The invisible and unknown pathologist!

Prof. dr. Jo Van Dorpe, dienst Pathologische Anatomie

UZ GENT

UNIVERSITEIT GENT

Inhoud

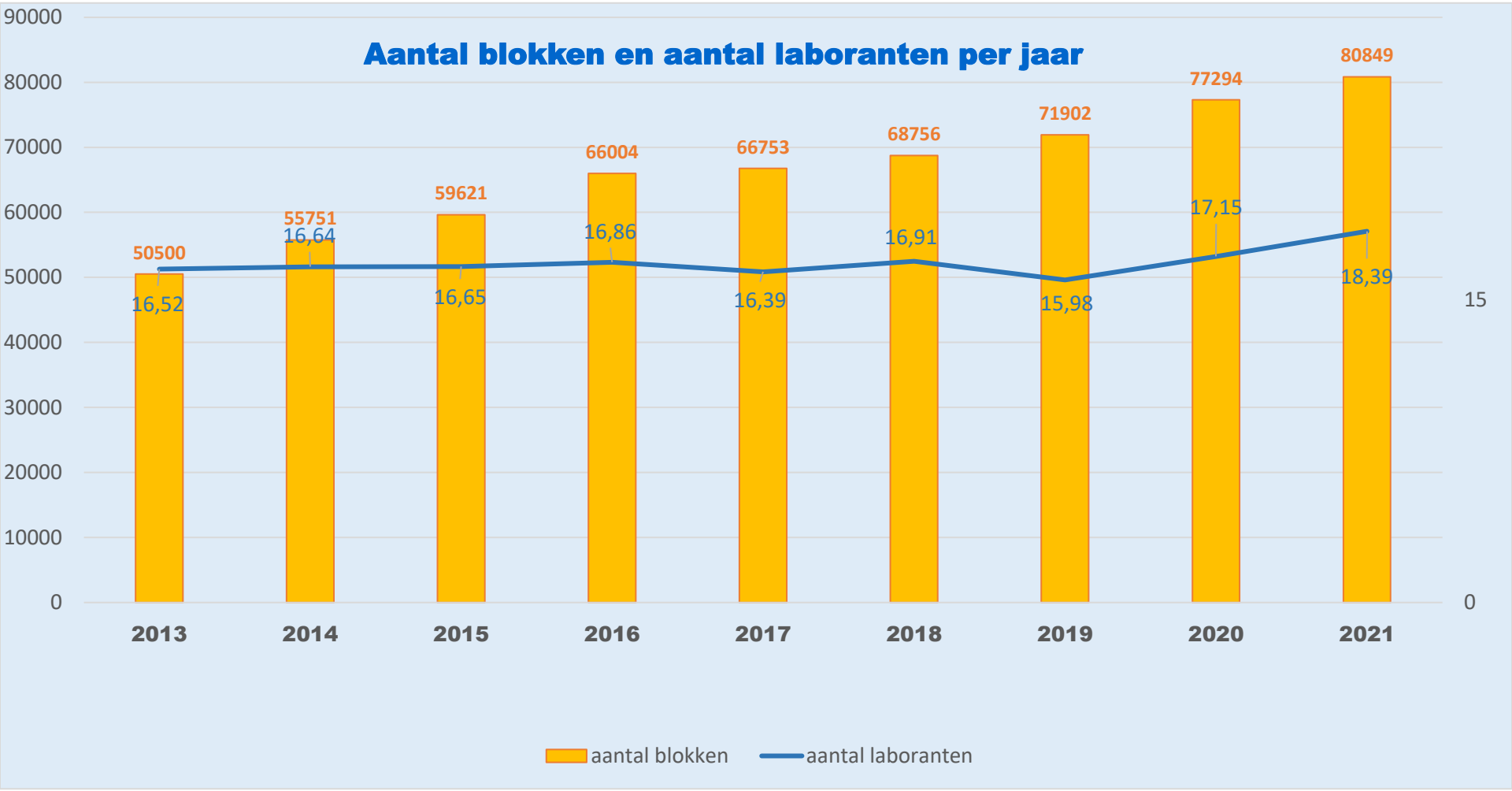
- Misverstanden over pathologie
- Beweringen over pathologie die waar zijn
- ‘Moderne’ pathologie
- De toekomst
- Conclusie

Misverstanden over pathologie (1)

- ‘Voor pathologie heb je geen *social skills* nodig’
- ‘Iets voor *nerds*’
- ‘Iets voor autisten’
- ‘De patholoog zit in een kelder’

Misverstanden over pathologie (2)

- ‘Weinig werken en veel koffie drinken’


Aantal blokken en aantal laboranten per jaar
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
15
0
50500
55751
59621
66004
66753
68756
71902
77294
80849
16,52
16,64
16,65
16,86
16,39
16,91
15,98
17,15
18,39
2013
2014
2015
2016
2017
2018
2019
2020
2021
aantal blokken
aantal laboranten

Misverstanden over pathologie (3)

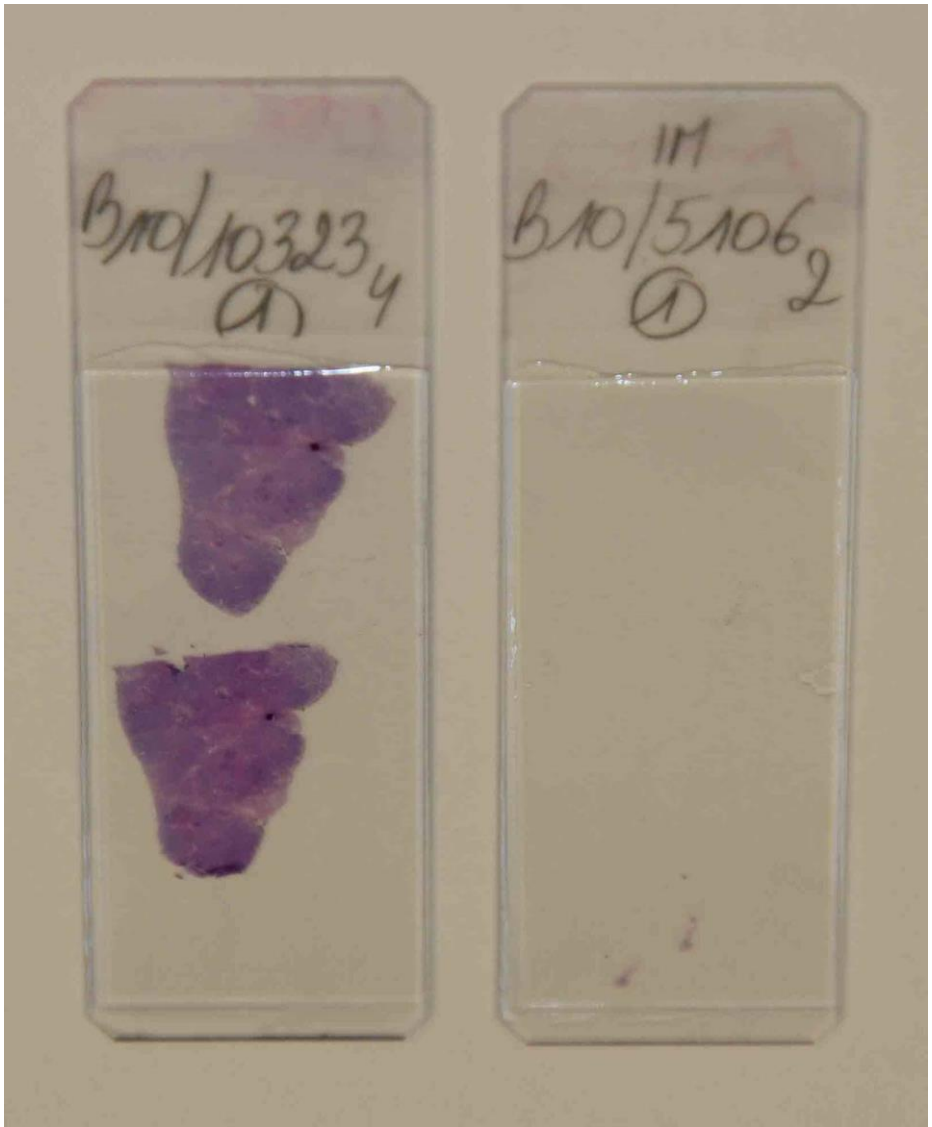
- ‘De patholoog is geen echte arts’
- ‘De patholoog ziet geen patiënten’

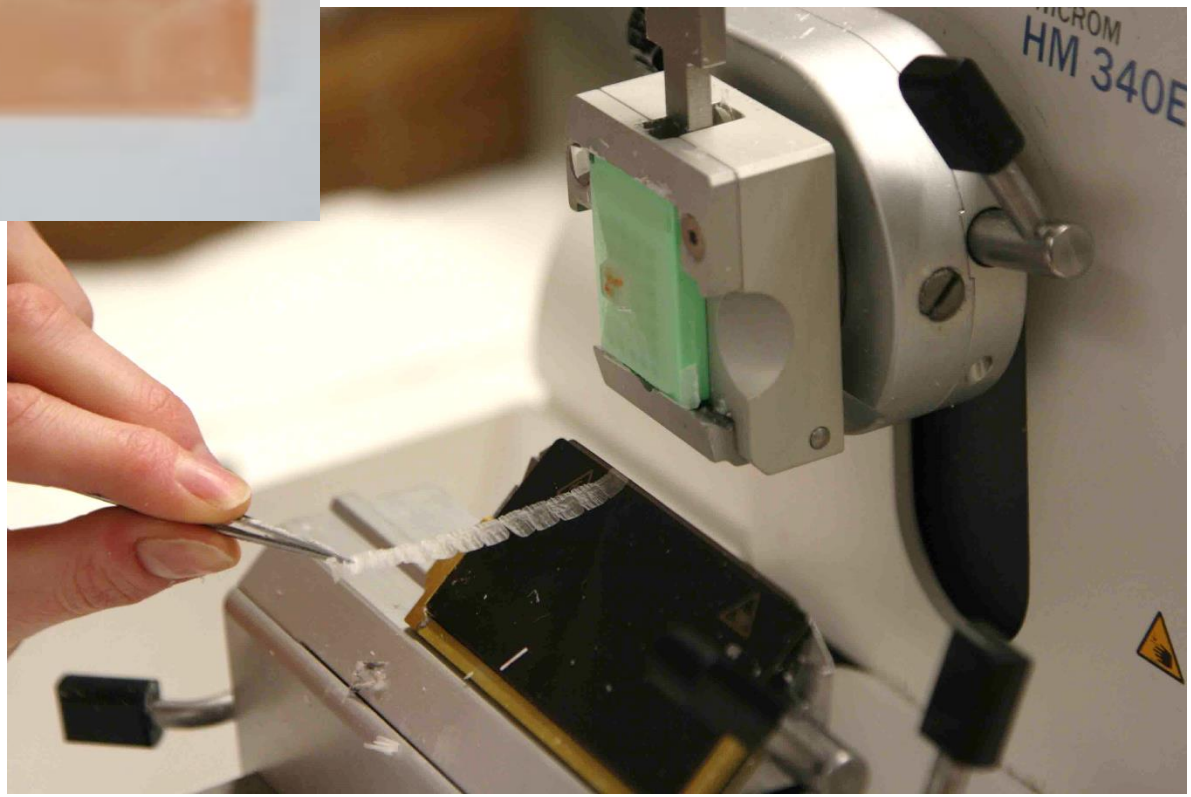
Misverstanden over pathologie (4)

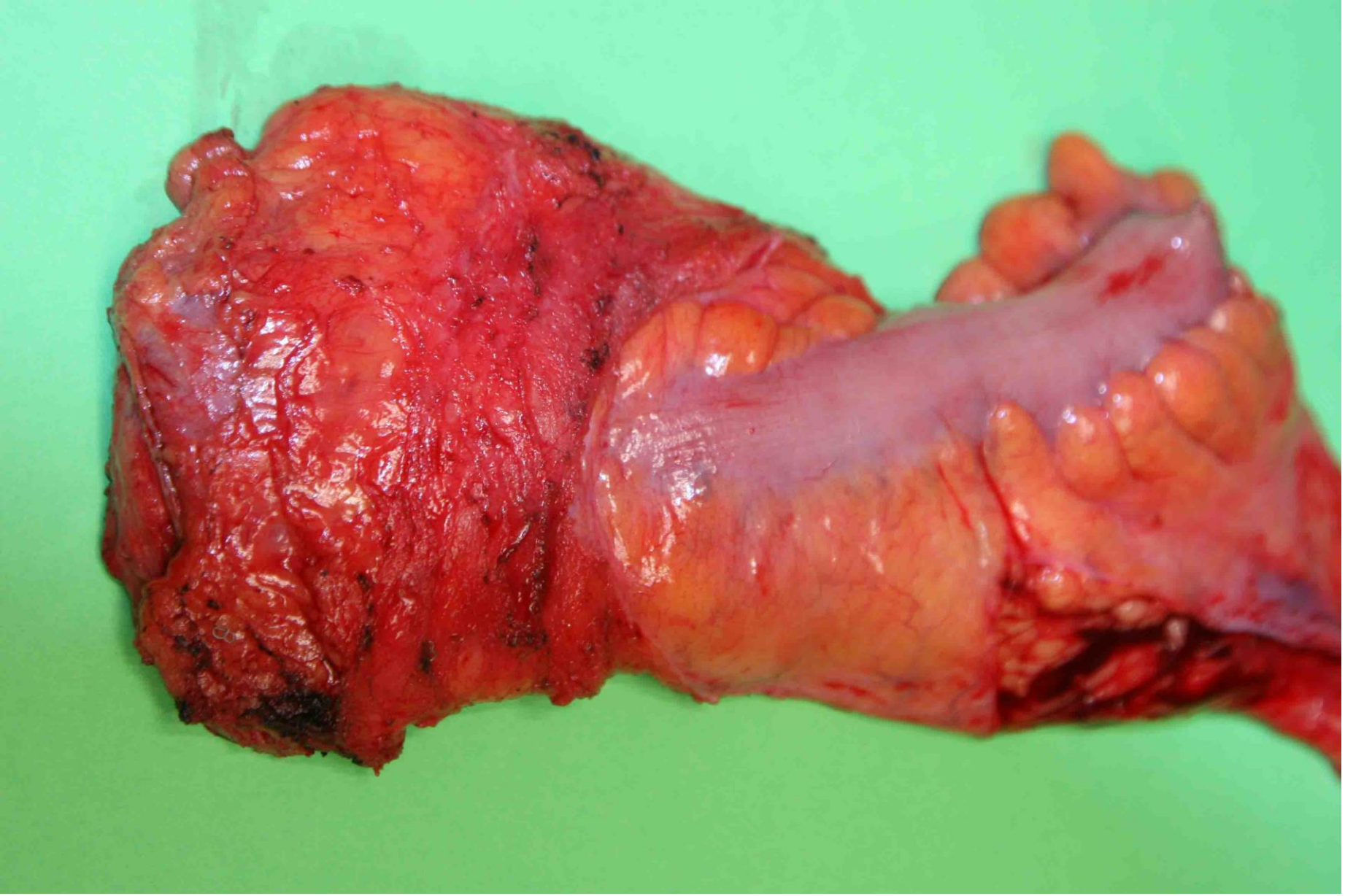
- ‘Pathologie is een laboratoriumspecialisme’

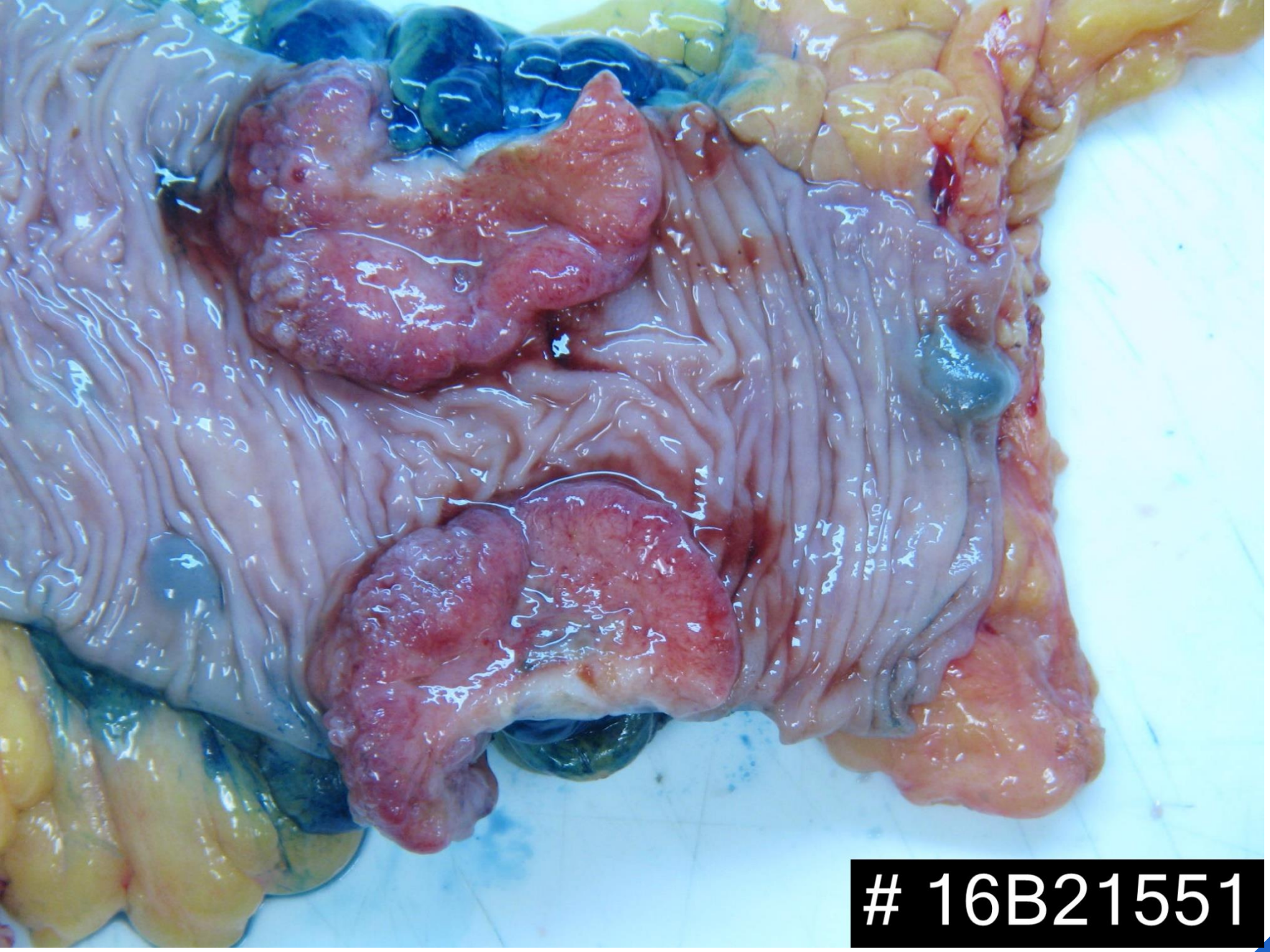
= WAAR en NIET-waar

Veel manuele stappen!
Erg arbeidsintensief!




HM 340E

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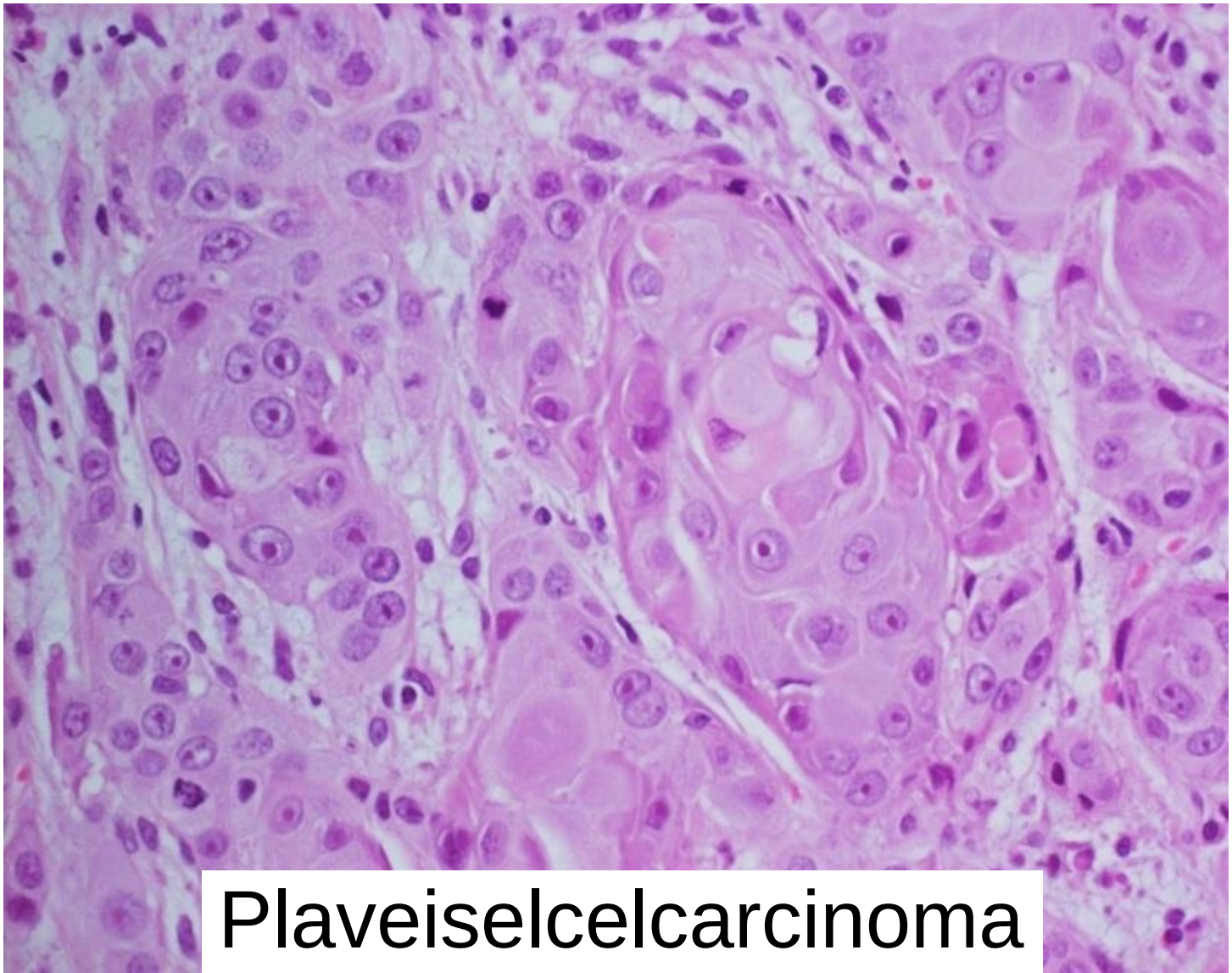
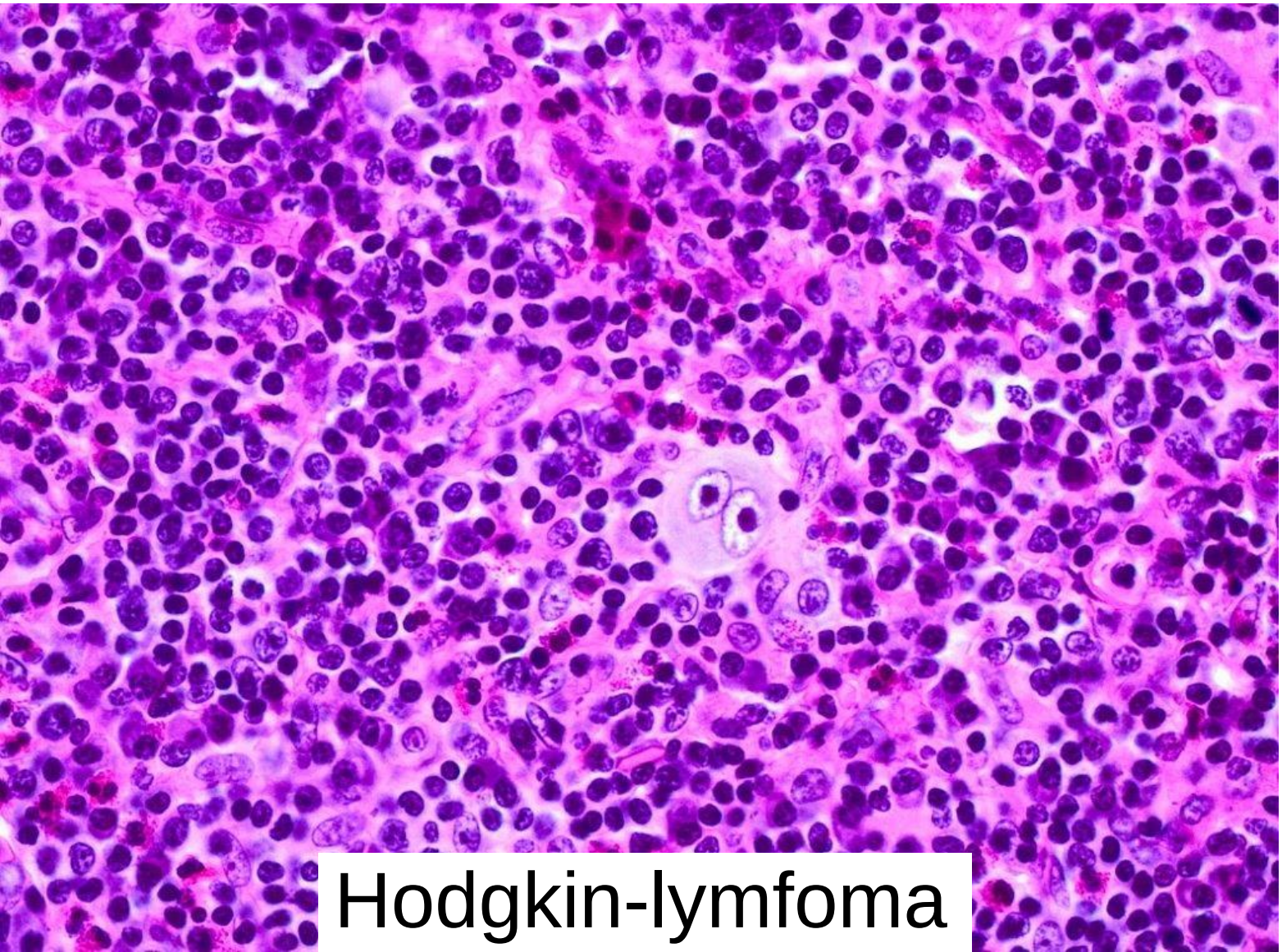
Pathologische anatomie = klinisch specialisme!



Plaveiselcelcarcinoma

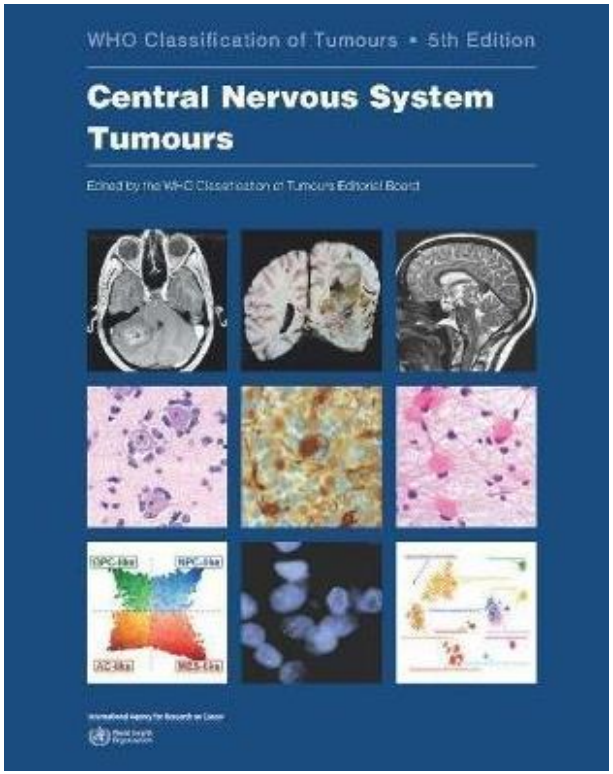


Hodgkin-lymfoma

Autopsies

Beweringen over pathologie die waar zijn (1)

- ‘Een patholoog moet veel kennen en kunnen’



Beweringen over pathologie die waar zijn (2)

- ‘Pathologen doen hun vak met veel passie’

Beweringen over pathologie die waar zijn (3)

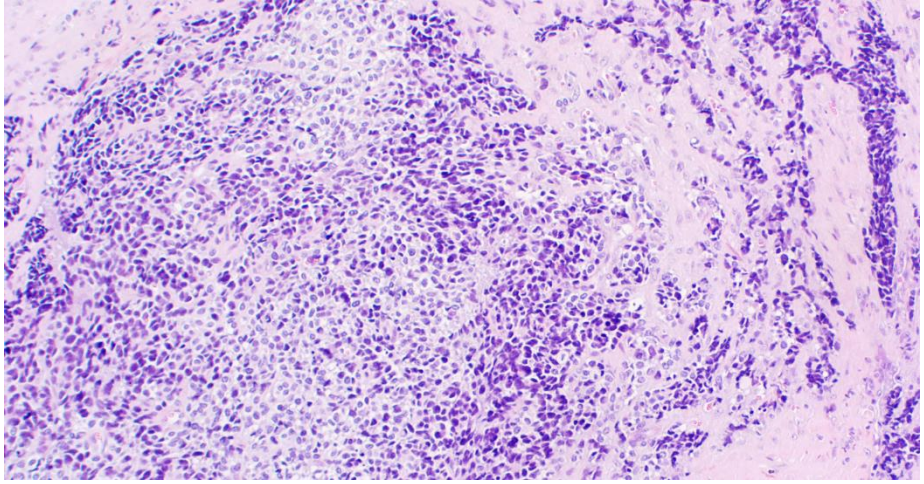
- ‘Geen oncologie zonder pathologie’

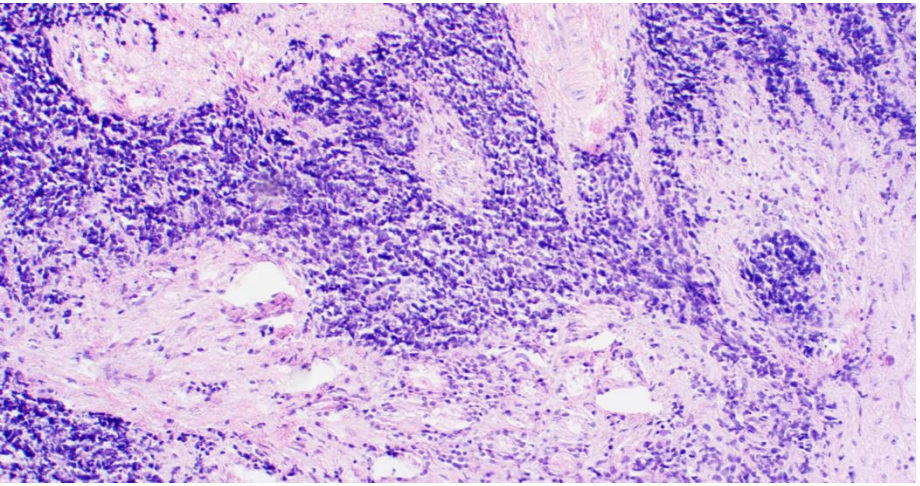
Beweringen over pathologie die waar zijn (4)

- ‘Pathologie is *service*-verlenend’

‘Moderne’ pathologie

- Immuunhistochemie
- Moleculaire pathologie





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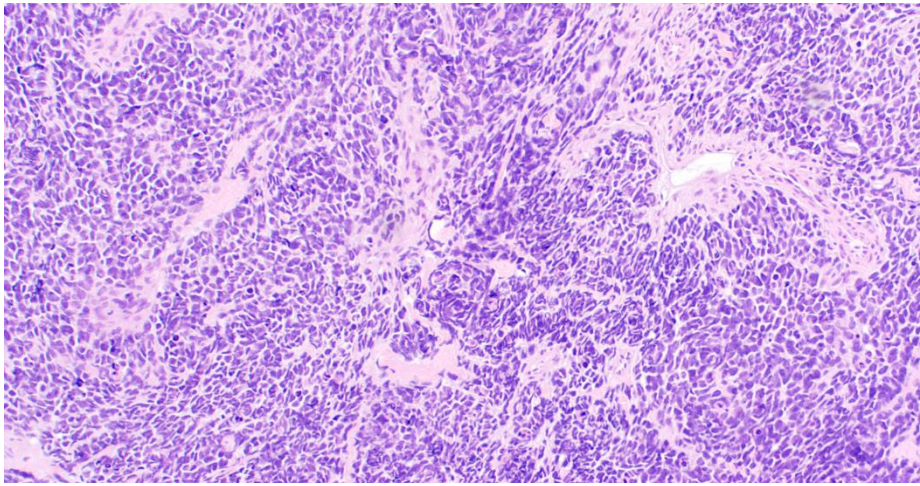
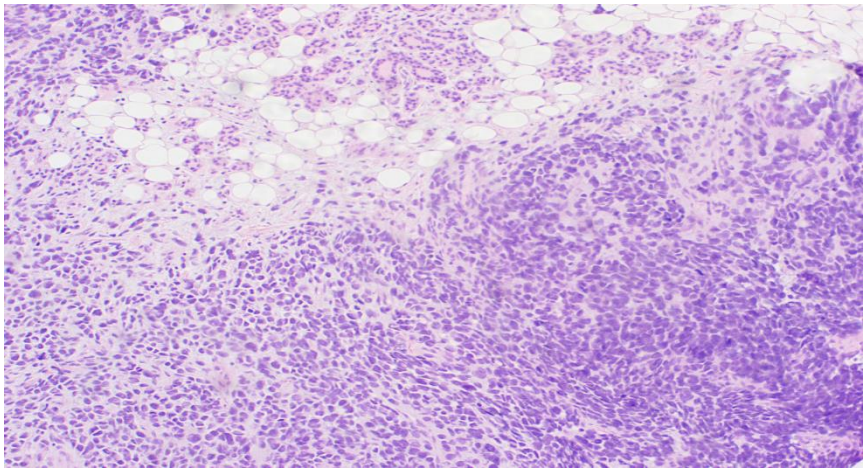
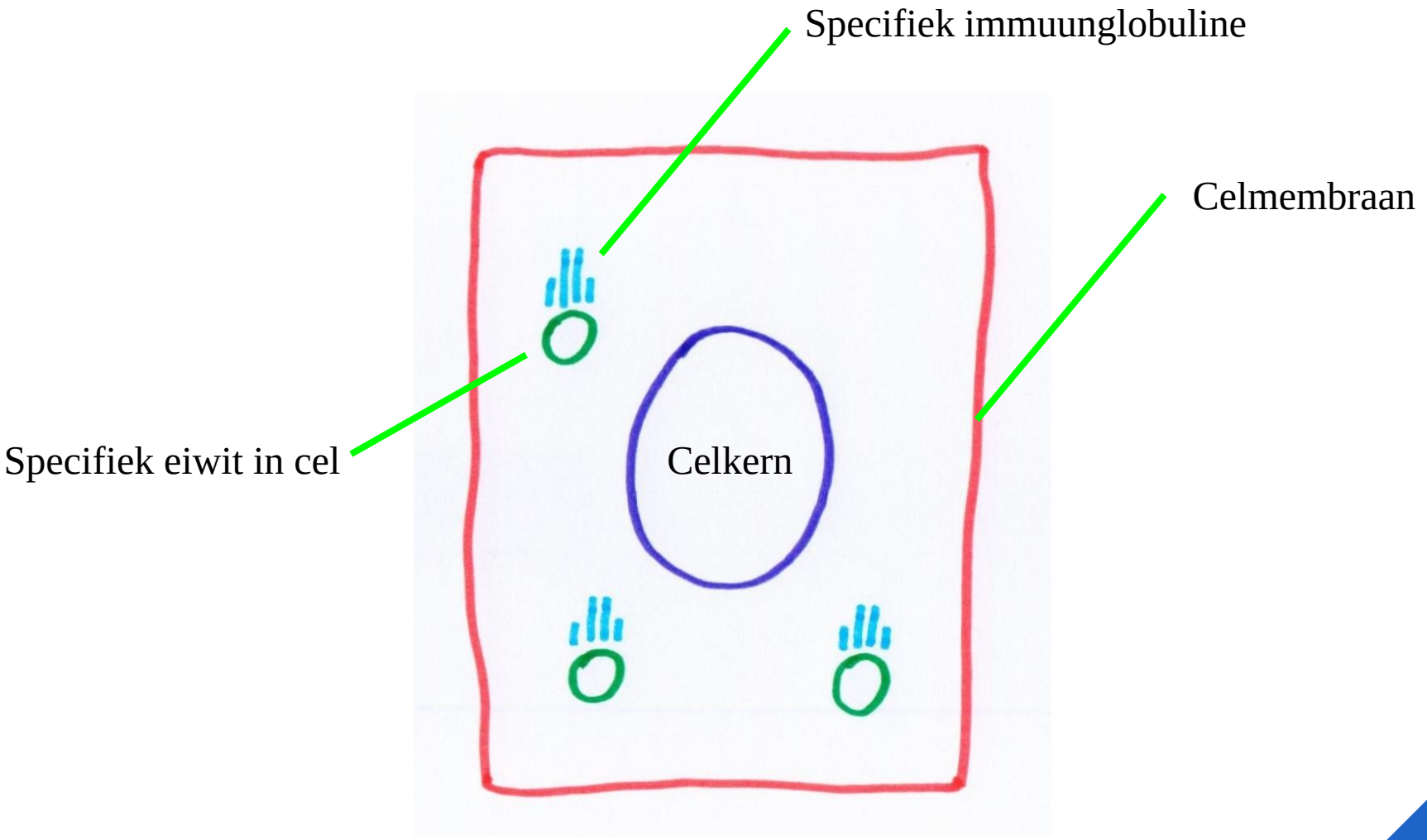
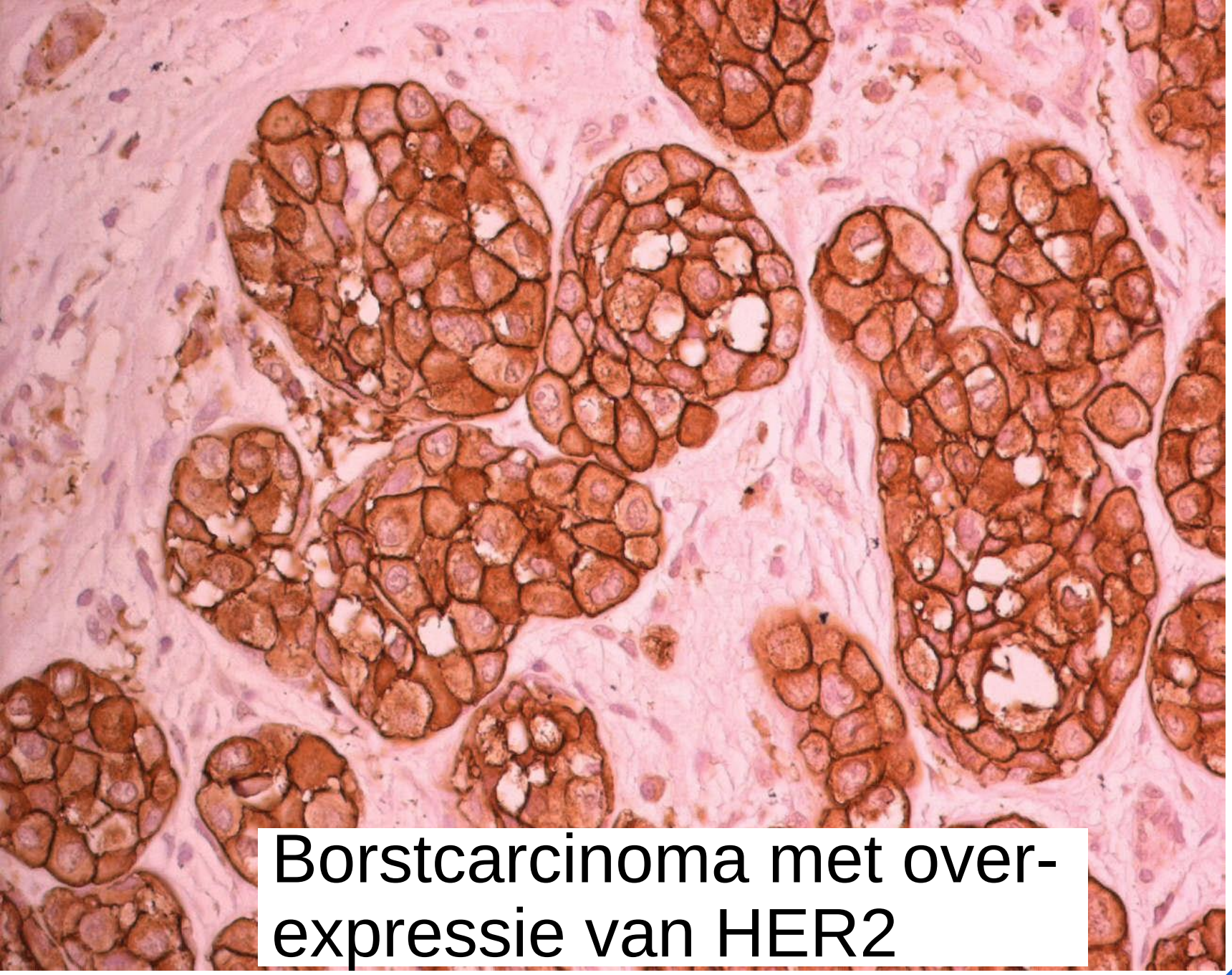




1) Immuunhistochemie = eiwitniveau

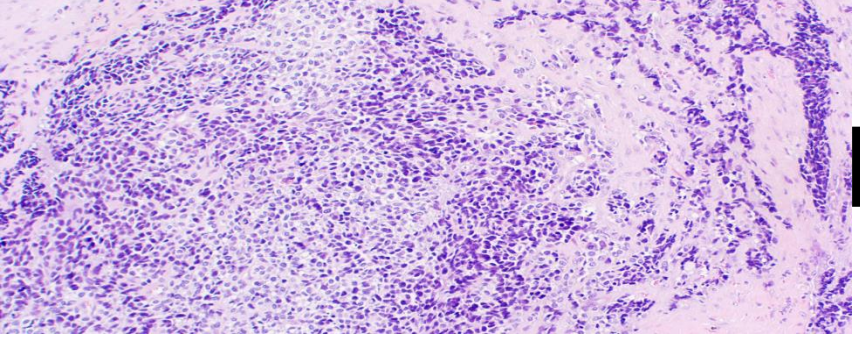




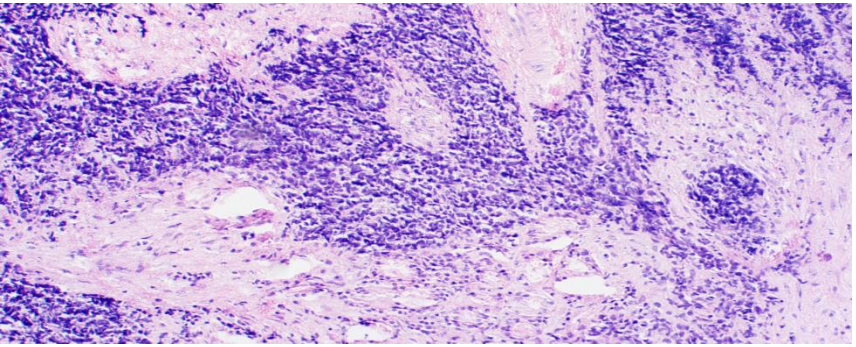
Borstcarcinoma met over-expressie van HER2

Immuunhistochemie

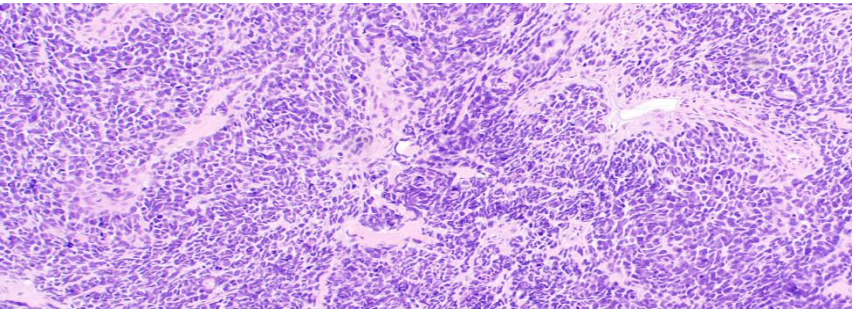
- Typering van tumoren
- Prognose
- Predictief
- Aantonen mutaties
- Identificatie van micro-organismen



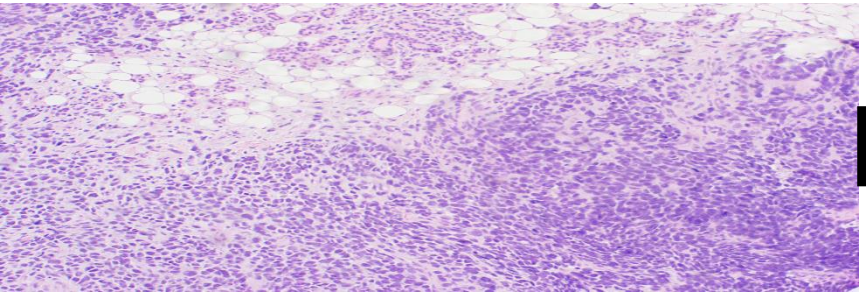
CD45+, CD20+ → B-cel lymfoom



S100+, SOX10+ → melanoma



CD99+, NKX2.2+ → .....

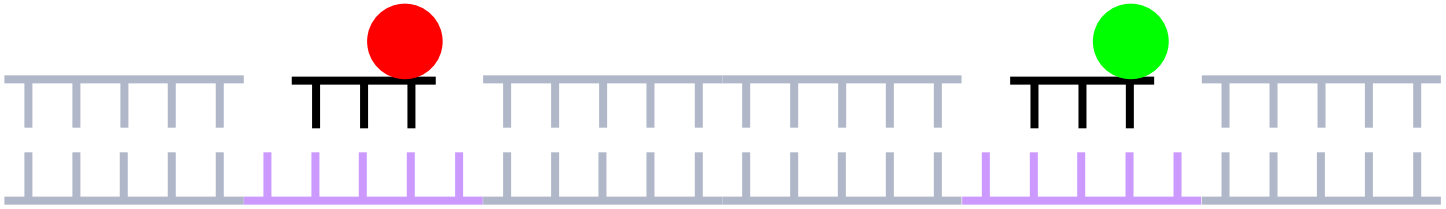


CD99+, NKX2.2 negatief → .....

2) Moleculaire pathologie = op DNA- en RNA-niveau

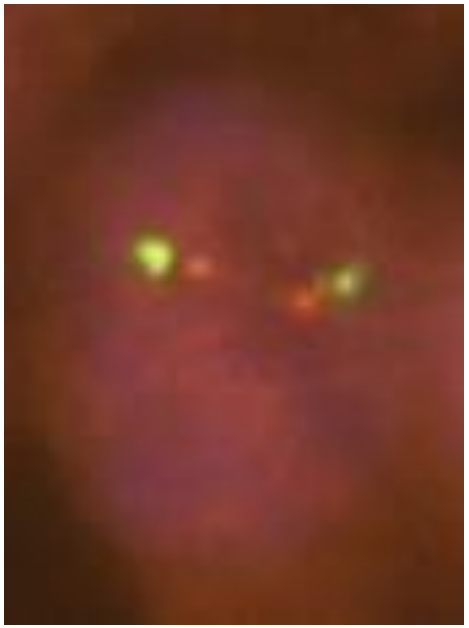
- FISH-analyse
- *Next generation sequencing*:
  - Op DNA-niveau
    - Op gen-niveau: mutatie-analyse
    - Op chromosomaal niveau: *copy number variant sequencing*
  - Op RNA-niveau: gen-fusie-detectie

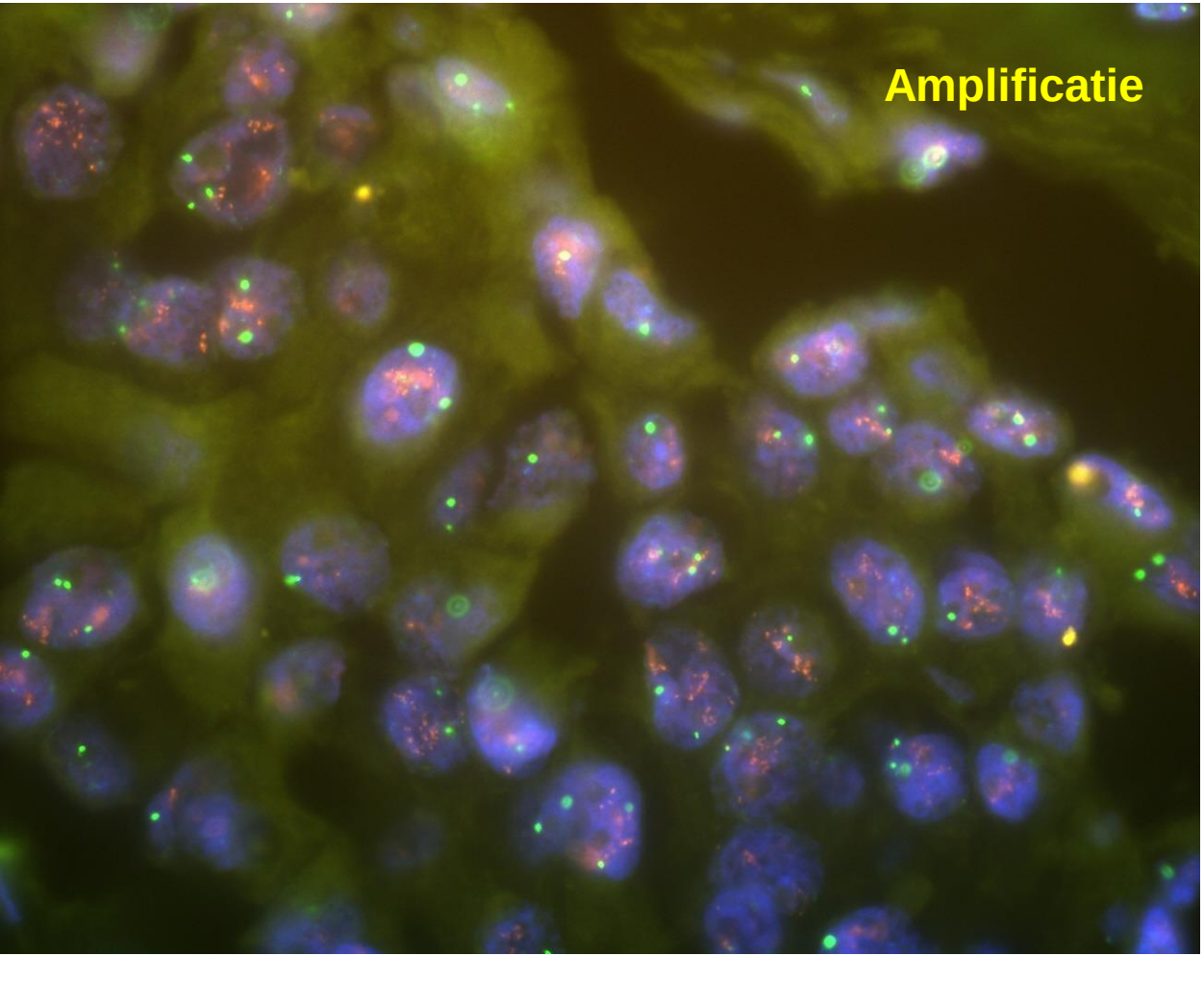
FISH-analyse (1)



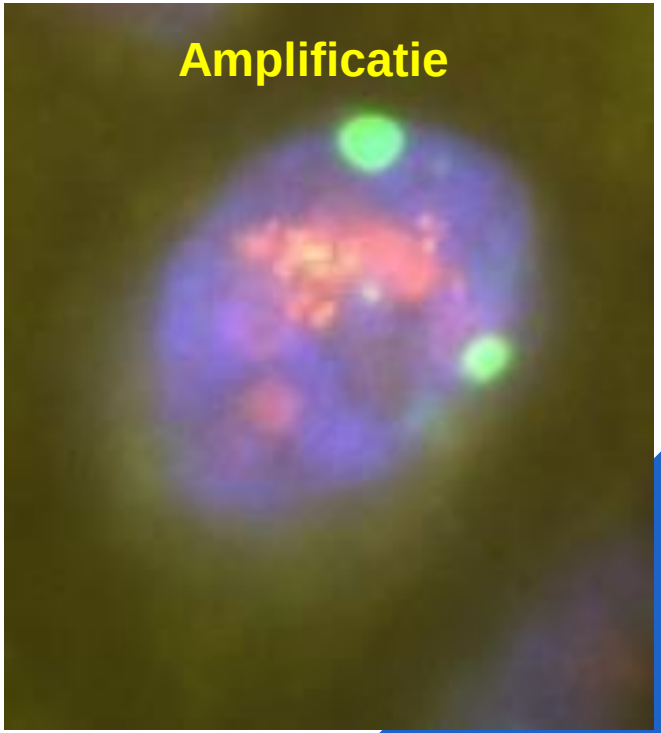
***HER2*- gen** **chromosoom 17 centromeer**

Normale cel

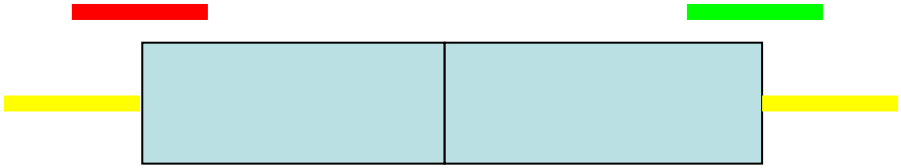




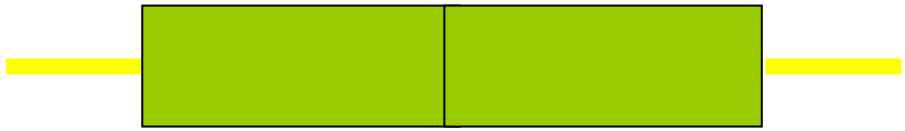
Borstcarcinoma



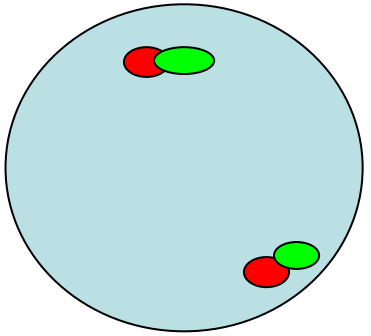
FISH-analyse (2)

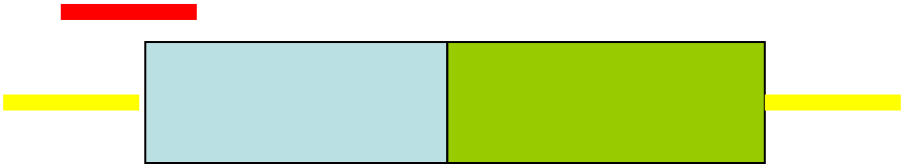


***EWS* 22**

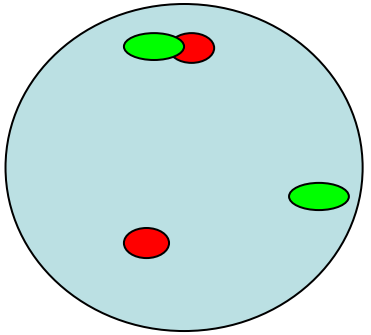


***FLI1* 11**

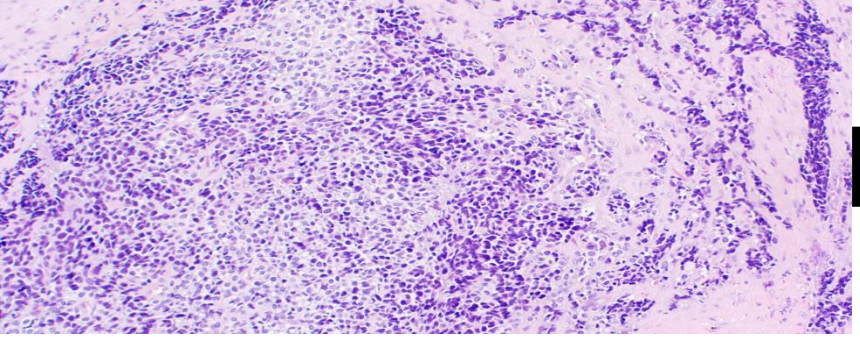




***EWS-FLI1* t(11;22)**



***FLI1-EWS* t(11;22)**



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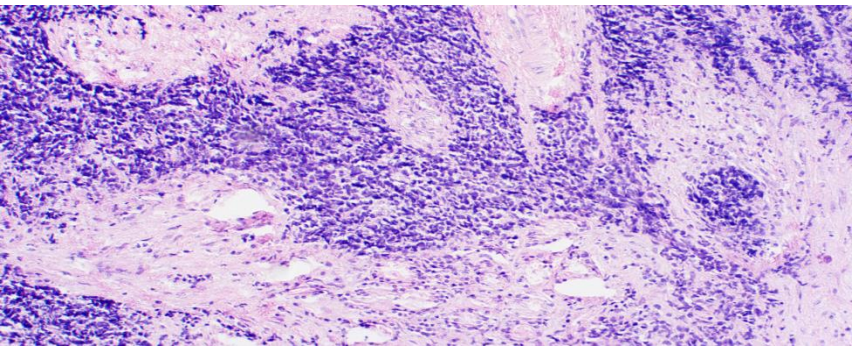

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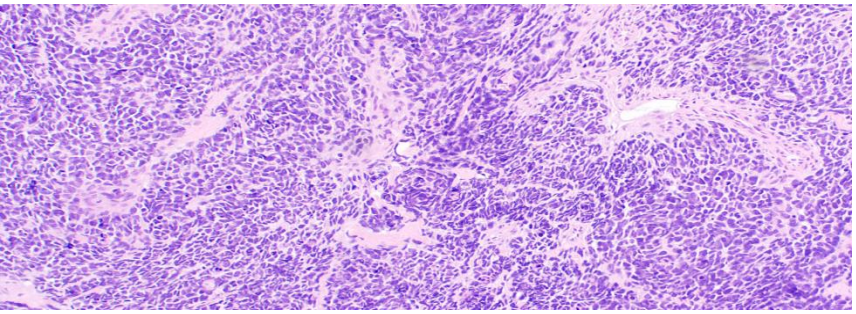
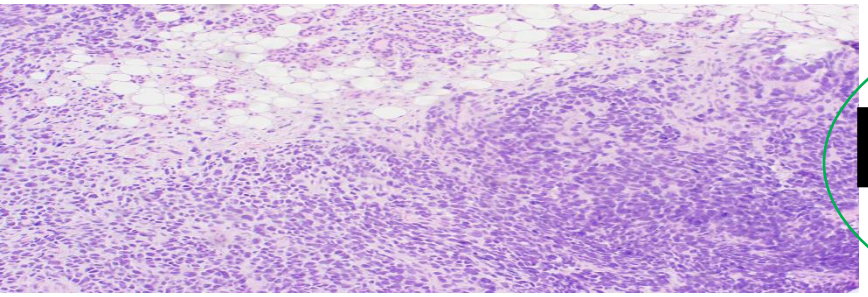


CD99+, NKX2.2+ → *FISH: EWSR1-herschikking* → Ewing-sarcoma

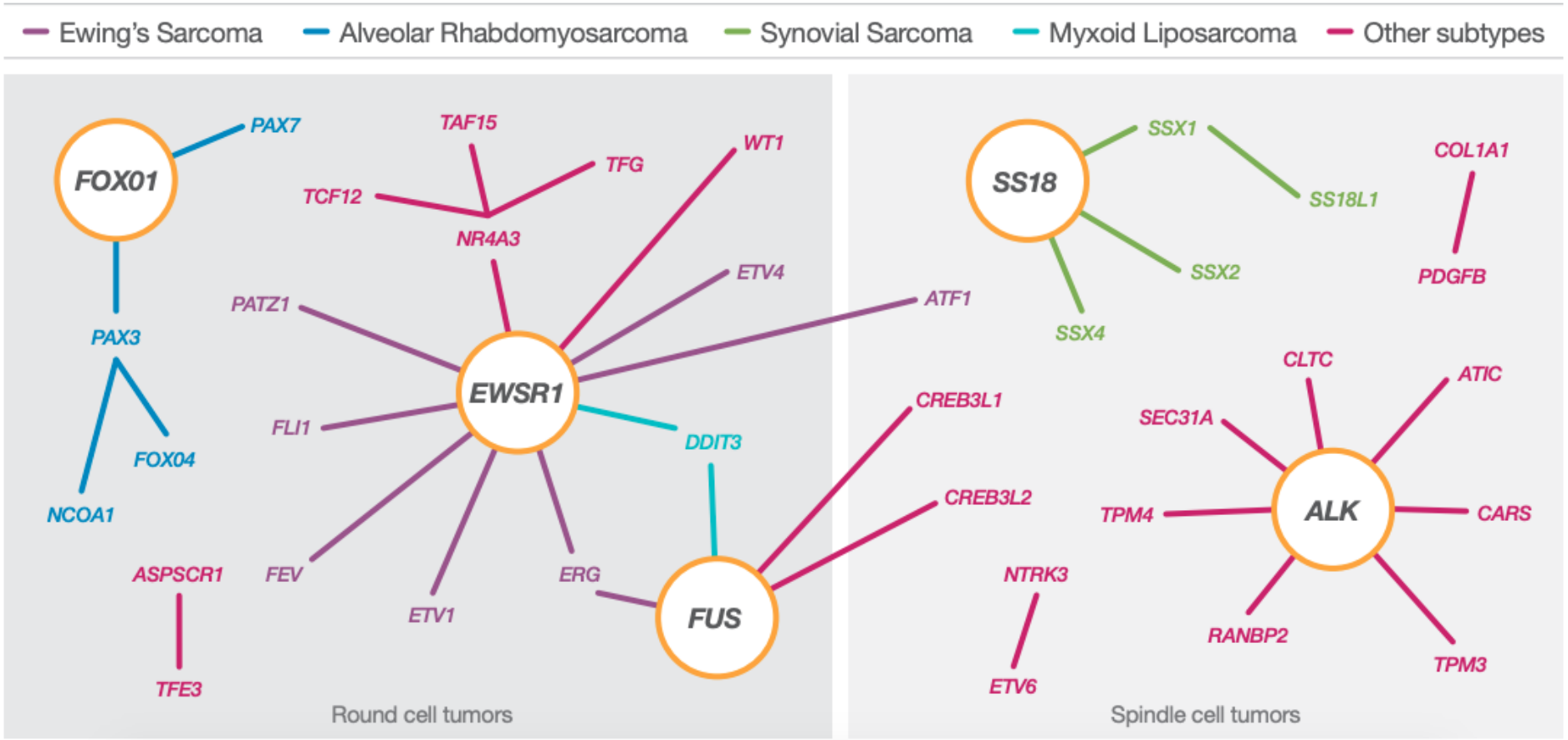


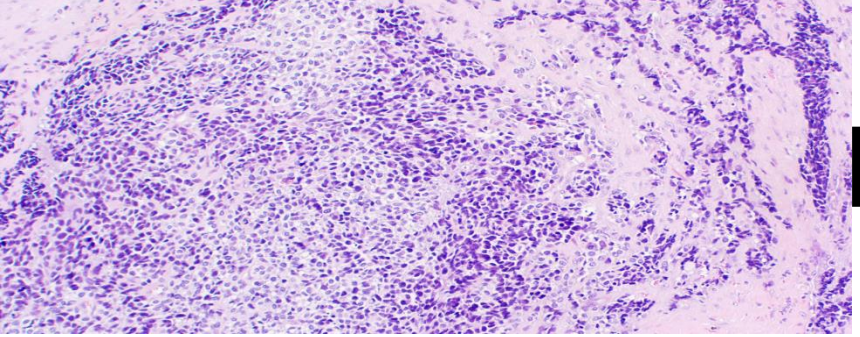
CD99+, NKX2.2 negatief → *FISH: EWSR1-herschikking* → ?

Moleculaire diagnostiek Gent (MDG)

RNA-niveau: gen-fusie-detectie

- *ALK, BCOR, BRAF, CAMTA1, CCNB3, CIC, CSF1, EPC1, EWSR1, FGFR1, FGFR2, FGFR3, FOSB, FOXO1, FUS, GLI1, HMGA2, JAZF1, MEAF6, MKL2, NCOA2, NR4A3, NTRK1, NTRK2, NTRK3, NUTM1, PAX3, PDGFB, PHF1, PLAG1, RET, ROS1, SS18, STAT6, TAF15, TCF12, TFE3, TFG, USP6, YWHAE*





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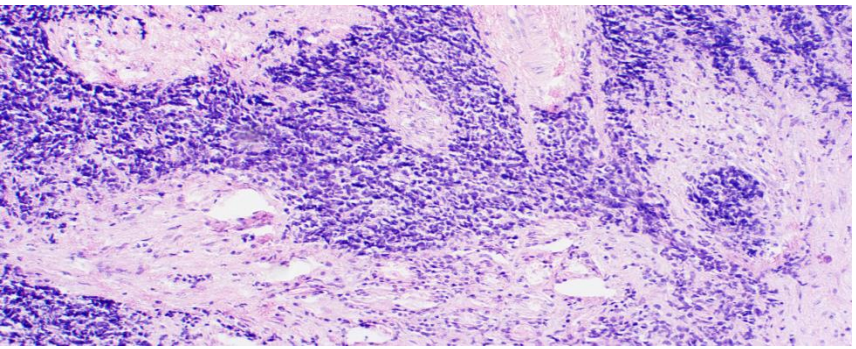

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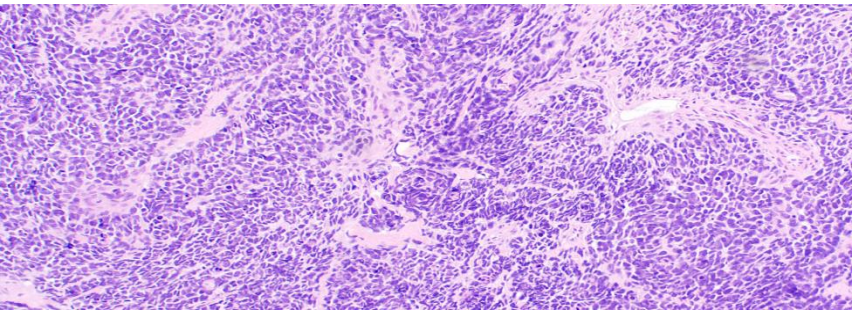

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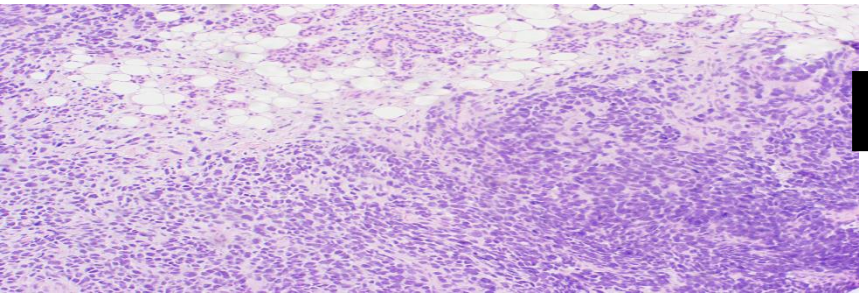


CD99+, NKX2.2 negatief → *EWSR1-SSX2-herschikking* → Ewing-like sarcoma met EWSR1-SSX2 fusie!!!

Received: 24 June 2021 | Revised: 31 August 2021 | Accepted: 14 September 2021
DOI: 10.1002/gcc.22999

BRIEF REPORT

WILEY

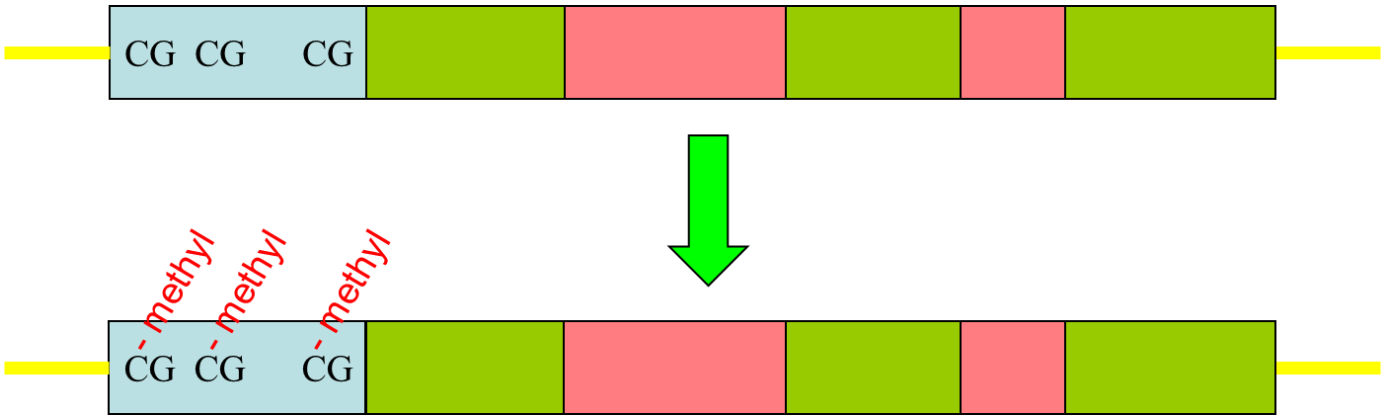
Undifferentiated sarcoma of bone with a round to epithelioid cell phenotype harboring a novel *EWSR1-SSX2* fusion identified by RNA-based next-generation sequencing

Fleur Cordier[1] | Joni Van der Meulen[2,3] | Bram Van Gaever[1] | Lore Lapeire[3,4] | Gwen Sys[3,5] | Jo Van Dorpe[1,3] | David Creytens[1,3]

Genes Chromosomes and Cancer, 2022 Jan; 61(1): 44-49.

De toekomst

- Moleculaire pathologie zal nog aan belang toenemen
- ***Liquid biopsies***
- Epigenetica: **methylatie-*profiling***



- Sub-specialistie: ***dedicated specialist*** in orgaan-specifieke tumordiagnostiek
- Digitalisatie en **artificiële intelligentie**

Raman et al. Genome Medicine (2020) 12:35
https://doi.org/10.1186/s13073-020-00735-4

Genome Medicine

RESEARCH Open Access

Shallow whole-genome sequencing of plasma cell-free DNA accurately differentiates small from non-small cell lung carcinoma

Lennart Raman[1,2†], Malaïka Van der Linden[1†], Kim Van der Eecken[1†], Karim Vermaelen[3], Ingel Demedts[4], Veerle Surmont[3], Ulrike Himpe[4], Franceska Dedeurwaerdere[5], Liesbeth Ferdinande[1], Yolande Lievens[6], Kathleen Claes[2], Björn Menten[2†] and Jo Van Dorpe[1*†]

Abstract

Background: Accurate lung cancer classification is crucial to guide therapeutic decisions. However, histological subtyping by pathologists requires tumor tissue—a necessity that is often intrinsically associated with procedural difficulties. The analysis of circulating tumor DNA present in minimal-invasive blood samples, referred to as liquid biopsies, could therefore emerge as an attractive alternative.

Methods: Concerning adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, our proof of concept study investigates the potential of liquid biopsy-derived copy number alterations, derived from single-end shallow whole-genome sequencing (coverage 0.1–0.5×), across 51 advanced stage lung cancer patients.

Results: Genomic abnormality testing reveals anomalies in 86.3% of the liquid biopsies (16/20 for adenocarcinoma, 13/16 for squamous cell, and 15/15 for small cell carcinoma). We demonstrate that copy number profiles from formalin-fixed paraffin-embedded tumor biopsies are well represented by their liquid equivalent. This is especially valid within the small cell carcinoma group, where paired profiles have an average Pearson correlation of 0.86 (95% CI 0.79–0.93). A predictive model trained with public data, derived from 843 tissue biopsies, shows that liquid biopsies exhibit multiple deviations that reflect histological classification. Most notably, distinguishing small from non-small cell lung cancer is characterized by an area under the curve of 0.98 during receiver operating characteristic analysis. Additionally, we investigated how deeper paired-end sequencing, which will eventually become feasible for routine diagnosis, empowers tumor read enrichment by insert size filtering: for all of the 29 resequenced liquid biopsies, the tumor fraction could be increased in silico, thereby "rescuing" three out of five cases with previously undetectable alterations.

(Continued on next page)

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†Lennart Raman, Malaïka Van der Linden, and Kim Van der Eecken contributed equally to this work.
Björn Menten and Jo Van Dorpe are considered shared last authors.
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ARTICLE

Shallow-depth sequencing of cell-free DNA for Hodgkin and diffuse large B-cell lymphoma (differential) diagnosis: a standardized approach with underappreciated potential

Ferrata Storti Foundation

Lennart Raman,[1,2,*] Malaïka Van der Linden,[1,2,*] Ciel De Vriendt,[3,*] Bliede Van den Broeck,[4] Kristoff Muylle,[5] Dries Deeren,[6] Franceska Dedeurwaerdere,[7] Sofie Verbeke,[1] Amélie Dendooven,[1,8] Katrien De Grove,[3] Saskia Baert,[3] Kathleen Claes,[2] Björn Menten,[2] Fritz Offner[3#] and Jo Van Dorpe[1#]

[1]Department of Pathology, Ghent University, Ghent University Hospital, Ghent; [2]Center for Medical Genetics, Department of Biomolecular Medicine, Ghent University, Ghent University Hospital, Ghent; [3]Department of Clinical Hematology, Ghent University, Ghent University Hospital, Ghent; [4]Department of Nuclear Medicine, Ghent University, Ghent University Hospital, Ghent; [5]Department of Nuclear Medicine, AZ Delta, Roeselare; [6]Department of Hematology, AZ Delta, Roeselare; [7]Deparment of Pathology, AZ Delta, Roeselare and [8]Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

*LR, MVDL and CDV contributed equally as co-first authors.

#JVD and FO contributed equally as co-senior authors.

Haematologica 2022
Volume 107(1):211-220

ABSTRACT

Shallow-depth sequencing of cell-free DNA, an inexpensive and standardized approach to obtain molecular information on tumors non-invasively, has been insufficiently explored for the diagnosis of lymphoma and disease follow-up. This study collected 318 samples, including longitudinal liquid and paired solid biopsies, from a prospectively-recruited cohort of 38 Hodgkin lymphoma (HL) and 85 aggressive B-cell non-HL patients, represented by 81 diffuse large B-cell lymphoma (DLBCL) cases. Following sequencing, copy number alterations and viral read fractions were derived and analyzed. At diagnosis, liquid biopsies showed detectable copy number alterations in 84.2% of HL patients (88.6% for classical HL) and 74.1% of DLBCL patients. Of the DLBCL patients, copy number profiles between liquid-solid pairs were highly concordant (r=0.815±0.043); and, compared to tissue, HL liquid biopsies had abnormalities with higher amplitudes (P=0.010). This implies that tumor DNA is more abundant in plasma. Additionally, 39.5% of HL and 13.6% of DLBCL cases had a significantly elevated number of plasma Epstein-Barr virus DNA fragments, achieving a sensitivity of 100% compared to the current standard. A longitudinal analysis determined that, when detectable, copy number patterns were similar across (re)staging moments in refractory or relapsed patients. Further, the overall profile anomaly correlated highly with the total metabolic tumor volume (P<0.001). To conclude, as a proof of principle, we demonstrate that liquid biopsy-derived copy numbers can aid diagnosis: e.g., by differentiating HL from DLBCL, random forest modeling is represented by an area under the receiver operating characteristic curve of 0.967. This application is potentially useful when tissue is difficult to obtain or when biop-

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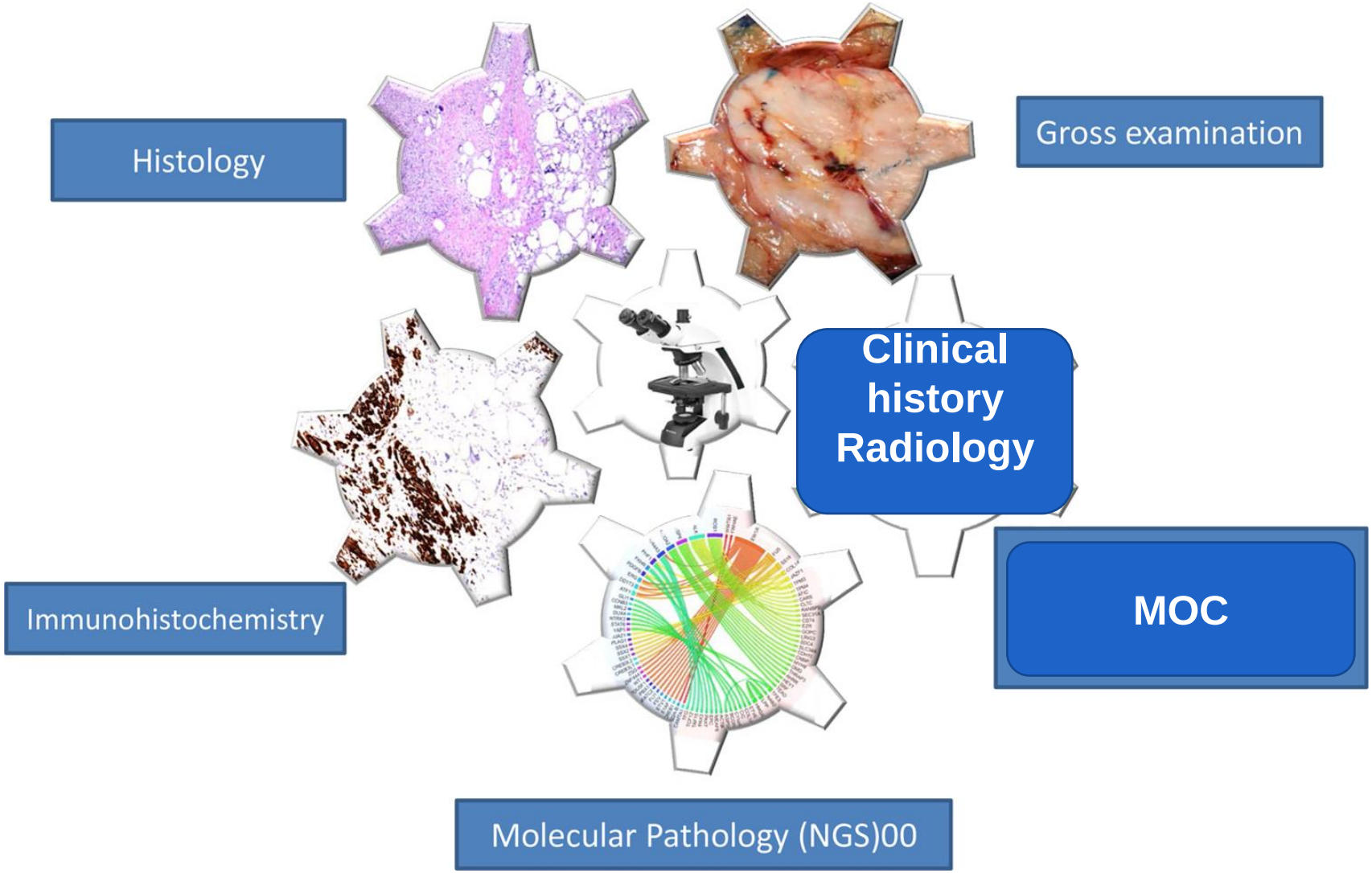
Conclusie

- Ruim, maar dan ook ruim het **boeiendste** van alle specialismen
- Echt iets voor **detectieven**
- **Klinische vaardigheid** gelinkt aan **theoretische kennis**
- Stellen van diagnose is **multidisciplinair**


Histology
Gross examination
Clinical history Radiology
Immunohistochemistry
MOC
Molecular Pathology (NGS)00

Bedankt voor de aandacht!