

Internal Medicine Review

Colon Cancer Update

April 7, 2023

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Sentinel Hotel, Portland

Outline

- SEER data- Incidence & mortality
- Presentation and risk factors
- Screening
- Staging
- Treatment colorectal cancers
- Survivalship

Projected Mortality Rates

Common Types of Cancer	Estimated New Cases 2022	Estimated Deaths 2022	
1. Breast Cancer (Female)	287,850	43,250	
2. Prostate Cancer	268,490	34,500	
3. Lung and Bronchus Cancer	236,740	130,180	1
4. Colorectal Cancer	151,030	52,580	2
5. Melanoma of the Skin	99,780	7,650	
6. Bladder Cancer	81,180	17,100	
7. Non-Hodgkin Lymphoma	80,470	20,250	
8. Kidney and Renal Pelvis Cancer	79,000	13,920	
9. Uterine Cancer	65,950	12,550	
10. Pancreatic Cancer	62,210	49,830	3

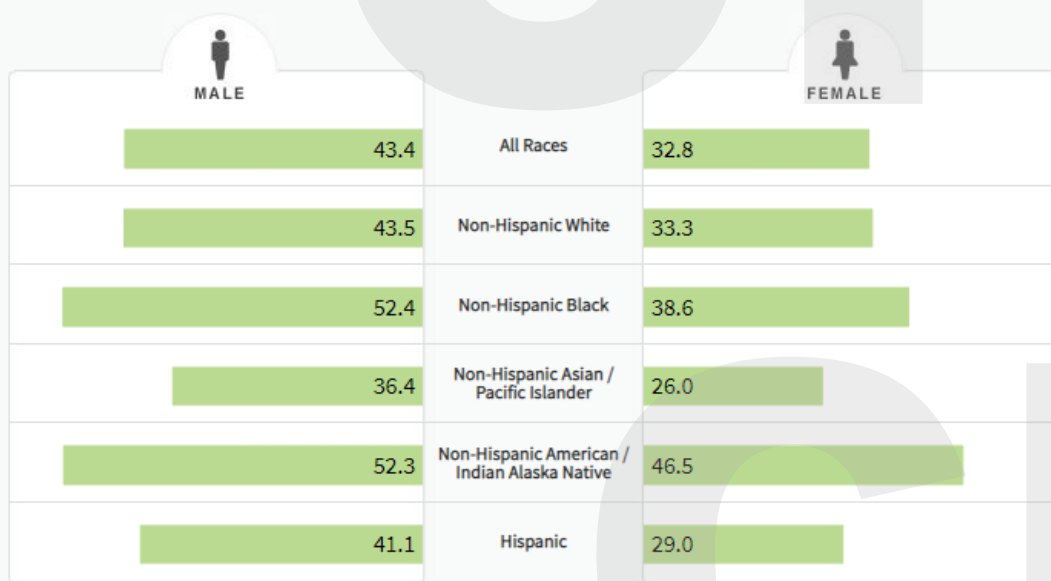
Colorectal cancer represents 7.9% of all new cancer cases in the U.S.



*SEER cancer statistics

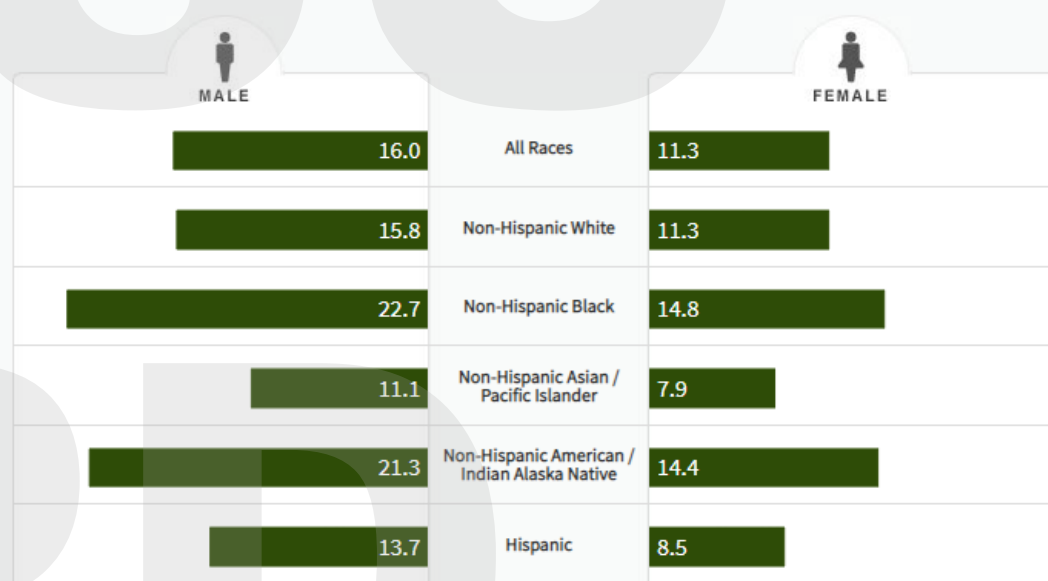
Rates by Race/Ethnicity/sex

Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer



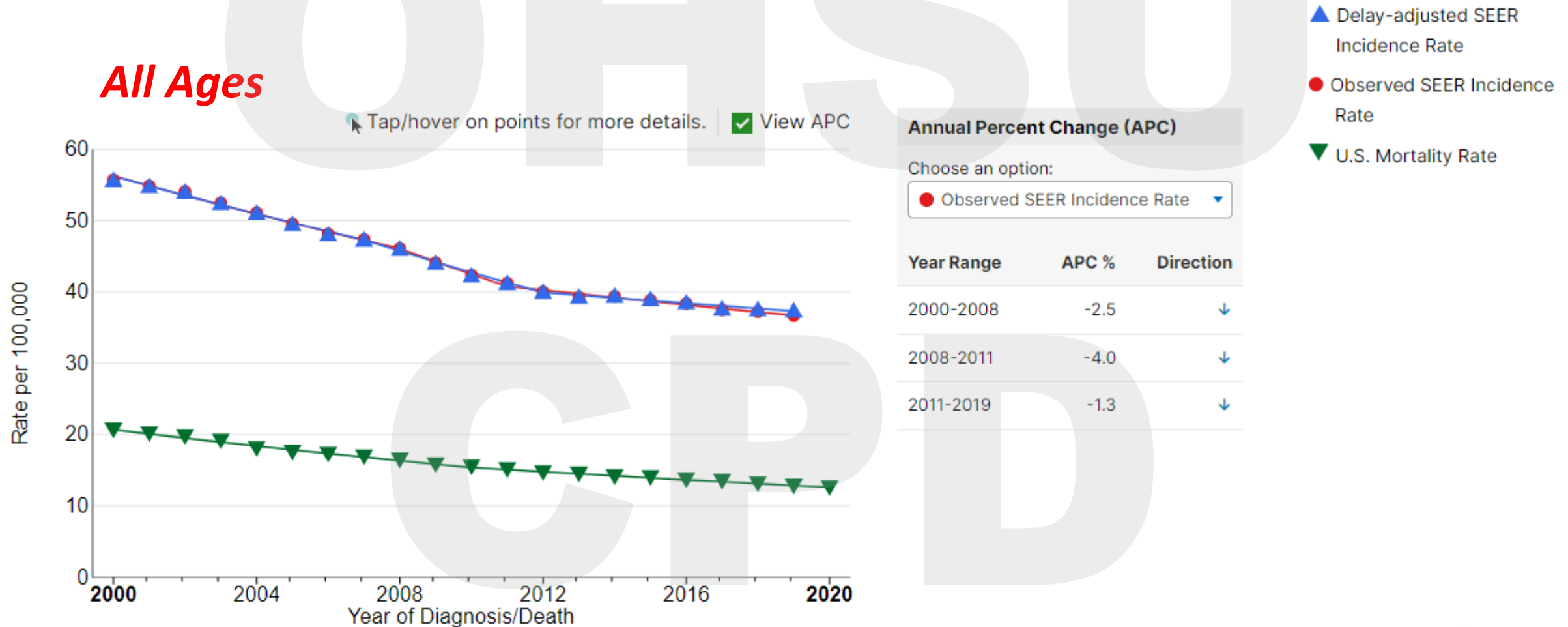
SEER 22 2015-2019, Age-Adjusted

Death Rate per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer



U.S. 2015-2019, Age-Adjusted

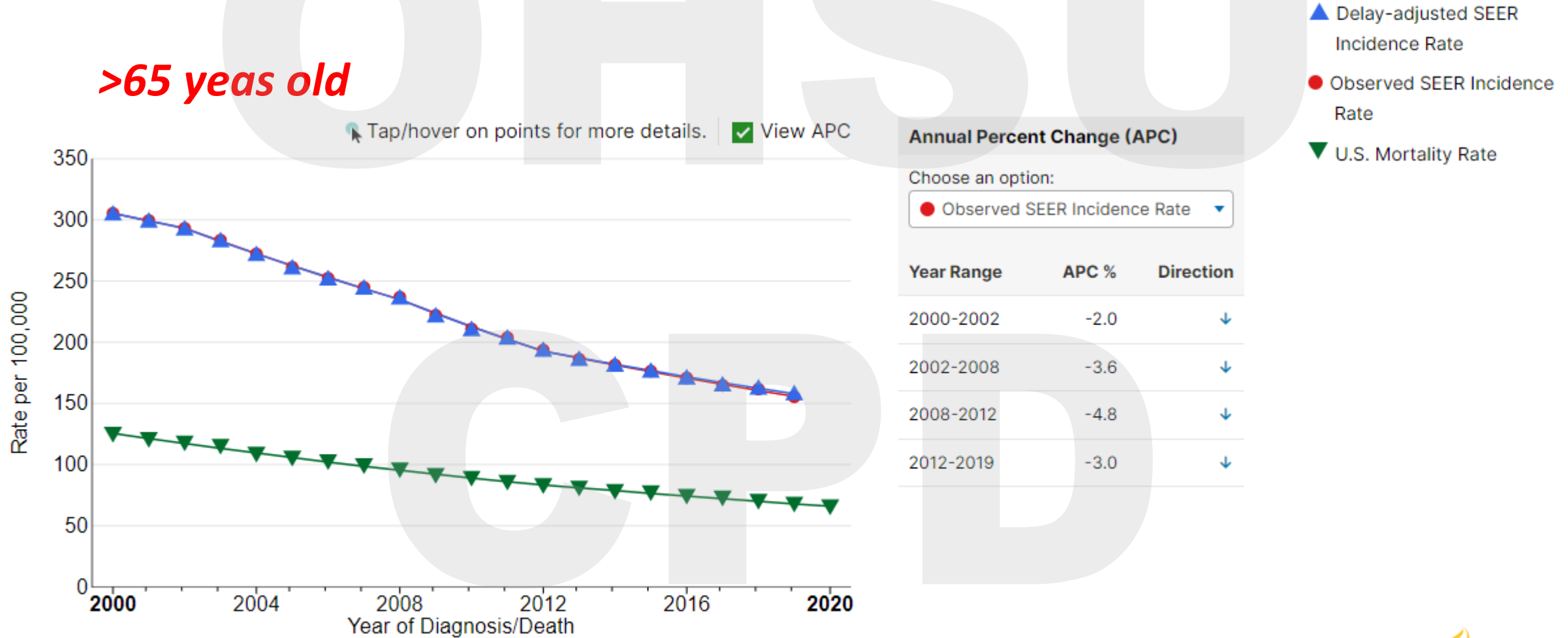
Recent Trends in SEER Incidence(2000-2019) and U.S. Mortality(2000-2020) Rates



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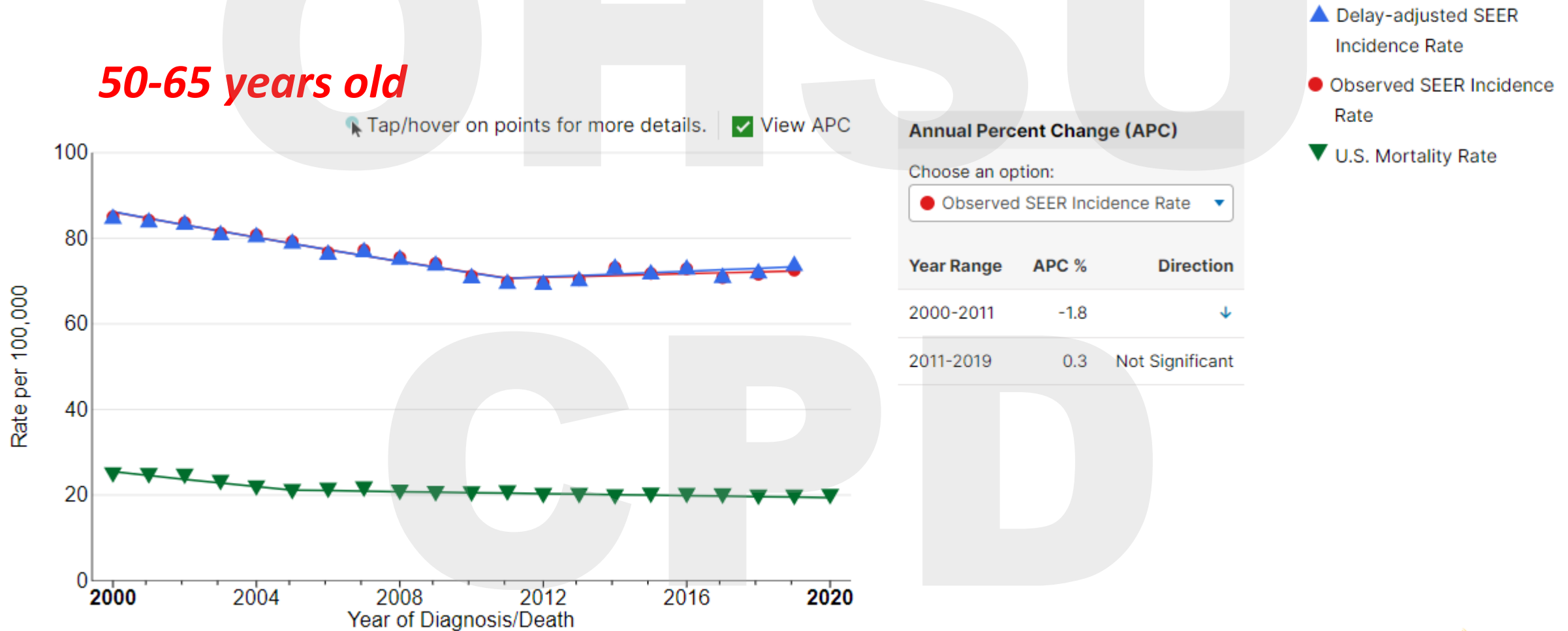
>65 years old



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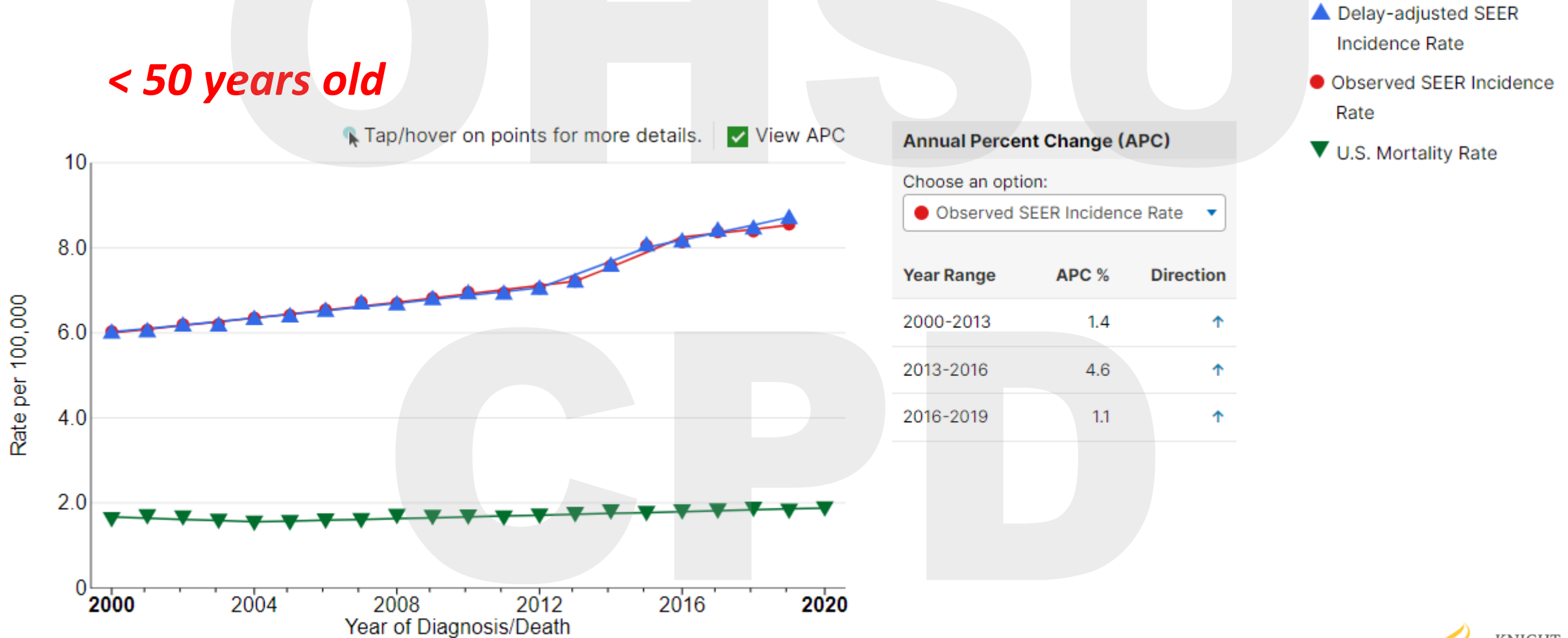
50-65 years old



*SEER cancer statistics

Recent Trends in SEER Incidence(2000-2019) and U.S. Mortality(2000-2020) Rates

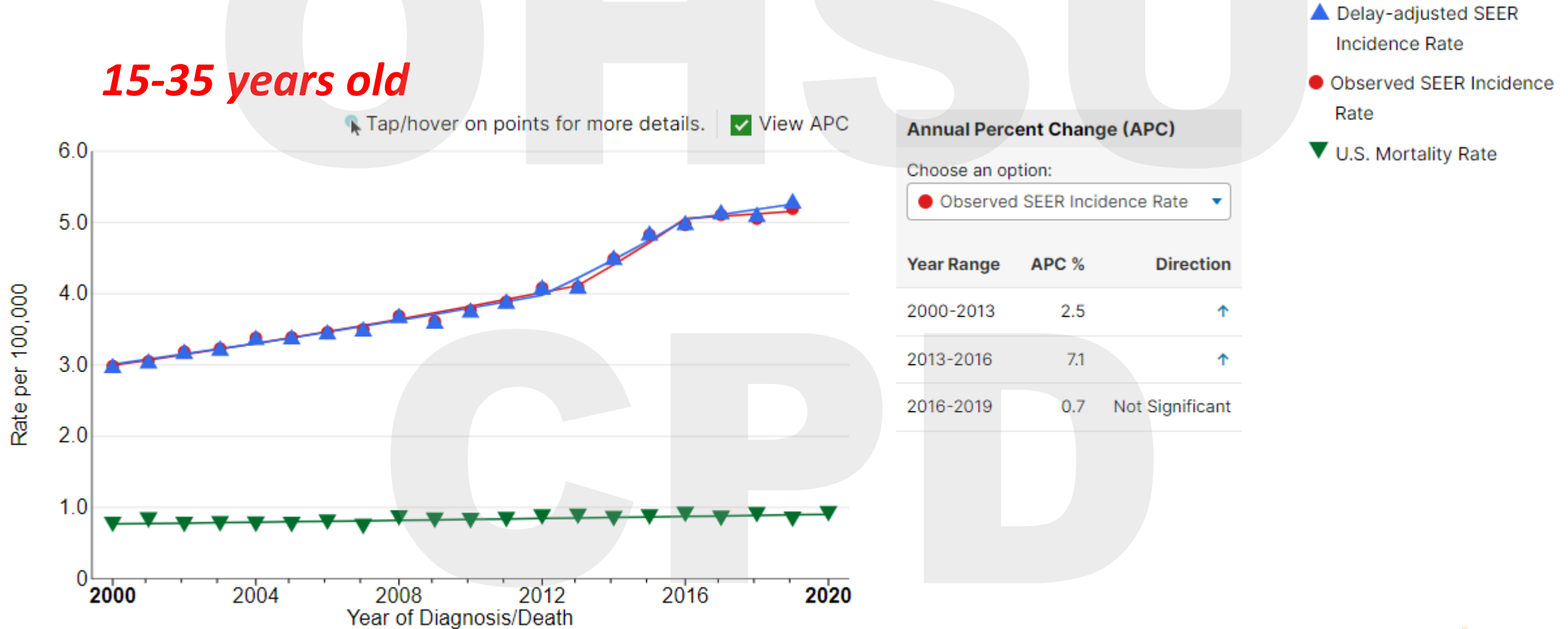
< 50 years old



*SEER cancer statistics

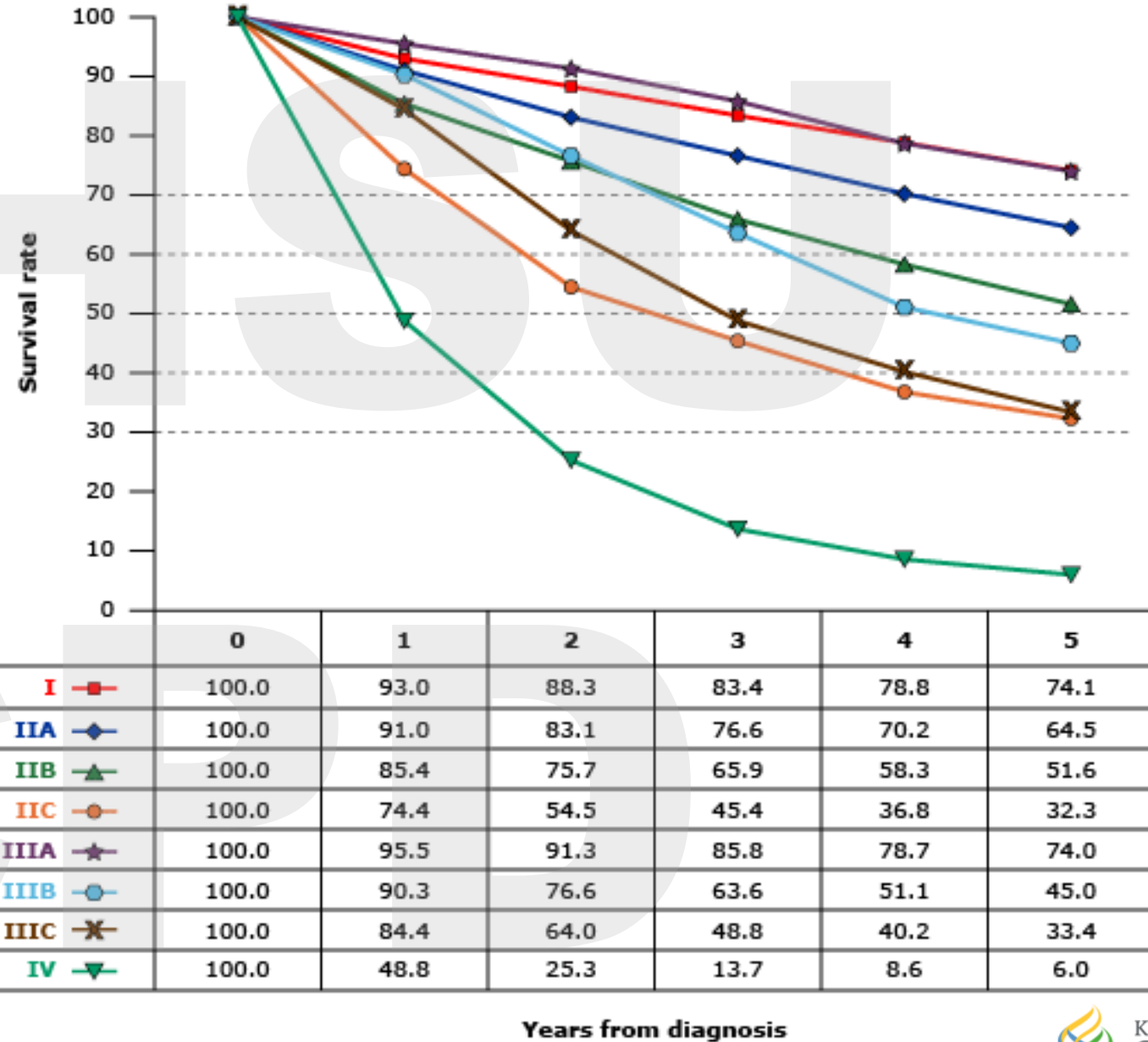
Recent Trends in SEER Incidence(2000-2019) and U.S. Mortality(2000-2020) Rates

15-35 years old



*SEER cancer statistics

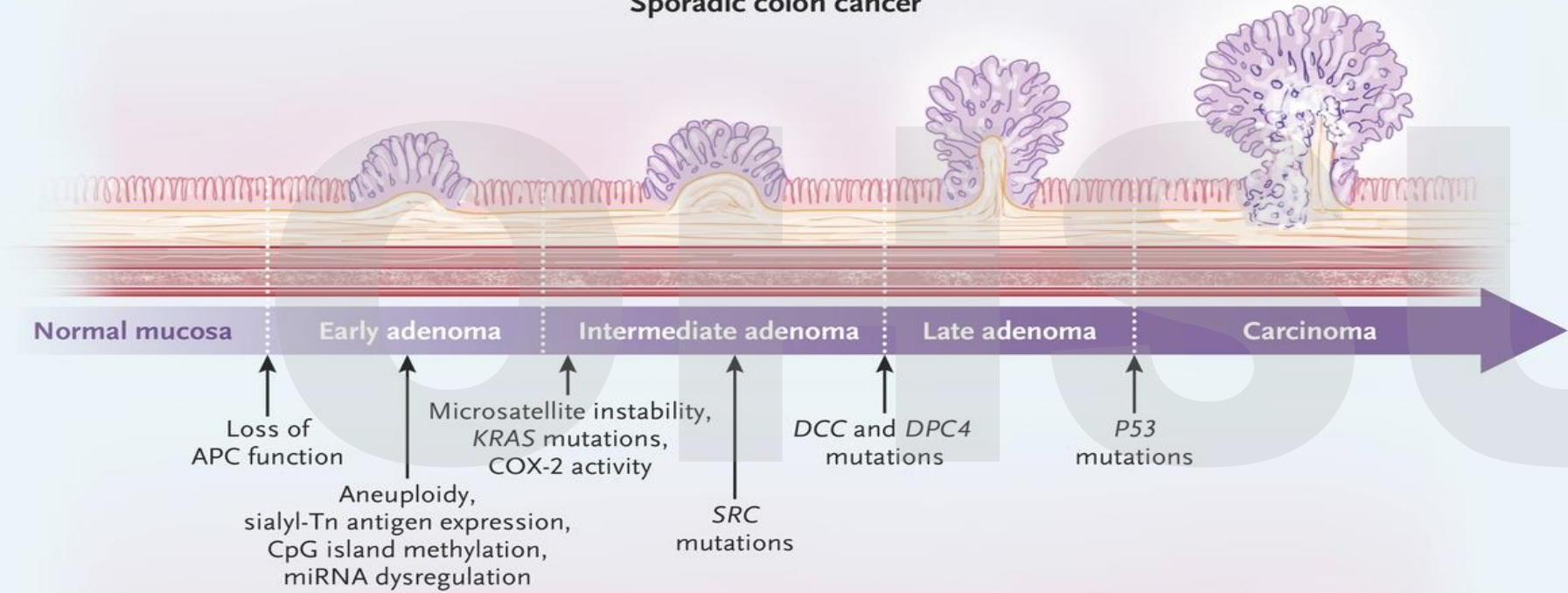
Survival Per Stage



SEER 1973-2005 Public Use File diagnosed in years 1998-2000

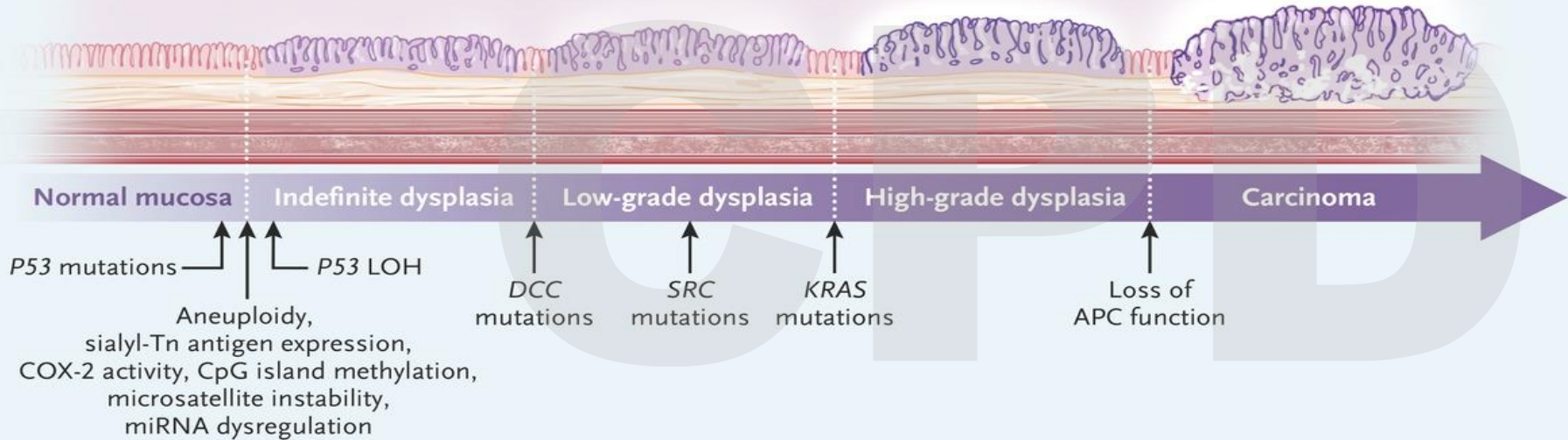
A

Sporadic colon cancer



**Multi-step
Model of
Carcinogenesis
= biologic
heterogeneity**

Colitis-associated colon cancer



**Slow process
years**

Risk Factors for Colorectal Cancer

Genetic susceptibility	FAP (risk approaches 100% by age 50) HNPCC (Lynch Syndrome) (lifetime risk approaches 80%)
Family history (first degree)	CRC (16% lifetime risk); adenoma (11% lifetime risk)
Medical history	Inflammatory bowel disease (pancolitis \geq 8 years or left-sided colitis \geq 15 years) (10-20% risk)
Characteristics	Age (91% of cases occur after age 50) Male sex (35% \uparrow in men) Race/ethnicity (15% \uparrow in African Americans) High dietary fat, red meat, low dietary fiber, smoking, excess alcohol, obesity, diabetes, low physical activity.

FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colon cancer syndrome; CRC = colorectal cancer.

Anderson FW, et al. *J Natl Cancer Inst.* 2002;94:1126-1133; *Colorectal Cancer Facts & Figures*. American Cancer Society; 2005; Levin B, et al. *NCCN*. v.1.2005; Lynch HT, et al. *Cancer*. 1995;76:2427-2433; Petersen GM, et al. *Cancer*. 1999;86(suppl):2540-2550; Winawer SJ, et al. *Gastroenterology*. 2003;124:544-560.

High Risk Syndromes- specific guidelines

- Lynch syndrome (hereditary nonpolyposis colorectal cancer)
- Classic familial adenomatous polyposis (FAP)
- Attenuated familial adenomatous polyposis (AFAP)
- *MUTYH*-associated polyposis (MAP)
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Serrated polyposis syndrome (SPS)
- Colonic adenomatous polyposis of unknown etiology
- Cowden syndrome/PTEN hamartoma tumor syndrome
- Li-Fraumeni syndrome

OHSU

- THE IMPORTANCE OF PRIMARY CARE !

CPCD

Presentation

- Many of the gastrointestinal symptoms caused by CRC, are common, often non-specific, and most people presenting with them will not have cancer.
 - Example; change in bowel habit
- Key diagnostic challenge for PCP
 - Identify the **small** number of symptomatic patients with cancer from the **large** number without

Presentation

- Most patients diagnosed with CRC will have presented in primary care with one or more abdominal complaints before diagnosis
- Lower gastrointestinal symptoms require clinical and family history, physical examination (including abdominal and rectal examination), and routine blood tests (to exclude anemia and other clinical features)
- Overlapping symptoms with diverticular disease or diverticulitis, IBD, and irritable bowel syndrome

Protective and risk factors for colorectal cancer

In the US, CRC has the second highest number of cancer cases and deaths attributed to lifestyle factors!

Protective lifestyle factors

- Consumption of dietary fibre
- Consumption of whole grains
- Consumption of dairy products
- Milk intake
- Calcium intake
- Physical activity
- Aspirin use
- Hormone replacement therapy

Lifestyle risk factors

- Consumption of processed meat
- Consumption of red meat
- Alcohol consumption
- Body fatness
- Abdominal fatness
- Tobacco smoking

Higher risk groups

(Including genetically determined conditions)

- Family history of CRC
- Personal history of CRC or colorectal adenoma
- Other diseases/conditions
 - Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
 - Acromegaly
 - Ureterosigmoidostomy
 - Cystic fibrosis
- Non-polyposis syndromes
 - Lynch syndrome
 - Familial CRC
- Adenomatous polyposis syndromes (e.g. Familial Adenomatous Polyposis or FAP)
- Non-adenomatous polyposis syndromes
- Genetic variants

Screening....

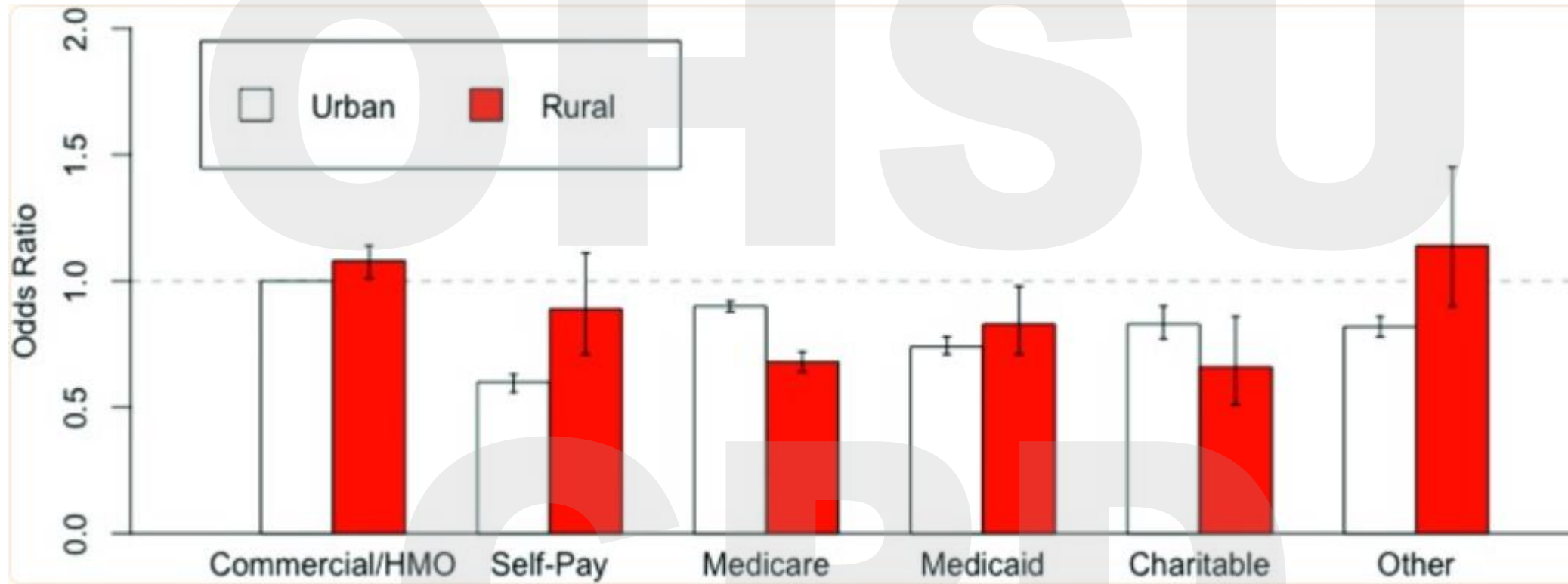
SCREENING REDUCE CRC MORTALITY!

- Stool-based tests
 - Fecal immunochemical test every y
 - High-sensitivity, guaiac-based fecal occult blood test every y
 - Multitarget stool DNA test every 3y
- Structural examinations
 - Colonoscopy every 10y
 - CT colonography every 5y
 - Flexible sigmoidoscopy every 5y
- **Colonoscopy – Preferred approach**
 - National Polyp Study: 76-90% reduction in expected rate of CRC
- **But...**

Winawer et al. N Engl J Med. 1993;329:1977-1981.

Rex, et al. Gastrointestinal Endoscopy. 2006;63:S16-28.

But WE aren't getting screened!



Adjusted odds ratio of seeing a specialist for the interaction of rurality with insurance.

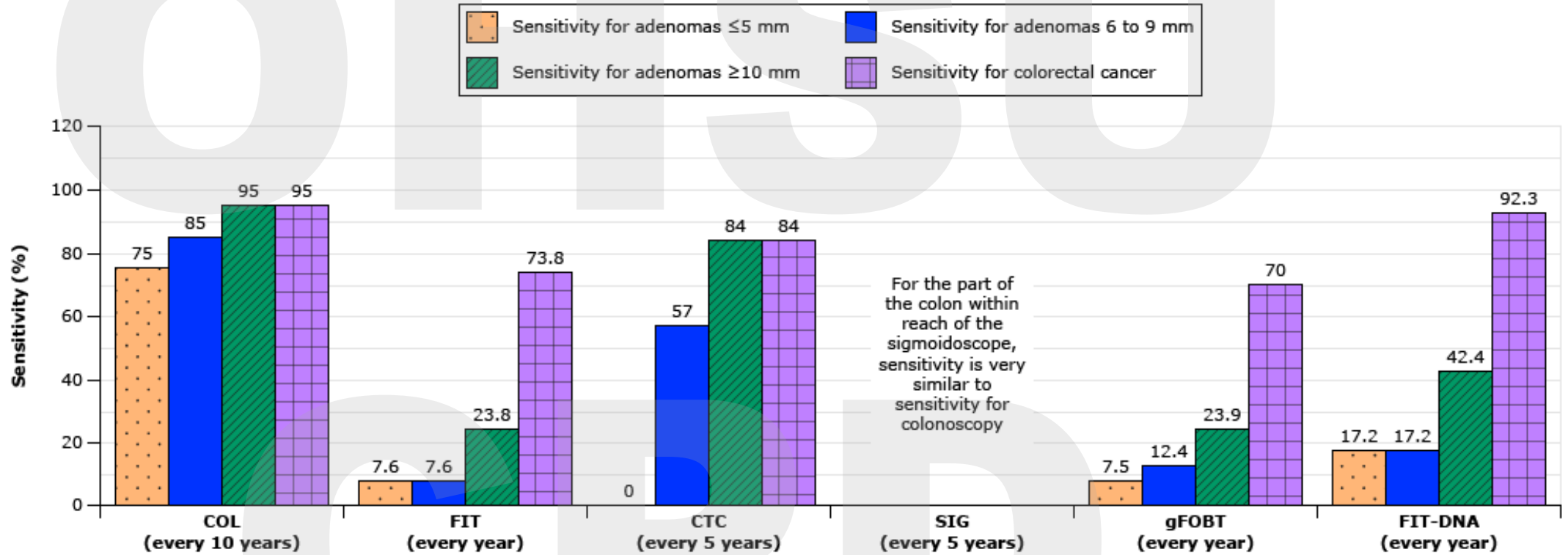
Screening

- Initiate screening at age 45 years in adults at average risk
 - USPSTF, American College of Gastroenterology, American Cancer Society...
- Discontinue screening should be individualized based on shared decision-making (avg age 75yo)
 - However, for older adults who have never been screened average risk assessment of cost effectiveness
 - colonoscopy was cost-effective to age 83 years,
 - sigmoidoscopy to 84 years,
 - fecal immunochemistry testing (FIT) to 86 year

Stool-based tests

- Faecal immunochemical test (FIT) vs guaiac Faecal occult blood test (gFOBT)
- FIT has several advantages over gFOBT
 - Increased sensitivity and specificity, better sensitivity to detect advanced adenomas, and only requires a single stool sample
 - Specific to human haemoglobin, does not require dietary restrictions, and the results are unaffected by NSAIDs and anticoagulants
- FIT (yearly) vs multitarget stool DNA testing (every 1-3 year-Cologuard)
 - Multitarget stool DNA testing detect significantly more cancers than FIT but had more false positive results.

Colorectal cancer screening strategy



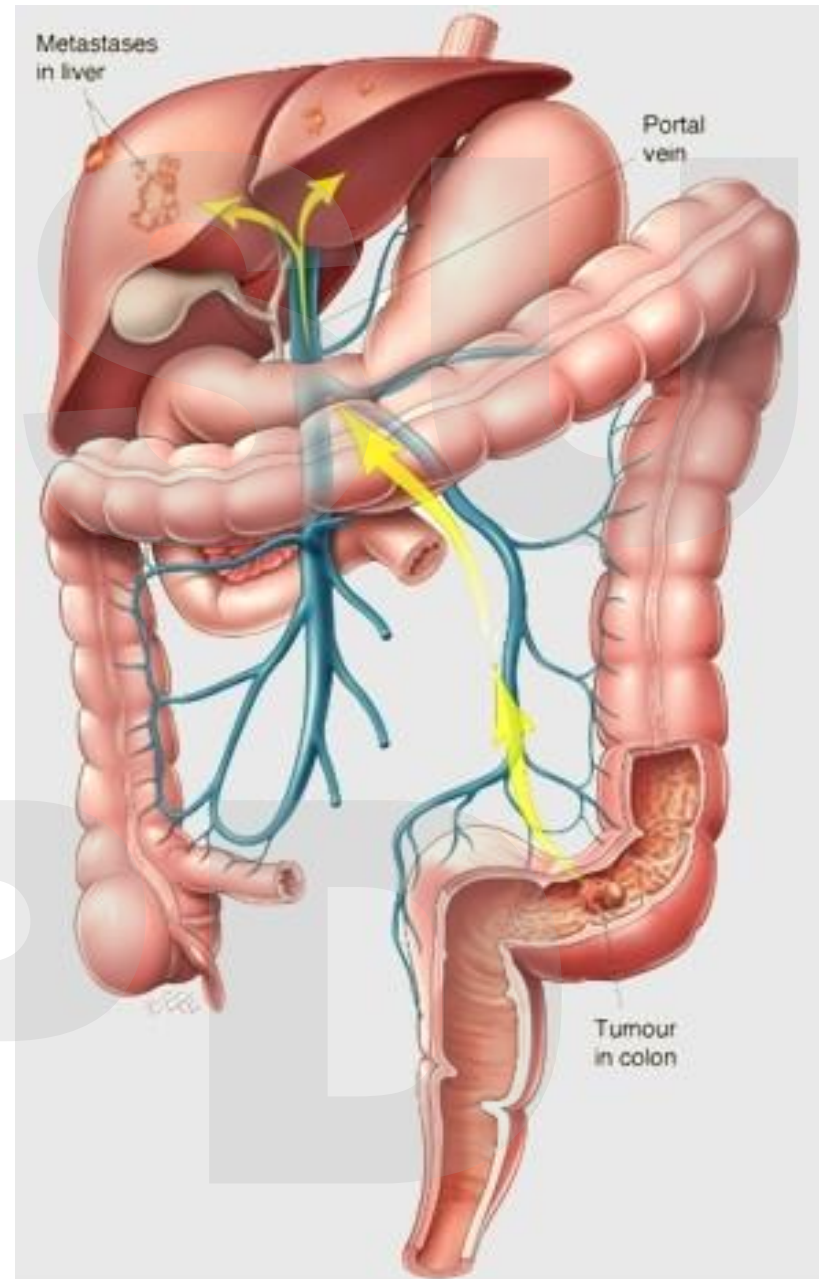
Test specificity	86	96.4	88	87	92.5	89.8
Colorectal cancer deaths averted per 1000 40-year-olds (n)*	22 to 24	20 to 23	16 to 24	16 to 21	20 to 23	21 to 24

Uptodate

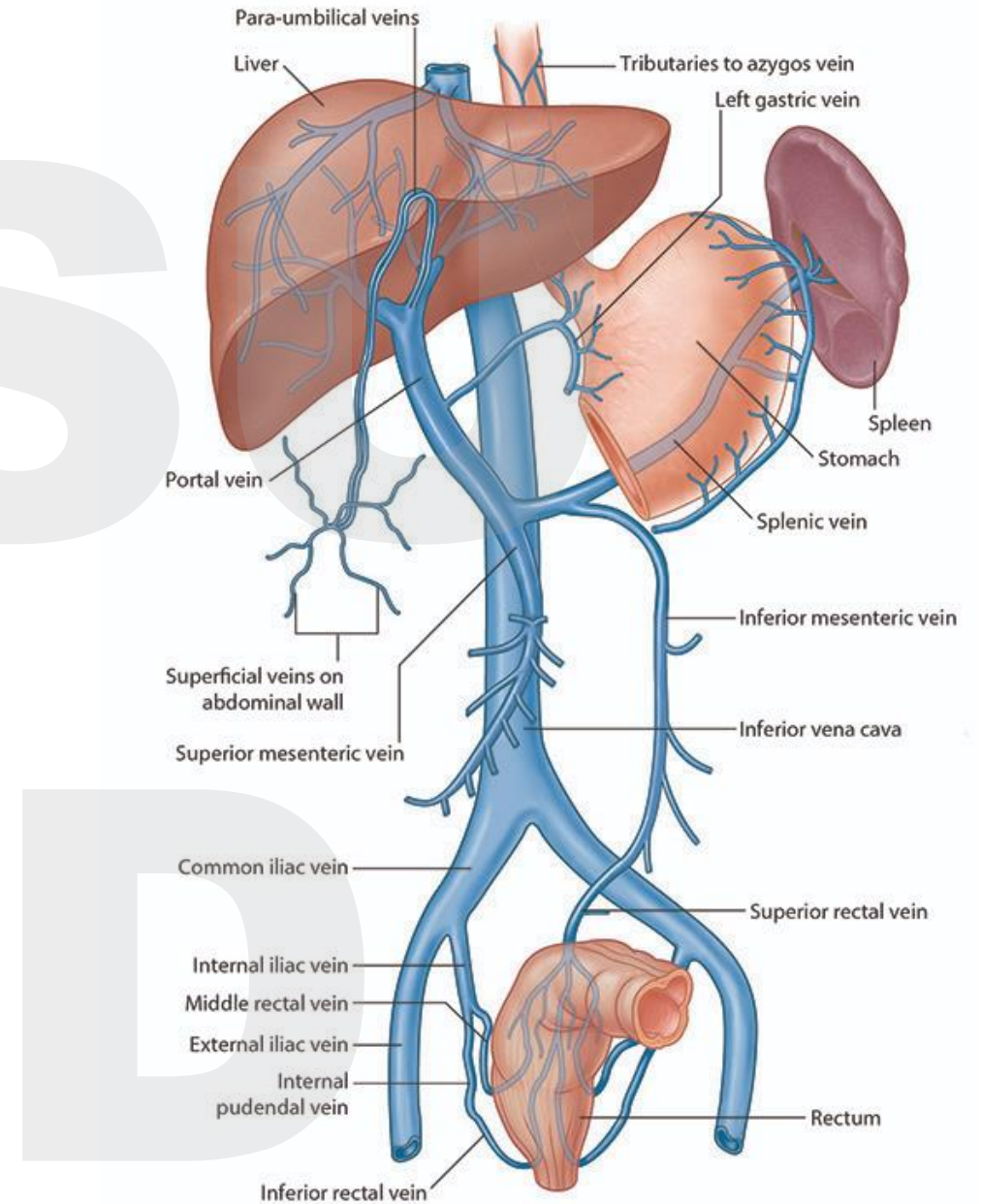
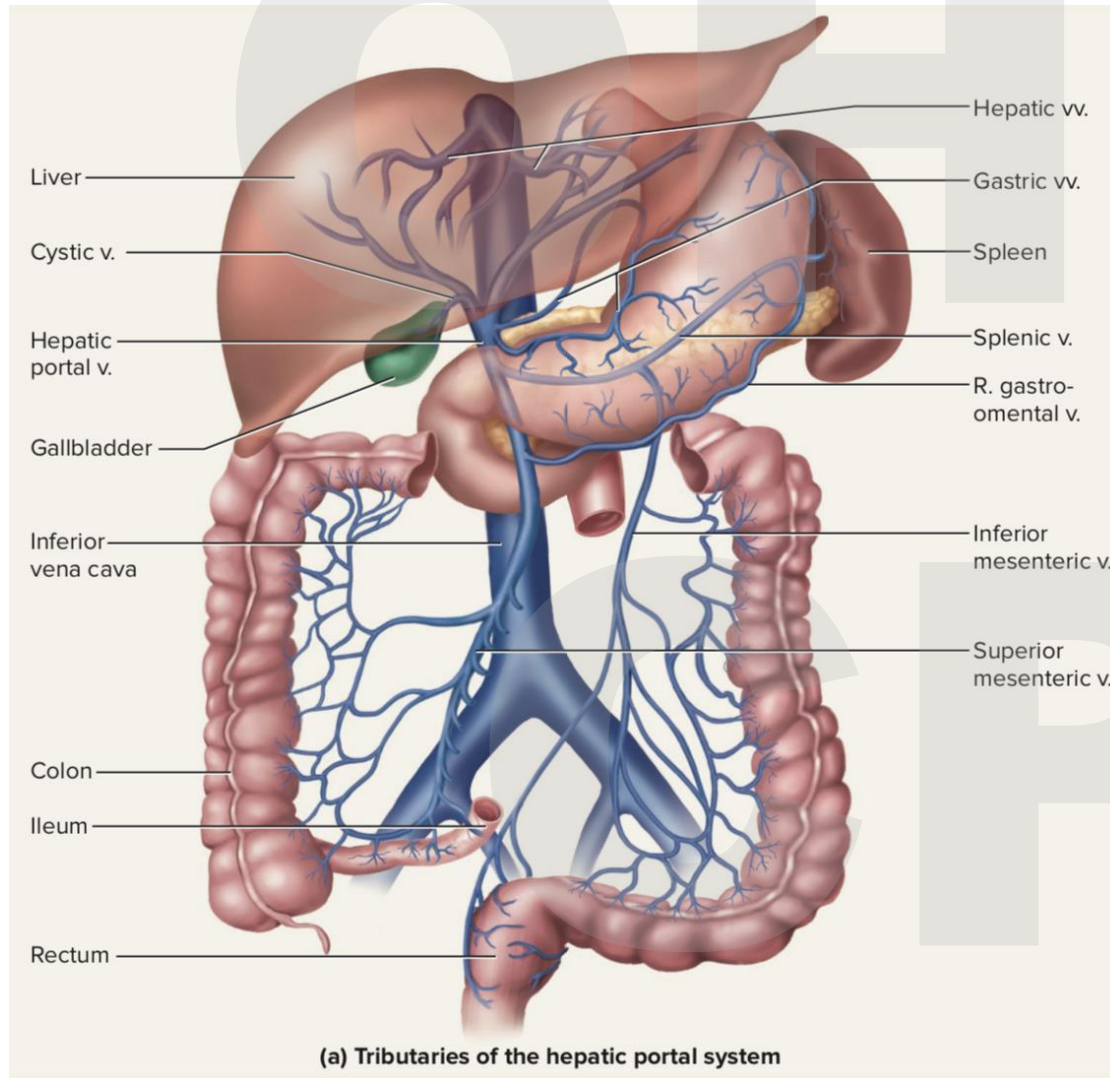
Zauber et al. AHRQ Publication No. 14-05203-EF-2. Agency for Healthcare Research and Quality; October 2015.

Knudsen et al. JAMA 2016; 315:2595.

ColoRECTAL Cancer



Venous Drainage

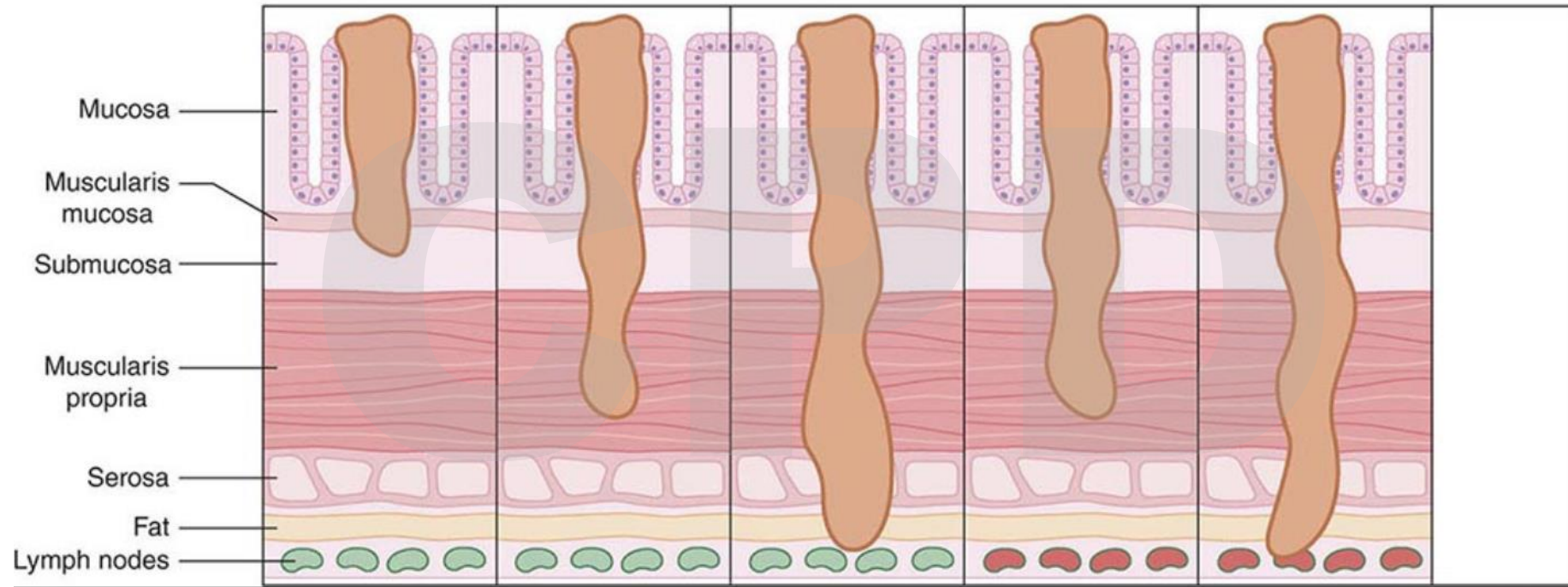


Stage

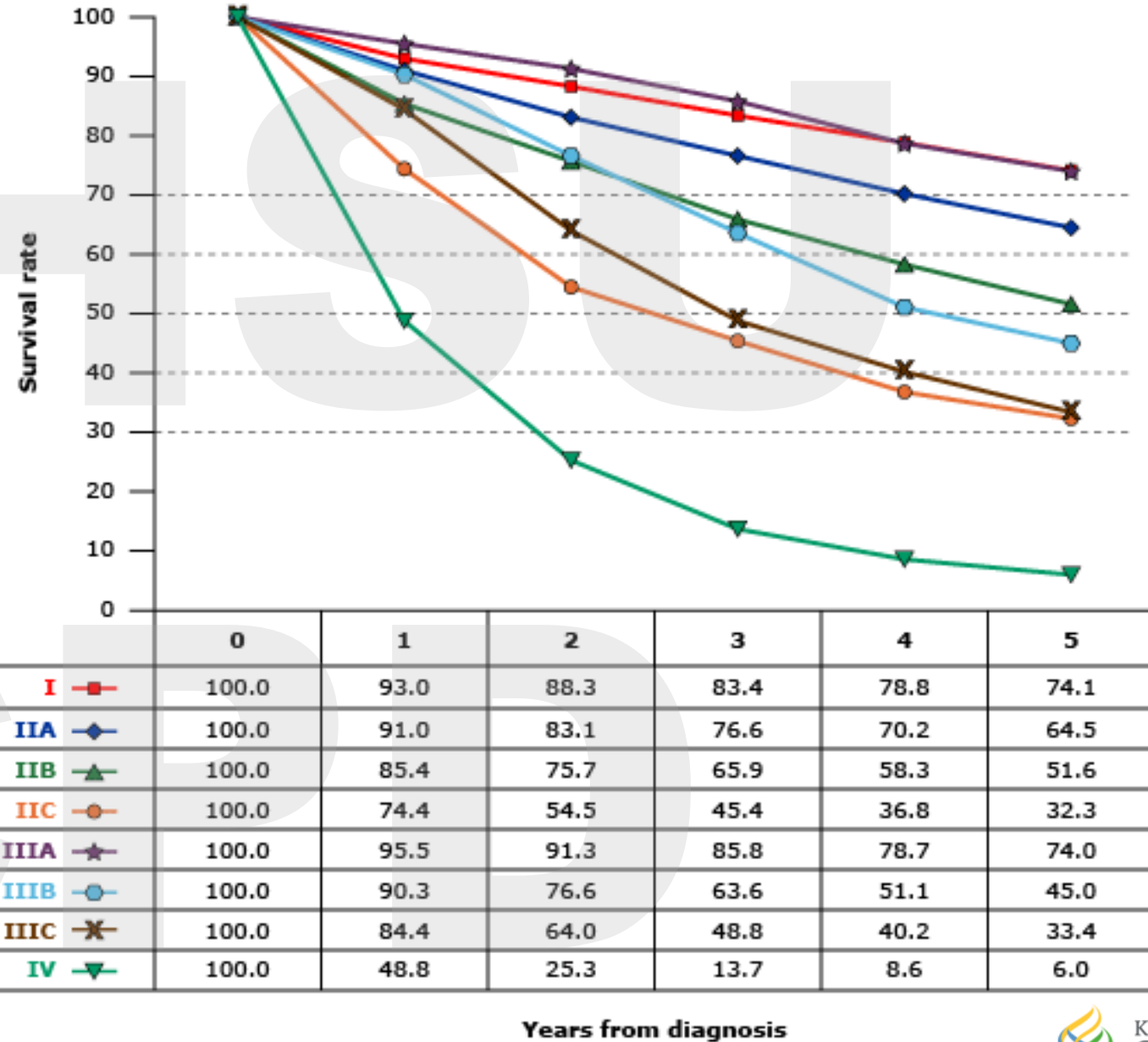
Staging of colorectal cancer

Stage	I		II	III		IV
	T1	T2	T3	N1	N2	M
Extent of tumor	No deeper than submucosa	Not through muscularis	Through muscularis	1-3 lymph node metastases	≥4 lymph node metastases	Distant metastases
5-year survival	>95%	>90%	70-85%	50-70%	25-60%	<5%
Stage at presentation	Colon 23%		31%	26%		20%
	Rectal 34%		25%	26%		15%

Surgery (Stages I-II)
 ?! (Stages II-III)
 Surgery + Systemic (Stages III-IV)
 Systemic (Stage IV)



Survival Per Stage



SEER 1973-2005 Public Use File diagnosed in years 1998-2000

Staging

- **Biopsy**, colonoscopy or metastatic site
- CT chest abdomen pelvis
- CEA- carcinoembryonic antigen
- MRI (important for RECTAL cancer)
- ctDNA
- No role for PET/CT

Treatment Non-Metastatic Rectal Cancer

- MRI (or US) clinical staging
- Stage I-
Surgery (mesorectal excision)
- Stage II/III (T3-T4/N+)
 - A. Chemo/radiation → Surgery → Adjuvant chemotherapy
 - B. Chemo/radiation → Neoadjuvant chemotherapy → Possible surgery (TNT)
- Abdominal –peritoneal resection (APR) → permanent colostomy

Treatment Non-Metastatic Colon Cancer

- Surgery! (pathological staging-TNM)
 - Stage I-
Surgery alone
 - Stage II-
 - IIA
Surgery alone*
 - IIB
Discussion with the patient*
 - IIC
Adjuvant chemotherapy (T4b)
 - Stage III-
Adjuvant chemotherapy
- *High risk factors
 - T4
 - >12 Lymph nodes evaluated
 - Lymphovascular invasion
 - Poorly differentiation G3
 - Clinical perforation or obstruction
 - Positive ctDNA

5-Fluorouracil; 5-FU

United States Patent Office

2,802,005
Patented Aug. 6, 1957

1

2,802,005

5-FLUOROURACIL

Charles Heidelberger, Madison, Wis., and
Robert Duschinsky, Essex Fells, N. J.

No Drawing. Application September 26, 1956,
Serial No. 612,088

12 Claims. (Cl. 260—260)

(22)

15 (23)

20

This invention relates to novel chemical compounds and to novel processes and novel intermediates useful in preparing the same. More particularly, the invention relates to 5-fluorouracil and salts thereof; to methods of preparing said 5-fluorouracil and salts; and to intermediates useful in practicing said methods.

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(19)

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FLOW SHEET—PROCESS II

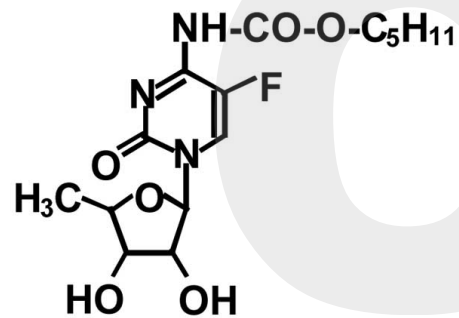
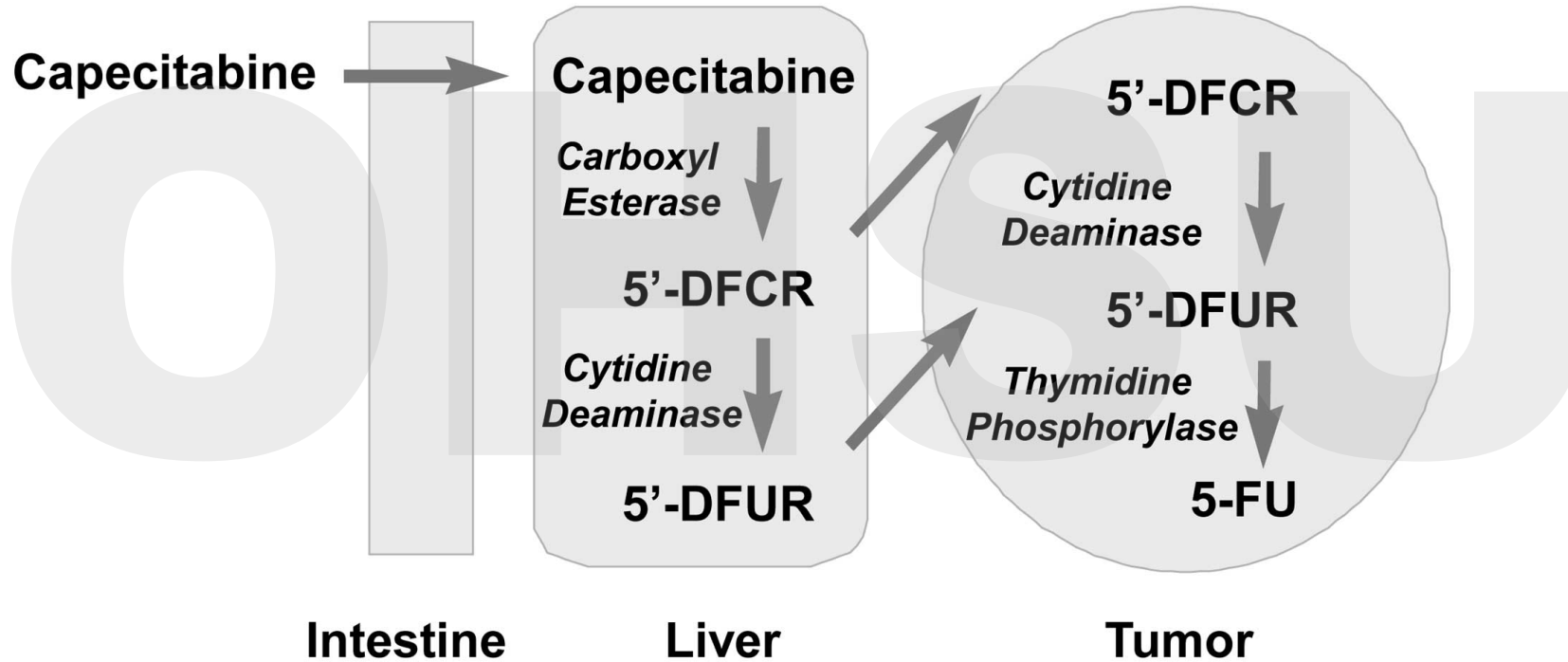
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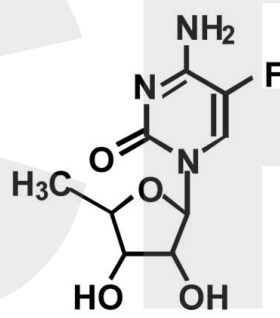
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 \text{FCH}_2\text{COOR}^0 \\
 \left. \begin{array}{l} \text{R}^1\text{OOC} \text{---} \text{COOR}^1 \\ + \\ \text{M}(\text{or } \text{M-O-R}^2) \end{array} \right\} \downarrow \\
 \begin{array}{c}
 \text{R}^a\text{-O-C(=O)-C-F} \\
 | \\
 \text{M-O-C(=O)-COOR}^1
 \end{array}
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(21)

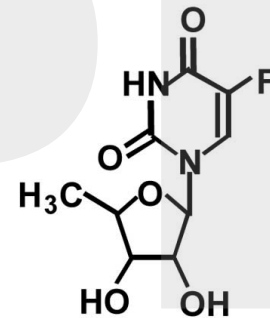
(24)



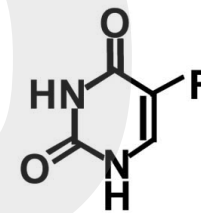
Capecitabine



5'-DFCR



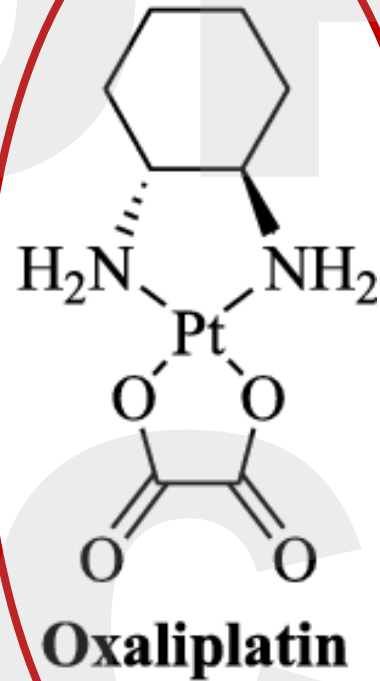
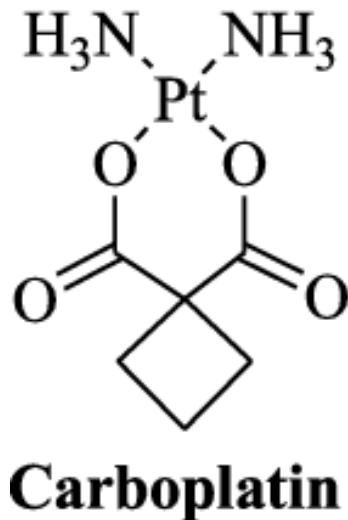
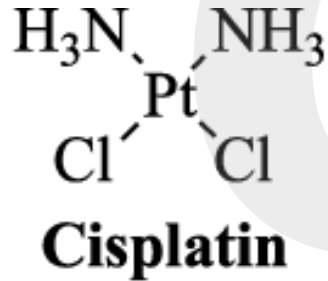
5'-DFUR



5-FU

Chemical Structure of Platinum Analogues

OXALIPLATIN, Eloxatin®

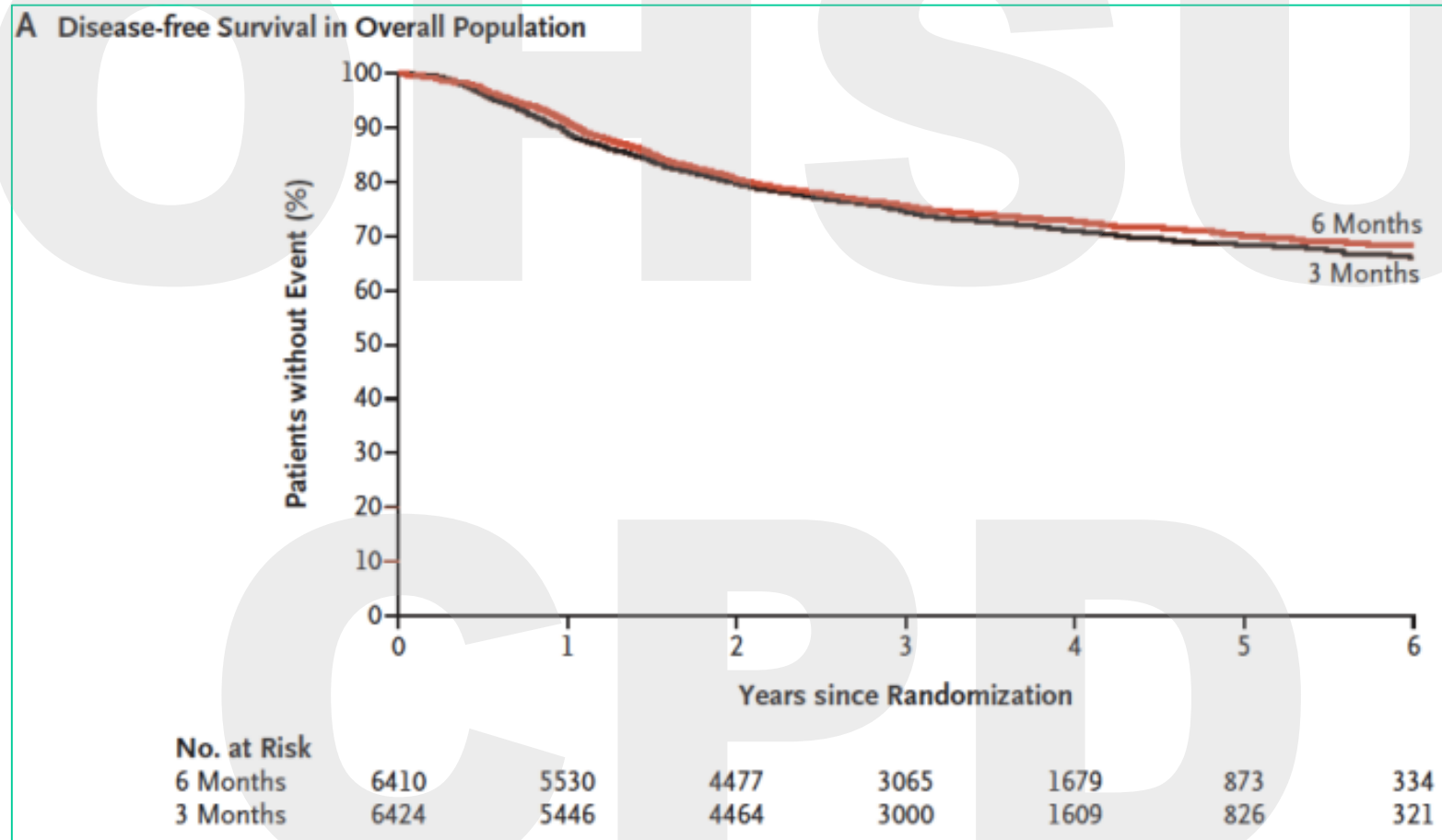


- Diaminocyclohexane (DACH) carrier ligand
- Active in NCI CRC cell lines
- DNA adducts, cross-links
- Hold if CrCL<20cc/min

Stage III- Oxaliplatin associated toxicity

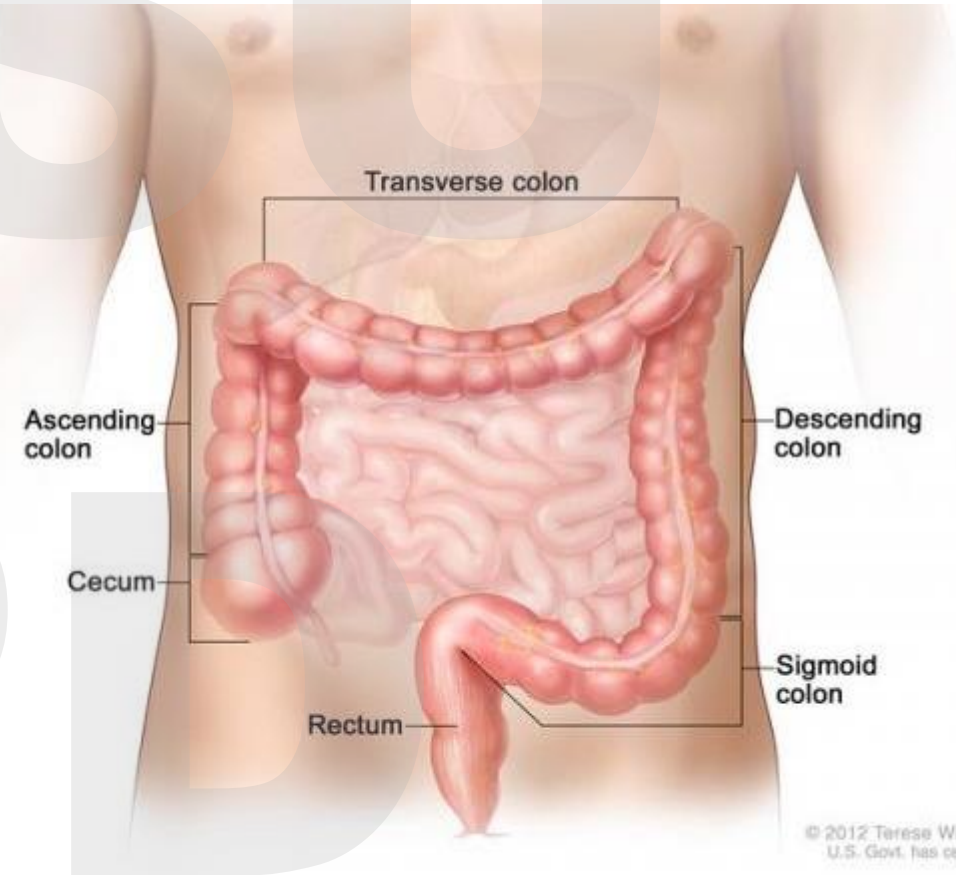
- 6 months of Oxaliplatin is associated with Neurotoxicity
 - Grade 3 peripheral neuropathy is observed in 12.5% of pts treated with FOLFOX for 6 mos.
- IDEA: Comparing 3 months vs. 6 months of adjuvant FOLFOX or CAPOX therapy in resected stage III colon cancer
- Shorter duration of adjuvant therapy decreases risk of peripheral neuropathy and saves health care costs

IDEA Primary Analysis



N Engl J Med. 2018;378(13):1177-1188.

Metastatic COLOrectal Cancer



Patient's
right

Patient's
left

Transverse colon

Ascending
colon

Descending
colon

Cecum

Sigmoid colon

Rectum

Midgut derivative

- ↑ Women
- ↑ Sessile serrated lesions
- ↑ Mucinous tumours

Overall worse prognosis*

- ↑ CIMP-high
- ↑ BRAF
- ↑ MSI-high
- ↑ MSI immune tumours (CMS1)
- ↑ Metabolic tumours (CMS3)
- (↑ KRAS)

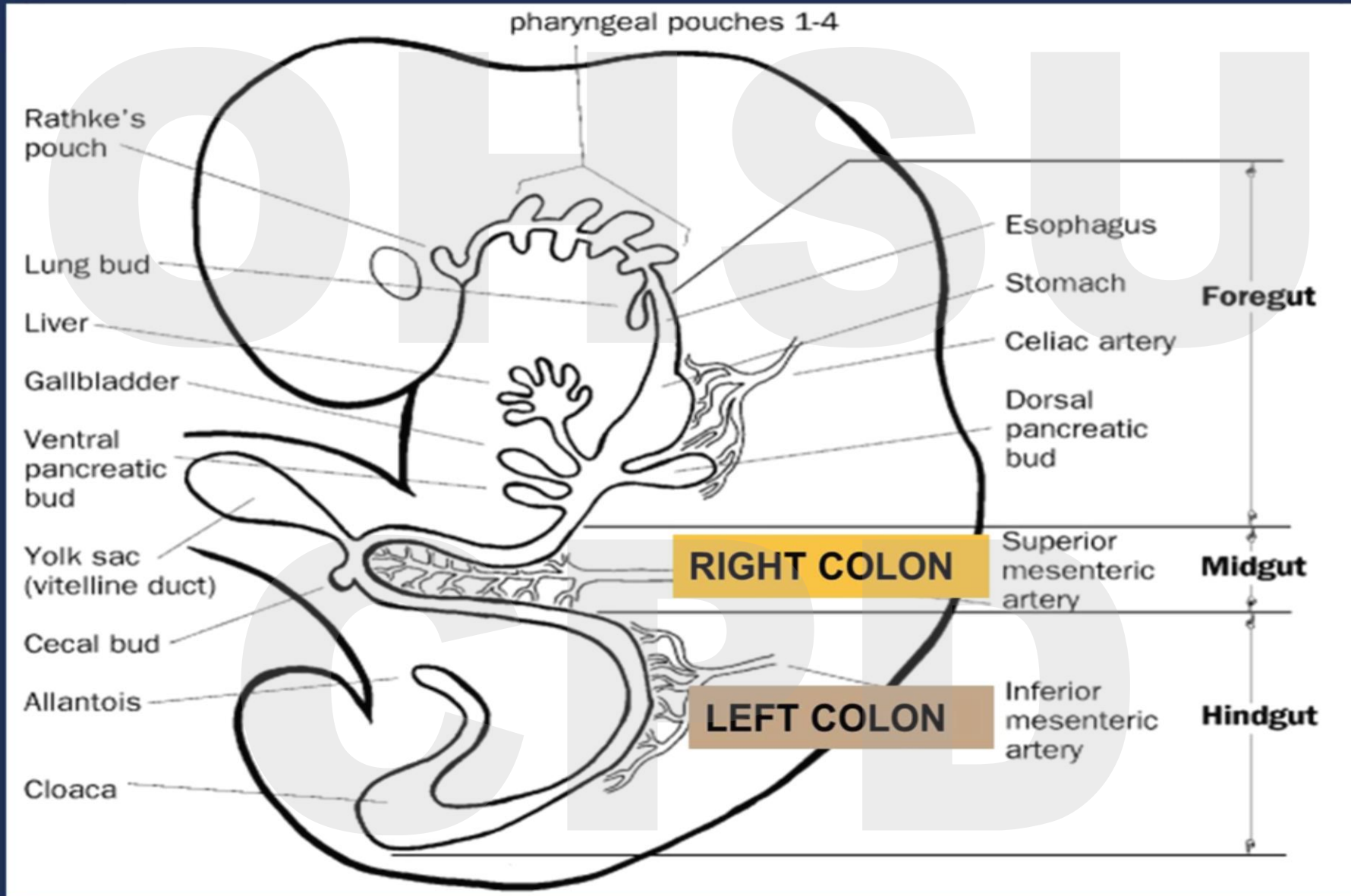
Hindgut derivative

- ↑ Men

Overall better prognosis*

- ↑ Mesenchymal (CMS4)
- ↑ Canonical (CMS2), distally
- ↑ TP53
- ↑ APC

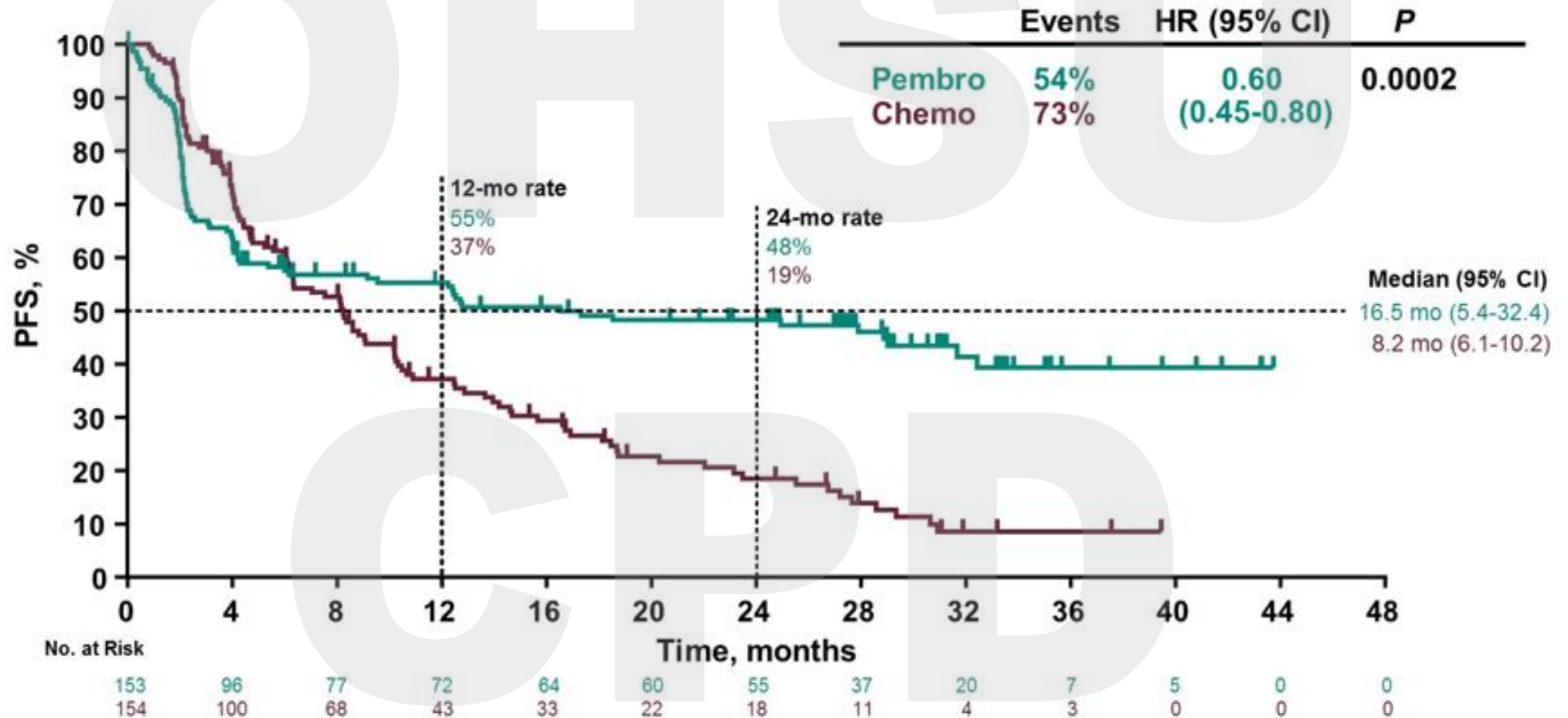
Embryology: The origin of the colon



First Line Treatment Metastatic Colorectal Cancer

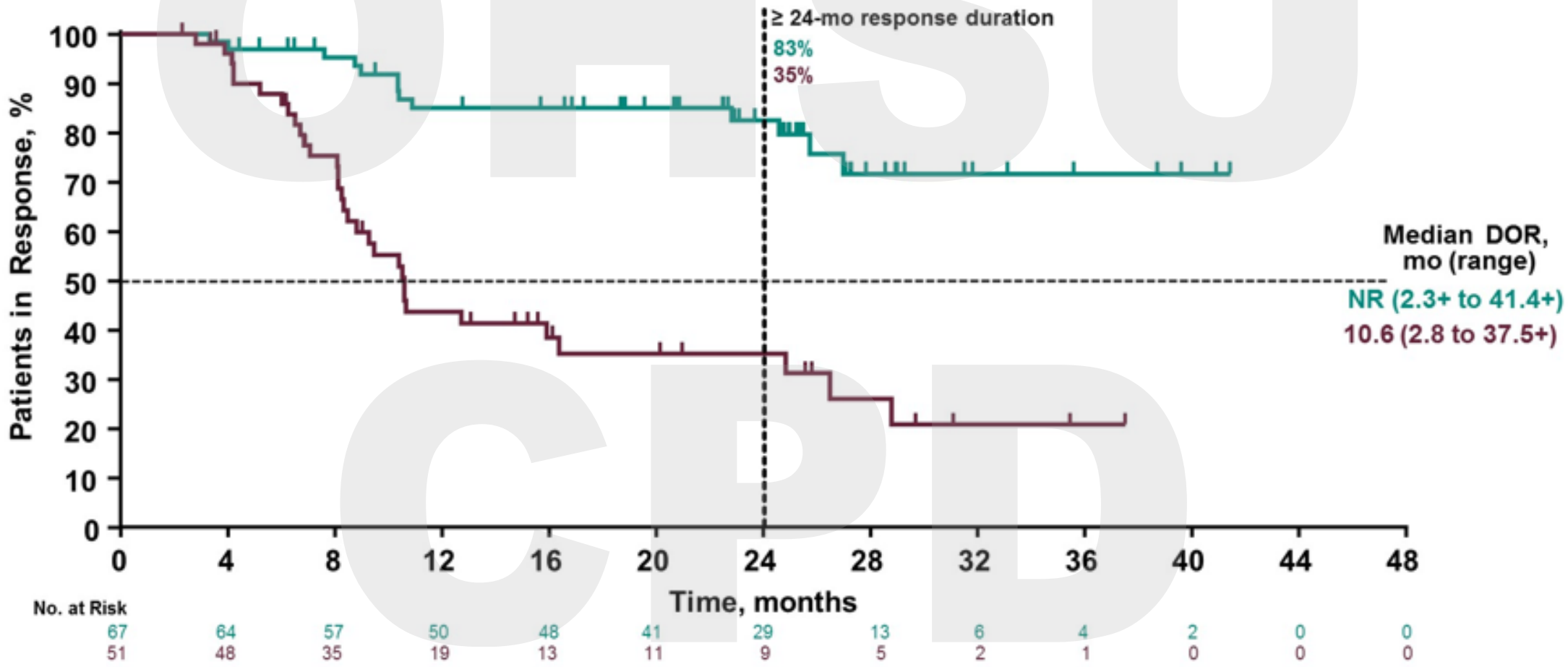
- Molecular status?
 - MMR/MSI
 - dMMR (MSI-H) (Mut-MLH1, MSH2, MSH6 and PMS2)
 - pMMR (MSS)
- RAS (KRAS, NRAS), BRAF
 - RAS Mut or BRAF Mut
 - RAS WT and BRAF WT
- HER2

Progression Free Survival



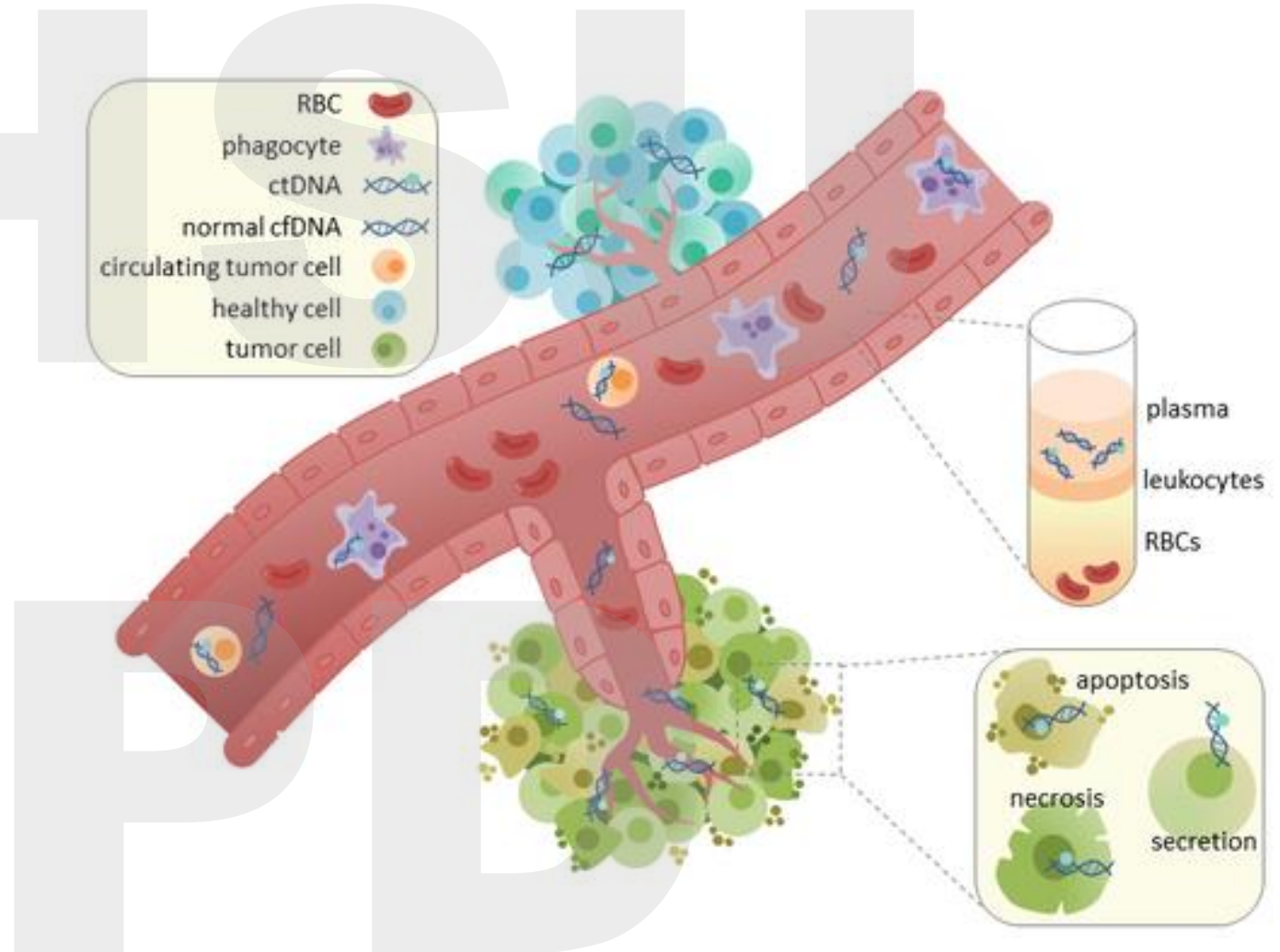
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided $\alpha = 0.0117$; Data cut-off: 19Feb2020.

Duration of Response

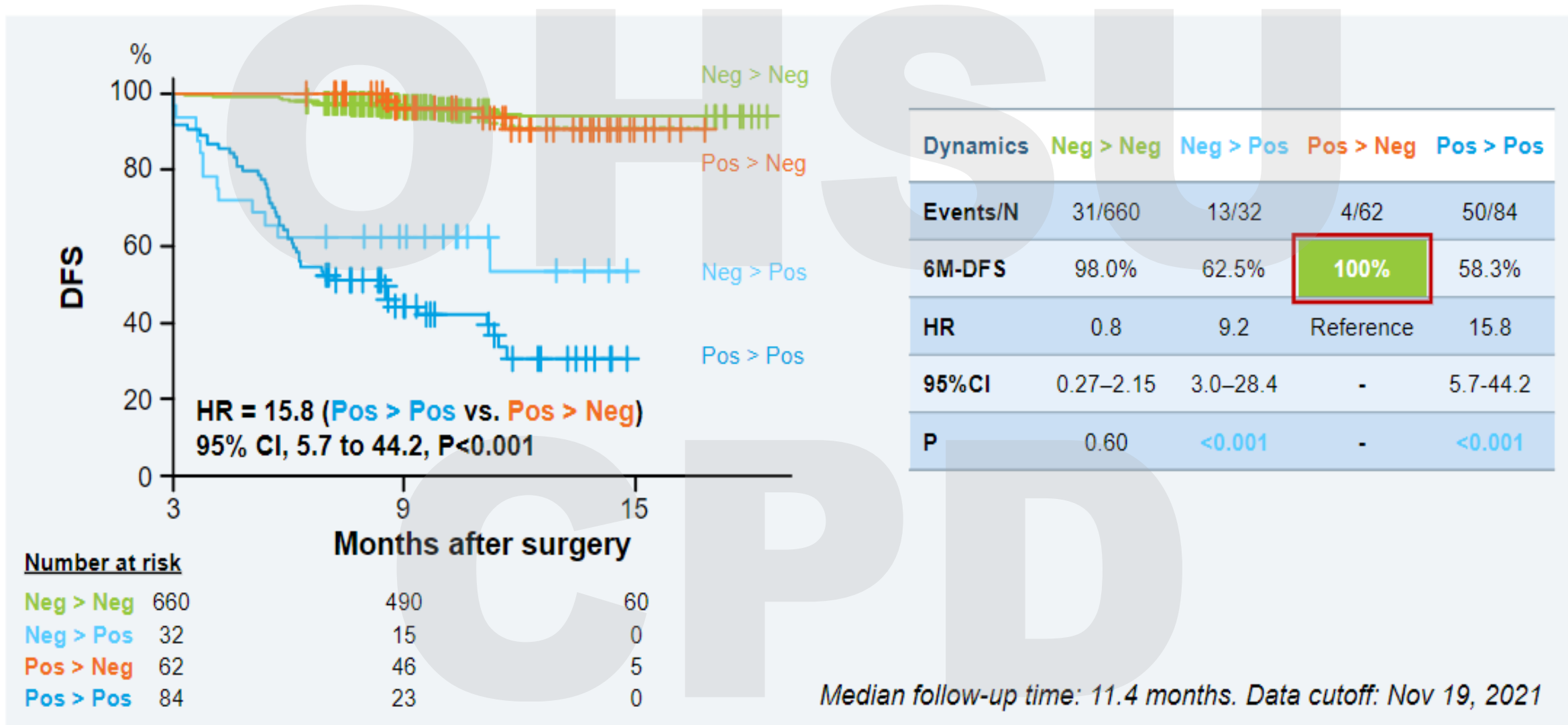


circulating tumor DNA (ctDNA)

- Cancer cells release circulating tumor DNA (ctDNA) into the bloodstream
- ctDNA is a powerful tool that can be measured to assess the absence or presence of molecular residual disease (MRD)
- Dynamic real-time biomarker: the normal half-life is less than an hour



ctDNA clearance predictive



Survival ship- Coordination between specialists and primary care

- **Components of post treatment follow-up include medical and psychosocial subjects**
- Prevention of recurrent- Screening **and** Prevention
 - Continue screening; Breast, prostate, Lung, CNS...others
 - Prevention; healthy life style
- Consequences of cancer and its treatment
 - Cardiac, Neurologic, Infectious, Hematologic, Endocrine...
 - medical problems; (lymphedema and sexual dysfunction)
 - symptoms (pain and fatigue)

Survival ship- Coordination between specialists and primary care

- Psychological distress (patient and their caregivers)
 - Depression, anxiety, fatigue, cognitive limitations, sleep problems, sexual dysfunction, pain, and opioid dependence or use disorder
 - Genetics
- Socioeconomical - employment, insurance, and disability
 - In one study, 25 percent of cancer survivors reported that they used up all or most of their savings in the process of cancer treatment*

*The USA Today/Kaiser Family Foundation/Harvard School of Public Health. National Survey of Households Affected by Cancer. 2006



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Thank you...

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CPD

