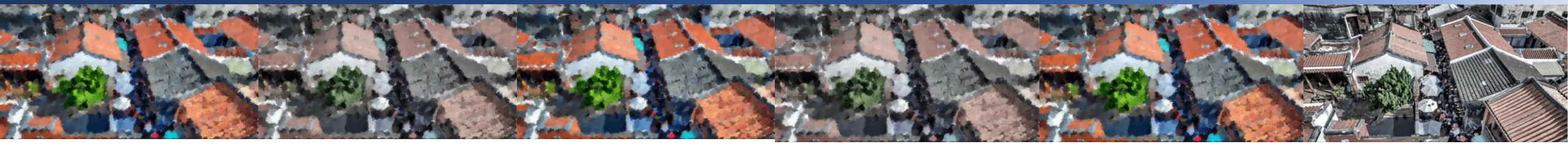


4P-based Colorectal Cancer Screening

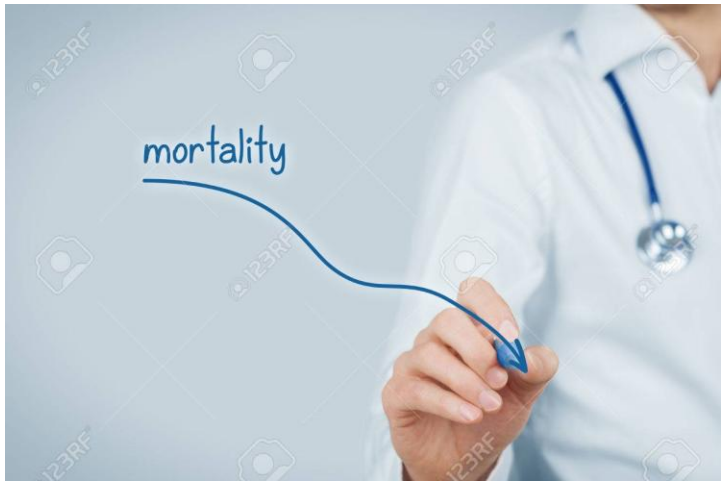
Han-Mo CHIU, MD, PhD.

Clinical Professor, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Principal Investigator, Taiwan Colorectal Cancer Screening Program

The ultimate goal of our efforts

- **Avoid CRC death** – by early detection of cancer
- **Avoid occurrence of CRC** - by detection (and removal) of adenoma



How much we would like to spend to:

- Avoid one CRC death
- Avoid one CRC

Short-term outcome: Stage shifting

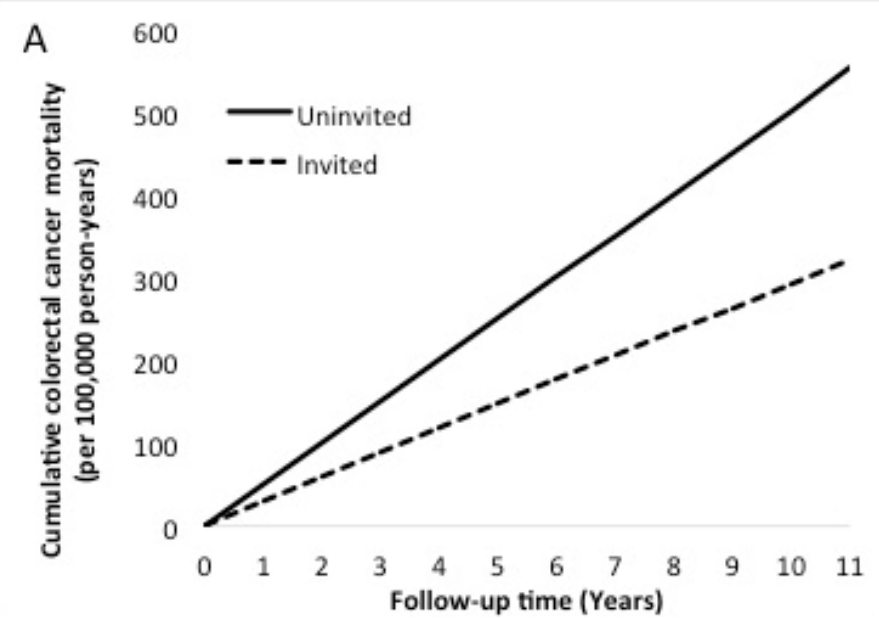
AJCC stage	CRC in unscreened group		CRC in screened group					
			Overall		First FIT screening		Subsequent FIT screening	
	N	%	N	%	N	%	N	%
0	2019	**6.7**	3568	**24.4**	2024	**21.5**	1544	**29.6**
I	4587	**15.1**	4268	**29.2**	2677	**28.5**	1591	**30.5**
II	7317	24.2	2274	15.6	1594	17.0	680	13.1
III	8812	29.1	3232	22.1	2195	23.4	1037	19.9
IV	7560	**25.0**	1268	**8.7**	910	**9.7**	358	**6.9**
Total	30295	100.0	14610	100.0	9400	100.0	5210	100.0

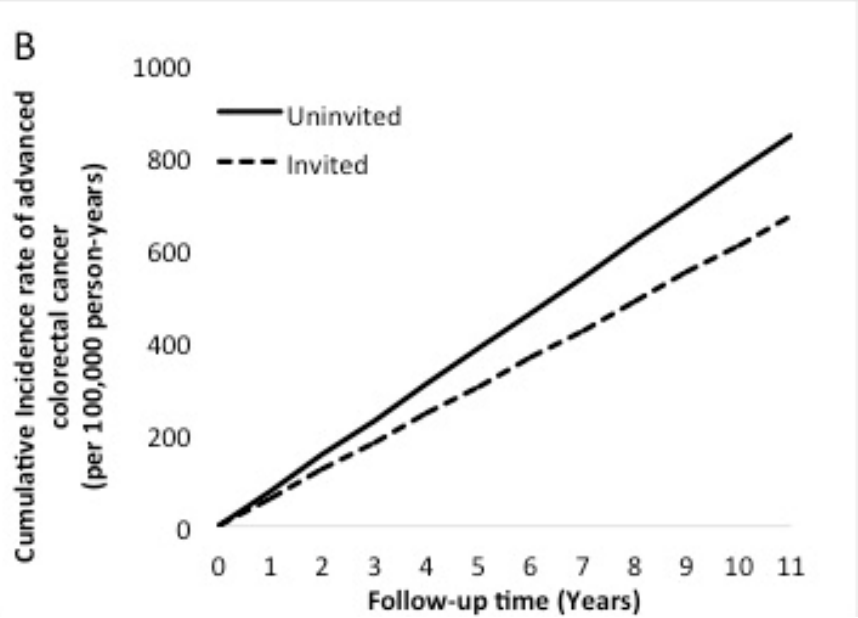
Taiwan Colorectal Cancer Screening Program

Chiu HM et al. Gut. 2021;70:2321-2329.

Long-term outcome:
Mortality and incidence of advanced stage CRC

CRC mortality	*Incidence of advanced stage CRC*





35% reduction
(aRR=0.60, 95%CI=0.57-0.64)

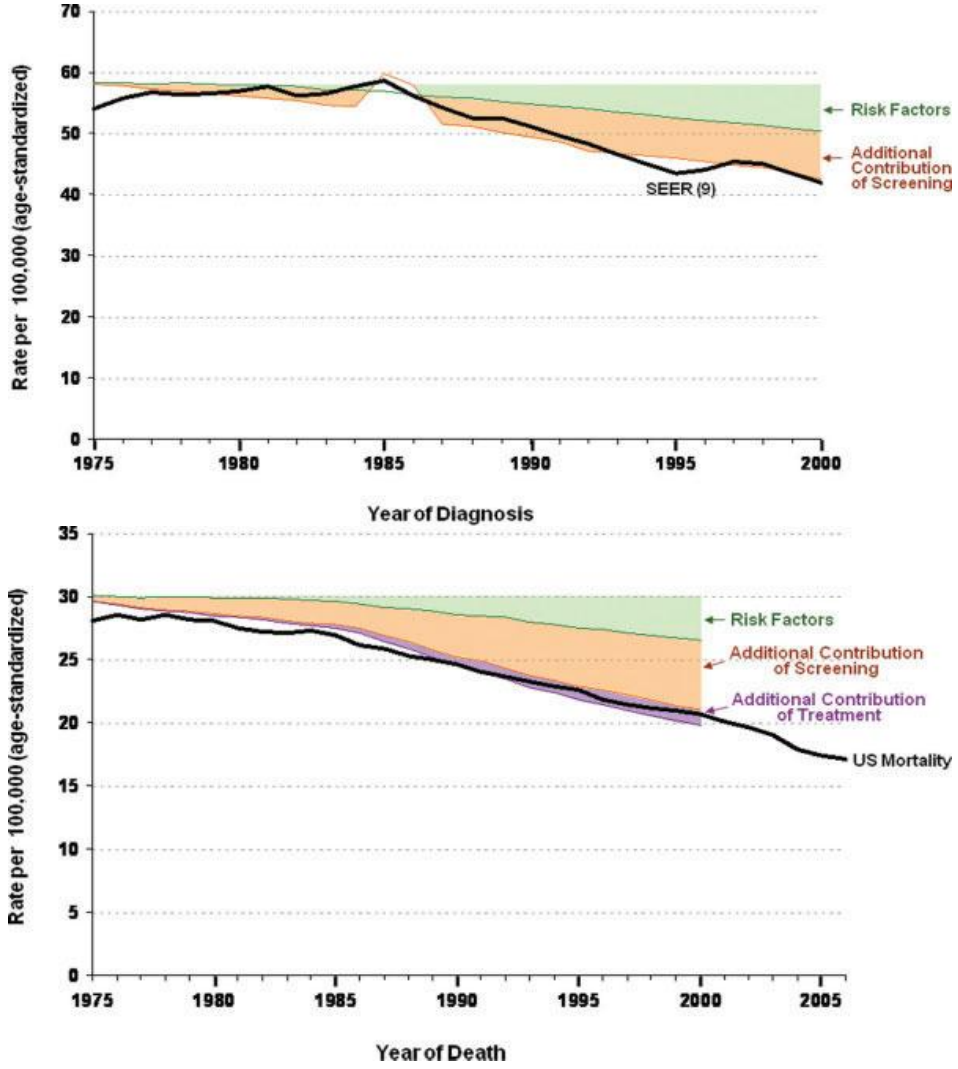
29% reduction
(aRR=0.66, 95%CI=0.63-0.70)

Chiu HM et al. Gut. 2021;70:2321-2329.

Current effort in the CRC screening community

- Improve participation
- Improve screening quality: FIT & Colonoscopy
- Improve resection techniques
- Improve safety
- Rely largely on RCTs and long-term cohort studies

Thinking beyond screening



- The United States was the first country to achieve reductions in both colorectal cancer incidence and mortality, with declines of 26% and 22%, respectively, between 1975 and 2006.
- **50 %** incidence reduction could be attributable to screening
- Mortality reduction attributable to:
  - ✓ Screening: **53%**
  - ✓ Life style modification: **35%**

Annual report of American Cancer Society
Edwards et al. Cancer 2010

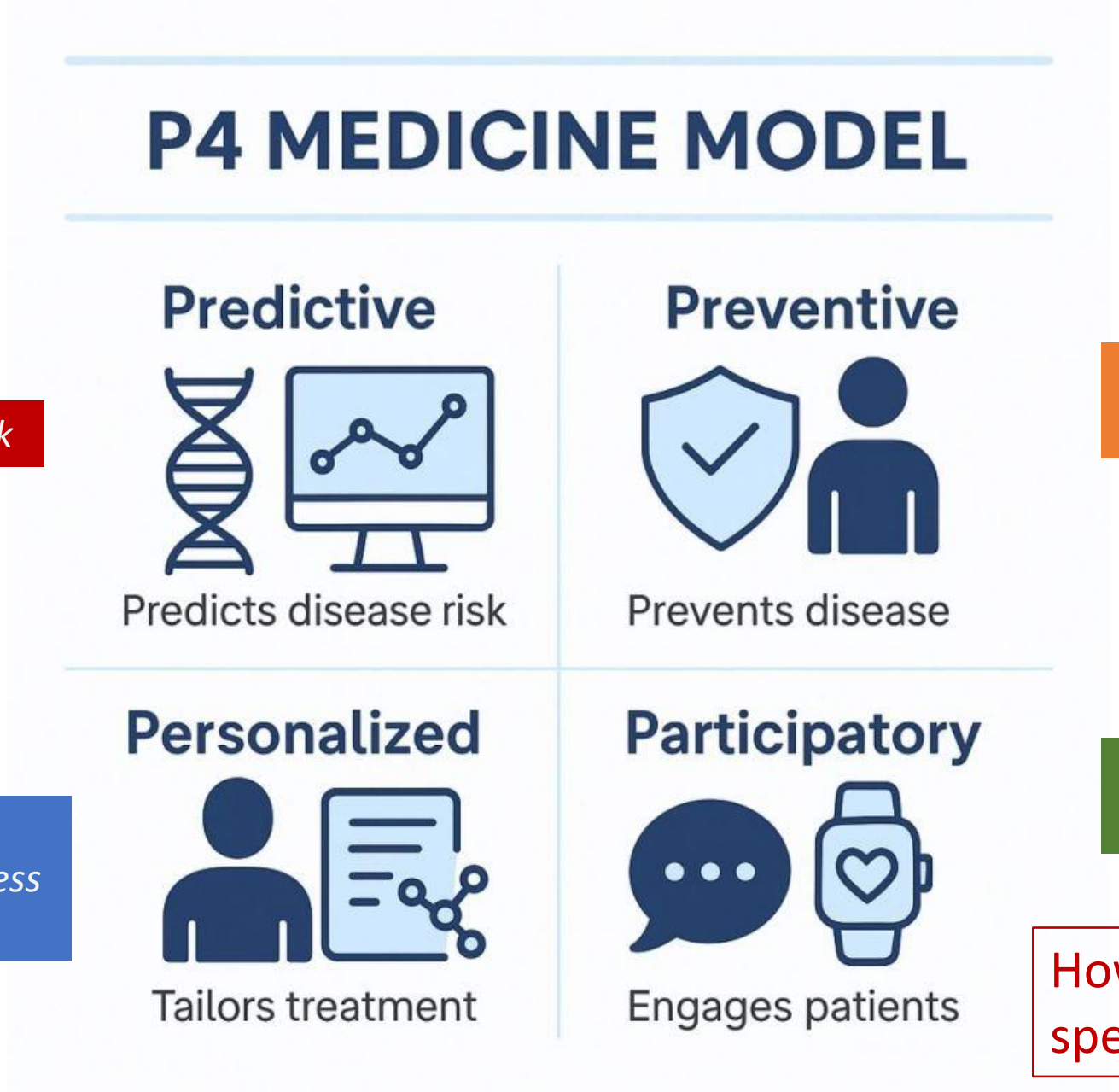
Spill over effect may exist

Screening regime	CRC (Duke A or B)	CRC (Duke C or D) or CRC death	CRC death	RR	95% CI
Multiple screening					
Annual	278.30	167.87	102.82	0.67	0.52-0.86
Biennial	253.48	192.69	113.94	0.74	0.58-0.94
Three-yearly	241.88	204.29	119.02	0.77	0.61-0.98
Four-yearly	234.96	211.21	121.91	0.79	0.62-1.00
Five-yearly	231.17	215.00	124.25	0.81	0.64-1.02
Single screening for CRC					
Annual	329.54	195.22	118.22	0.77	0.60-0.97
Biennial	300.17	224.58	131.24	0.85	0.67-1.07
Three-yearly	286.43	238.33	137.18	0.89	0.71-1.12
Four-yearly	278.20	246.55	140.57	0.91	0.73-1.15
Five-yearly	273.70	251.05	143.35	0.93	0.74-1.17
Control	250.50	274.25	154.17	1	

CRC + Other NCD

CRC only

Yang KC et al. J Med Screen 2006;13 Suppl 1:S8-13



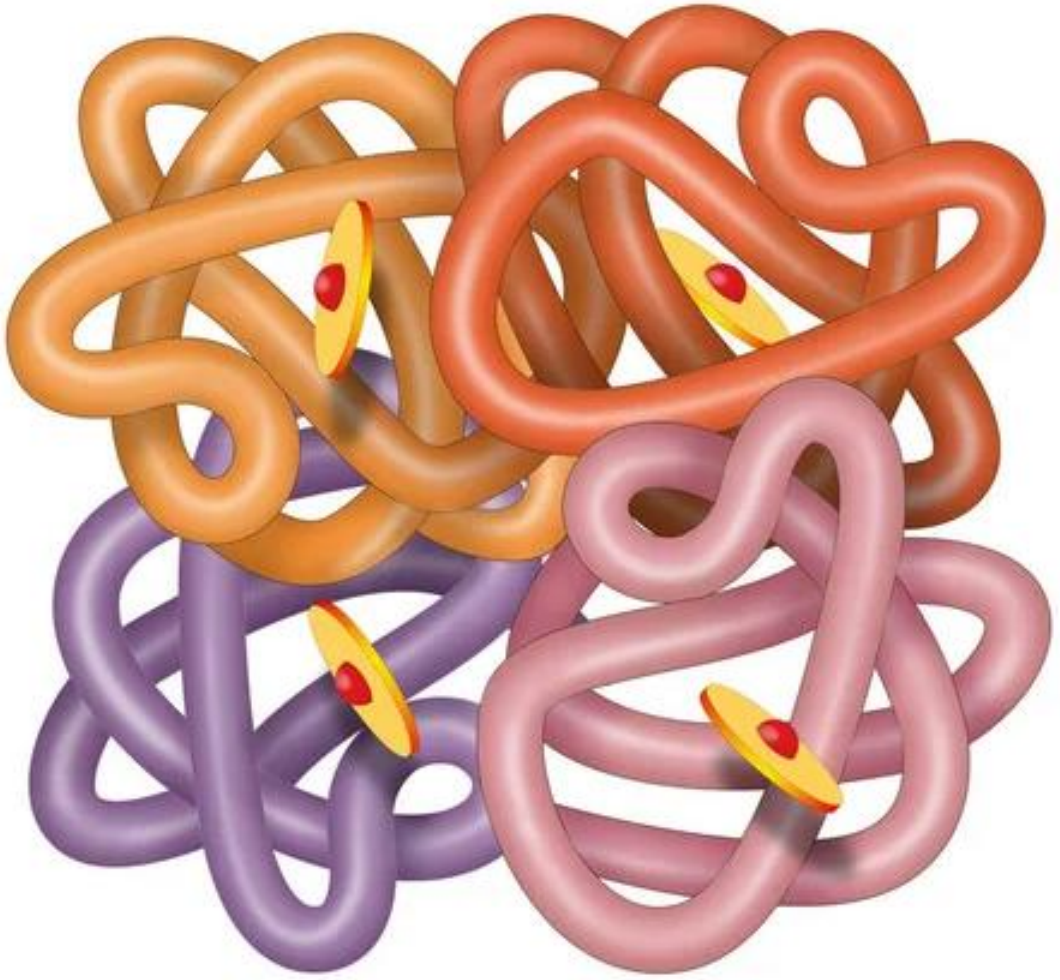
Predict future CRC risk

Prevent CRC death
Prevent CRC

Risk stratification
- *Enhance effectiveness*
- *Enhance efficiency*

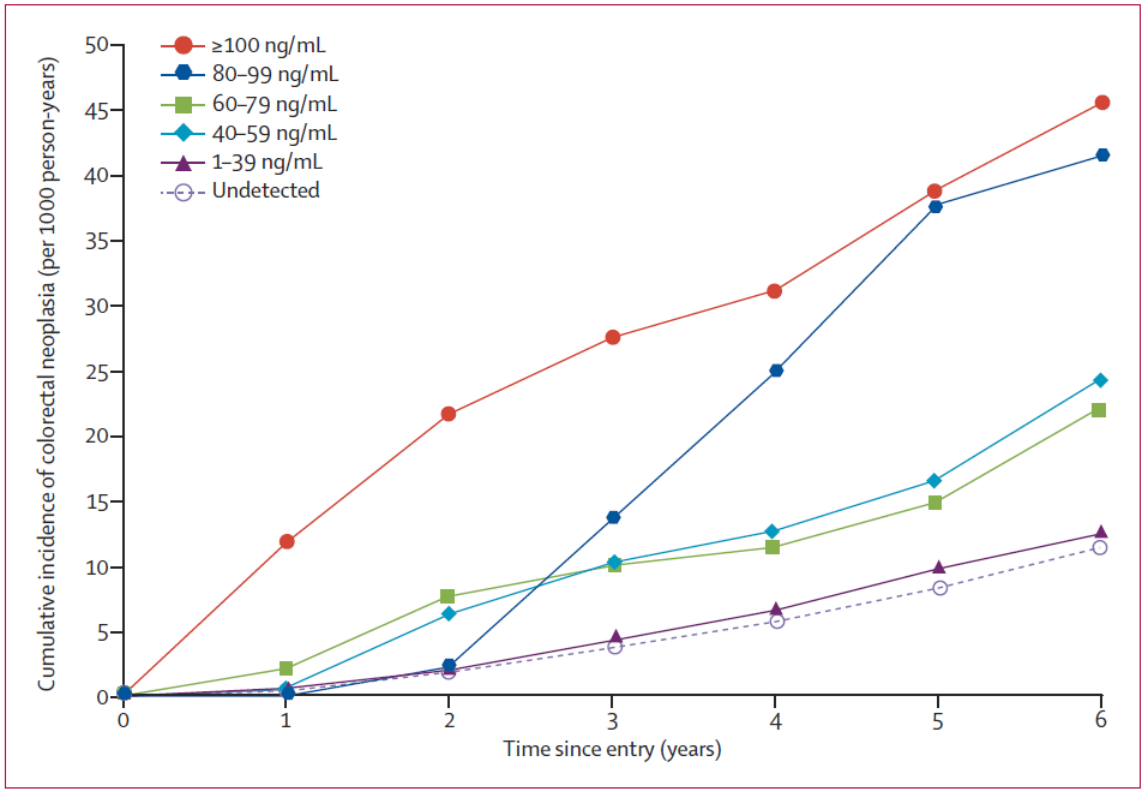
Increase screening participation
Enhance colonoscopy compliance

How much are we willing to spend to achieve these ?



Fecal Hemoglobin as a Trigger of 4P CRC Screening

Our very early findings set the scene for f-Hb-based precision CRC screening



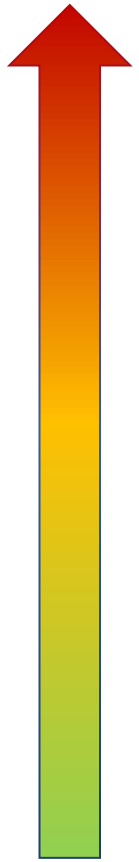


Figure 2: **Cumulative incidence of adenoma and colorectal cancer, by faecal Hb concentration**
Hb=haemoglobin.

Chen LS et al. Lancet Oncology 2011;12:551-558

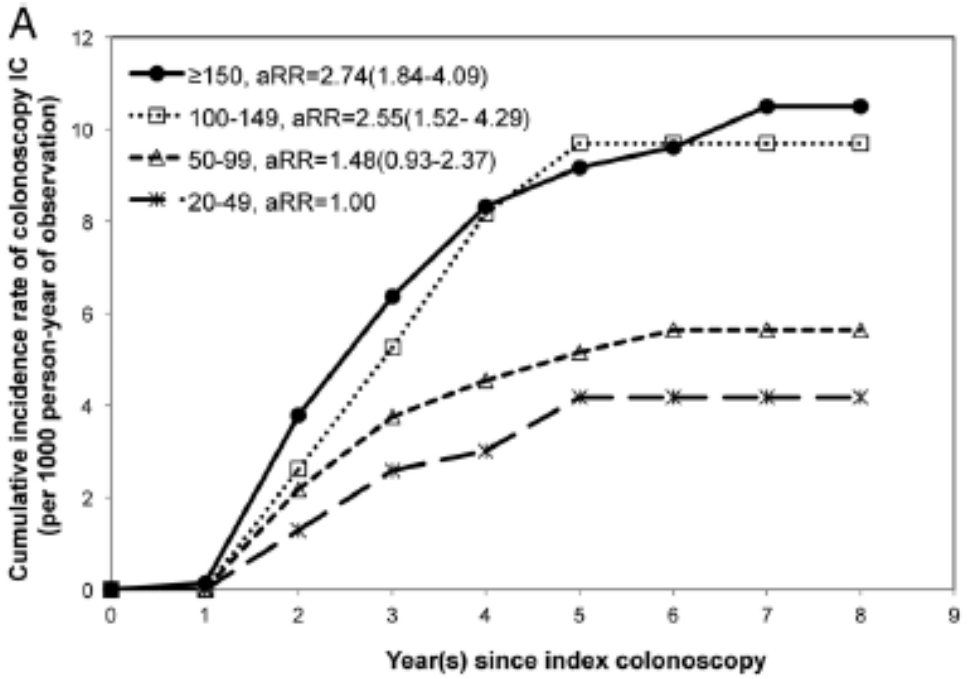
f-Hb is associated with the risk of advanced neoplasm

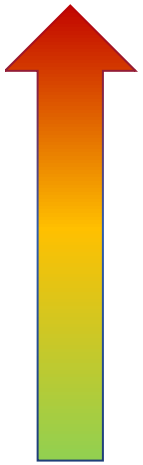
FHbC (μg/g feces)	Subjects with non-AA only, n	PPV for non-AA, %	Subjects with AA, n	PPV for AA, %	Subjects with CRC, n	PPV for CRC, %
20-49	3956	25.5 (23.9-27.1)	1398	9.0 (7.4-10.6)	304	**2.0 (0.4-3.5)**
50-99	2165	24.9 (22.8-27.0)	1005	11.6 (9.5-13.7)	283	**3.3 (1.2-5.4)**
100-149	875	23.8 (20.6-27.1)	512	14.0 (10.7-17.2)	183	**5.0 (1.8-8.2)**
≥150	2183	19.9 (18.1-21.8)	1737	15.9 (14.0-17.7)	1190	**10.9 (9.0-12.7)**

Chiu SY Chiu HM et al. Gut. 2017;66:293-300.

F-Hb predicts PCCRC risk

Overall





"Your colonoscopy quality is poor, and that's why f-Hb is associated with the risk of PCCRC after negative colonoscopy in your cohort"

Chiu SY, Chiu HM et al. Gut. 2017;66:293-300

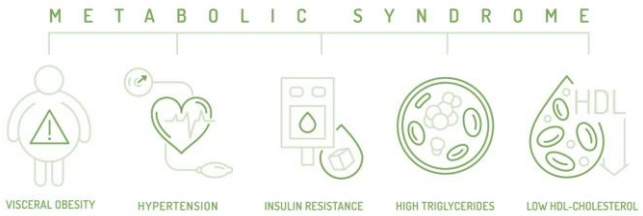
Inflammation and GI cancer: not uncommon

Diseases	Biomarker	Consequences
Chronic hepatitis B and C	Abnormal AST / ALT	Hepatocellular carcinoma
H.pylori infection chronic gastritis	Reddish discoloration of colonic mucosa	Gastric cancer
Inflammatory bowel disease	Inflammation of colonic mucosa Stool calprotectin	Colitic cancer
Colorectal neoplasm	**FIT?**	CRC

MetS increases the risk of advanced neoplasms occurrence

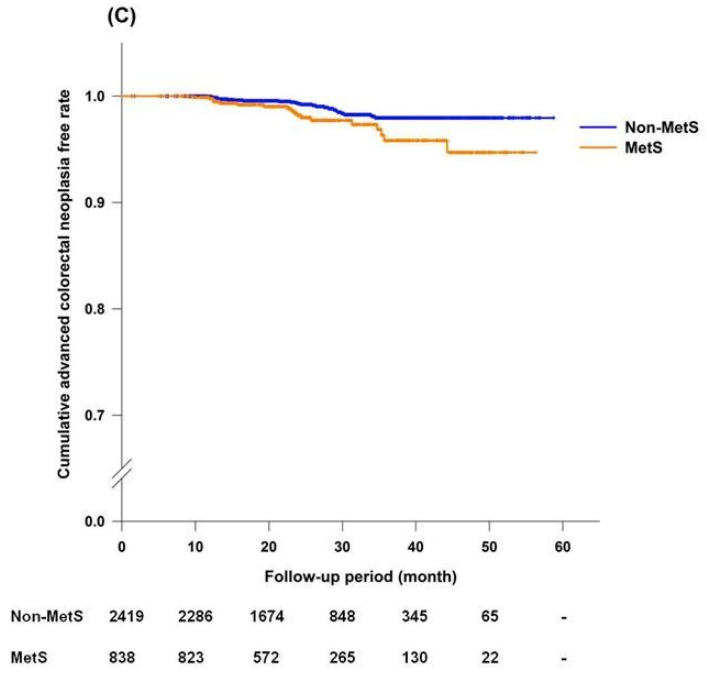
Endoscopic group	Overall N=4,483
Normal group (5y)	1.3%
Low-risk group (5y)	2.4%
High-risk group (3y)	8.5%

*:$P<0.05$

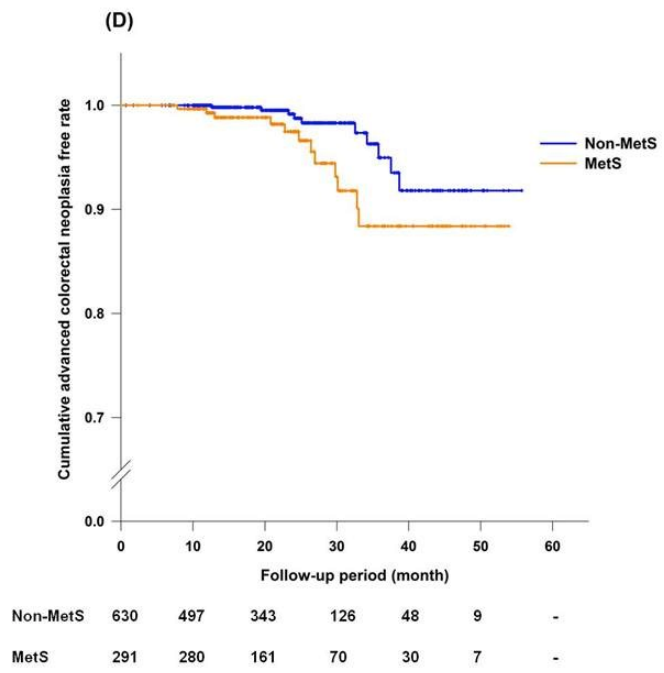


Chiu HM et al. Clin Gastroenterol Hepatol. 2015;13:1134-42.

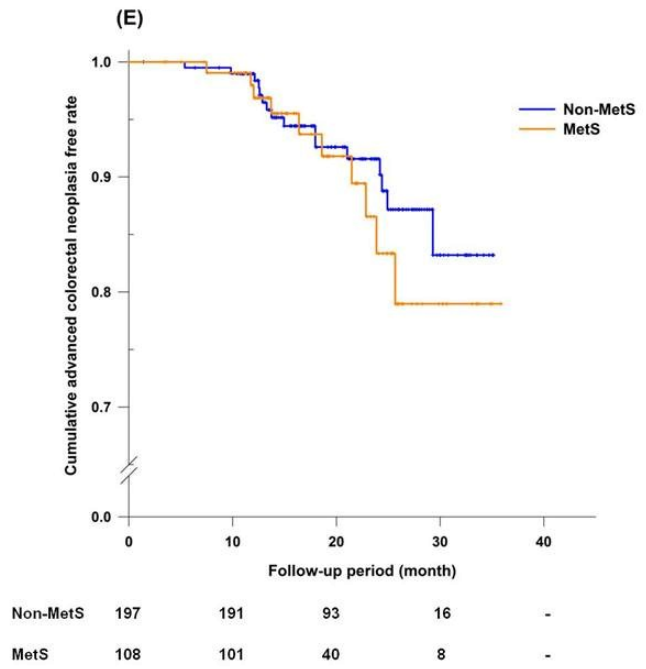
MetS increases the risk of advanced neoplasms occurrence



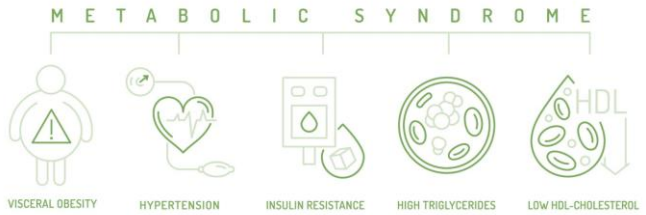
Normal group: *P*<0.001



Low-risk group: *P*=0.04



High-risk group: *P*=0.48



Chiu HM et al. Clin Gastroenterol Hepatol. 2015;13:1134-42.

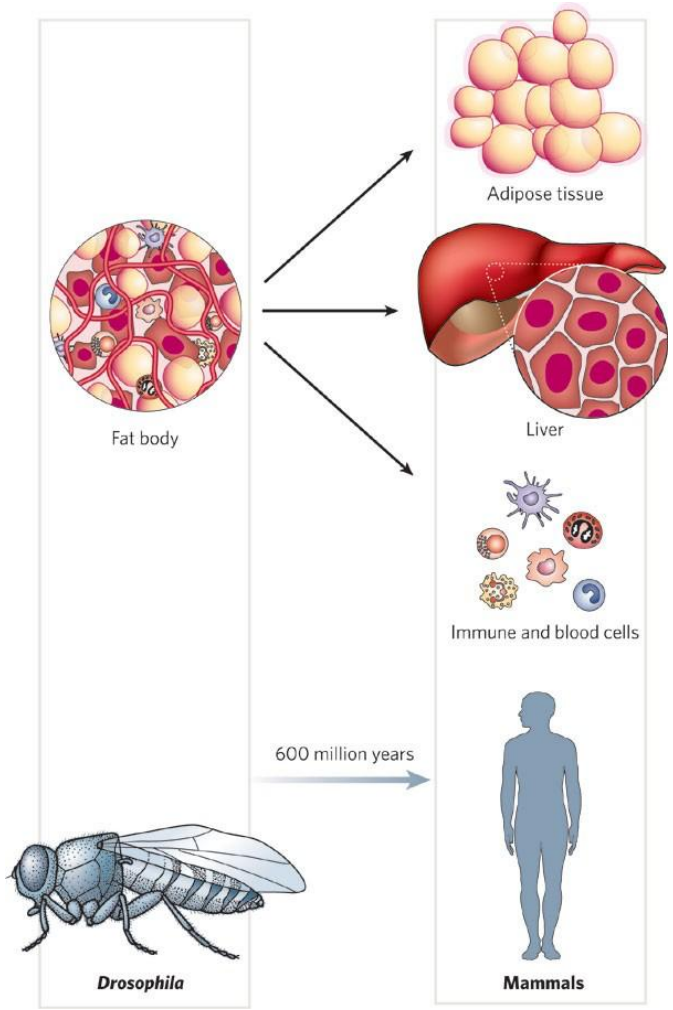
Low grade inflammation and colorectal neoplasia

	Neoplasia		Advanced neoplasia		Synchronous neoplasia		Concurrent synchronous & advanced neoplasia	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Q1	1	-	1	-	1	-	1	-
Q2	1.05 (0.85-1.31)	0.64	1.41 (0.87-2.28)	0.16	1.29 (0.80-2.08)	0.29	1.36 (0.53-3.50)	0.52
Q3	1.06 (0.85-1.31)	0.62	2.07† (1.33-3.23)	0.001	1.89† (1.22-2.92)	0.004	3.24† (1.43-7.37)	0.005
Q4	0.89 (0.70-1.12)	0.32	2.17† (1.38-3.39)	0.0008	1.49 (0.94-2.38)	0.092	2.48† (1.05-5.87)	0.038

Q: quartile of plasma CRP:
Q1: CRP<0.5 mg/dL, Q2: 0.5 mg/dL ≤CRP<0.8 mg/dL,
Q3: 0.8 mg/dL ≤CRP<1.4 mg/dL, Q4: 1.4 mg/dL ≤CRP

Chiu HM et al. Am J Gastroenterol 2008;103:2317-25.

Adipose tissue · Hematopoietic organ · Liver

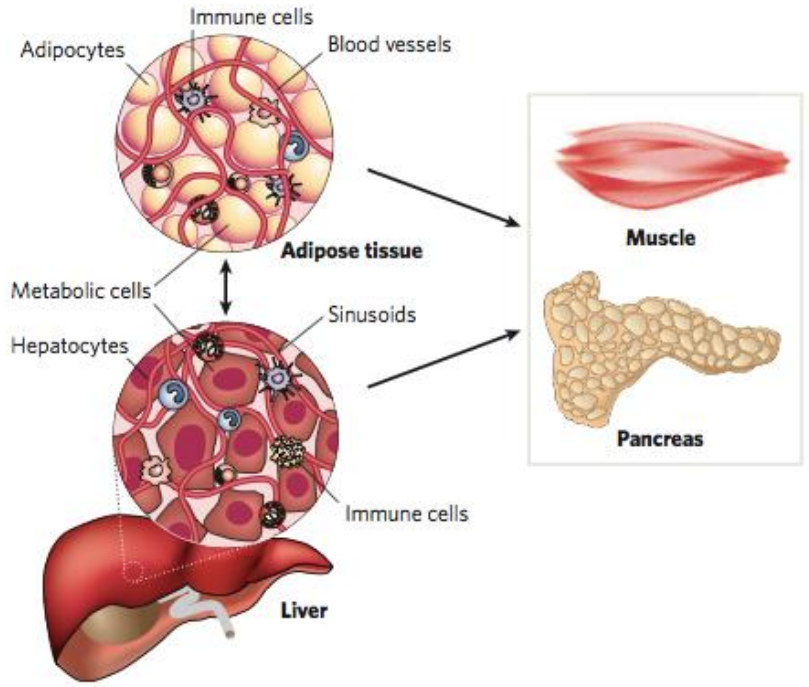


The adipose tissue, liver and hematopoietic system are all organized in one functional unit in *Drosophila melanogaster*, known as the 'fat body'. This developmental heritage may underlie the highly overlapping biological repertoire of these organs, their effects on metabolic and immune cells, and the close link between immune and metabolic response systems.

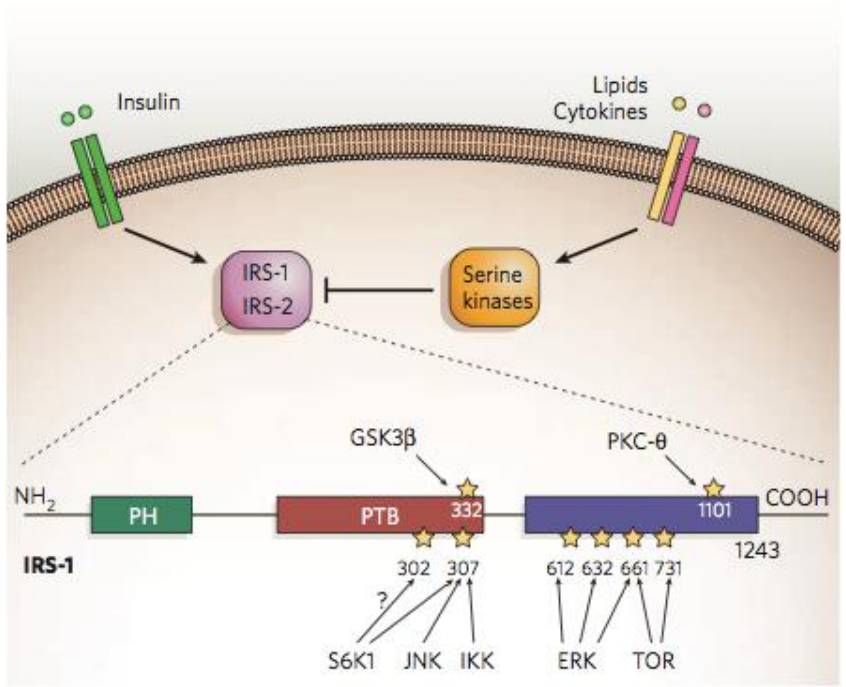
Hotamisligil et al. Nature 2006; 444: 860

“Metaflammation”

– *Fat tissue, immune system, and liver are connected*



Organization and proximity of principal metabolic and immune cells in adipose tissue and liver

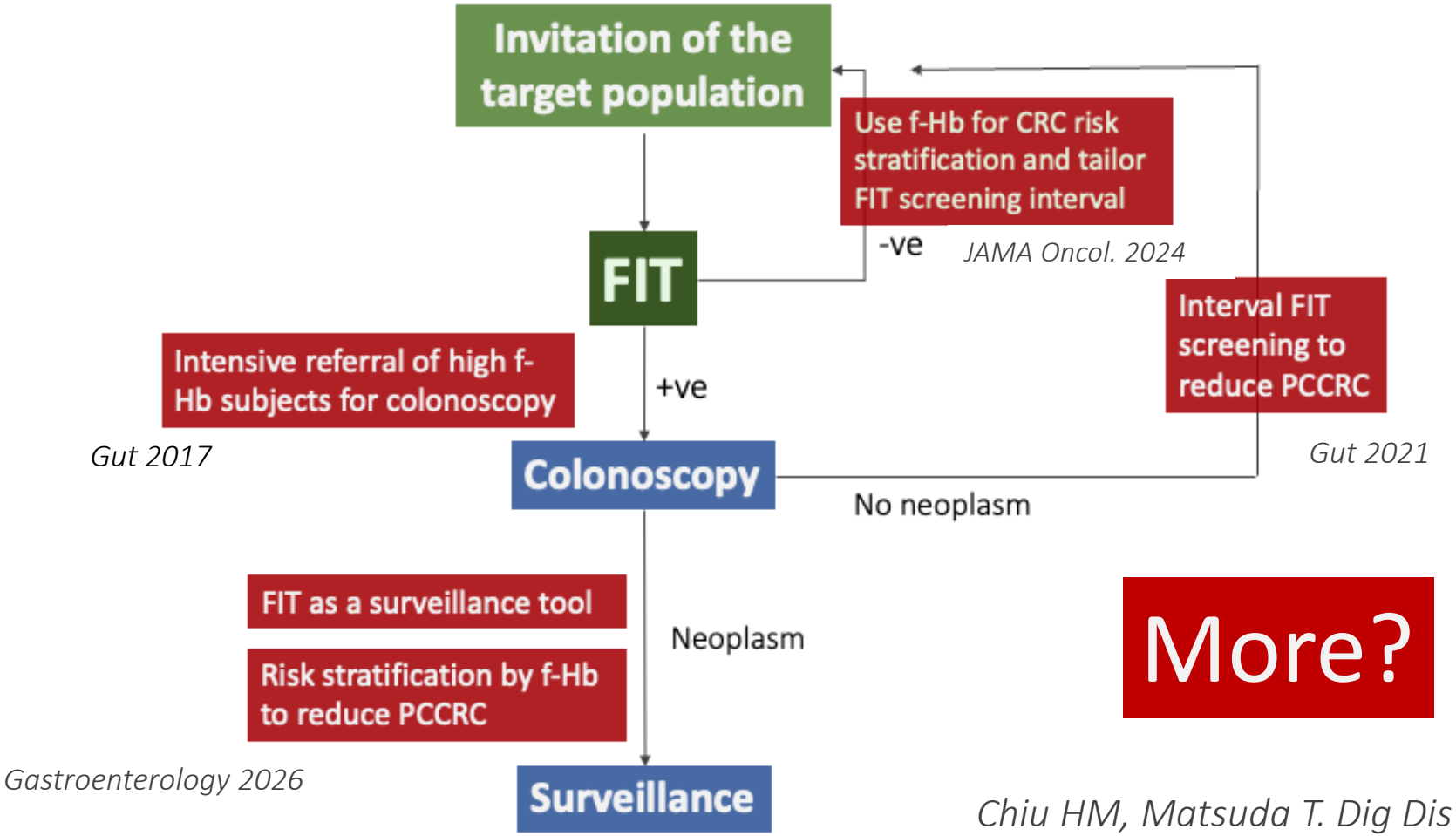


Insulin-receptor signaling interfaces with inflammatory signaling

Hotamisligil et al. Nature 2006; 444: 860

Colorectal Cancer Screening 2.0

-f-Hb plays a pivotal role in precision CRC screening



Chiu HM, Matsuda T. Dig Dis Sci 2025;70:1616-1624.

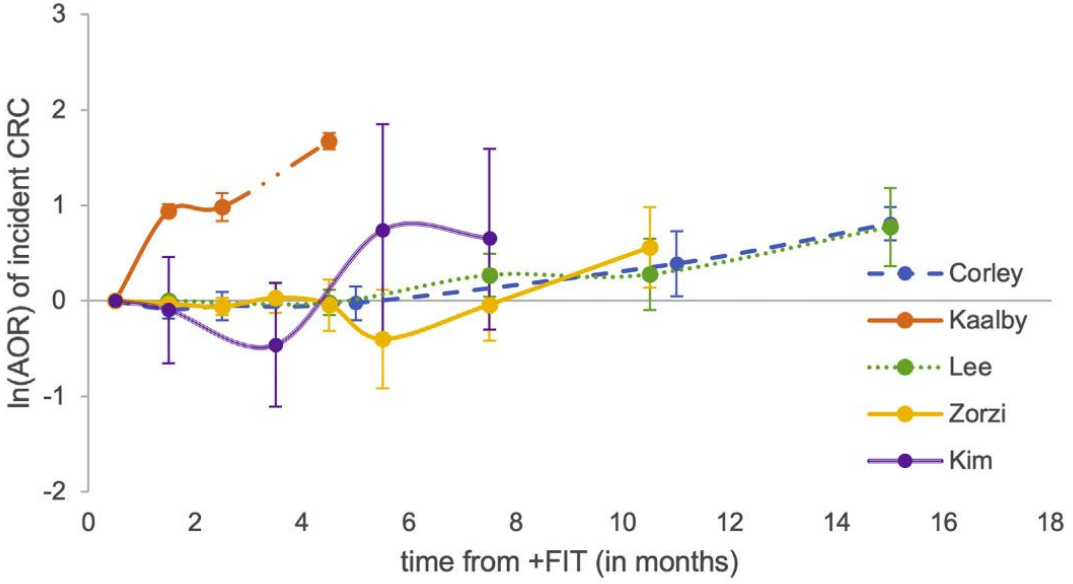
Timely colonoscopy after +ve FIT is crucial

Time from FIT to colonoscopy	CRC risk	Advanced stage CRC risk
Within 6 month	Ref	Ref
6-9 months	↑30%	2X
9-12 months	↑30%	2X
> 12 months	2X	2.8X

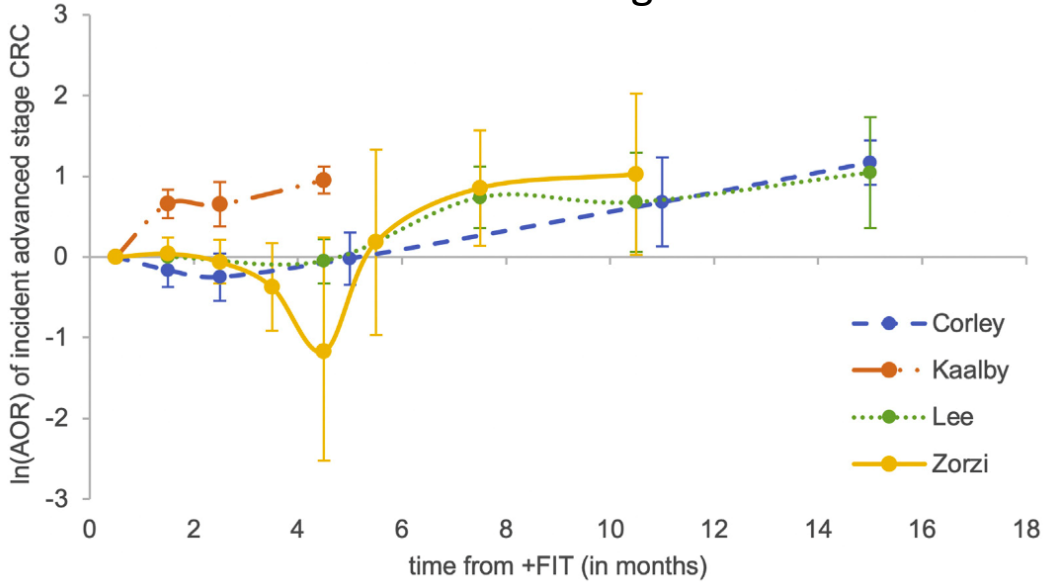
Modified from: Lee YC et al. Clin Gastroenterol Hepatol. 2019;17:1332-1340.

Timely colonoscopy after +ve FIT is crucial

CRC risk



Advanced stage CRC risk



Forbes N et al. Clin Gastroenterol Hepatol. 2021;19:1344-1354.

Timely colonoscopy after +ve FIT is crucial, but f-Hb can further tailor it

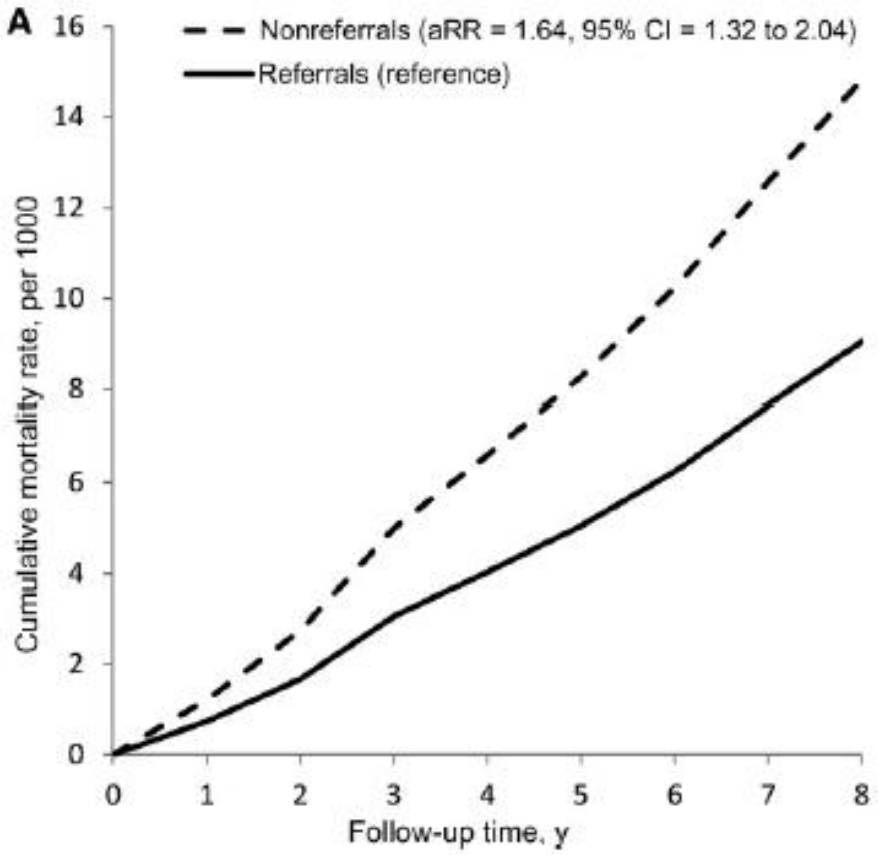
FIT to colonoscopy interval	CRC risk	Advanced CRC risk
within 6 mon	Ref	Ref
6-9 mon	**↑30%**	**2-fold**
9-12 mon	**↑30%**	**2-fold**
> 12 mon	**2-fold**	**2.8-fold**

Baseline f-Hb (μg Hb/g feces)	CRC risk	Advanced CRC risk
20–49	1	1
50–99	**1.5-fold**	**1.6-fold**
≥100	**4.3-fold**	**6.7-fold**

Taiwan Colorectal Cancer Screening Program

Modified from: Lee YC et al. Clin Gastroenterol Hepatol. 2019;17:1332-1340.

Non-compliance to colonoscopy

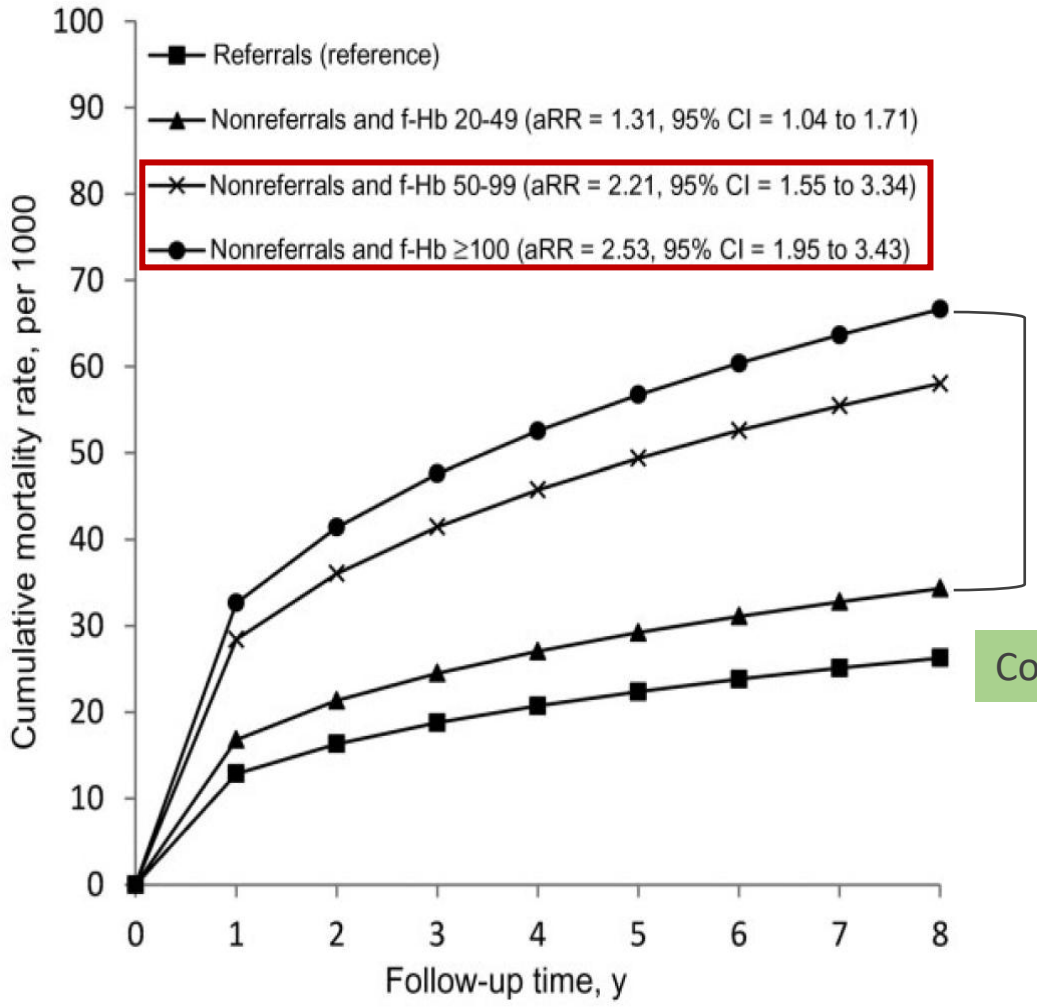


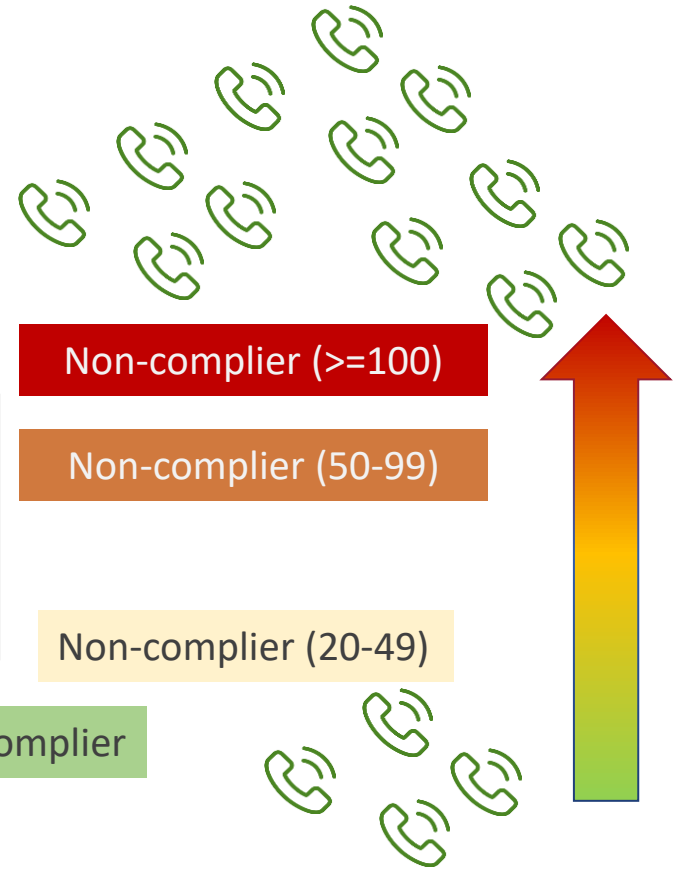
CRC death increased by **64%** if not undergo colonoscopy

Lee YC et al. J Natl Cancer Inst. 2017;109(5).

FHbC can set priority for colonoscopy referral

Subjects with high f-Hb should be **more intensively** contacted for colonoscopy after positive FIT





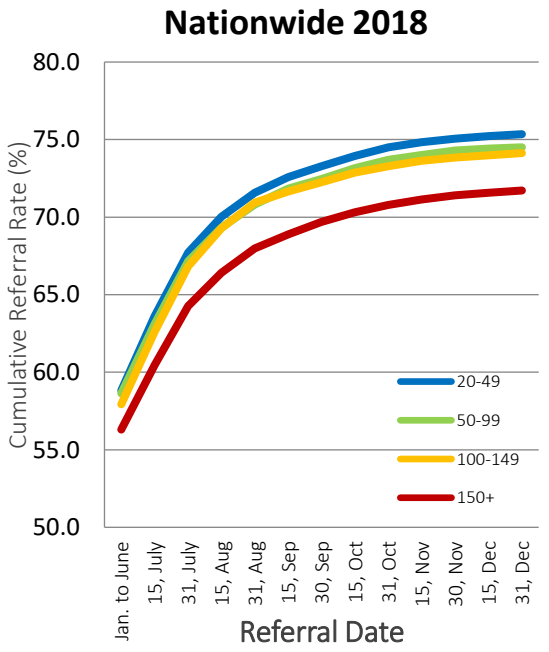
Lee YC et al. J Natl Cancer Inst. 2017;109(5).

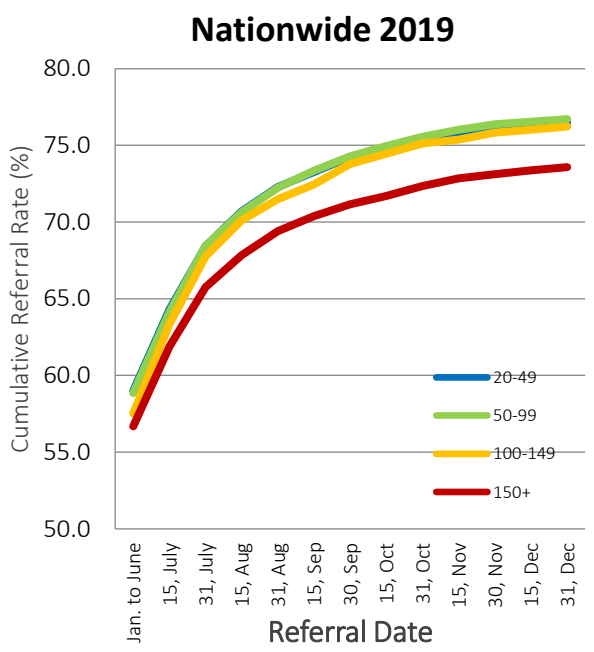
Set priority for colonoscopy based on FHbC during COVID

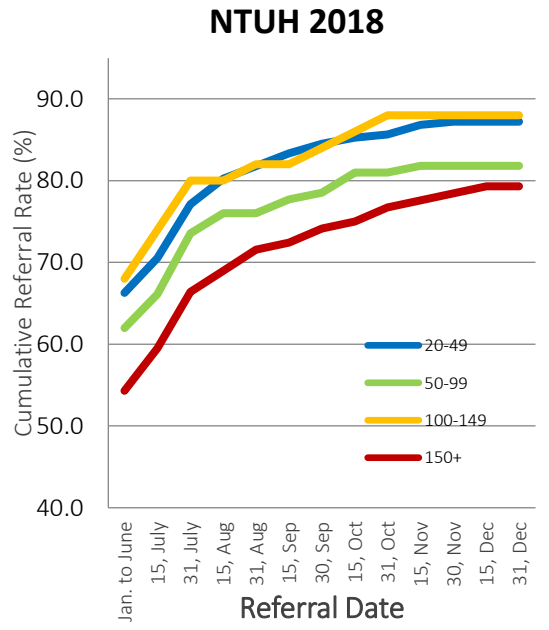
PPV (based on 2020 data)	FHbC (μg Hb/g)	FIT positive, n		Colonoscopy rate, %		Backlog	Expected No. of CRC
		Jan-Apr	May-July	Jan-Apr	May-July	Jan-July	Jan-July
7.8%	>=150	8654	2322	58.9%	21.5%	5384	418
2.4%	100-149	3537	868	59.5%	23.6%	2095	51
1.7%	50-99	9132	2288	60.7%	22.8%	5356	92
0.9%	20-49	18515	4739	59.7%	21.6%	11181	104
2.8%	TOTAL	39838	10217	59.7%	22.0%	24016	665

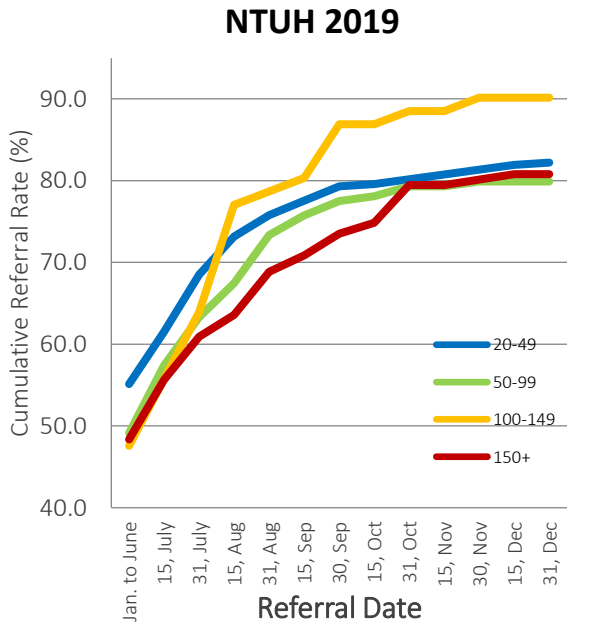
An interesting finding that we observed before COVID pandemic…

Those who had high f-Hb were less compliant to colonoscopy after positive FIT

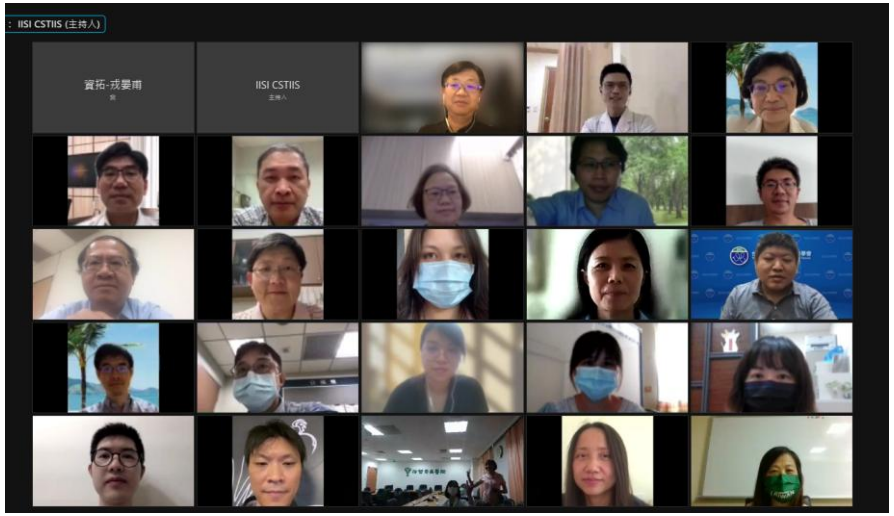




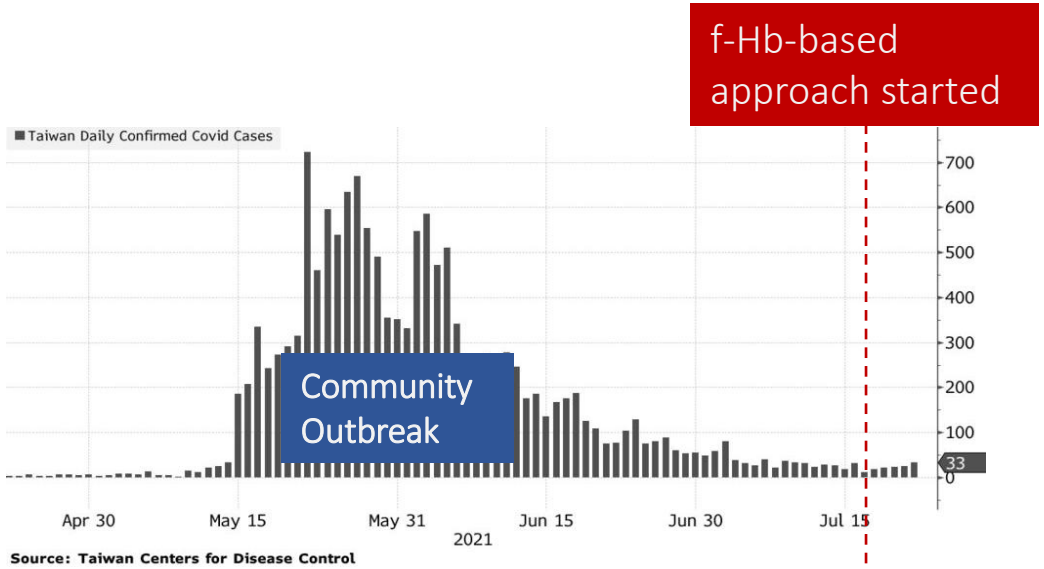


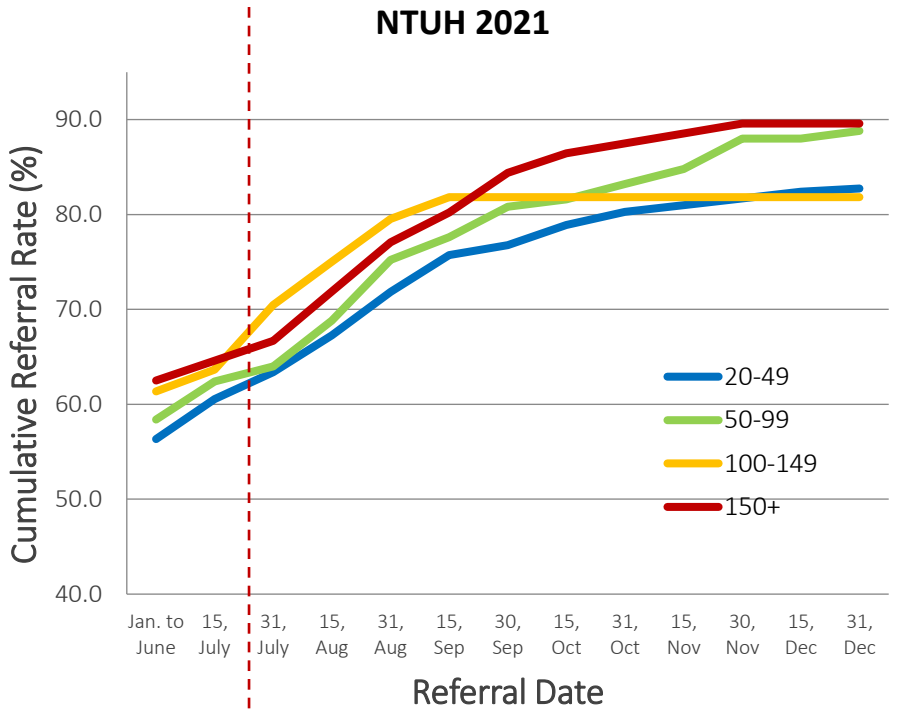


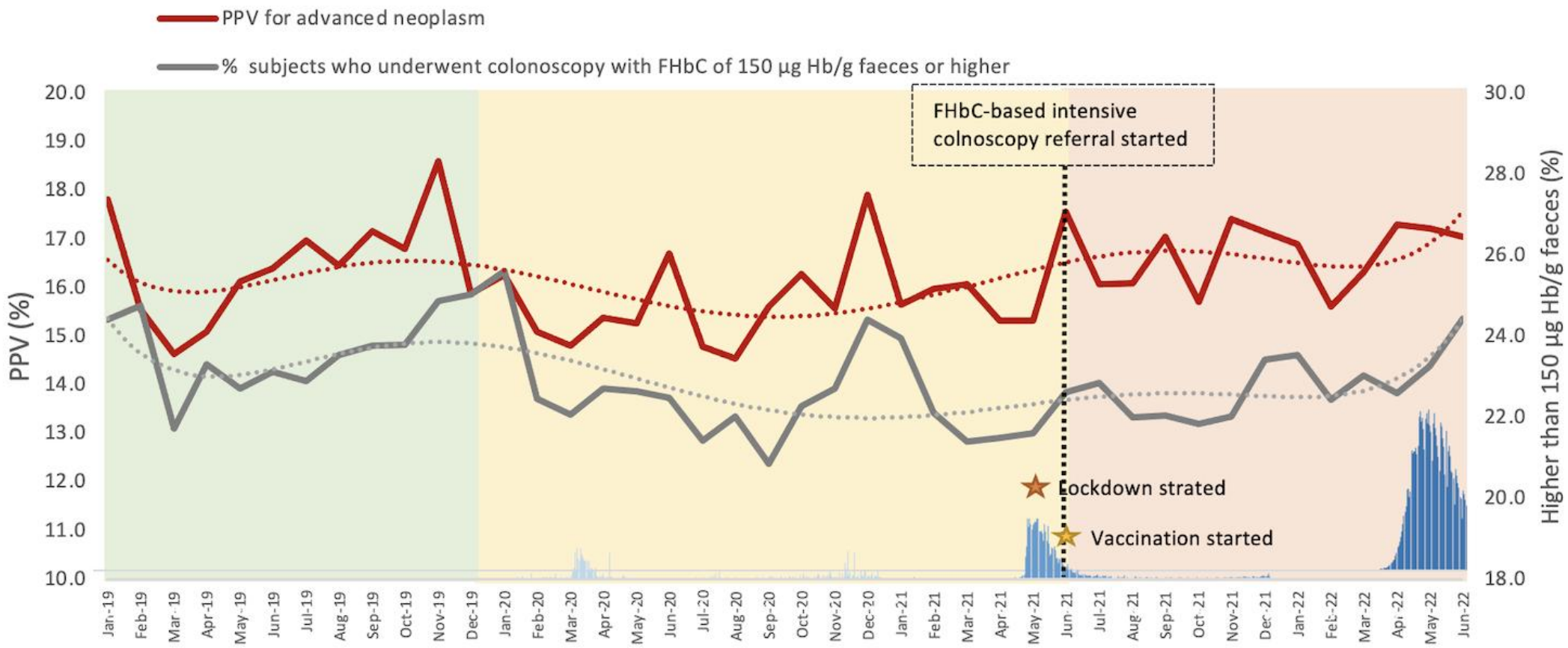
"Public health in action" meeting



Nationwide endoscopy unit meeting

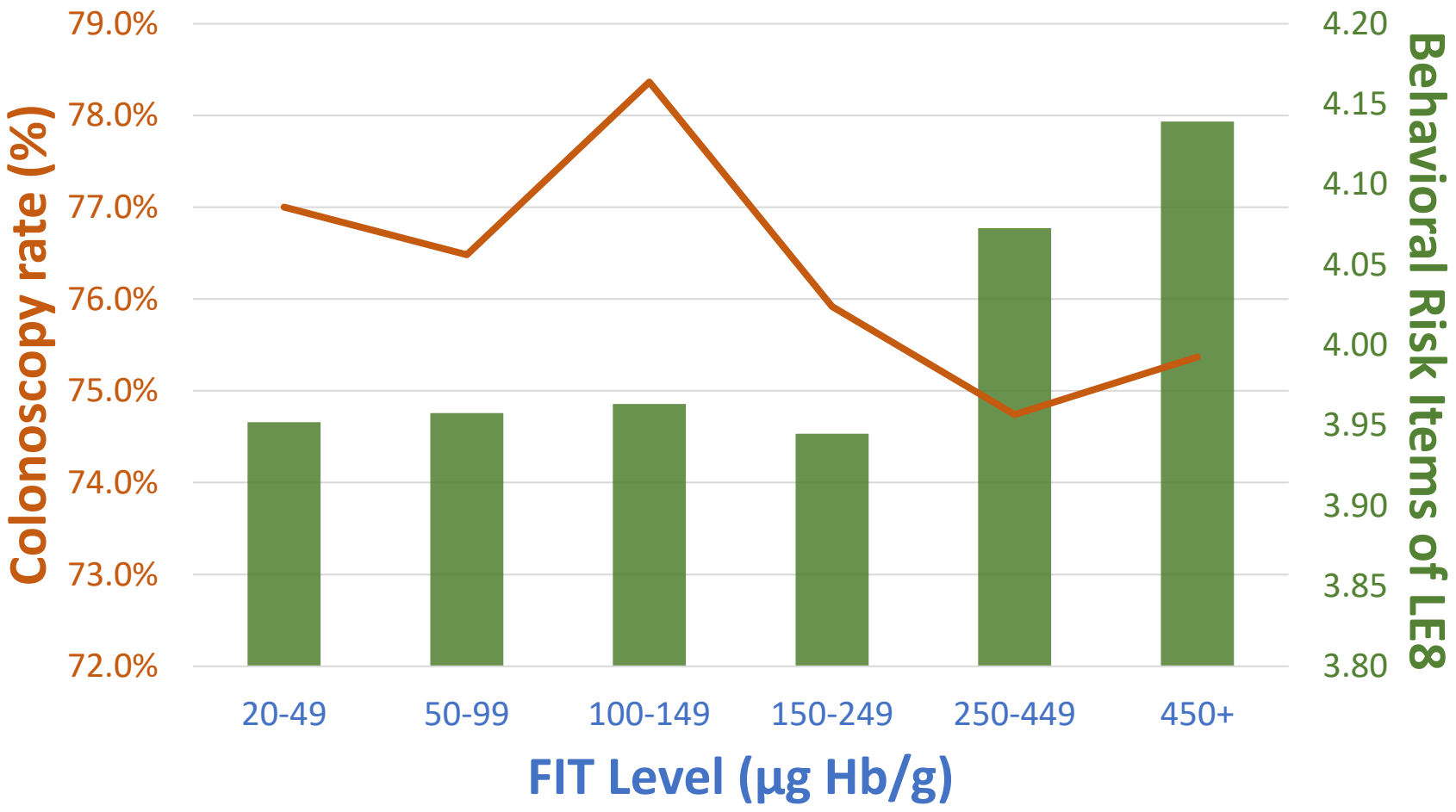






Although we performed far fewer colonoscopies, we detected a similar number of CRC during the pandemic

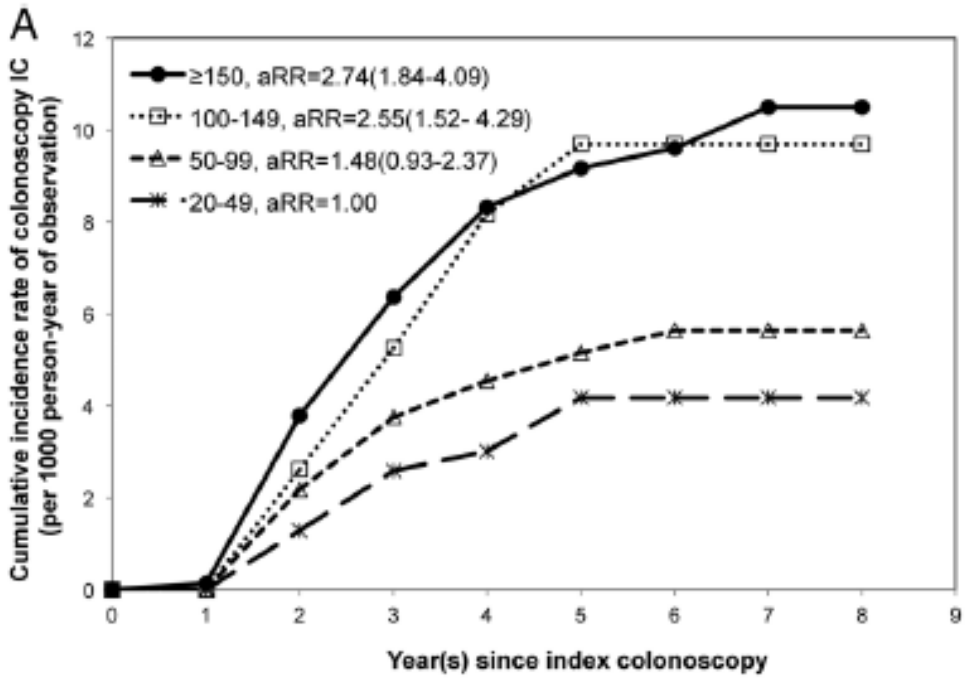
Chiu HM et al. DDW 2022



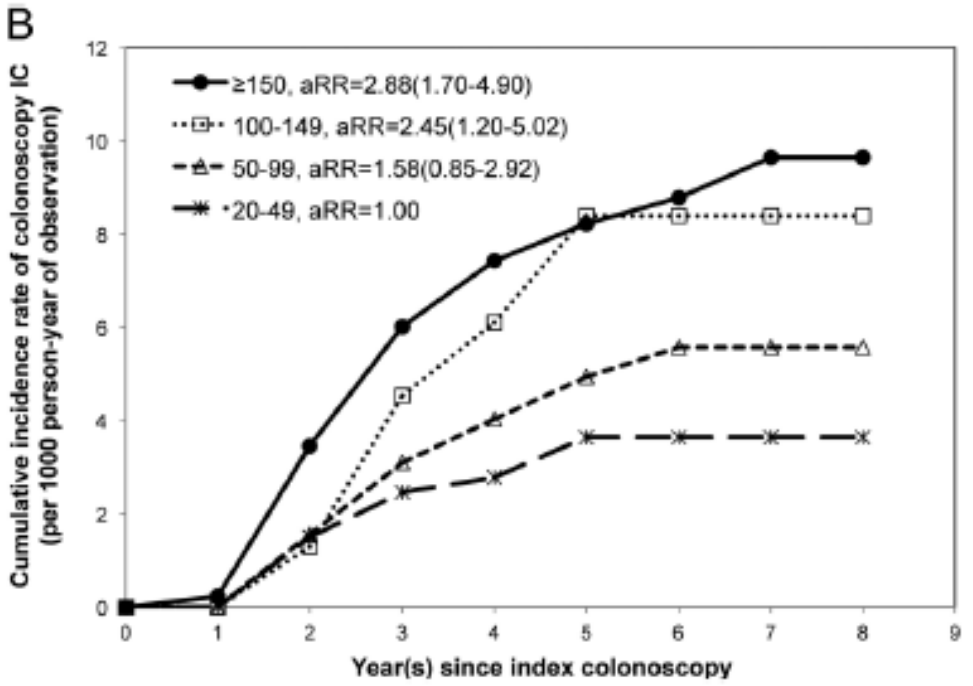
Changhua Community-based Integrated Screening

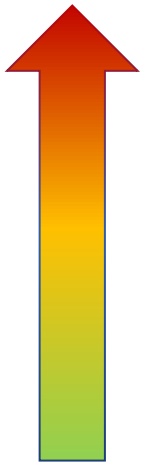
F-Hb predicts PCCRC risk

Overall



Negative colonoscopy



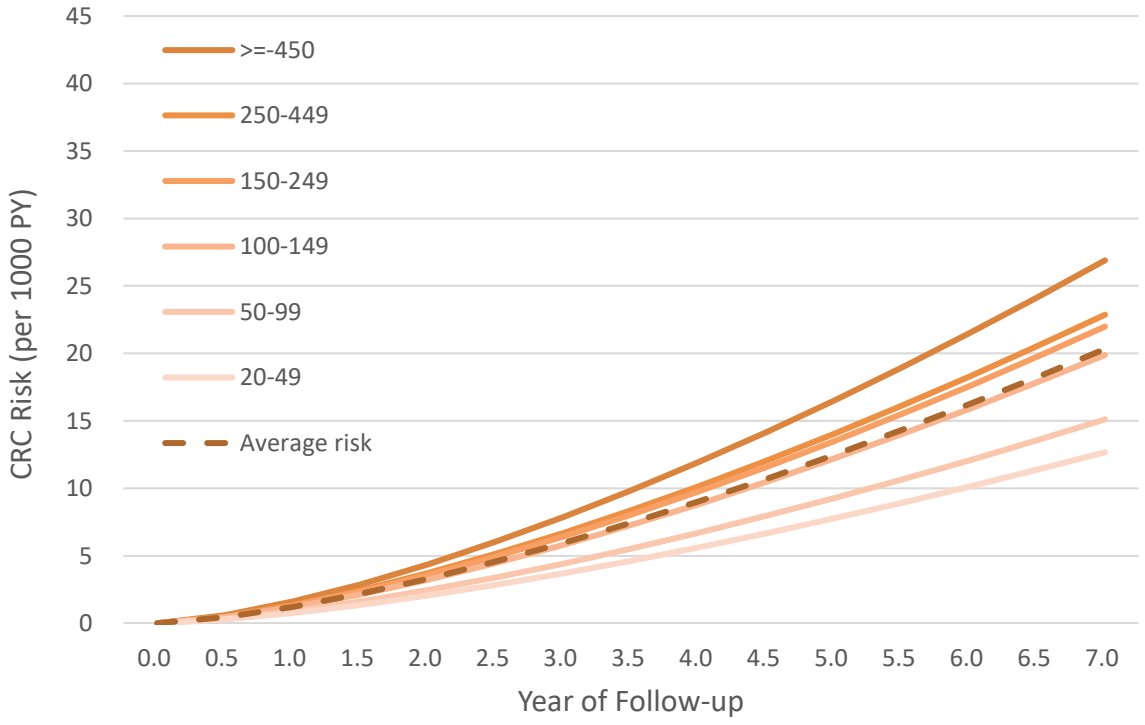


Tailored surveillance interval recommendation incorporating current guidelines and f-Hb

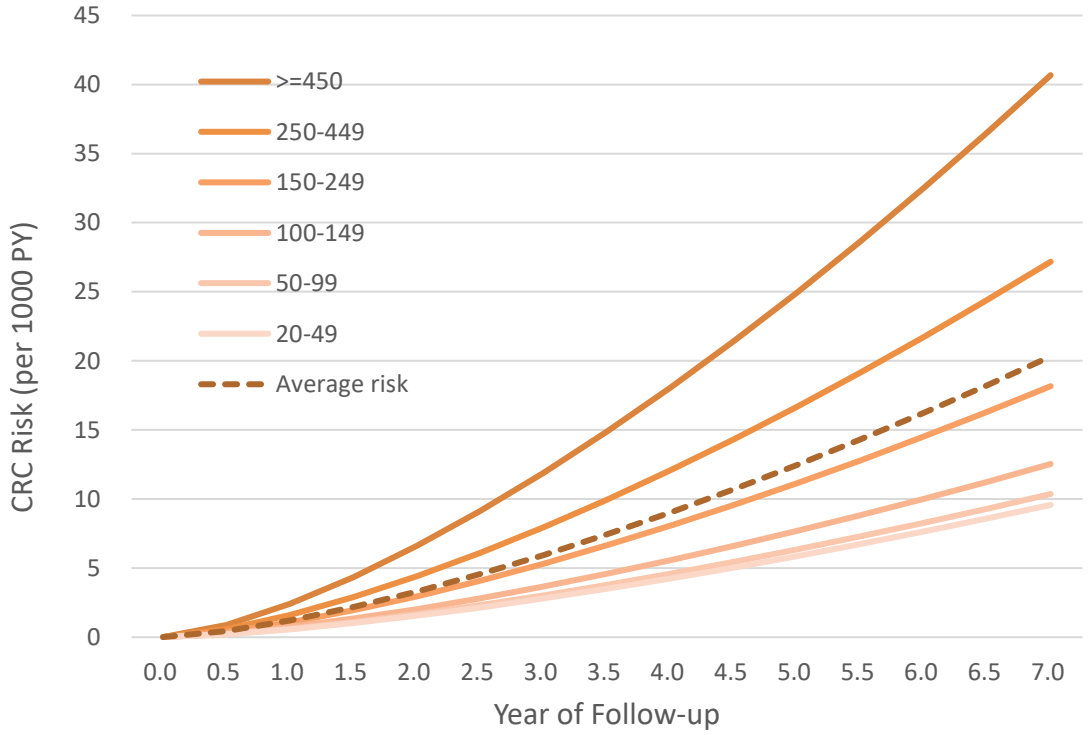
Chiu SY, Chiu HM et al. Gut. 2017;66:293-300

Precision surveillance based on f-Hb to reduce PCCRC

High-risk group



Low-risk group



Chuang MP et al. Gastroenterology 2026 (In press)

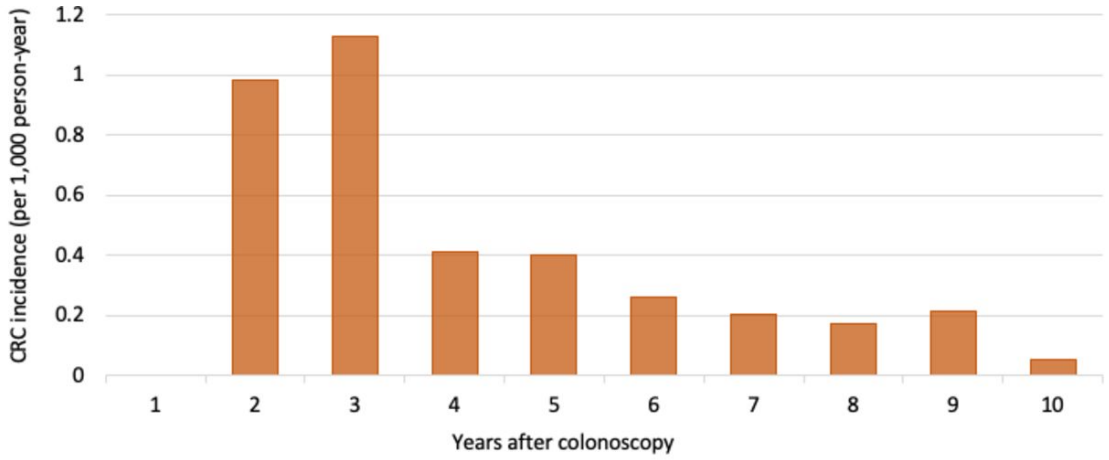
Reduced PCCRC risk and surveillance colonoscopy workload

Comparator strategy	Colonoscopy demand	CRC risk		Change in colonoscopy demand
		Low-risk (7 years)	↓ 4.0% (CI: 3.1%- 4.9%)	↓ 28,930 (↓ 63.8%)
USMSTF guidelines	134,165	High-risk (3 years)	↓ 13.4% (CI: 12.6%- 14.1%)	↑ 8,781 (↑ 9.9%)
		Overall	**↓ 8.6% (CI: 8.2%- 9.1%)**	**↓ 20,149 (↓ 15.0%)**
		Low-risk (10 years)	↓ 1.2% (CI: 0.3%- 2.1%)	↓ 33,397 (↓ 63.1%)
ESGE guidelines	163,395	High-risk (3 years)	↓ 15.5% (CI: 14.6%- 16.3%)	↑ 15,004 (↑ 13.6%)
		Overall	**↓ 8.2% (CI: 7.8%- 8.7%)**	**↓ 20,149 (↓ 11.3%)**

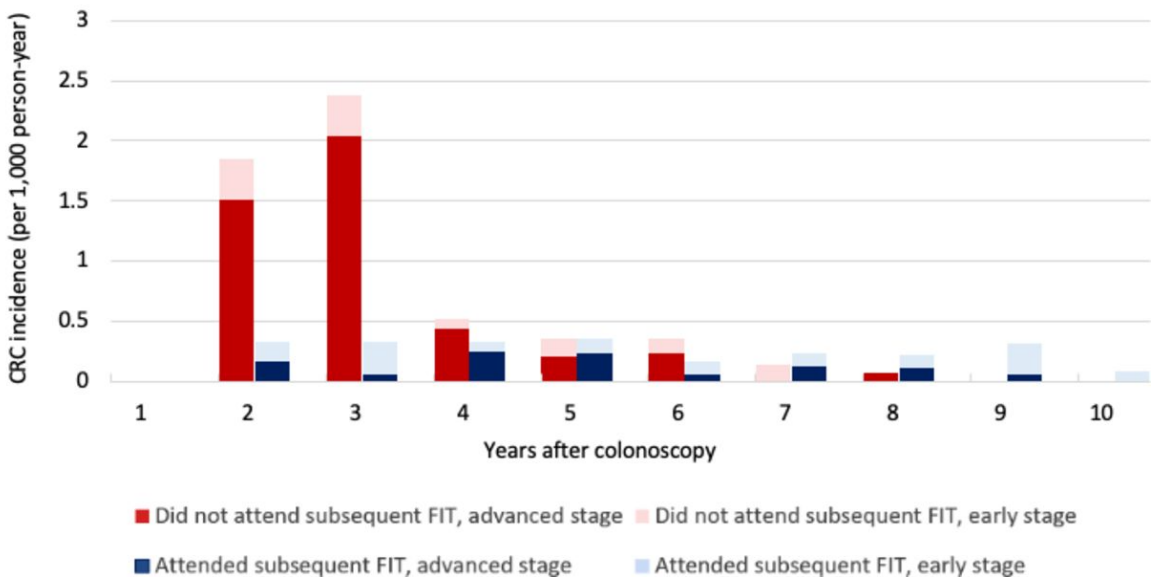
Chuang MP et al. Gastroenterology (In press)

Interval FIT as a surveillance tool to reduce PCCRC

A



B



Peng SM, Chiu HM et al. Gut. 2021;70:1318-1324.

		Adjusted HR (95% CI)	
	Crude HR (95% CI)	Model 1	Model 2
Age	1.02 (0.99 to 1.06)	1.00 (0.96 to 1.03)	1.00 (0.96 to 1.03)
Gender			
Male vs female	1.37 (0.93 to 2.01)	1.23 (0.83 to 1.81)	1.23 (0.84 to 1.81)
Subsequent FIT			
No	1	Ref	1
Yes	0.44 (0.30 to 0.64)	0.47 (0.31 to 0.71)	–
1.5–3 years	0.48 (0.29 to 0.77)	–	0.53 (0.32 to 0.88)
3–5 years	0.43 (0.25 to 0.74)	–	0.45 (0.26 to 0.79)
>5 years	0.36 (0.18 to 0.74)	–	0.37 (0.18 to 0.77)
Adenoma detection rate			
>49%	Ref	ref	ref
42%–49%	1.66 (1.01 to 2.72)	1.42 (0.86 to 2.34)	1.47 (0.89 to 2.43)
<42%	1.96 (1.19 to 3.23)	1.61 (0.97 to 2.67)	1.66 (1.00 to 2.77)
FHbC of baseline FIT (µg hemoglobin/g faeces)			
20–39	Ref	Ref	Ref
40–59	1.98 (1.07 to 3.66)	1.94 (1.05 to 3.58)	1.93 (1.04 to 3.56)
60–99	1.00 (0.47 to 2.11)	0.95 (0.45 to 2.01)	0.95 (0.45 to 2.00)
100–149	2.40 (1.23 to 4.70)	2.28 (1.17 to 4.46)	2.26 (1.16 to 4.43)
≥150	2.59 (1.54 to 4.37)	2.46 (1.45 to 4.15)	2.44 (1.44 to 4.12)
CRC family history in first-degree relatives			
No	Ref	–	–
Yes	1.11 (0.27 to 4.50)	–	–
FIT kit			
HM-JACK	Ref	–	–
OC-Sensor	1.15 (0.63 to 2.10)	–	–

ADR

F-Hb

f-Hb-based tailored inter-screening intervals

Parameters	Regular coefficient	SD	Estimated mortality (per 100 000)
Intercept	−13.49	0.12	NA
Age	0.08	0.002	NA
Sex			
Male vs female	0.35	0.03	NA
f-Hb, μg Hb/g			
Undetected	−0.35	0.03	10.25
1-9	0	NA	14.55
10-19	0.12	0.04	16.38
20-49	0.75	0.05	30.71
50-99	1.26	0.07	51.23
100-149	1.27	0.08	51.65
≥150	2.29	0.04	143.64

f-Hb, μg Hb/g	Relative risk	Screening interval, y	
		Theoretical recommendation	Pragmatic recommendation
Undetected	0.33	6.00	6
1-9	0.47	4.22	4
10-19	0.53	3.75	3
20-49	1.00	2.00	2
50-99	1.67	1.20	1
100-149	1.68	1.19	1
≥150	4.68	0.43	0.5

Variable	No.		
		f-Hb-guided personalized CRC screening	
	Universal biennial screening	60% Referral rate	80% Referral rate
Tests	19 917 993	10 233 766	NA
Reduction in tests	1 [Reference]	9 684 228	NA
Reduction in tests, %	1 [Reference]	49	NA
Colonoscopies	1 279 680	686 570	915 427
Reduction in colonoscopies	1 [Reference]	593 110	364 253
Reduction in colonoscopies, %	1 [Reference]	46	28

Given a colonoscopy rate of 60%:

- Reduce FIT by **49%**
- Reduce colonoscopy work load by **46%**

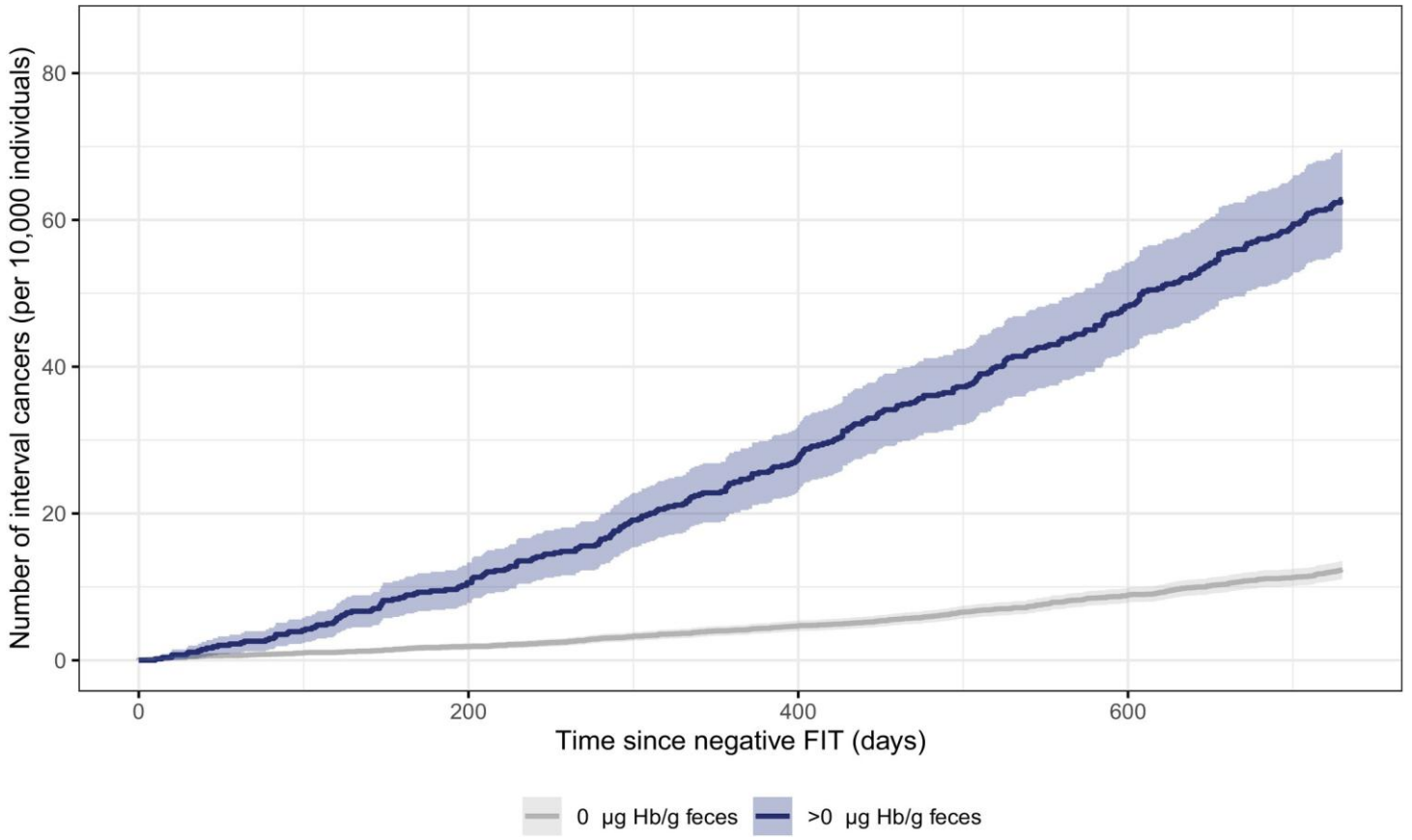
Yen MF et al. JAMA Oncol. 2024;10:765-772.

New definition of FIT positivity

Risk per 1000		FIT 2 (μg Hb/g)						
		<10	10-14	15-19	20-49	50-99	100-149	150+
FIT 1 (μg Hb/g)	<10	0.9	3.1	4.3	4.6	6.0	8.1	13.2
	10-14	2.8	4.4	7.1	7.7	12.5	13.7	25.0
	15-19	3.3	7.7	9.8	7.4	13.5	15.6	28.8
FIT 1 [a] (μg Hb/g) PCCRC	20-49	2.3	4.1	5.3	6.2	7.3	10.3	18.3
	50-99	2.6	4.8	4.8	7.6	9.3	15.3	22.5
	100-149	3.0	6.3	3.0	6.3	11.7	11.4	17.2
	150+	2.4	5.0	8.9	7.0	12.0	13.5	24.2
FIT 1 [b] (μg Hb/g)	20-49	2.9	6.5	7.3	9.6	14.9	16.5	31.4
	50-99	3.6	6.7	6.5	14.9	17.7	26.9	47.0
	100-149	4.6	6.0	5.6	12.3	21.0	13.0	45.3
	150+	4.5	12.6	12.2	19.9	21.9	28.0	55.6

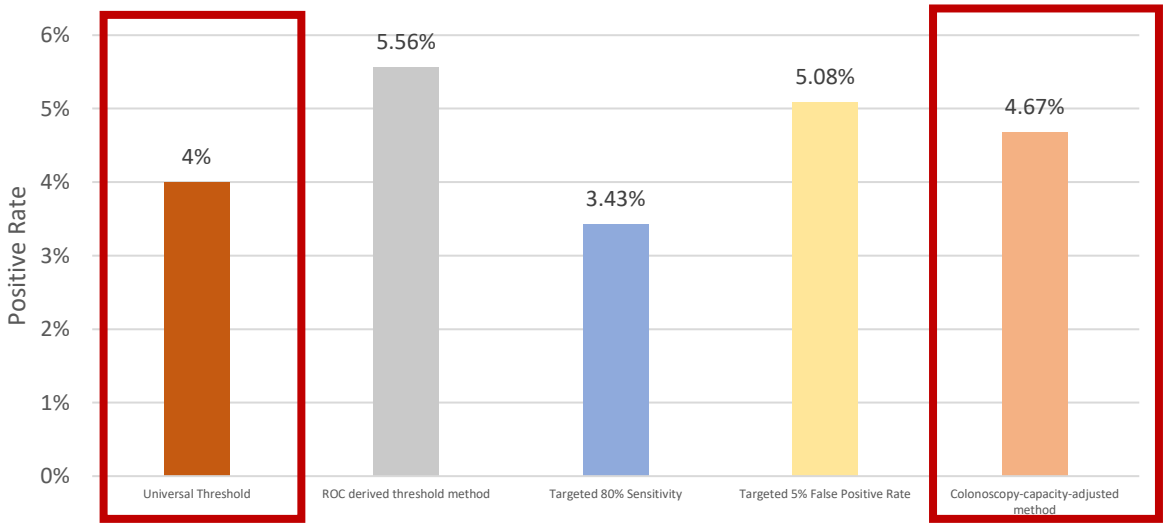
Su CW et al. DDW 2026

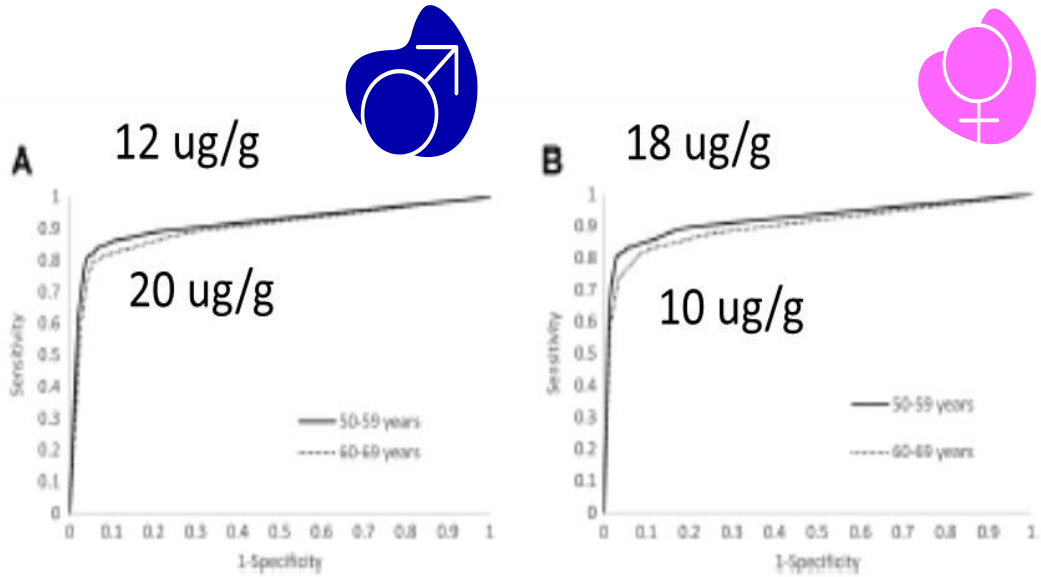
Interval CRC risk for individuals with and without detectable f-Hb in their last screening



van Stigt BJ et al. Int J Cancer. 2025;156:1783-1790.

Cutoff can be tailored based on age, gender, and colonoscopy capacity





Chen SL, Young GP et al. Cancer Epidemiol Biomarkers Prev. 2018;27:704-709.

Entire eligible population

PCCRC risk

CRC death risk

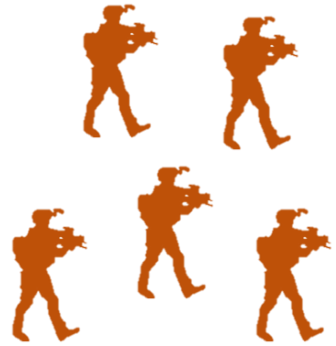
Which is better?

FIT IC risk

PCCRC risk

CRC death risk

Selected high-risk population



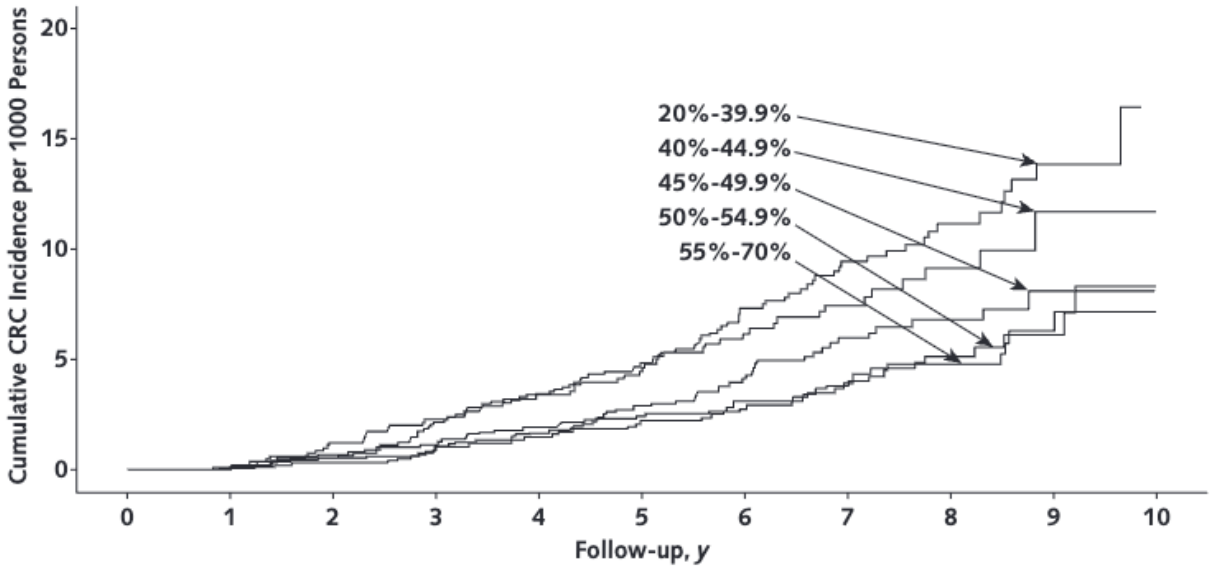
High ADR endoscopist

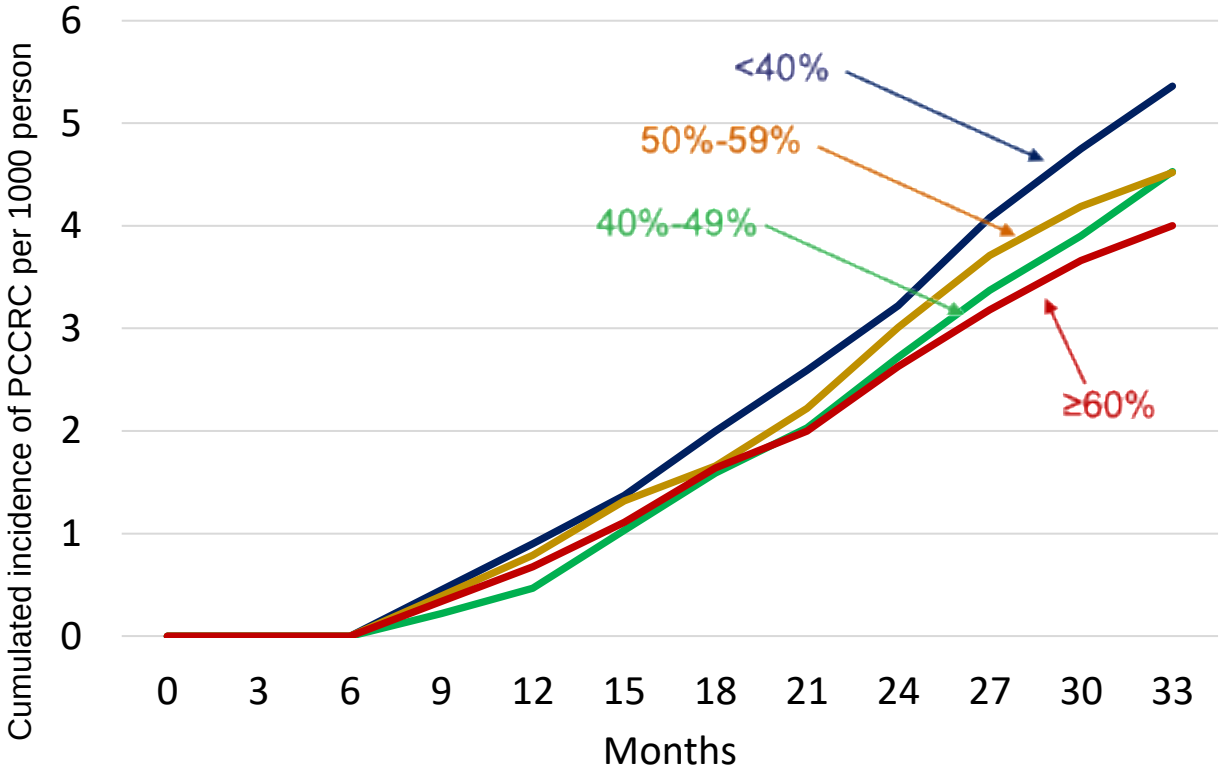
Average ADR endoscopist

Low ADR endoscopist

How can we further reduce PCCRC risk in the FIT screening program?

PCCRC risk overlaps across upper ADR tiers

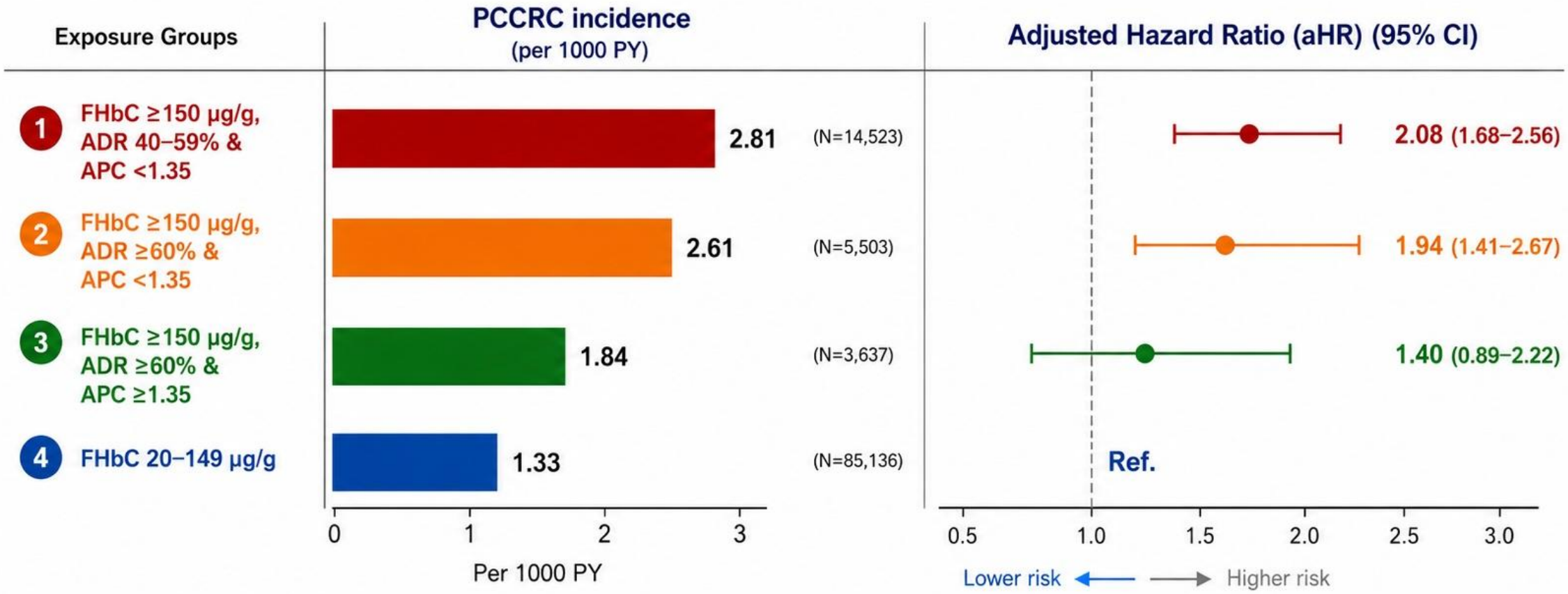




Zorzi M, et al. Ann Intern Med. 2023;176:303-310.

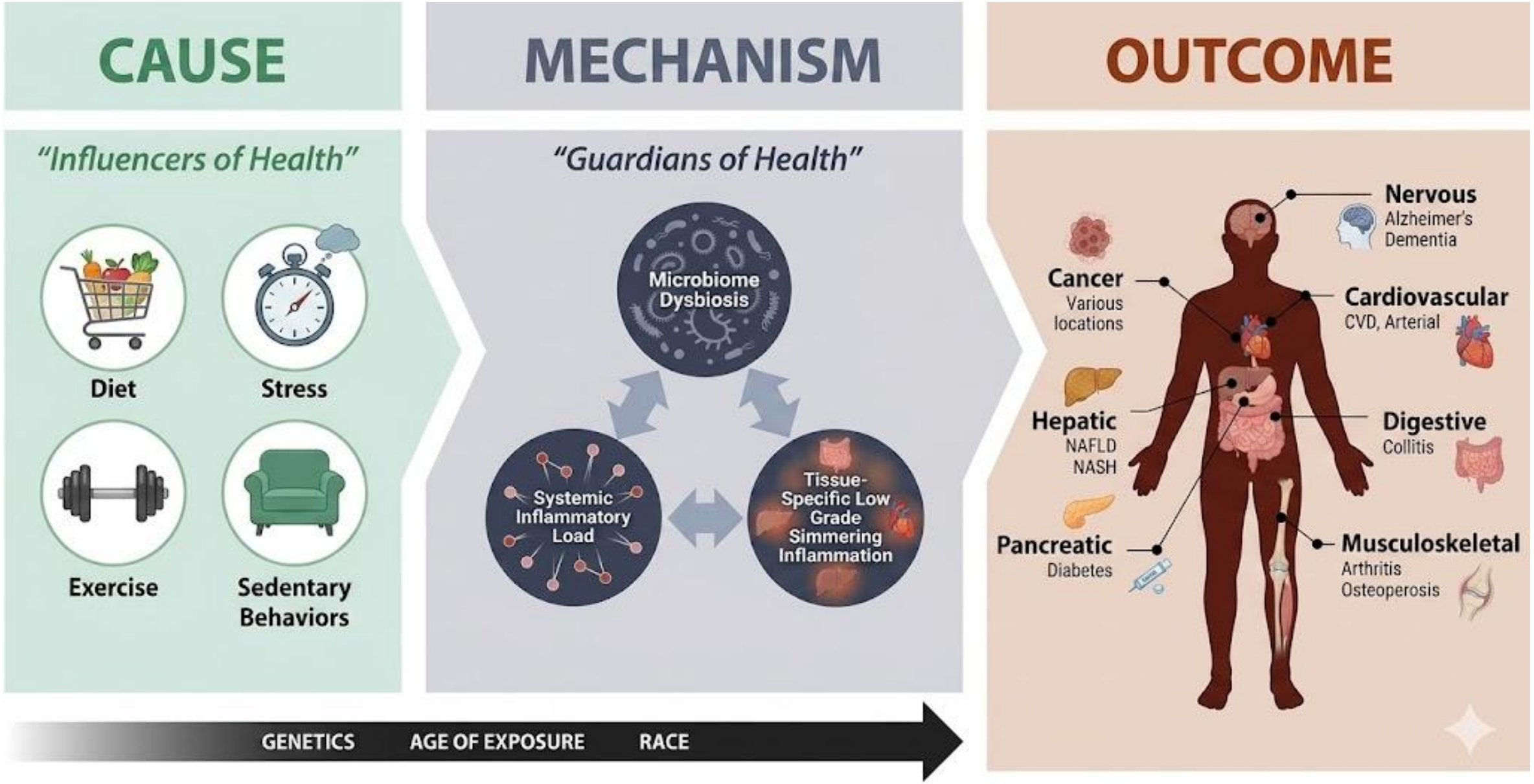
Taiwan Colorectal Cancer Screening Program

Tailored colonoscopy referral based on f-Hb



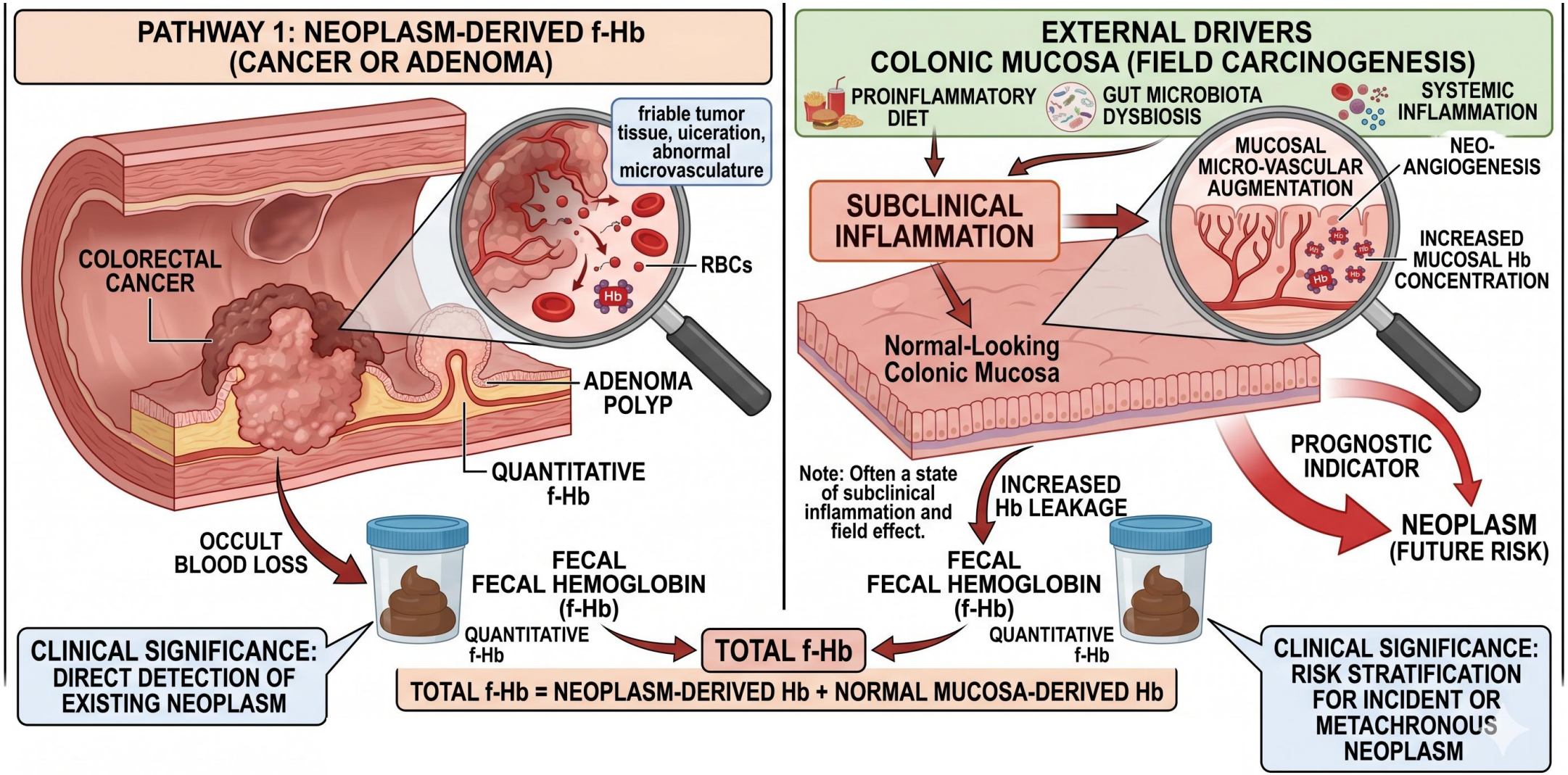
APC (adenoma per colonoscopy)= Total No. of adenoma / Total No. of colonoscopy

Hsu WF, Chiu HM et al. DDW 2026



Modified from: Hofseth LJ et al. Diet and acute and chronic, systemic, low-grade inflammation. In book: Diet, Inflammation, and Health (pp.85-111)

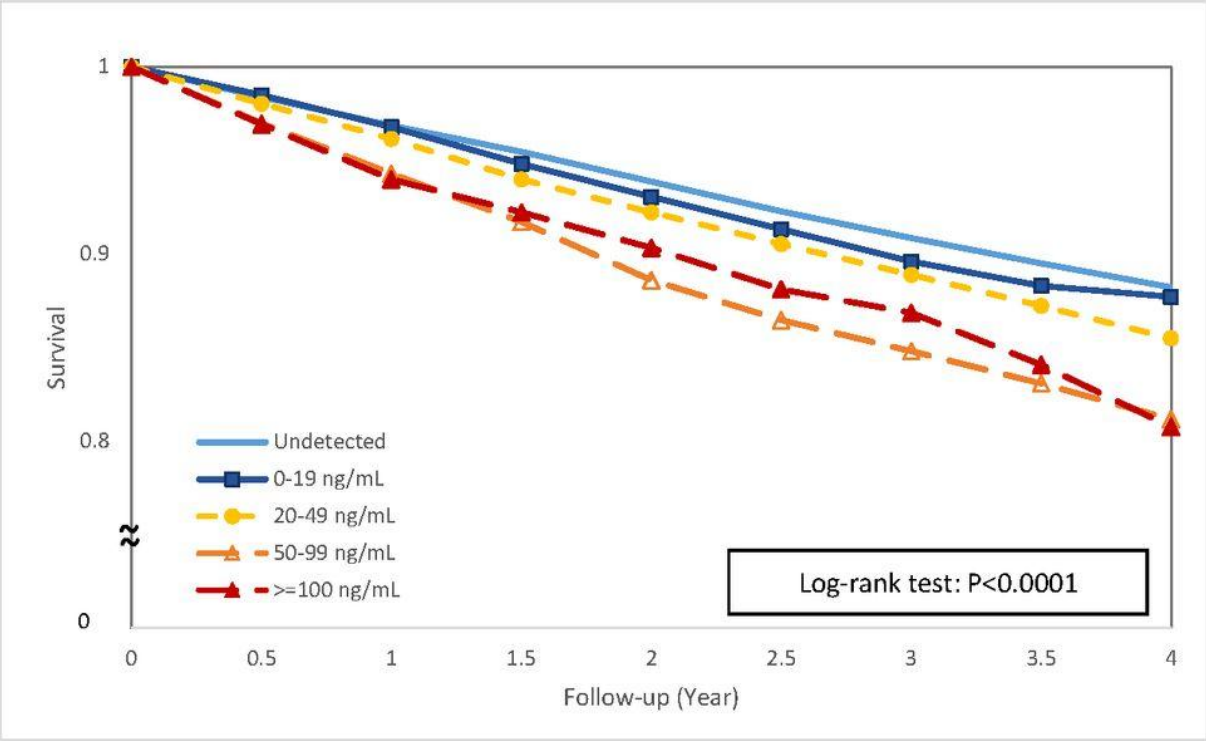
Neoplasm is probably not the sole origin of f-Hb



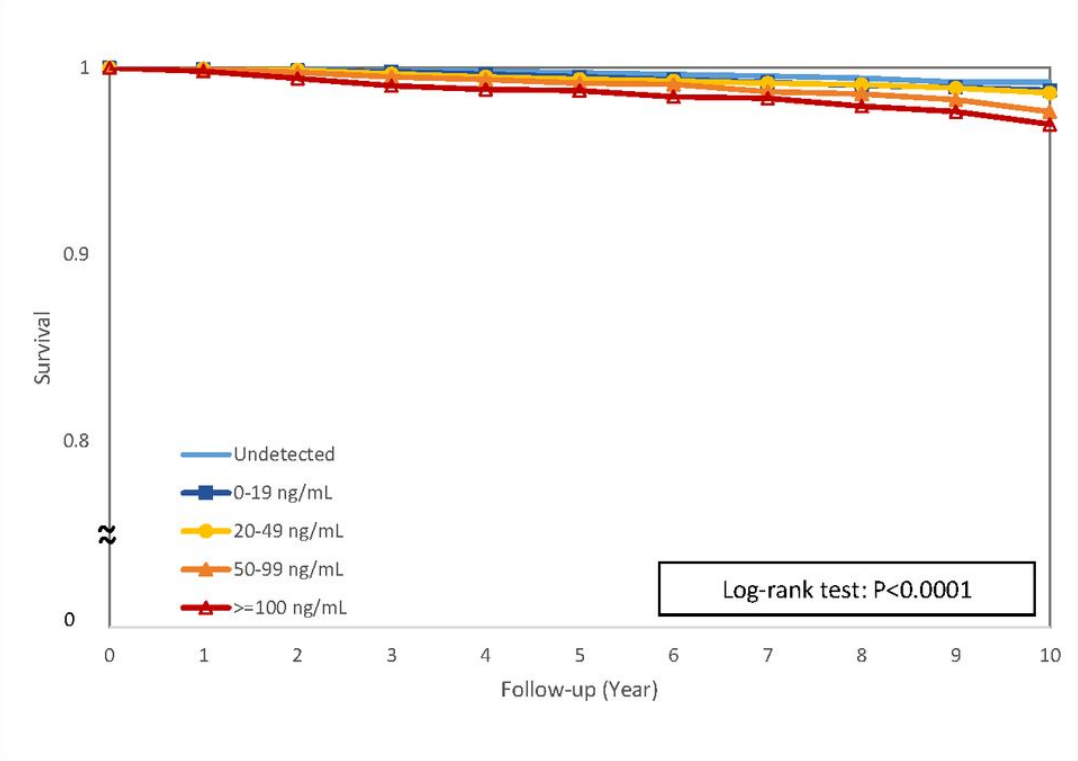
Made by Gemini

F-Hb concentration and cardiovascular risk

Cardiovascular risk

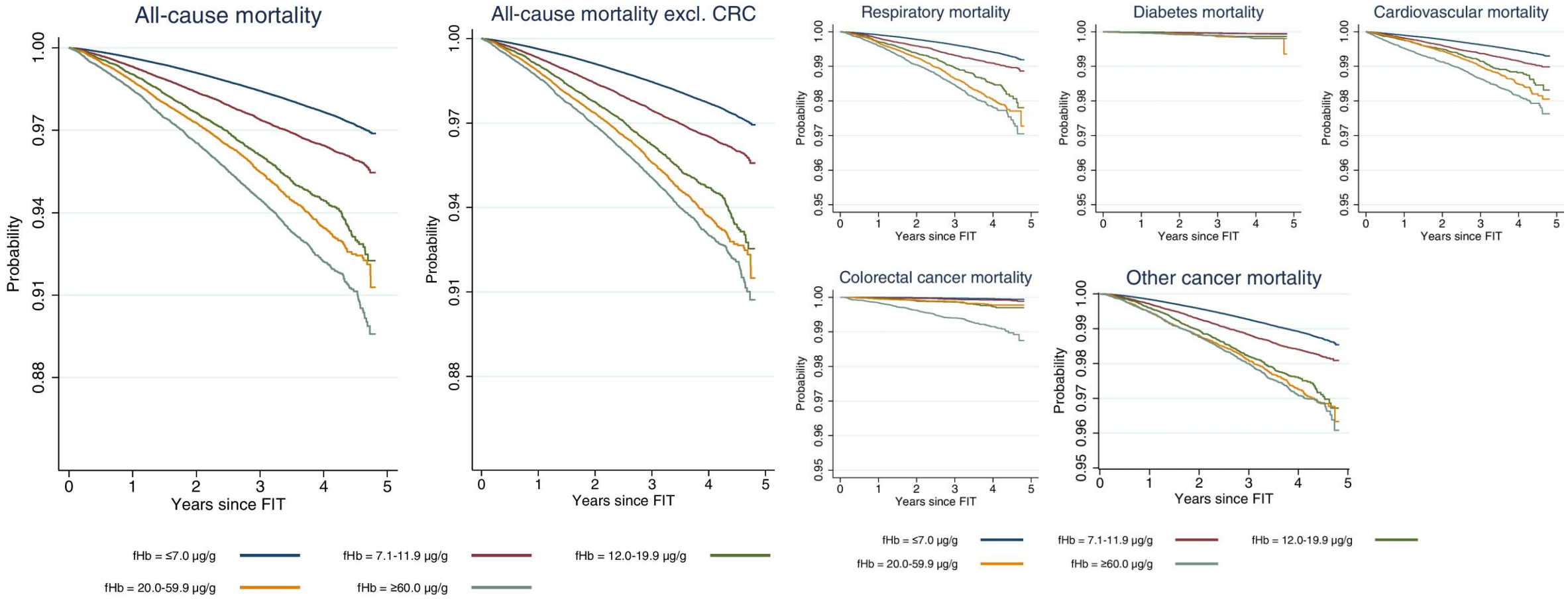


Cardiovascular death risk

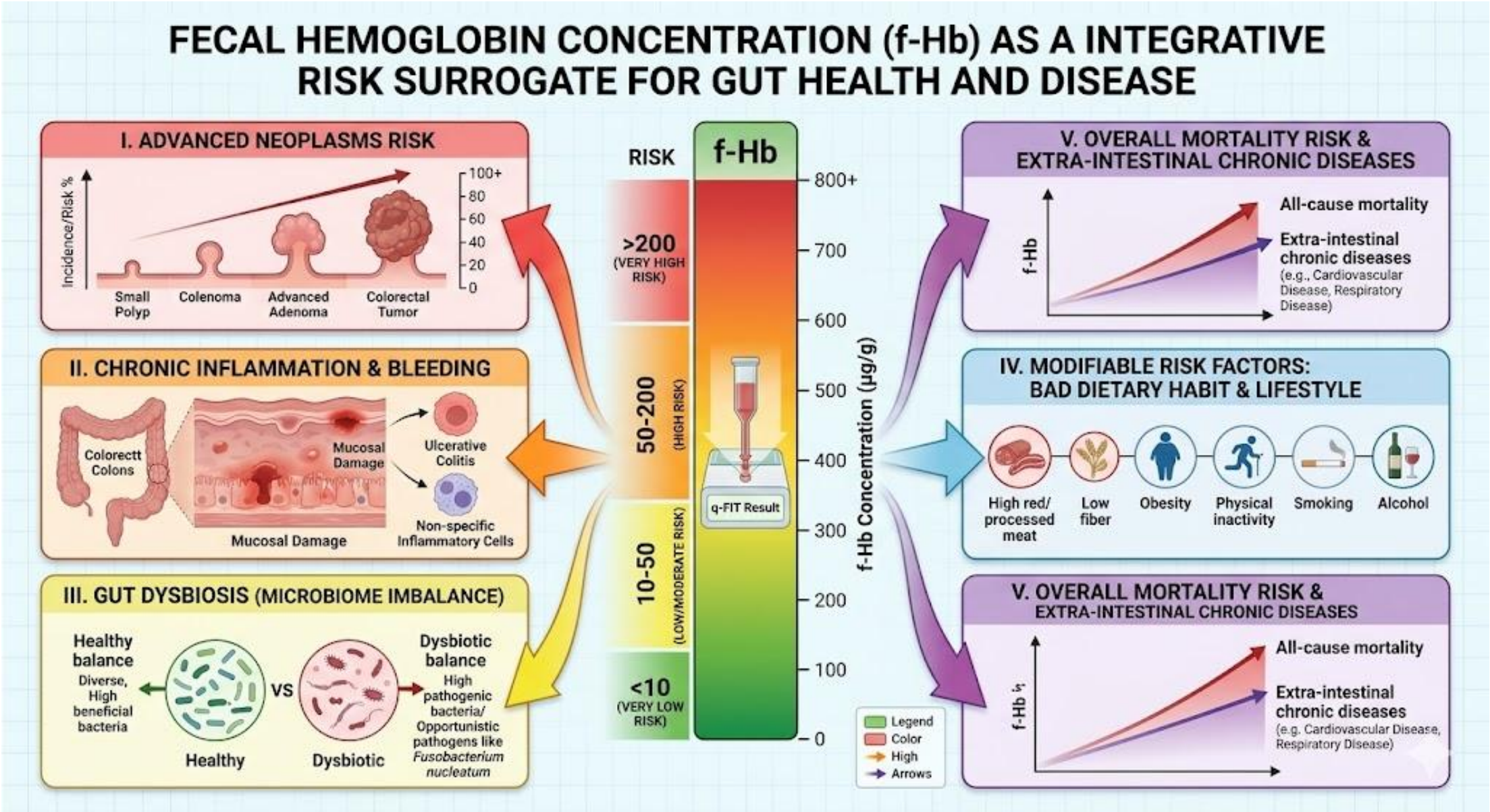


Chien KL et al. BMJ Open. 2020;10(6):e032633.

F-Hb concentration and other causes of death

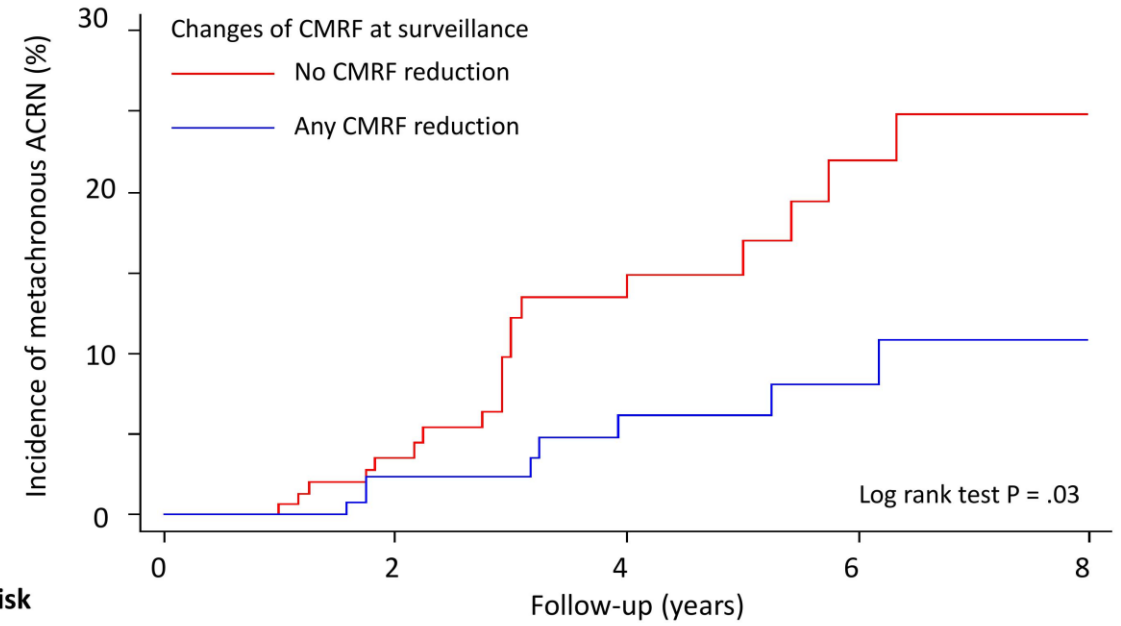


Kaalby L et al. BMC Med. 2023;21:29.



Made by Gemini

Exercise after polypectomy can reduce the risk of metachronous AN in MASLD patient



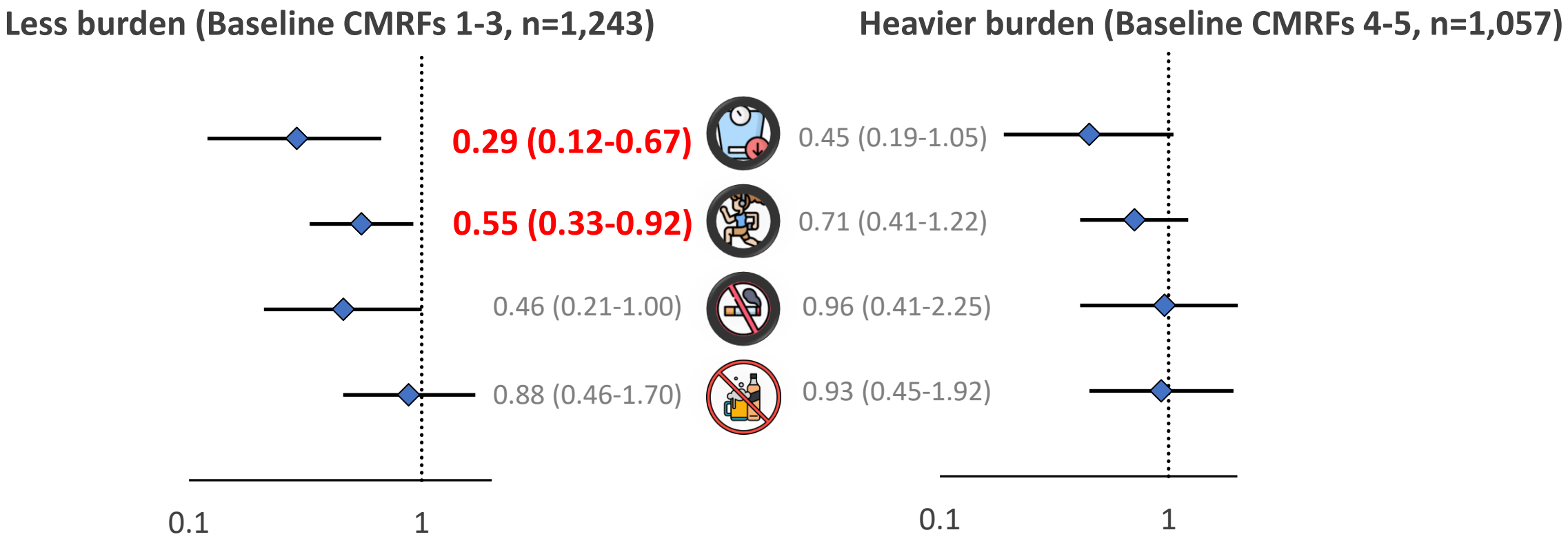
Number at risk

No CMRF reduction	162	118	59	29	14
Any CMRF reduction	150	117	66	40	20

Chang WY, Chiu HM et al. JAMA Network Open 2026 (In press)

Lifestyle and the risk of metachronous AN in MASLD population

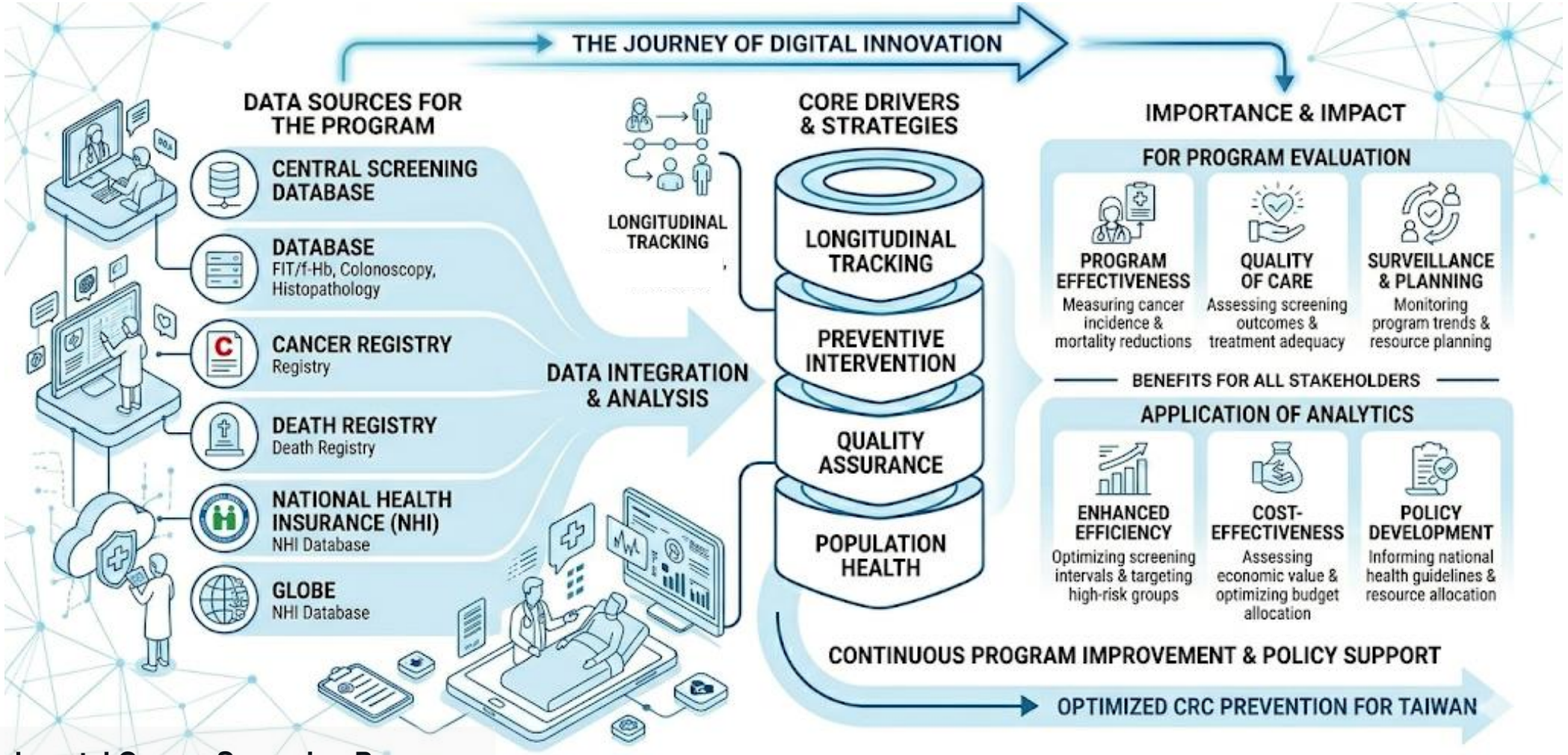
Each lifestyle goal and aHR (95% CI) of meta-ACRN



Chang WY, Chiu HM et al. DDW 2026

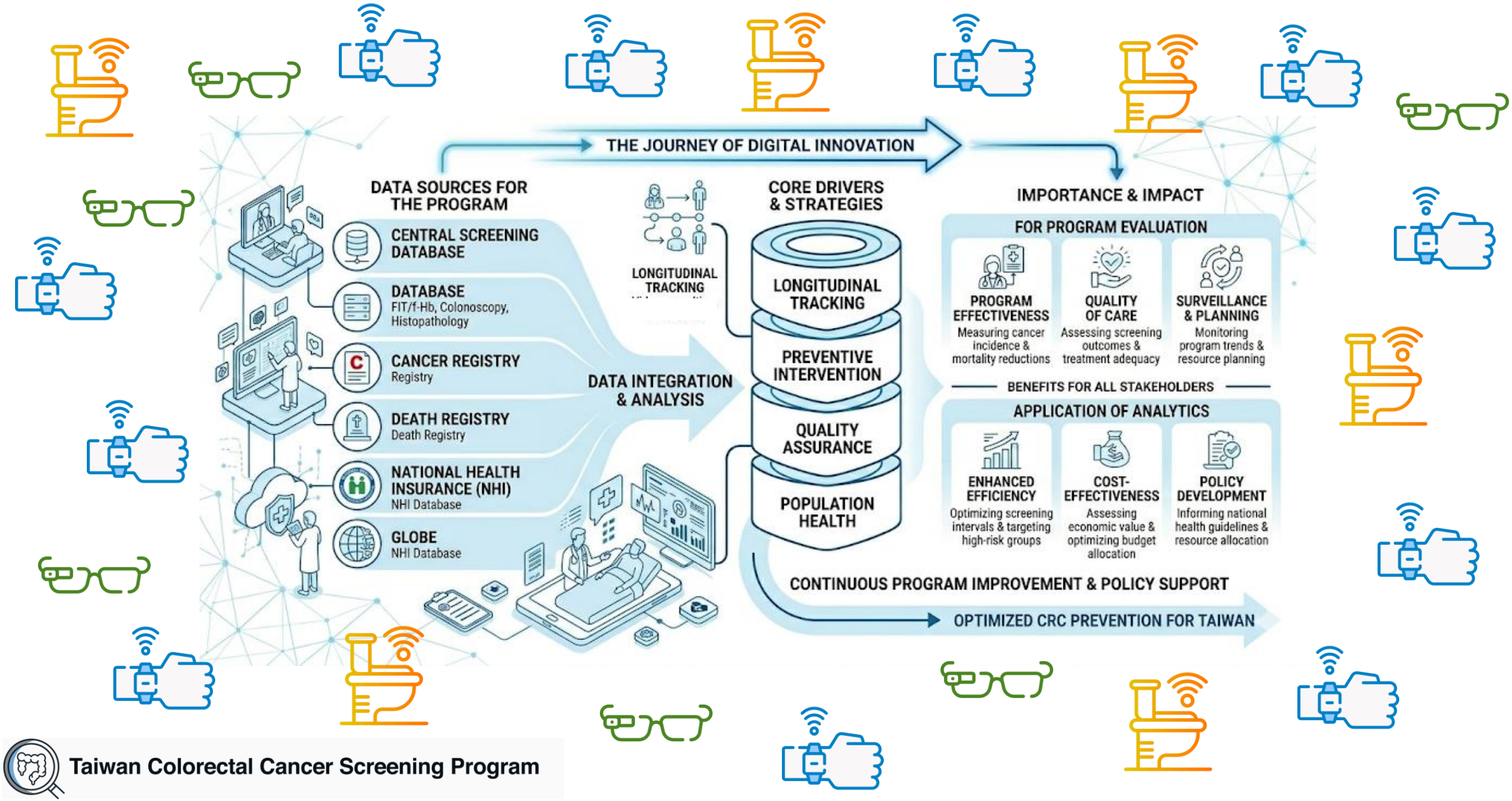
Our dream will come true

-Turning bold ideas into real-world impact



Taiwan Colorectal Cancer Screening Program

Made by Gemini



Taiwan Colorectal Cancer Screening Program

1. Physical Data Layer

Individuals with personal features & longitudinal FIT history

Individual A

Age: 58 | Smoker | Obesity | Family history: No | Diabetes: No | Alcohol: Occasional | PPI use: No

FIT history (f-Hb, μg/g)

2016	2016	2020	2022	2024
4	5	8	15	22

Individual B

Age: 66 | Non-smoker | Metabolic syndrome | Family history: Yes | Diabetes: Yes | Alcohol: Regular | PPI use: Yes

FIT history (f-Hb, μg/g)

2016	2018	2020	2022	2024
12	18	25	55	80

Individual C

Age: 73 | Former smoker | Hypertension | Family history: Yes | Diabetes: Yes | Alcohol: Rare | PPI use: No

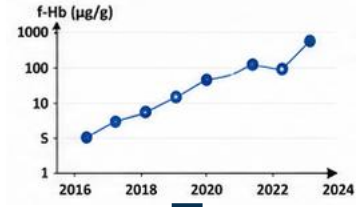
FIT history (f-Hb, μg/g)

2016	2018	2020	2022	2024
6	9	14	28	45

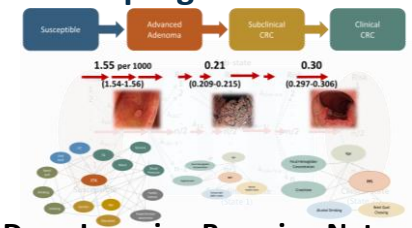
2. Computational Layer

Digital Twin: personalized risk modelling (Dynamic FIT + Features)

Dynamic f-Hb trajectory

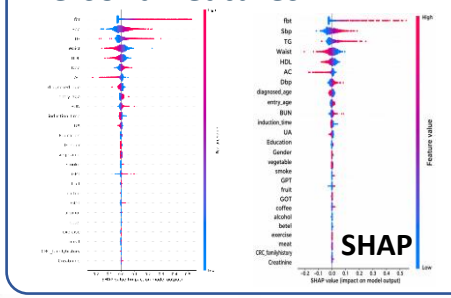


Disease progression



Deep Learning Bayesian Network

Personal features



3. Decision-supported Layer

(eg. Inter-screening Interval & Emerging detection modality)

Dynamic f-Hb concentration (μg/g)

Personal risk score (tmt (fom BN)

	<10	10–14	15–19	20–49	50–99	100–149	≥150
Extremely High Risk	Surveillance (<1 year)	1 year	1 year	1 year	1 year	<1 year	<1 year
High Risk	2 years	2 years	1–2 years	1–2 years	1 year	1 year	<1 year
Moderate Risk	3 years	3 years	2–3 years	2 years	1–2 years	1–2 years	1 year
Low Risk	6 years	6 years	3–6 years	3 years	2–3 years	2 years	1–2 years
Extremely Low Risk	6 years	6 years	6 years	6 years	3–6 years	3 years	2–3 years

Longer interval (lower risk) ← → Shorter interval (higher risk)

Notes:

- Risk score is derived from the Bayesian Network (personal features).
- f-Hb trajectory is dynamically updated over time.
- Map is learned from the Digital Twin (multistate model).
- Interval recommendations balance benefit, harm, and resource use.

4. Personalized Service Layer

Individual A

Recommended interval:

6-year Interval

Next screening: 2030

Individual B

Recommended interval:

3-year Interval

Next screening: 2026

Individual C

Recommended interval:

2-year Interval

Next screening: 2027

Reinforcement Learning

5. Intervention Layer

Primary Prevention and Surveillance & Early awareness of CRC

Courtesy of Prof Tony Hsiu-Hsi Chen

Gastro
aga American Gastroenterological Association

Bringing Primary and Secondary Prevention Into Play in Community Prevention of Gastrointestinal Cancers

See "Potential impact of time trend of lifestyle risk factors on burden of major gastrointestinal cancers in China," by Wu Y, Li Y, Giovannucci E, on page 1830.

The epidemiological pattern of malignancies has changed markedly in recent decades, and many countries have experienced "cancer transition," which is represented by the decline or stabilization of smoking, a traditionally well-established carcinogen, and infection-related cancers. Obesity-related cancers, such as cancer of the colorectum, corpus uteri, gallbladder, kidney, multiple myeloma, and pancreas, have increased substantially in many countries as a result of economic development. Globally, in 2012, it was estimated that 3.6% (n = 481,000) of all new cancer cases in adults older than 30 years were attributable to a high body mass index (BMI).[1] This is speculated to be due to a change in dietary, metabolic, hormonal, and reproductive factors, which are the result of rapid societal and economic transitions.[2]

Although the etiologies of different digestive cancers vary, most of them are closely or partially associated with lifestyle factors. In this issue of *Gastroenterology*, Wu and colleagues[3] report on the impact lifestyle factors have on risk of major gastrointestinal (GI) cancers in China. In this study, it was revealed that 56.5% of colorectal cancers (CRC), 59.8% of gastric cancers, 48.5% of esophageal cancers, and 35.2% of liver cancers in China were attributable to lifestyle risk factors in 2011.[3] The GI cancer cases attributable to lifestyle factors, for example, high sodium intake, low dietary fiber intake, and smoking habits, were reduced from 1991/1997 to 2011. However, other factors, such as high BMI, high red or processed meat consumption, and low physical activity, are expected to continue to contribute to increasingly more GI cancer beyond 2011 and into the future.

High BMI, especially in individuals with visceral obesity, is a well-established risk factor for noncommunicable diseases (NCDs), including some cancers, and is associated with increases in their related mortality. Although prevalence varies widely, the incidence of being overweight or obese has been increasing worldwide, and is closely related to the Human Development Index, raising concerns about the impact on health in many countries with a rising Human Development Index.[1] China has experienced many drastic social and economic changes and shifts in people's lifestyles since the 1990s, in parallel with the fast-rising prevalence of obesity. Several cohort studies from China have demonstrated that such changes in overweight and obesity were associated with increased risks of NCDs, such as hypertension, type 2 diabetes, cardiovascular disease, and the aforementioned obesity-related cancers.[4–9]

Lifestyle intervention, either via the improvement of the obesogenic environment, such as improving the food environment and establishing a healthy built environment and a supportive social information environment; or via health education in schools and the community, is a feasible and effective way to reduce obesity-related health problems.[4] Primary prevention through vaccination or chemoprevention is also an effective way to reduce the disease burden of some GI cancers. Hepatitis B vaccination during childhood and early adulthood has proven effective in preventing liver cancer.[10] Chemoprevention by eradication of *Helicobacter pylori* was also associated with a significant reduction in incident gastric cancer by 50%.[11–13] These strong interventions might have impacted the burden of these cancers, and their effects are expected to increase alongside the implementation of such public health interventions and improved accessibility to health care services.

Another effective way to reduce the disease burden of those cancers is screening, which could counteract the effect of increasing exposure to lifestyle risk factors. For example, it was demonstrated that screening for CRC could remarkably reduce its related death rate and even incidence. According to the results of a microsimulation study, it was revealed that the overall observed decline in CRC mortality in the United States was 26% for 1975–2000. The model predicted that, with changes in risk factors only, CRC mortality would decrease by 9%, explaining 35% of the observed mortality decline. Screening decreased mortality by another 14%, explaining 53% of the mortality reduction, and treatment added another 3% decline, explaining the final 12% of the observed decline in CRC mortality.[14] CRC screening is also considered cost-effective in urban areas of upper middle-income countries, where incidence rates approach levels similar to those in high-income countries (age-standardized rate of 30 or more per 100,000 in men).[15] As many regions of China have a CRC incidence exceeding or approaching such a level, population-level screening interventions should be seriously considered. Given the disparity in health care resources among different areas in China with such a large population, a fecal immunochemical test–based approach would be a more practical choice than colonoscopy for large-scale population-level screening. Recent studies from Taiwan, where fecal immunochemical test is used for organized population screening, have reported that fecal immunochemical test screening not only reduced CRC mortality in those who participated in screening, but also in the entire population, given sufficiently high screening participation.[16,17]

The potential synergistic effect of primary and secondary preventions is an intriguing issue and cannot be ignored. Many obesity-related cancers share common risk factors with NCDs, such as obesity, type 2 diabetes, or dyslipidemia. Screening for multiple NCDs other than cancer could not only help to prevent unfavorable health outcomes, but also intensify the effectiveness of screening. For example, dietary habits, such as high calorie and red meat consumption, or sedentary lifestyles, such as low physical activity, which collectively lead to obesity and metabolic derangements, are not only risk factors for cardiovascular and cerebrovascular disease, but also CRC. Therefore, identifying and controlling NCDs could also contribute to the prevention of CRC.[18] Such a multiple screening framework for NCDs is a more cost-effective approach, as it not only detects diseases at preclinical phases, but also lessens the need for repeated invitations for screening for different diseases, thereby reducing related costs and improving willingness to participate by the public.

Last but not least, lifestyle interventions should be delivered early in life. Early exposure to some lifestyle risk factors can increase susceptibility to carcinogenic processes later in life, causing life-long consequences. Recent studies revealed that early-onset CRC is related to prolonged sedentary television viewing time, a surrogate for a sedentary lifestyle, and adolescent simple sugar and sugar-sweetened beverage intake was associated with a higher risk of colorectal neoplasms.[19,20] It is, however, a major challenge to implement effective lifestyle interventions early in life and requires multifaceted and multilevel systematic changes, from socioecological and behavioral levels to downstream health services and medical interventions.

HAN-MO CHIU
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan

Gastroenterology. 2021;161:1787-1789.

Summary

- CRC screening must evolve to the next stage
- FIT should be used beyond a simple positive/negative threshold
- Harness the synergistic effects of primary and secondary prevention
- Modern technologies enable precision, risk-stratified screening and prevention
- Thinking outside the box

Thank you