

Prof. Søreide, del III

Patogenese og Genetikk

Patogenese og genetikk

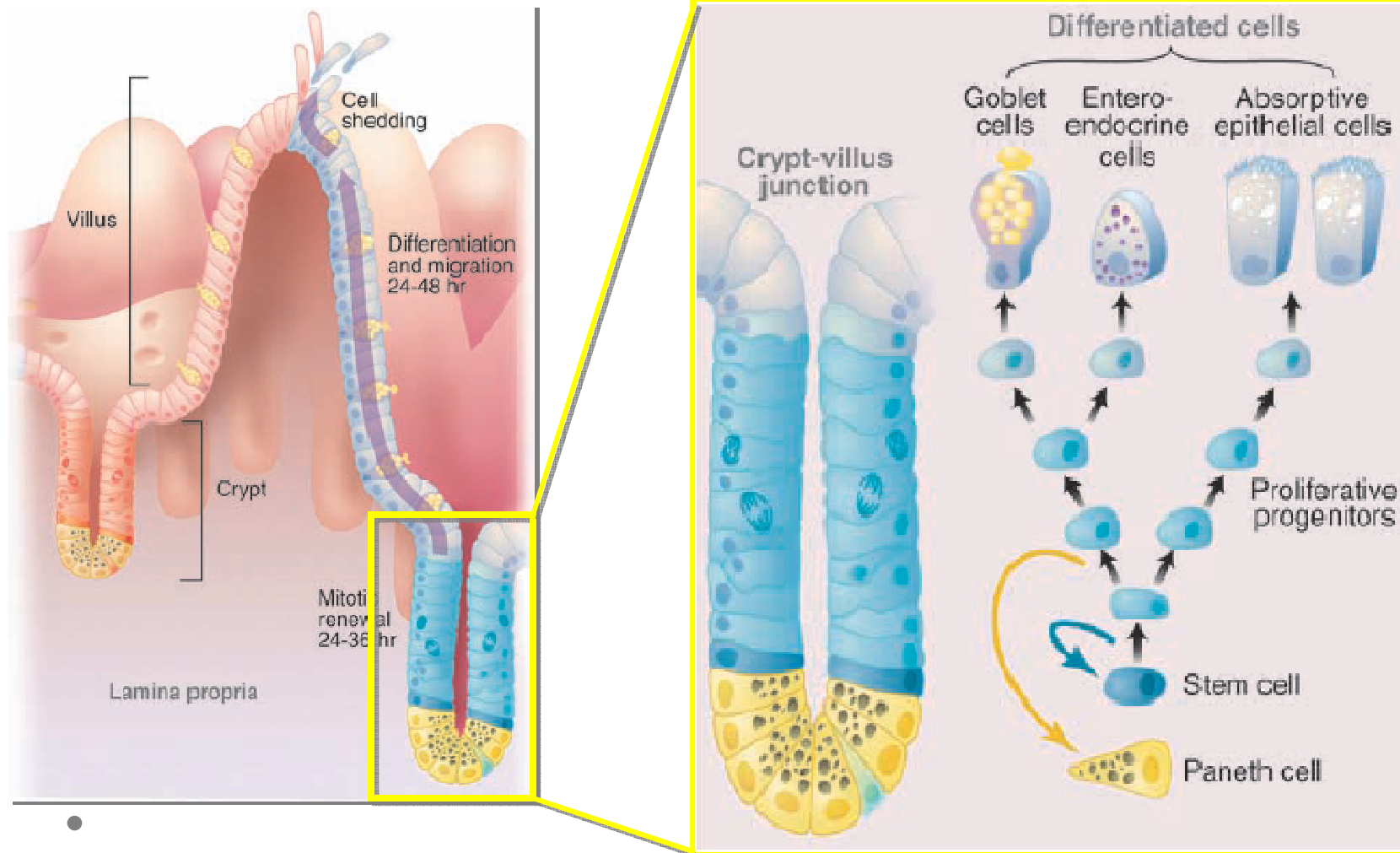
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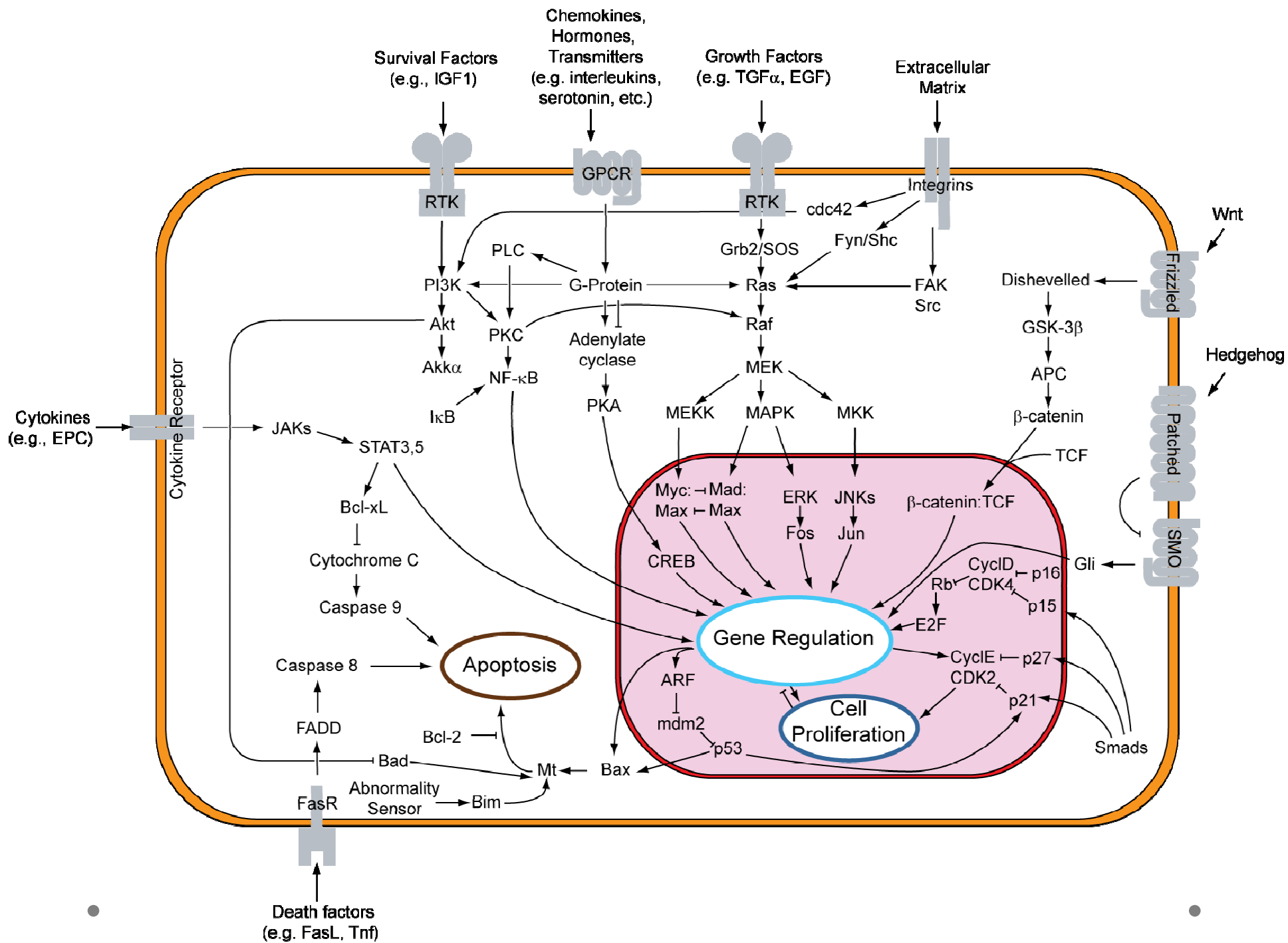
MODELLSYKDOM



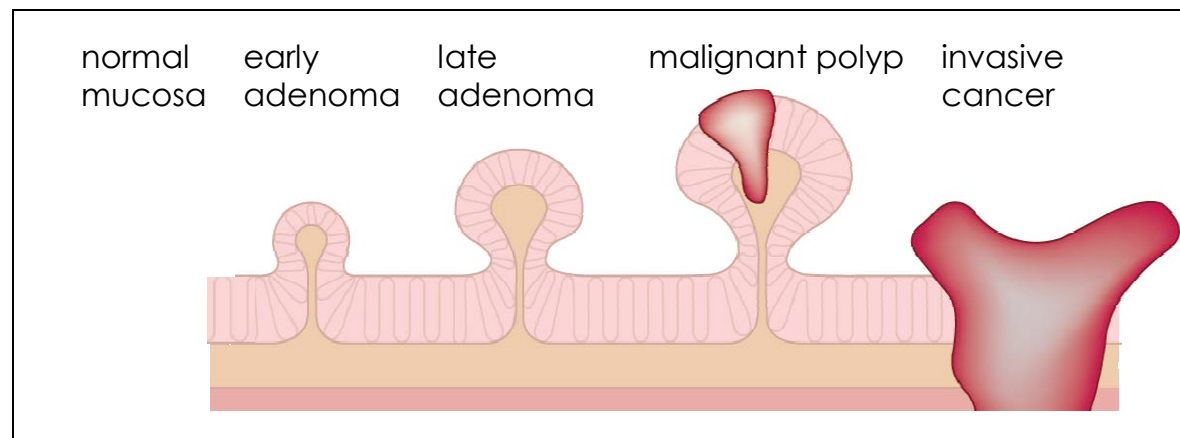
Stamceller i colonkrypt

Science, 2005



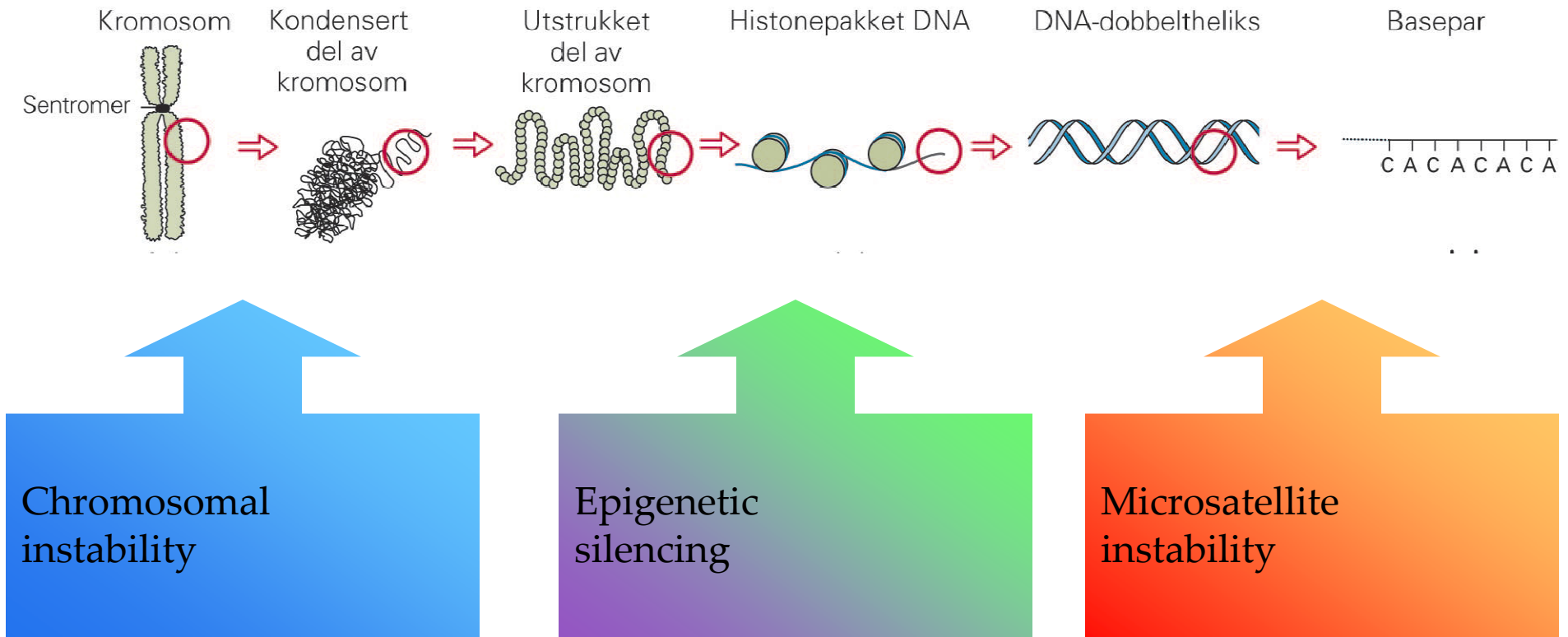


"Adenoma-carcinoma sequence"

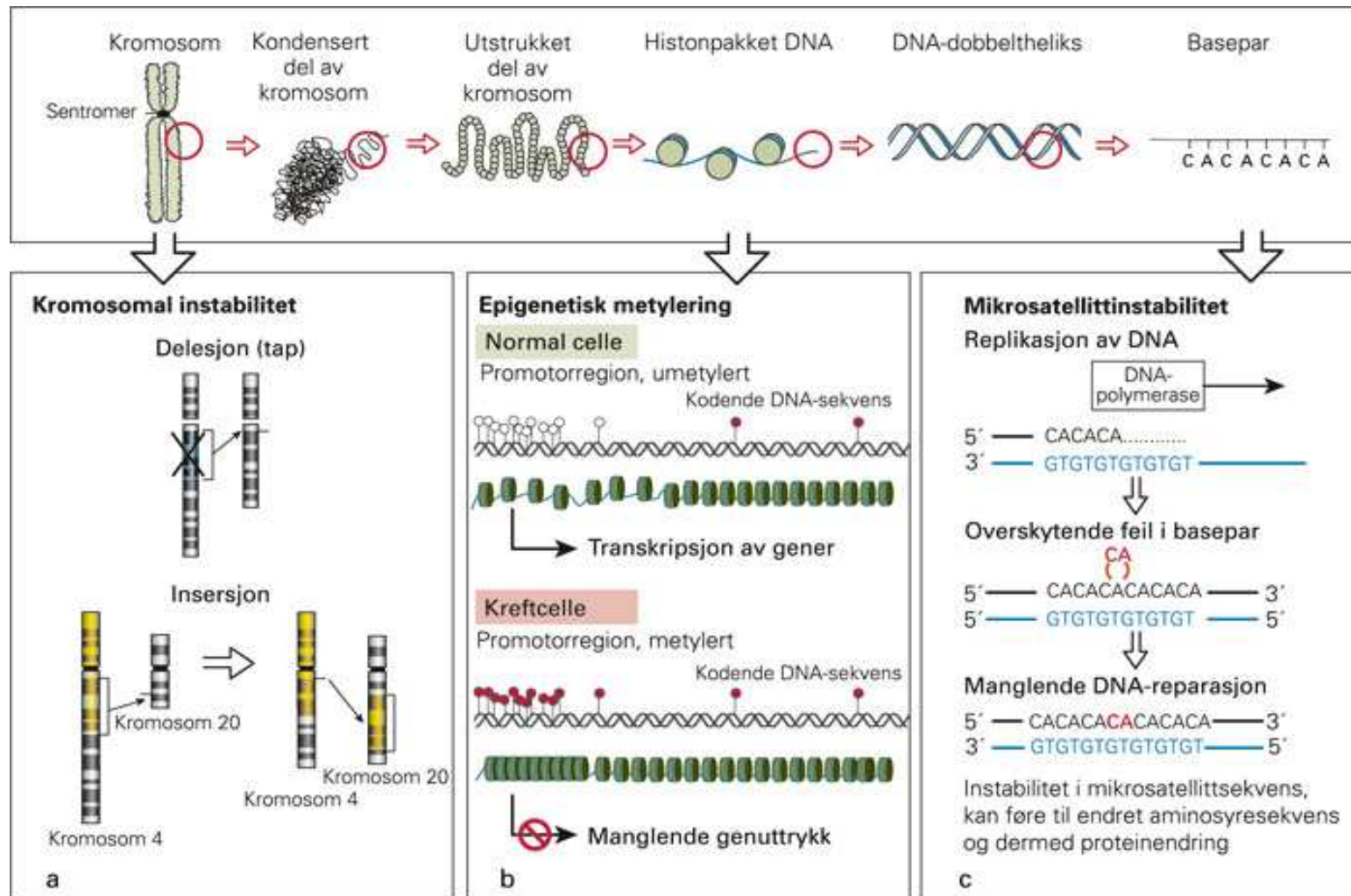


10-15 years

...økt forståelse av genetisk instabilitet



Genetisk instabilitet i kolorektal cancer



Chromosomal instability (CIN) pathway

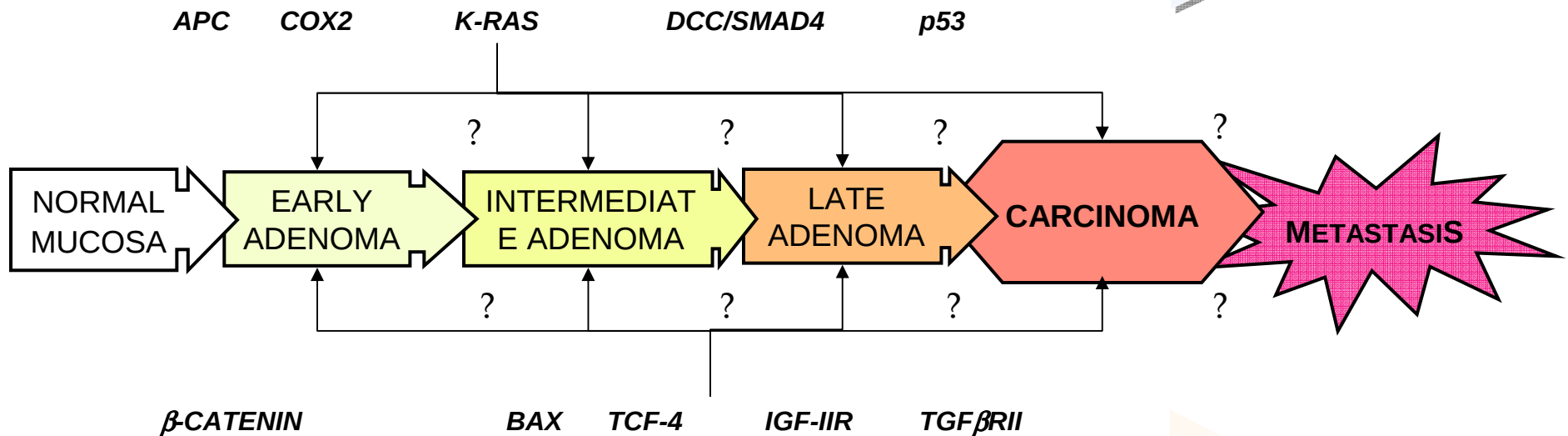
Genetic alterations through chromosomal losses and gains

Del 1p

Del 8p

LOH 17p

LOH 18q



MLH1

MSH2

MSH6

Epigenetics

CIMP

hypermethylation

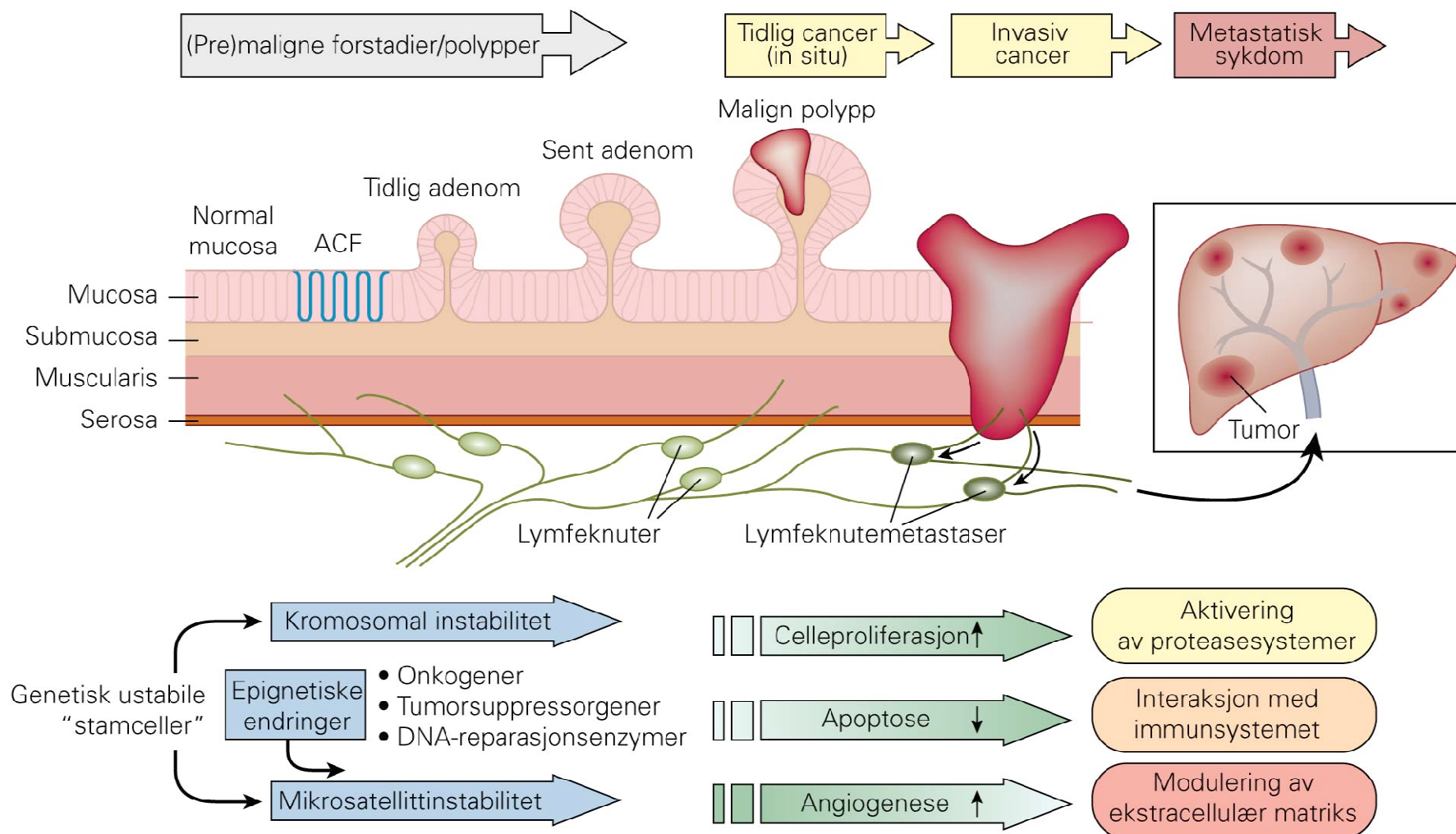
Microsatellite instability (MSI) pathway

Genetic alterations through defective DNA mismatch repair proteins

Molekylær klassifisering

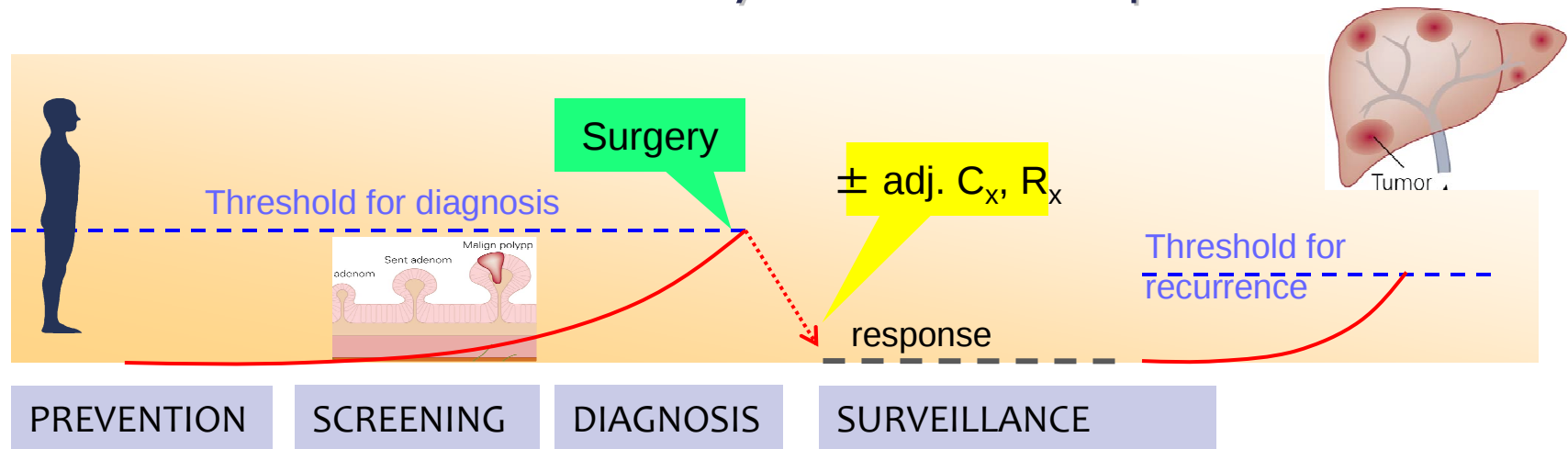
Table 2. Proposed Molecular Classification of Colorectal Cancers.		
Type	Genetic Instability	Morphologic Correlate
Type 1	CIMP high, MSI-H, B-raf mutation	“Serrated pathway”
Type 2	CIMP high, MSI-L or MSS, B-raf mutation	“Serrated pathway”
Type 3	CIMP low, MSS or MSI-L, KRAS mutation	“Any polyp”
Type 4	CIMP neg, MSS	“Adenoma-carcinoma-sequence”
Type 5 (Lynch syndrome)	CIMP neg, MSI-H	“Adenoma-carcinoma-sequence”

Discovery Medicine, Volume 12, Number 66, November 2011

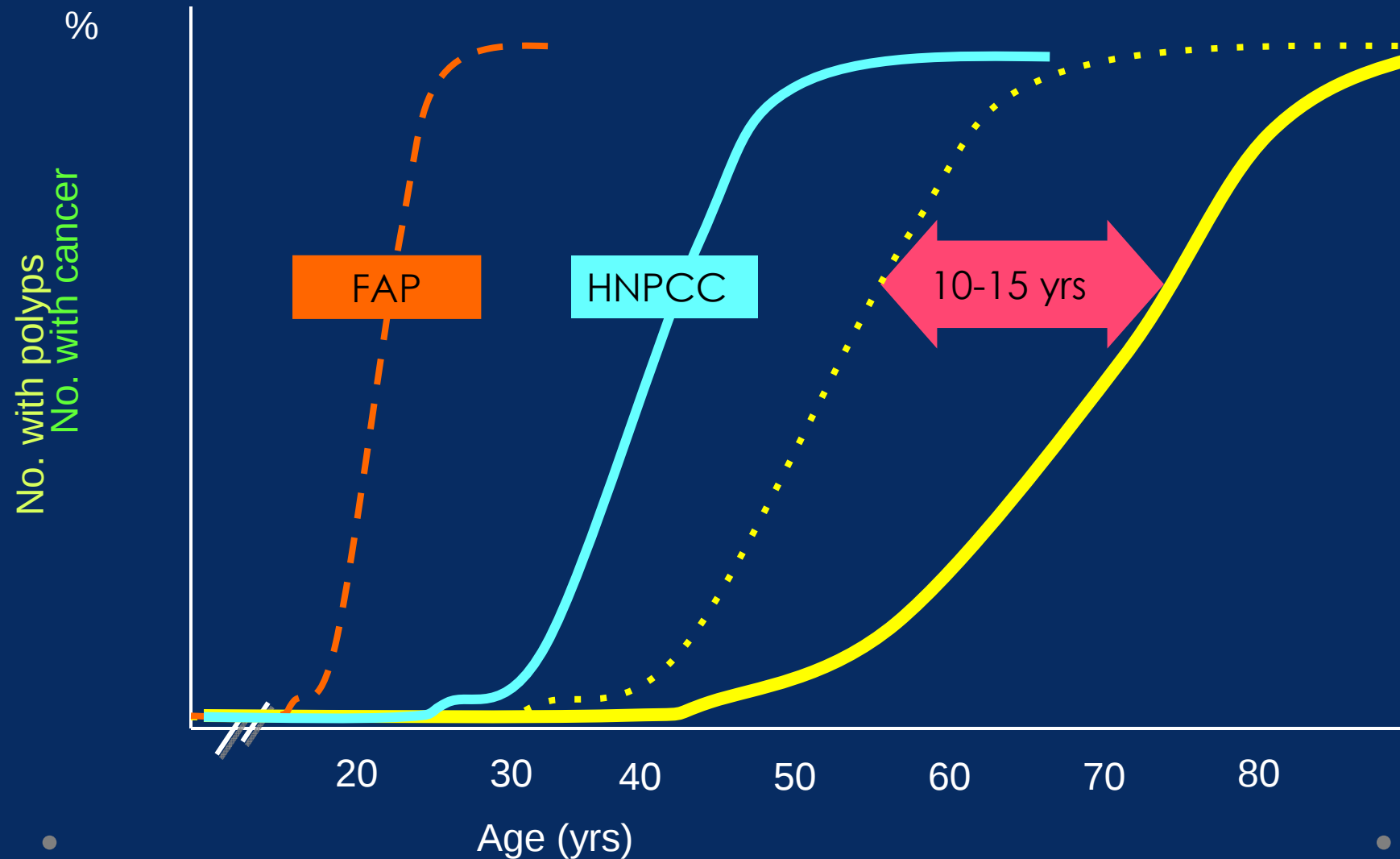


Colorectal Cancer - sykdomsforløp

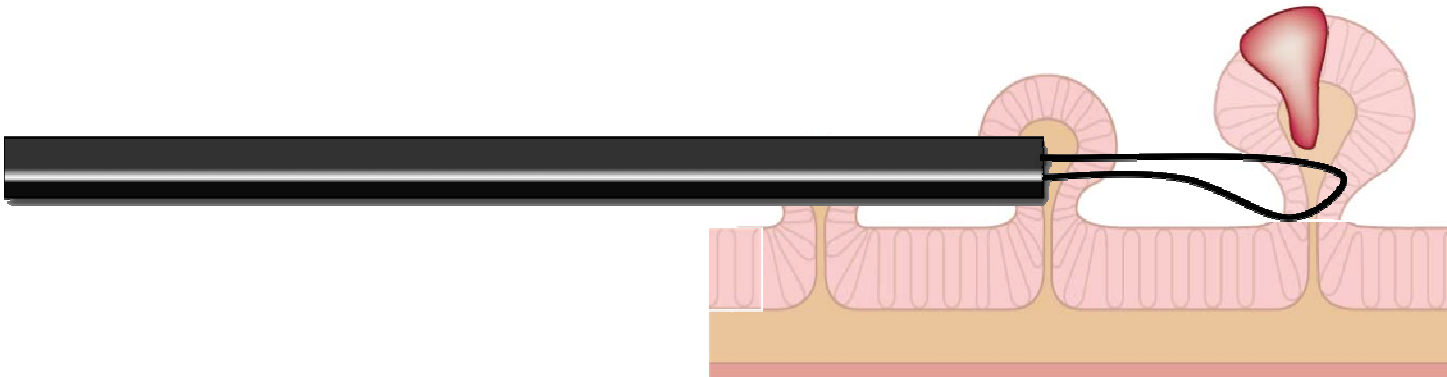
TUMOR BURDEN



“Window of opportunity”



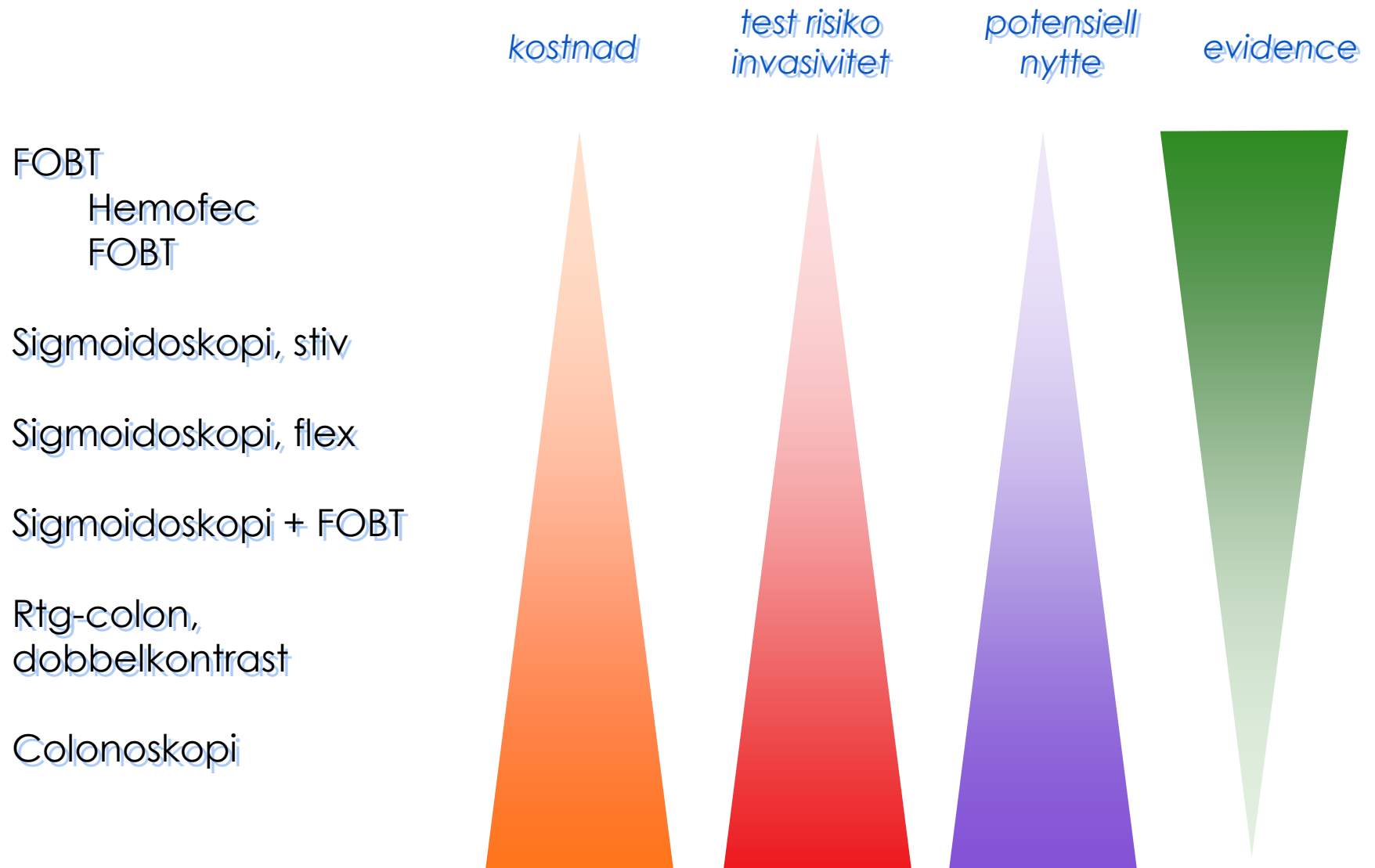
Polypectomy - prevents cancer !



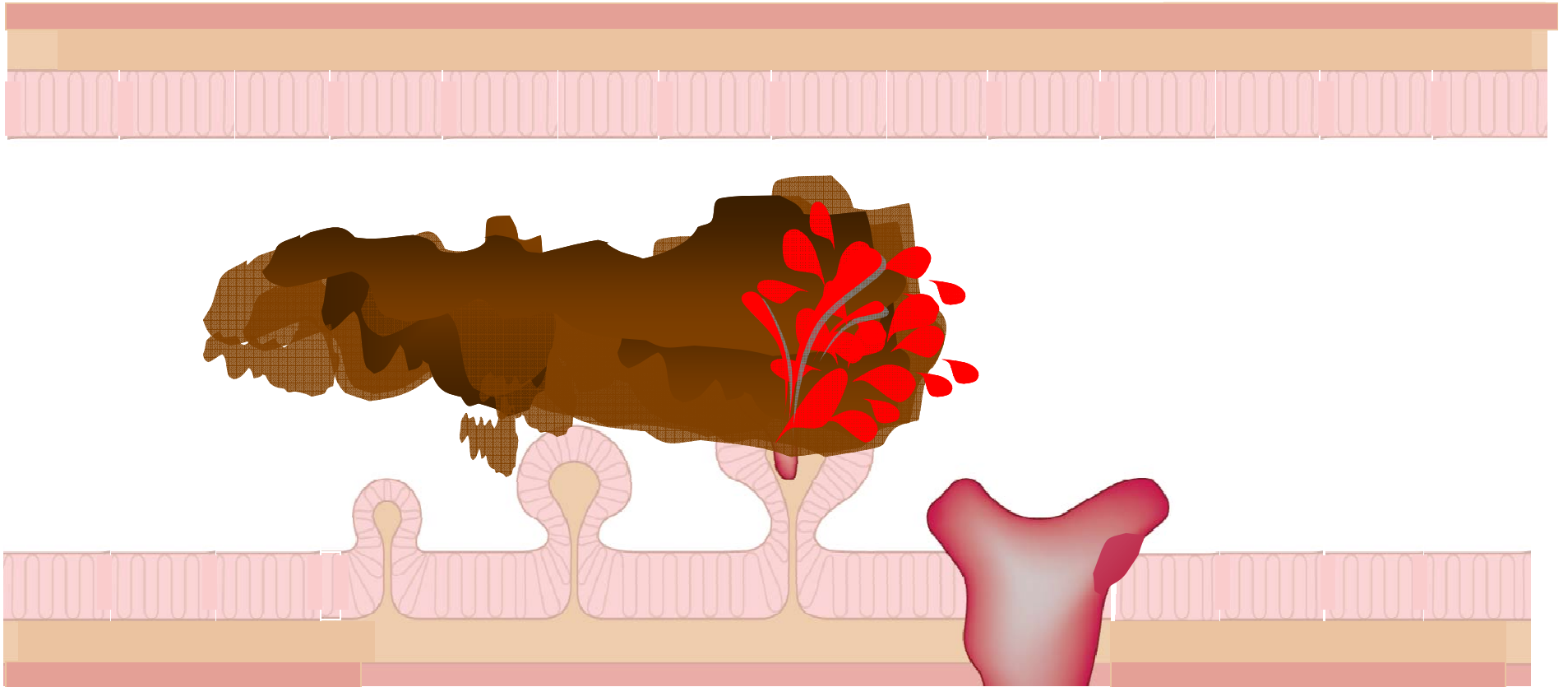
Perforation rate estimated at 0.2% = 2 in every 1000

Mortality 1-3 in every 10 000

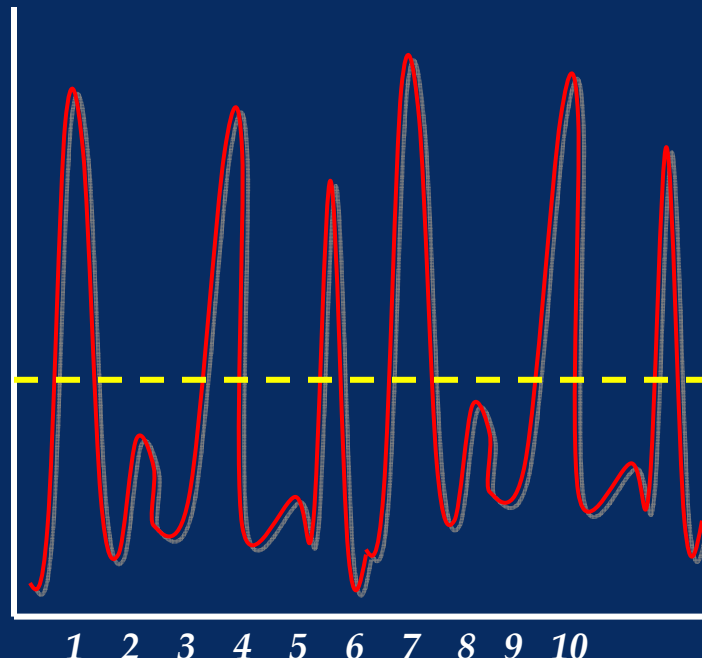
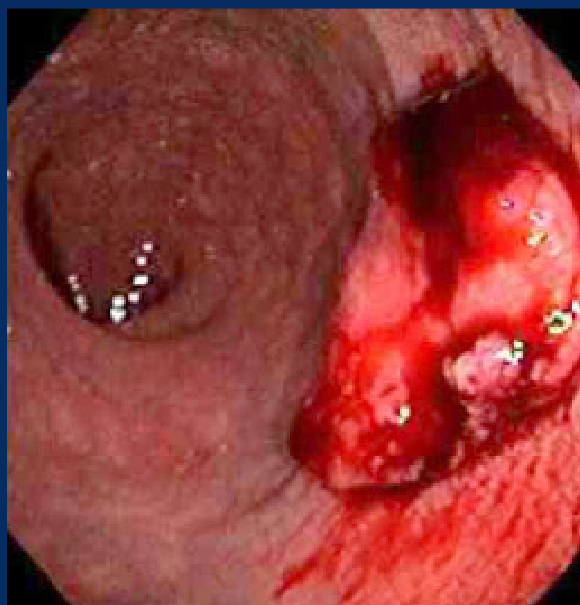
Valg av screening test



Leakage...



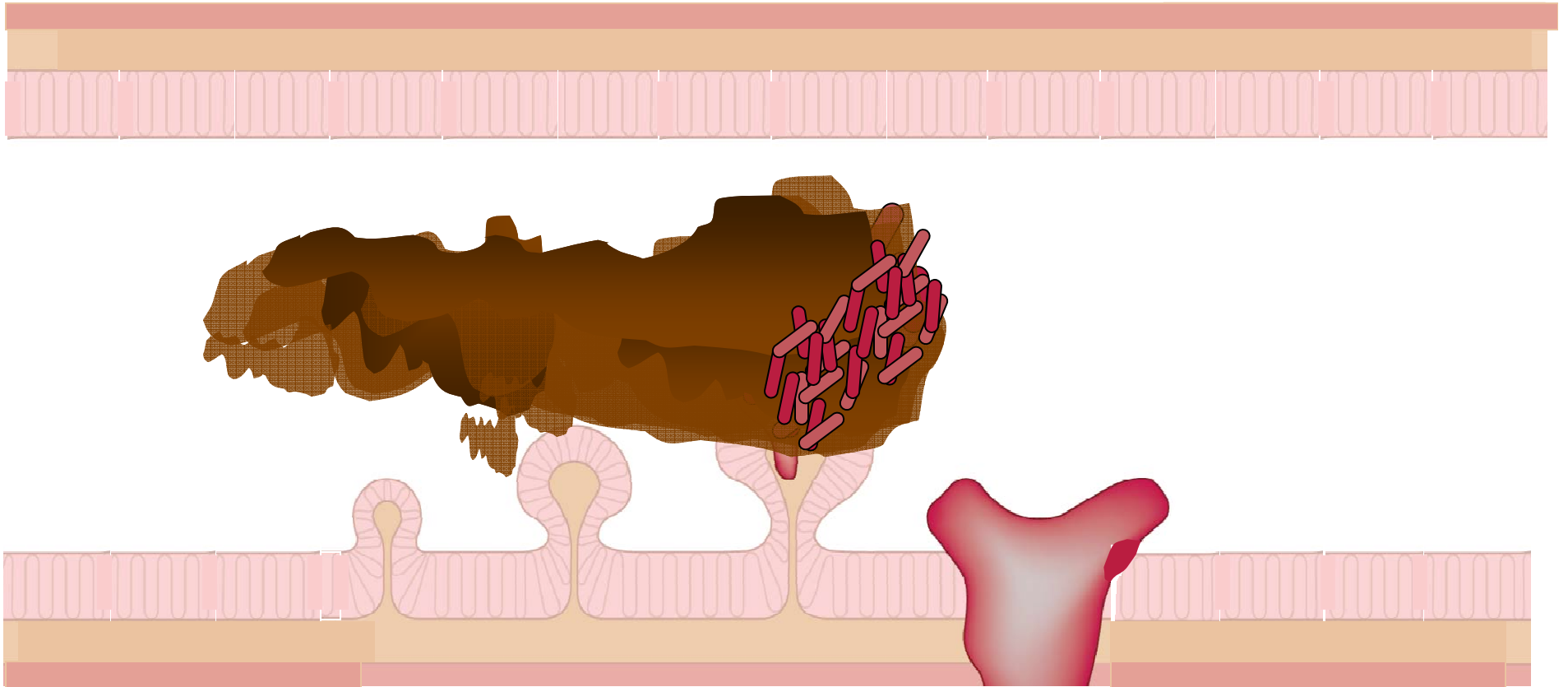
Fecal occult blood tests (FOBT)



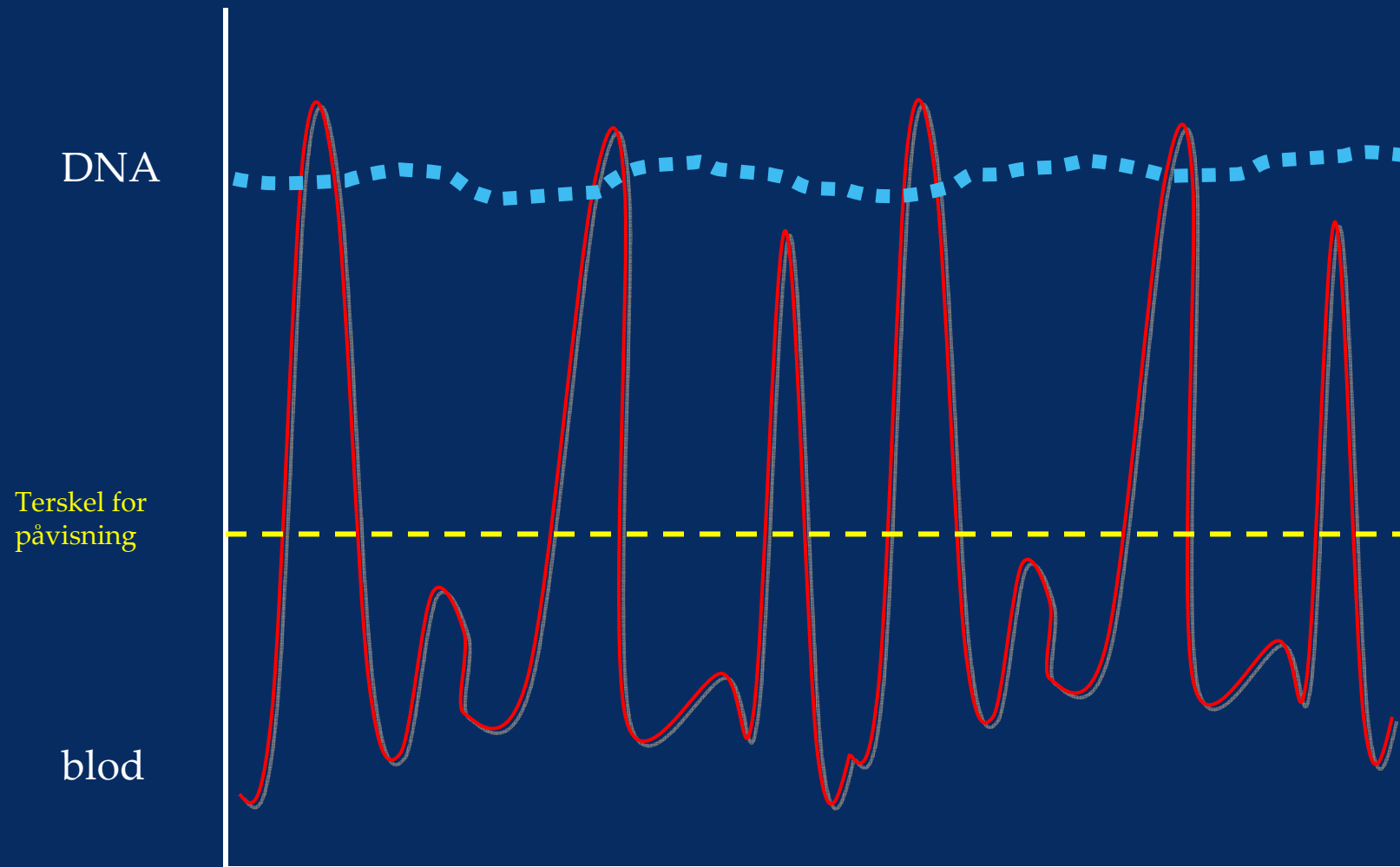
- 3+ RCTs ; > 320,000 pts; 10-18 yrs fo-up
- 15-33% reduced CRC *mortality* ²⁻⁴
- 25% relative risk reduction (RR 0.75, 95% CI 0.66 - 0.84)

Several drawbacks (false-pos, compliance, diet-restr. ...)

Exfoliated cells...

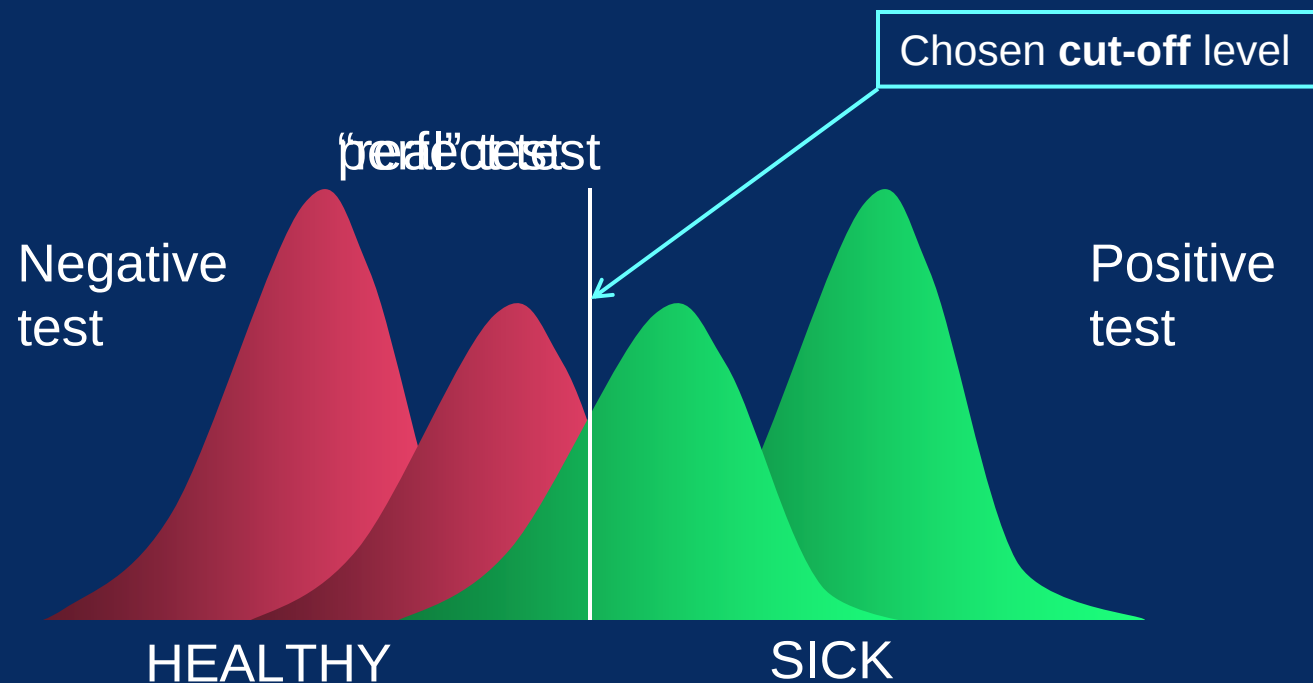


...kontinuerlig utskillelse...

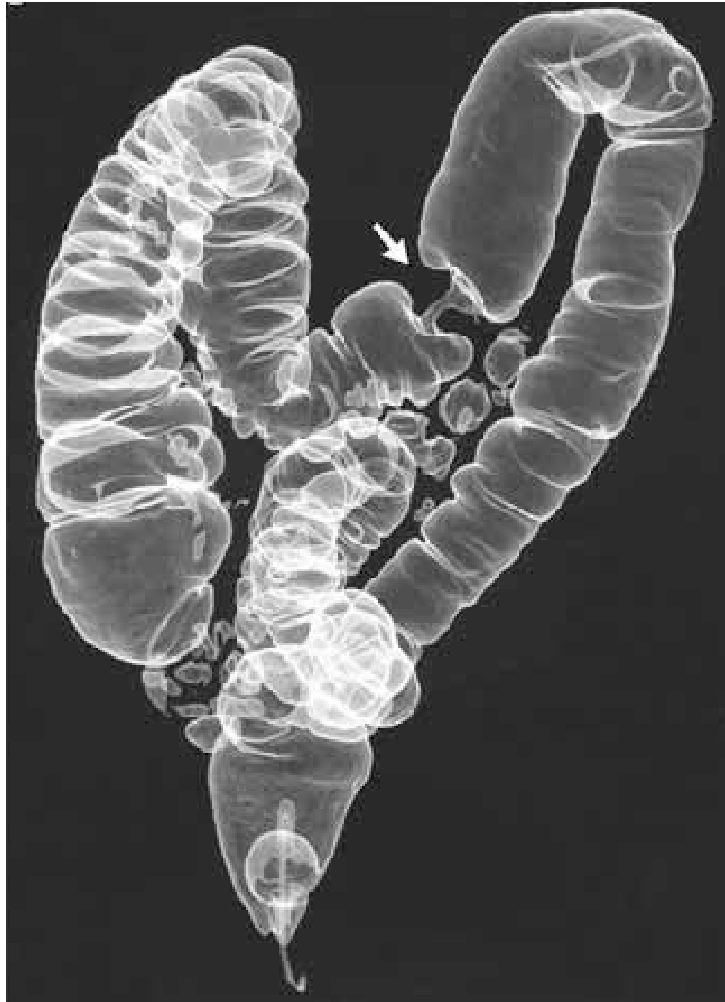


Screening test needs...

- High sensitivity (=True positives)
 - o To rule **IN** those with disease
- High specificity (=True negatives)
 - o To rule **OUT** those without disease



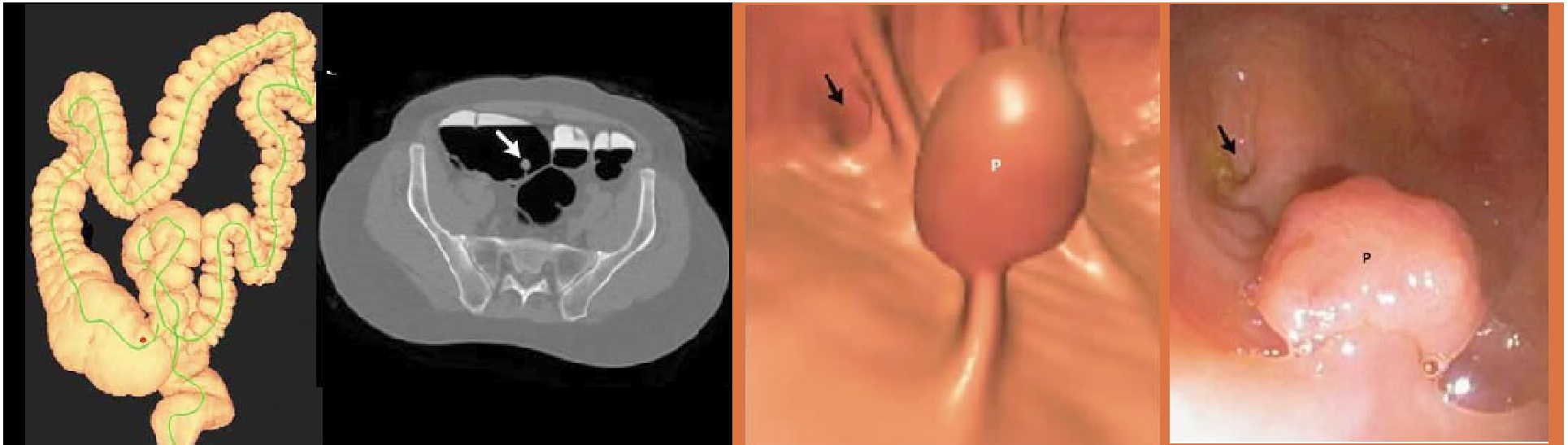
Barium enema



*"I don't want another X-ray.
The last one didn't help one bit."*

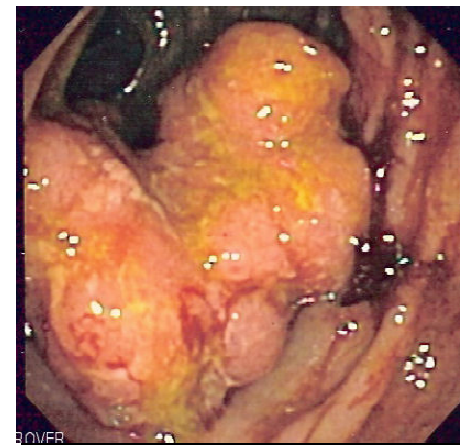
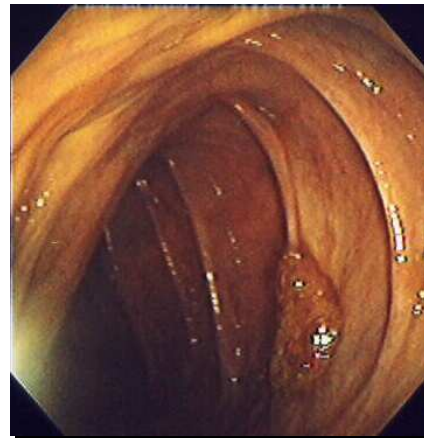
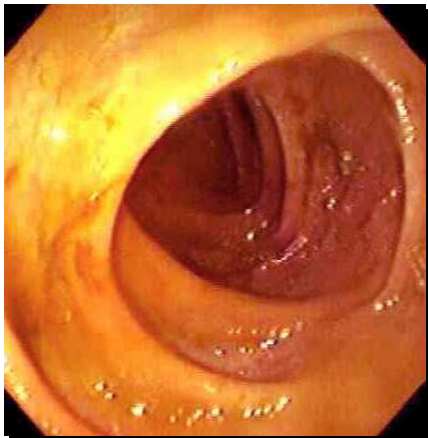
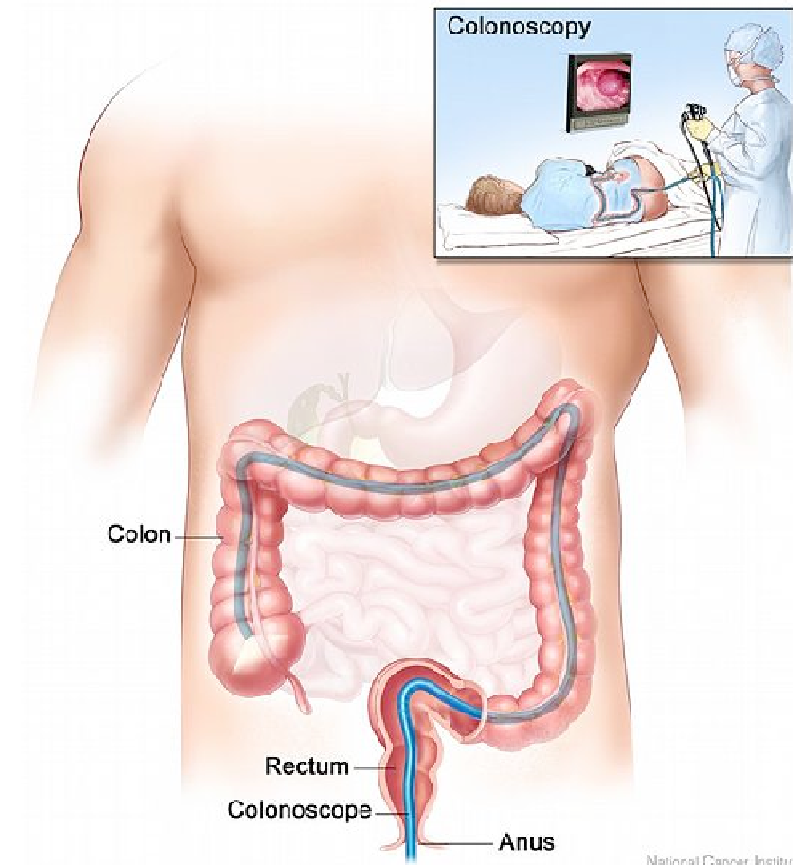
CT colography

"virtual colonoscopy"



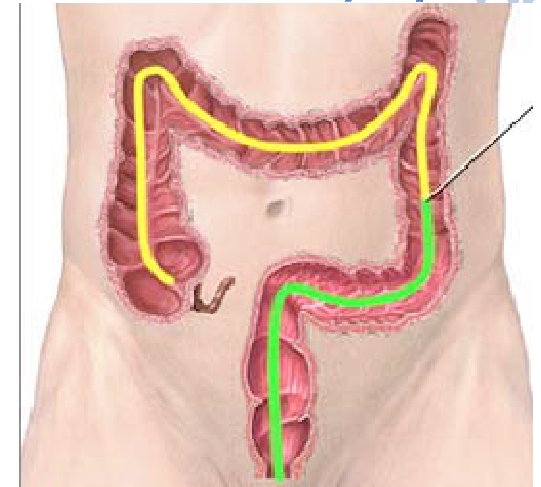
- pooled per-patient sensitivity of CT colonography ¹
 - **polyps >10 mm (0.82, 95% CI, 0.76-0.88)**
 - **polyps 6-10 mm (0.63, 95% CI, 0.52-0.75)**
 - **polyps 0-5 mm (0.56, 95% CI, 0.42-0.70)**
- comparable diagnostic ability to colonoscopy, fewer polypectomies ²

Koloskopi



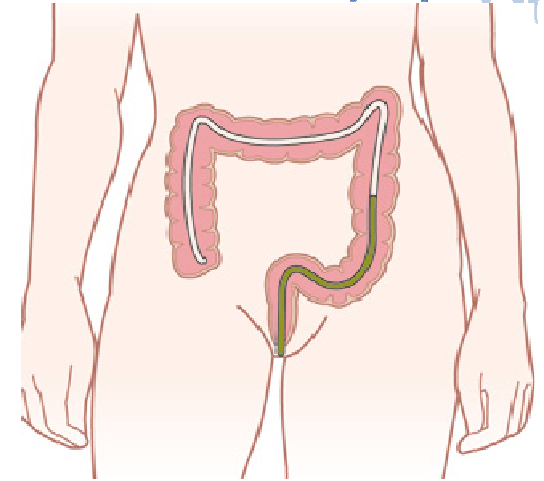
Sigmoidoscopy

- Most adenomas in distal part
- Effect on CRC incidence
 - TPS-1 study; 80% reduction (but wide 95% CI)
 - 3 RCTs (NORCCAP-1)
- Colonoscopy required for whole colon!

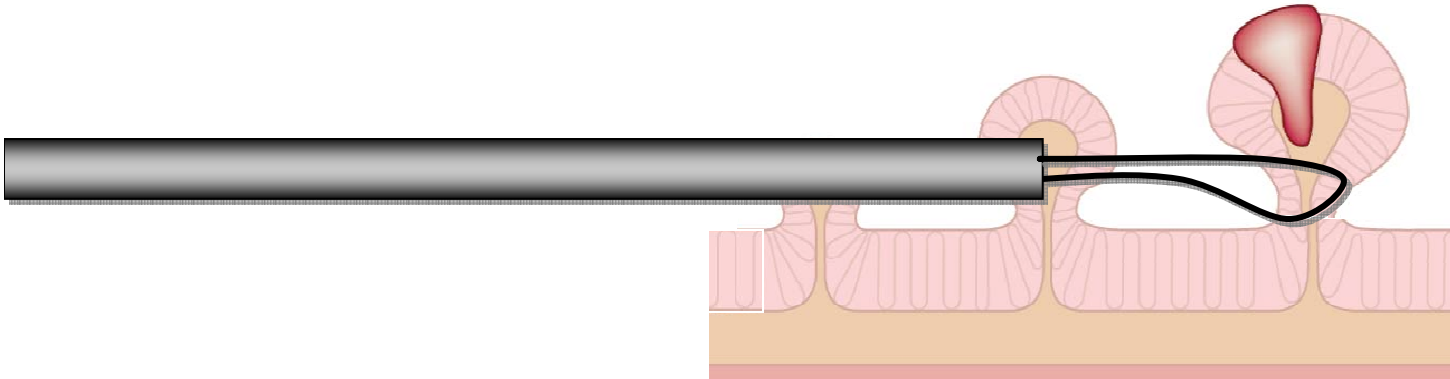


Colonoscopy

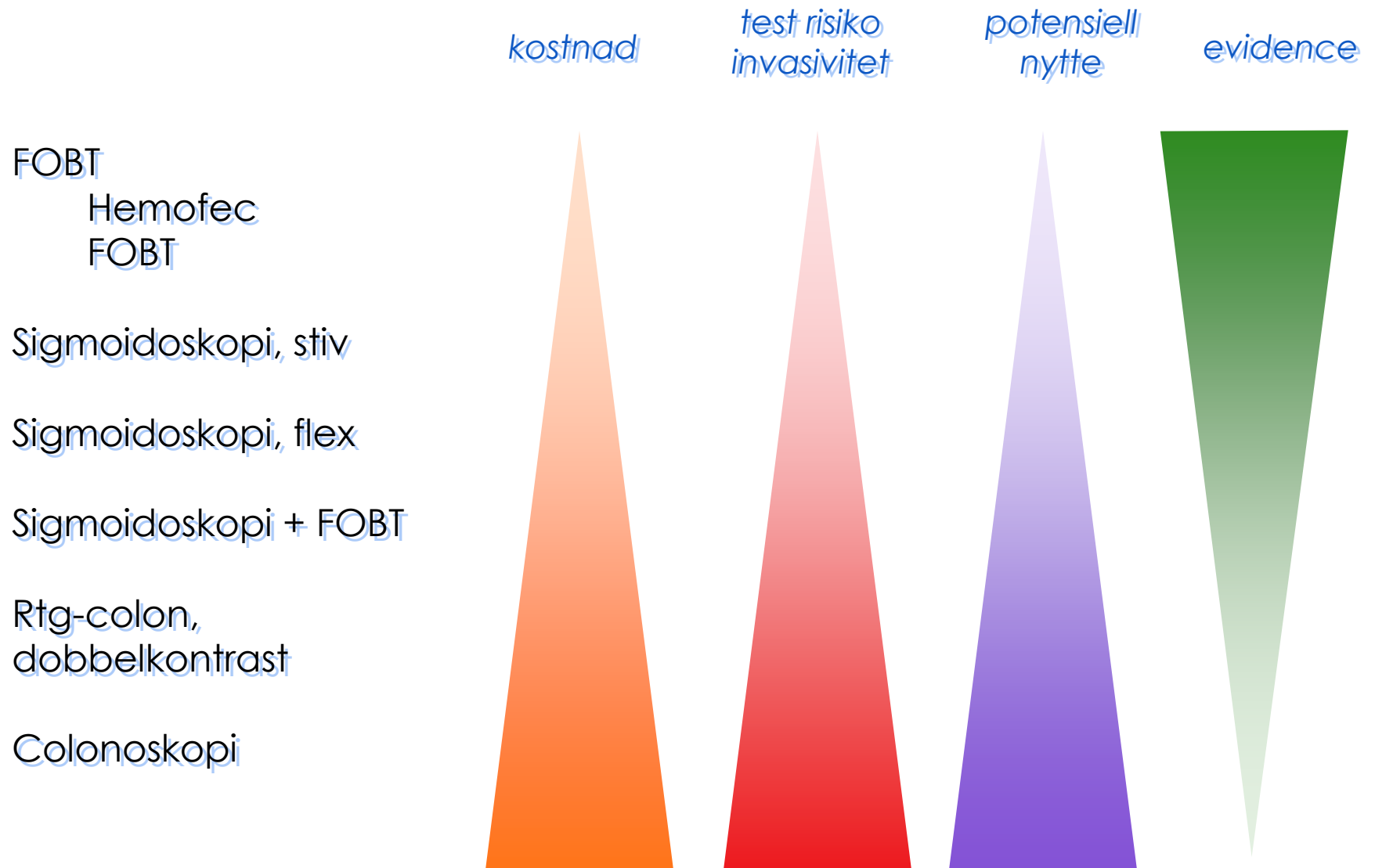
- Reaches entire colon!
 - High sens/spec: >95%
- Theoretically more effective
 - Est. 50-90% mortality reduction
 - Est. 70-90% incidence reduction
- Recommended and implemented
 - Guidelines & Nat'l programmes (USA, Germany, Poland...)
- No RCTs



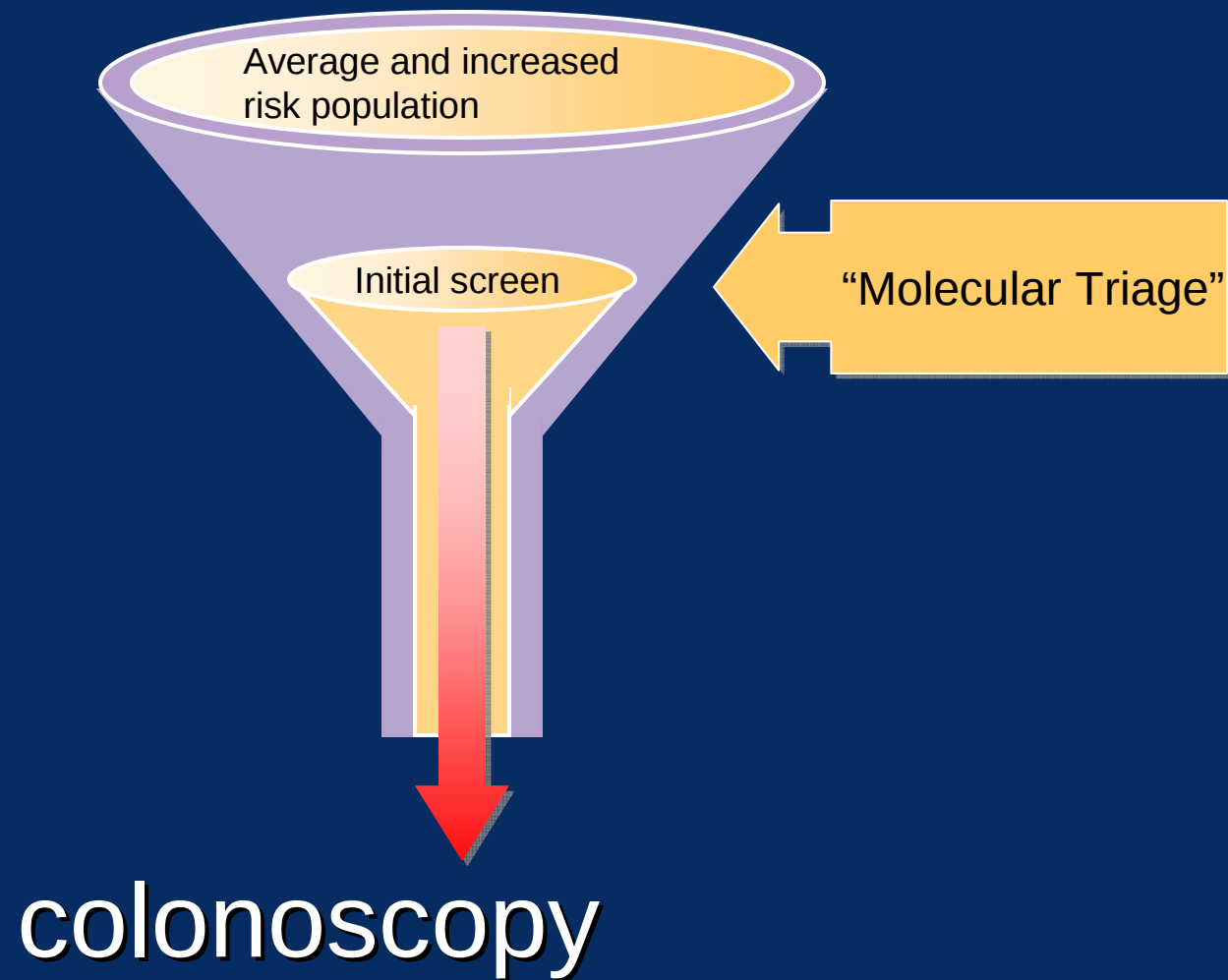
Polypectomy prevents cancer !



Valg av screening test



...forhåndsseleksjon av risikopersoner:

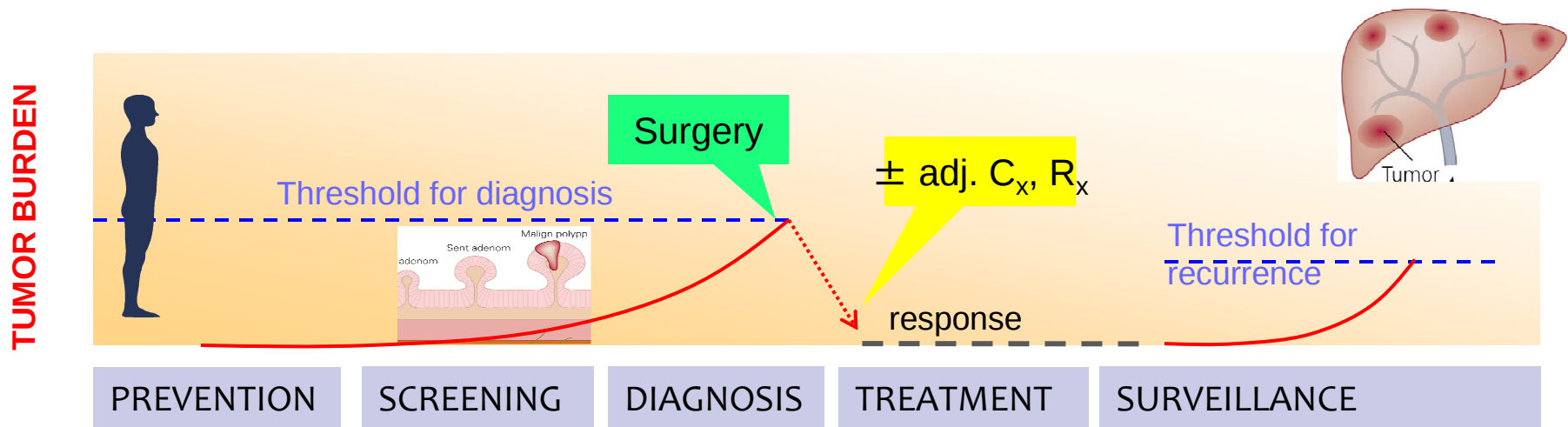




Screening

- **I 2012 kommer 140 000 kvinner og menn i alderen 50-74 år fra Østfold, Akershus og Buskerud til å bli invitert til å være med i et pilotprosjekt:**
 - o Et forprosjekt på masseundersøkelse (screening) for CRC
- teste ut to alternativer mot hverandre:
 - o En immunokjemisk test for usynlig blod i avføringen (iFOBT) oppdager ca. seks av ti tilfeller av tarmkreft og
 - o sigmoidoskopi detekterer ca. syv av ti.
 - o Falske positive tester er et problem ved iFOBT (åtte av ti positive prøver er "fask alarm"), men metoden er ikke-invasiv i motsetning til sigmoidoskopi og prøvetakingen skjer hjemme.

Colorectal Cancer

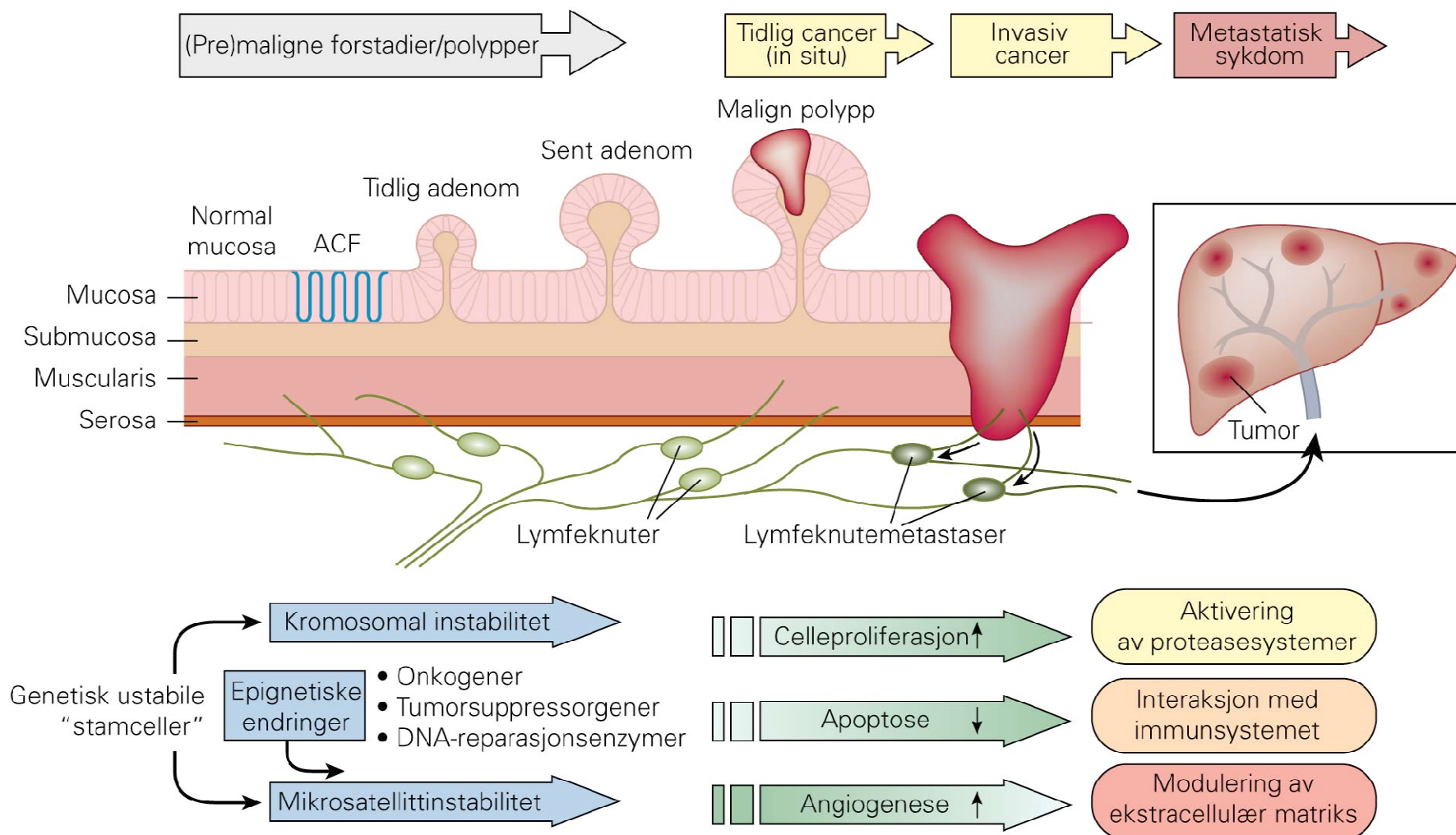


Insidens
Mortalitet

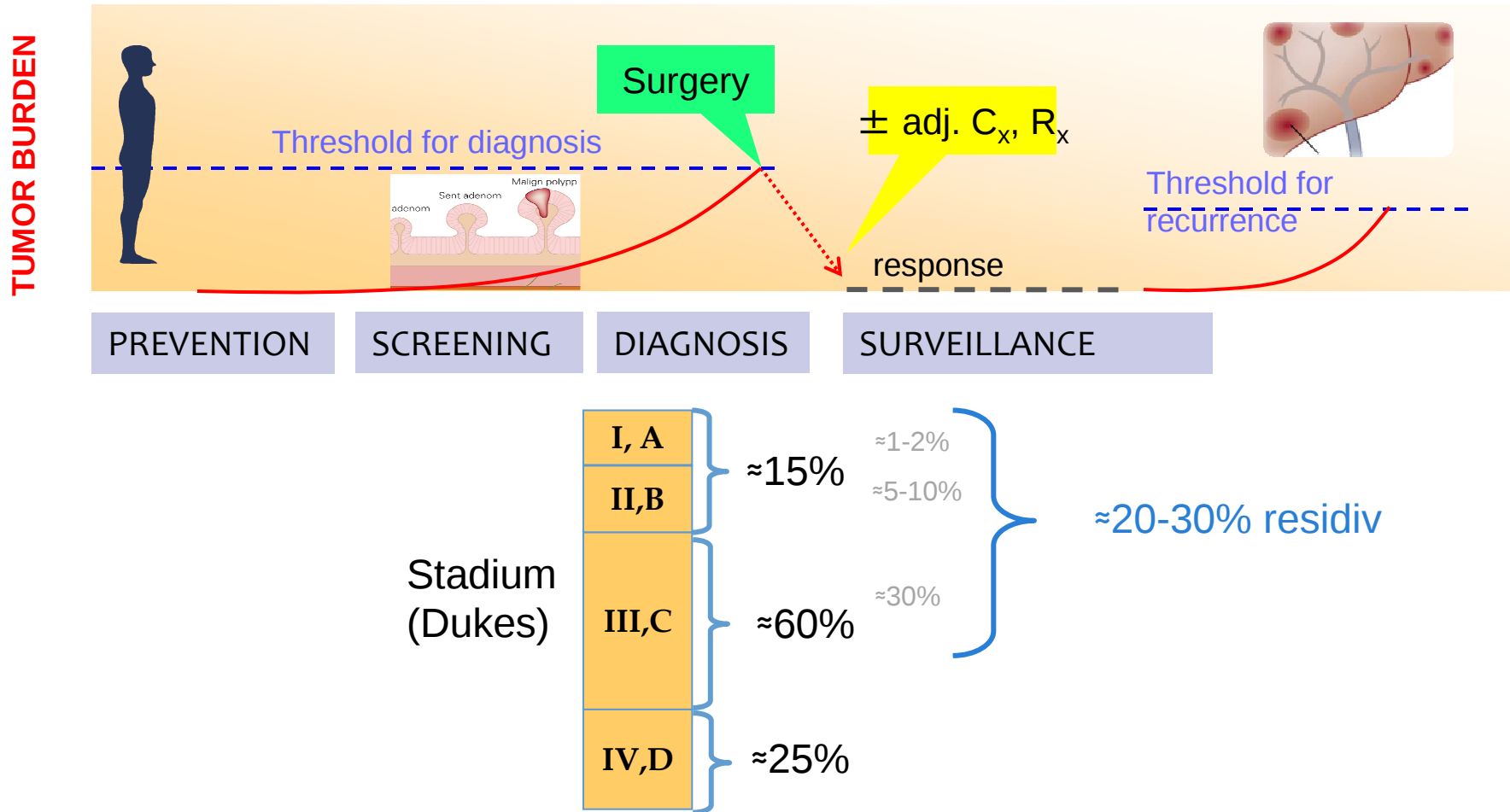
Test-type ??

RCT (NORCAPP,
NORDICC)

Stool DNA
(epigenetiske)



Colorectal Cancer - sykdomsforløp



Follow-up etter CRC kirurgi

Follow-up strategies for patients treated for non-metastatic colorectal cancer (Review)

Jeffery M, Hickey BE, Hider PN

- Intensiv oppfølging:
 - Økt **overlevelse** ved intensiv surveillance
 - OR 0.73 (95% CI 0.59-0.91)
 - Flere får kurativ kirurgi ved tilbakefall
 - (28 vs 12%)
 - Antall residiv likt, tid til oppdagelse noe kortere

Konflikten

- "Best-evidence" tyder på økt overlevelse

Rehnan AG, et al. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials.
BMJ 2002;324:813

Jeffery GM, et al. Follow-up strategies for patients treated for non-metastatic colorectal cancer.
Cochrane Database Syst Rev. 2007

- "Noe" bør gjøres - men hva ?

Kørner H, Søreide K, Stokkeland PJ, Trøeland JH, Søreide JA.
Oppfølging etter kirurgi for kolorektal cancer.
Tidsskr Nor Lægeforen, 2008

Oppfølging etter CRC kirurgi

- Nasjonale retningslinjer i Norge, NGICG-1997:

	Surveillance, post-operative months											
	3	6	9	12	18	24	30	36	42	48	54	60
CEA	●	●	●	●	●	●	●	●	●	●	●	●
US of liver		⊙		⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
Chest X-ray		⚡		⚡	⚡	⚡	⚡	⚡	⚡	⚡	⚡	⚡
Colonoscopy				∩								∩

Oppfølging etter CRC kirurgi

- Compliance er begrenset, kostnadene høye
 - Compliance lavest for coloscopi, 55%

Kørner H, Søreide K, Stokkeland PJ, Søreide JA. Systematic follow-up after curative surgery for colorectal cancer in Norway: a population-based audit of effectiveness, costs, and compliance.

J Gastrointest Surg 2005;9(3):320-8

- Diagnostisk treffsikkerhet ved CEA suboptimal

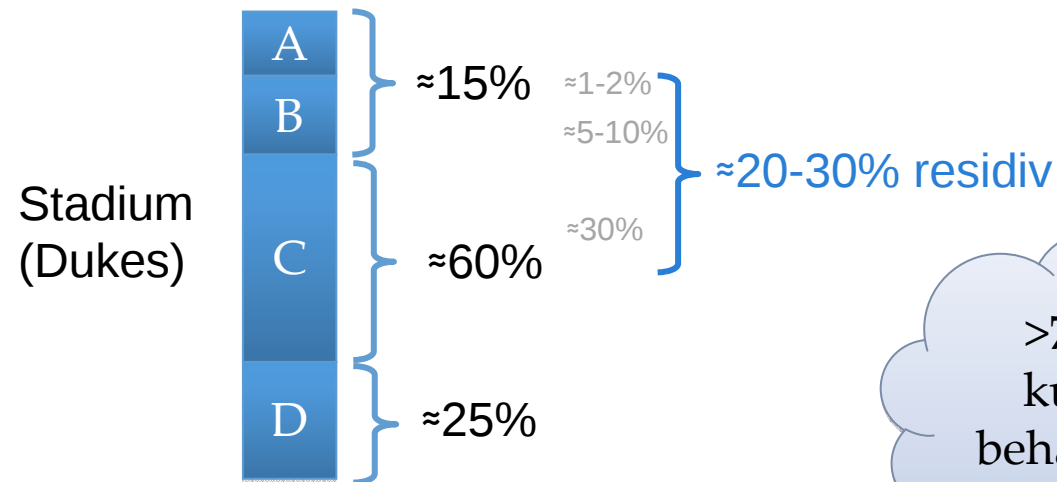
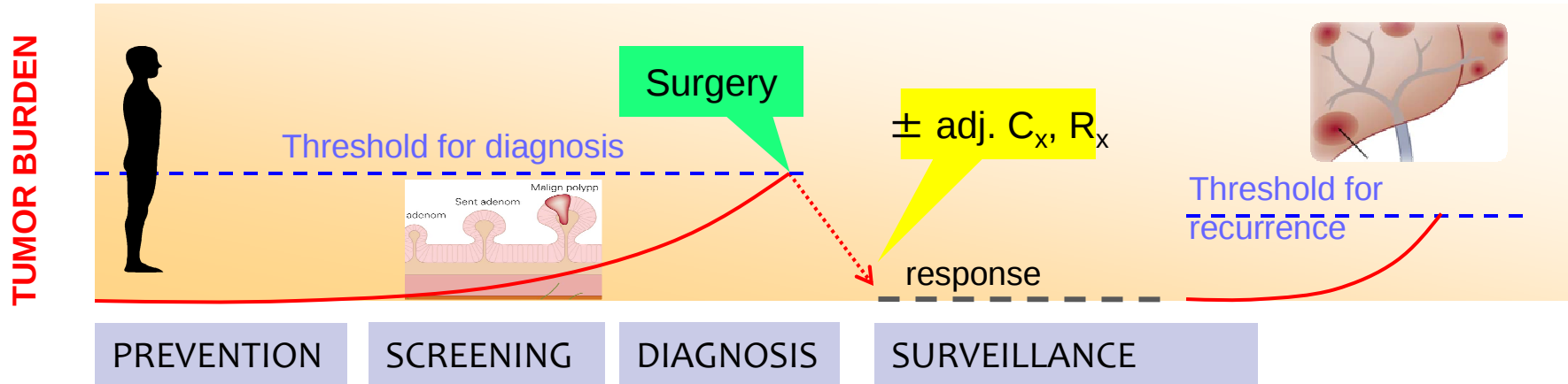
Kørner H, Søreide K, Stokkeland PJ, Søreide JA. Diagnostic accuracy of serum-carcinoembryonic antigen in recurrent colorectal cancer: a receiver operating characteristic curve analysis.

Ann Surg Oncol 2007;14(2):417-23

Spørreundersøkelse 2007

- Alle sykehus svarte (kir. avd., n=46)
- Alle hadde oppfølging etter kirurgi for CRC
 - o De fleste NGICG, eller "modifisert"
 - o De fleste på sykehus, andre via fastlegen
 - Colon-ca gjerne hos fastlege
 - Alle fulgte rectum-ca på sykehus
- Økt bruk av billediagnostikk
 - o CT og MR
 - o = i tråd med de nye anbefalingene til Hdir 2010
 - o Colorect Dis (in press 2012)

Colorectal Cancer



>70% er
kurativt
behandlet !!!

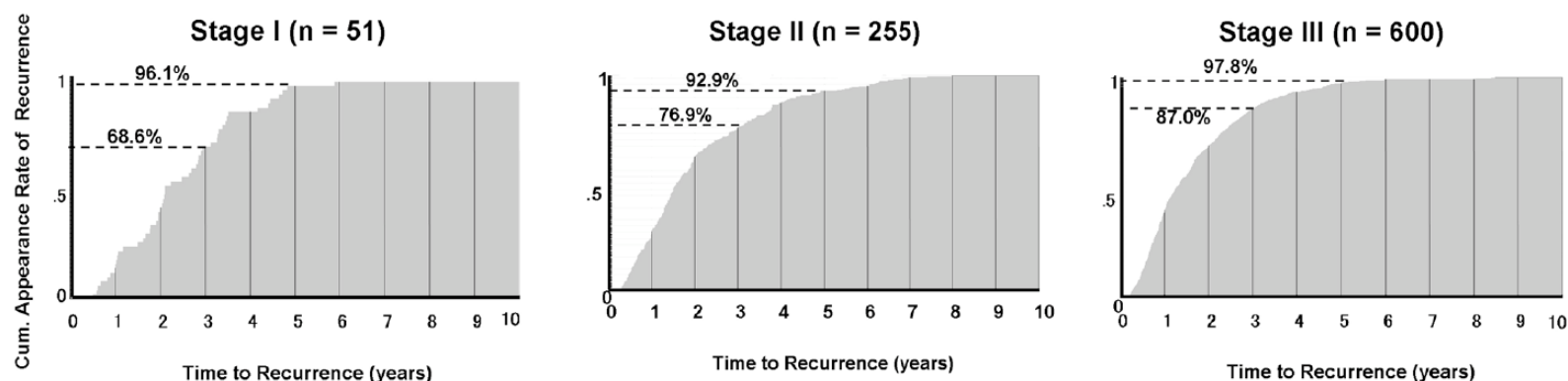
Lokalisasjon for residiv etter kurativ kirurgi

• Lever	30%
• Lunge	20-30%
• "Locoregional"*	5-15%
• Annet sted	<5%
• Ny/metakron cancer	1-3%

Økt rolle/bruk av
billeddiagnostikk
(CT, MR, PET)

- * obs! data basert på gamle tall; pre-TME era etc. •

Timing for follow-up?



Kobayashi et al, Surgery 2007; Japan; n≈5,300

- Residiv generelt:
 - Fleste residiv kommer innen 3 år fra kirurgi
 - Nær "alle" innen 5 år
- Metakron cancer:
 - Median tid til metakron CRC ≈18 mdr
 - Forekomst høyere enn screening populasjoner; SEER, NPS
 - Ann Intern Med, 2002; >3000 stage II + III crc
 - MSI er risikofaktor for metakron CRC
 - Dis Colon Rectum, 2002 etc

anbefalinger

kolon

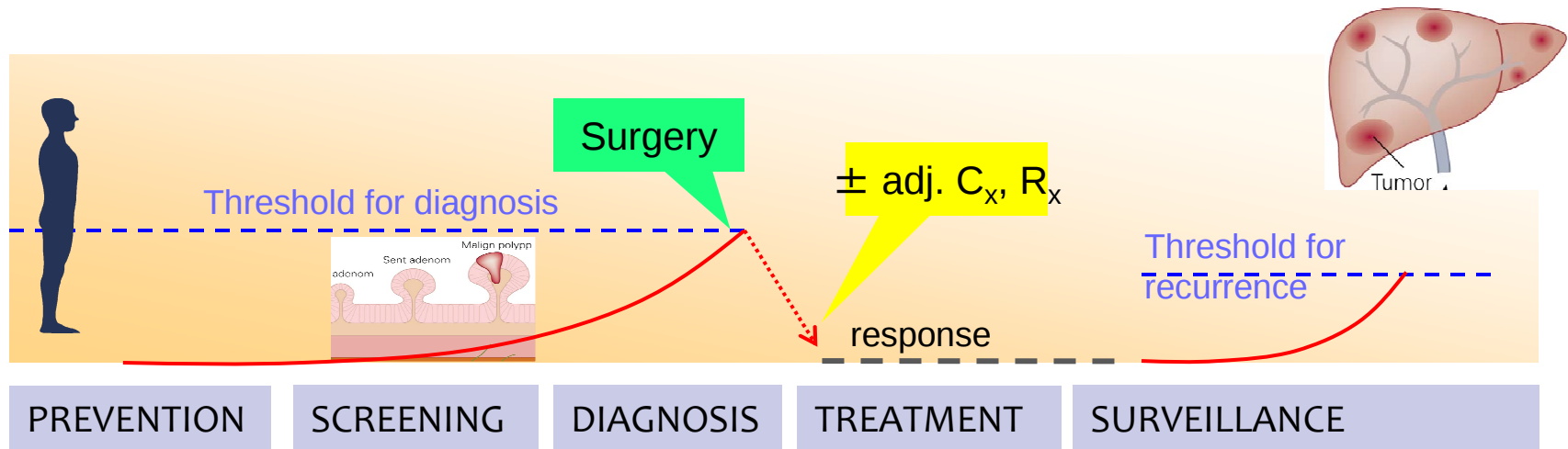
Måneder postop.	1 ¹	6	12	18	24	30	36	48	60
CEA	•	•	•	•	•	•	•	•	•
CT-lever/abdomen		• ²							•
UL-lever med kontrast (CEUS) ²			•	•	•	•	•	•	
Lavdose CT-thorax			•		•		•	•	
Colon-undersøkelse ³									•

rektum

Måneder postop.	1 ¹	6	12	18	24	30	36	48	60
CEA	•	•	•	•	•	•	•	•	•
CT-lever/abdomen/bekken ²		•							•
UL-lever med kontrast (CEUS) ²			•	•	•	•	•	•	
Lavdose CT-thorax			•		•		•	•	
Colon-undersøkelse ⁴									•
Undersøkelse av rectum/perineum ³		•	•	•	•	•	•	•	•

Colorectal Cancer

TUMOR BURDEN



Billedfokusert (US, CT, MR)



Prognose & staging

Lymfeknuter

pN-status fortsatt viktigste prognostiske
markør etter kirurgi for CRC

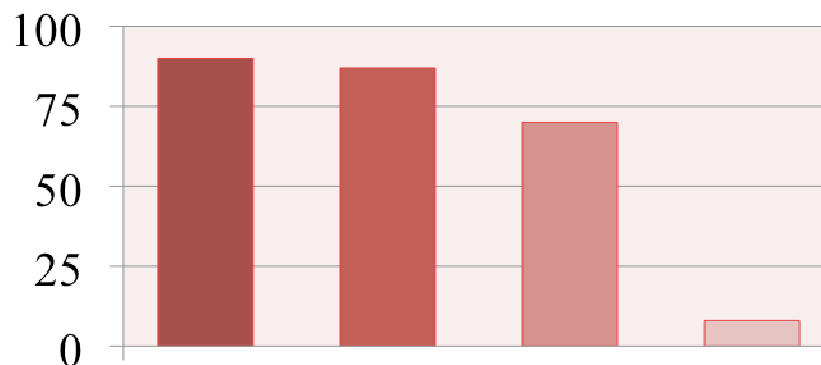
Relativ 5-års overlevelse i Norge

etter TNM-stadium og Dukes' klassifikasjon

TNM-klassifisering av kolorektal kreft

- TNM-systemet (Tumor Node Metastasis)
- TX: Tumors utbredelse kan ikke vurderes
- Tis: Tumor in situ
- T1: Tumor i submucosa
- T2: Tumor i muscularis propria
- T3: Tumor i perirektalt/perikolisk fettvev
- T4: Tumor invaderer naboorganer
- N0: Ingen regionale lymfeknute-metastaser
- N1: Metastase i 1–3 lymfeknuter
- N2: Metastaser i 4 eller flere lymfeknuter
- M0: Ingen fjernmetastaser
- M1: Fjernmetastaser

Stadium	Klassifisering	Relativ femårsoverlevelse (%)
<i>Lokalisert</i>		
I	T1-2, N0, M0	Dukes A
II A	T3, N0, M0	Dukes B
II B	T4, N0, M0	Dukes B
<i>Regional spredning</i>		
III A	T1-2, N1, M0	Dukes C
III B	T3-4, N1, M0	Dukes C
III C	T(alle), N2, M0	Dukes C
<i>Fjernmetastaser</i>		
IV	T(alle), N(alle), M1	Dukes D



5-års overlevelse

LK stasjoner

Tarmnære

Epicolic / paracolic i amerikansk klassifisering

N1-stasjoner i japansk klassifisering

(obs: har ingenting med TNM å gjøre)

Ligger nær tarmveggen, omkring eller perifert for arkade-karene

Intermediære

N2-stasjoner i japansk klassifisering

Ligger sentralt for arkadene, langs kar med anatomisk benevning, for eksempel ileocolica, colica dxt., colica media (men ikke helt sentralt ved avgangen) colica sinistra, sigmoidal-arterier, hemorrhoidalis superior

Sentrale

Central / apical / high i amerikansk klassifisering

N3 stasjoner i japansk klassifisering

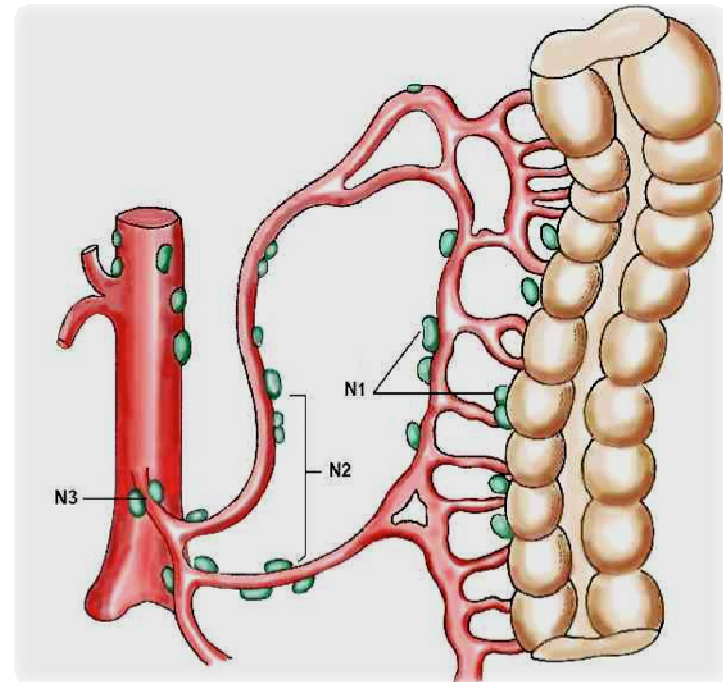
Ligger sentralt ved hovedkarene

Ved mesenterica superior karene ved hø.sidig og transversum cancer (inkl. flexurer)

Ved aorta, sentralt ved mesenterica inferior karene ved ve.sidig cancer

Obs: Paraaortale glandler ovenfor avgangen av mesent. sup / inf. er stasjon N4 = fjernmetastase

Tilsvarende terminologi for å beskrive omfanget av lymfeknutedisseksjon er D1-, D2- og D3-disseksjon i japansk terminologi; tarmnær, intermediær eller sentral (high tie) i vestlig terminologi.



LK: Betydning og kontroverser

- Avgjør adjuvant kjemo +/-
- Influeres av flere faktorer
 - o Avhengig av disseksjon/kirurg
 - o Avhengig av patolog (bruk av mal)
 - o Avhenger av biologi (bl.a. lokalisasjon og MSI)
- Varierende "cut-off"
 - o fra 6 til 40 stk
 - o ≥ 12 LK som "standard" i Norge (anbefalt UICC)
- Betydning av negative vs positive vs "LN-ratio"
 - o Flere studier viser økt overlevelse ved høyere LK antall
- Størst betydning?
 - o Antall (totalt, positive vs negative)
 - o Lokalisasjon (plassering, sentinel)
 - o Innhold (isolerte tumor celler, micrometastaser, immunoprofil)

Lymph node ratio (LNR) - stadium III

- Eur J Surg Oncol, 2008
 - o The lymph node ratio, the quota between the number of lymph node metastasis and assessed lymph nodes, is a highly significant ($p < 0.001$) prognostic factor in stage III colon cancer.
- Am J Surg, 2007
 - o The metastatic lymph node ratio predicts survival in colon cancer.
- Am J Surg, 2007
 - o The relationship of lymph node dissection and colon cancer survival in the Veterans Affairs Central Cancer Registry.

LYMFEKNUTER OG COLON CA

...

"Will Rogers phenomenon"



Will Rogers fenomen

commenting on geographic migration during the economic depression of the 1930s, the American humourist Will Rogers is alleged to have said:

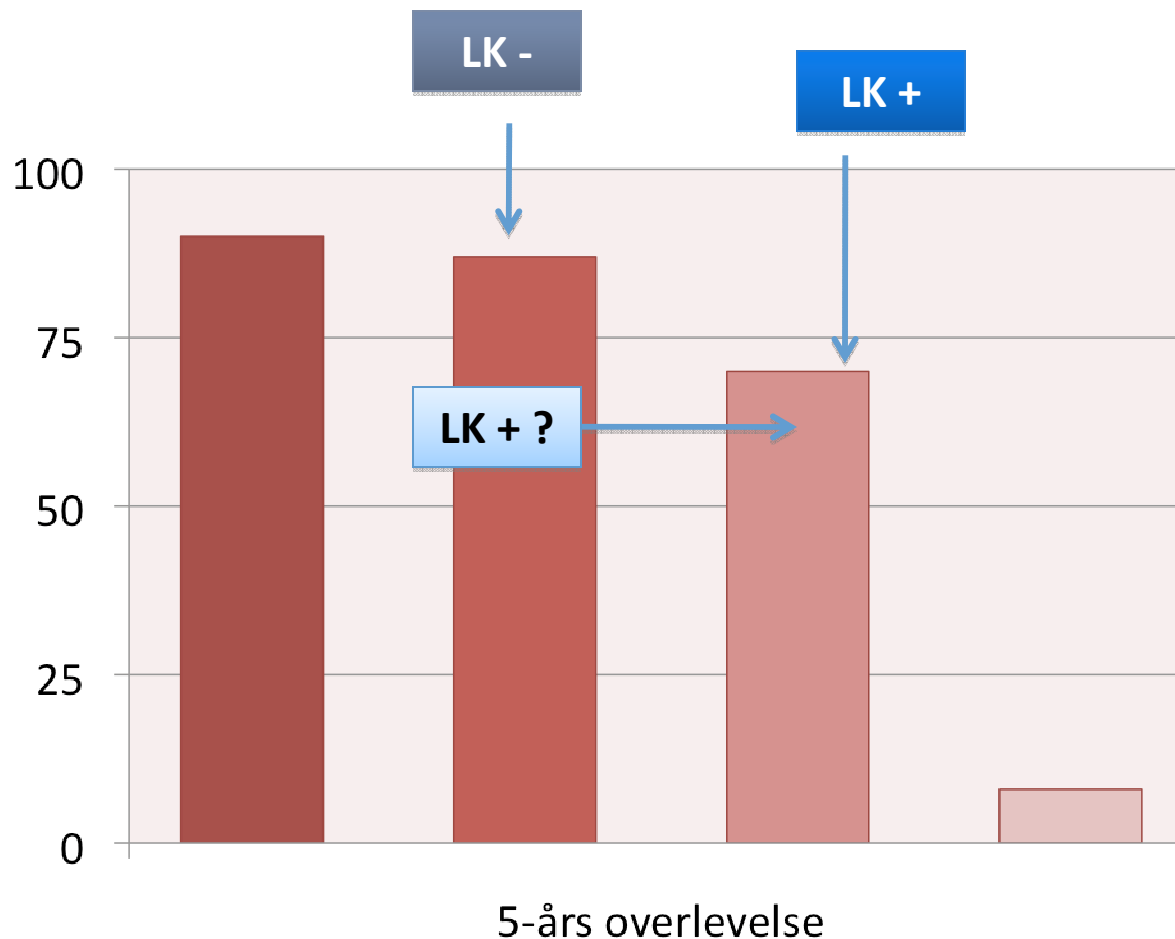
" When the Okies left Oklahoma and moved to California, they raised the average intelligence levels in both states"



The effect will occur when both of these conditions are met:

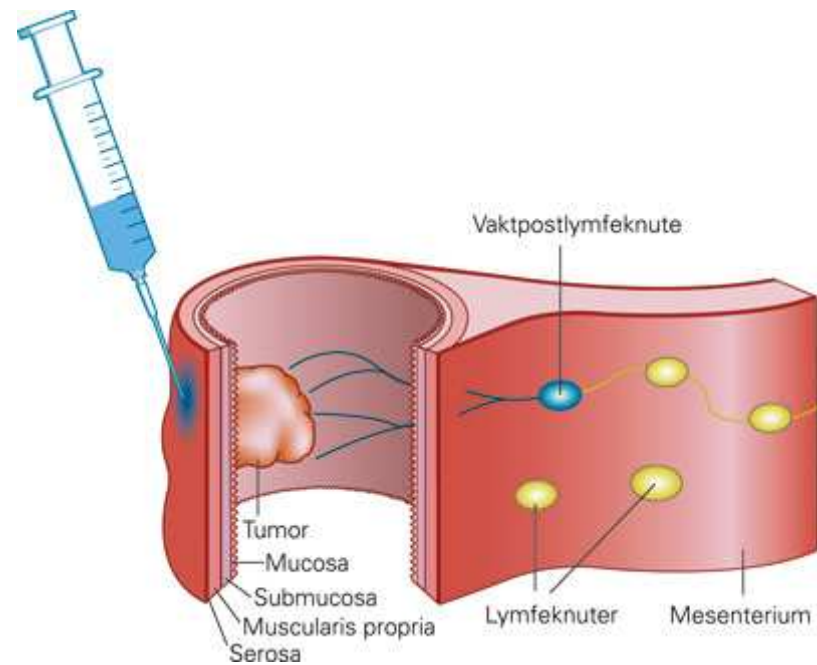
1. The element being moved is below average for its current set. Removing it will, by definition, raise the average of the remaining elements
2. The element being moved is above the current average of the set it is entering. Adding it to the new set will, by definition, raise the average

...gjelder “stage migration” i medisin!

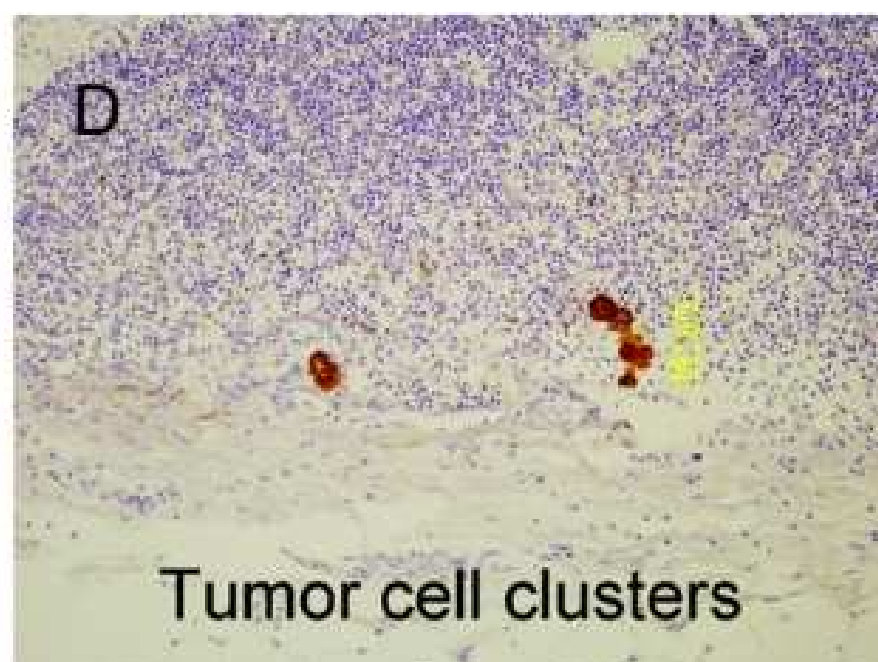
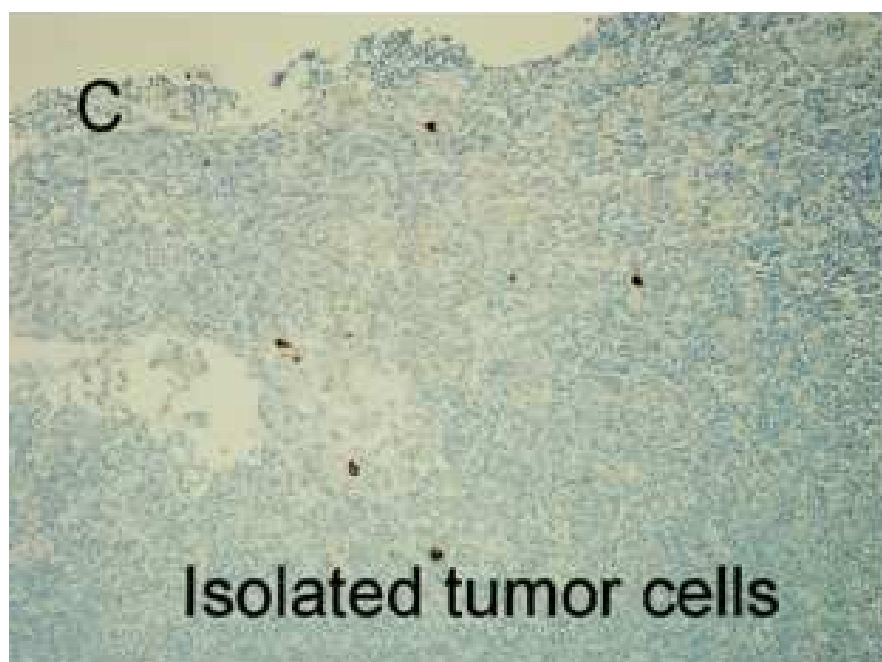


- If a population of patients is **more accurately staged** it will **improve the survival of all stages** because patients with **subtle advanced disease** will be **upstaged** ●

Vaktpostlymfeknuder ved tykktarmskreft (sentinel node)

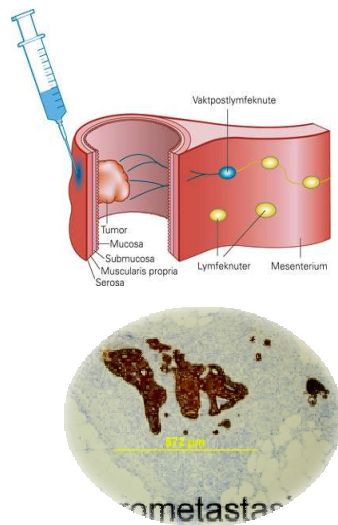


Mikrometastaser og isolerte tumor celler (ITC)

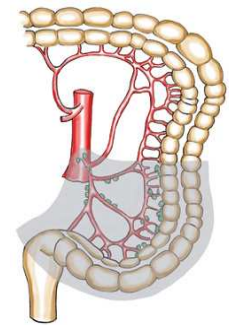


LK: diagnostisk eller terapeutisk ???

“Ta den rette”



“Ta alt”





Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm

