City of Hope

ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Revolutionizing Gastrointestinal Cancer Care Through AI

Stephen B. Gruber, MD, PhD

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Vice President, City of Hope National Medical Center

Disclosures

- Grant/Research Support from AbbVie, AstraZeneca, Eisai, GenVivo, HaloDx, Invitae & NIH / NCI.

The presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Objectives

1

Liquid Biopsy for Early Detection:

Review selected liquid biopsy tests for colorectal cancer or multi-cancer detection.

2

Immunology & AI:

Recognize prognostic and predictive potential of immune measures in colorectal cancer and advances in computing and AI.

3

High Risk Management:

Apply advances in identifying and managing individuals & populations with genetic risk.

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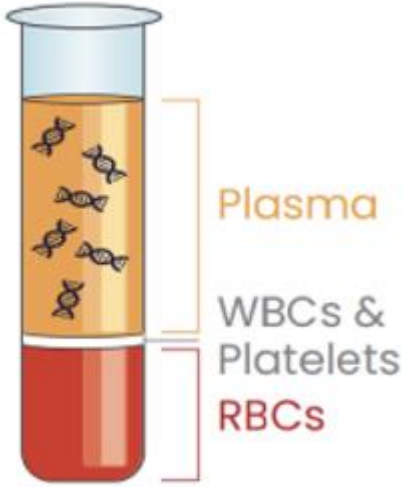
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2024 VOL. 390 NO. 11

A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening

Daniel C. Chung, M.D., Darrell M. Gray II, M.D., M.P.H., Harminder Singh, M.D., Rachel B. Issaka, M.D., M.A.S., Victoria M. Raymond, M.S., Craig Eagle, M.D., Sylvia Hu, Ph.D., Darya I. Chudova, Ph.D., AmirAli Talasaz, Ph.D., Joel K. Greenson, M.D., Frank A. Sinicrope, M.D., Samir Gupta, M.D., M.S.C.S., and William M. Grady, M.D.



CONCLUSIONS

In an average-risk screening population, this cfDNA blood-based test had 83% sensitivity for colorectal cancer, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions. (Funded by Guardant Health; ECLIPSE ClinicalTrials.gov number, NCT04136002.)

What do you do with a positive **Guardant SHIELD** test?

- Colonoscopy

What do you do with a negative **Guardant SHIELD** test?

- Reassure
- Repeat every 3 years

Liquid Biopsy - Early Detection

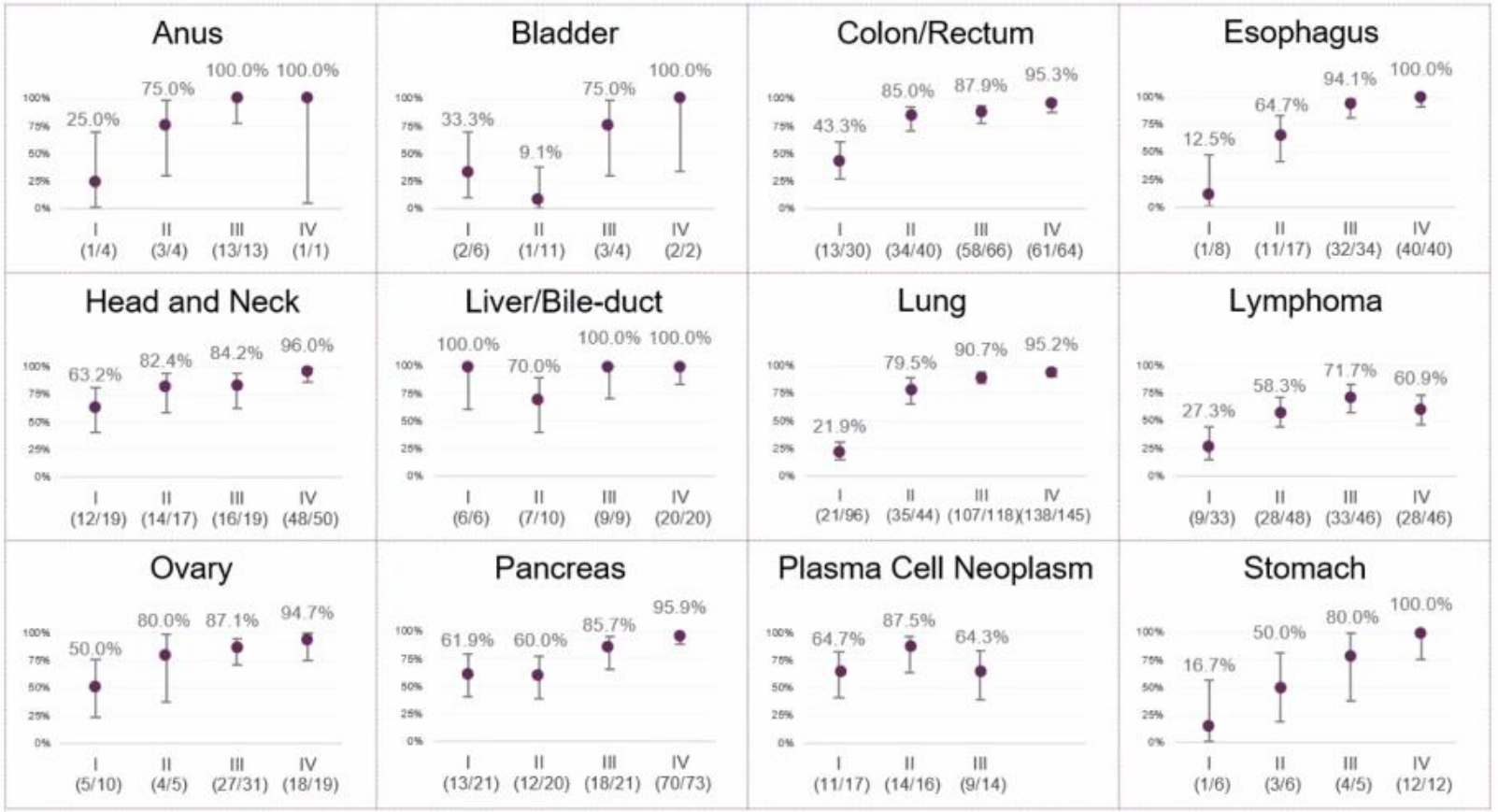
- Commercially available – **Guardant SHIELD**
  - Blood-based colorectal cancer
  - FDA-approved in 2024
  - Covered by Medicare

- Commercially available – **GRAIL Galleri**
  - Blood-based Multi-cancer early detection test
  - Cash pay – not covered by insurance
  - $949

- Clinical Trials at City of Hope

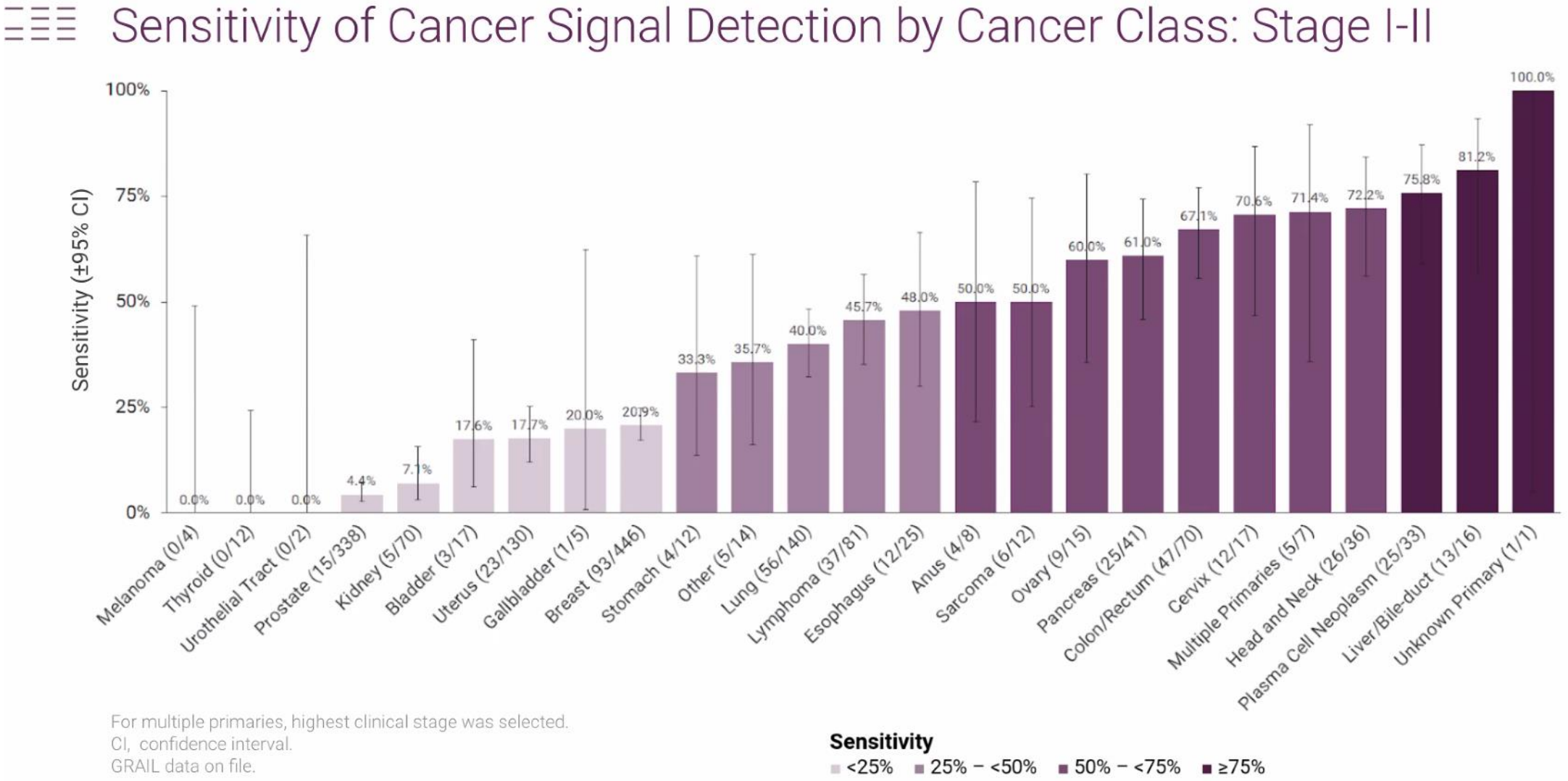
GRAIL Galleri

Sensitivity of Cancer Signal Detection by Stage in 12 Pre-Specified Cancers Responsible for Two-Thirds of Cancer Deaths



List of 12 cancers that account for 62% of US cancer deaths from American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf.
Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

GRAIL Galleri

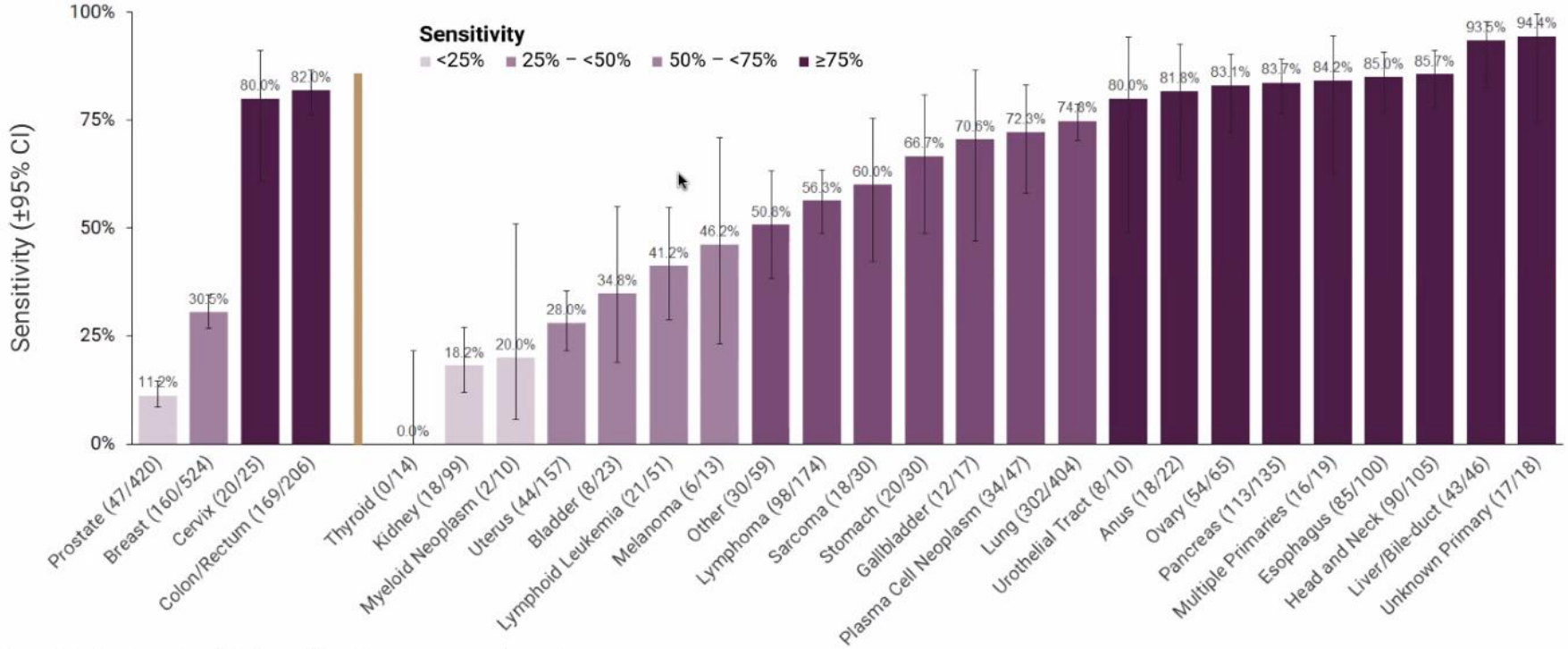


GRAIL Galleri

Sensitivity of Cancer Signal Detection in Cancers With and Without Common Screening

With Common Screening Options:
33.7% (95% CI: 31.1–36.5%)

Without Common Screening Options:
63.8% (95% CI: 61.4–66.1%)



For multiple primaries, highest clinical stage was selected.
CI, confidence interval.
Klein E, et al. Ann Oncol. 2021 Sep;32(9):1167-1177. doi: 10.1016/j.annonc.2021.05.806..

Ongoing Studies of GRAIL Galleri Test

- **United Kingdom**
  - United Kingdom - NHS study of 140,000 people
  - Goal – Does Galleri test lead to a reduction in diagnosis of Stage IV cancers?
  - Results expected 2025-2026

- **United States**
  - Medicare demonstration project 50,000 people
  - “REACH” study – 1st pt enrolled July 2024)
    - Usual care + annual Galleri test vs. Usual care alone

What do you do with a positive **GRAIL Galleri** test?

- See your doctor
- Additional testing
  - CT, MRI, PET scan
  - Blood tests
  - Biopsy

What do you do with a negative **Grail Galleri** test?

- Continue to screen with approved screening
  - Mammogram
  - Colonoscopy
  - PSA

Objectives – Epidemiology of Immune Responses

1

Access:

Explore potential impact of universal germline genetic testing for all cancer patients.

2

Immunology & AI:

Recognize prognostic and predictive potential of immune measures in colorectal cancer and advances in computing and AI.

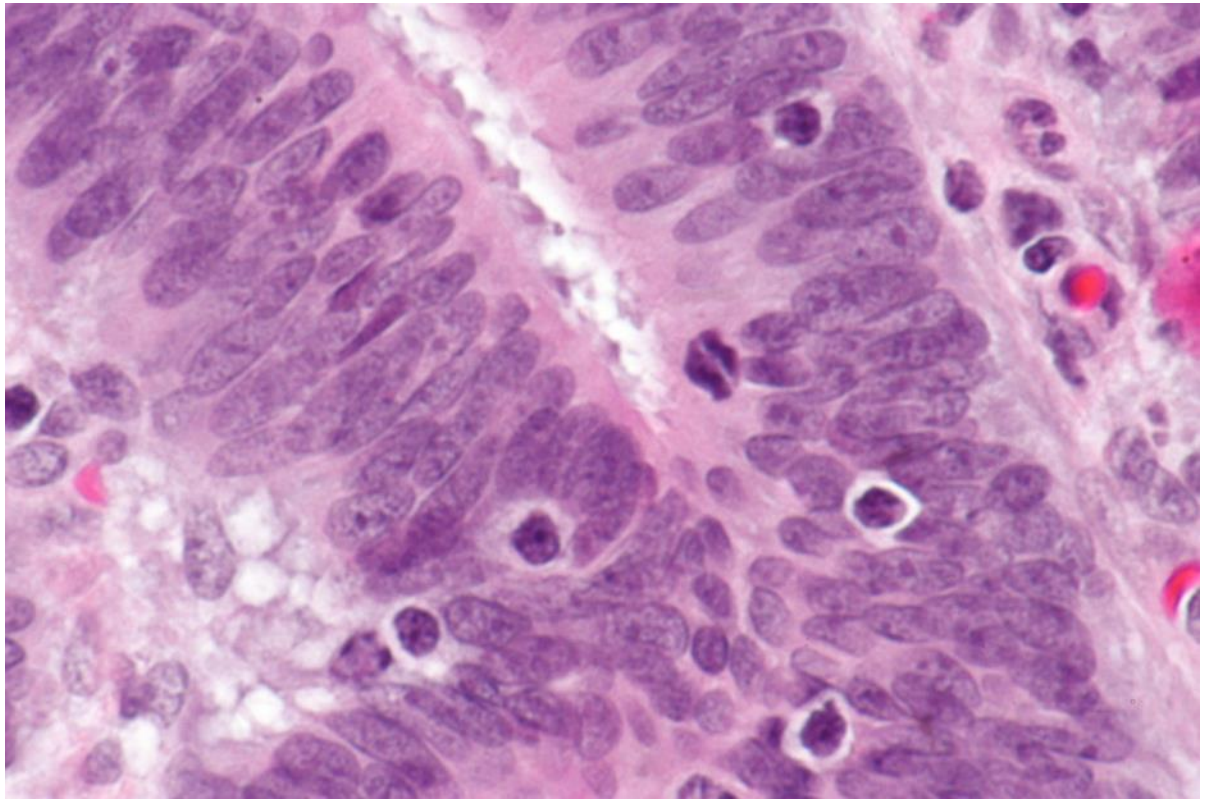
3

High Risk Management:

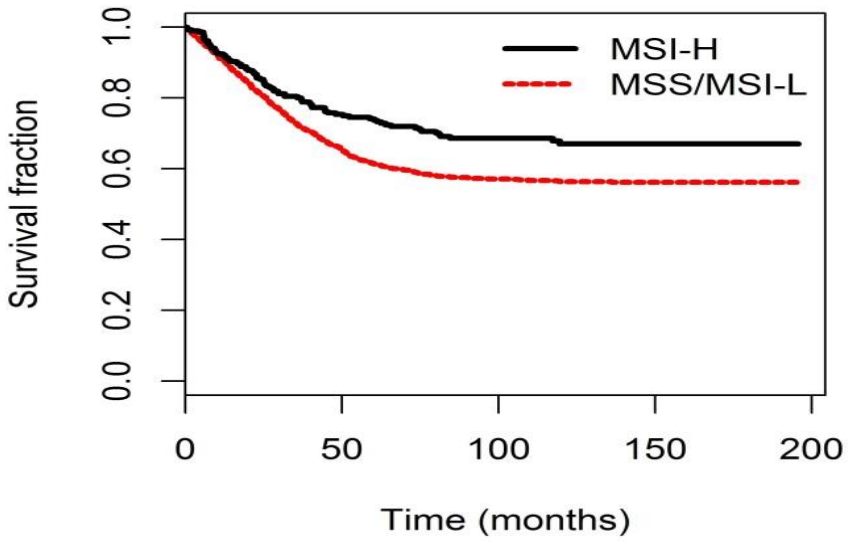
Apply advances in identifying and managing individuals & populations with genetic risk.

Epidemiology of Immune Responses in Colorectal Cancer

R01 CA197350



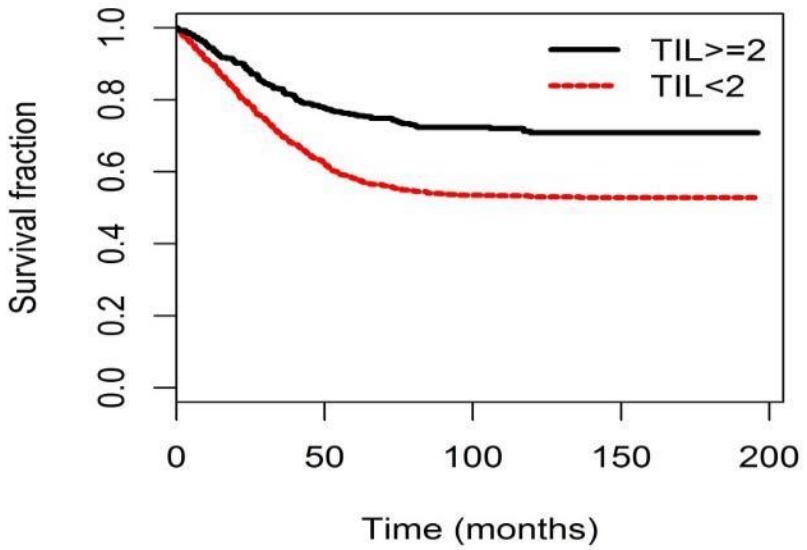
Microsatellite Instability



No. at risk	Survival Time (months)			
	0	50	100	150
MSI-H	296	189	122	33
MSS/MSI-L	1,675	949	646	2

Rozek, Schmit et al, *JNCI,* 2016

Tumor Infiltrating Lymphocytes



No. at risk	Survival Time (months)			
	0	50	100	150
TIL≥2	539	364	248	87
TIL<2	1,449	781	523	171

Rozek, Schmit et al, *JNCI,* 2016

Artificial Intelligence

- Deep Learning especially useful for image recognition
- Predicting dichotomous biomarkers – transformer based
- Predicting continuous biomarkers – regression based

Deep Learning – AI Approaches to Precision Medicine

Digital pathology has potential to improve:

- **Tumor detection/diagnosis**
- **Mutation profiles**
- **Treatment Response**
- **Survival**

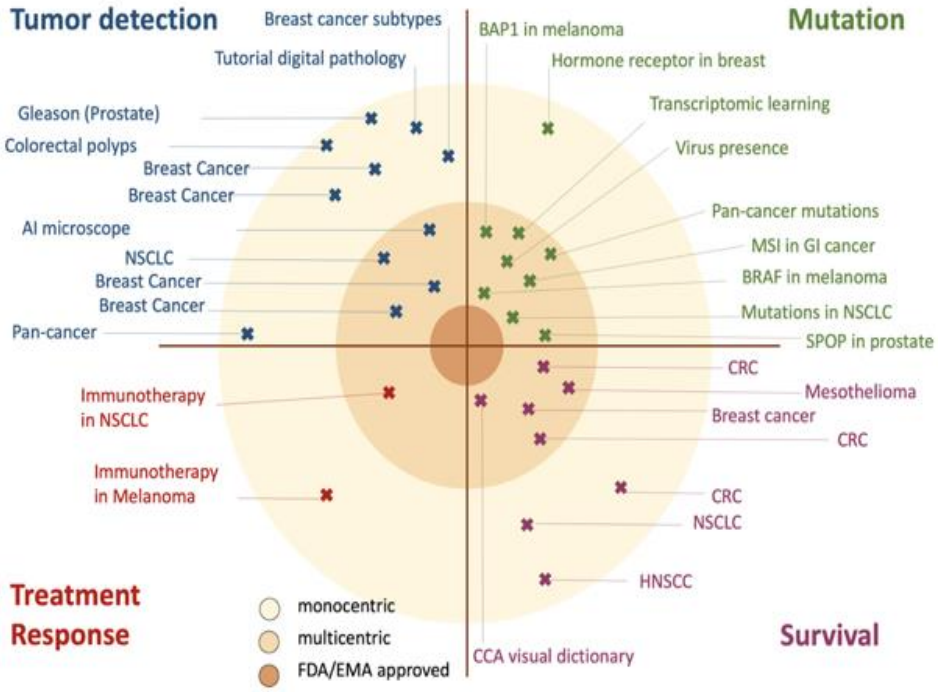
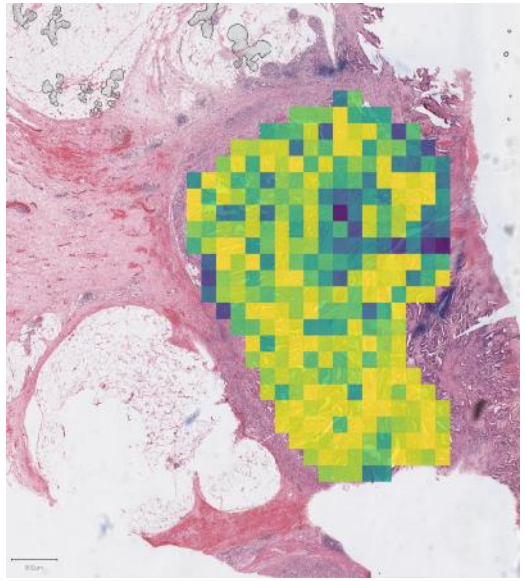


Figure 1: Scientific context of our proposed project. Selected relevant articles of deep learning histopathology arranged by level of evidence (single center, multicentric, or FDA/EMA approved). AI = artificial intelligence, NSCLC = non-small-cell lung cancer, WSI = whole slide image, ER = estrogen receptor, MSI = microsatellite instability, GI = gastrointestinal, HNSCC = head and neck squamous cell carcinoma, CCA = cholangiocarcinoma, FDA = Food and Drug Administration, EMA = European Medicines Agency.

EPICO
Epidemiology, Pathology, Immunology, and Colorectal Cancer Outcomes
R01 CA263318



- “Our **overarching goal** is to shift the paradigm of how CRC is diagnosed and molecularly characterized through histologic, genomic, and immune features derived from routinely collected images.”

Pathologic Predictors of Microsatellite Instability

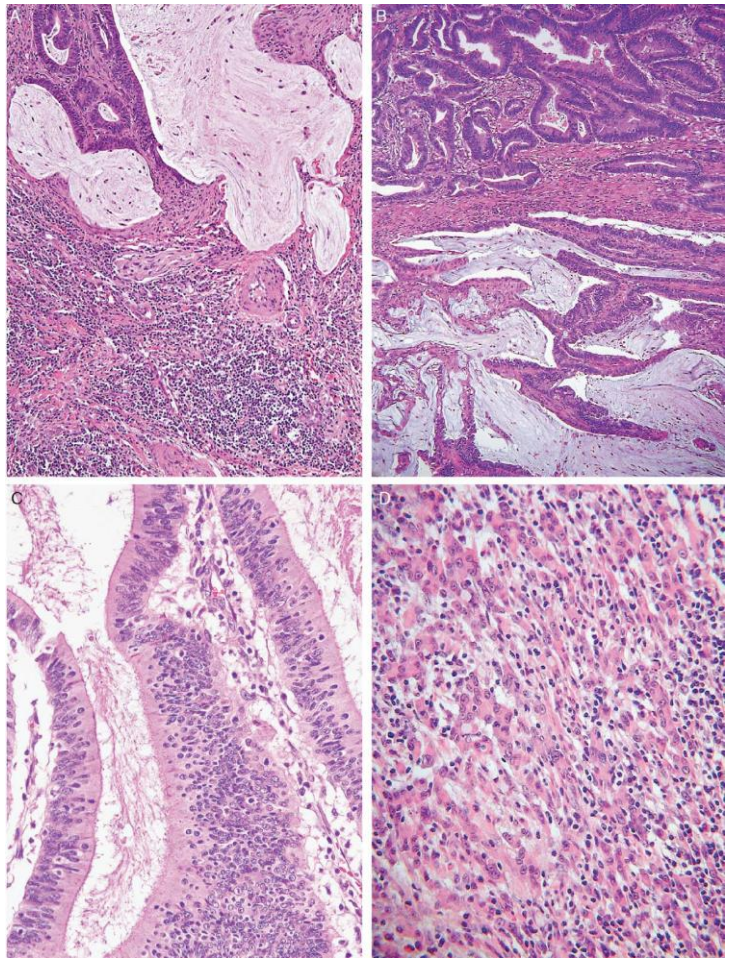


TABLE 5. MSI Probability Scoring System

Pathologic Feature	Coefficient Score
>2 TIL/HPF	1.3
Two or less TIL/HPF	0
Well or poorly differentiated	1.2
Moderately differentiated	0
Age < 50	1.1
Age 50 or greater	0
Crohn-like reaction present	0.8
Crohn-like reaction absent	0
Right-sided location (cecum, ascending or transverse)	0.8
Left-sided location (descending, sigmoid or rectum)	0
Lack of dirty necrosis	0.6
Dirty necrosis present	0
Any mucinous differentiation	0.5
No mucinous differentiation	0
MSI probability score	Total:

HPF indicates high-powered field; MSI, microsatellite instability; TIL, tumor-infiltrating lymphocytes.

Greenson et al, *Am J Surg Path*, 2009

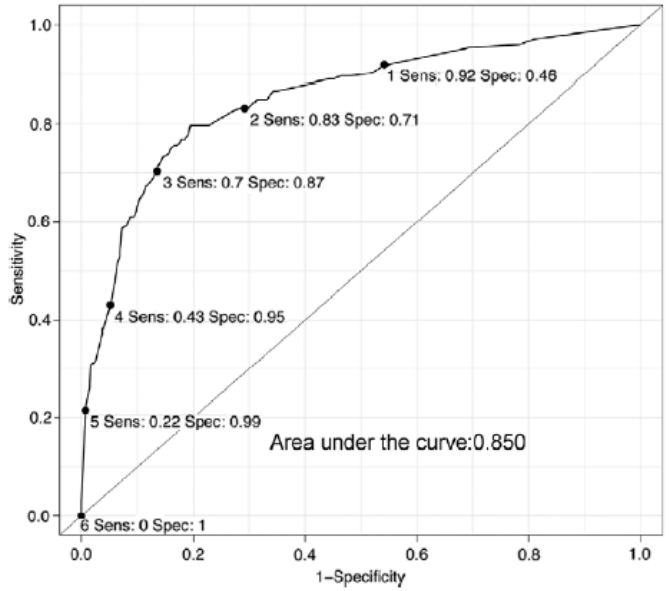
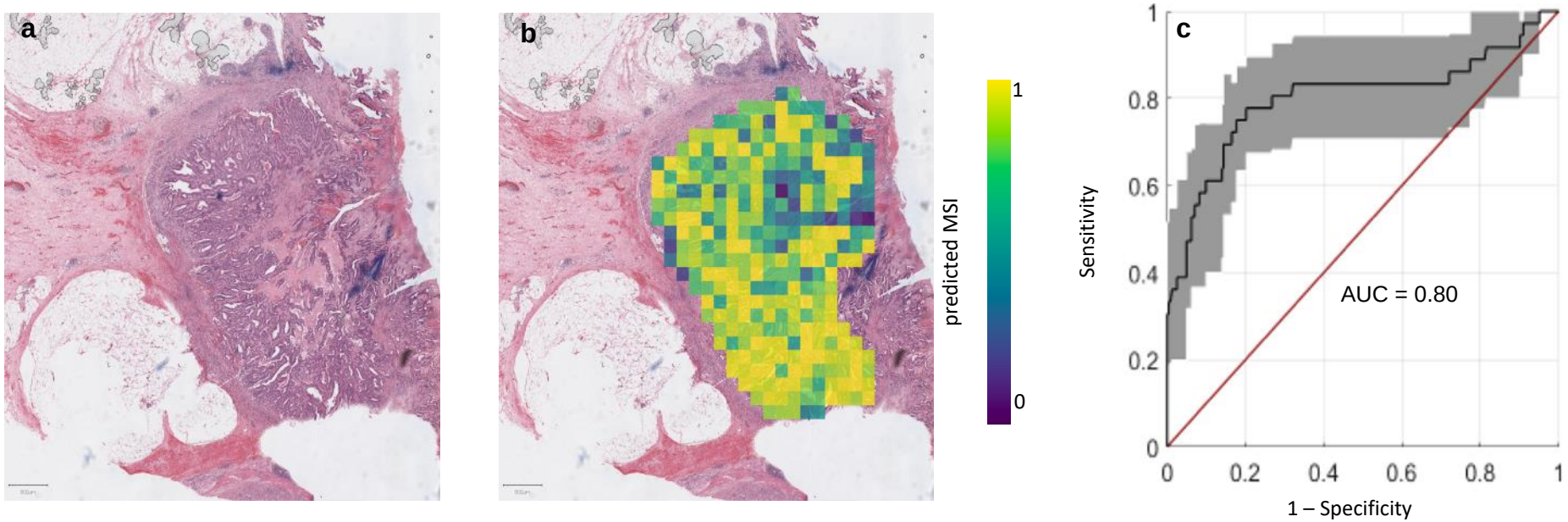


FIGURE 4. This receiver operator characteristic curve shows an area under the curve of 0.850. The sensitivity and specificity for a given MSI probability score is listed. Note that for a MSI probability score of 1, the sensitivity is 92% and the specificity is 46%. MSI indicates microsatellite instability.

Predicting Microsatellite Instability from H&E Slides

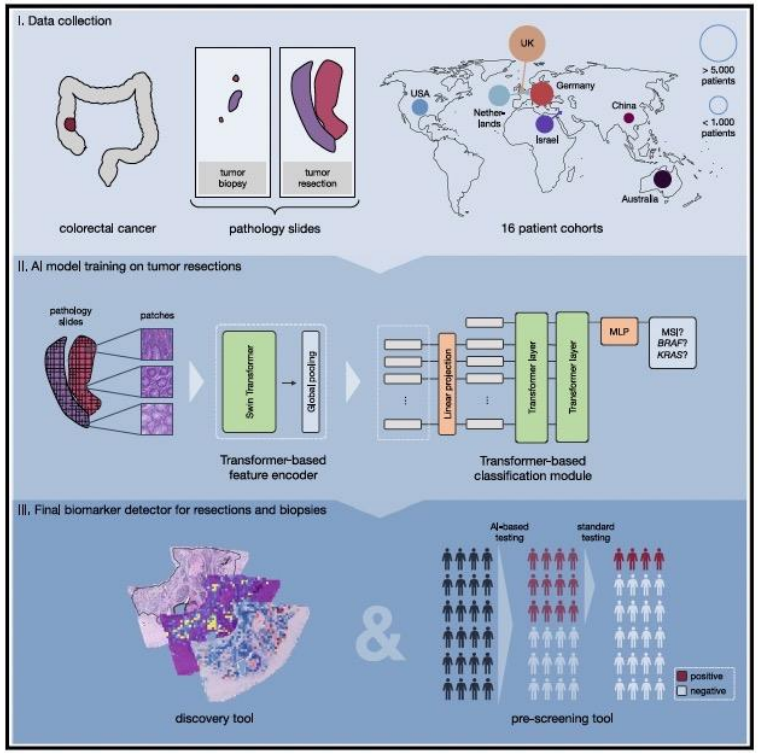


Tumor detection and MSI prediction in H&E histology. **a)** High resolution scanned image from FFPE recut H&E stained slide from MECC case 10248, an MSI-H tumor shown at low power magnification. **b)** Spatial patterns of predicted MSI score from MSIDetect network algorithm, applied to MECC 10248. **c)** Receiver-operator curve predicting MSI among 279 MECC cases, yielding AUC = 0.80, (95% confidence interval, 0.74 - 0.89)

Cancer Cell

Transformer-based biomarker prediction from colorectal cancer histology: A large-scale multicentric study

Graphical abstract



Highlights

- AI-based prediction of biomarkers (MSI, *BRAF*, and *KRAS*) using transformers

Authors

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Correspondence

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In brief

Wagner et al. show that transformer-based prediction of biomarkers from histology substantially improves the performance, generalizability, data efficiency, and interpretability as compared with current state-of-the-art algorithms. The method significantly outperforms existing approaches for microsatellite instability detection in surgical resections and reaches clinical-grade performance on biopsies of colorectal cancer, solving a long-standing diagnostic problem.

13,000 patients

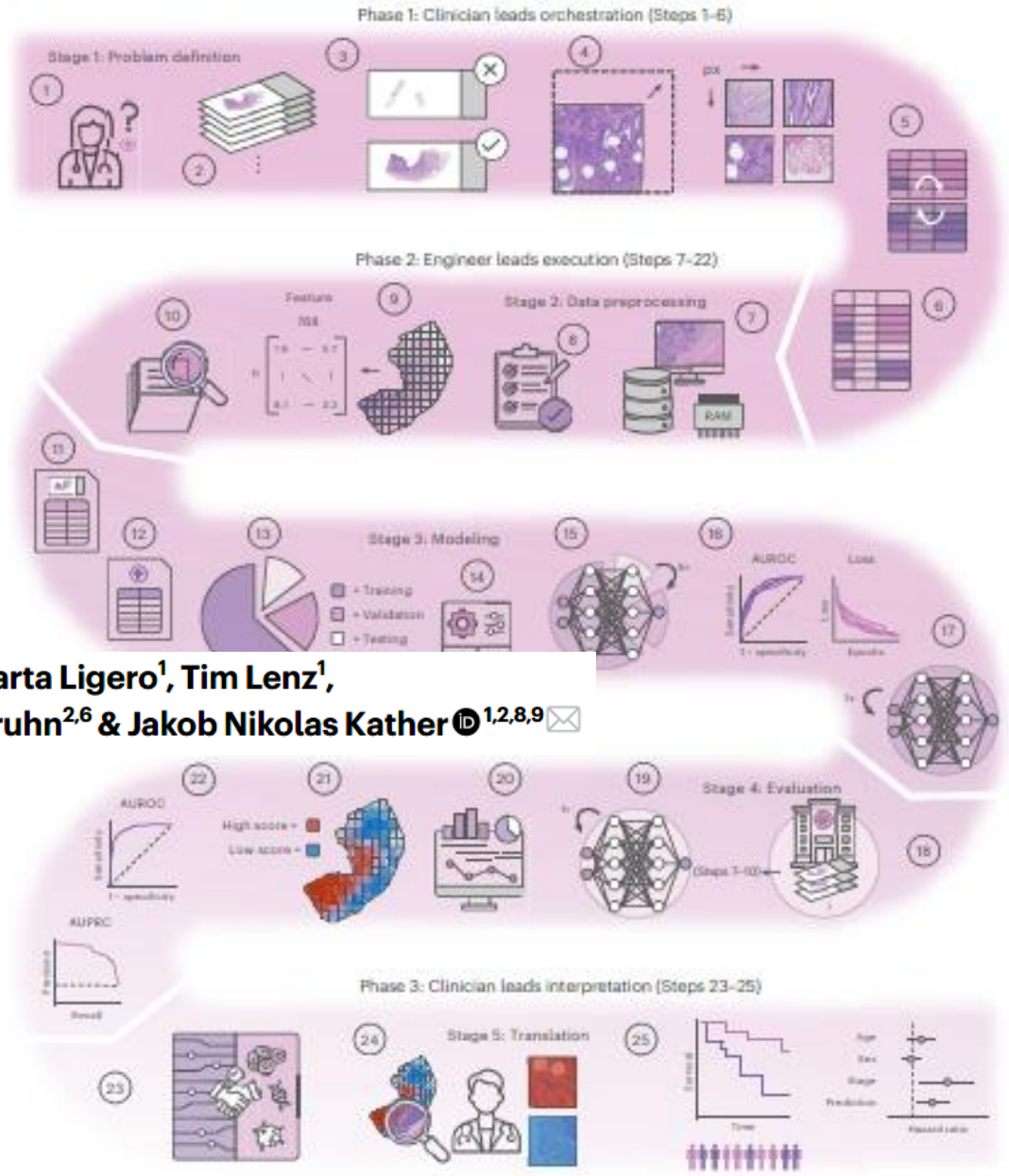
16 CRC cohorts

- MSI prediction
- BRAF
- KRAS

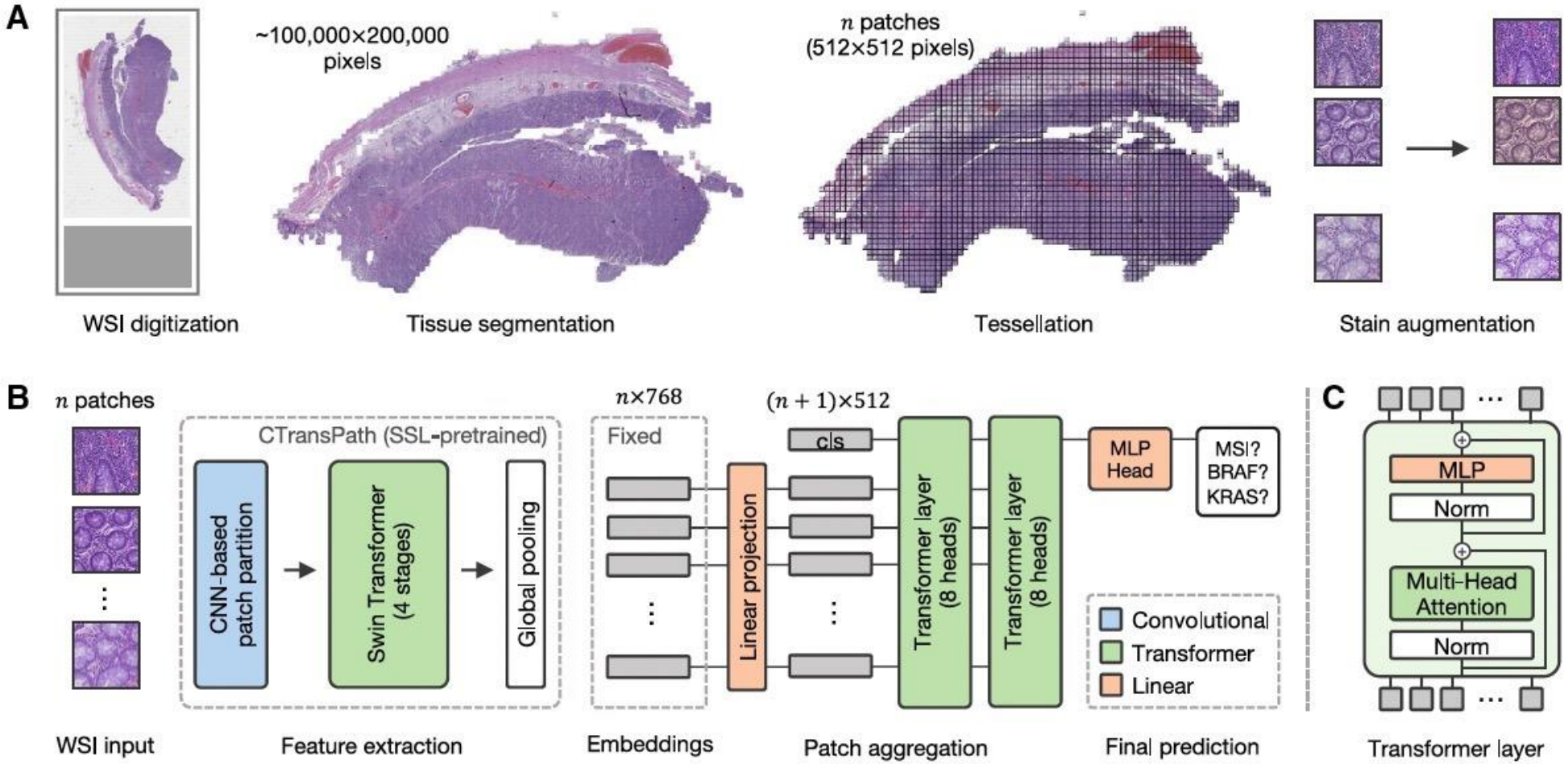
From whole-slide image to biomarker prediction: end-to-end weakly supervised deep learning in computational pathology

Omar S. M. El Nahhas[1,2], Marko van Treeck[1], Georg Wölflein[3], Michaela Unger[1], Marta Ligero[1], Tim Lenz[1], Sophia J. Wagner[4,5], Katherine J. Hewitt[1], Firas Khader[2,6], Sebastian Foersch[7], Daniel Truhn[2,6] & Jakob Nikolas Kather[1,2,8,9]

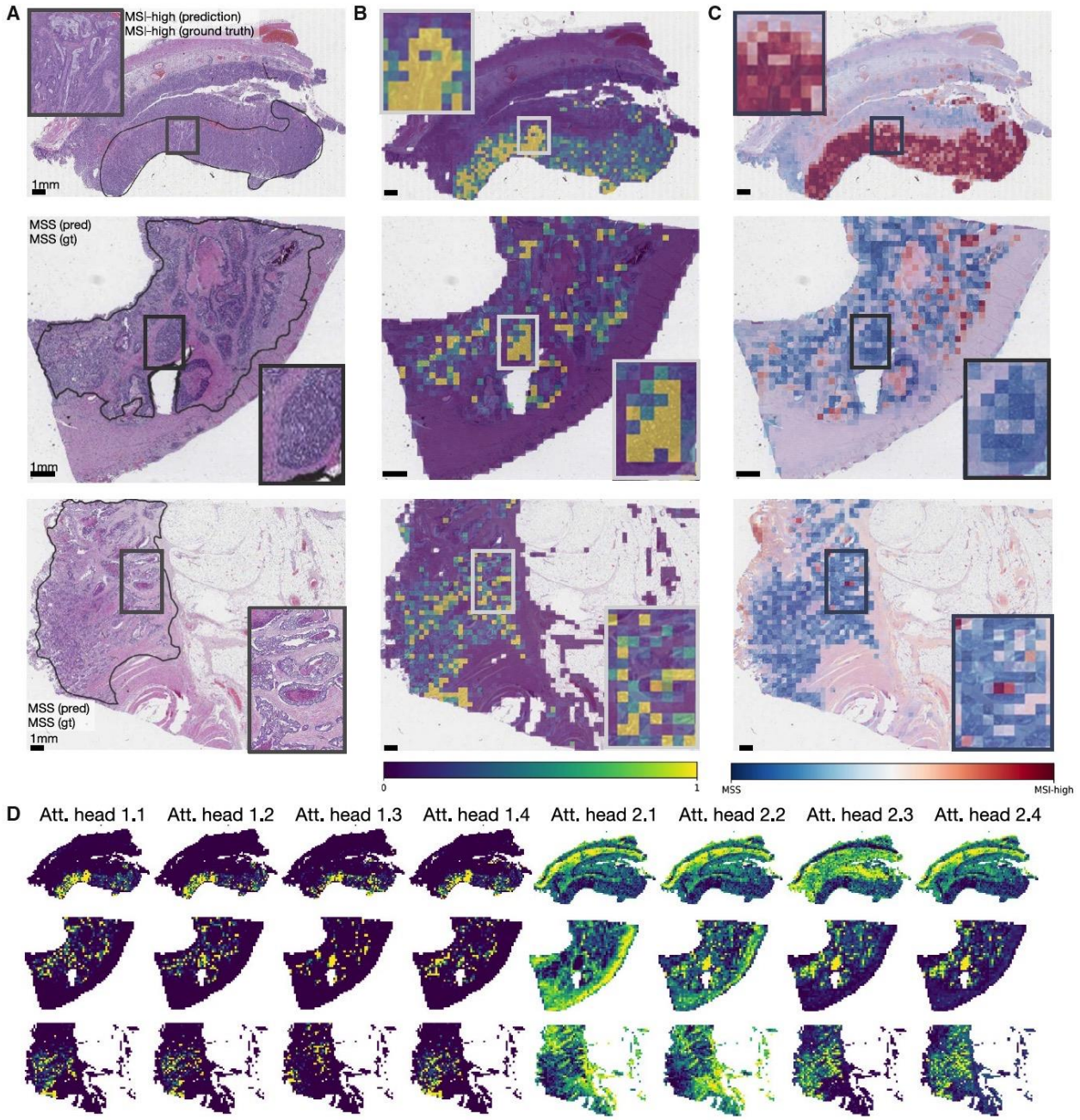
Nature Protocols | Volume 20 | January 2025 | 293–316



Workflow



Wagner et al, Cancer Cell 2023

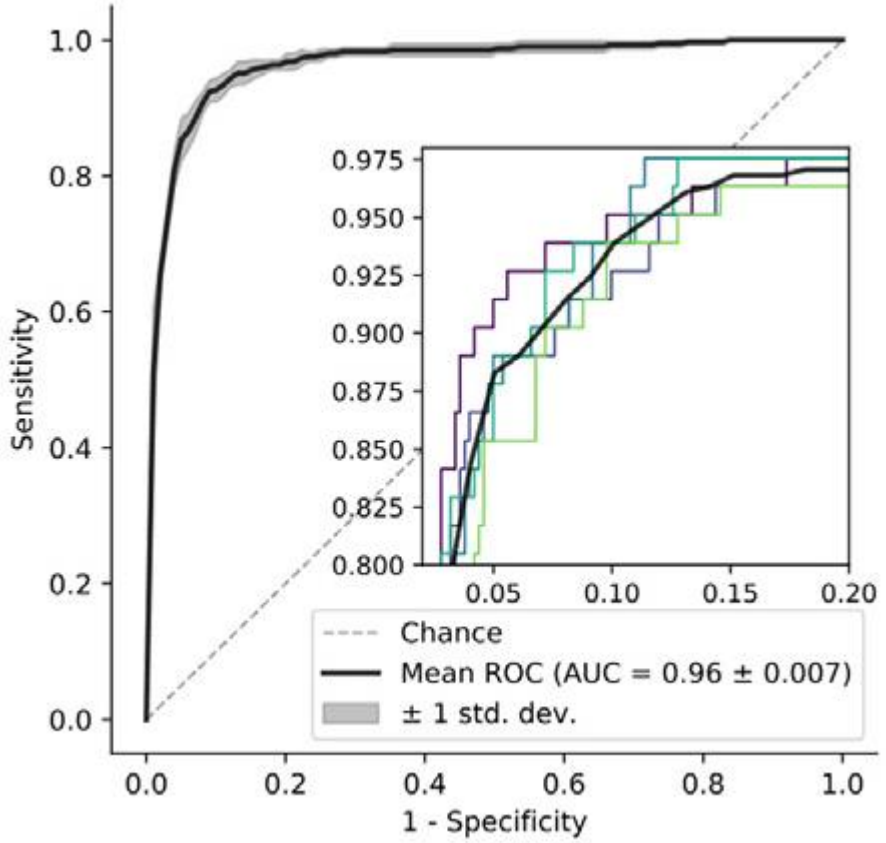


Attention allows interpretability

What are the relevant features and how they relate among each other

Wagner et al, Cancer Cell 2023

Predicting MSI status from histologic images: transformer-based

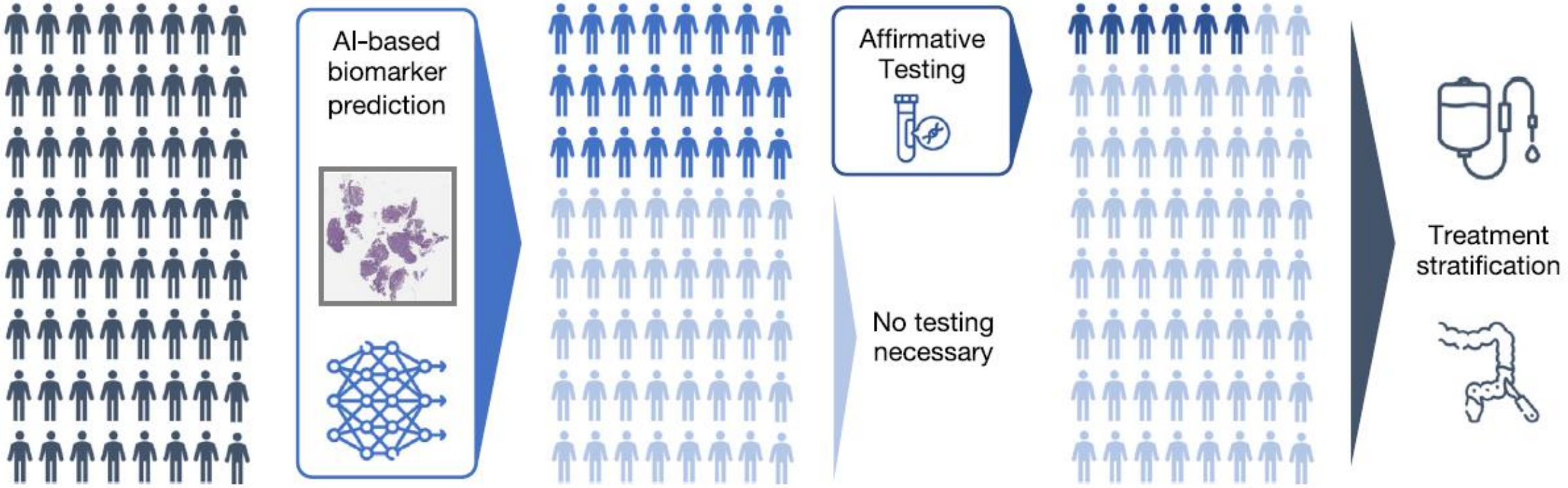


Predicting MSI from surgical resection specimens is highly accurate (AUC = 0.96)

Clinical-grade performance on biopsy specimens from two external cohorts (AUC = 0.92 and AUC = 0.86)

Wagner et al, Cancer Cell 2023

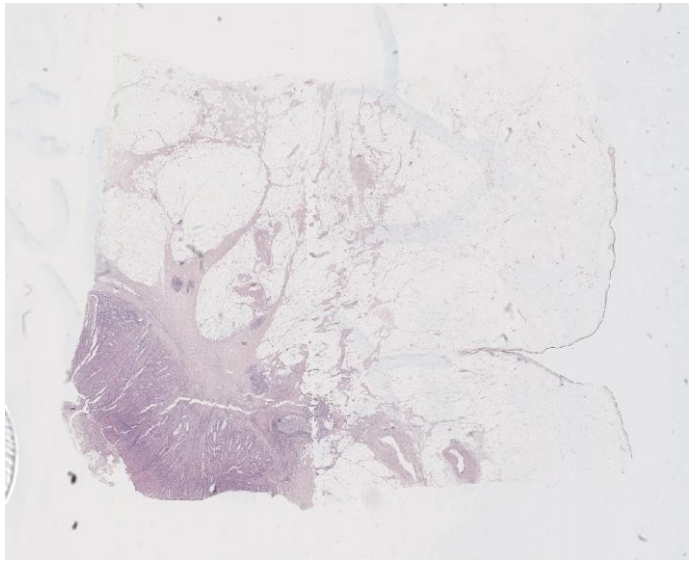
Envisioned clinical workflow from MSI analysis of biopsies

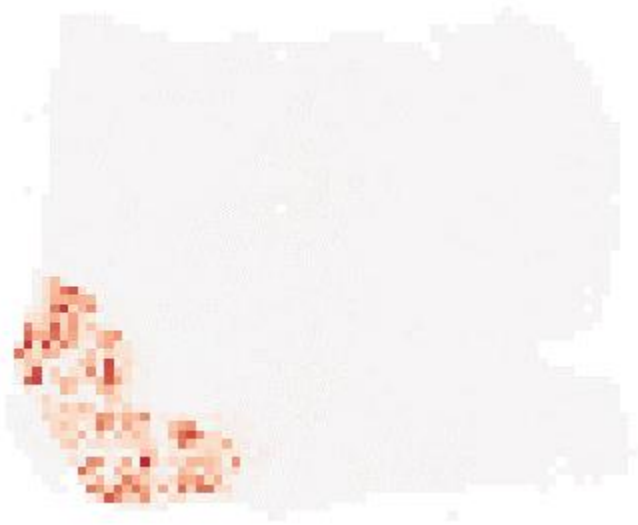


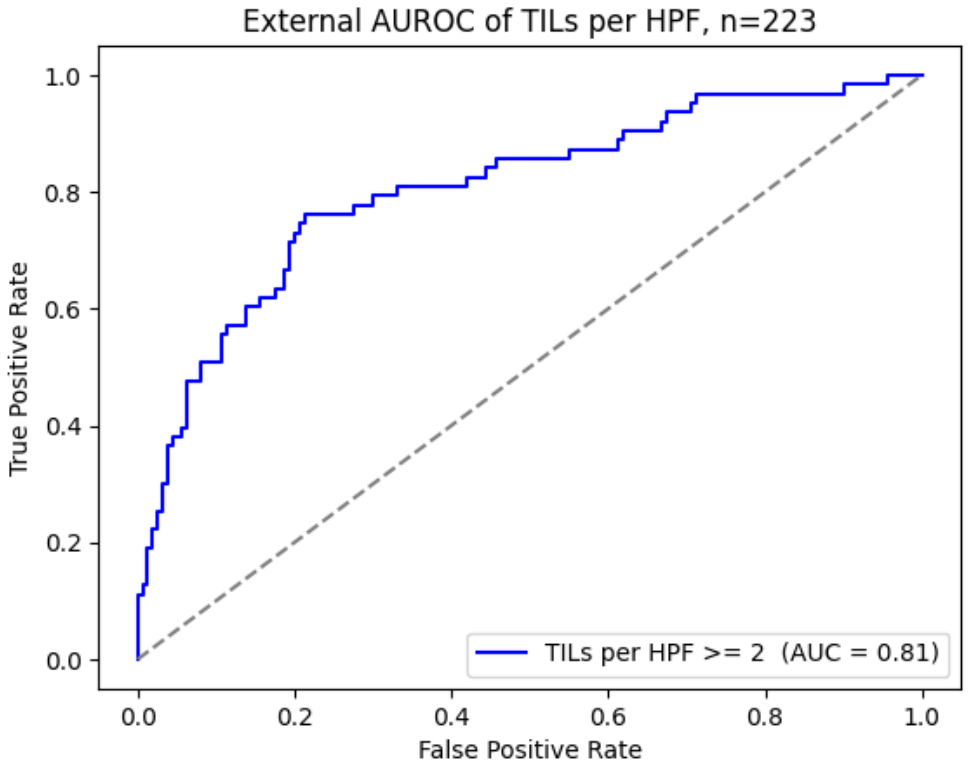
Wagner et al, Cancer Cell 2023

Predicting TILs/hpf with Regression-based AI

Pathologist-counted TILs/hpf = 10.0
AI-Predicted TILs/hpf = 8.41



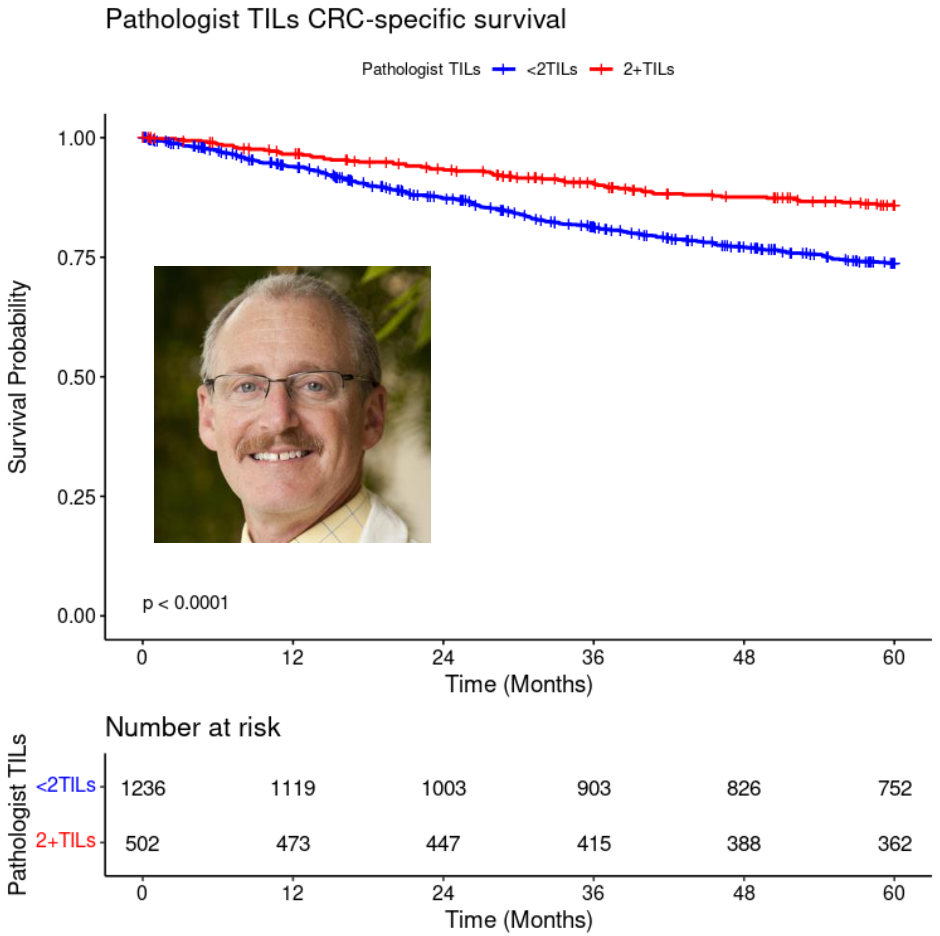


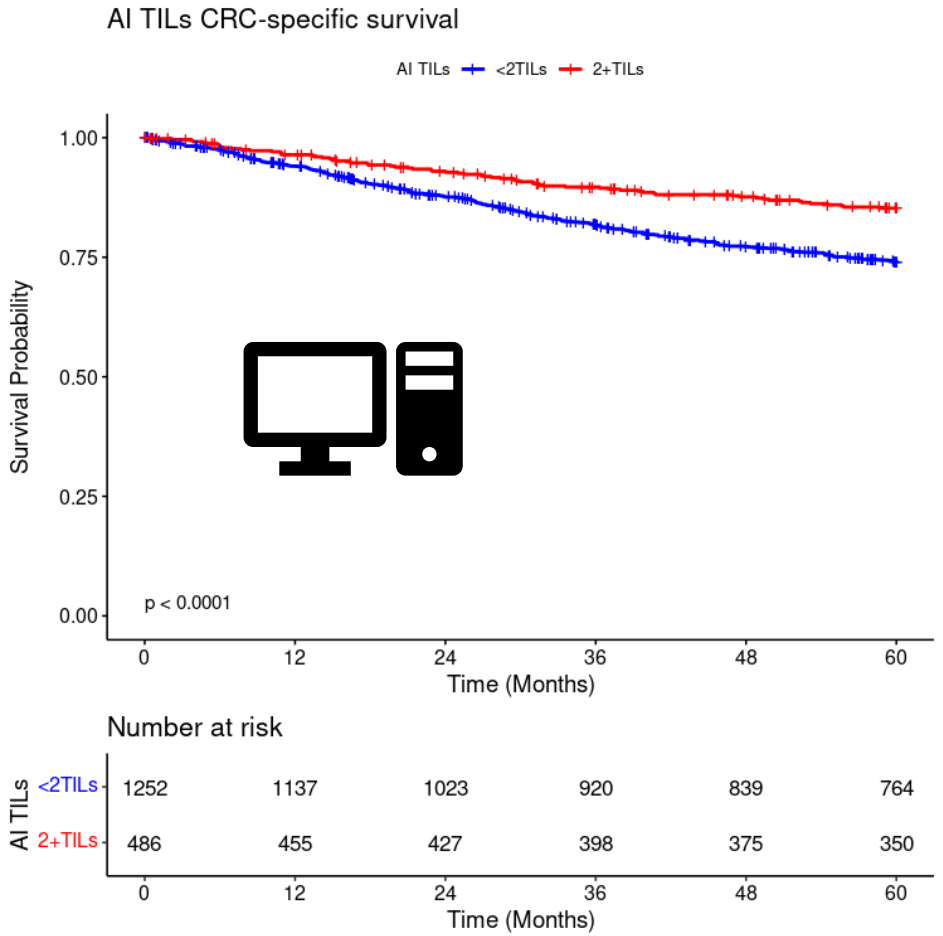


Gruber *et al*, AACR 2024

El Nahhas *et al*, AACR 2024

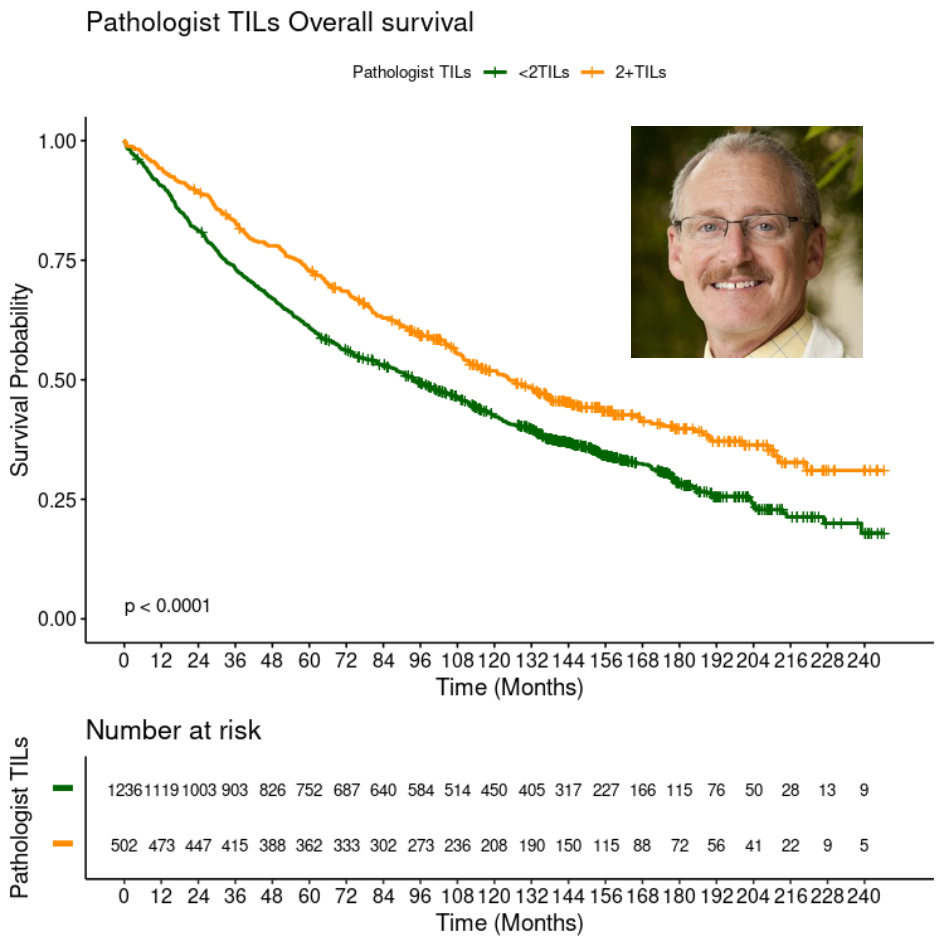
5-Year Colorectal Cancer Specific Survival - HopeSTIL™

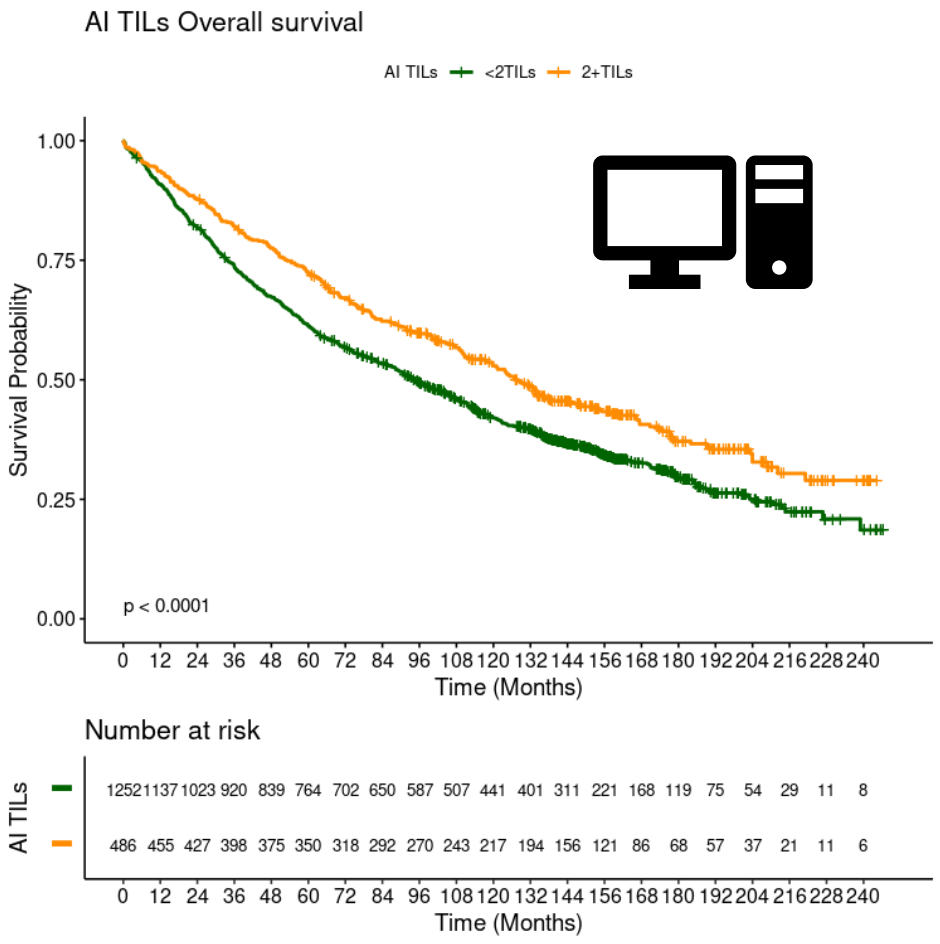




Gruber et al, AACR 2024

20-Year Overall Survival - HopeSTIL™





Gruber et al, AACR 2024

Multivariate Cox Proportional Hazards Model

5-Year Cancer-Specific Survival

Variable	Hazard Ratio	95% Confidence Interval	p-value
AI-Predicted TILS	**0.70**	**(0.52 – 0.94)**	**0.018**
Age (continuous)	1.01	(1.00 – 1.02)	0.058
Sex (M vs. F)	1.00	(0.80 – 1.25)	0.990
Stage (III/IV vs. I/II)	6.69	(5.24 – 8.53)	<0.001
Microsatellite Instability (MSI-H vs MSS)	0.83	(0.60 – 1.16)	0.278

Gruber et al, AACR 2024

Objectives – High Risk Management

1

Access:

Explore potential impact of universal germline genetic testing for all cancer patients..

2

Immunology & AI:

Recognize prognostic and predictive potential of immune measures in colorectal cancer and advances in computing and AI.

3

High Risk Management:

Apply advances in identifying and managing individuals & populations with genetic risk.

Models for Managing Individuals

Dana-Farber Cancer Institute

share this tool:

Home | Get My Cancer Risks

MyLynch: A Cancer Risk Tool for People with Lynch Syndrome

MyLynch was built by cancer researchers and statisticians from the BayesMendel lab at Dana-Farber Cancer Institute and Harvard University to help people with Lynch Syndrome (LS) understand how their LS can increase the risk of different cancers and to show them what they can do to lower their risks.

MyLynch is new and we are seeking YOUR input to help us improve this website; there will be a link to a user survey at the end of the tool so please give us feedback.

What is Lynch Syndrome?

Lynch Syndrome (LS) is a condition passed down through families that affects about 1 in 300 people in the United States. People with LS have a significantly increased likelihood of developing one or more cancers throughout their lifetime, with colorectal cancer being the most common. As LS research has evolved, many other cancers have also been linked to LS however, advances in medicine have also found effective ways to prevent and treat these cancers.

LS is caused by a pathogenic mutation on one of five genes:

- MLH1
- MSH2
- MSH6
- PMS2
- EPCAM

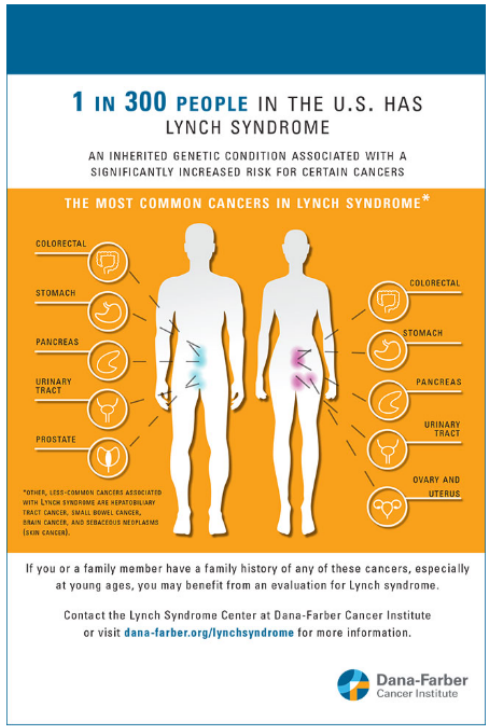
There are tests available for LS, both commercially and through your doctor, to detect if you have a pathogenic mutation on one of the genes above. If someone in your family has been diagnosed with LS, or your family has a history of cancer, you may have LS and you should talk with your doctor about getting tested.

People diagnosed with LS are often referred to a medical specialist called a genetic counselor. Your genetic counselor will work with your doctor to make a plan to manage your LS.

Dana-Farber has a dedicated site for LS where you can learn more: click here

What Does MyLynch Do?

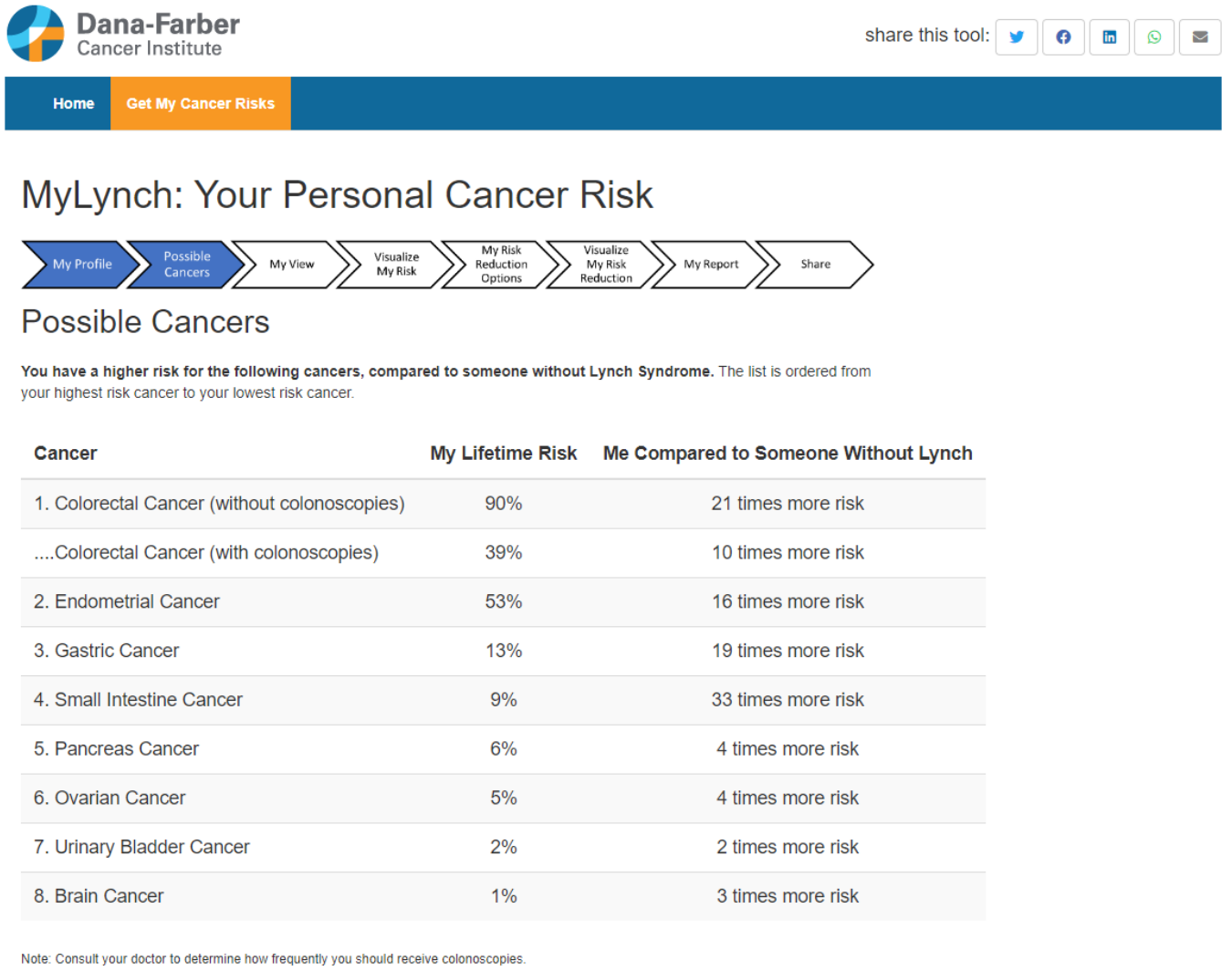
This tool is based on a large body of medical research that links specific LS genes to different cancer types. The research shows that for people with LS, risk for these cancers varies widely from person-to-person based on several factors such as which gene is causing their LS, their sex, their age, and other factors. This tool will lead your through a series of steps and in the end, you can get a personalized report that tells you:



https://hereditarycancer.dfci.harvard.edu/mylynch/

MyLynch

- Case Example - hypothetical
- 35 yo Black woman, non-Hispanic, with MLH1 and no prior history of cancer
- 5’4” 160lbs (BMI 27.5)



Dana-Farber Cancer Institute

share this tool:

Home | Get My Cancer Risks

MyLynch: Your Personal Cancer Risk

My Profile | Possible Cancers | My View | Visualize My Risk | My Risk Reduction Options | Visualize My Risk Reduction | My Report | Share

Possible Cancers

You have a higher risk for the following cancers, compared to someone without Lynch Syndrome. The list is ordered from your highest risk cancer to your lowest risk cancer.

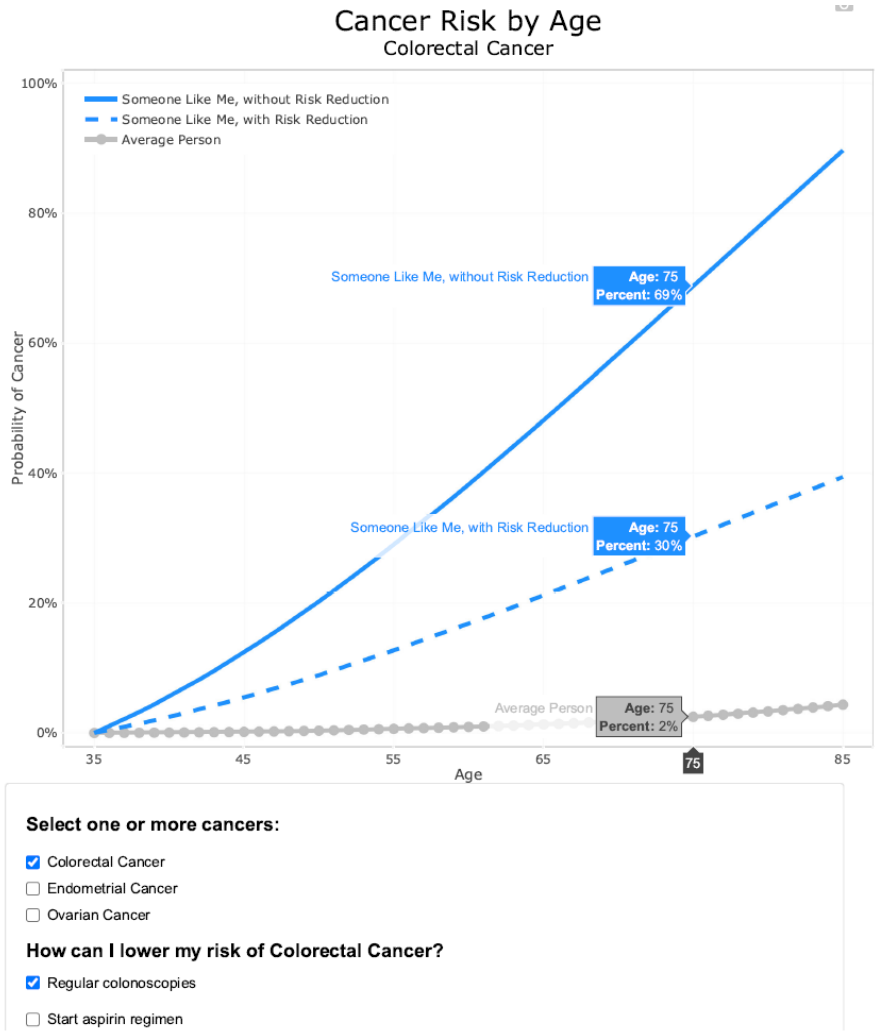
Cancer	My Lifetime Risk	Me Compared to Someone Without Lynch
1. Colorectal Cancer (without colonoscopies)	90%	21 times more risk
....Colorectal Cancer (with colonoscopies)	39%	10 times more risk
2. Endometrial Cancer	53%	16 times more risk
3. Gastric Cancer	13%	19 times more risk
4. Small Intestine Cancer	9%	33 times more risk
5. Pancreas Cancer	6%	4 times more risk
6. Ovarian Cancer	5%	4 times more risk
7. Urinary Bladder Cancer	2%	2 times more risk
8. Brain Cancer	1%	3 times more risk

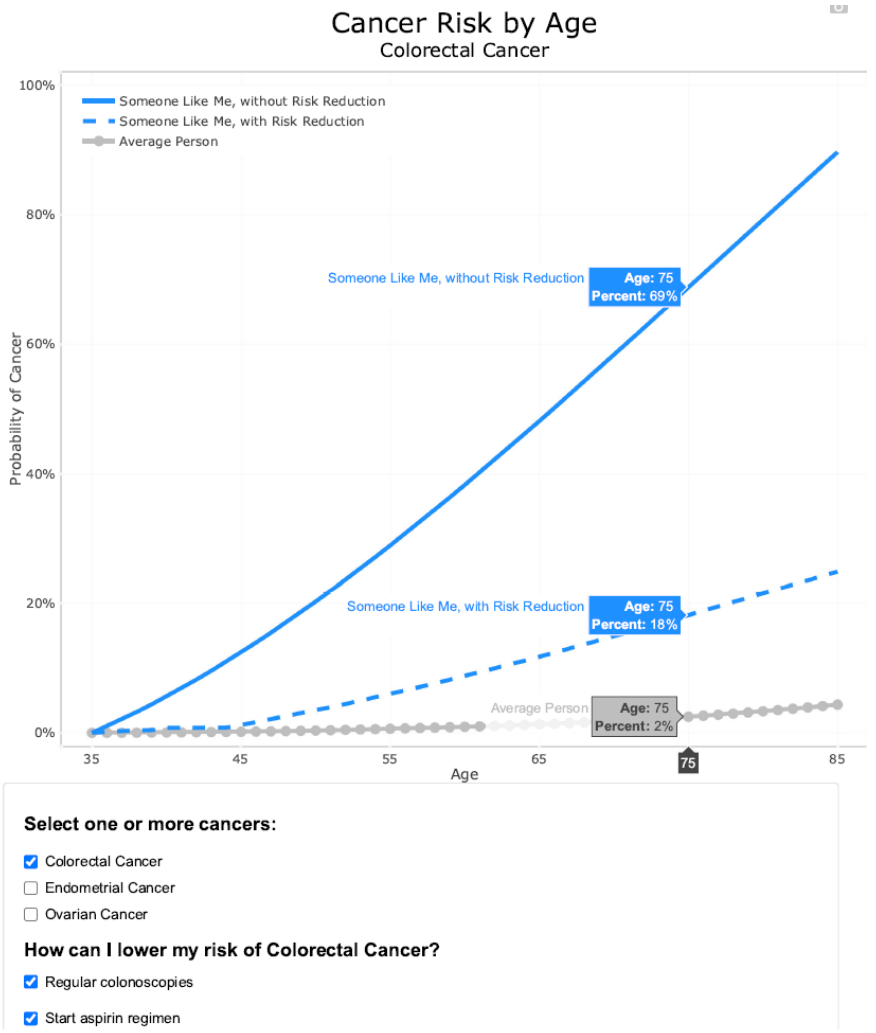
Note: Consult your doctor to determine how frequently you should receive colonoscopies.

https://hereditarycancer.dfci.harvard.edu/mylynch/

Hypothetical Case – MyLynch

- Case Example
- 35 yo Black woman, non-Hispanic, with MLH1 and no prior history of cancer
- 5’4” 160lbs (BMI 27.5)
- No screening or chemoprevention…risk of CRC at age 75 is **69%**
- Colonoscopy, but NO aspirin… risk of CRC at age 75 is **30%**.
- Colonoscopy WITH aspirin…risk of CRC at age 75 is **18%**.





Summary

- **Liquid biopsy holds promise** as technologies continue to emerge with improved performance
- Artificial Intelligence identifies features from digital pathology to predict clinically relevant outcomes
- Quantitative tools point patients towards preventive management of colorectal cancer risk