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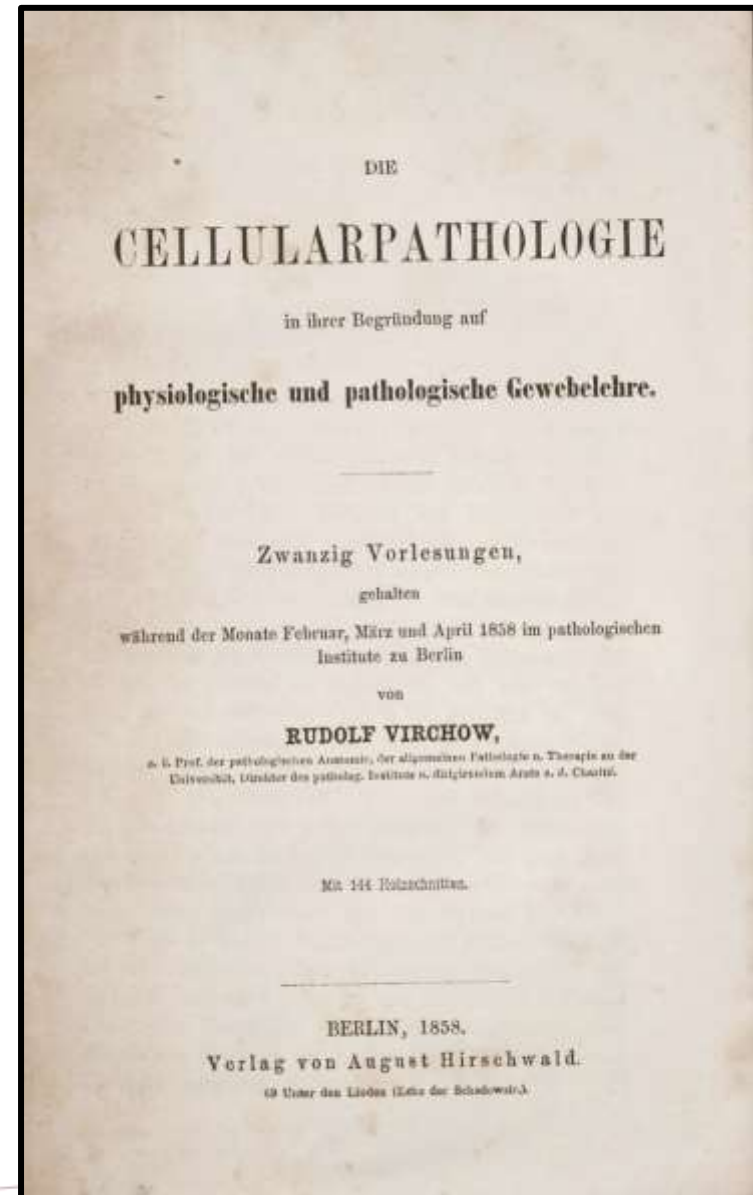
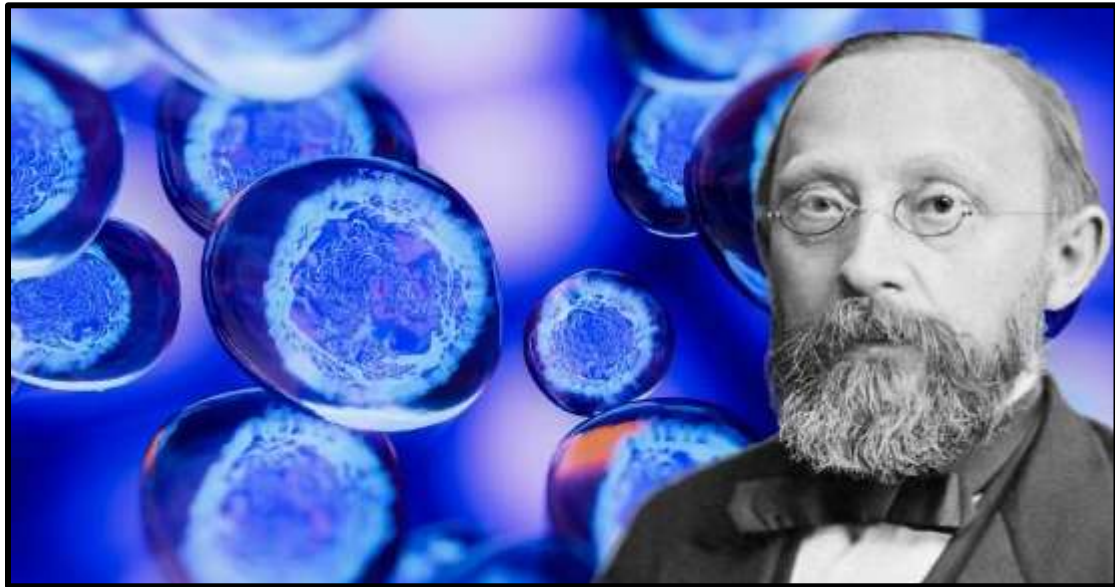
Pathologie van tumoren – GE pathologie

José van den Berg, patholoog

Disclosures

- Geen disclosures

Cellularpathologie = De basis van ziekte zit in de cel



plaveiselcelcarcinoom

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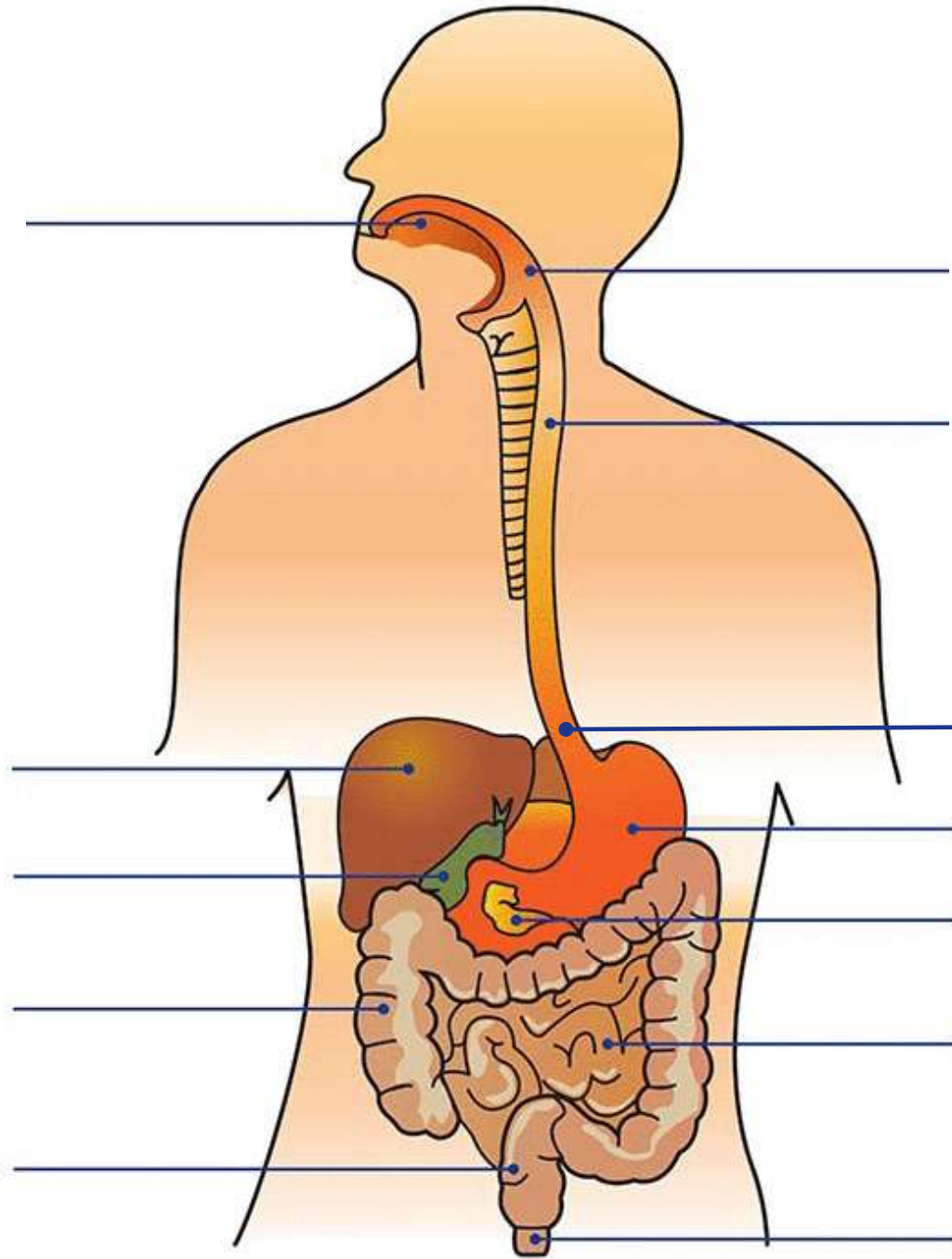
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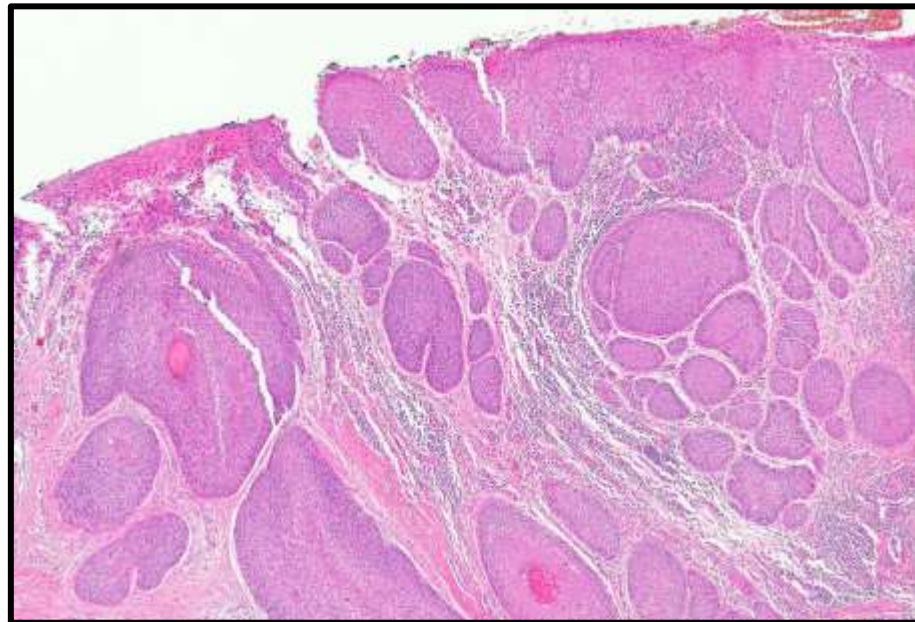
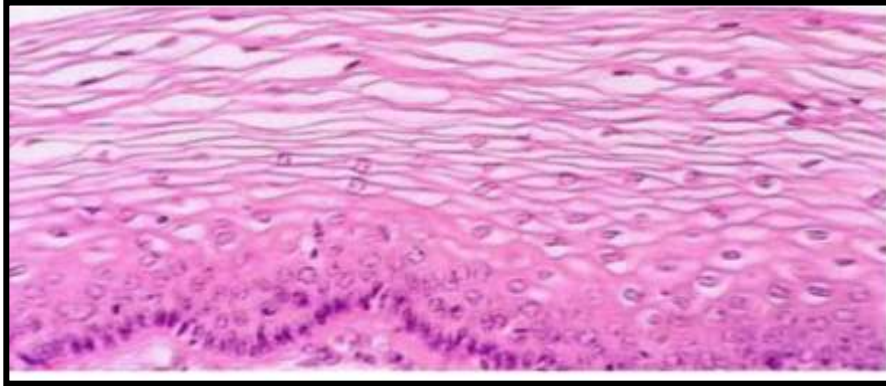
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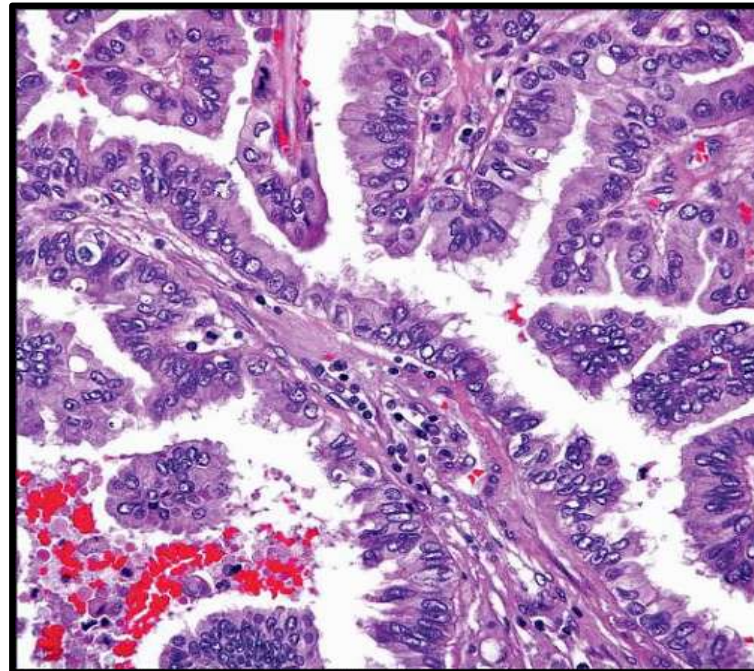
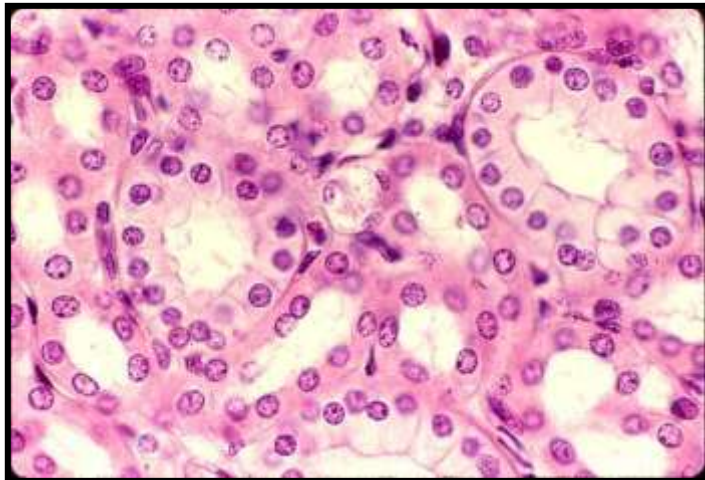


Classificatie van tumoren o.b.v. morfologie



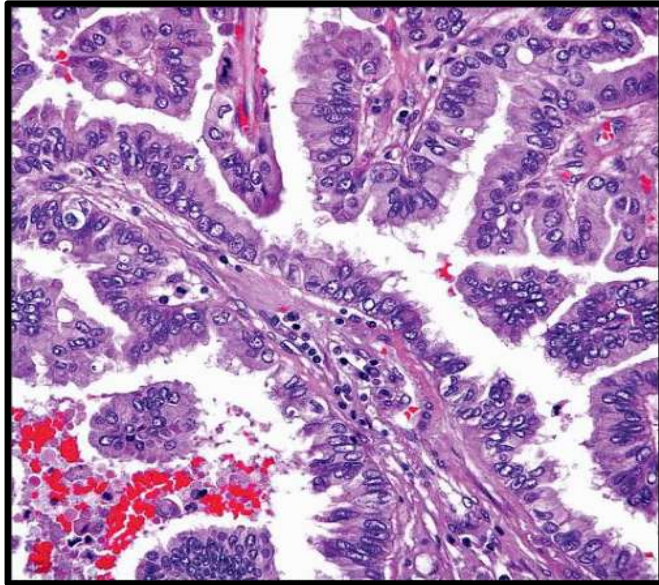
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Classificatie van tumoren o.b.v. morfologie



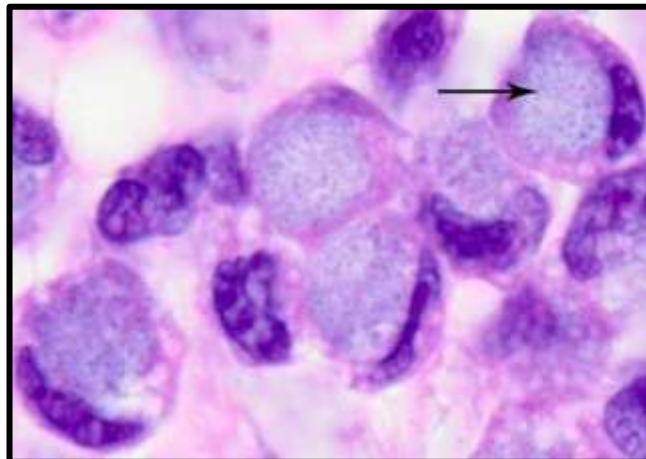
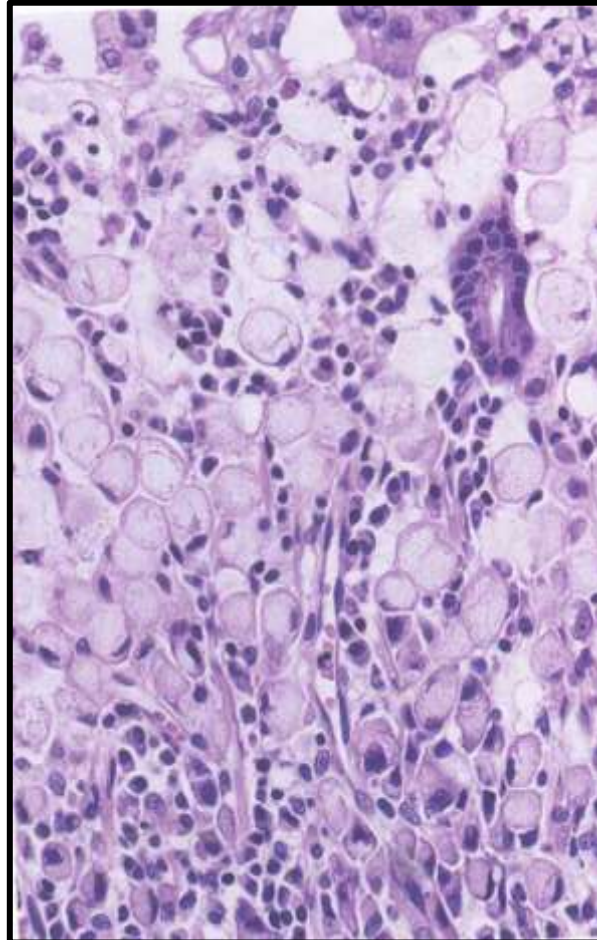
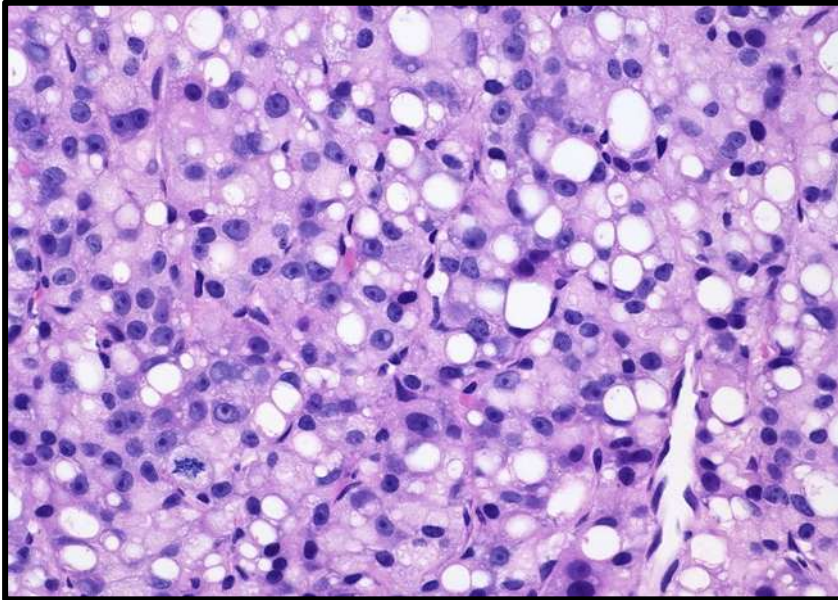
adenocarcinoom

Classificatie van tumoren o.b.v. morfologie

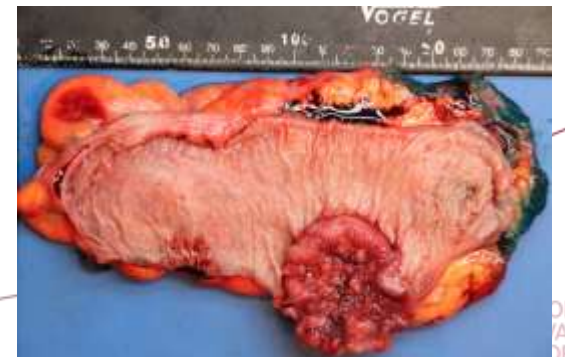
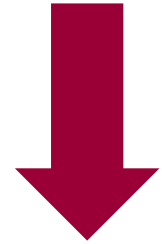
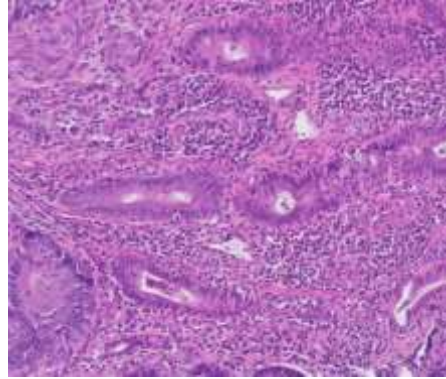
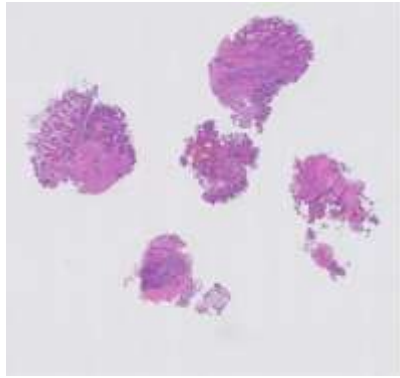


Intestinaal type adenocarcinoom

Classificatie van tumoren o.b.v. morfologie



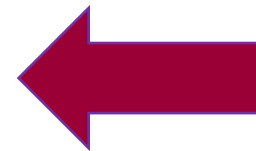
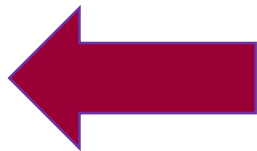
Zegelringcelcarcinoom



Maligne

Classificatie
Graad
TNM
snijvlakken

Evt adjuvante
therapie



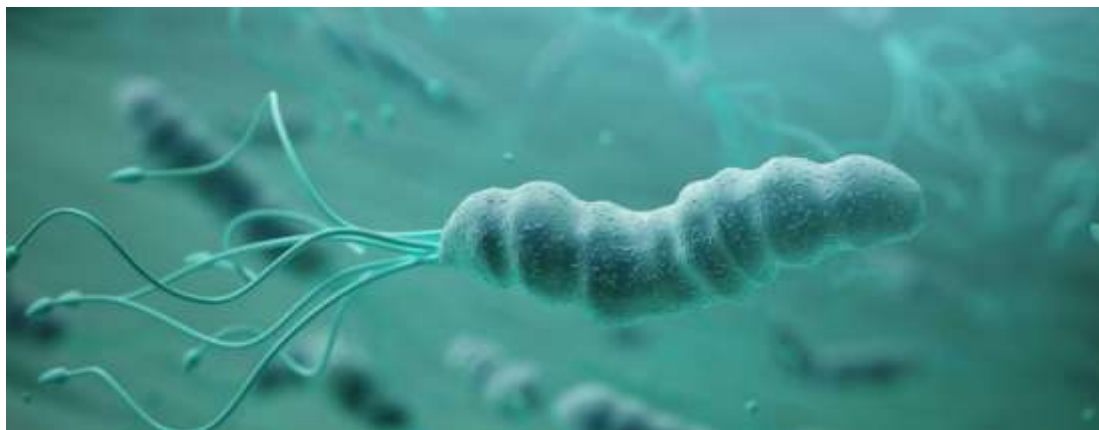
Oude pathologie

- Classificatie op basis van morfologie
- Niet per se gerelateerd aan ontstaanswijze
- Vaak ook eigennamen

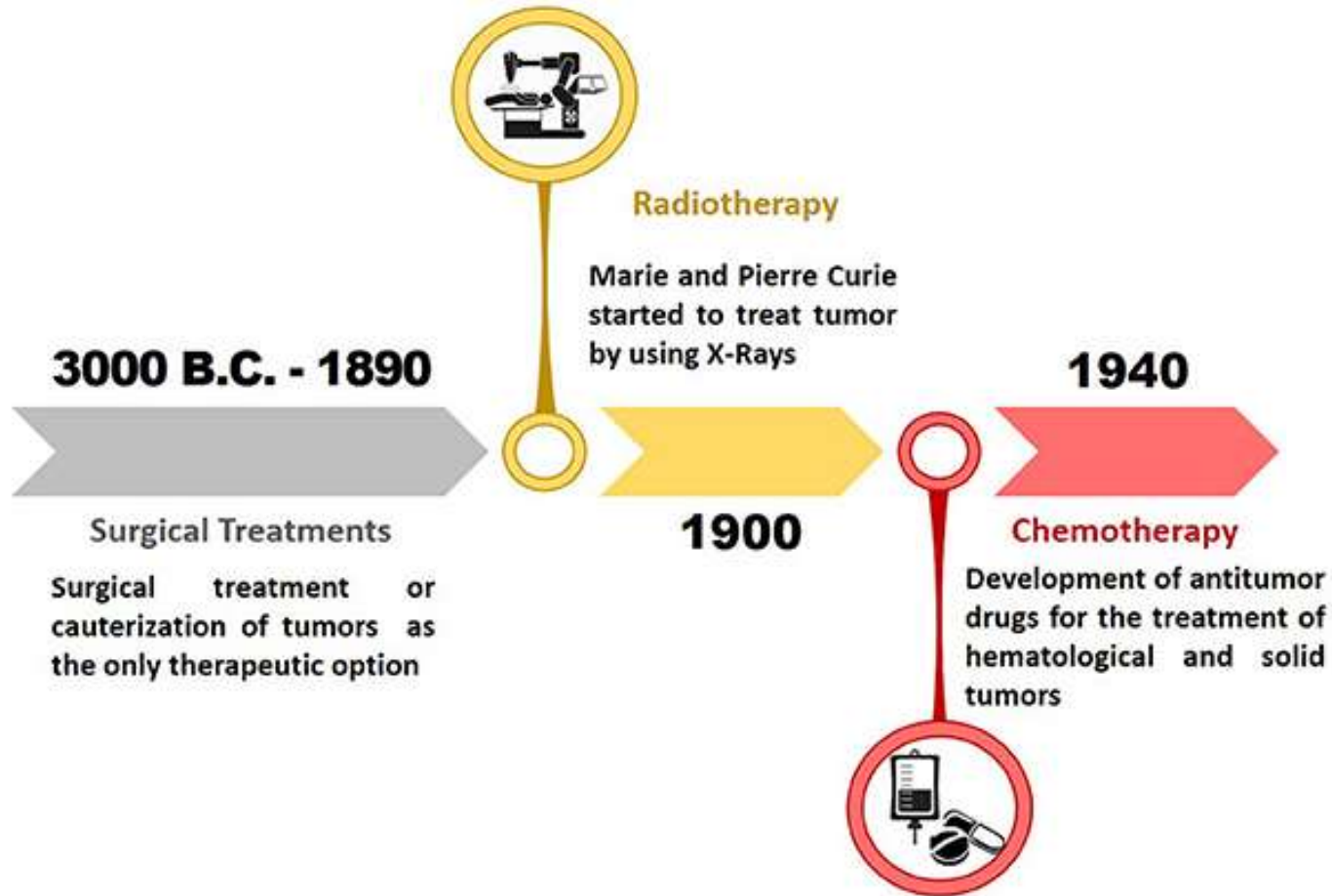


- Begrip over ontstaan van ziekte nodig om ziekte gericht te kunnen behandelen

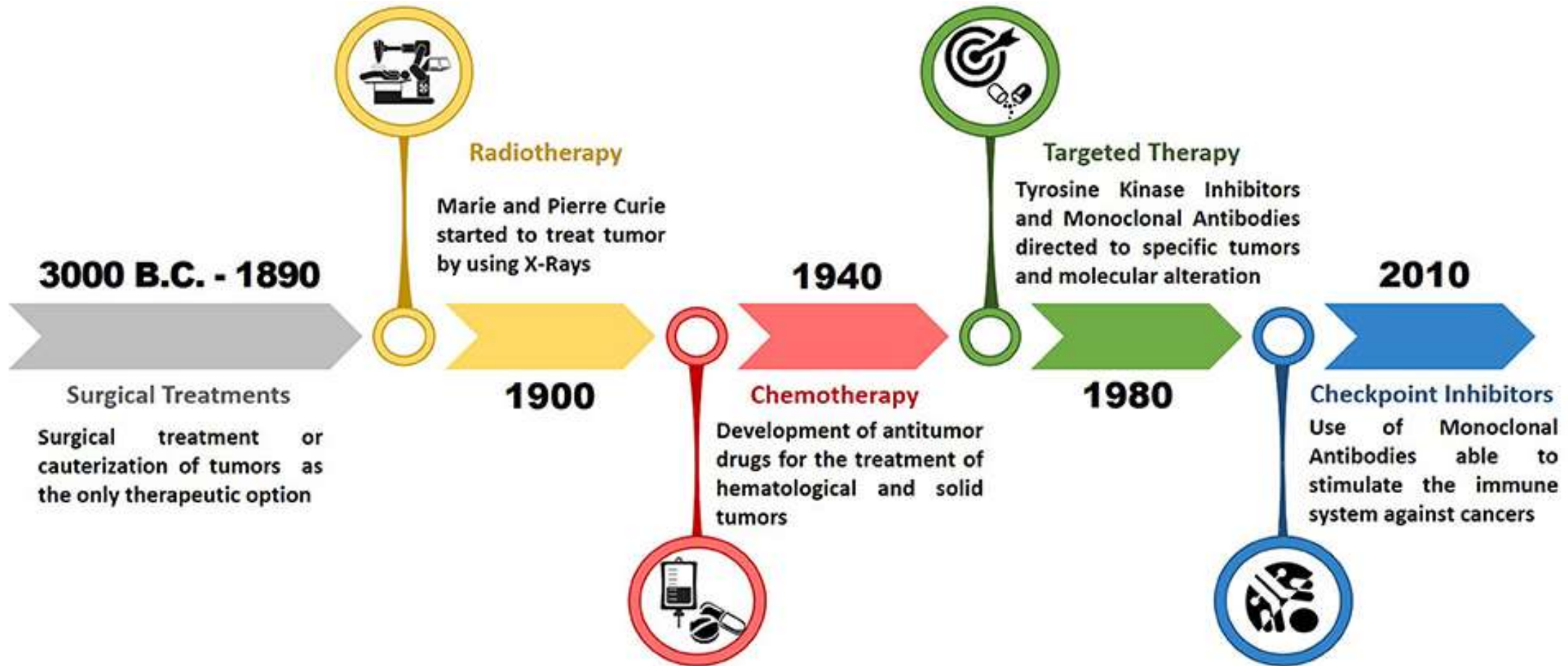
Begrip over ontstaan van ziekte nodig om ziekte gericht te kunnen behandelen



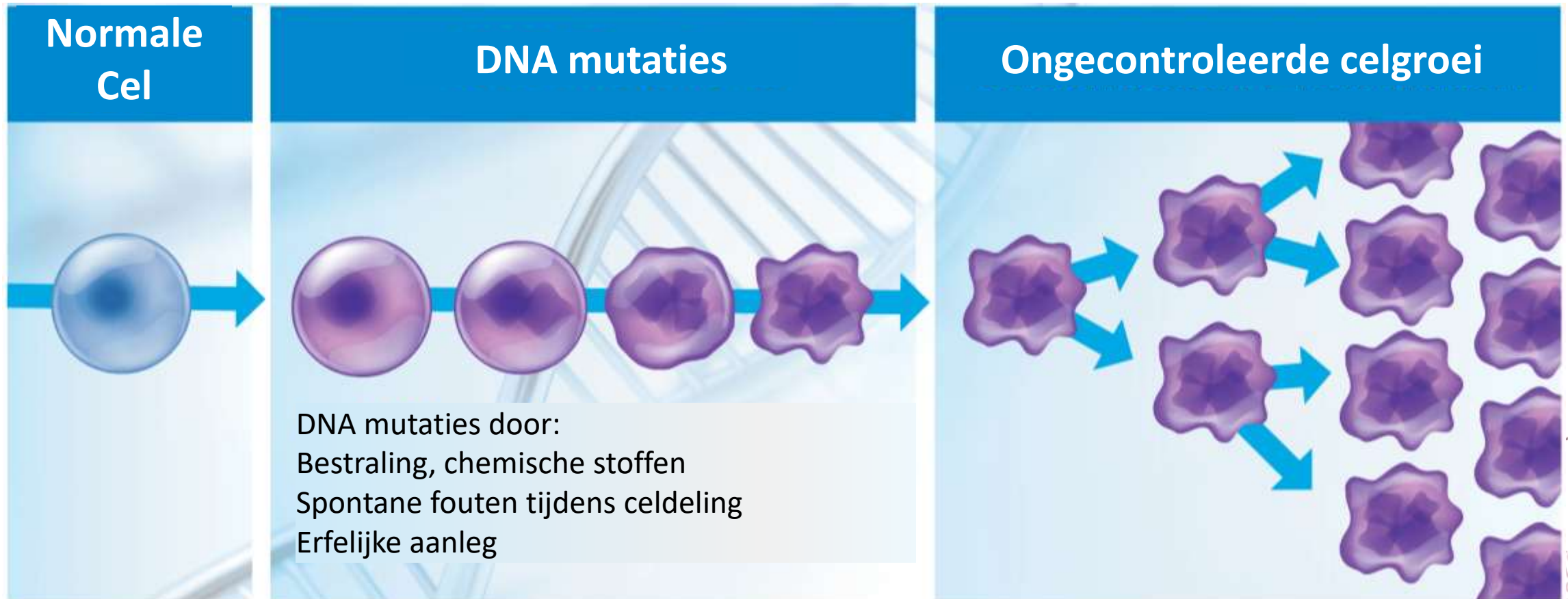
Veranderingen in de behandeling van kanker



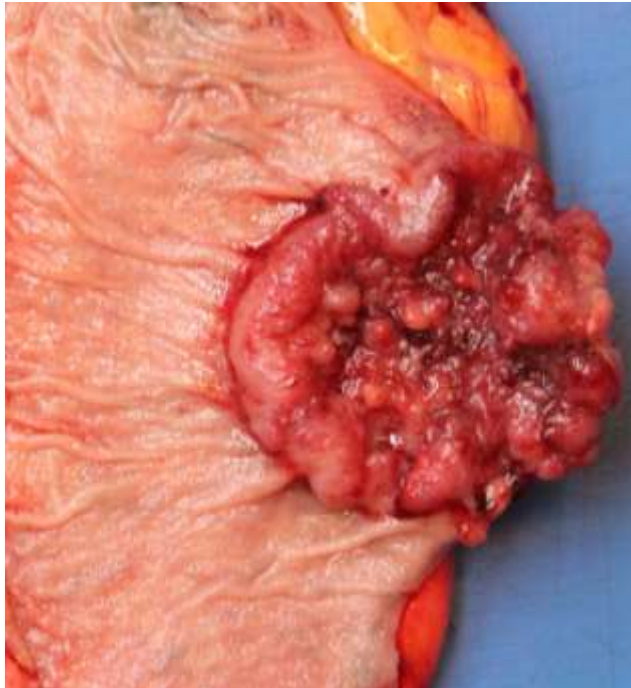
Veranderingen in de behandeling van kanker



Kanker: ongecontroleerde groei van cellen door fouten in het DNA



Ongecontroleerde groei leidt tot een tumor



darm

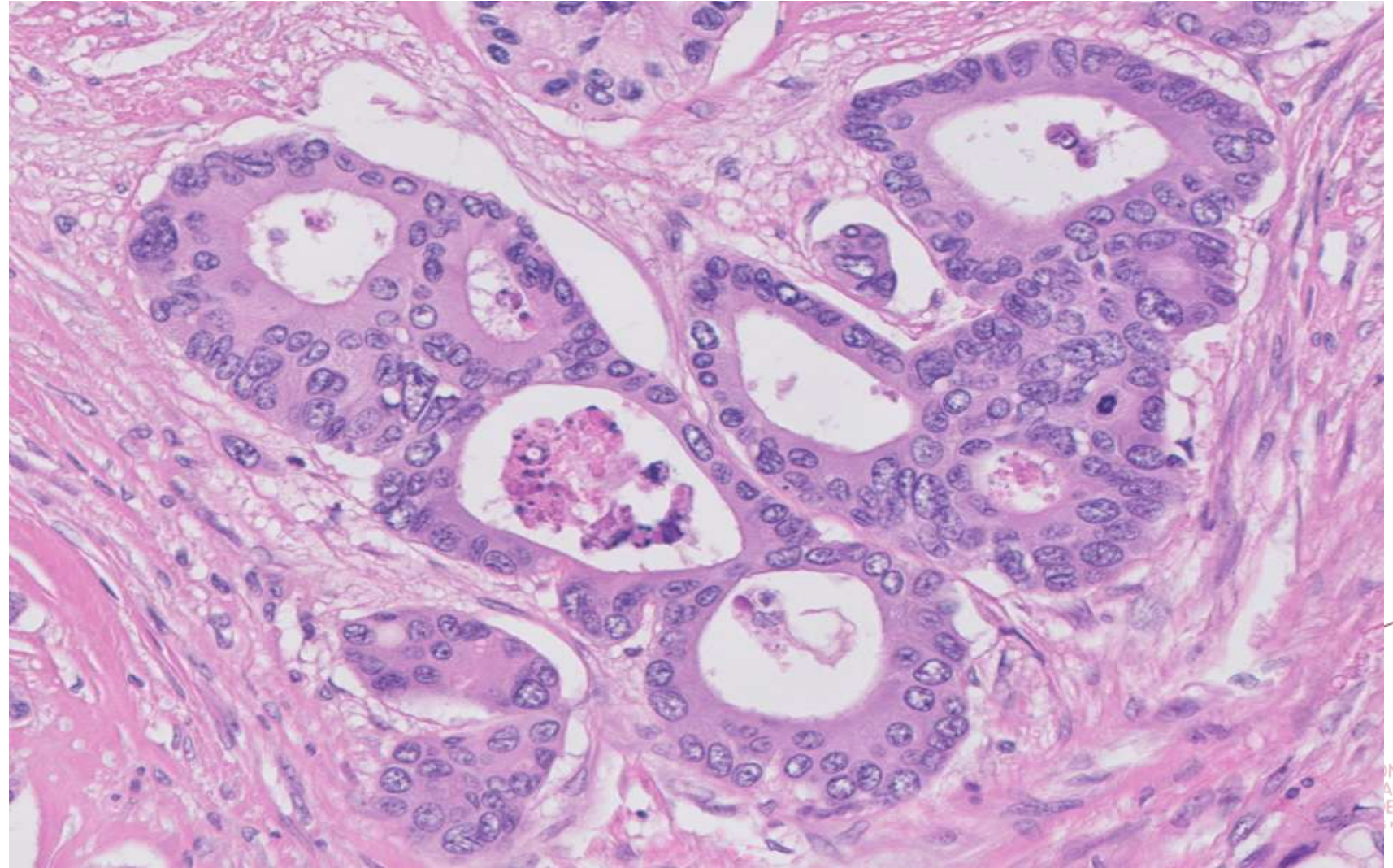
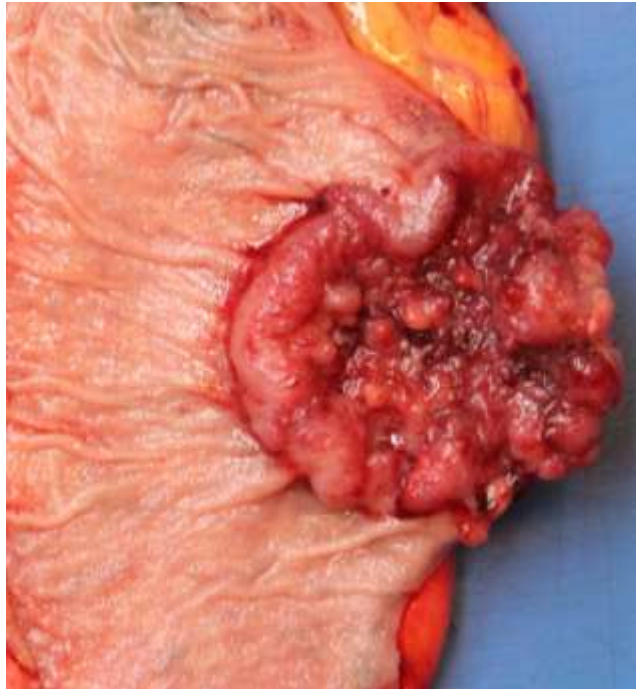


borst

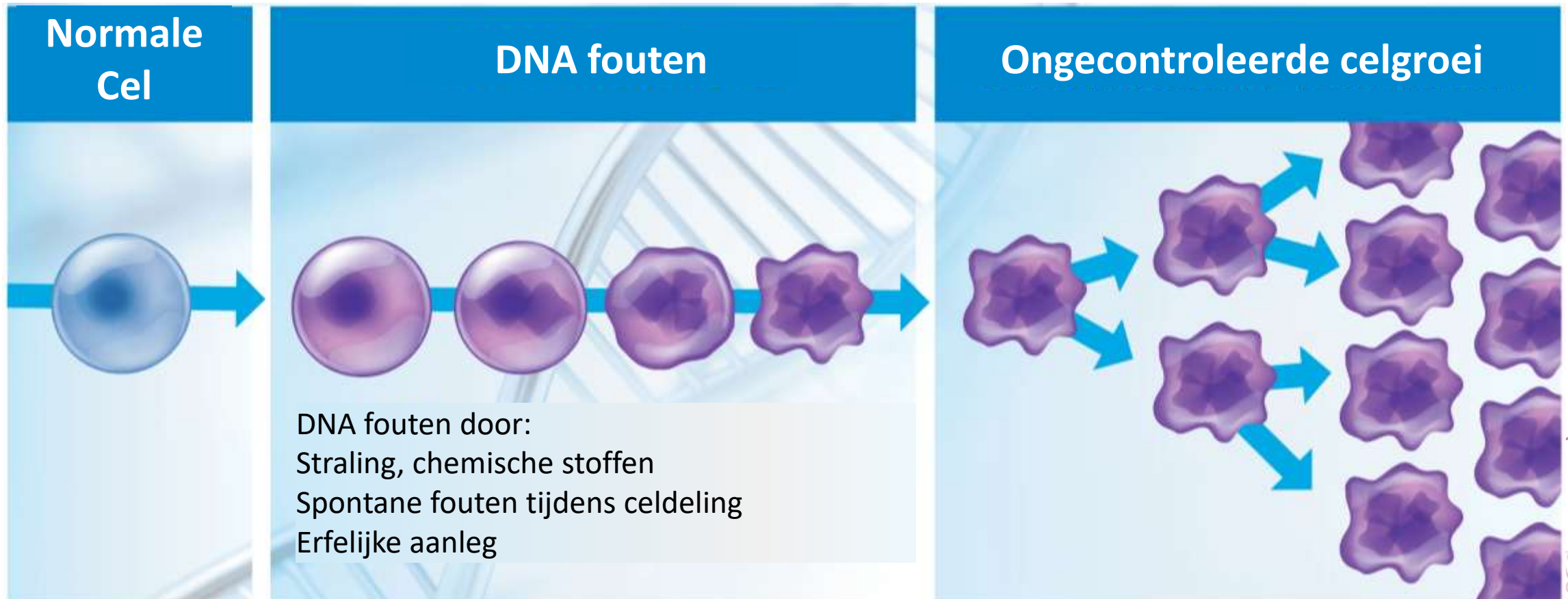


long

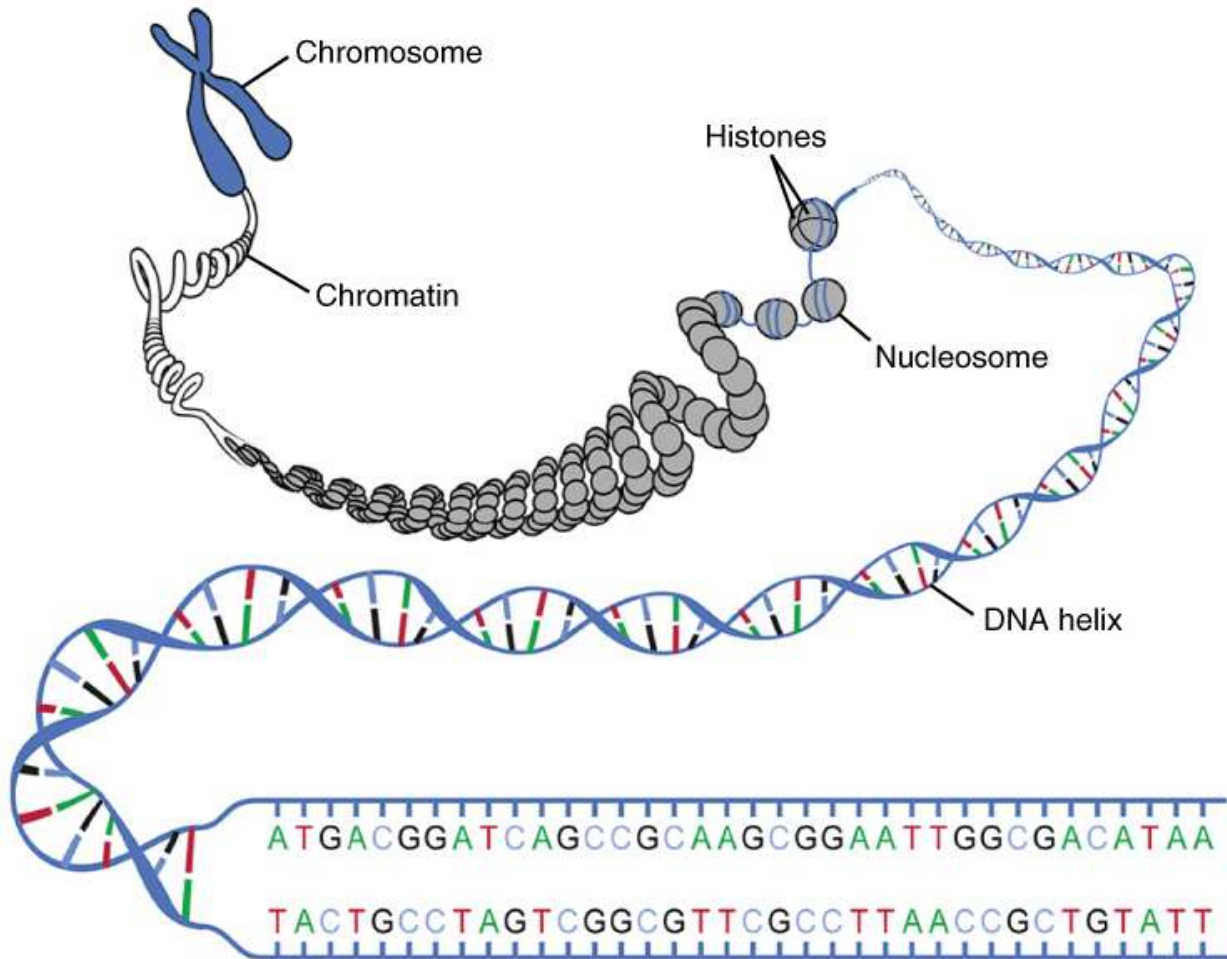
Ongecontroleerde groei leidt tot een tumor



Kanker: ongecontroleerde groei van cellen door fouten in het DNA



DNA



- DNA zit in de celkern
- 46 chromosomen (22 paar + X/Y)
- ~19,000 - 20,000 genen
- >3 miljard bouwstenen (A,C,T,G)
- 2,5 meter DNA in 1 cel

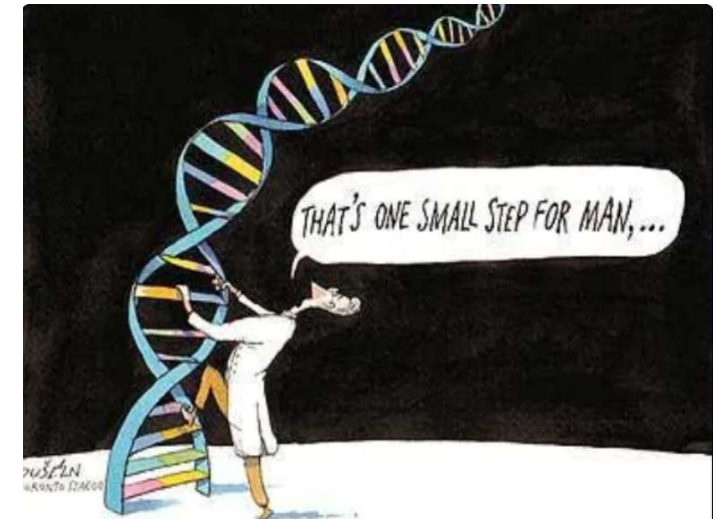
Human genome project: het hele DNA van één mens in kaart brengen

- Start 1 oktober **1990**
- 20 instituten, meer dan 2800 onderzoekers wereldwijd
- Eerste versie: februari **2001**
- Kosten: **2,7 miljard USD**

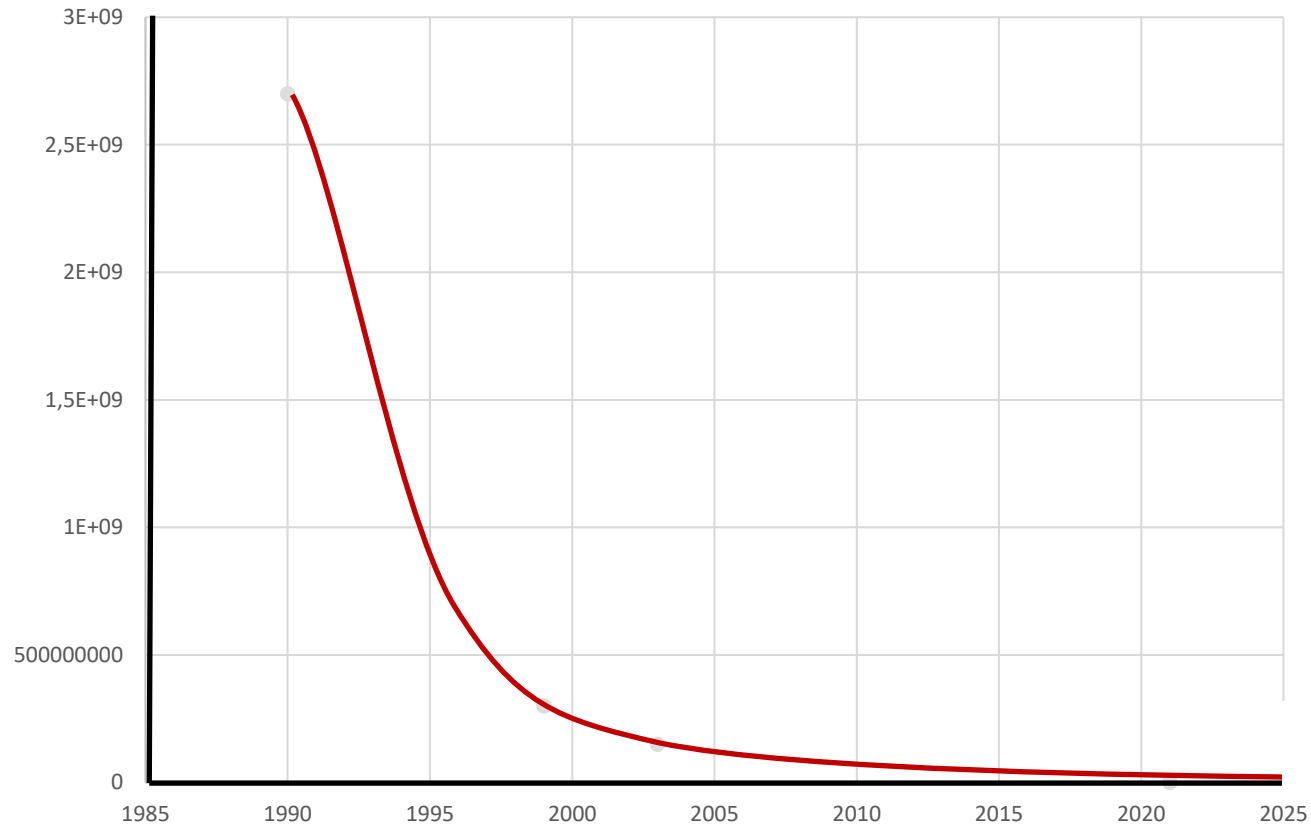


Whole genome sequencing: het hele DNA van een tumor in kaart brengen

- Sinds 2020 in het AVL in samenwerking met HMF
- Alle DNA (fouten) van een tumor in 1 keer
- Uitslag na 7 – 10 werkdagen
- De test levert een soort vingerafdruk van de tumor
 - Voorspellen van reactie op therapie
 - Informatie over ontstaanswijze van de tumor
 - Draagt bij aan kankeronderzoek
 - Mogelijkheid om neo-antigenen te identificeren/voorspellen

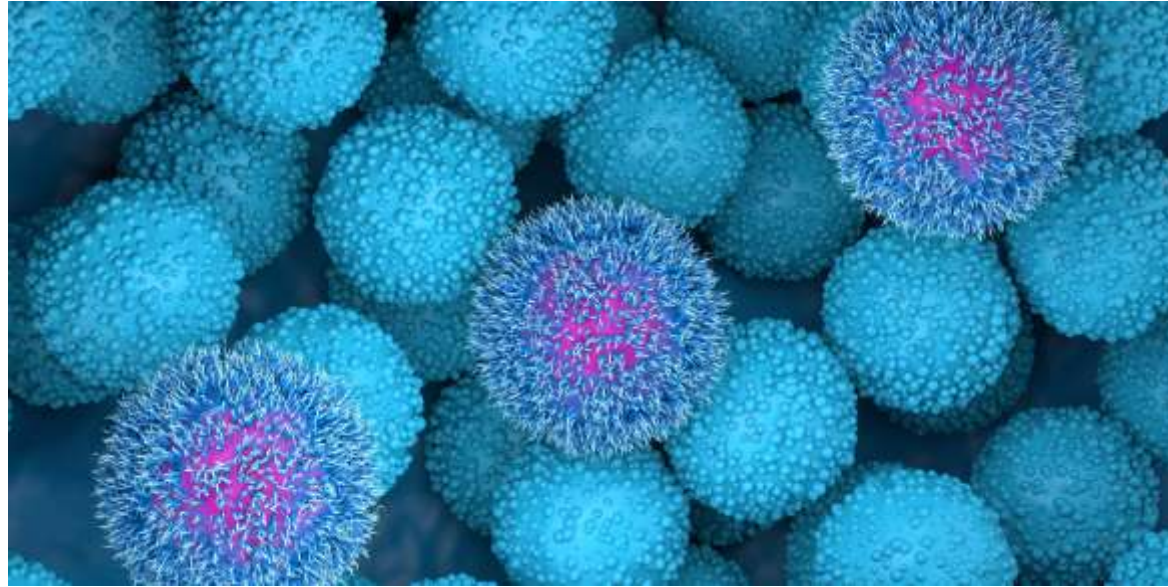
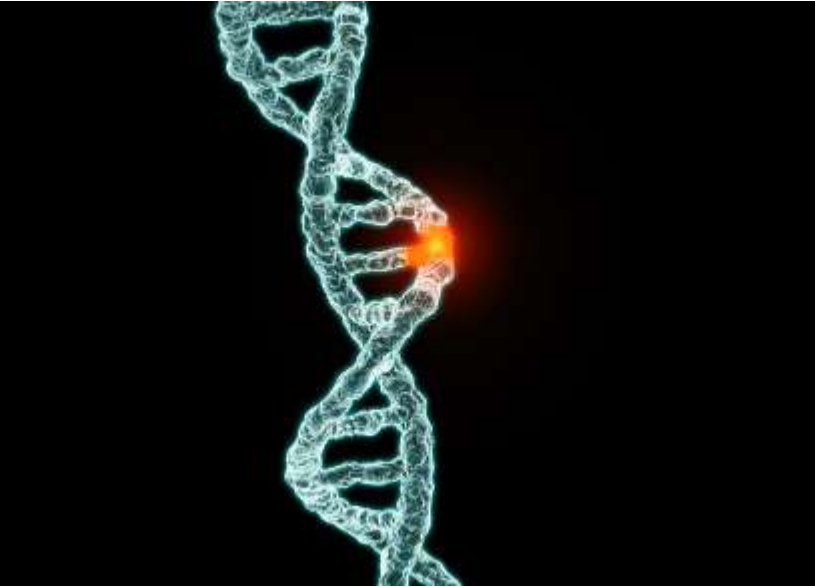


Kosten sequencing human genoom

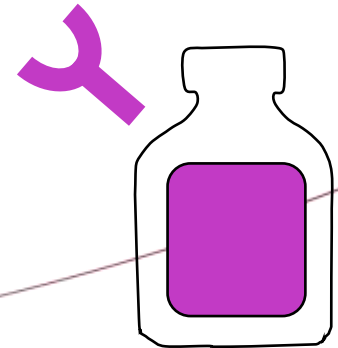
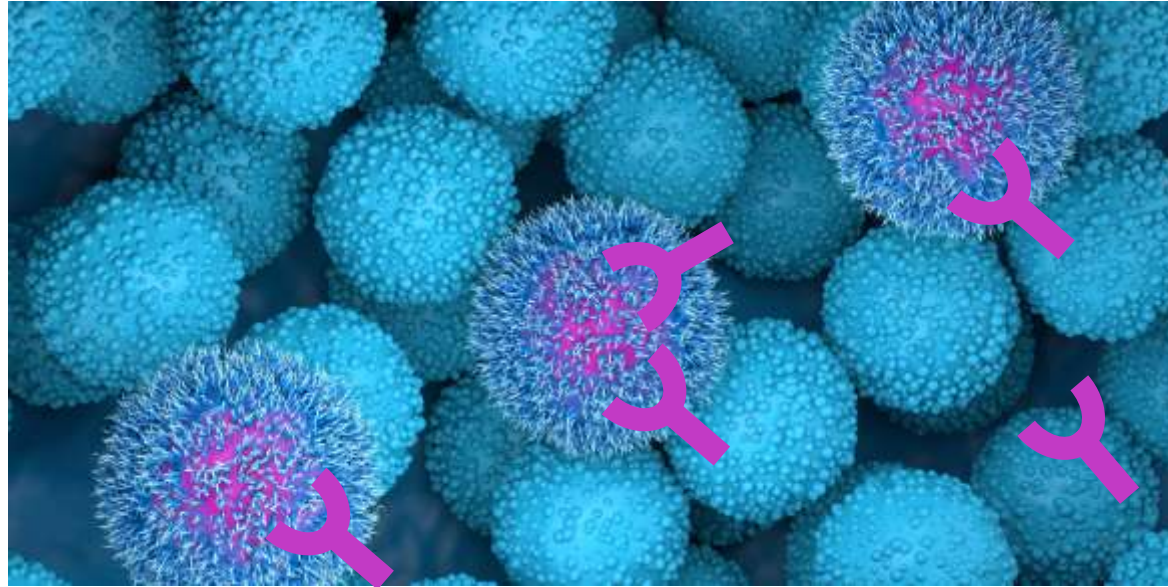
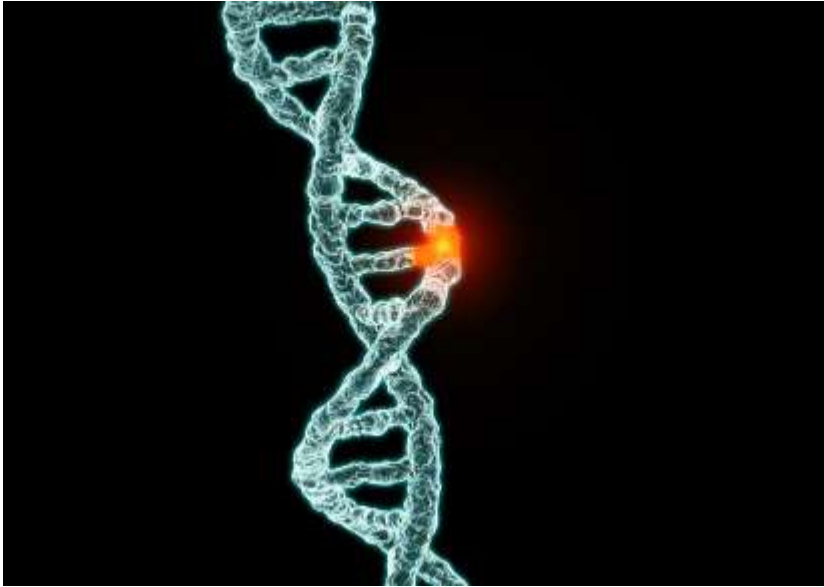


Kosten WGS anno 2025:
2400 euro

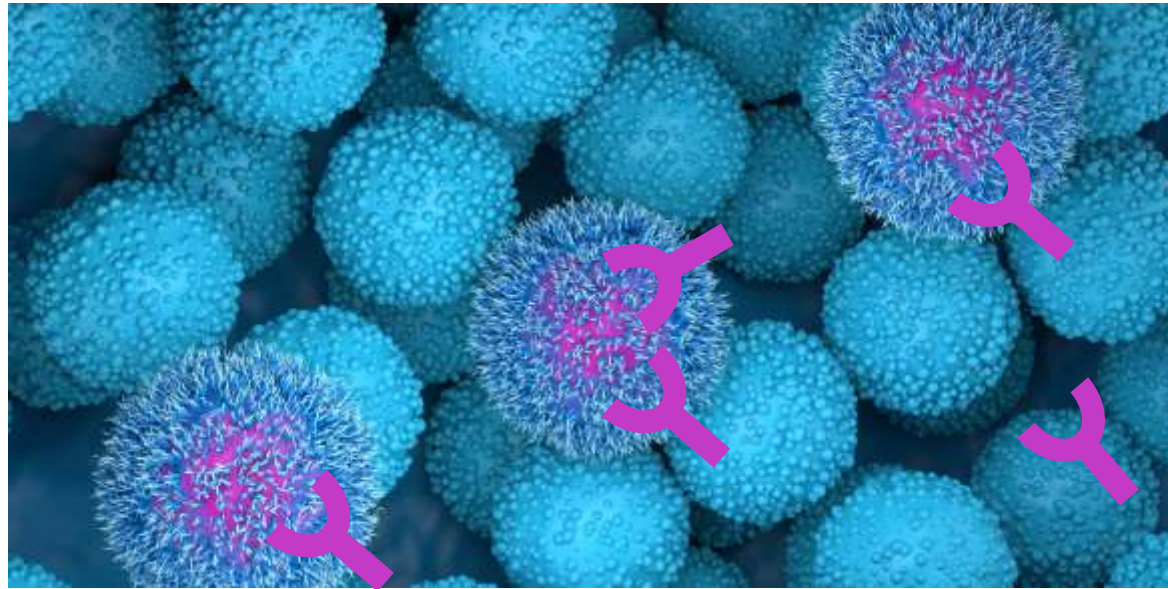
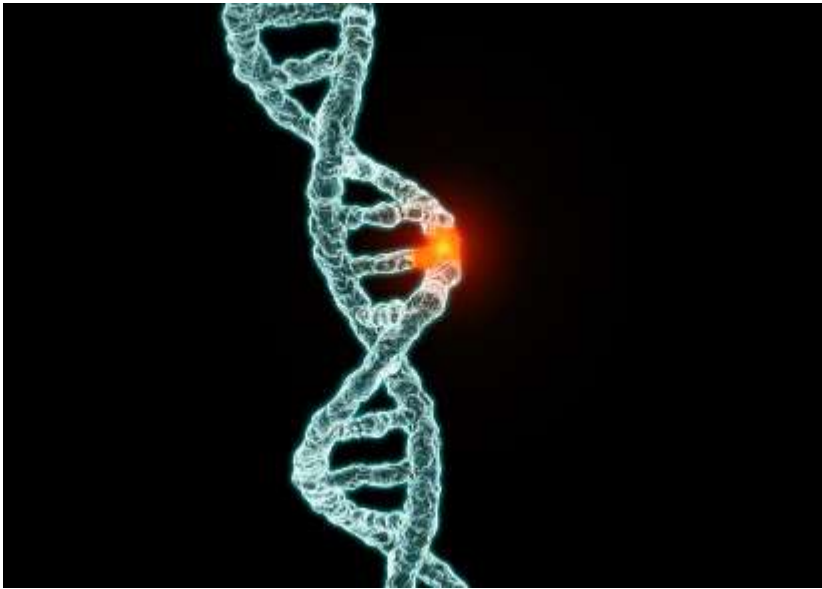
De fout in het DNA zorgt voor celgroei maar kan ook de Achilleshiel zijn van de tumor



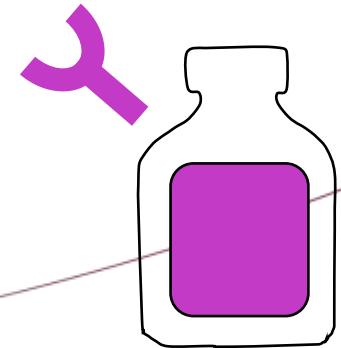
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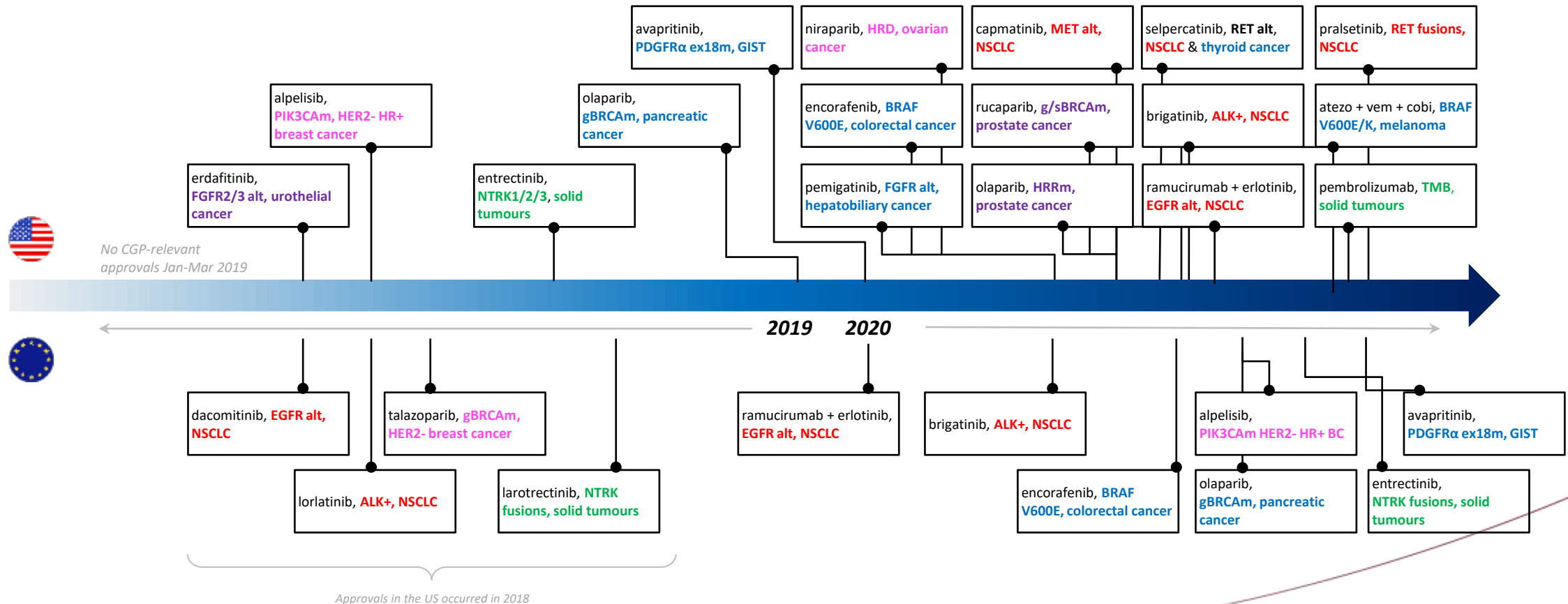


Gerichte therapie

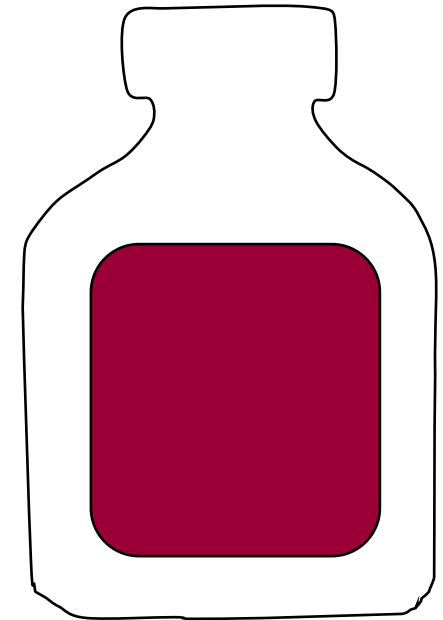
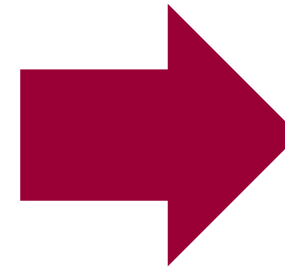
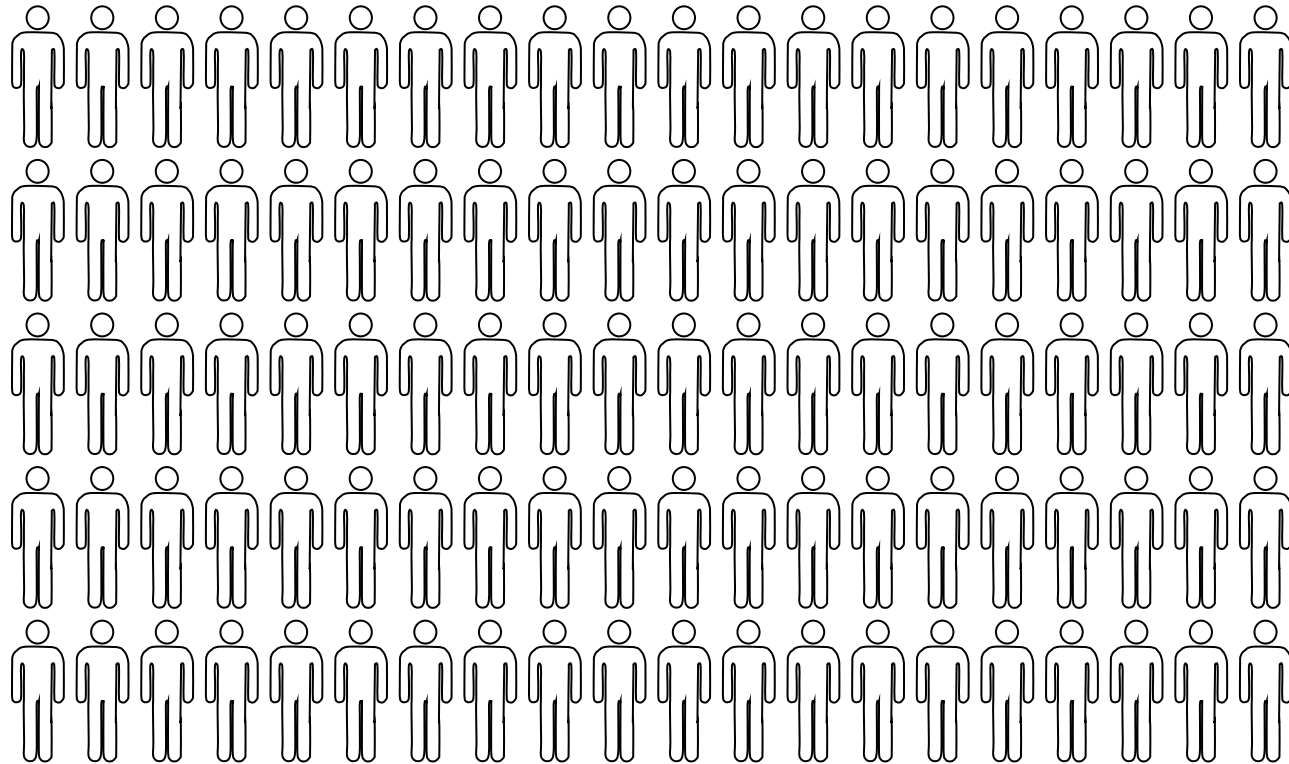


Ontwikkeling van gerichte therapie gekoppeld aan biomarkers die door moleculaire tests worden aangetoond

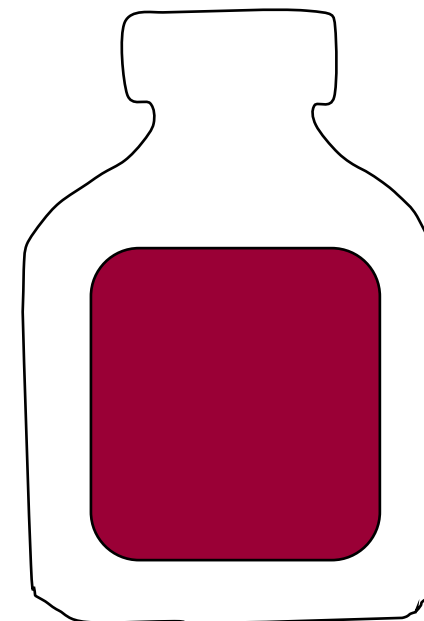
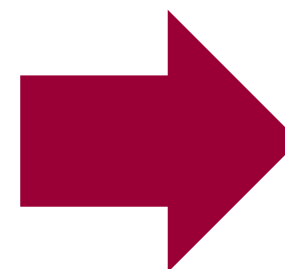
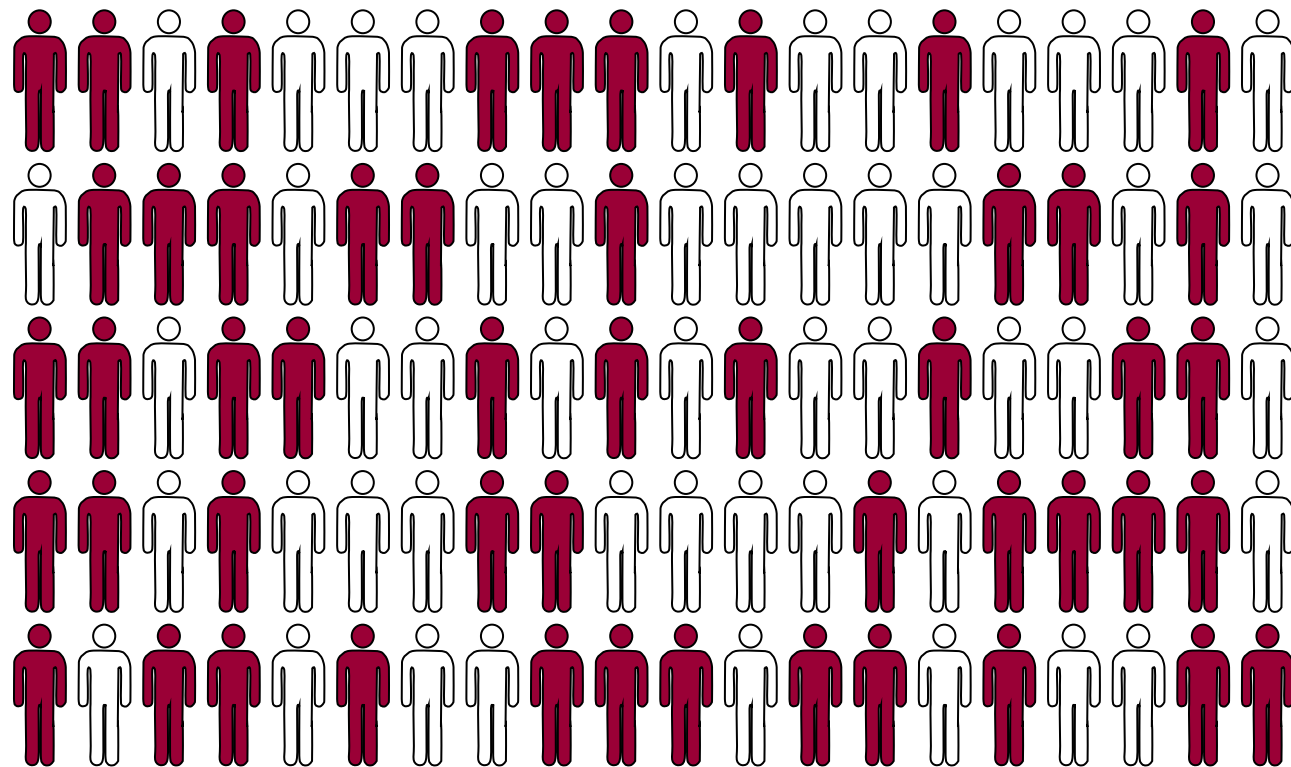
Recent Biomarker-Specific Solid Tumour Approvals



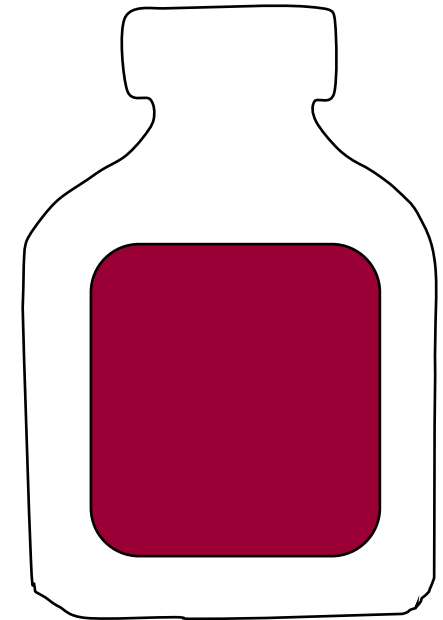
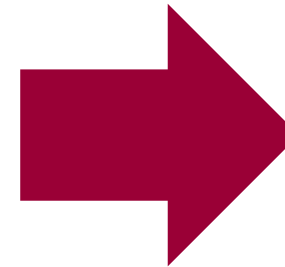
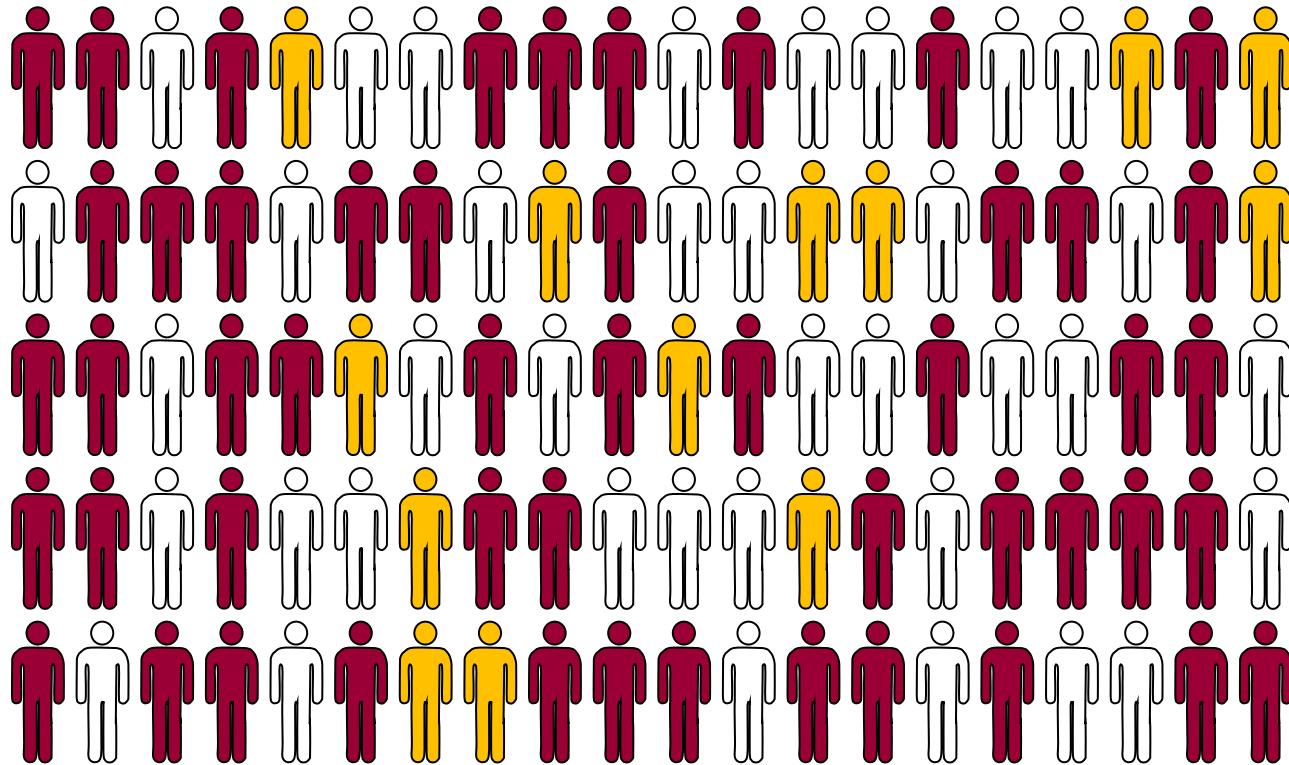
Behandeling op maat



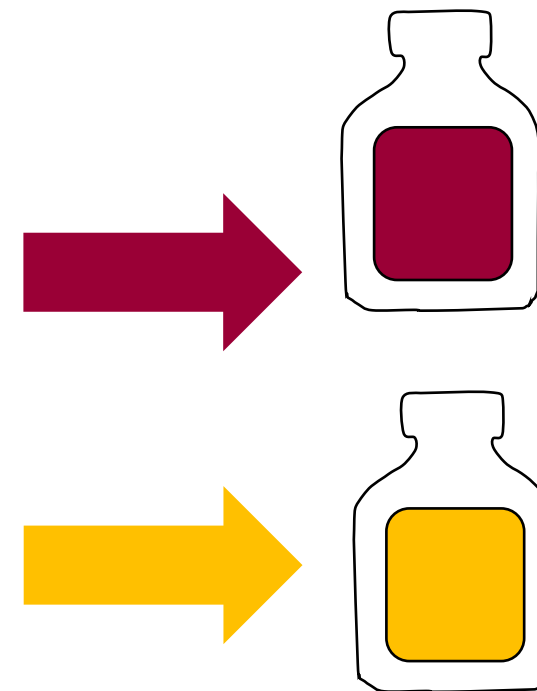
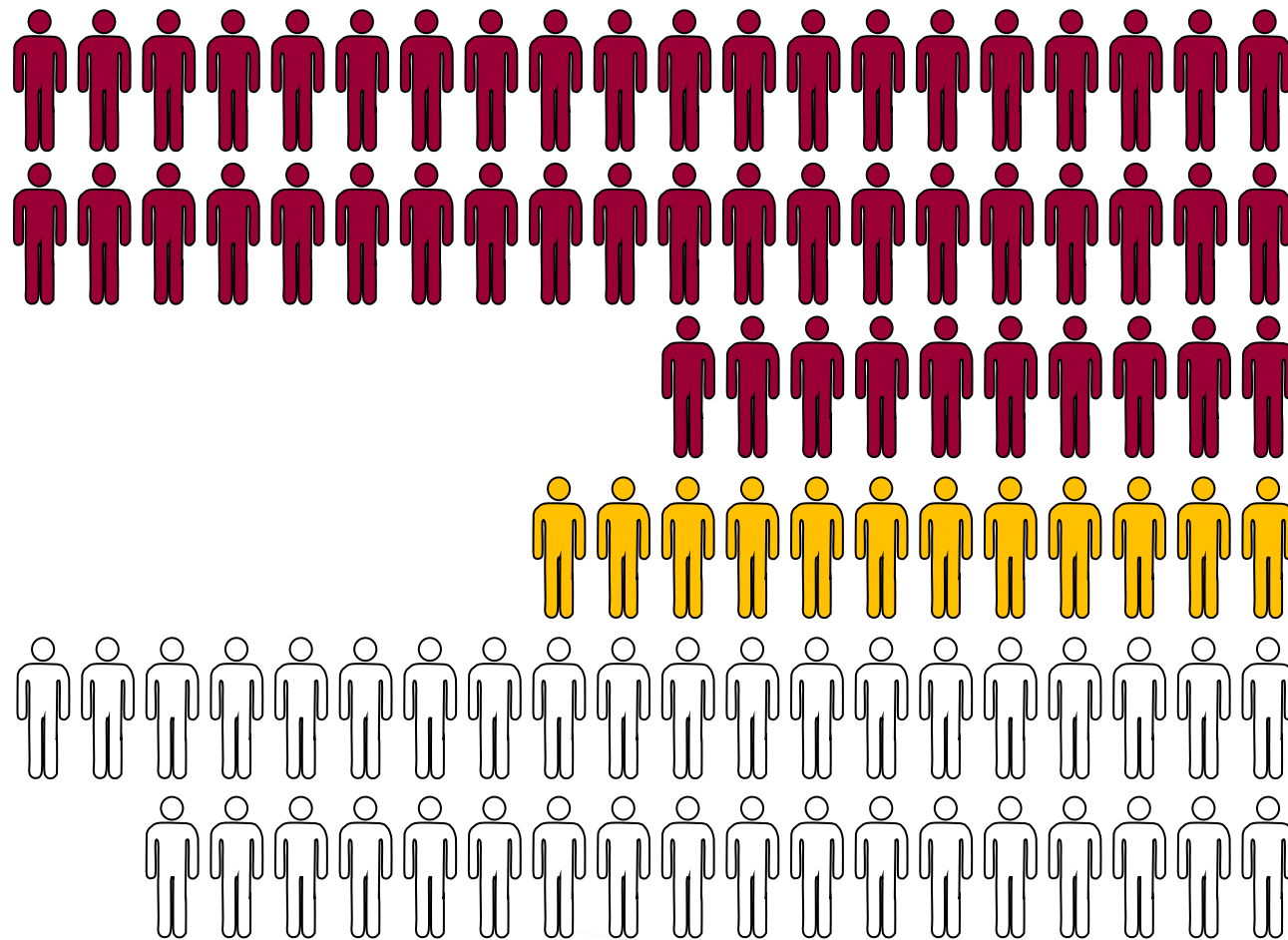
Behandeling op maat



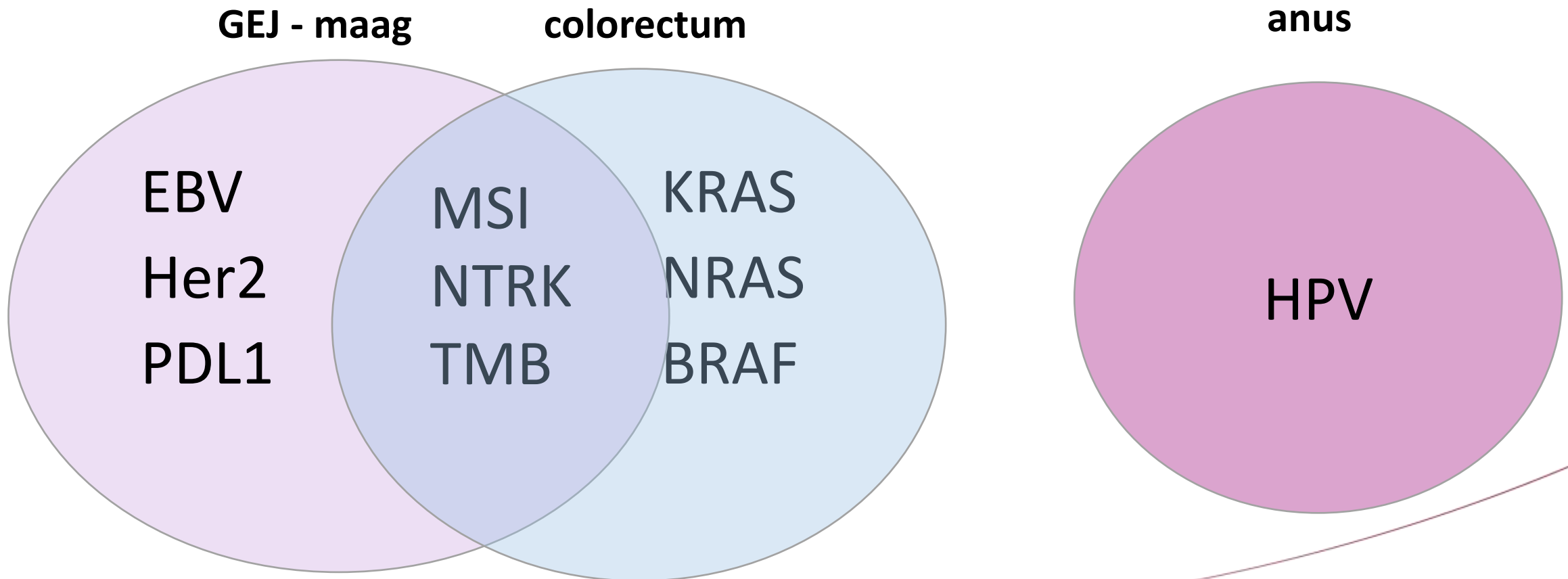
Behandeling op maat



Behandeling op maat



PA biomarkers bij carcinoom in de tractus digestivus



MSI – microsatellite instabiliteit

Waarom belangrijk?

MSI – microsatellite instabiliteit

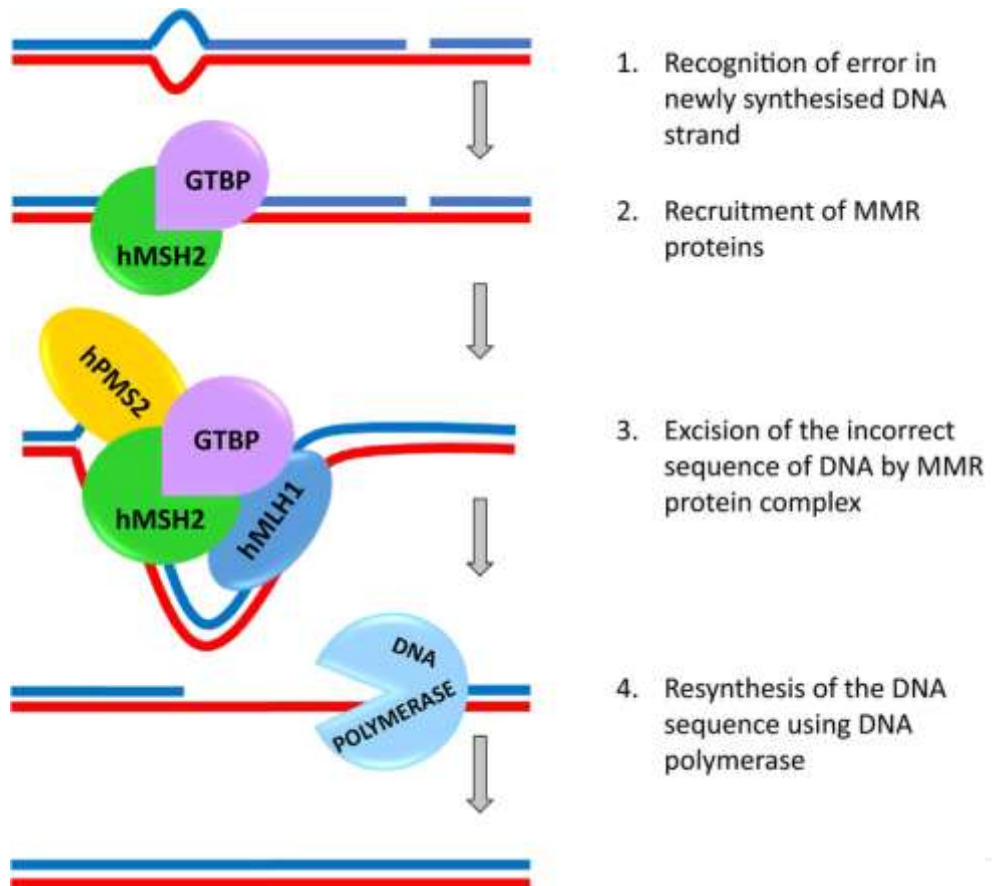
Waarom belangrijk?

- Lynch syndroom – erfelijke aanleg voor kanker
- Biomarker voor respons op immuuntherapie

MSI- Microsatelliet instabiliteit

Mismatch repair eiwit (MMR)

Corrigeert fouten van DNA polymerase



Defect in 1 van de
4 MMR eiwitten



Fouten van DNA polymerase
worden niet hersteld



Hypergemuteerde tumor:

- accumulatie van mutaties in tumor suppressor genen en oncogenen

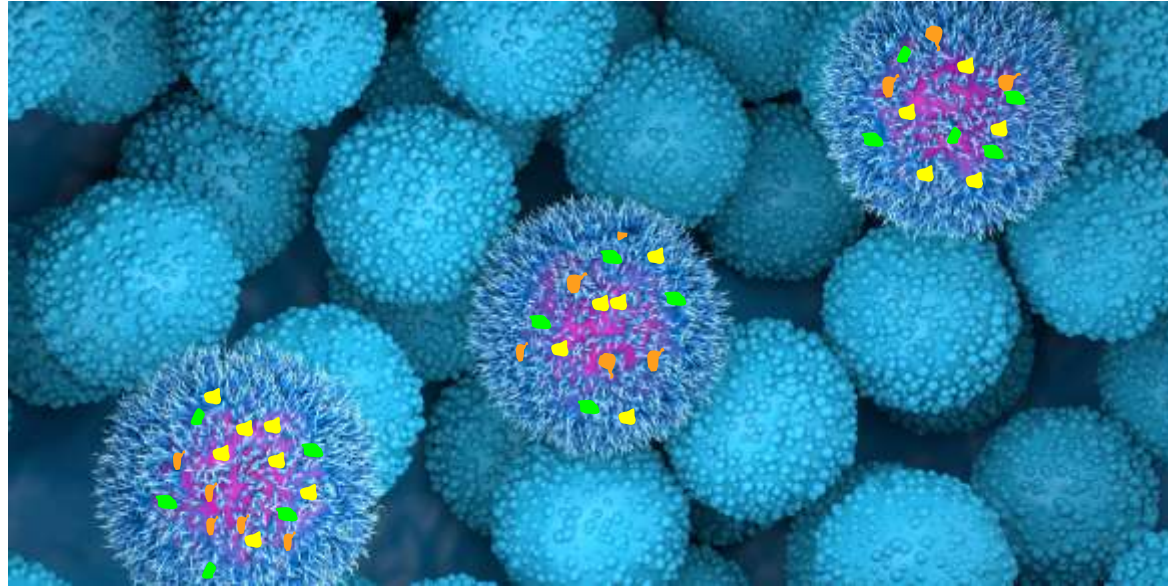
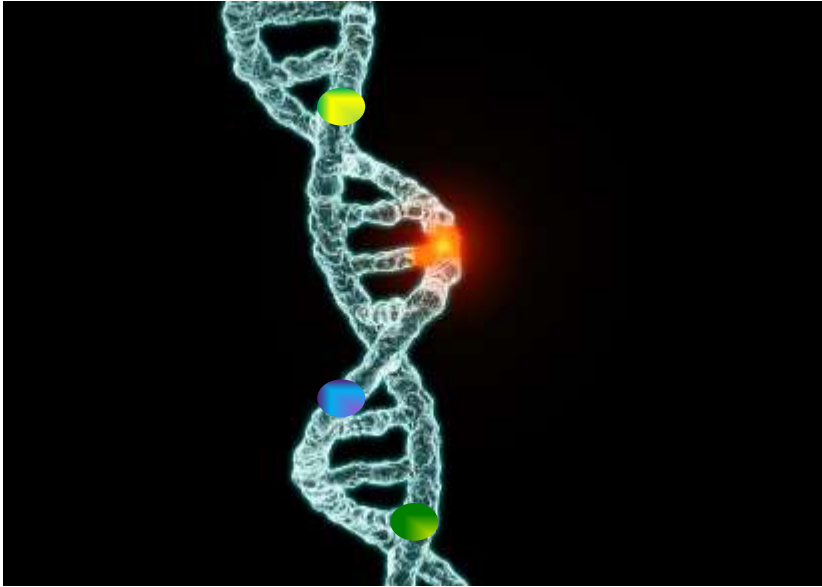
- **Microsatelliet instabiliteit**

MSI – microsatellite instabiliteit

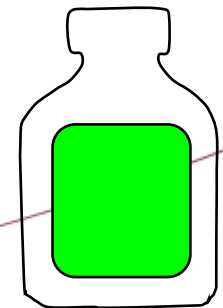
Waarom belangrijk?

- Lynch syndroom – erfelijke aanleg voor kanker
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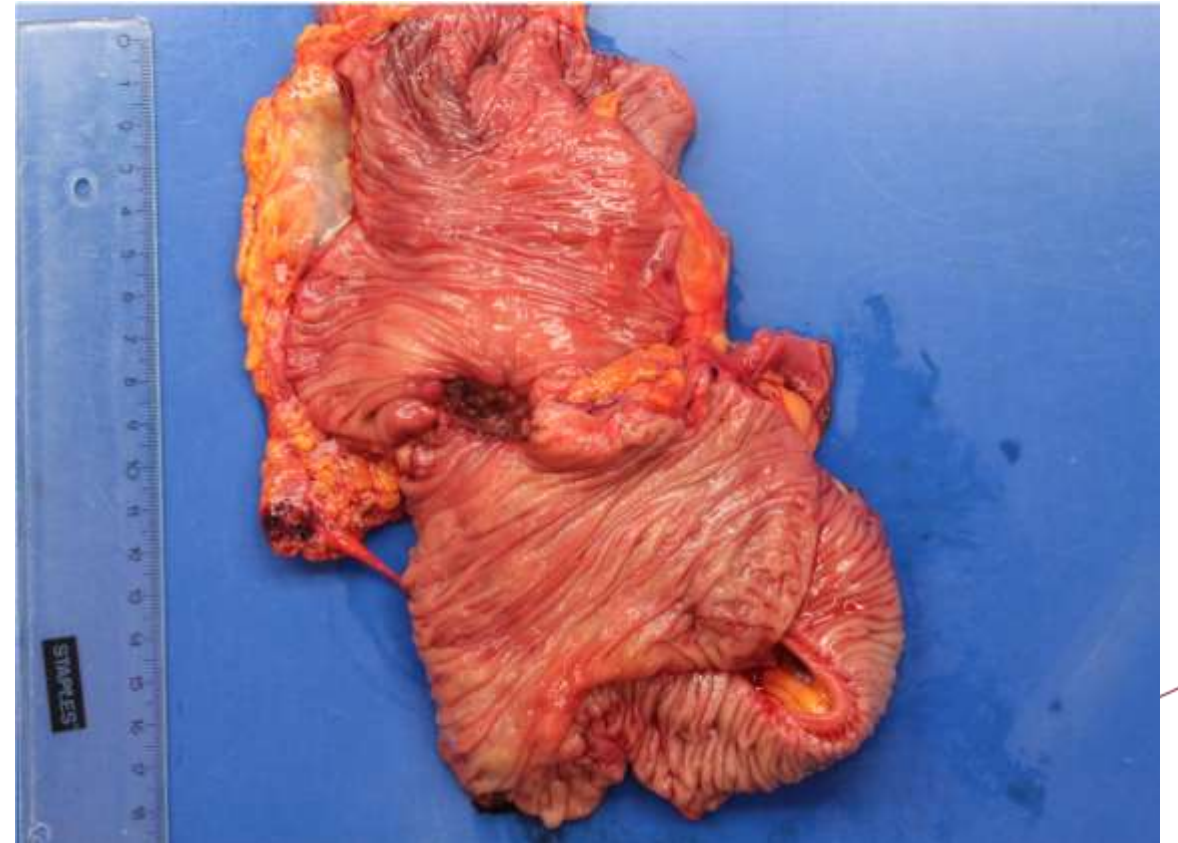
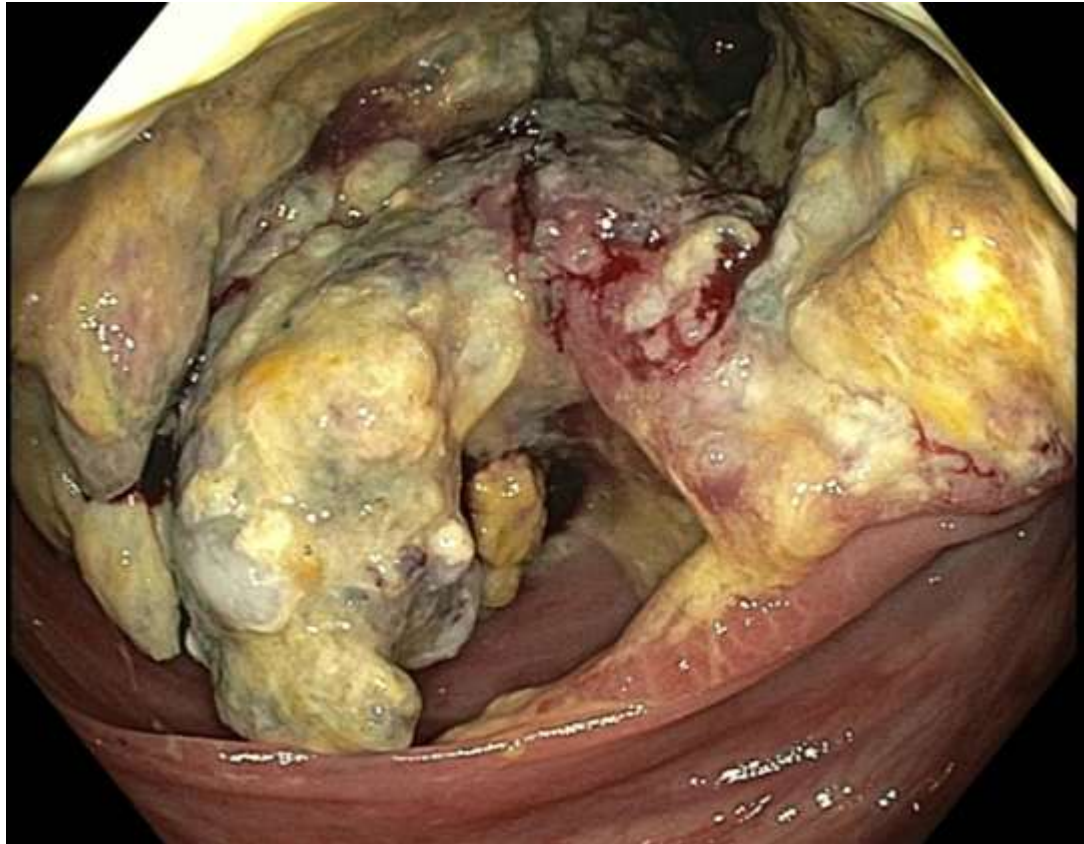
Veel fouten maken een tumor gevoelig voor immuuntherapie

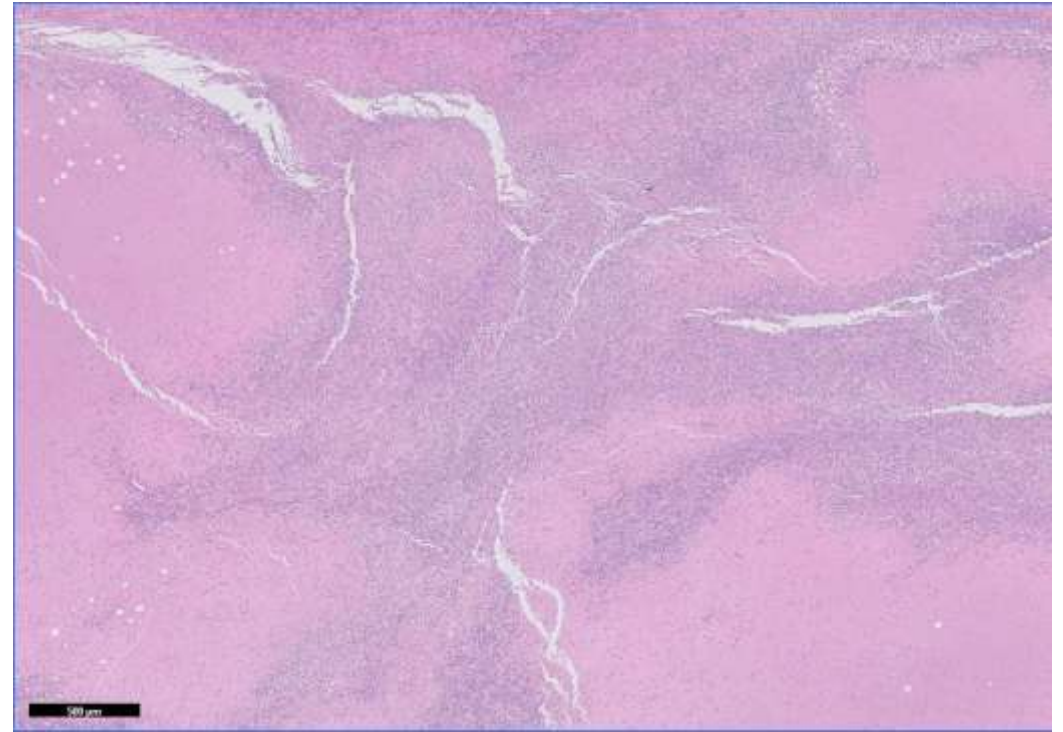
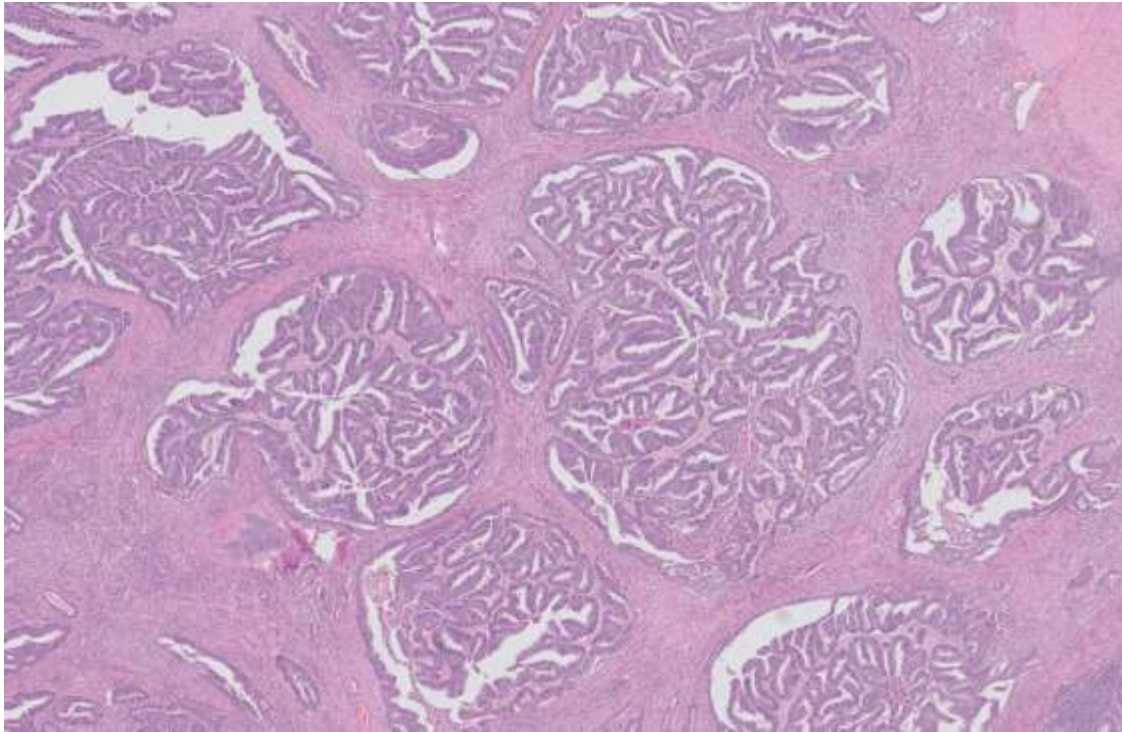


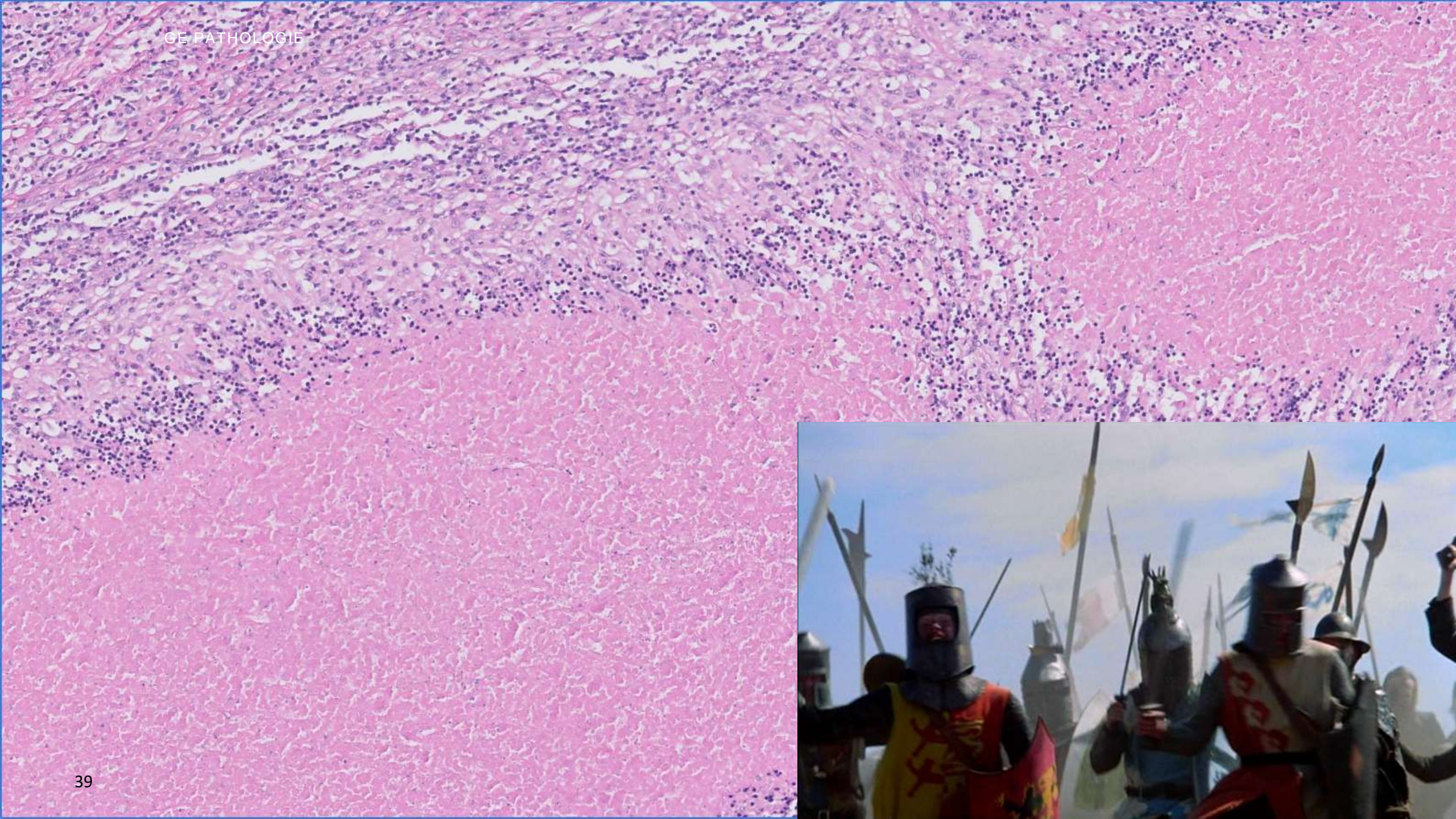
immuuntherapie



Coloncarcinoom na immuuntherapie – NICHE trial







MSI als een predictieve biomarker

ARTICLES

<https://doi.org/10.1038/s41591-020-0805-8>

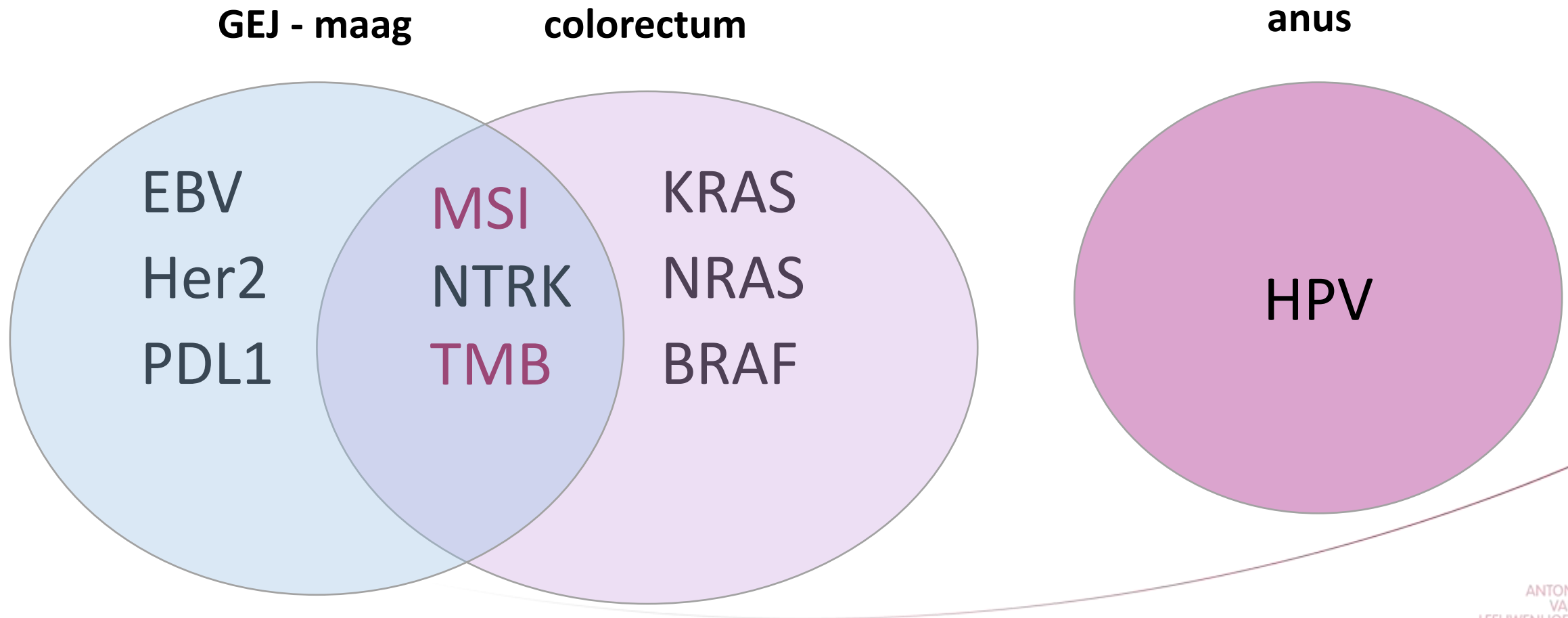
nature
medicine
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Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi^{1,2,3}, Lorenzo F. Fanchi^{2,4,17}, Krijn K. Dijkstra^{2,4,17}, José G. Van den Berg^{5,17}, Arend G. Aalbers⁶, Karolina Sikorska⁷, Marta Lopez-Yurda^{7,8}, Cecile Grootsholten¹, Geerard L. Beets^{6,9}, Petur Snaebjornsson⁵, Monique Maas¹⁰, Marjolijn Mertz¹¹, Vivien Veninga^{2,4}, Gergana Bounova^{4,12}, Annegien Broeks¹³, Regina G. Beets-Tan^{9,10}, Thomas R. de Wijkerslooth¹, Anja U. van Lent¹⁴, Hendrik A. Marsman¹⁵, Elvira Nuijten⁷, Niels F. Kok⁶, Maria Kuiper¹, Wieke H. Verbeek¹, Marleen Kok^{3,16}, Monique E. Van Leerdam¹, Ton N. Schumacher^{2,4}, Emile E. Voest^{1,2,4,17} and John B. Haanen^{2,3,17}

PD-1 plus CTLA-4 blockade is highly effective in advanced-stage, mismatch repair (MMR)-deficient (dMMR) colorectal cancers, yet not in MMR-proficient (pMMR) tumors. We postulated a higher efficacy of neoadjuvant immunotherapy in early-stage colon cancers. In the exploratory NICHE study (ClinicalTrials.gov: NCT03026140), patients with dMMR or pMMR tumors received a single dose of ipilimumab and two doses of nivolumab before surgery, the pMMR group with or without celecoxib. The primary objective was safety and feasibility; 40 patients with 21 dMMR and 20 pMMR tumors were treated, and 3 patients received nivolumab monotherapy in the safety run-in. Treatment was well tolerated and all patients underwent radical resections without delays, meeting the primary endpoint. Of the patients who received ipilimumab + nivolumab (20 dMMR and 15 pMMR tumors), 35 were evaluable for efficacy and translational endpoints. Pathological response was observed in 20/20 (100%; 95% exact confidence interval (CI): 86–100%) dMMR tumors, with 19 major pathological responses (MPRs, $\leq 10\%$ residual viable tumor) and 12 pathological complete responses. In pMMR tumors, 4/15 (27%; 95% exact CI: 8–55%) showed pathological responses, with 3 MPRs and 1 partial response. CD8⁺PD-1⁺ T cell infiltration was predictive of response in pMMR tumors. These data indicate that neoadjuvant immunotherapy may have the potential to become the standard of care for a defined group of colon cancer patients when validated in larger studies with at least 3 years of disease-free survival data.

PA biomarkers bij carcinoom in de tractus digestivus



Virussen en kanker

THE JOURNAL OF EXPERIMENTAL MEDICINE V OL. XII.

PLATE LXVI.



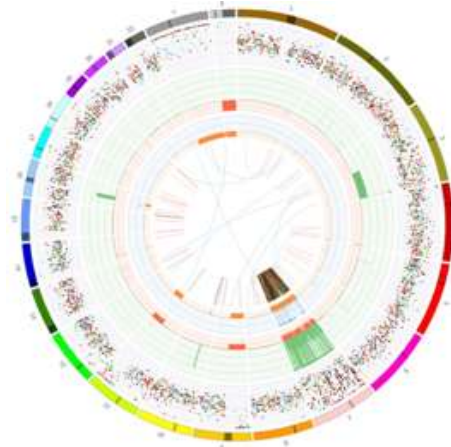
FIG. 1.

A photo of the original hen from Rous' study and her tumor. Sadly she was unnamed.

WGS genereert nog veel meer informatie

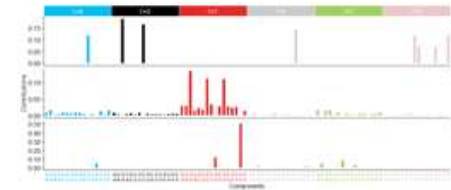


To inform medical specialists on clinical actionability and relevance for cancer patients

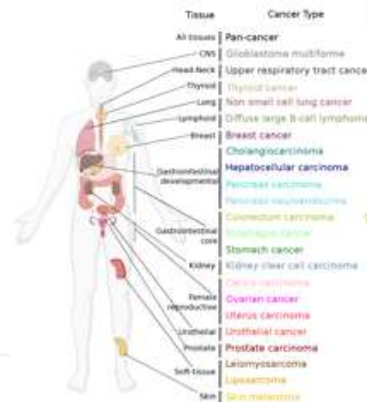


- Cancer drivers from genome-wide variant calling
- small and structural variants
 - purity and ploidy
 - bi-allelic, subclonal, driver vs passenger
 - optimized for diagnostic cancer genes

- Complex biomarkers
- DNA repair status (MSI, HRD)
 - mutational signatures



Viral presence 



Tissue	Cancer Type
All tissues	Pan-cancer
Brain	Glioblastoma multiforme
Head/neck	Upper respiratory tract cancer
Thyroid	Thyroid cancer
Lung	Non-small cell lung cancer
Lymphoid	Diffuse large B-cell lymphoma
Breast	Breast cancer
Cholangiohepatic development	Cholangiocarcinoma
Hepatobiliary development	Hepatocellular carcinoma
Peritoneal development	Peritoneal carcinoma
Neuroectodermal development	Neuroblastoma
Gastrointestinal core	Colorectal carcinoma
Stomach	Gastric cancer
Kidney	Kidney clear cell carcinoma
Female reproductive	Ovarian cancer
Uterus	Uterine carcinoma
Prostate	Prostate carcinoma
Soft tissue	Liposarcoma
Skin	Skin melanoma

Tissue of origin and Tumor (sub)typing



Germline information

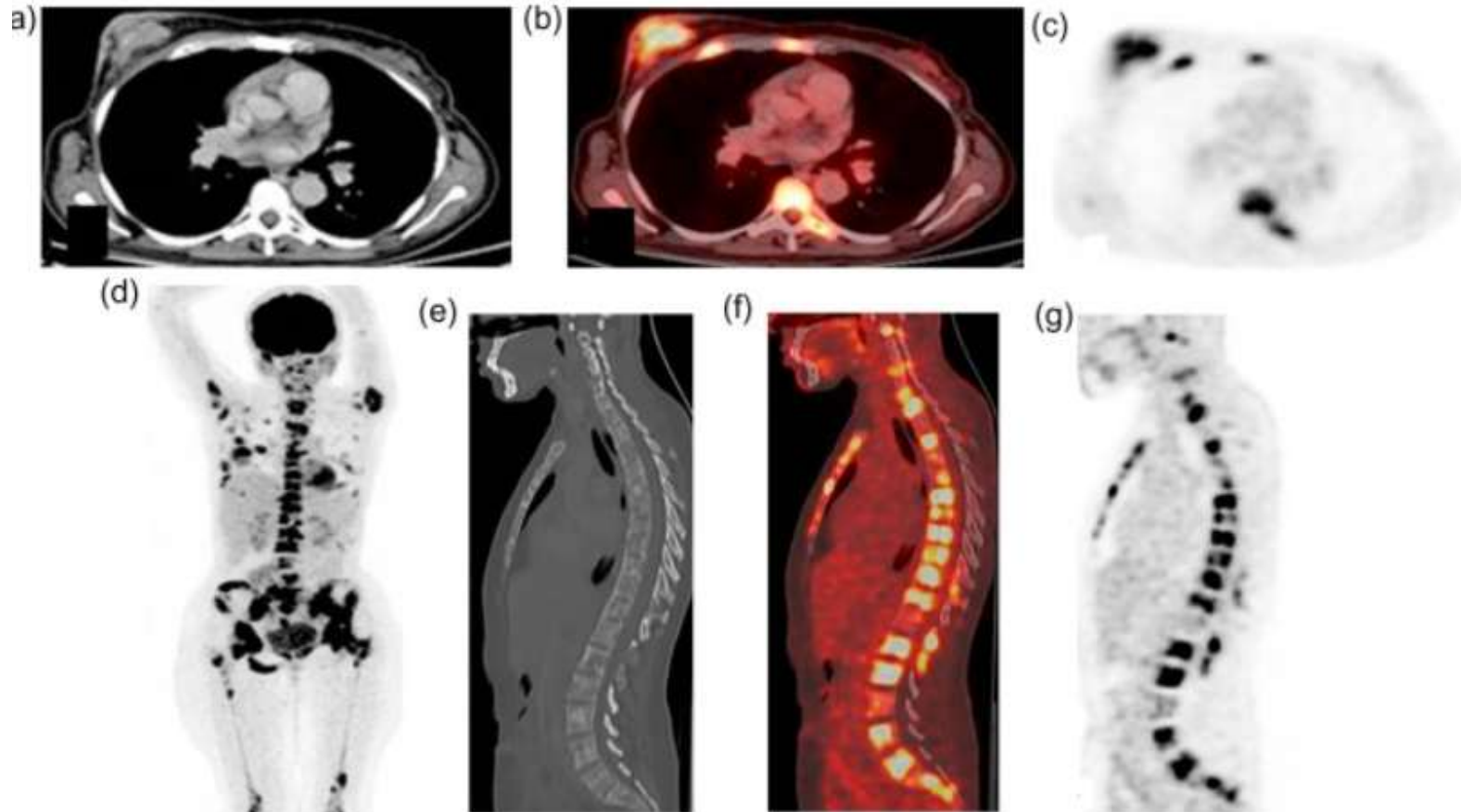
- cancer predisposition
- pharmacogenetics



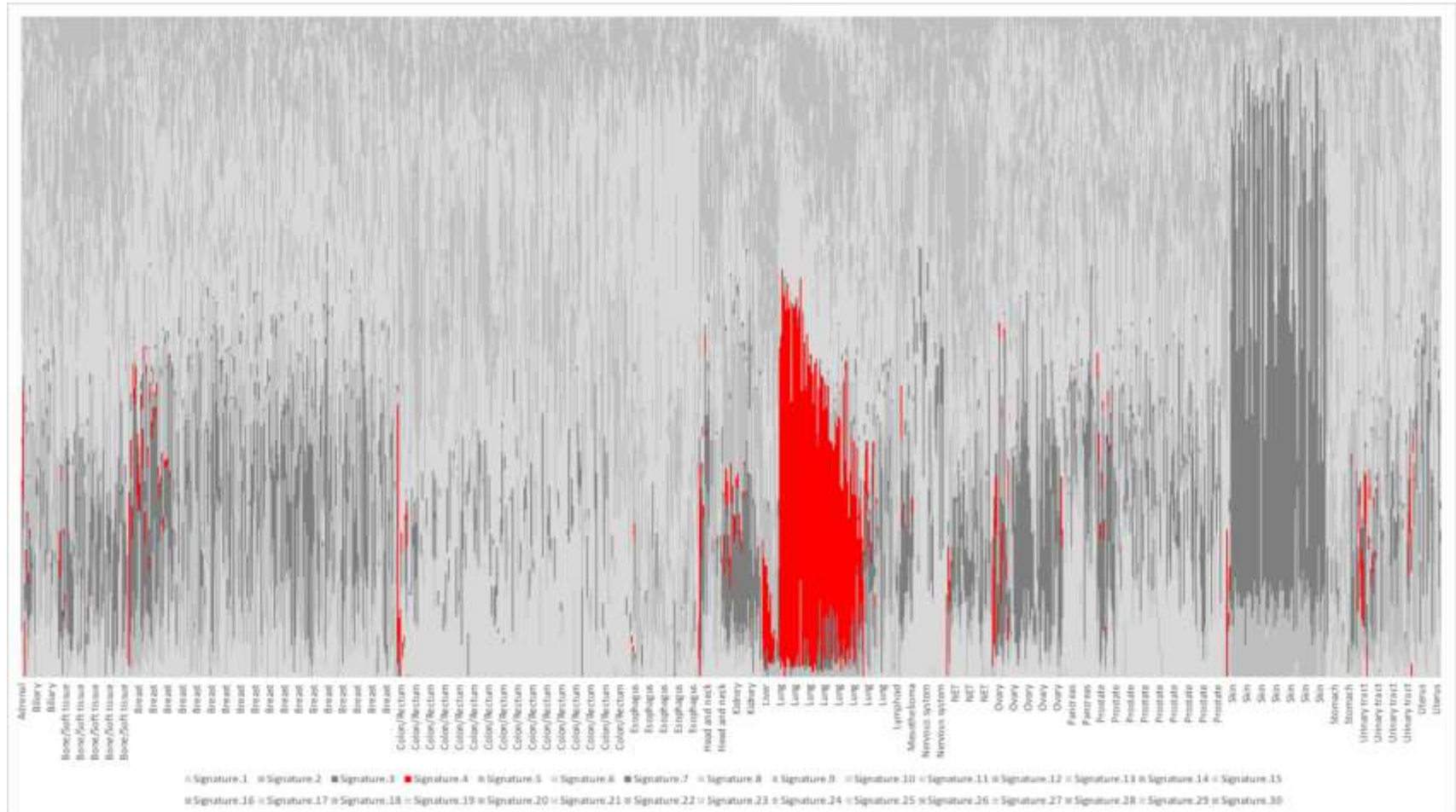
HLA typing and neopeptides

- immunotherapy
- vaccination

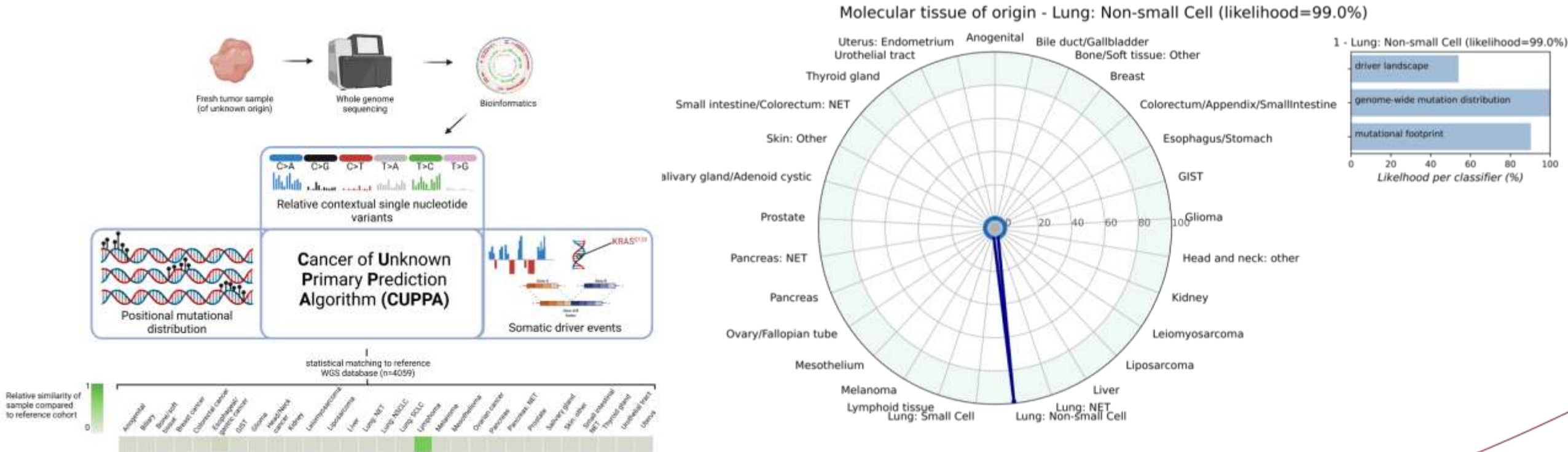
Primaire tumor onbekend

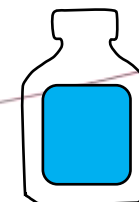
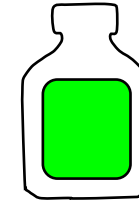
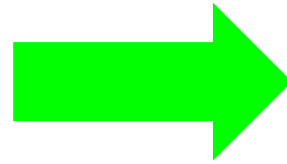
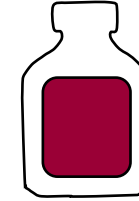
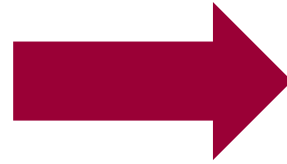
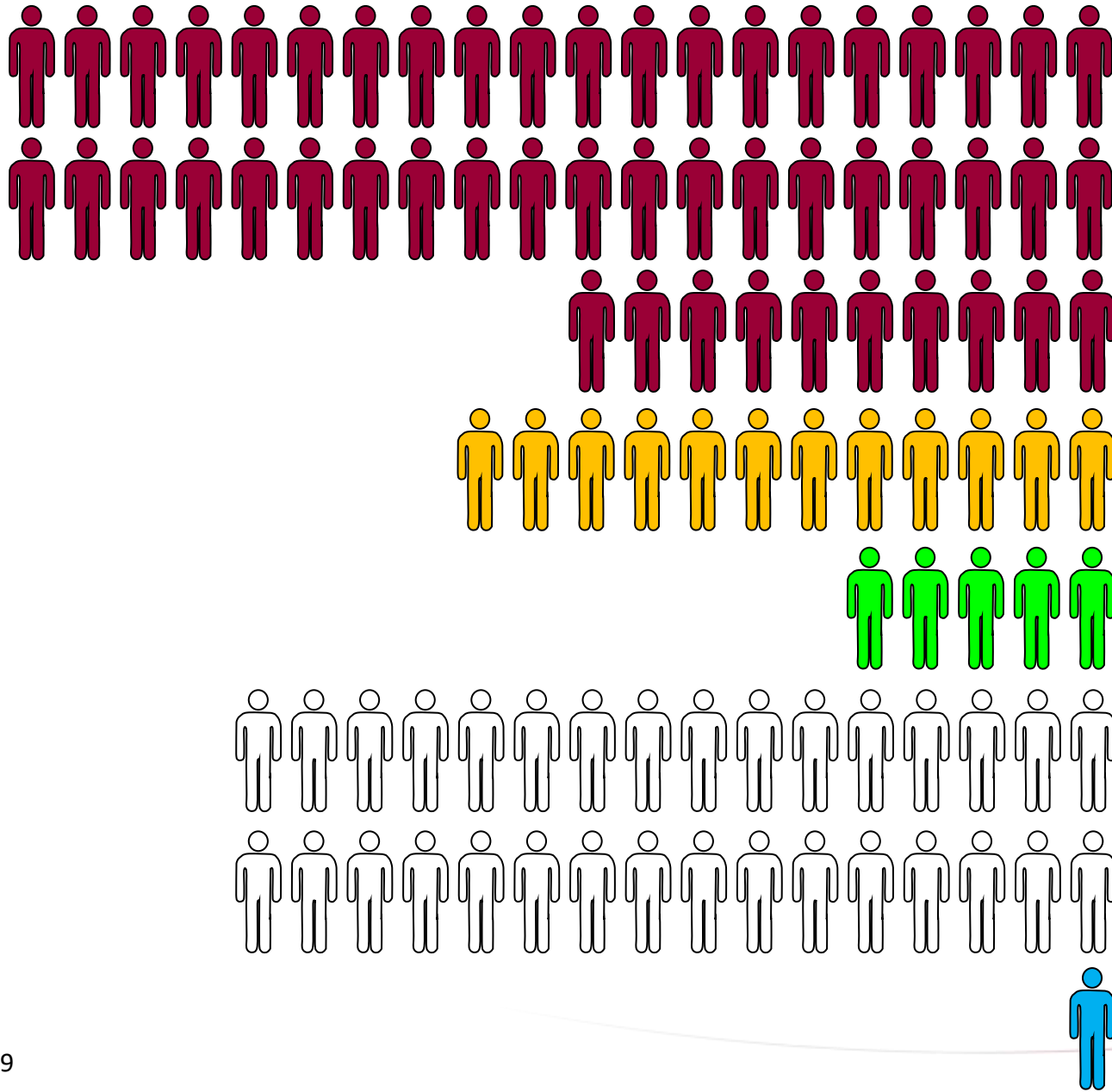


Met behulp van WGS en computertechnologie kunnen we **aanwijzen** wat de **primaire tumor** is

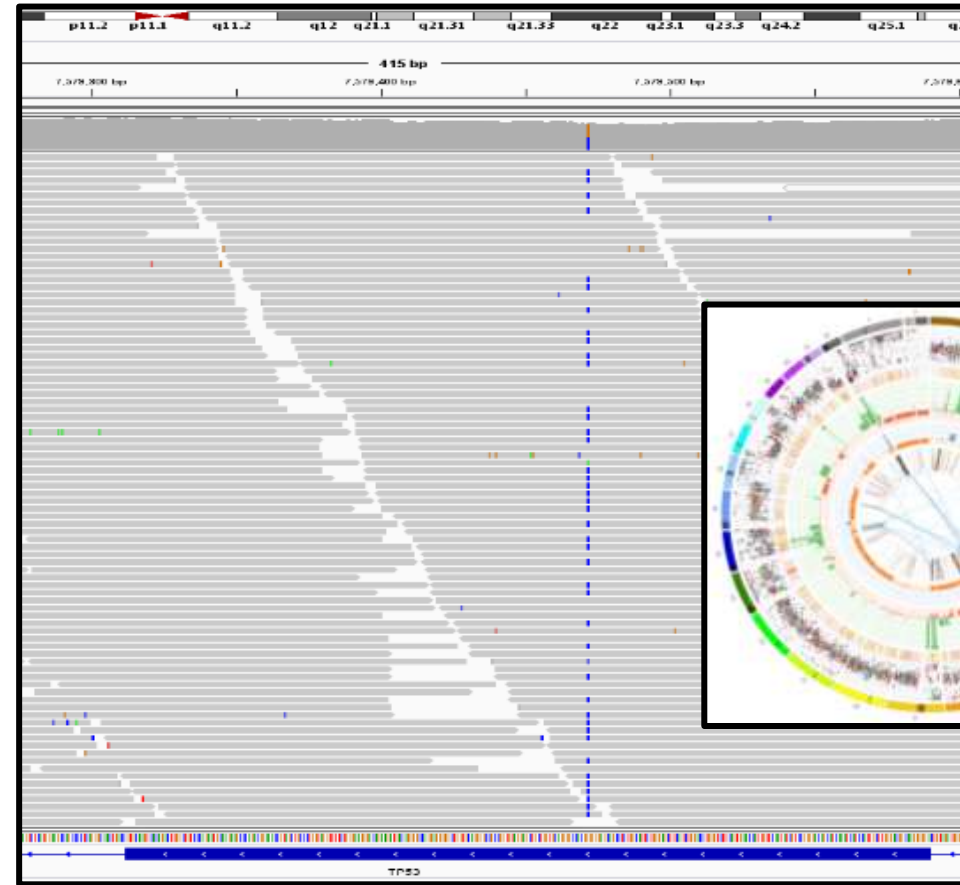
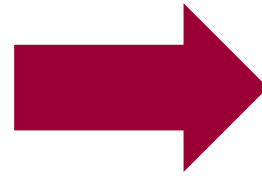
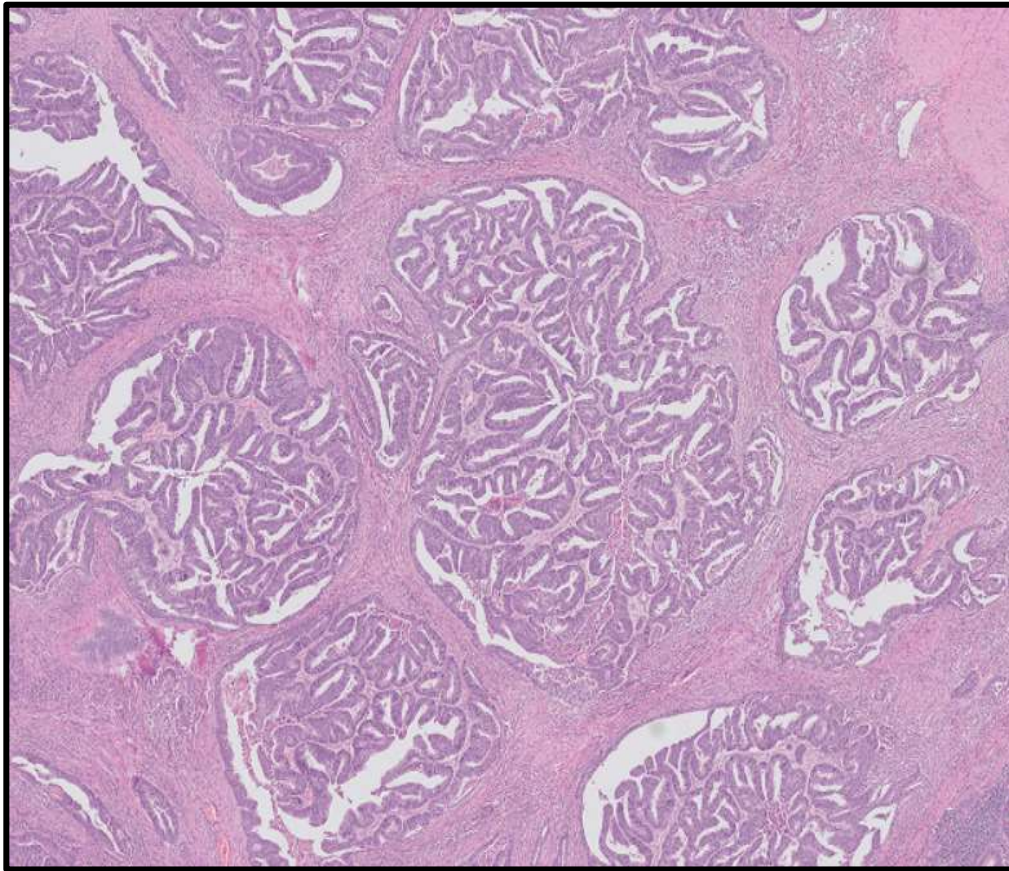


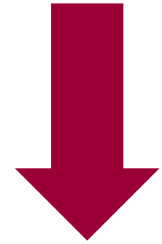
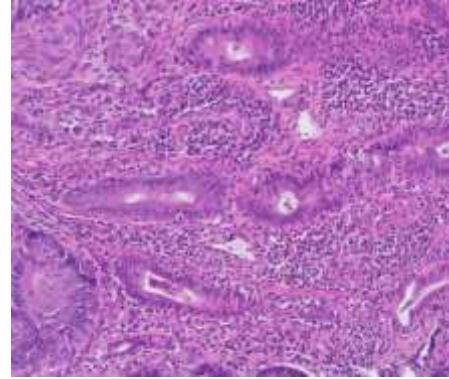
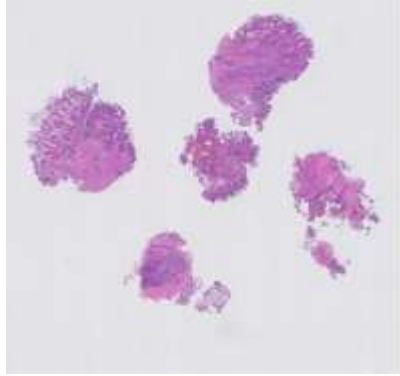
WGS helpt bij het opsporen van de oorspronkelijke tumor





Moderne pathologie

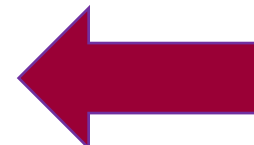




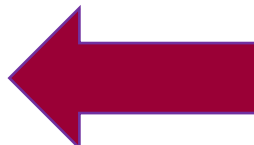
Maligne

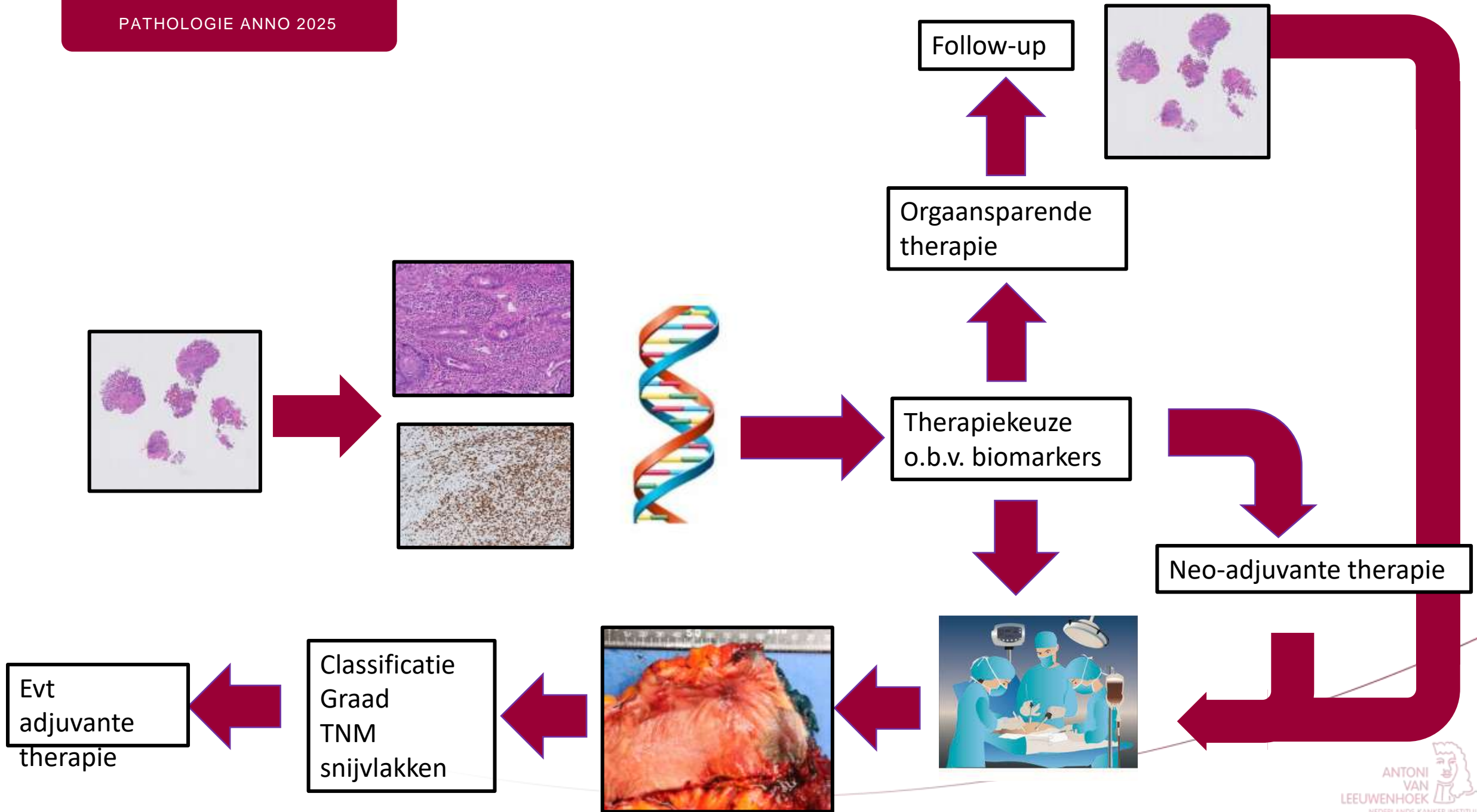


Classificatie
Graad
TNM
snijvlakken

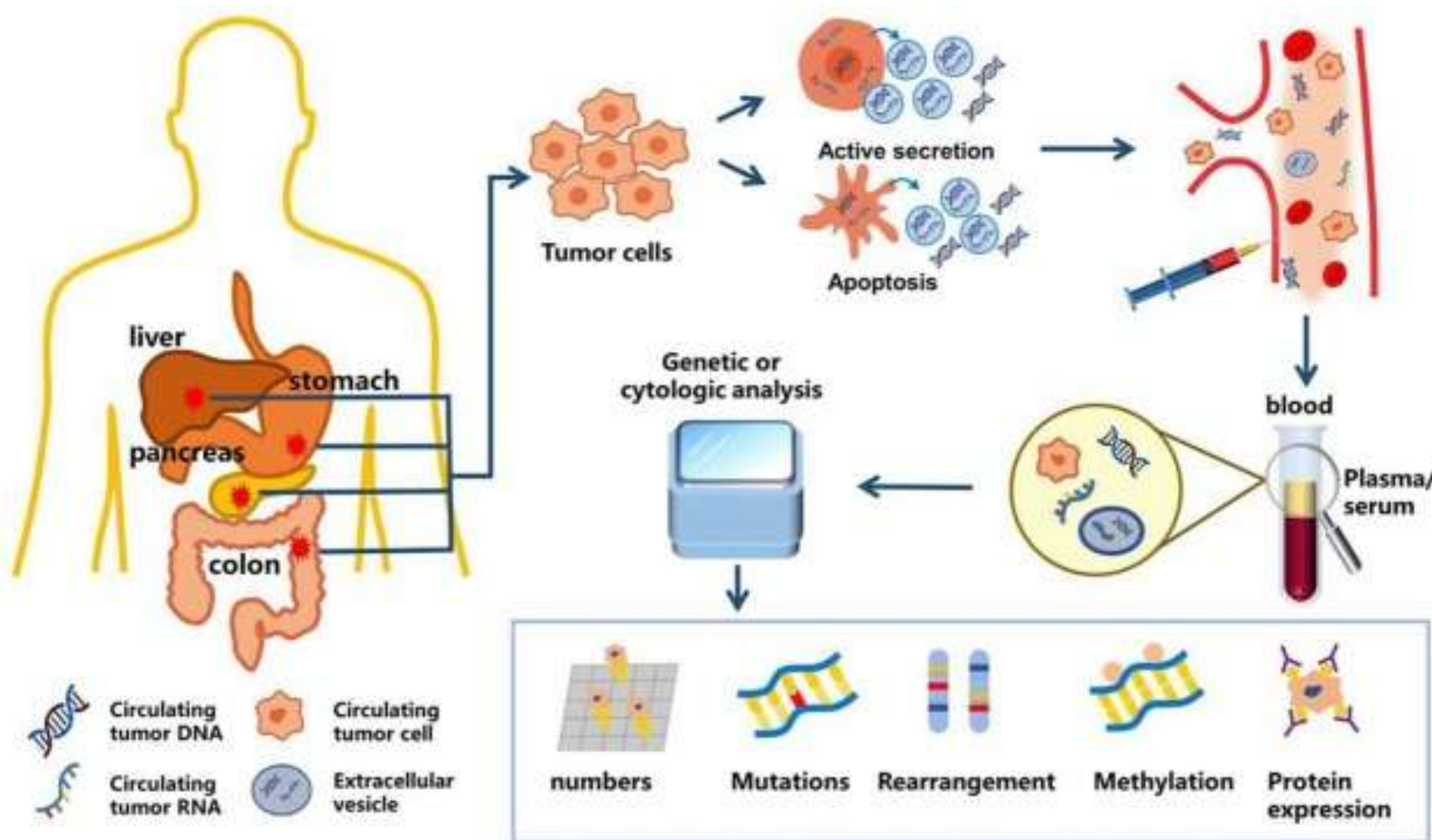


Evt adjuvante
therapie





Tumor DNA kan ook in bloed worden aangetoond



MEDQCC

STAND UP TO CANCER

Tumor DNA kan ook in andere vochten worden aangetoond

Oncogene

www.nature.com/onc

BRIEF COMMUNICATION

Check for updates

Improving diagnostic accuracy of identifying gastric cancer patients with peritoneal metastases: tumor-guided cell-free DNA analysis of peritoneal fluid

Karen van der Sluis¹, Johanna W. van Sandick¹, Marieke A. Vollebergh², Jolanda M. van Dieren², Niek Hugen¹, Koen J. Hartemink¹, Alexander A. F. A. Veenhof¹, Els Verhoeven³, José G. van den Berg³, Petur Snaebjornsson^{3,4}, Michael Noe³, Tom van Wezel³, Mirjam C. Boelens^{3,5} and Liudmila L. Kodach^{3,5}

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Detection of peritoneal dissemination (PD) in gastric cancer (GC) patients remains challenging. The feasibility of tumor-guided cell-free DNA (cfDNA) detection in prospectively collected peritoneal fluid (ascites and peritoneal lavage) was investigated and compared to conventional cytology in 28 patients. Besides conventional cytology, next generation sequencing was performed on primary tumor DNA and cell-free DNA from peritoneal fluid. Patients were retrospectively grouped into: a *positive group* (with PD) and a *negative group* (without PD). Detectable mutations were found in the primary tumor of 68% ($n = 19$). Sensitivity of PD detection by tumor-guided cfDNA analysis was 91%, compared to 64% by conventional cytology. Within the positive group ($n = 11$), tumor-guided cfDNA was detected in all patients with ascites samples (4/4, 100%) and in 86% (6/7) of the lavage samples, opposed to 4/4 (100%) patients with ascites and 43% (3/7) with lavage by conventional cytology. Within the negative group ($n = 8$), conventional cytology was negative for all samples. In two patients, tumor-guided cfDNA was detected in peritoneal lavage fluid. Interestingly, these 2 patients developed PD within 6 months, suggesting a prognostic value of tumor-guided cfDNA detection. This study showed that tumor-guided cfDNA detection in peritoneal fluids of GC patients is feasible and superior to conventional cytology in detecting PD.

Oncogene; <https://doi.org/10.1038/s41388-024-03034-z>

Samenvattend.....

Het vak van de patholoog is in beweging

1. Nieuwe classificaties op basis van tumor DNA
2. Biomarker onderzoek en neo-adjuvante therapie
3. Digitale pathologie en de mogelijkheden van AI



cat



dog

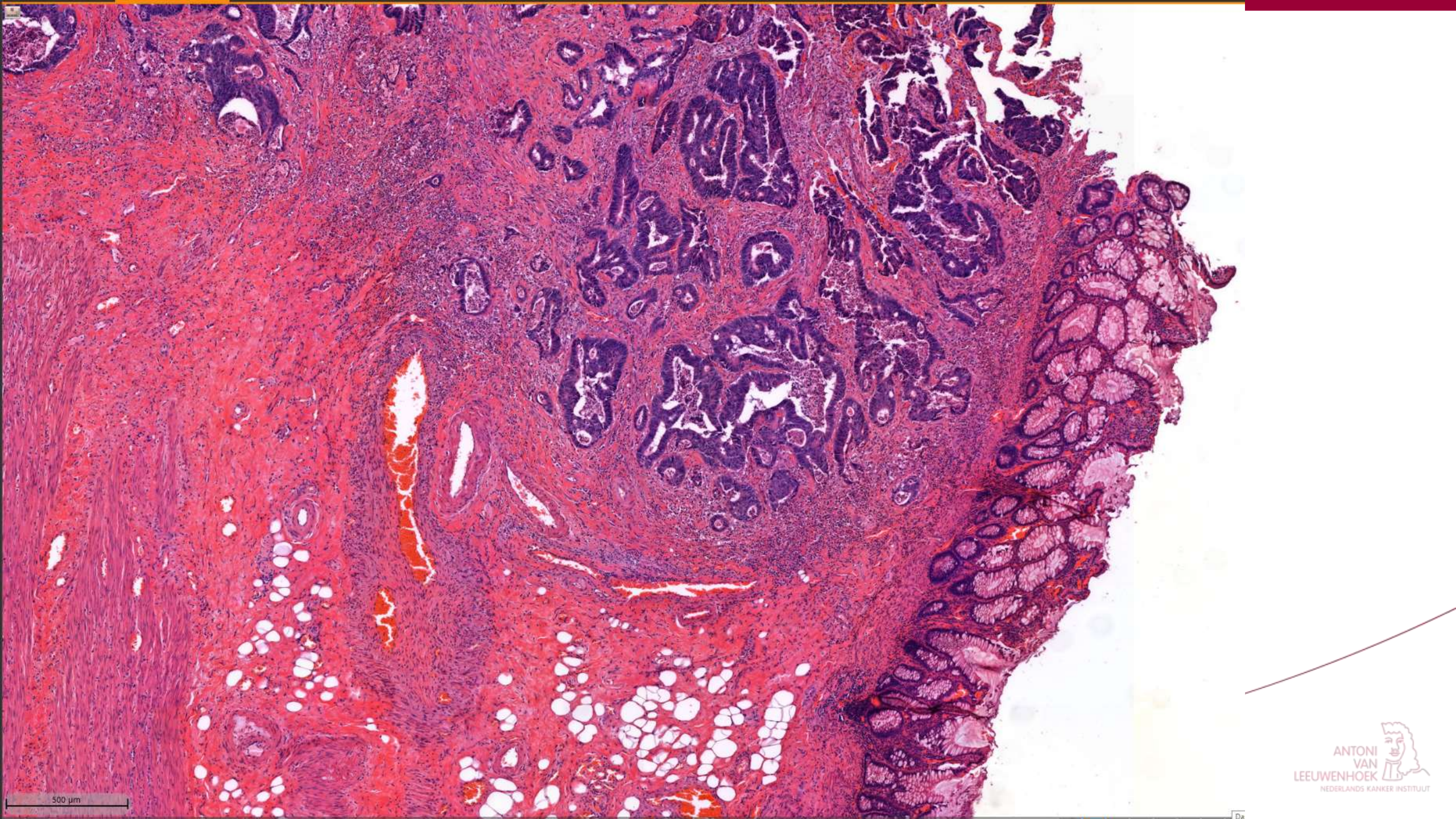


mug

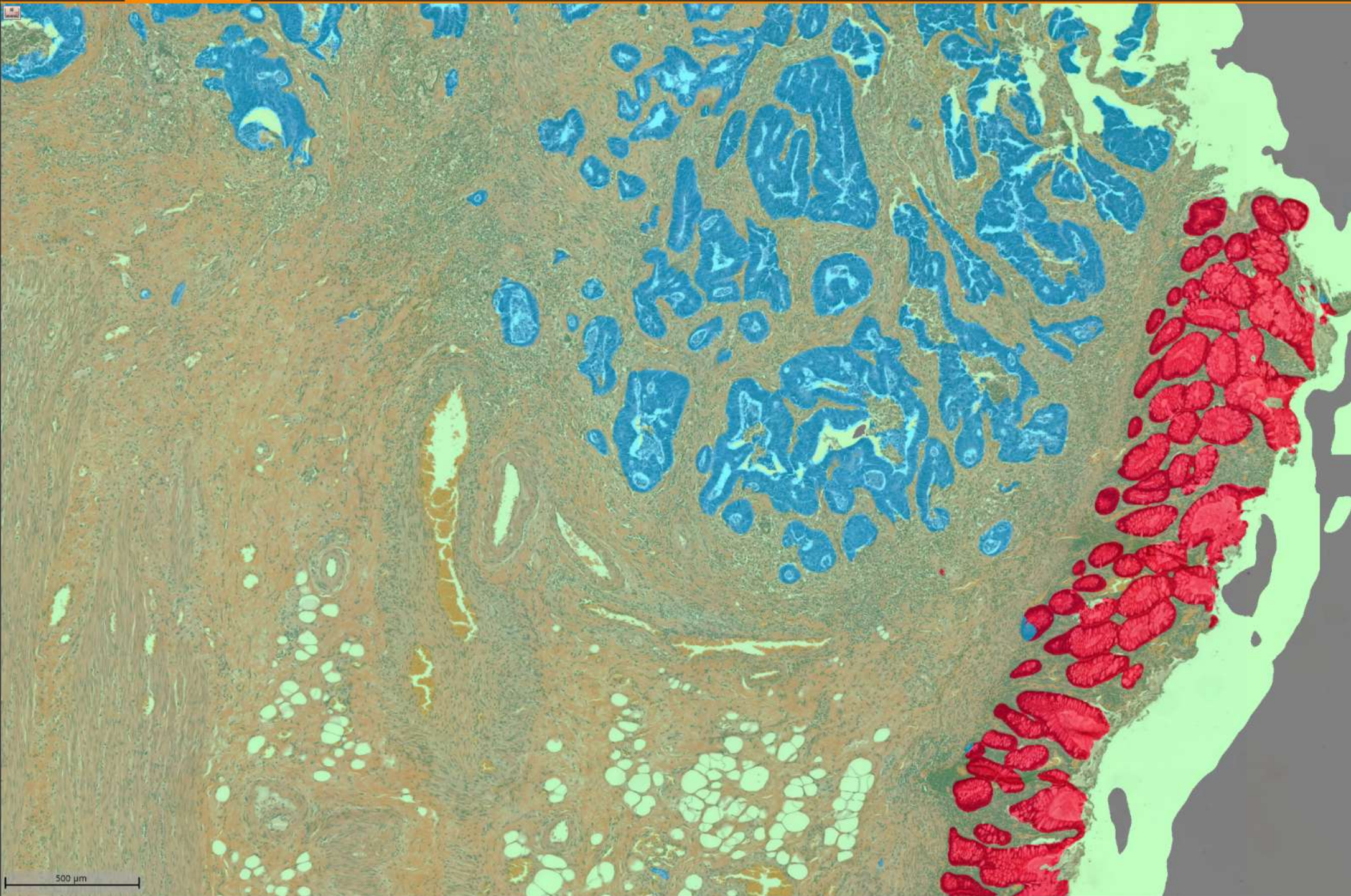


hat





500 μ m

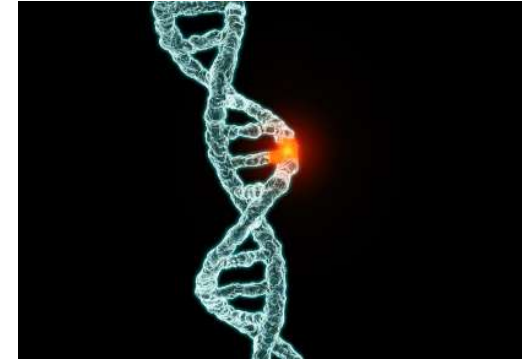


500 μ m

Het vak van de patholoog is in beweging

1. Nieuwe classificaties en beter begrip door DNA onderzoek
2. Neo-adjuvante therapie

o.b.v. biomarkers



3. Digitale pathologie en de mogelijkheden van AI

