS*



T. H. Morgan – 1933: Nobel Prize for Genetic linkage study



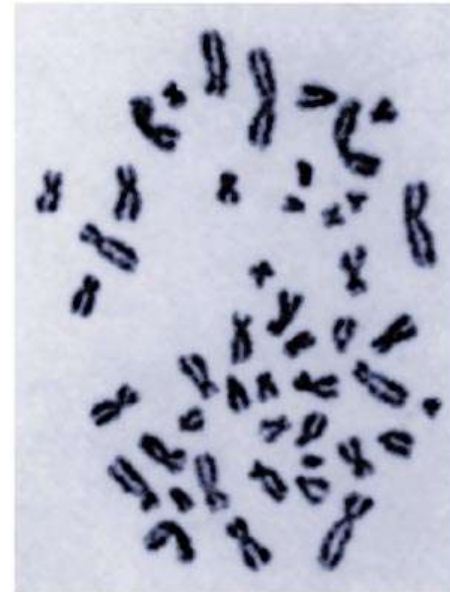
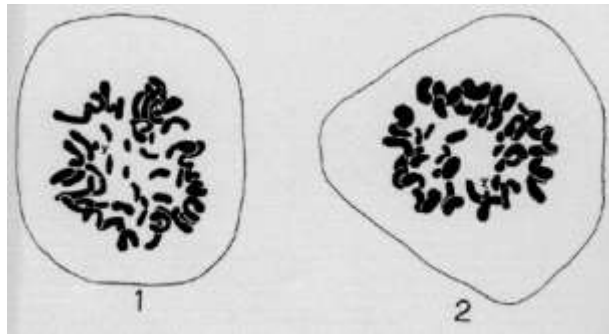
T. H. Morgan – 1944: DNA is the carrier of the genetic information



J. D. Watson, F. Crick, M. McCarty – 1953: Structure of DNA molecule

Chromosomes

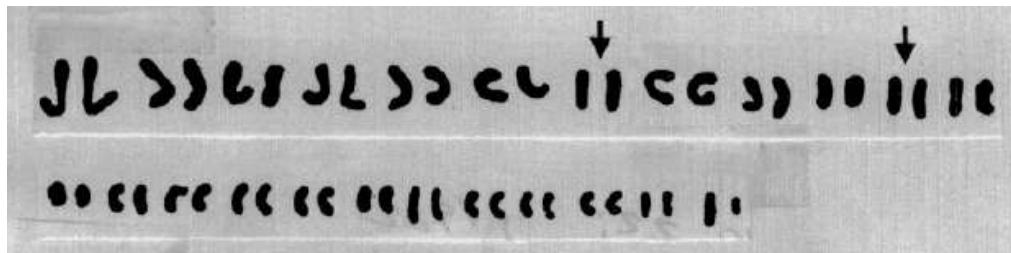
23 chromosome pairs



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Down syndrome

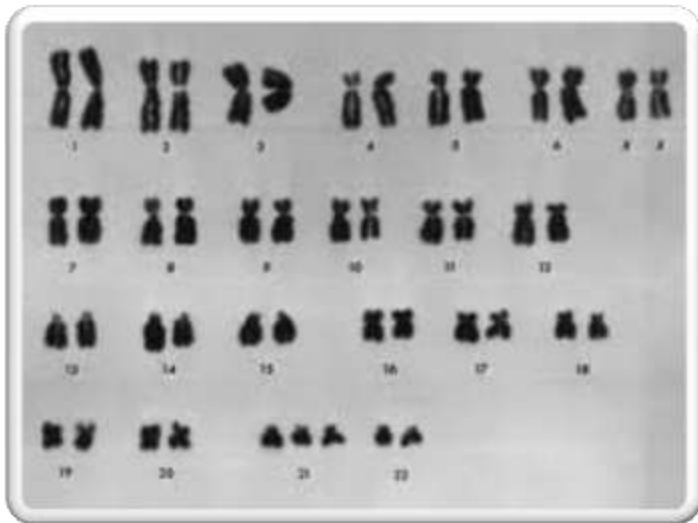


John Langdon Down – 1866

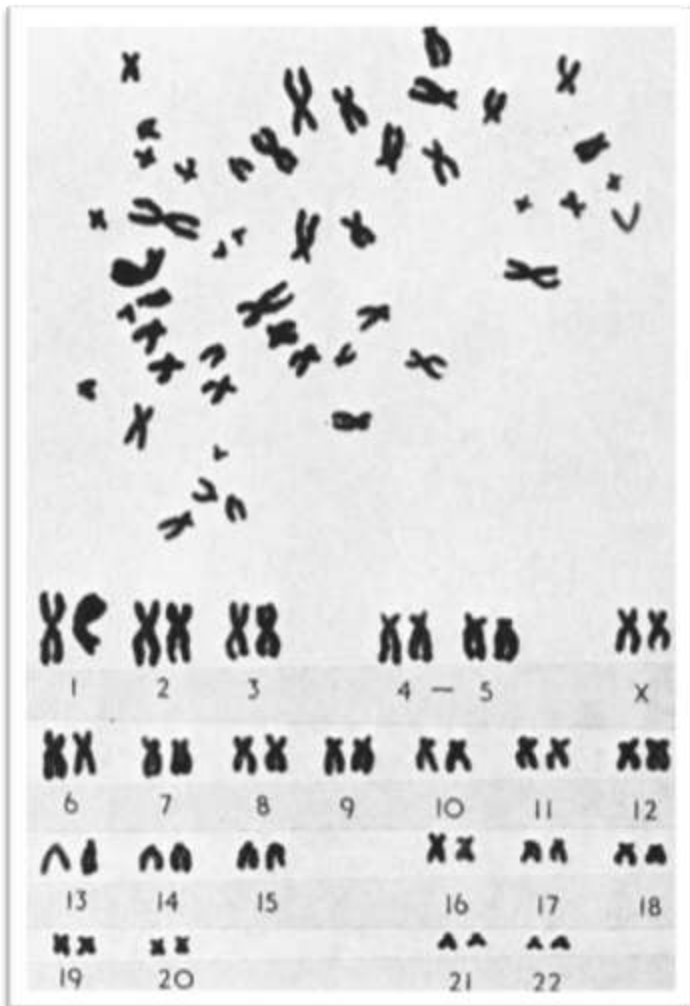
Observations on an Ethnic Classification of Idiots

Jérôme Lejeune – 1959

Etude des chromosomes somatiques de neuf enfants mongoliens



Cri du chat syndrome



Jérôme Lejeune – 1963

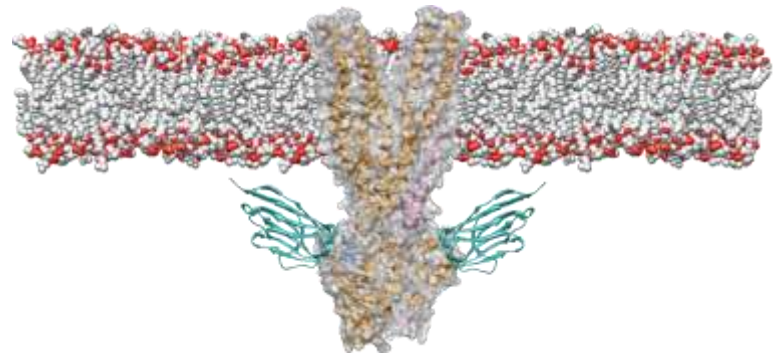
3 Cases of partial deletion of the short arm of chromosome 5



Molecular genetics



1985 - PCR reaction invented by Kary B. Mullis



1989 – CFTR gene mutation discovered by Francis Collins and Lap-Chee Tsui

Clinical Genetics



Victor A. McKusick
1921 – 2008

1957 – One of the first departments of clinical genetics was founded at John Hopkins Medicine in Baltimore

today

McKusick-Nathans Institute of Genetic Medicine



www.omim.org

Role of clinical genetics

Clinical genetics (medical genetics) is an independent branch of medicine

In the European Union the medical genetics is an **individual specialization**

Departments of clinical genetics have their own laboratories and the clinical (ambulatory) part. Departments with their own beds are very rare.

The main goals of clinical genetics are as follows:

- Diagnosis
- Prevention
- Treatment
- Registration

The counseling should be **strictly non-directive**

Most important diagnoses

Congenital Malformation is a congenital anomaly of the structure of some body part.

Birth Defect or Congenital Disorder are nearly synonyms for the term Congenital Anomaly.

Chromosomal Aberrations are the numerical or structural abnormalities of the karyotype.

Genetic Disorders are the conditions caused by the mutation of the gene(s).

Cooperation

Pediatrics (congenital anomalies, mental retardation, dysmorphic features, small stature, disorders of sexual development, metabolic disorders)

Gynecology and obstetrics (prenatal diagnosis, fetal abnormalities)

Oncology (hereditary cancer syndromes, oncocyto-genetics)

Neurology (muscle dystrophies, epileptic syndromes, hereditary ataxias, hereditary neurodegenerative disorders)

Internal medicine (hemocoagulation disorders, hereditary diseases of the kidneys, hereditary cardiomyopathies and arrhythmias, hereditary forms of DM, hereditary jaundice, congenital immunodeficiencies etc.)

And others...

Clinical geneticists provide counseling for other departments

Indication for genetic examination

Prenatal

- abnormal results of prenatal screening (biochemical, combined)
- abnormal findings during prenatal ultrasound examination of the fetus
- higher age of the mother (35 years and more...)
- fetal death or spontaneous abortion in previous pregnancies
- congenital anomalies in the family history
- genetic disorders in family history

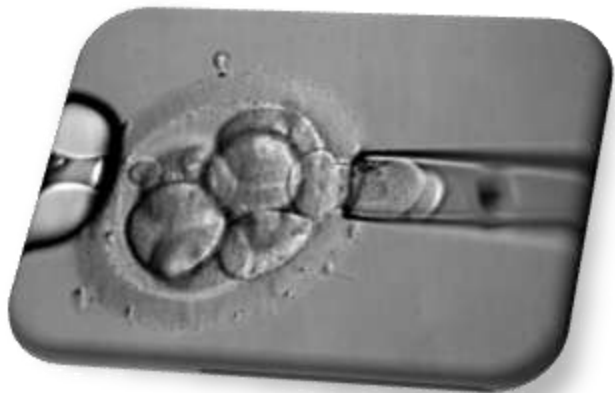
Indication for genetic examination

Postnatal

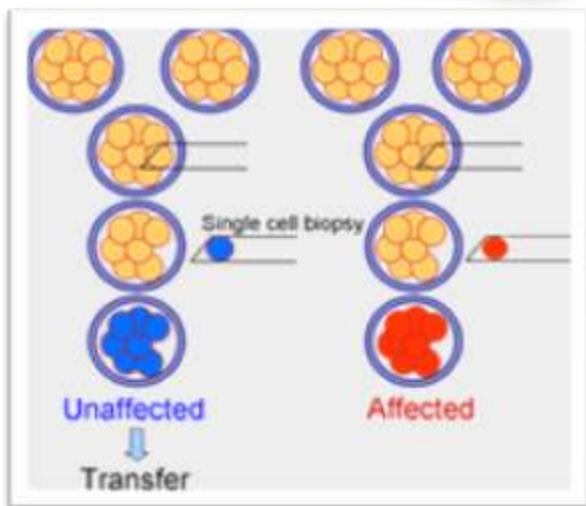
- Congenital anomaly
- Psychomotor retardation
- Sexual development disorders
- Abnormal growth
- Psychic disorders, autism
- Genetic disorder in family history
- Poor reproduction history (sterility / infertility)
- Multiple cancer diagnoses in family history

Indication for genetic examination

Preimplantation genetic diagnosis (PGD)



- Known genetic disorder in the family
- Exact mutation must be known
- Balanced chromosomal aberration in one of the parents
- IVF method is required
- Only the embryo without defect will be implanted



Genetic counselling

Genetic counsel is a special talk between clinical genetician and **proband**

Proband provides information about the problem (indication) and about family history (special forms are useful for collecting these information).

The other medical specialist **reports** are welcomed and sometimes **required**.

The genetician **informs** the proband about the (proposed) diagnose (or diagnose at risk) – clinical signs, prognosis, possible treatment, risk for other family members

The genetician **proposes** next steps (genetic diagnostics, prenatal tests)

Genetician only informs - It is up to the proband to decide!

It is recommended to give some extra time for proband's decision.

Genetic counselling

Informed consent is an important part of clinical genetic practice

The agreement or disagreement of the proband with proposed test examination or procedure has to be confirmed by his or her signature.

The informed consent includes:

- Name of the procedure (test, examination...)
- The reason and/or indication for this procedure
- Possible alternatives to the proposed procedure
- Possible risks of the proposed procedure
- Proband's decision upon the future of the sample (DNA bank)
- Geneticists and probands declaration of validity of the consent

Genetic examination

Syndromologic examination is a very important part of clinical genetics practice.

The phenotype of the proband is examined closely and characteristic features are compared to the features of known genetic diseases and or syndromes.

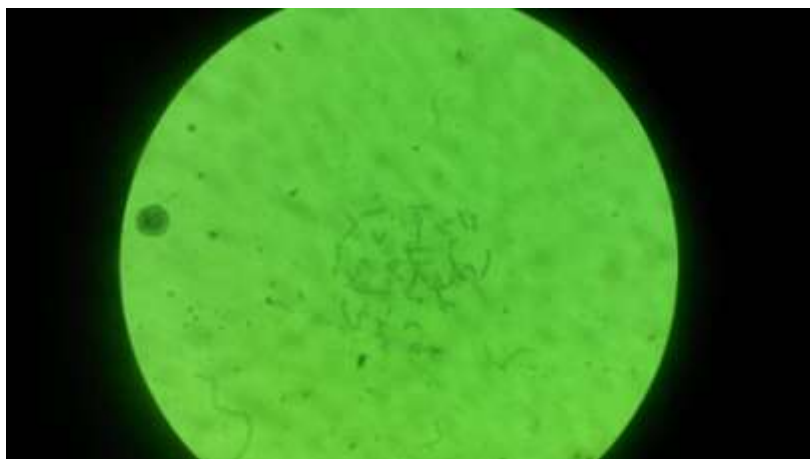
Dysmorphic features of certain syndromes can be very specific.

However, this process is very difficult and time consuming and the diagnosis are rarely made „on the first look“.

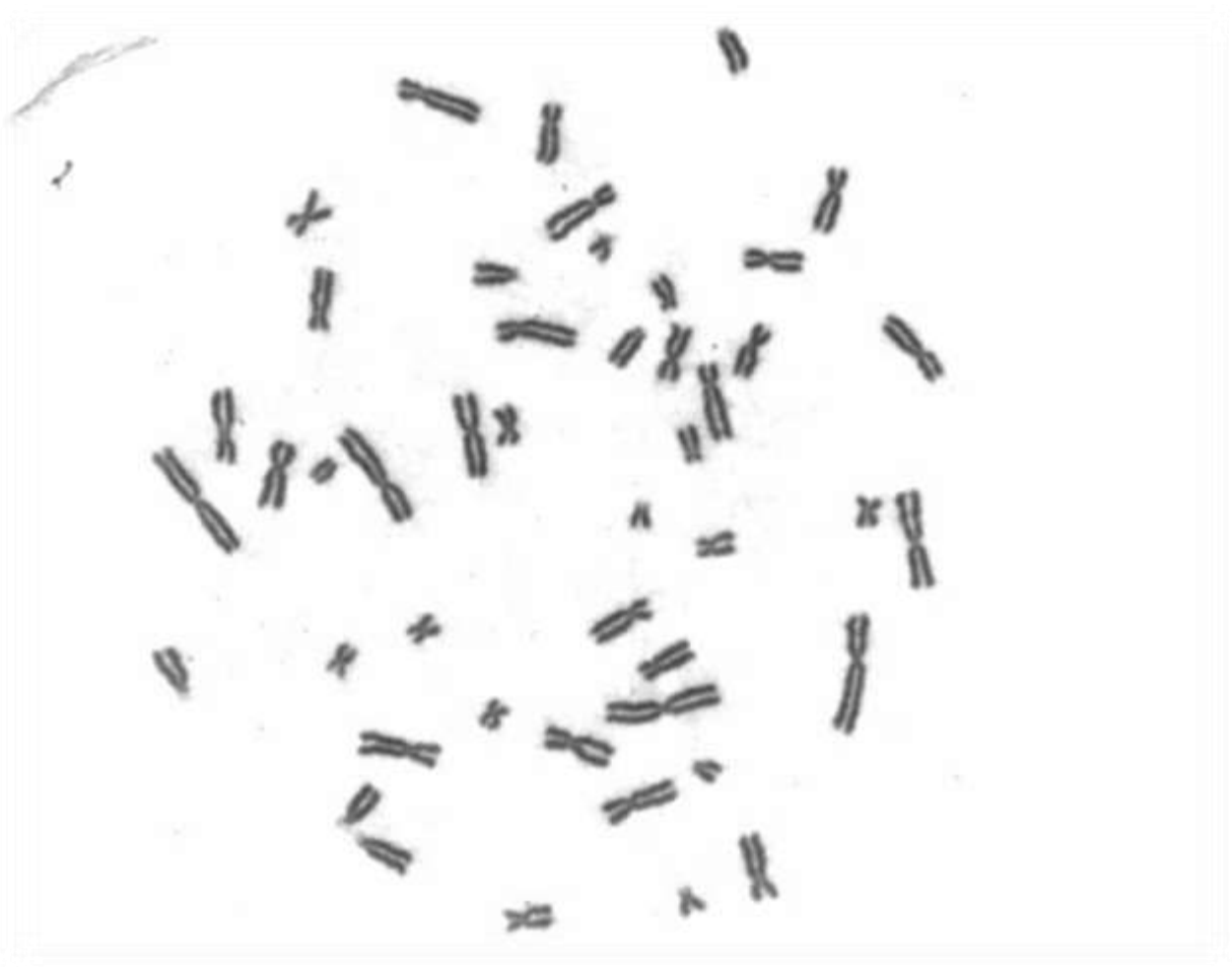
More specific tests are sometimes needed to confirm the proposed diagnosis

- **Genetic tests** (cytogenetic, molecular-cytogenetic or molecular-genetic)
- **Other** (Ultrasonography, MRI, RTG, ECHO, ECG, biochemical or hematological examination etc.)

Cytogenetics



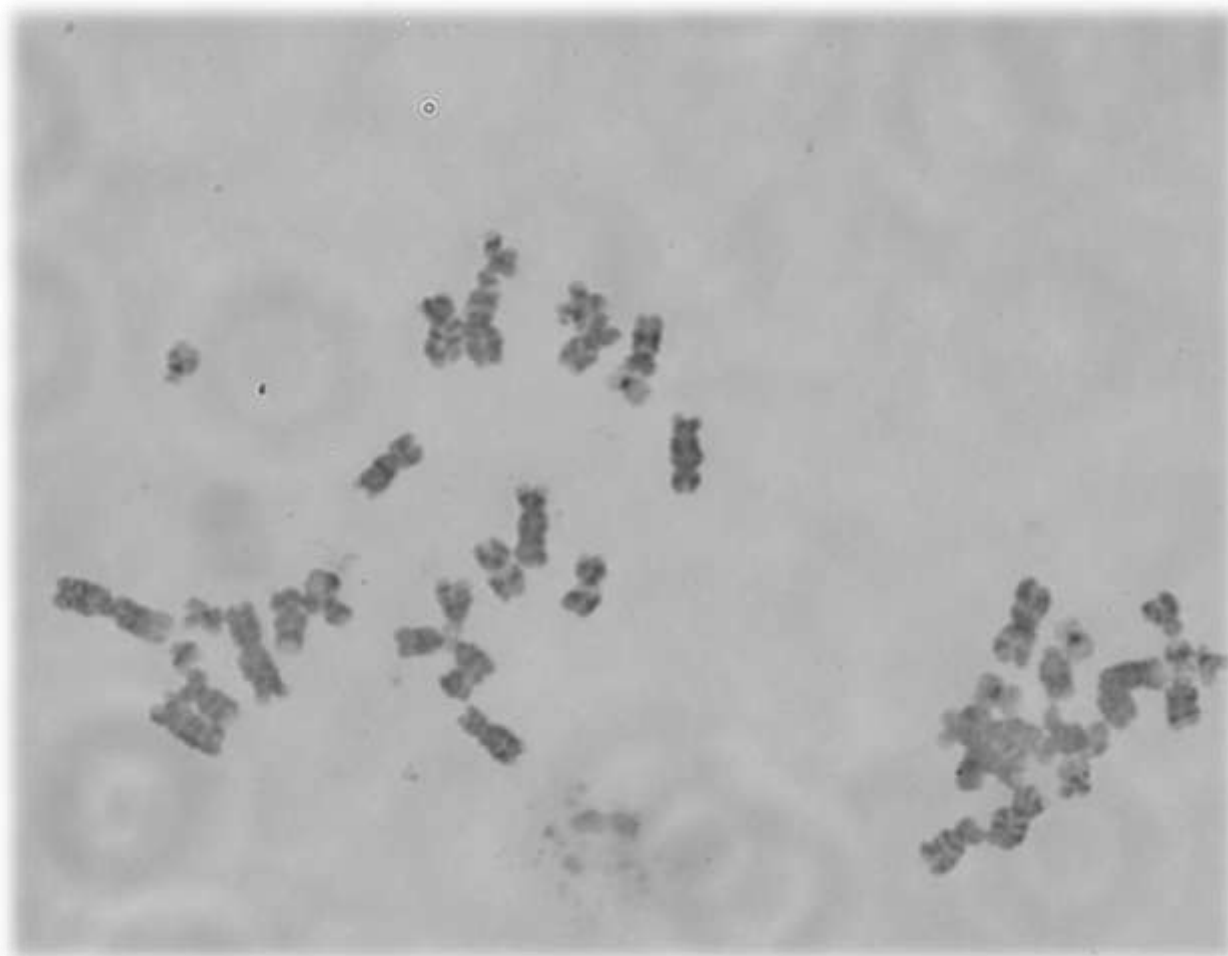
Classical staining



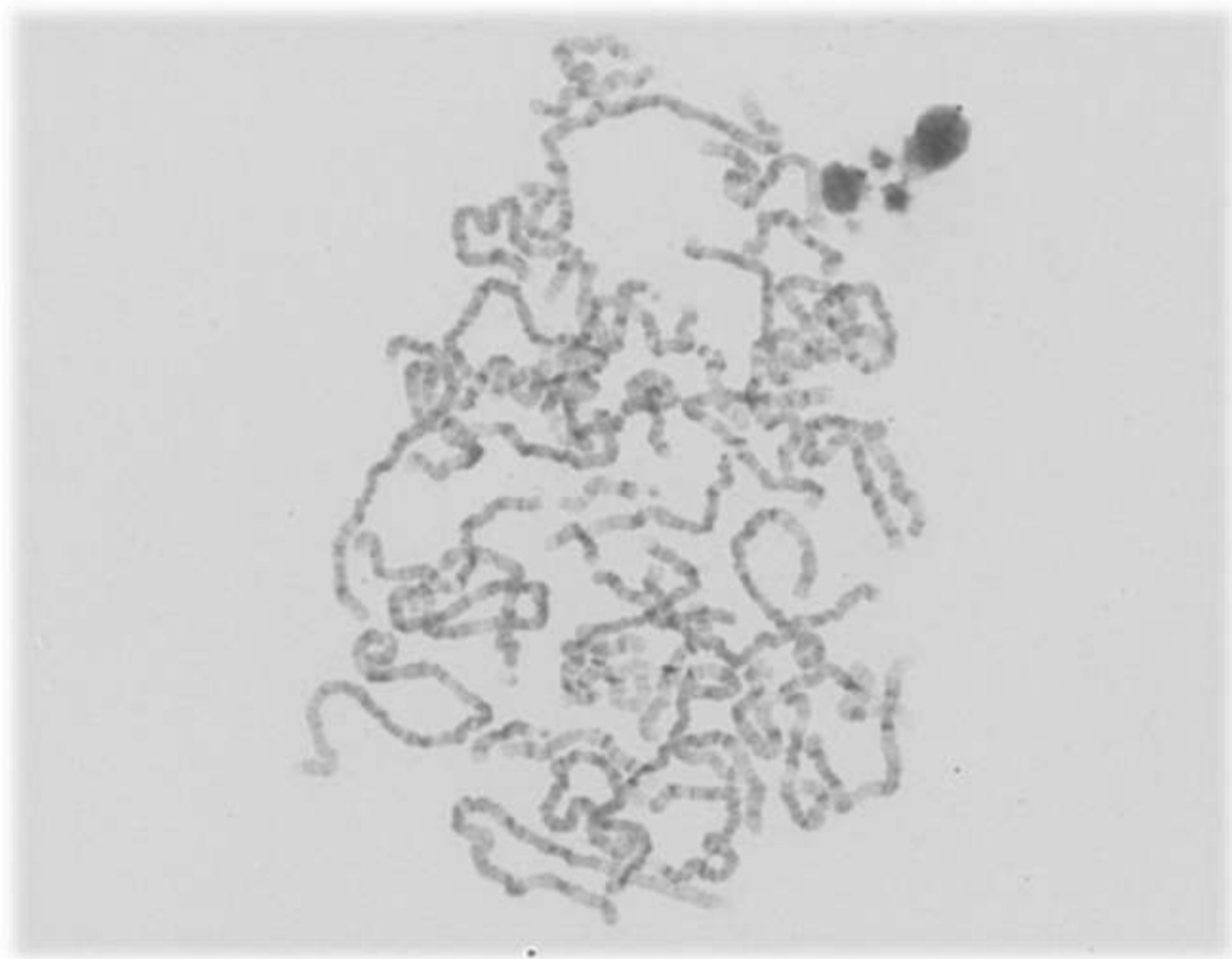
G-banding



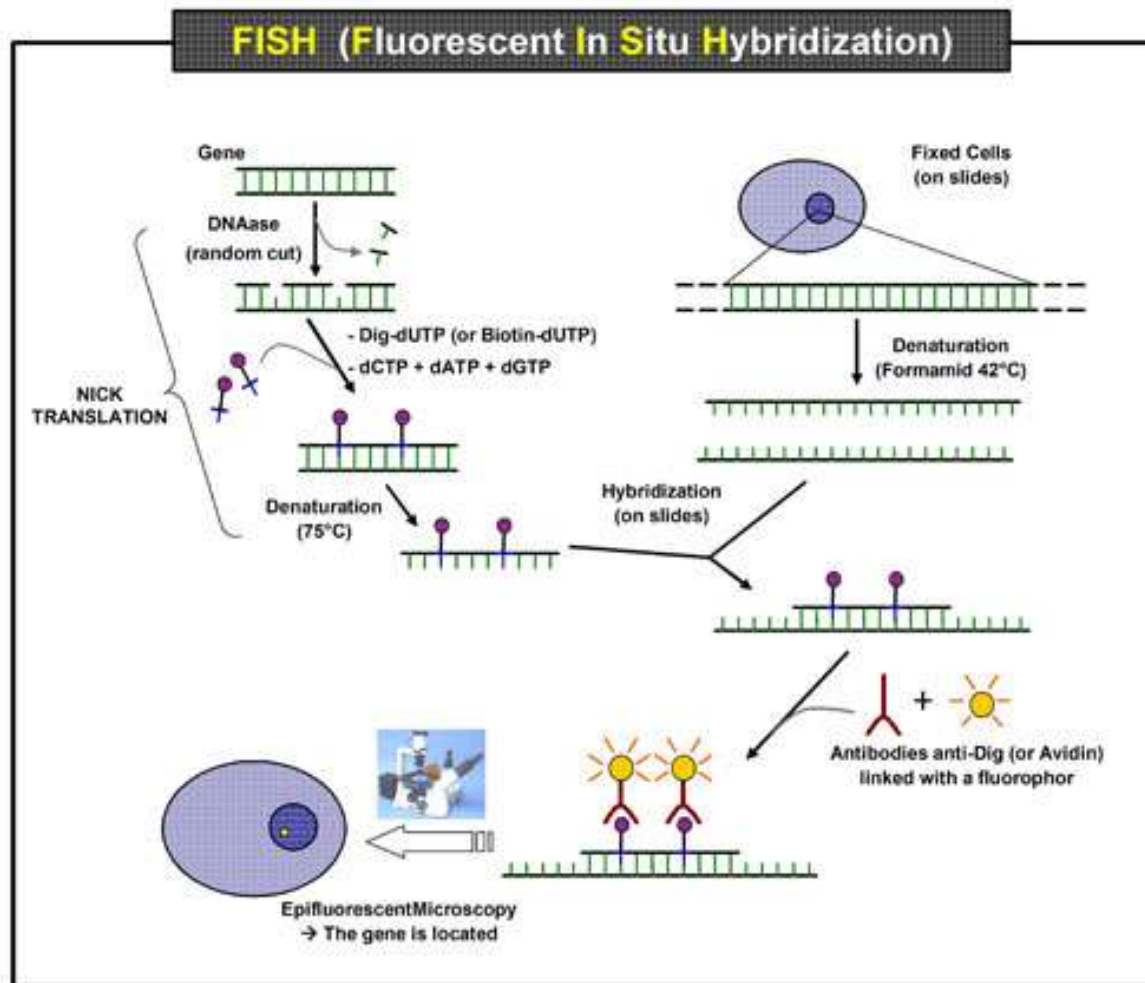
G-banding (CVS)



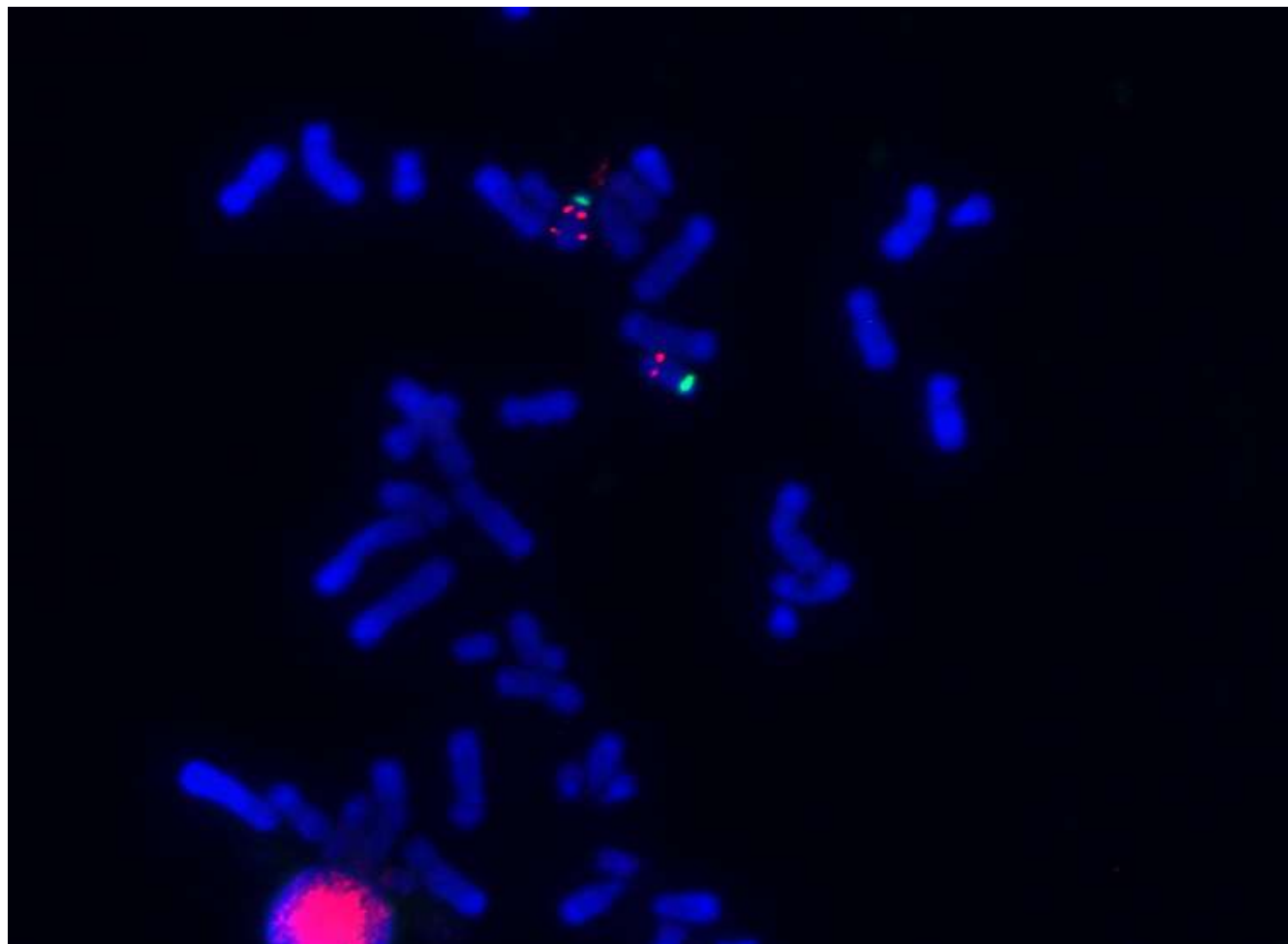
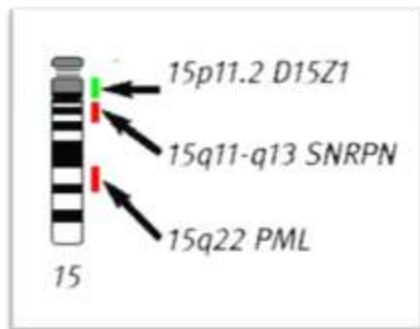
HRT



FISH

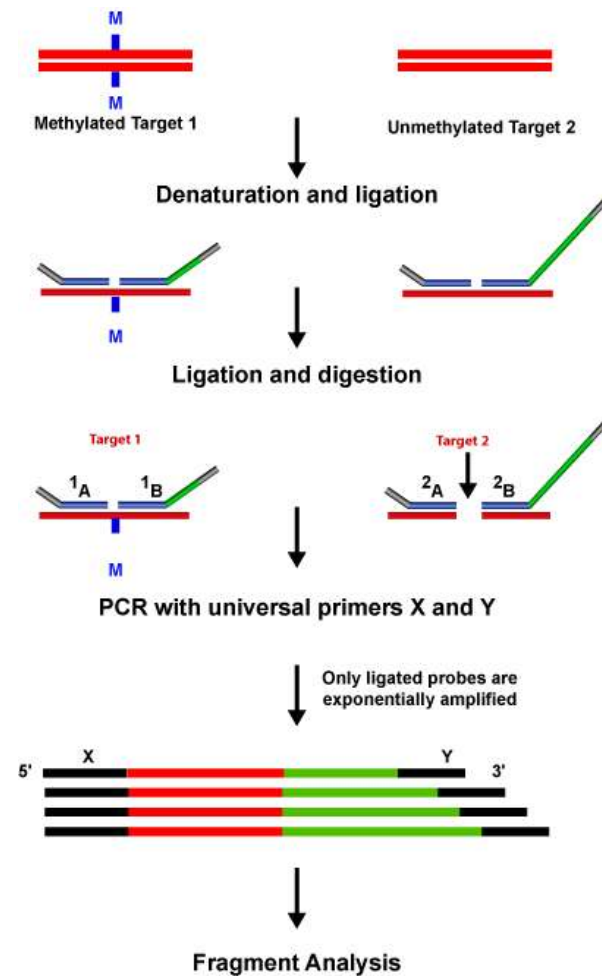
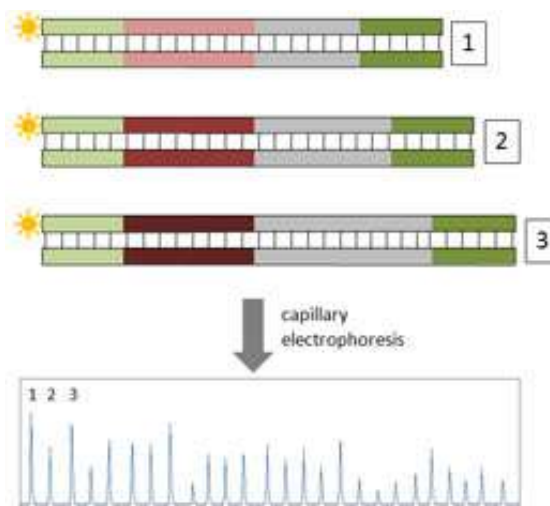
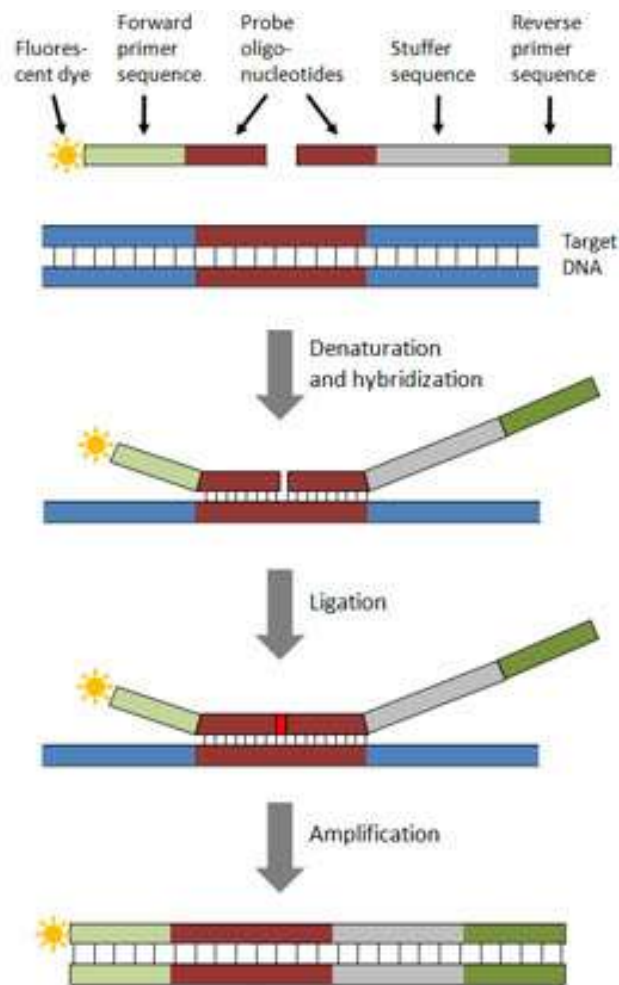


FISH



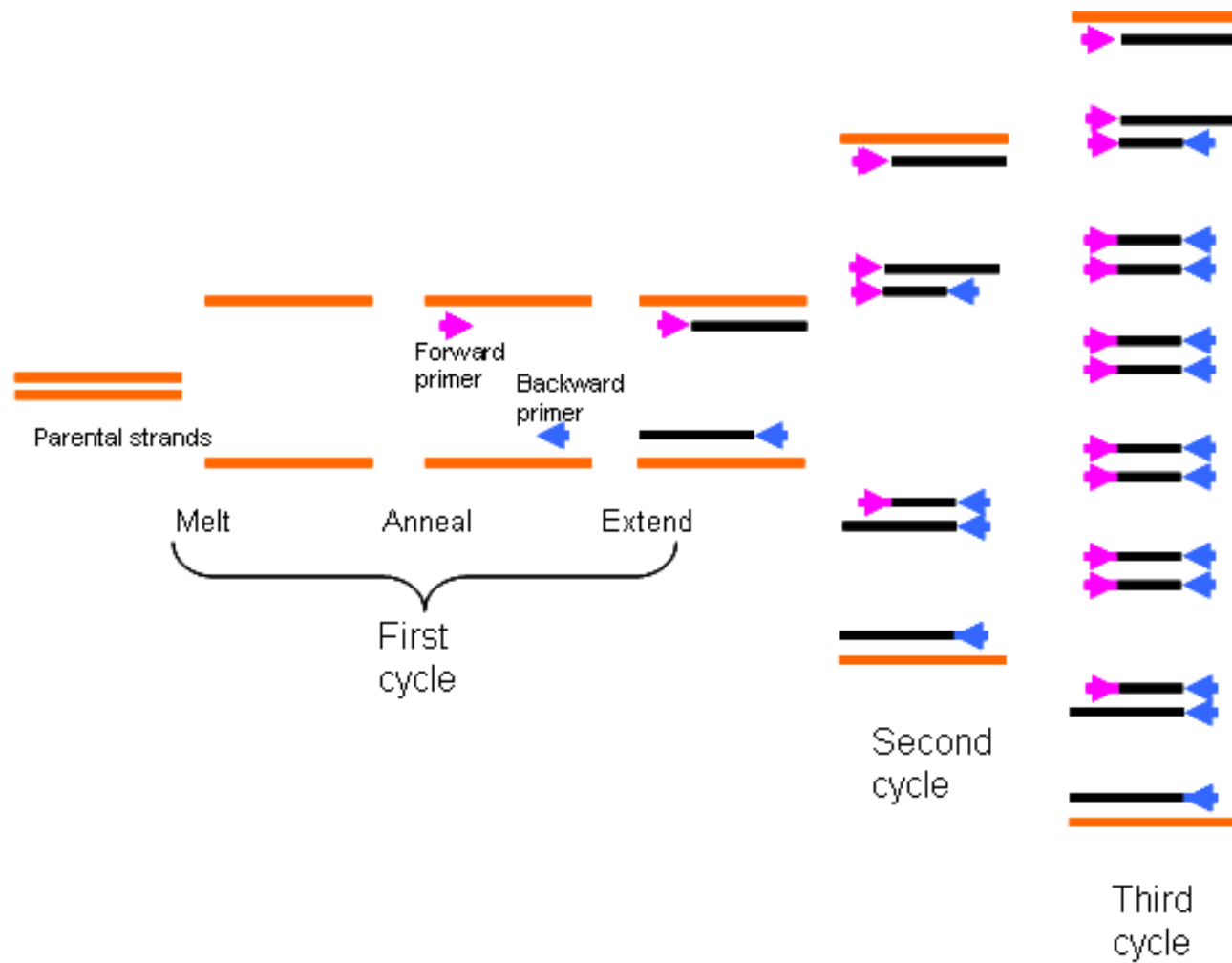
MLPA

Multiplex ligation-dependent probe amplification

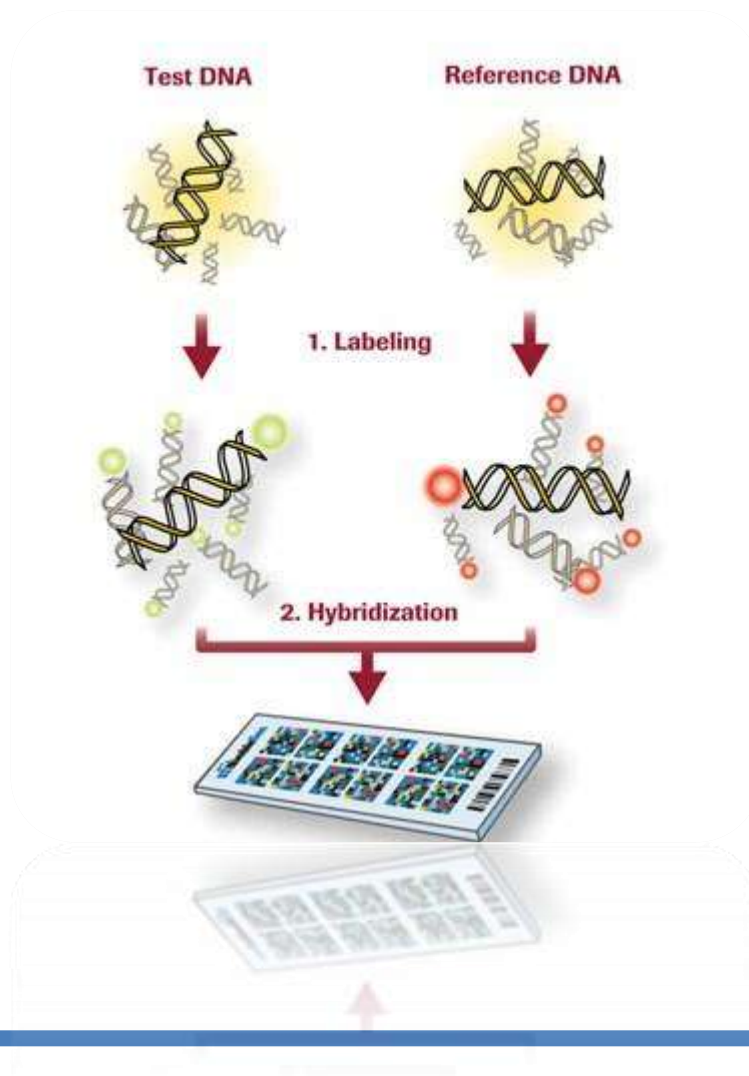


PCR

Polymerase Chain Reaction

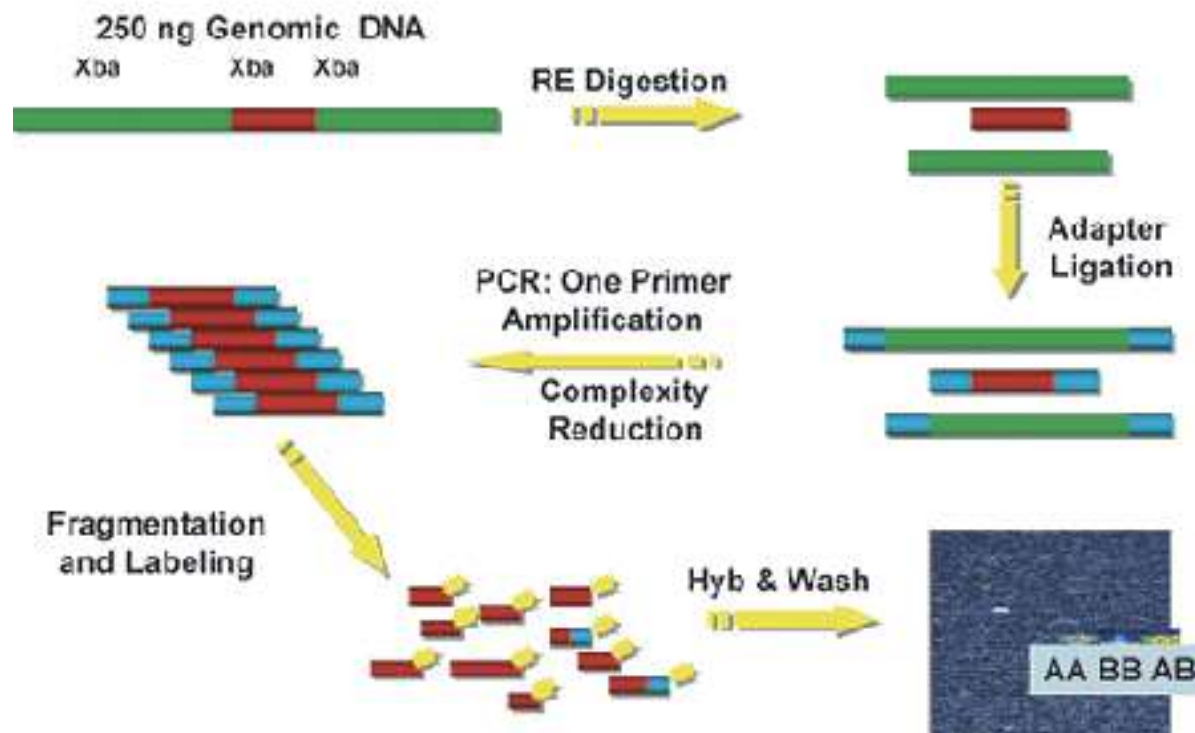


Array-CGH

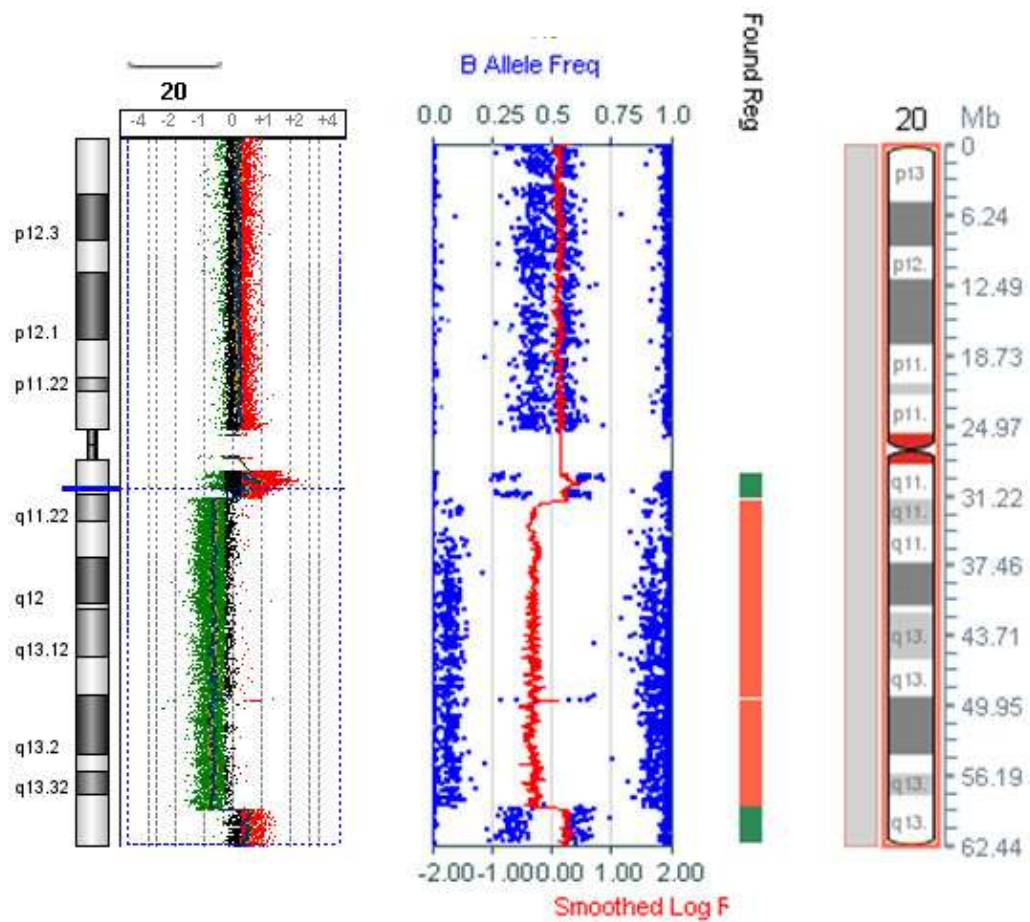


SNP-Array

Genotyping Mapping Assay Overview



Array methods



BM 26 day

Primary prevention

- The main goal is to **prevent** anomaly or malformation **before** they develop (that means before conception or during pregnancy).
- The women should avoid the pregnancy in very low or very high age. **The pregnancy should be planned.**
- The parents should avoid any contact with **mutagens** or **teratogens**.
- No stress, smoking, drugs and alcohol during pregnancy.
- Clinical geneticist should be consulted in advance – if necessary (repeated abortions, congenital anomalies in family, genetic diseases).
- Good compensation of mother's diseases (DM, PKU etc.)
- Supplementation with folic acid**

Secondary prevention

- The main goal is to **prevent** the birth of a child with a congenital anomaly. However, the **termination itself is not a prevention.**
- We can terminate the pregnancy in order to prevent such a birth.
- However, the termination may not be legal in each country.
- In the Czech Republic it is legal to terminate the pregnancy because of severe genetic reasons **till 24th week** of pregnancy.
- Prenatal diagnosis is therefore very important, because we need the best information available about the condition of the fetus. If a severe condition is diagnosed, we may offer **termination** of pregnancy, prenatal **therapy** or **special treatment** in perinatologic period.

Registration

National Registry of Congenital Anomalies of the Czech Republic (NRCA)

- Unofficial monitoring in former Czechoslovakia started in **1961**
- Official monitoring started on 1st of January **1964**
- **First stage (1964 – 1974)** – only **36** selected diagnoses of congenital anomalies (CA) were registered
- **Second stage (1975 – 1993)** – **60** diagnoses of CA registered
- **Present time: (1994 – now)** – **all cases** in terminations of pregnancies (TOPs), stillbirths and live births are registered (age limit for reporting = **15 years**)

Cooperating centre:



europa
cat
european surveillance of
congenital anomalies

Registration

Registry: population based (whole area of the Czech Republic)

Law: The registration is compulsory, required by the Internal Law of Ministry of Health (nr. 14/2001). The database is run by the Institute of Health Information and Statistics of the Czech Republic

Cases: all cases in TOPs, live births and stillbirths (above 1000g) are reported

Coding: ICD-10 (international), no verbal description

Sources: Multiple sources, including departments of medical genetics, genetic laboratories, pediatric and neonatology departments, delivery units, ultrasound diagnostics departments etc.

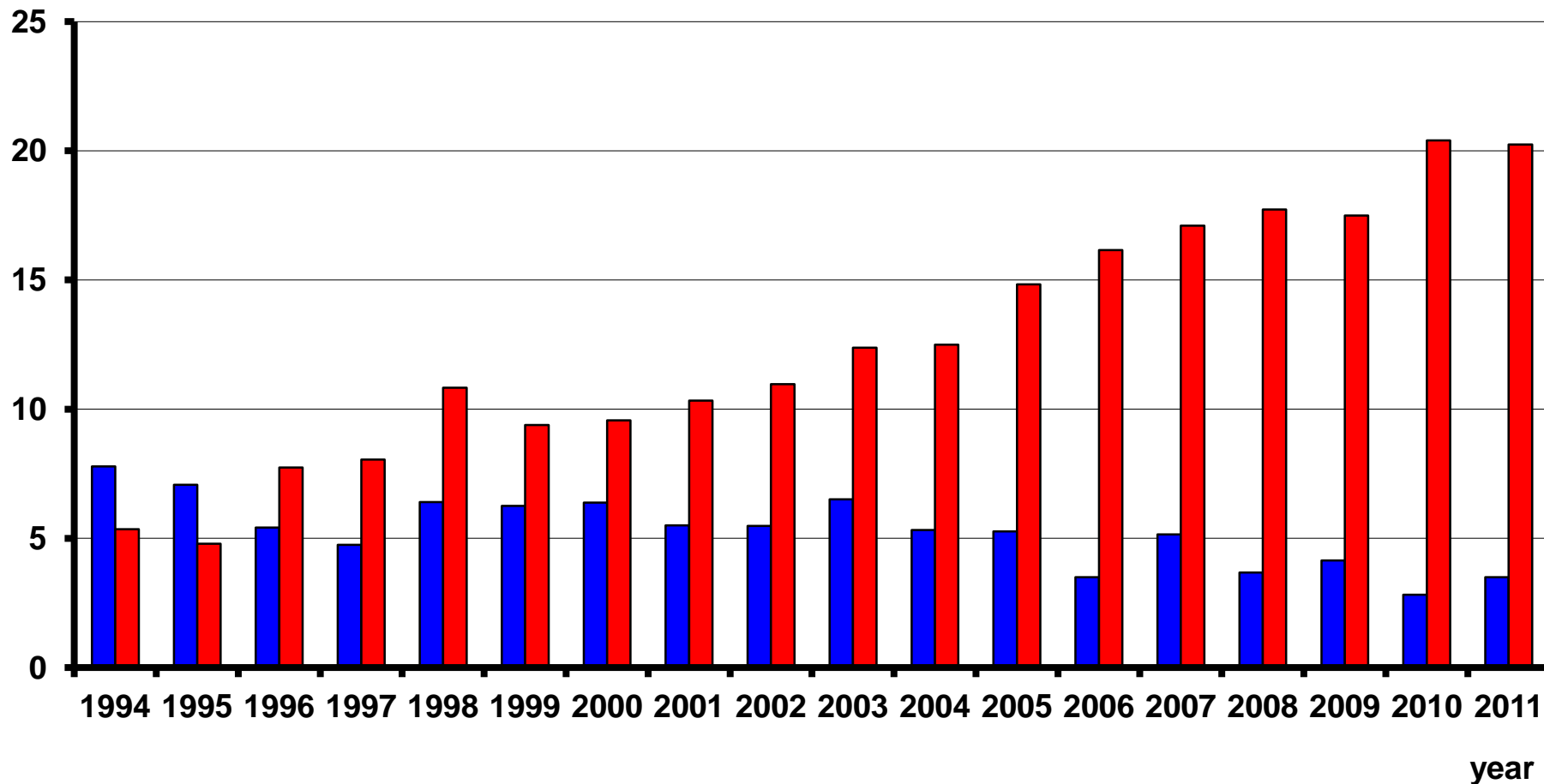
Termination of Pregnancy: Legal, up to the 24th week of gestation (from genetic reasons)

Down syndrome

Per 10 000 live births

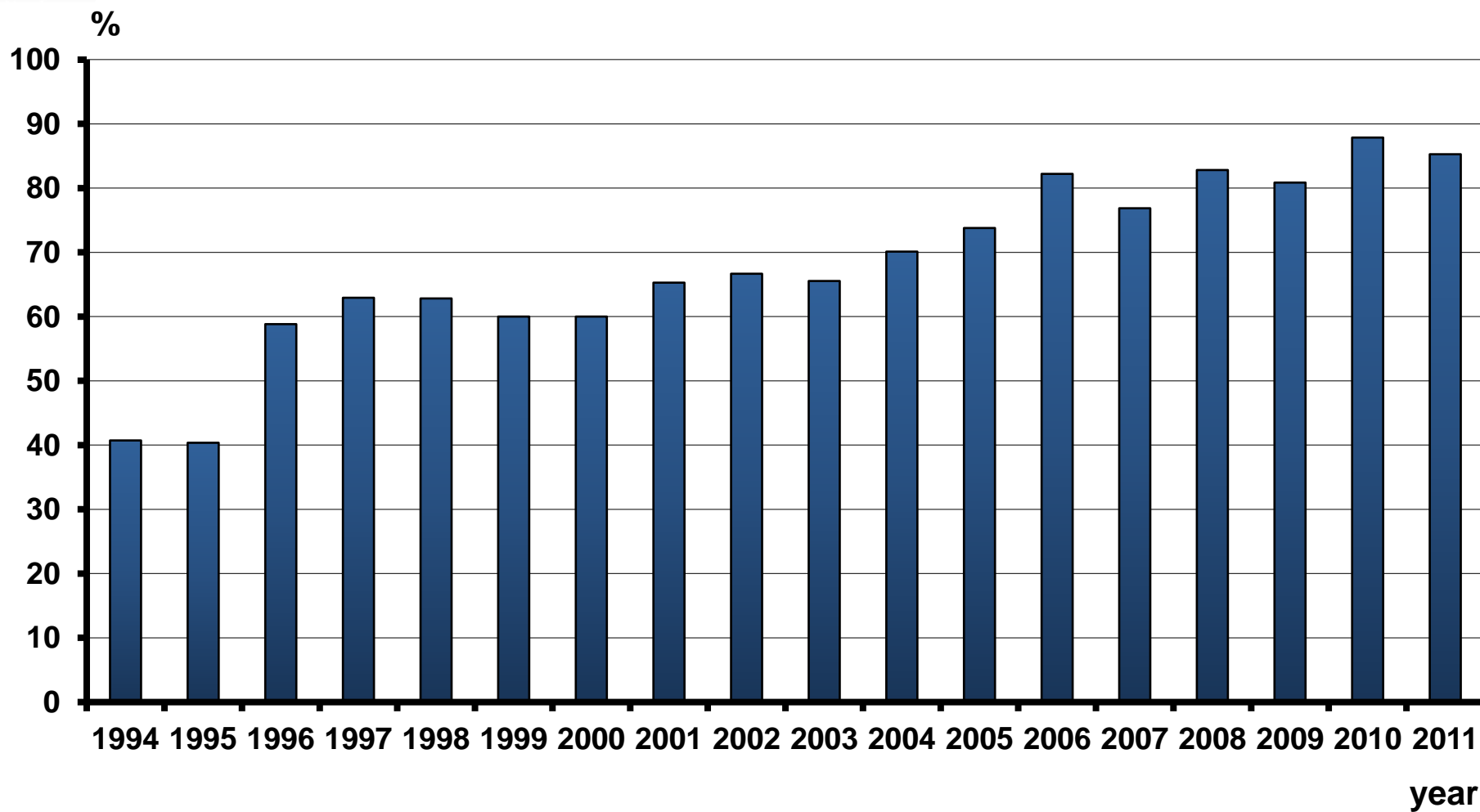
■ Births

■ Prenatal diagnosis



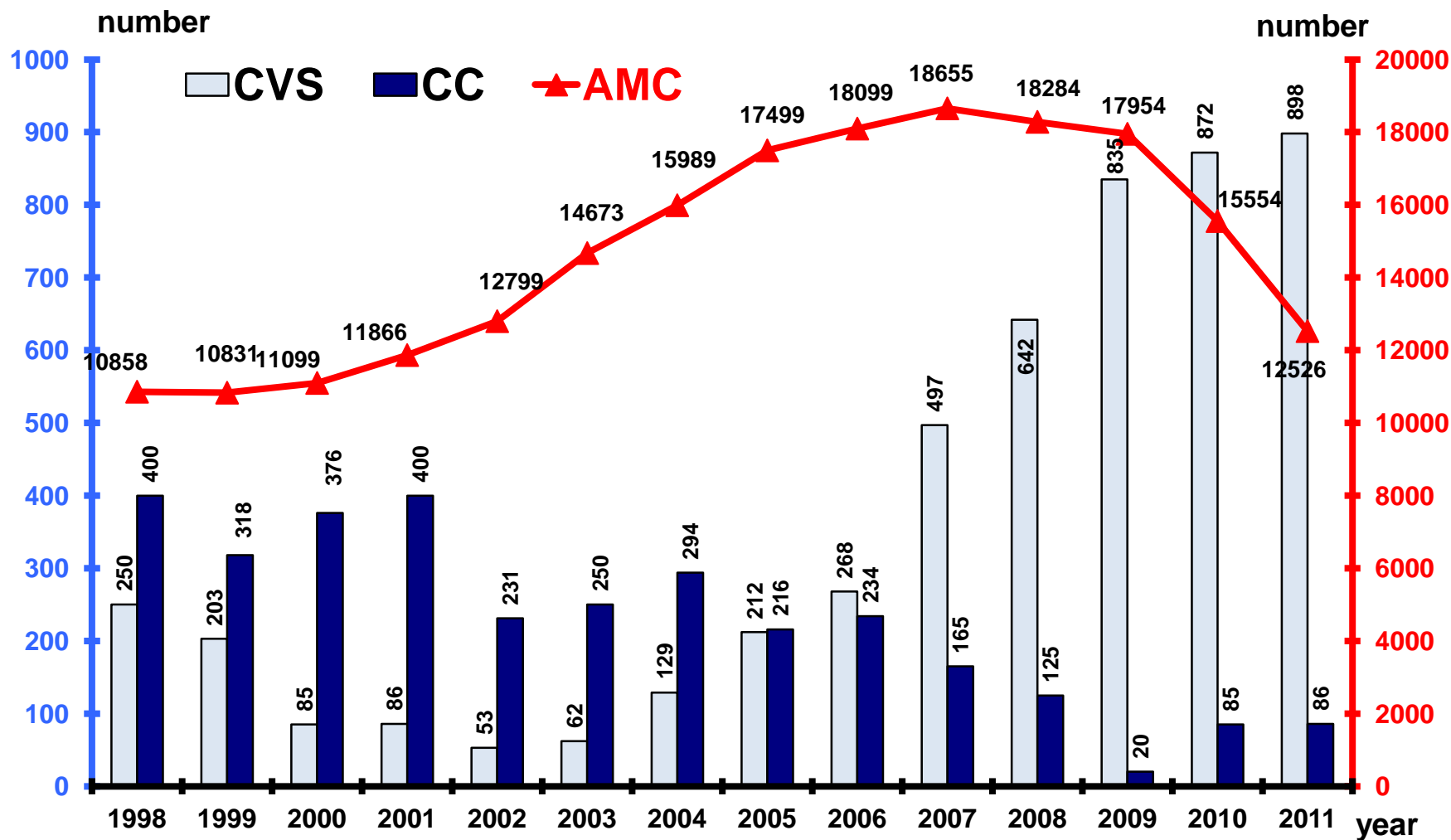
Down syndrome – All cases in live births and prenatal diagnosis

Down syndrome

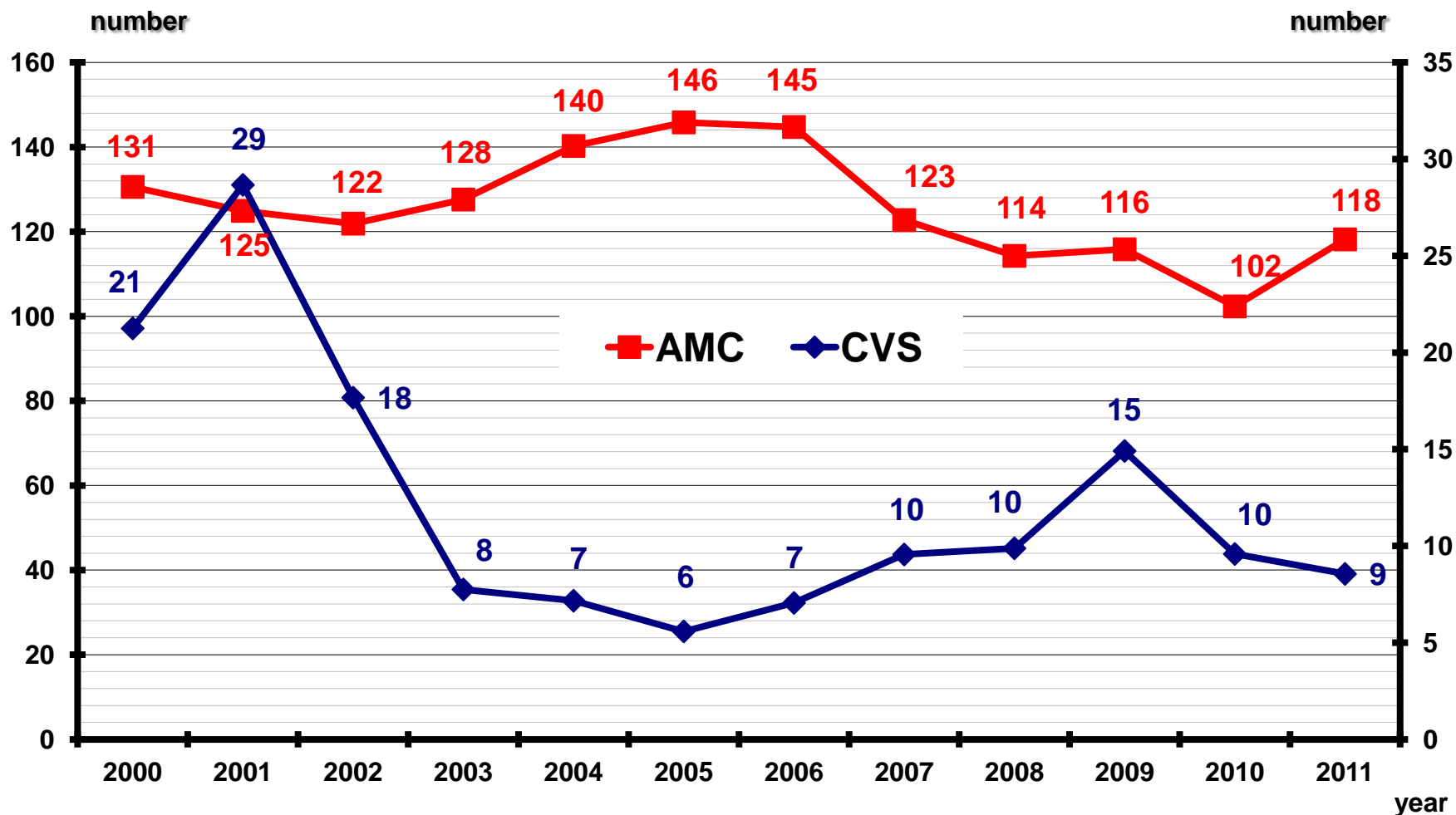


Down syndrome – relative number of prenatally diagnosed cases (%)

Invasive prenatal diagnosis

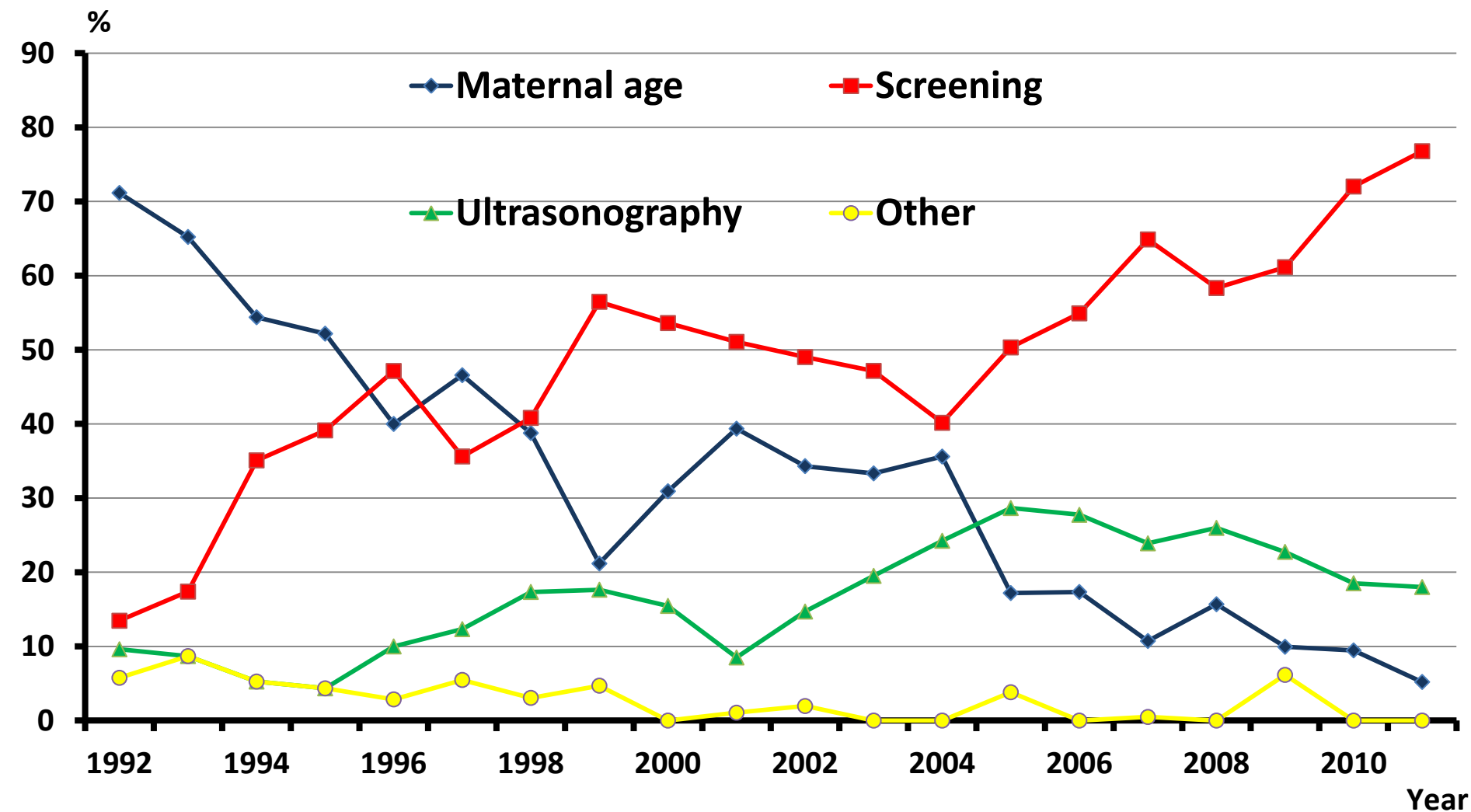


Effectiveness

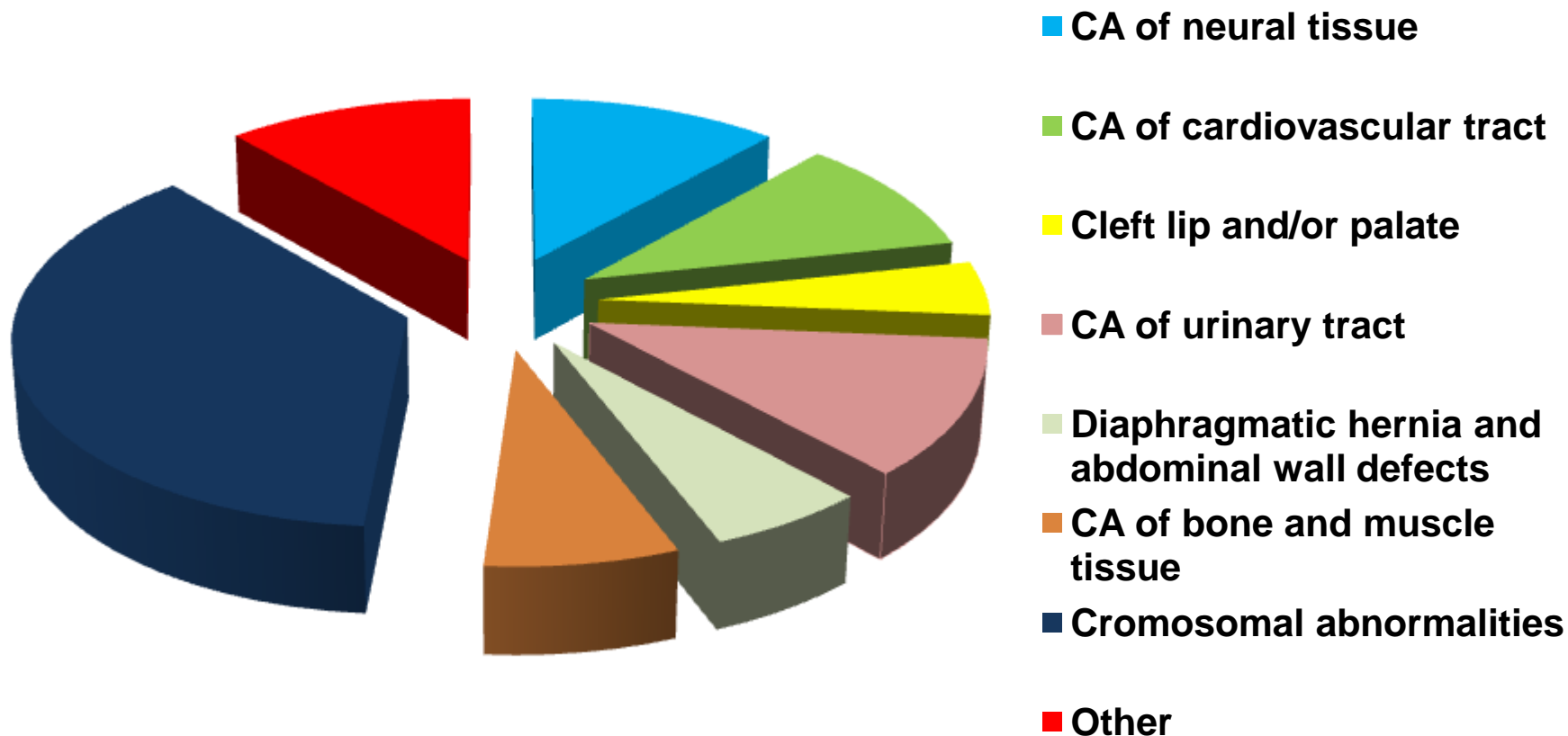


Number of invasive procedures needed for one diagnosis of Down syndrome

Prenatal diagnosis - Indications

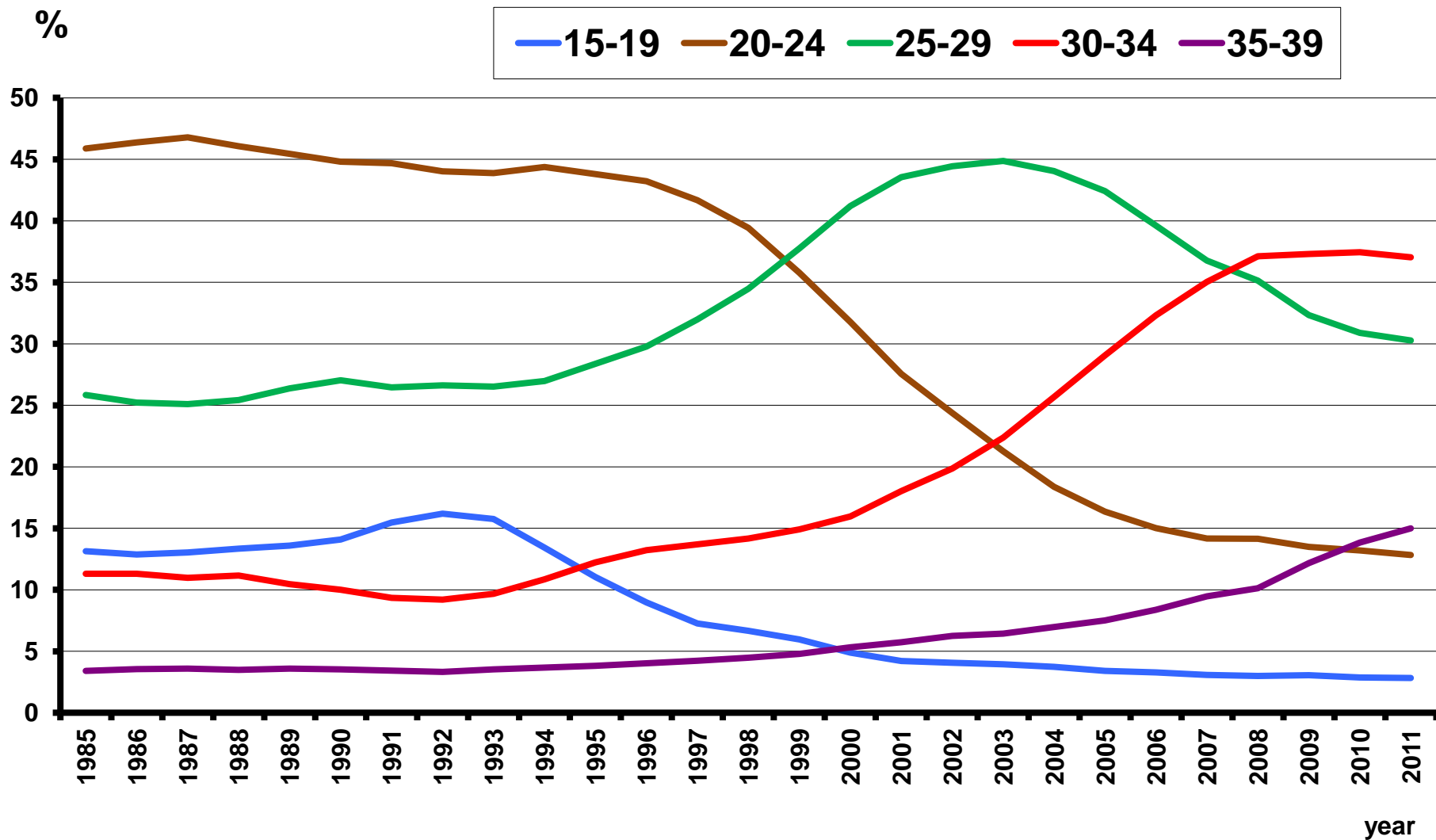


Spectrum of diagnoses



Spectrum of diagnoses – Prenatal diagnosis – All cases

Maternal age – Time trends



Summary

Clinical genetics (medical genetics) is an independent branch of medicine

The most important diagnoses for clinical genetician are **genetic disorders, chromosomal abnormalities and congenital anomalies.**

The counseling should be **strictly non-directive**

For the testing – the patient's consent is **required.**

Not only diagnostics, but also **prevention is very important.**

Thank you for your attention!



antonin.sipek@lf1.cuni.cz

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