Clinical Genetics

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Dept. of Medical genetics

- Genetic ambulance

genetic counselling

- Laboratory part
- Cytogenetic laboratories

Prenatal cytogenetics

Postnatal cytogenetics

Oncocytogenetics

Molecular – cytogenetics

- Lab. for DNA and RNA analysis (clinical genetics and oncogenetics)

Characteristic of Medical Genetics

- Preventive Medicine
- Interdisciplinary cooperation
- Information from genetics (disease, posibilities of testing, prenatal analysis)
- Voluntary choice for patients
- Informed agreement

Primary genetic prevention

- **Before pregnancy**
- Folic acid (cca 0,8 mg/day, 3+3 months)
- Vaccination (rubella)
- Genetic counselling
- Contraception, family can opt for adoption or donor of gamets (oocytes, sperm)
- Pregnancy planning
- Rediction of environmental hazards (drugs, radiation, chemicals…)

Reproduction of the optimal age

- In women increases the risk of accidental congenital chromosomal aberrations in the offspring

- In men may increase the risk of de novo mutations in some monogenic diseases (Neurofibromatosis I, Achondroplasia..)

Prevention of spontaneous and induced mutations

- Healthy Lifestyle

- The restriction of harmful substances - drugs, environmental hazards

Vacctination, infection prevention

- Prevention of rubella embryopathie

  Prevention of congenital toxoplasmosis

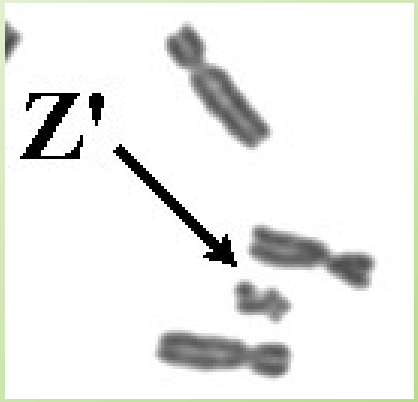
- Testing for infectious disease risk in mothers (CMV, varicella-zoster virus, ...)

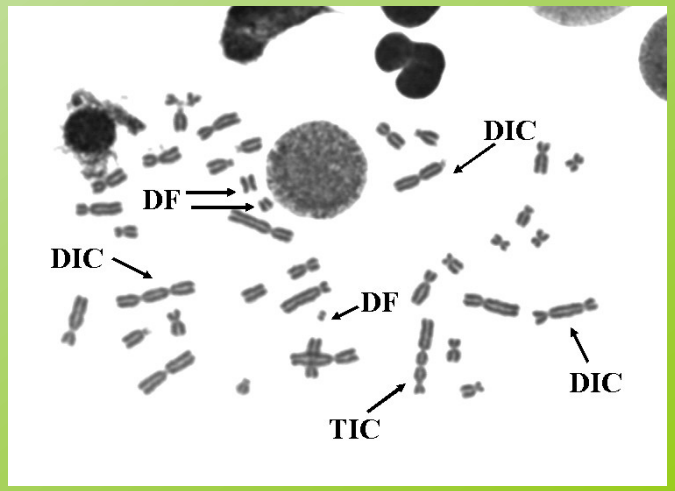
Vitamin prevention of neural tube defects, anterior abdominal wall defects, clefts

- Folic acid at a dose of 0.8 mg daily (twice the dose in non-pregnant) for 3-6 months prior to conception and till the end of 12. week of pregnancy

Examination of acquired chromosomal aberrations

- Preventive examinations of persons exposed to environmetal risks at work or persons with risk of long-term therapy (immunosuppressants, cytostatics, ...)
- The possibility of vitamin therapy to improve repair of DNA (3-6 months)





Contraception, sterilization

- Contraception - temporarily prevents conception in the limited impact of risk (treatment)

- Sterilization - the long-term inhibition of pregnancy in a high risk of disease in the offspring (Hereditary disease)

Adoption

- Alternative family care as an option at high genetic risk families

Donation

- of sperm, oocytes and embryos
- reduction in high genetic risk
- reproductive problems

Secondary genetic prevention

- Prenatal diagnosis
- Prenatal screening
- Prenatal tests
- Genetic counselling
- Termination of pregnancy (the law in Czech Republic- end of 24. week of gestation)
- Postnatal screening
- Newborn screening

Genetics diseases

- Chromosome abnormalities
- about 0,6 - 0,7%

- Monogen diseases
- about 0,36%

(study in 1 000 000 newborns)

- most then 90% of monogen diseases occur in childhood

- Multifactorial (polygenic or complex) disorders
- Occur in about 80% in the population

Patients on genetic departements

- Dead person
- Adults
- Pregnant women
- Fetuses
- Children

Patients on genetic departements

- Positive family history (chromosome abnormality, congenital malformations, mental retardation, diseases…)
- Pregnant women with encrease risk for the fetus
- Infertility – sterility, repeated fetal loss
- Donors (gamets)
- Patients with tumours

Children

- Congenital malformations

Children

- Suspition of mongenic hereditary diseases or inherited metabolic disorders and their families

Children

- Suspition on congenital chromosom aberations (children with congenital malformations, abnormal face, atipical visage, pre- or postnatal growth retardation, premature birth)

Children

- early or delayed puberty
- Malformations of the external or internal genitalia
- Low or high figure

Children

- Preventiv genetic examinatioun before adoption

Children or adults

- Mental retardation
- Psychomotor retardation
- Developmental delay

Children and adults

- Gender identity disorder

Children and adults

- people with long-term exposure to environmental pollutants
- (alcohol, cigarettes, drugs, radiation)

Children and adulds

- patients with suspected hereditary cancer
- patients with cancer (sporadic occurrence)

Adults

- Donors of gametes

(preventive tests)

Adults

- Related partners

(increased risk for hereditary disease with AR inheritance)

adults

- Infertility
- Repeated spontaneous abortions

Pregnant women

- With unfavorable family history

Pregnant women

- with adverse pregnancy history (chronic diseases with established therapies, acute disease in early pregnancy - temperature, drugs, X-rays, CT, vaccinations, toxoplasmosis, rubella, ...)

Pregnant women

- Prenatal biochemical screening

(Pathological results)

Pregnant women

- Ultrasound prenatal screening – pathological results
- Congenital malformations in the fetus
- Risk of chromosomal abnormality in the fetus

Genetic counselling

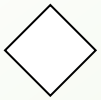
- Anamnesis
- Family history
- Pedigree analysis
- Examination of the patient
- Laboratory analysis
- Other examinations - neurology, psychology, hematology, CT, MRI …

Three-generation pedigree

- Patient
- Siblings
- Children siblings
- Parents
- Parents siblings
- Children of parents siblings
- Parents parents

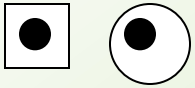
man

woman

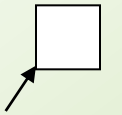


Unknown gender

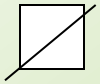
diseased



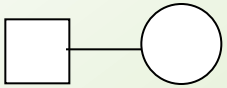
carrier



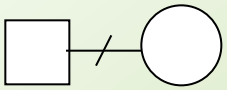
proband



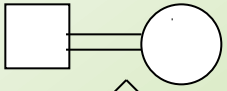
dead person



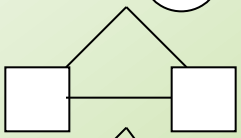
marriage



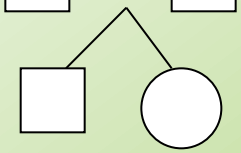
divorce



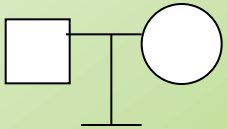
konsanguinity



monozyg. twins



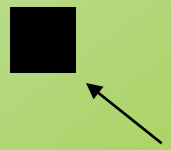
dizygot. twins



childless

miscarriage

Pedigree



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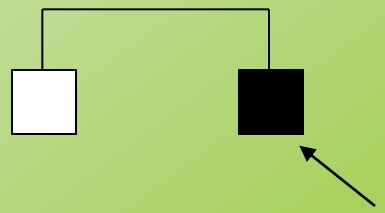

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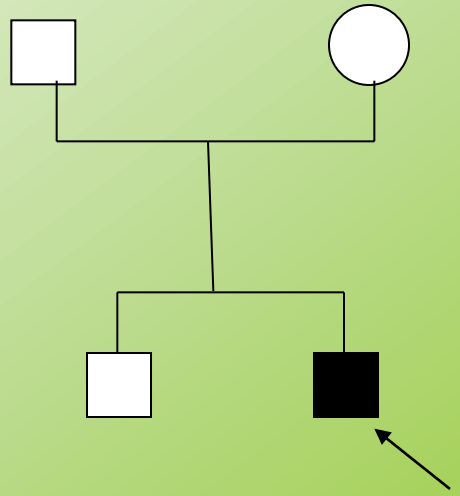

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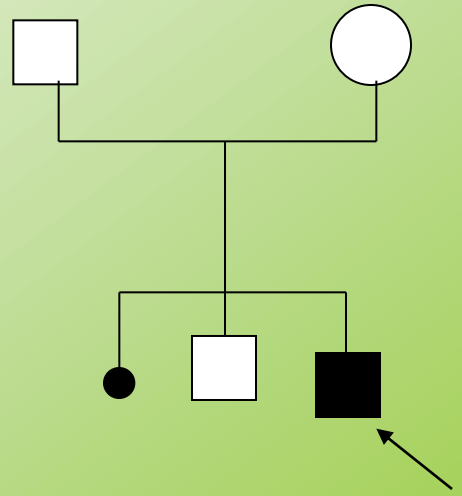

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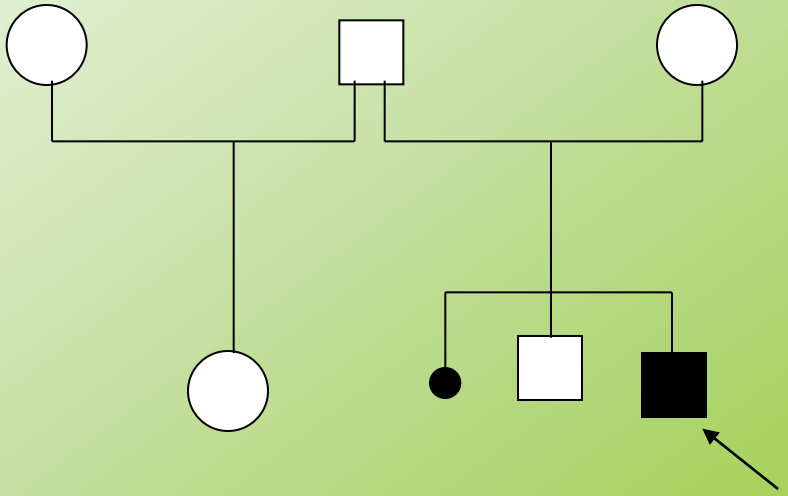

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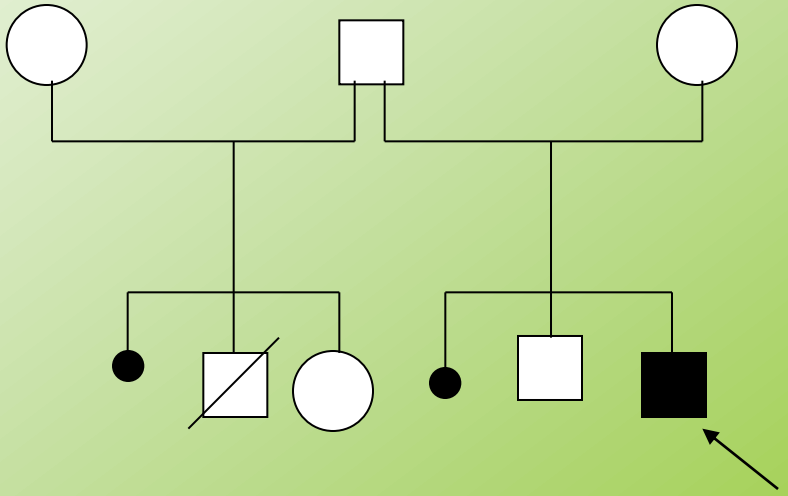

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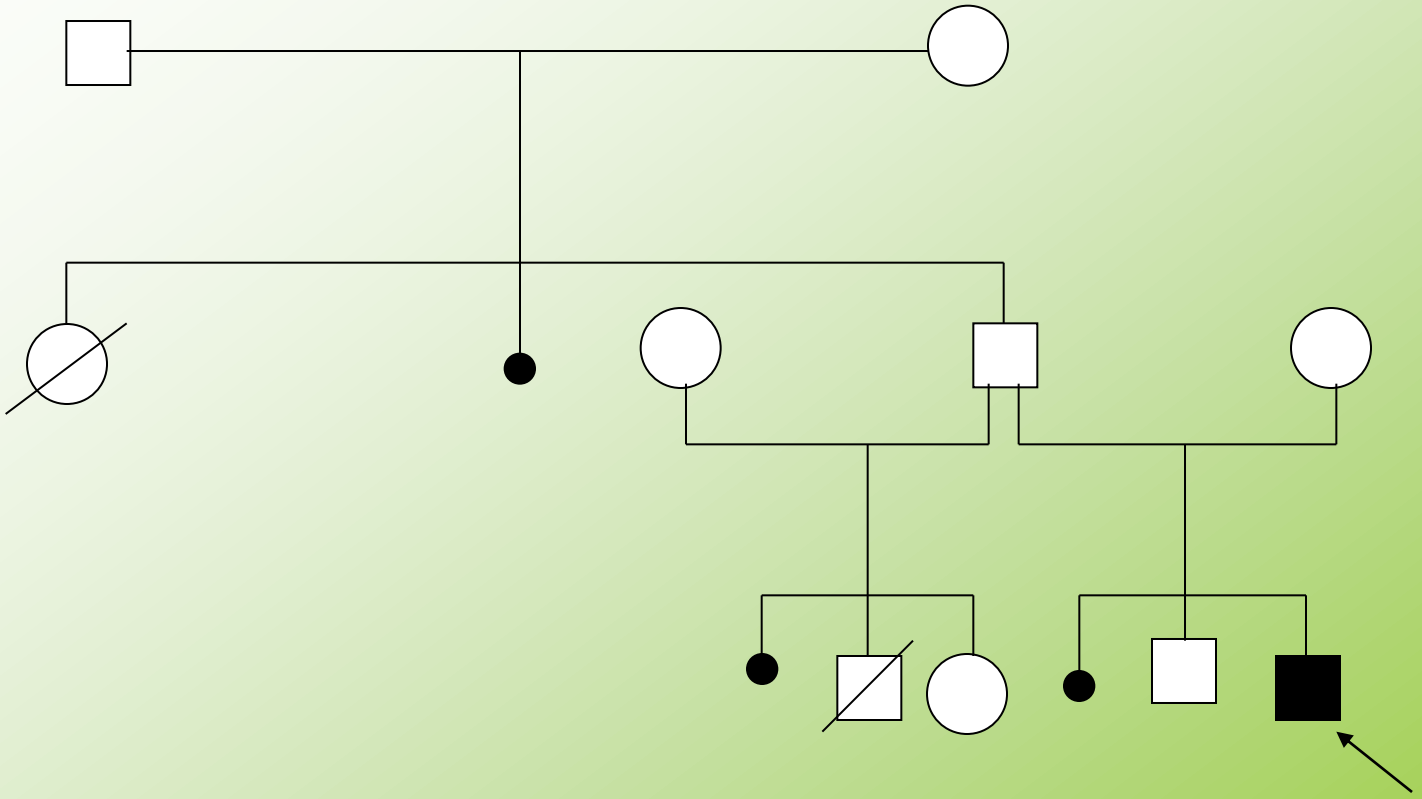

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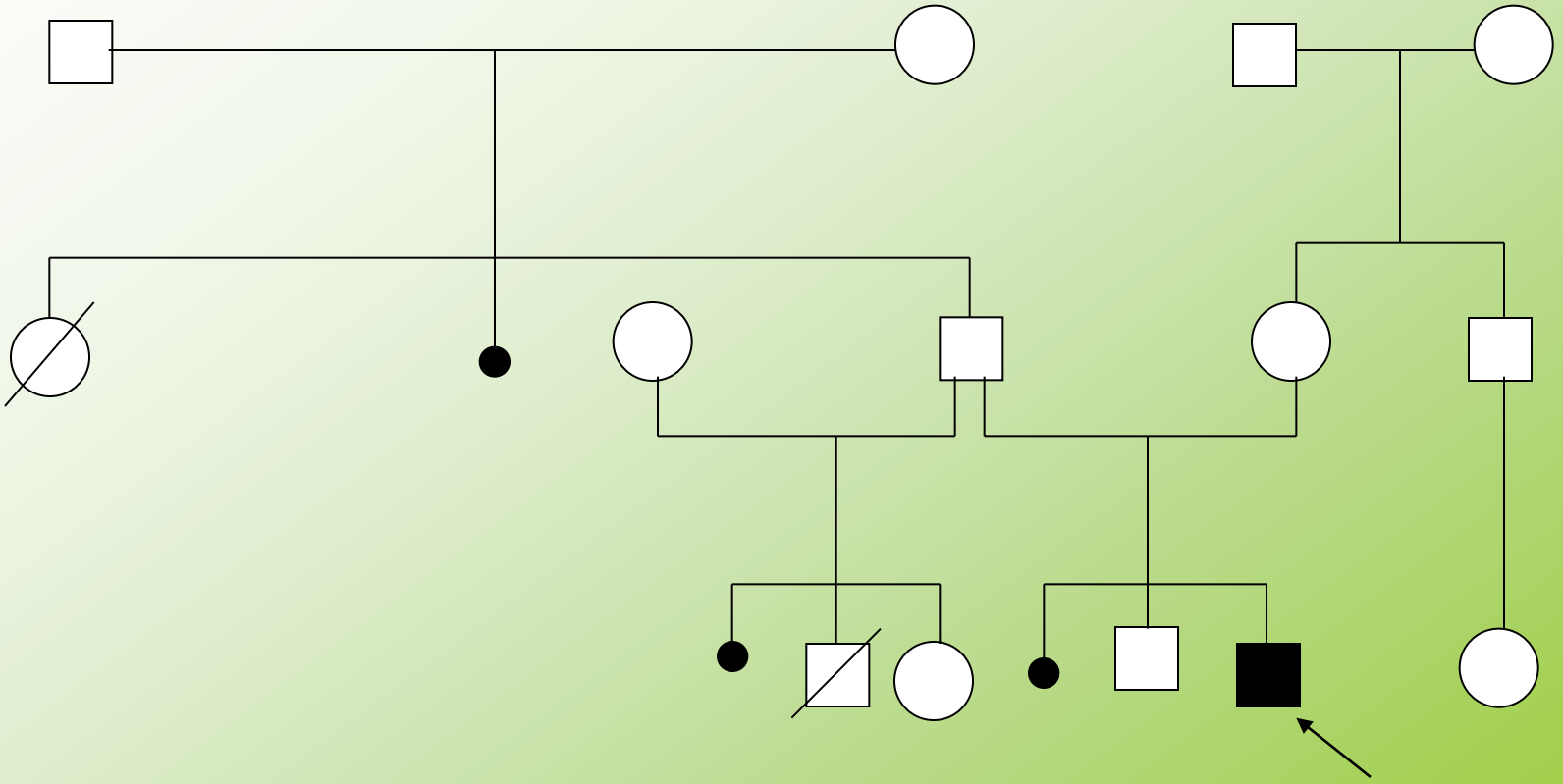


Clinical examination

Next steps

- Recommend the laboratory genetic testing
- Recommend other specialists if needed
- Require medical records
- Make photodocumentation

The result of genetic counselling

- **Specify exact diagnosis** (if possible)

- **Determine genetic prognosis**
- Is the disease hereditary?
- Type of inheritance
- Genetic risks for other family members
- Posibilities of treatment, prenatal analysis

Patient

Cell

Chromosome

DNA

Patient

Reproductive Genetics

Preconceptional testing
Genetic counselling and analysis
in couples with reproductive disorders
Prenatal diagnosis
Preimplantation genetic diagnosis
Examination of potential donor gametes

Secondary prevention of genetic

- The procedures in pregnancy - prenatal diagnosis and early postnatal diagnosis

Prenatal diagnosis

- Non invasive methods- screening
- Screening

- Invasive methods
- CVS – after the 10. week of gestation
- AMC – 15.-18. week of gestation
- Cordocentesis – after the 20. week of gestation

Prenatal diagnosis results

- CVS – karyotype – about 5 days
- AMC – karyotype – about 14-21 days

- DNA analysis (monogen diseases)
- About 5-15 days
- DNA from amniocytes after cultivation - exclusion contamination by maternal tissues

Prenatal analysis of most frewquent aneuploidias
QF PCR

- Examination of the most common numerical changes in chromosomes 13, 18, 21, X and Y
- The result for 24-48 hours

Prenatal screening (CR)

- Ultrasound (12. - 2 0. - 33. week)
- Ultrasound 20.week – cong. defect
- Ultrasound 20-22. week – cong. heart defect
- 10-14. week of gestation
- Free beta hCG, PAPP-A, US-NT,NB..
- 16.-18.week of gestation
- AFP, hCG, uE3

NIPT - non-invazive prenatal testing

examination of fetal DNA in maternal plasma

- aneuploidy (21, 13, 18, X/Y and others – microdetetions…)
- Rh in the fetus
- SRY in the fetus – in X linked diseases in the family
- Some mongenic diseases in the fetus (achondroplasie)

Indications for prenatal examination / genetic counselling

- US screening – congenital defects
- Family history of known conditions for which diagnosis is possible (DNA analysis)
- Known chromosomal abnormality (de novo finding in previous child, structural change in parents)
- Positive prenatal screening for chromosomal abnormalities
- Advanced maternal, paternal age

Preimplatation Genetic Diagnostics

Preimplatation Genetic Diagnostics

- IVF – assisted reproduction

- Preimplantation genetic screening
- aneuploidy - array- CGH, chip technology
- (FISH -13,18,21,X,Y, 15,16,22)

- Preimplantation Genetic Diagnostics
- Structural chromososmal aberations
- (parents are carries of balanced rearangement)
- Monogenic diseases (known in family history)

PG Diagnostic
X
PG Screening

- PGD high genetic risk

- PGS (most common) aneuploidies

Genetic counselling in infertility

Infertility

- Is the infertility one aspect of a genetic disorder that might be transmitted?
- Will correction if infertility give an increased risk of malformations in the offspring?

- Genetic testing before use of metods of asisted reproduction.

Infertility

- Patological examination of the abortus where possible, this may identify major structural malformations.
- Cytogenetic study of parents, this is especialy important where a structural abnormality is present.
- In general the finding of a chromosome abnormality in the abortus but not in parent is not likely to be relevant or affect the genetic risks.

Infertility

- A search for possible lethal mendelian causes (consanguinity- risk for AR diseases, X-linked dominant disorders lethal in male, myotonic dystrophy which gives heavy fetal loss in the offspring of mildly affected women)
- Inherited trombophilias in women with recurrent abortions (factor V Leiden, factor II - G20210A, hyperhomocystinaemia ? (MTHFR - C677T)

Factor V - Leiden

- frequency in the white European population of about 5 - 9%
- AD inheritance
- increased risk of thromboembolism in homozygots for FVL 50-100x, in heterozygots 5-10x

- increased risk of fetal loss after the 10. week of gestation

Sterility in male

- Klinefelter syndrome and other chromosomal aberations

- AZF (azoospermia factor) deletions of the DAZ gene Yq (deleted in azoospermia)
- Infertile man – 4-5%
- Men with azoospermia – about 15%

- CFTR mutations and polymorphisms

Postnatal care and neonatal screening

- Early diagnosis

  Dispensary

  Specialized Care

Prenatal and perinatal managment of prenagncies with malformation or genetic disease in the fetus

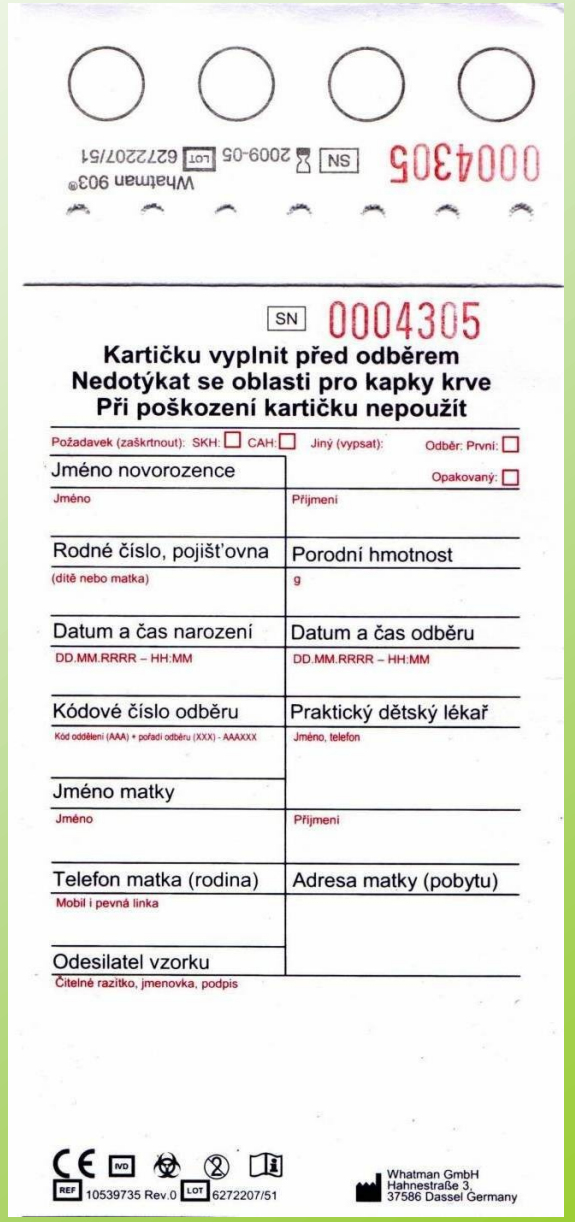
- Consultation with experts, who will continue to take care of the pregnant woman - ultrasound specialist, gynecologist, obstetrician, psychological support ..

  Consultions with specialists, who will care after the birth of newborns with disabilities

  The planned delivery of specialized care workplace - kardiocentrum, pediatric surgery, cardiology…

Newborn screening

Sampler card



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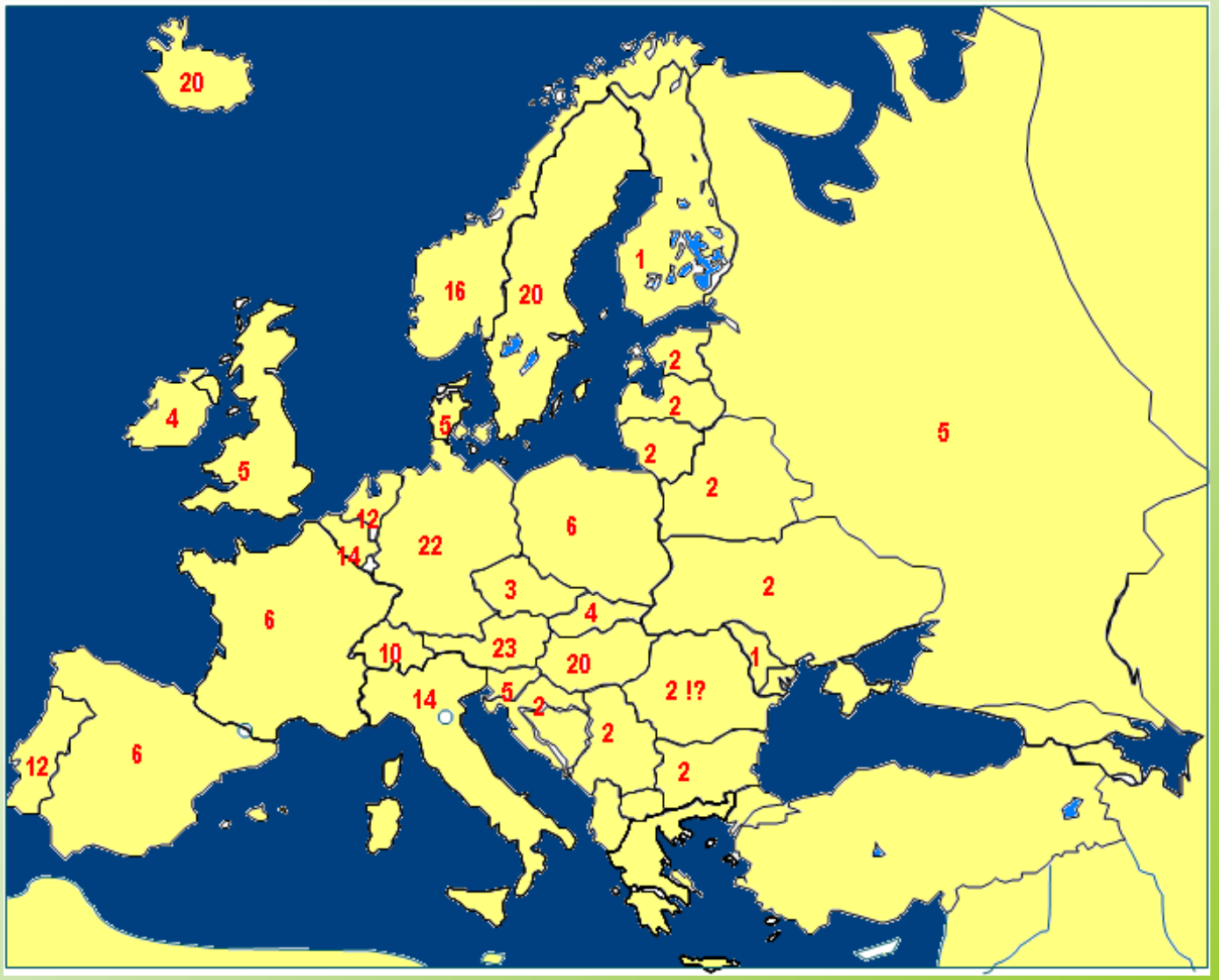
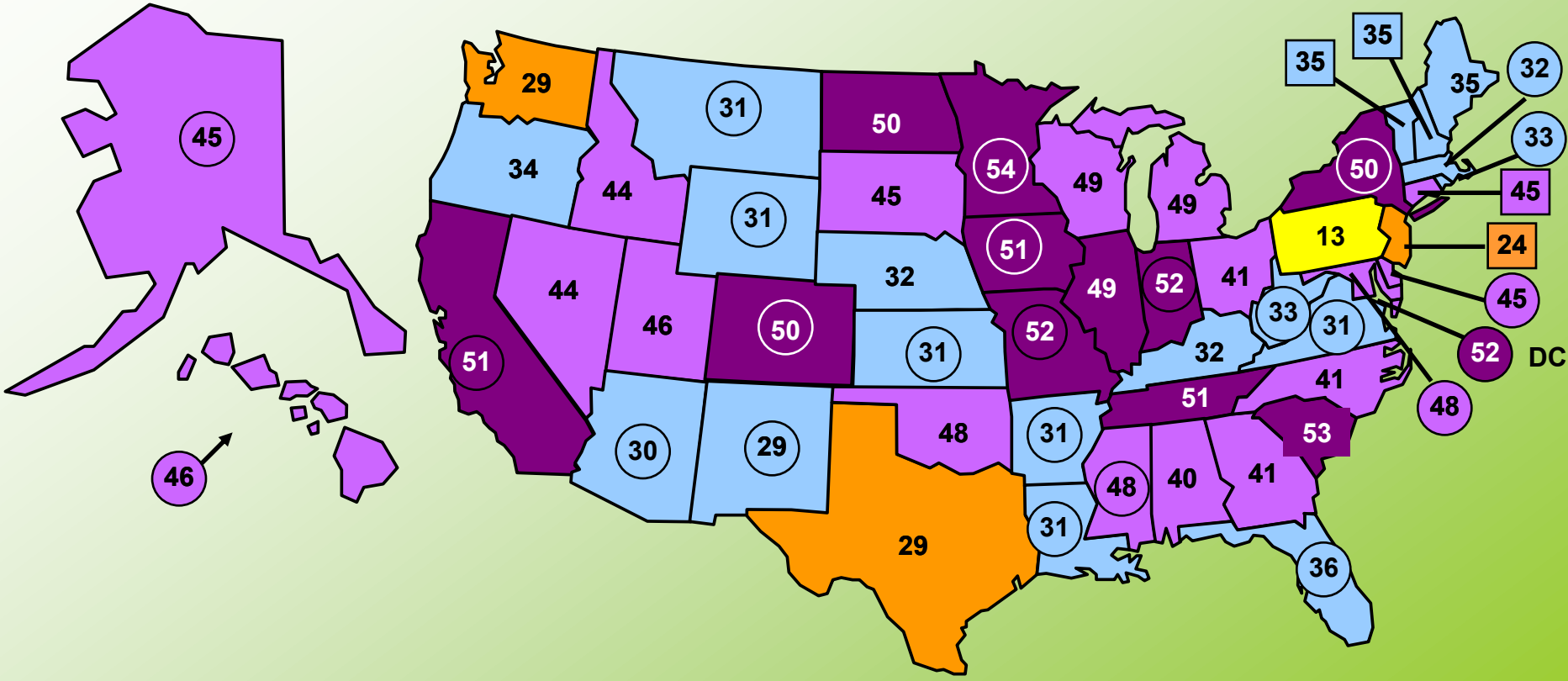


NS USA-2009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Screened diseases in CR from 10/2009

- Kongenital hypothyreosis
- Kongenital adrenal hyperplasia – CAH

(cumulative risk 1/2900)

Screened diseases in CR from 10/2009

- **Inborn errors of metabolism**
- Fenylketonuria (PKU, HPA)
- Leucinosis
- MCAD
- LCHAD
- VLCAD
- Def.karnitinpalmitoyltransferasis I a II
- Def.karnitinacylkarnitintranslocasis
- Glutaric aciduria
- Izovaleric acidurie

(cumulative risk 1/4000)

Screened diseases

- Cystic fibrosis

(1/4000)

- cumulative risk of all 13 screened diseases in CR - 1/1200