Introduction & haematological malignancies

Coding issues

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European Commission

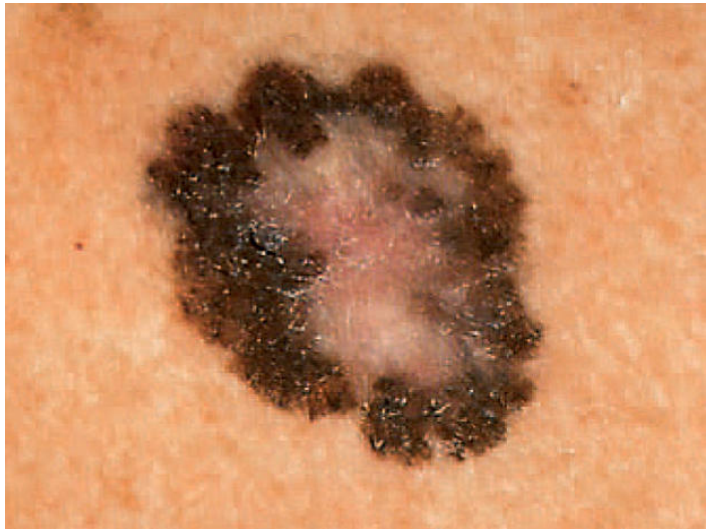
Introduction

- For most (solid) cancers, the primary site of the most important factor for the prognosis and the choice of treatment
- For other cancers, especially haematological malignancies, but also for an increasing number of solid cancers, the morphological classification is the most important factor

How is a cancer diagnosis made?

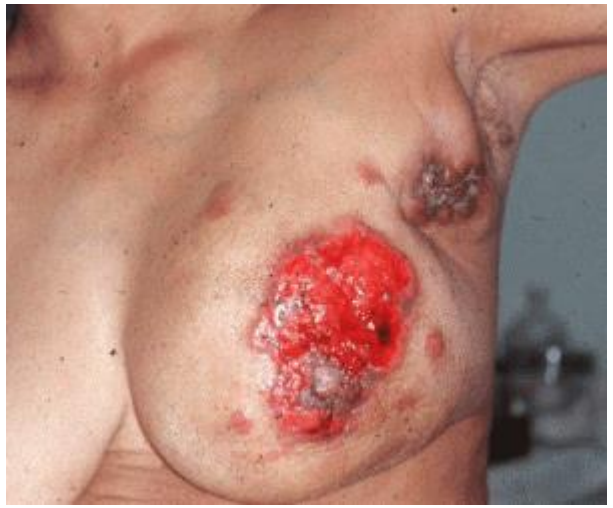
1. Clinical features
2. Microscopy
   - Large cells / small cells
   - Specific characteristics (colour, amount of cytoplasm, type of cell nucleus, etc)
3. Specific tests for proteins in the cytoplasm/cell nucleus/on the surface (immunohistochemistry)
4. Immunophenotyping
5. Cytogenetics

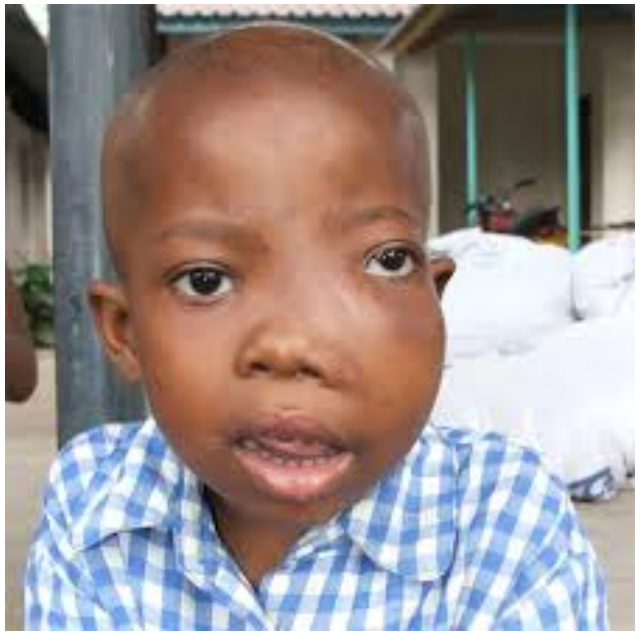
1. Clinical diagnosis



melanoma

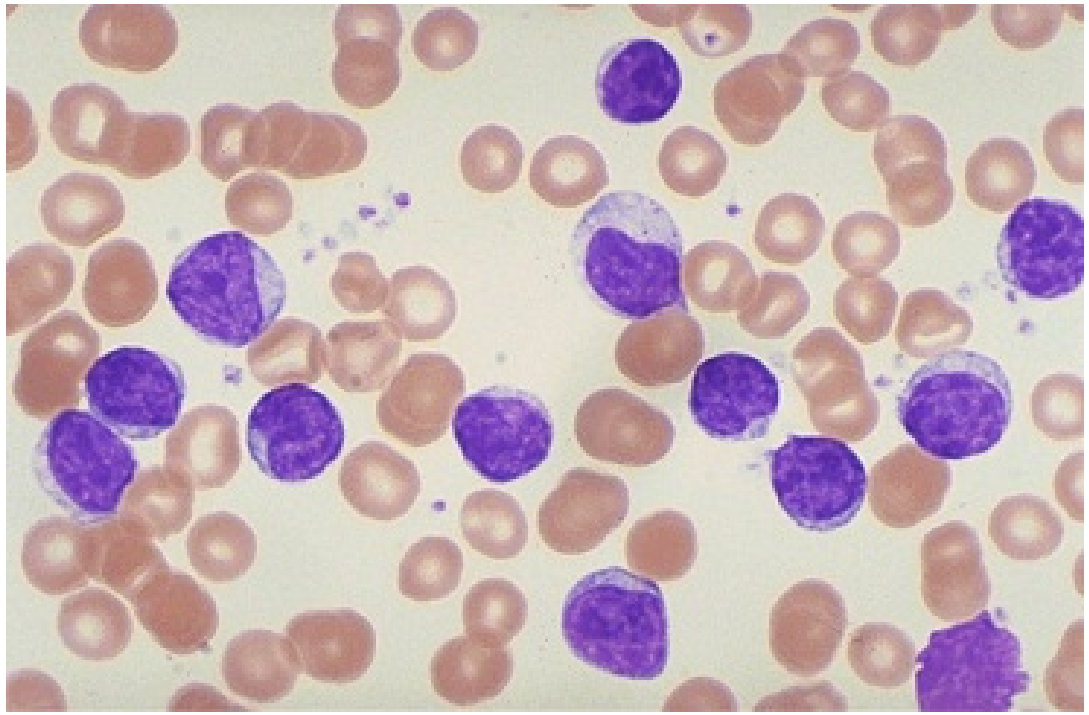
breast cancer



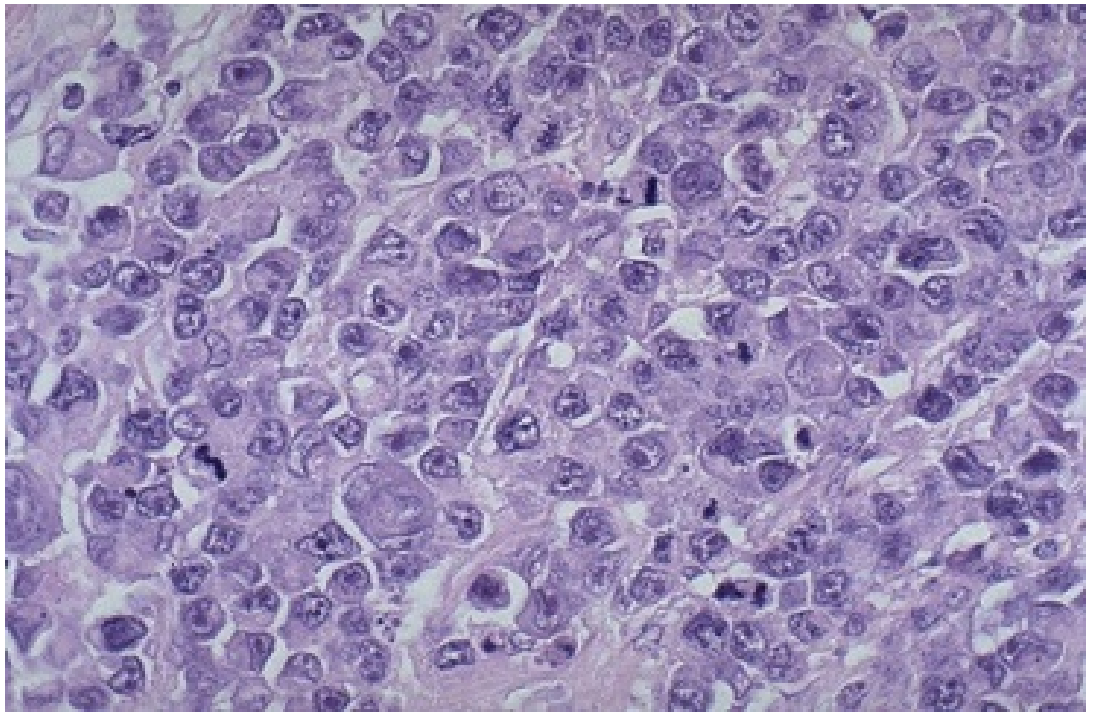


Burkitt lymphoma

2. Microscopy

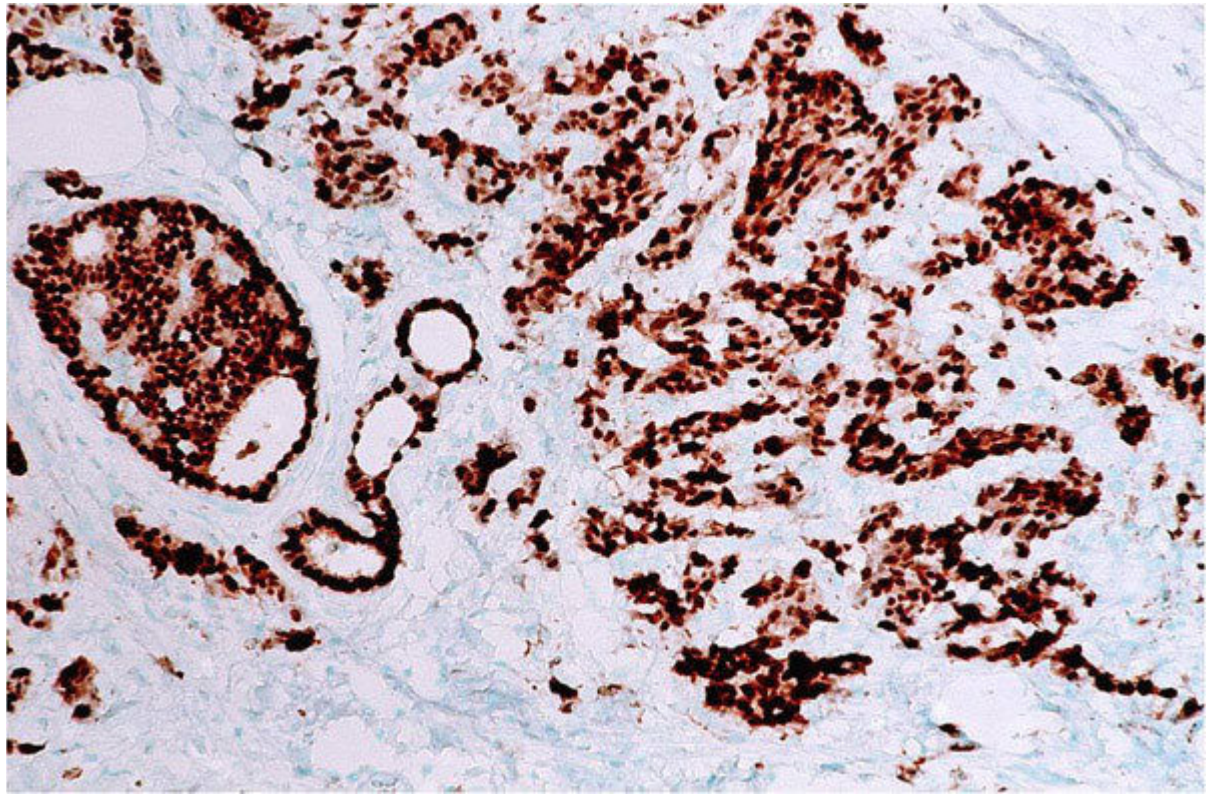


Small, mature cells with little cytoplasm, no mitoses (CLL)



Large cells (cytoplasm ++), prominent nucleoli, mitoses (DLBCL)

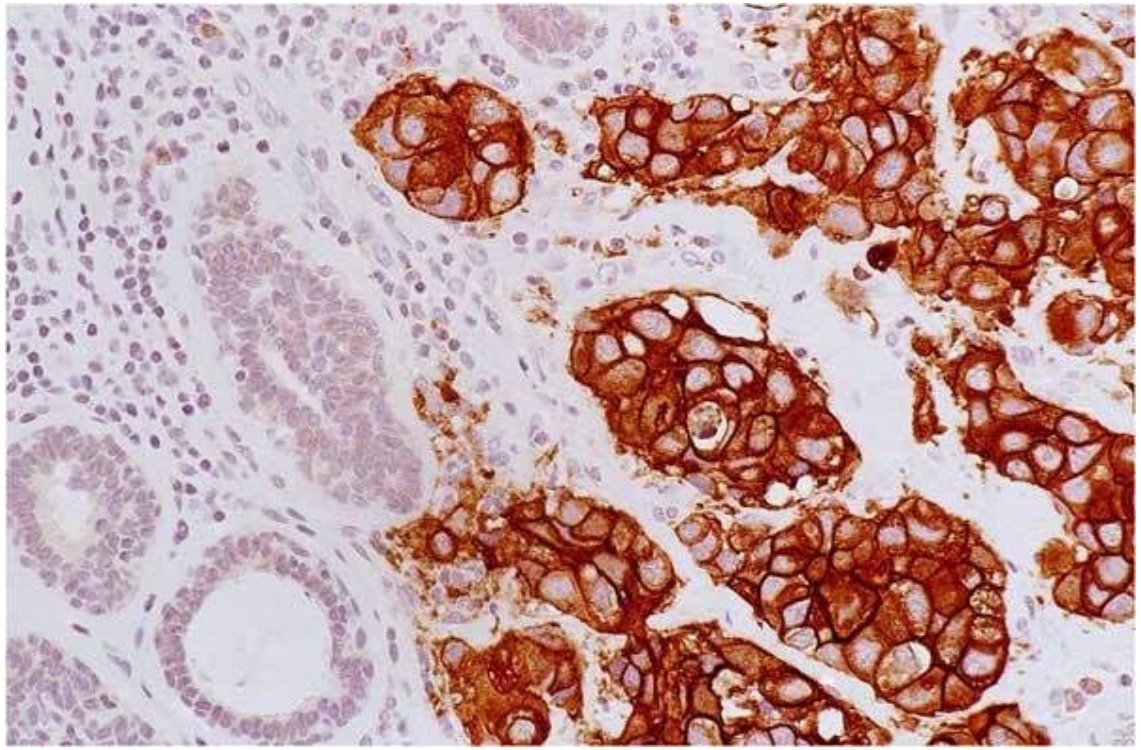
3. Immunohistochemistry



Expression of the estrogen receptor (ER) by using an immunostain for ER.

The immunostain binds to the ER protein in the nucleus of the cancer cells and is detected by a positive brown colour

3. Immunohistochemistry



Expression of HER2 by using an immunostain for HER2.

The immunostain binds to the HER2 protein on the surface of the cancer cells and is detected by a positive brown colour

4. Immunophenotyping

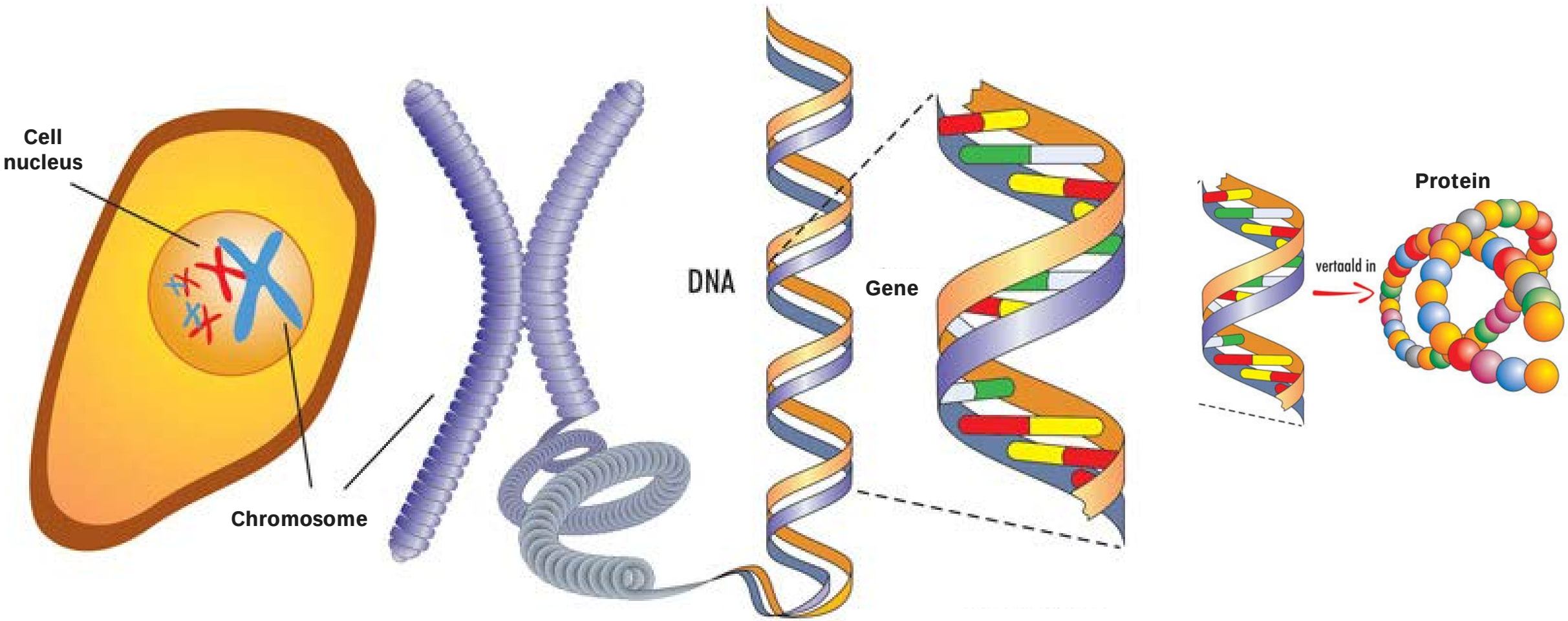
- Technique for the detection of proteins in the cell membrane of cancer cells
  - Tissue
  - Blood
  - Bone marrow
- If a certain protein is absent of present this gives an indication for the type of cell

4. Immunophenotyping

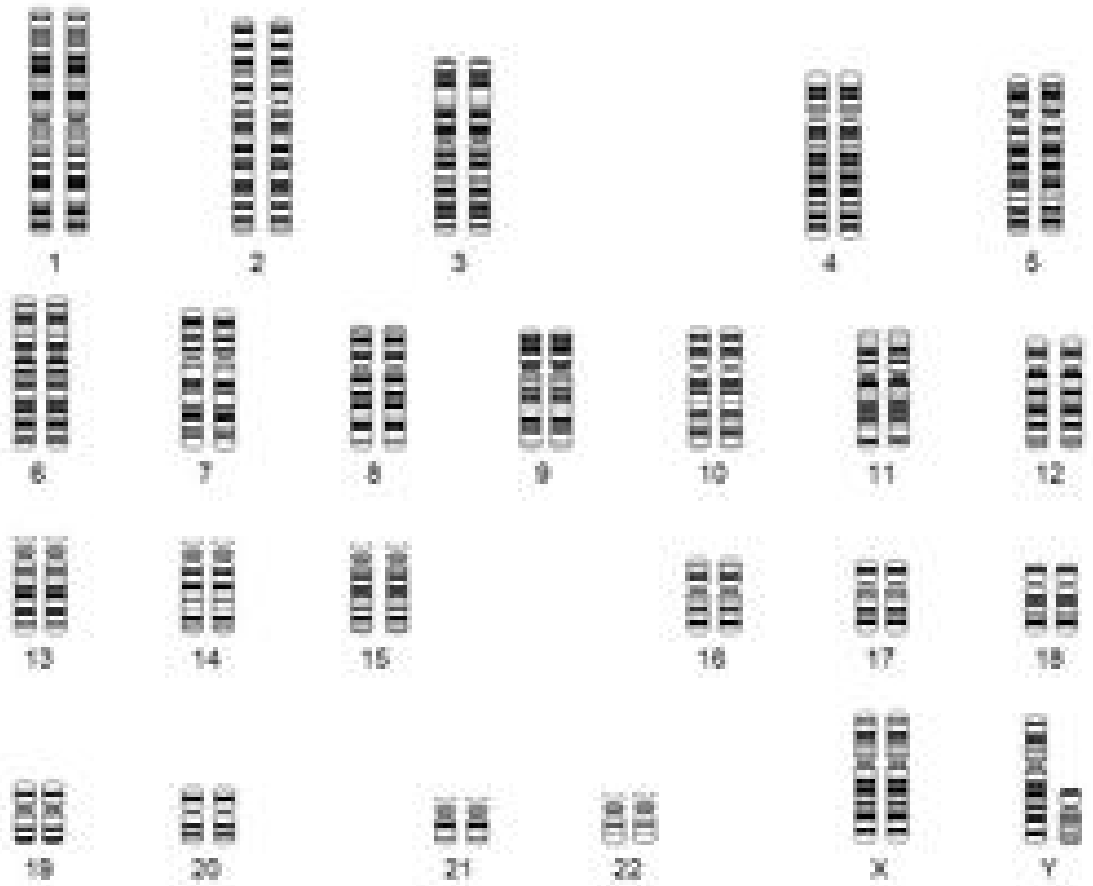
5. Cytogenetics & molecular diagnostics

- Most cancer cells have ‘errors’ in the DNA (cytogenetic aberrations)
- With cytogenetics & molecular diagnostics these aberrations can be detected
- Many aberrations are not clinically relevant, but others are, because specific drugs can target specific cytogenetic aberrations, e.g. imatinib for BCR-ABL+ chronic myeloid leukaemia (‘targeted therapy’)
- Often, aberrations can be detected with different techniques

5. Cytogenetics & molecular diagnostics



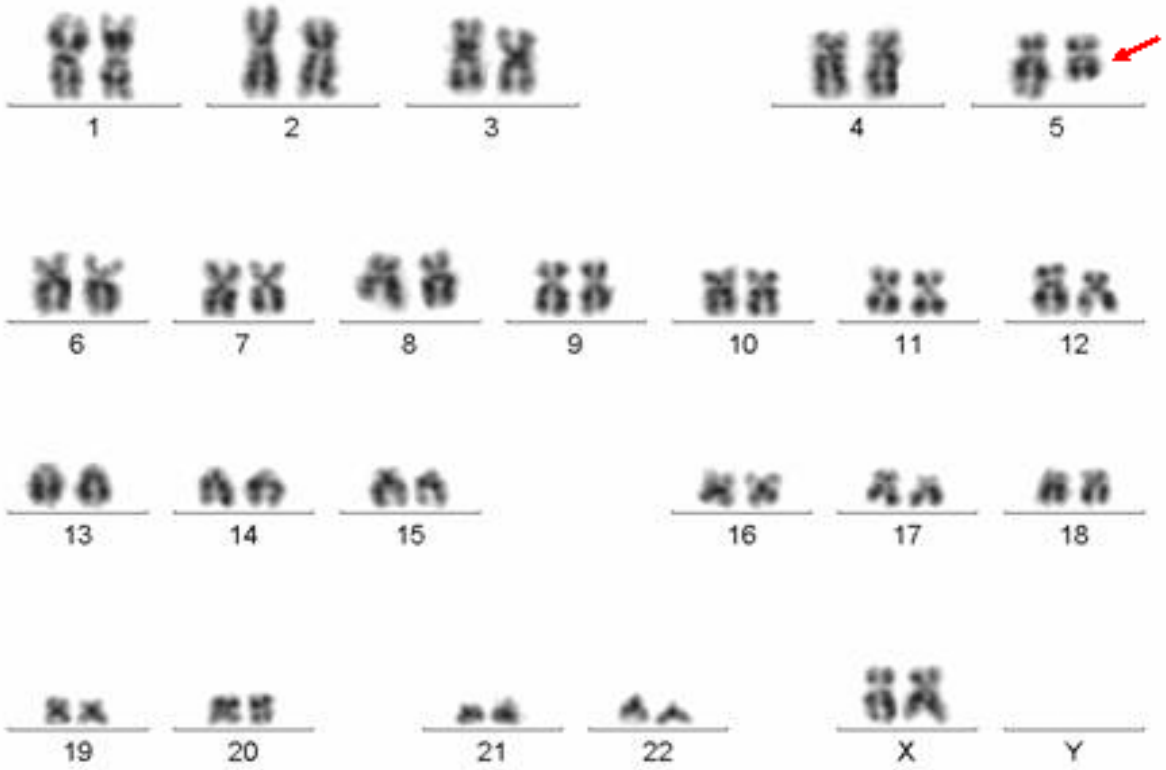
5. Cytogenetics: karyotyping



- Photo of the chromosomes
- Each (normal) cell has 46 chromosomes
- In cancer cells a (part of a) chromosome can be missing, duplicated or displaced

5. Karyotyping: example

- Patient with MDS
- A part the long arm (q) of chromosome 5 is missing (=deletion)
- Diagnosis: MDS with 5q-
- Morphology code: 9986

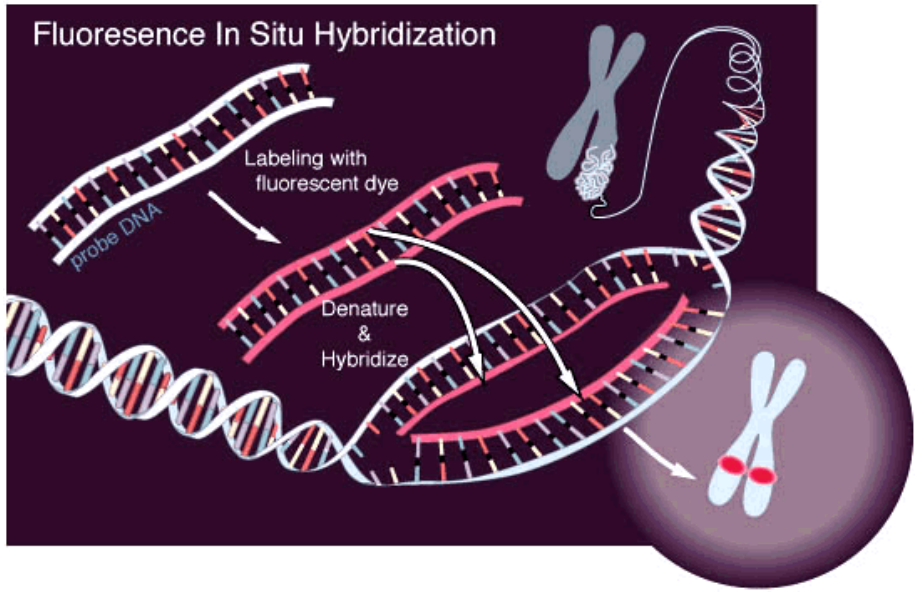


5. Aberrations visible with karyotyping

- Deletion→ MDS with 5q- = M9986
- Translocation → t(9;22) in CML =M9875
- Inversion → AML with inv(3) = M9869
- Trisomy (3 chromosomes in stead of 2) → Down syndrome (trisomy 21)
- Monosomy (1 chromosome in stead of 2)
- Hypodiploidy (<46 chromosomes) → hypodiploid ALL = M9816
- Hyperdiploidy (>46 chromosomes) → hyperdiploid ALL = M9815

5. Cytogenetics: Fluorescence *in situ* hybridisation (FISH)

- A fragment of RNA ('probe') is labelled with a fluorescent dye
- The probe binds to specific parts of the DNA (a gene or a larger part of the DNA)
- If the probe binds to a gene or part of DNA you see a fluorescent dot



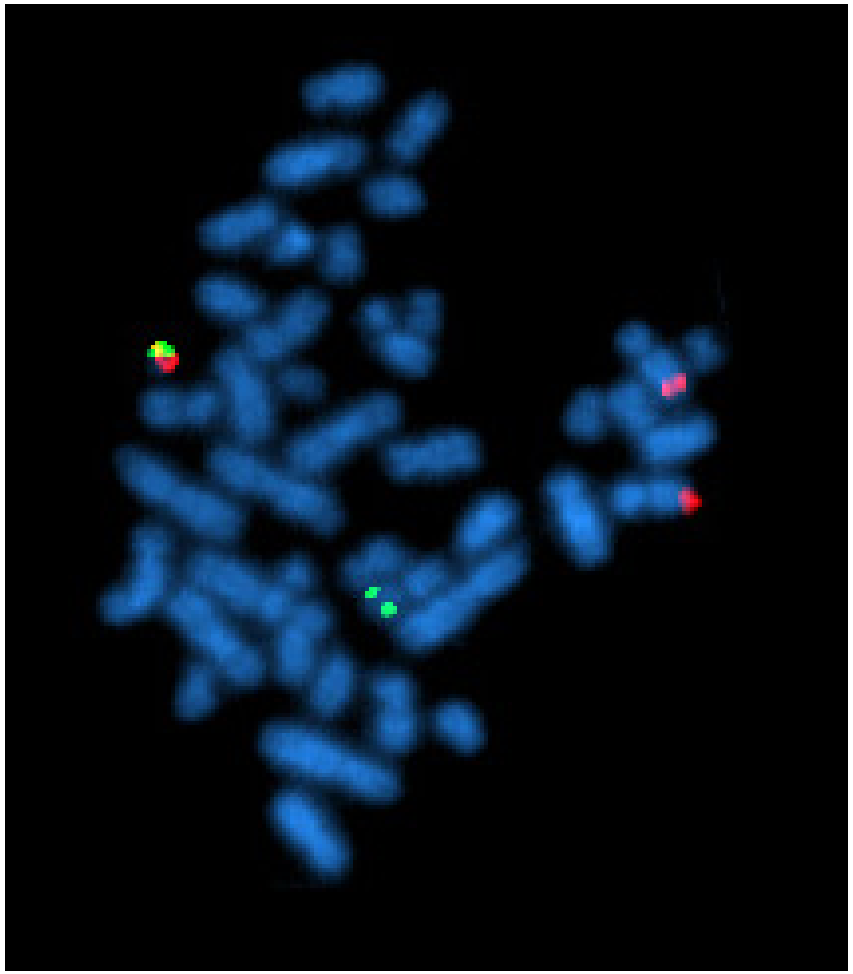
5. FISH: example

In CML there is a translocation of chromosomes 9 and 22 = t(9;22)

Chromosome 9 is labelled red and chromosome 22 green.

The normal situation is that you see 2 pairs of dots of the same colour (4 dots in total of each colour).

If there is a combination red/green, the translocation is present.



5. Molecular diagnostics

If a gene (or combination of genes = ‘fusion genes’) codes for a specific protein.

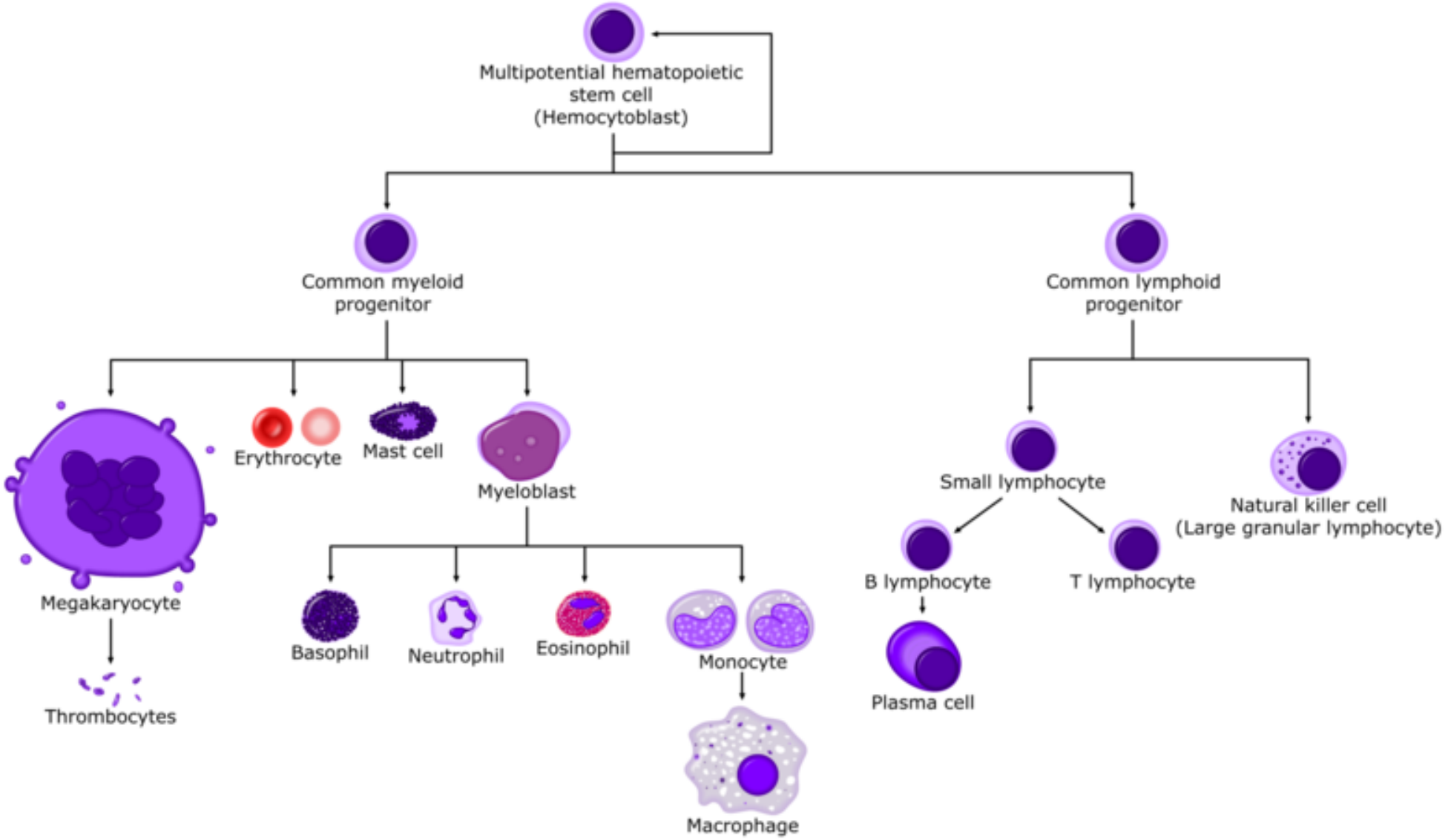
The fusion gene in CML produces the protein BCR-ABL.

The presence of the fusion gene BCR-ABL can be measured by detecting BCR-ABL RNA in the blood.

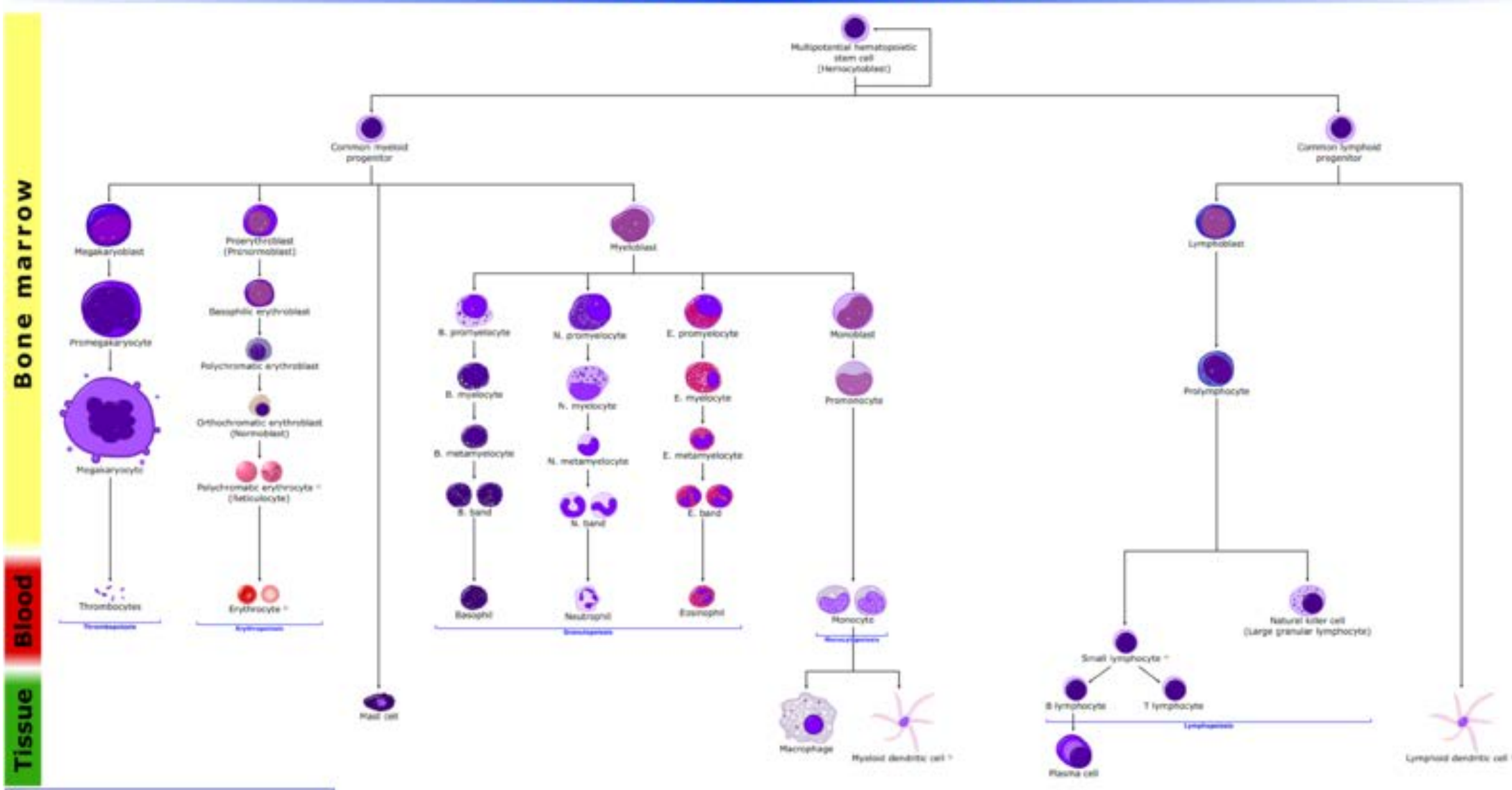
Haematological malignancies

European Commission

Haematopoiesis (overview)



Hematopoiesis in humans



Classification of haematological malignancies

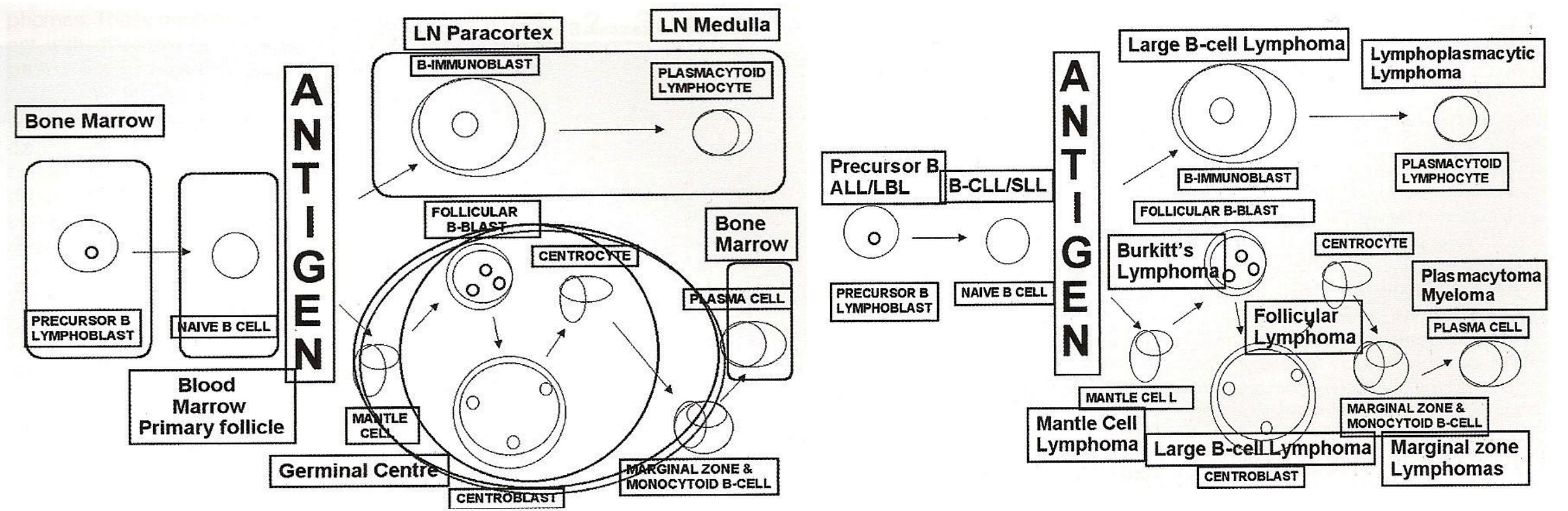
Aim:

- To determine the cell type and ‘the normal counterpart’
- To determine subtypes which are relevant for the prognosis and/or the treatment

Examples

Haematological malignancy	Normal counterpart
Multiple myeloma	plasma cell
Follicular lymphoma	germinal centre B-cell
B-ALL	haematopoietic stem cell or a B-cell progenitor cell
Mantle cell lymphoma	peripheral B-cell of the inner mantle zone (of a lymph node)

B-lymphocyte development with the malignant counterpart



Rules for classification

- Classify to the most specific (WHO) diagnosis
- Use all information from the different diagnostics
- Take into account that indolent haematological malignancies can transform to aggressive haematological malignancies
- For lymphoid malignancies the site of the tumour (lymph node, bone marrow) can also give an indication for the tumour type

Site of lymphoma

- Hodgkin lymphoma → lymph nodes
- Follicular lymphoma → mostly lymph nodes
- Lymphoplasmocytic lymphoma → bone marrow
- DLBCL → any site (including extranodal sites)
- T-ALL/LBL → bone marrow, thymus/mediastinal nodes

New morphology codes in 2nd revision of ICD-O-3

Code	Term
9715/3	Anaplastic large cell lymphoma, ALK negative Breast implant-associated anaplastic large cell lymphoma
9819/3	B lymphoblastic leukemia/lymphoma, BCR-ABL1–like
9877/3	Acute myeloid leukemia with mutated NPM1
9878/3	Acute myeloid leukemia with biallelic mutation of CEBPA
9879/3	Acute myeloid leukemia with mutated RUNX1
9912/3	Acute myleoid leukemia with BCR-ABL1
9968/3	Myeloid and lymphoid neoplasms with PCM1-JAK2
9993/3	Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia

Changes in behaviour code in 2nd rev. of ICD-O-3

A non-malignant variant of the disease was recognized

Code	Term
9673/1	In situ mantle cell lymphoma/neoplasia
9695/1	In situ follicular lymphoma/neoplasia
9702/1	Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
9709/1	Primary cutaneous CD4-positive small/medium T-cell lymphoma/lymphoproliferative disorder

A malignant variant of the disease was recognized

Term	Old code	New code
Lymphomatoid granulomatosis, grade 3	9766/1	9766/3

The disease was reclassified

Term	Old code	New code
Hydroa vacciniforme-like lymphoma	9725/3	9725/1

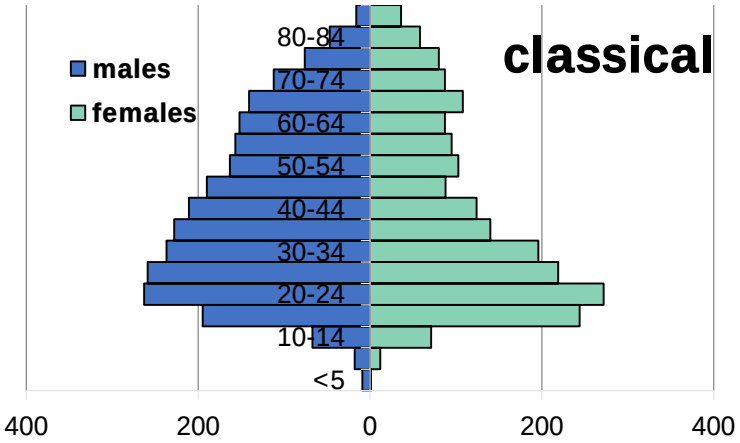
Langerhans histiocytosis: changes over time

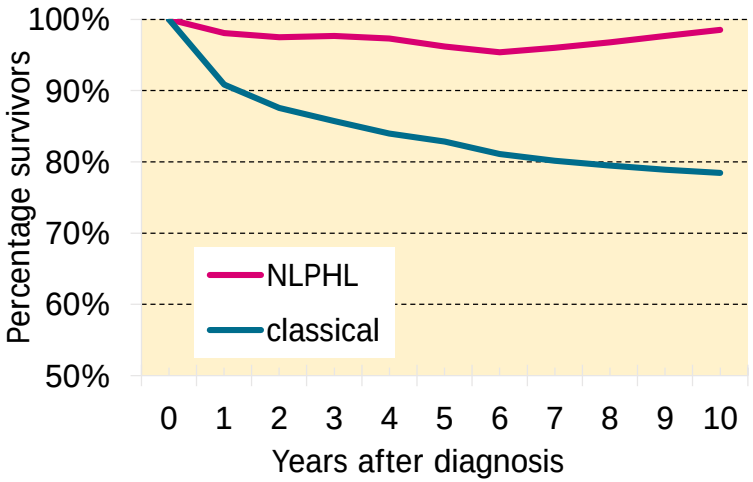
Term	ICD-O-2	ICD-O-3	ICD-O-3 1st revision	ICD-O-3 2nd revision
Langerhans cell histocytosis, NOS	-	9751/1	9751/3	9751/1
Langerhans cell histocytosis, mono-ostotic/unifocal	-	9752/1	9751/3	9751/1
Langerhans cell histocytosis, poly-ostotic/multifocal	-	9753/1	9751/3	9751/1
Langerhans cell histocytosis, disseminated/generalized	9722/3	9754/3	9751/3	9751/3

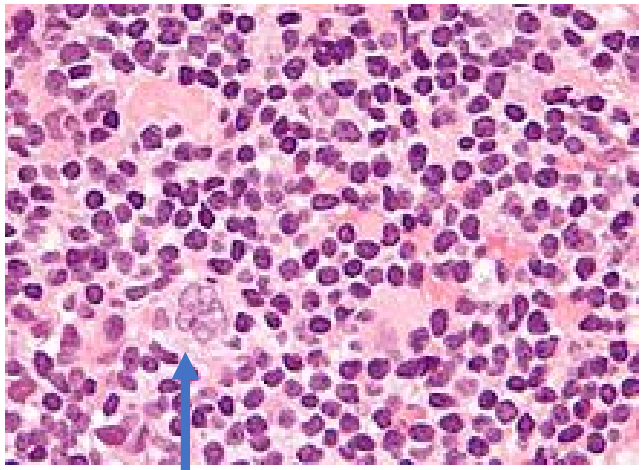
Hodgkin lymphoma: NLPHL versus classical HL

NLPHL (~8% of all cases)

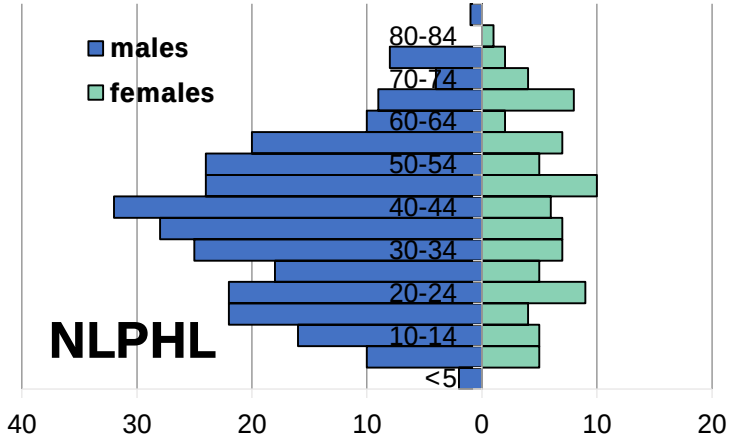
- higher survival, less aggressive treatment
- In the long run: risk of transformation to DLBCL







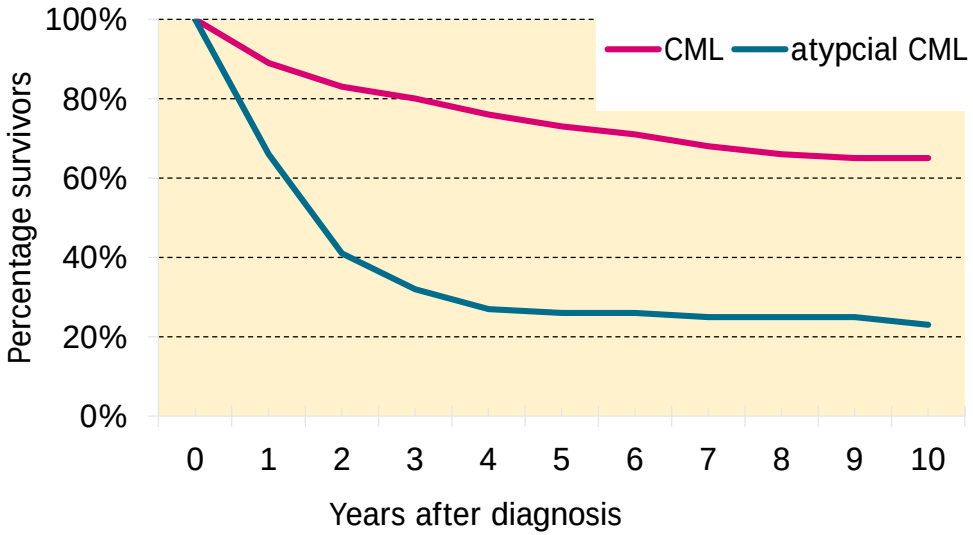
Reed-Sternberg cell (1900)

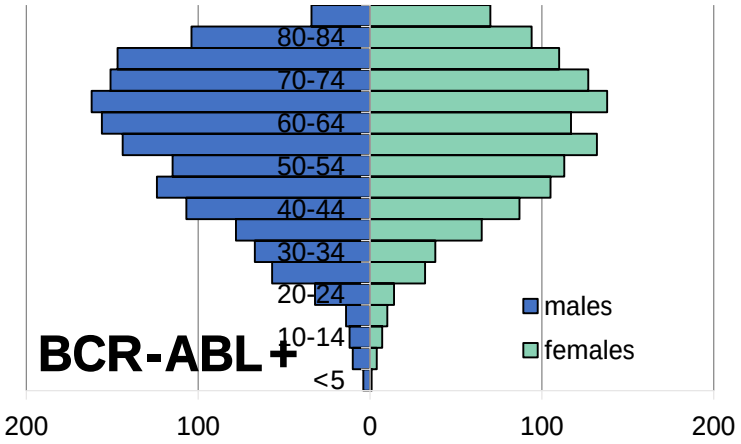


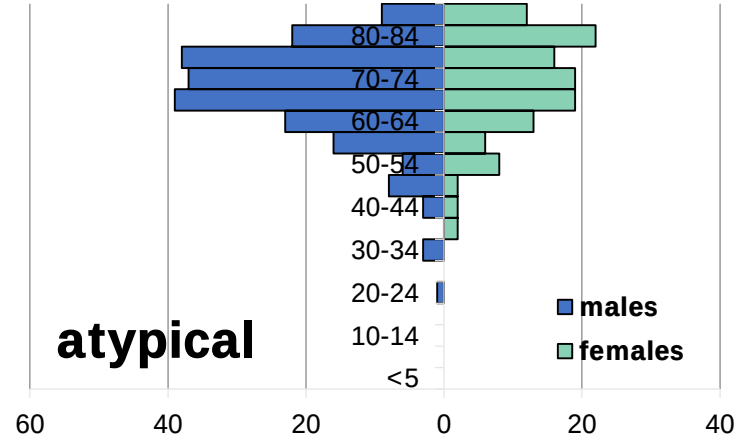
CML: BCR-ABL+ versus atypical

Atypical CML (~10% of all 'CML')

- Absence of t(9;22)
- No treatment with TKI (imatinib) → poor survival







Acute myeloid leukaemia

- *De novo* or as transformation of MDS or MPN
- In case of multiple diagnoses, code to the most specific category (1 > 2 > 3 > 4)
  1. With cytogenetic aberrations (9865, 9866, 9869, 9871, 9896, 9897, 9912)
  2. Myelodysplasia related (9895)
  3. Therapy related (9920)
  4. Other, not specified

Acute myeloid leukaemia

Examples

- Acute megakaryoblastic leukaemia (9910), therapy related (9920) → 9920
- Acute myeloid leukaemia, t(8;21) (9896), therapy related (9920) → 9896
- Acute myelomonocytic leukaemia (9867), t(8;21) (9896) → 9896

EXERCISES

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