

# Screening e Ricerca

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# Conflict of interest

- None

# Colorectal Cancer Screening

- Target population (50-69) followed longitudinally
- Collecting data (and possibly samples) prospectively from thousands of patients on
  - Procedures
  - Subject characteristics
  - Findings
    - Cancers
    - Polyps
    - Others...

**Huge source of data, samples → the ideal platform for research**

# CRC screening as a platform for research

- Epidemiological data/risk factors → policy makers; adoption of new strategies
- Quality in endoscopy → screening colonoscopy setting best standards for endoscopy
- Understanding the natural history of polyps and cancer
- Developing new strategies for CRC screening
- Understanding risk factors leading to polyps and cancers
- Molecular determinants in sporadic CRC vs hereditary
- New technological developments in endoscopy and imaging

# Faecal haemoglobin concentration among subjects with negative FIT results is associated with the detection rate of neoplasia at subsequent rounds

**Table 2** Predictors of the DR of CRC, advanced adenoma and AN at the third FIT

		CRC		Advanced adenoma		AN	
		OR	95% CI	OR	95% CI	OR	95% CI
Gender	Women	1		1		1	
	Men	1.34	1.00 to 1.79	1.63	1.46 to 1.83	1.60	1.43 to 1.78
Age (years)	50–54	0.54	0.32 to 0.91	0.67	0.55 to 0.82	0.65	0.55 to 0.79
	55–59	0.75	0.47 to 1.17	1.02	0.86 to 1.22	0.98	0.83 to 1.15
	60–64	0.95	0.67 to 1.36	1.00	0.86 to 1.16	0.99	0.87 to 1.14
	65–69	1		1		1	
	≥70	1		1		1	
Interval since last fit (months)	18–22	0.67	0.30 to 1.49	0.80	0.59 to 1.08	0.78	0.58 to 1.03
	23–27	1		1		1	
	28–32	0.92	0.61 to 1.37	0.98	0.83 to 1.16	0.97	0.83 to 1.13
	33–36	0.96	0.39 to 2.40	1.23	0.86 to 1.77	1.19	0.85 to 1.67
	37–60	1.10	0.51 to 2.36	1.49	1.14 to 2.00	1.44	1.11 to 1.87
Cumulative f-Hb level at previous 2 FIT tests (FIT1 + FIT2) µg Hb/g faeces	0	1		1		1	
	0.1–3.9	2.26	1.47 to 3.46	1.75	1.47 to 2.07	1.81	1.55 to 2.12
	4–9.9	4.01	2.51 to 6.39	4.64	3.93 to 5.49	4.58	3.91 to 5.36
	10–14.9	10.11	6.04 to 16.93	9.13	7.48 to 11.15	9.32	7.73 to 11.23
	15–19.9	11.63	6.42 to 21.07	12.84	10.32 to 16.00	12.42	10.43 to 15.76
	≥20	38.92	22.50 to 67.31	30.40	24.09 to 38.38	32.52	26.19 to 40.39

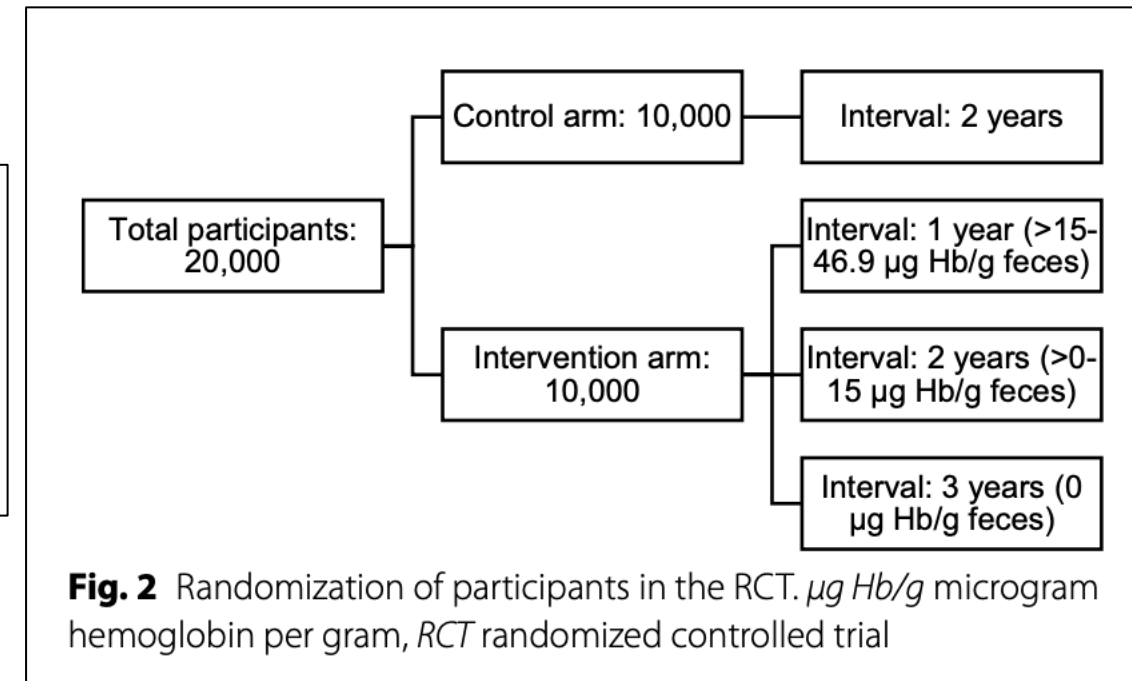
AN, advanced neoplasia; CRC, colorectal cancer; DR, detection rate; FIT, faecal immunochemical test.

# Personalized colorectal cancer screening: study protocol of a mixed-methods study on the effectiveness of tailored intervals based on prior f-Hb concentration in a fit-based colorectal cancer screening program (PERFECT-FIT)

**Table 1** Risk of AN and/or CRC in subsequent screening rounds in high-risk individuals compared to low-risk individuals

Program	FIT cut-off	Comparison high- vs. low-risk individuals	Main outcome	Risk of AN and/or CRC in subsequent round
Dutch pilot studies <sup>14</sup>	10 µg Hb/g feces	8–10 µg Hb/g feces vs. 0 µg Hb/g feces	AN	Hazard ratio: 8
Flemish CRC screening program <sup>15</sup>	15 µg Hb/g feces	Males aged 74 and 200 µg Hb/g feces vs. females aged 56 and 15 µg Hb/g feces	CRC	Odds ratio: 15
Dutch CRC screening program <sup>16</sup>	47 µg Hb/g feces	15–46.9 µg Hb/g feces vs. 0 µg Hb/g feces	AN	Odds ratio: 23
Scottish CRC screening program <sup>17</sup>	80 µg Hb/g feces	60.0–79.9 µg Hb/g feces vs. 0.0–19.9 µg Hb/g feces	AN	Odds ratio: 38

*CRC colorectal cancer, FIT fecal immunochemical testing, µg Hb/g microgram hemoglobin per gram, AN advanced neoplasia*



# Lifestyle factors and risk for colorectal polyps and cancer at index colonoscopy in a FIT-positive screening population

	NO LESIONS ( <i>n</i> = 1751)	HIGH-RISK ADENOMAS ( <i>n</i> = 1349)	
	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI)
<b>BMI</b>			
Underweight	12 (0.7)	6 (0.4)	0.74 (0.27–2.02)
Normoweight	738 (42.2)	547 (35.1)	1.0
Overweight	694 (39.7)	597 (44.3)	1.18 (1.0–1.39)
Obesity	306 (17.5)	272 (20.2)	1.29 (1.05–1.60)
<b>Ever smoking</b>			
No	1300 (74.2)	905 (67.1)	1.0
Yes	451 (25.8)	444 (32.9)	1.45 (1.24–1.71)

	NO LESIONS ( <i>n</i> = 1751)	CRC ( <i>n</i> = 224)		COLON CANCER ( <i>n</i> = 174)		RECTAL CANCER ( <i>n</i> = 49)	
	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI)	<i>n</i> (%)	OR (95% CI)	<i>n</i> (%)	OR (95% CI)
<b>BMI</b>							
Underweight	12 (0.7)	1 (0.4)	0.57 (0.07–4.60)	1 (0.6)	0.81 (0.1–6.51)	0	–
Normoweight	738 (42.2)	89 (39.7)	1.0	61 (35.1)	1.0	27 (55.1)	1.0
Overweight	694 (39.7)	85 (37.9)	0.89 (0.64–1.24)	67 (38.5)	1.03 (0.71–1.49)	18 (36.7)	0.62 (0.33–1.15)
Obesity	306 (17.5)	49 (21.9)	1.14 (0.77–1.68)	45 (25.9)	1.50 (0.98–2.29)	4 (8.2)	0.33 (0.11–0.96)
<b>Ever smoking</b>							
No	1300 (74.2)	148 (66.1)	1.0	116 (66.7)	1.0	31 (65.3)	1.0
Yes	451 (25.8)	76 (33.9)	1.5 (1.10–2.04)	58 (33.3)	1.43 (1.01–2.02)	17 (34.7)	1.58 (0.86–2.90)
<b>Alcohol</b>							
No	1717 (98.1)	211 (94.2)	1.0	161 (92.5)	1.0	49 (100)	1.0
Yes	34 (1.9)	13 (5.8)	2.29 (1.15–4.58)	13 (7.5)	3.09 (1.53–6.23)	0	–

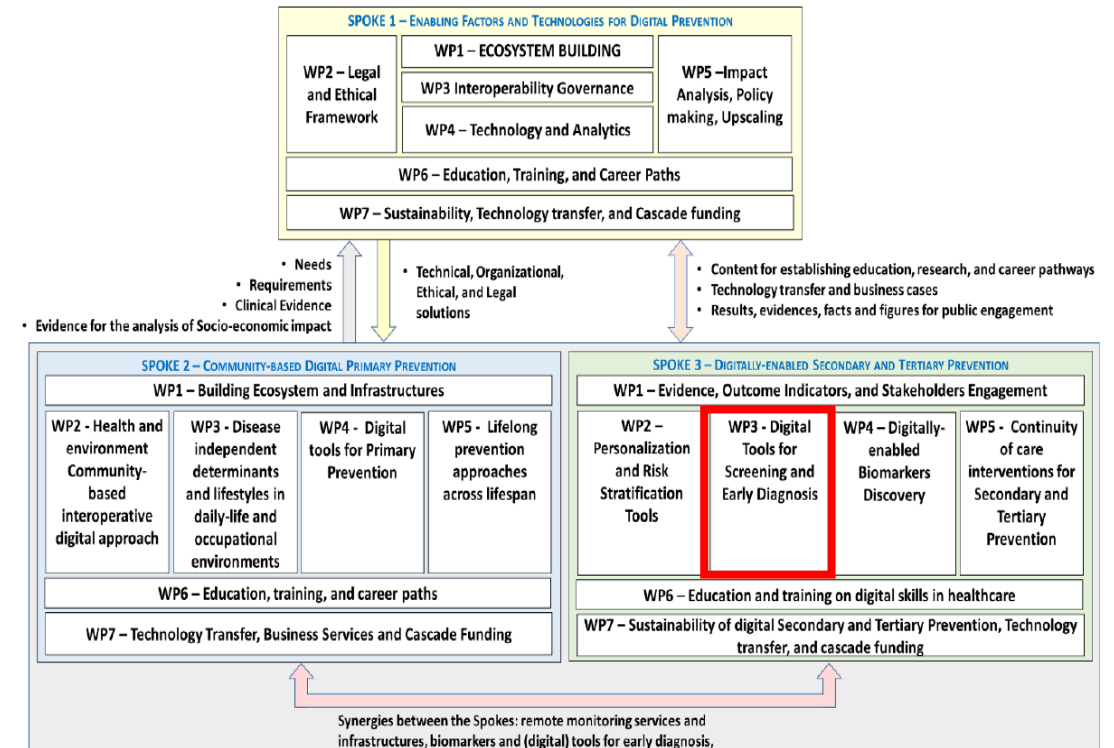
(continued)

## Generating AI-risk stratification strategies for improved colorectal cancer screening

**Scope:** Personalizing colorectal cancer screening and surveillance

**Population of interest:** *colorectal cancer screening*

**Relevance for secondary/tertiary prevention and connection with digital health:** *secondary prevention*





# AIM of the study

- Develop risk-based predictors, and tailor procedures to individuals' risk profile, offering more intensive screening to high-risk patients, to detect precancerous lesions and early cancers, while reducing the burden by offering less intensive screening to low-risk subjects.
- Providing precise and personalized strategy for screening and early detection through the biomarker assessment integrated with risk-based model tested in large scale populations.

# Impact of SARS-CoV-2 pandemic on colorectal cancer screening delay: effect on stage shift and increased mortality

A procedural model considering delays in the time to colonoscopy and estimating the effect on mortality due to up-stage migration of patients → The number of expected CRC cases computed by using the data of the **Osservatorio Nazionale Screening**. Estimates of the effects of delay to colonoscopy on CRC stage, and of stage on mortality assessed by a meta-analytic approach.

Prevalence (and corresponding expected number of CRC) of early and advanced stages for colorectal cancers detected at delayed screening, according to increasing time delays to the access to colonoscopy (estimates by the “DS” meta-analysis).

Diagnostic delay (mo.)	Stage at diagnosis	Stage Prevalence	95% CI <sup>#</sup>	Expected CRC <sup>\$</sup>	p-value <sup>&amp;</sup>
0-3	I-II	0.74	(0.69 – 0.80)	2356	Ref.
	III-IV	0.26	(0.20 – 0.31)	828	
4-6	I-II	0.76	(0.71 – 0.81)	2420	0.068
	III-IV	0.24	(0.19 – 0.29)	764	
7-12	I-II	0.71	(0.66 – 0.77)	2261	0.008
	III-IV	0.29	(0.23 – 0.34)	923	
>12	I-II	0.67	(0.57 – 0.77)	2133	<0.001
	III-IV	0.33	(0.23 – 0.43)	1051	

Expected number of deaths at 5-years for colorectal cancer detected at delayed screening, according to diagnostic delays and stage at diagnosis.

Diagnostic delay (mo.)	Stage at diagnosis	Expected Deaths <sup>\$</sup>	Relative change (%)	p-value <sup>&amp;</sup>	All stages		
					Expected deaths <sup>\$</sup>	Relative change (%)	p-value <sup>&amp;</sup>
0-3	I-II	353	Ref.	--	858	Ref.	--
	III-IV	505					
4-6	I-II	363	2.8	0.294	829	-3.4	0.427
	III-IV	466	-7.7				
7-12	I-II	339	-4.0	0.139	902	5.1	0.228
	III-IV	563	11.5				
>12	I-II	320	-9.3	<0.001	961	12.0	0.005
	III-IV	641	26.9				

# Modelling optimal use of temporarily restricted colonoscopy capacity in a FIT-based CRC screening program: Application during the COVID-19 pandemic

**Table 1. The efficiency of strategies to reduce colonoscopy demand predicted by MISCAN-Colon.**

	Reduction in colonoscopy demand in 2020, 2021 and 2022 (%)	Excess CRC incidence (2020–2050, %)	Increase in CRC incidence per colonoscopy not performed	Excess CRC deaths (2020–2050, %)	Increase in CRC deaths per colonoscopy not performed	Excess LYs lost (2020–2050, %)	Increase in LYs lost per colonoscopy not performed
<i>Increasing the cut-off value</i>							
50 µg Hb/g faeces	11,700 (7.3%)	400 (0.08%)	0.04	200 (0.09%)	0.01	1,400 (0.25%)	0.18
55 µg Hb/g faeces	15,000 (10.2%)	600 (0.12%)	0.04	300 (0.15%)	0.02	2,400 (0.43%)	0.15
60 µg Hb/g faeces	18,700 (12.7%)	700 (0.14%)	0.03	300 (0.19%)	0.02	3,200 (0.58%)	0.17
70 µg Hb/g faeces	25,100 (17.0%)	900 (0.18%)	0.03	400 (0.26%)	0.02	4,400 (0.80%)	0.18
<i>Skipping screening ages</i>							
55-year-olds	9,200 (6.2%)	200 (0.04%)	0.02	100 (0.08%)	0.02	2,700 (0.48%)	0.29
63-year-olds	7,400 (5.0%)	200 (0.05%)	0.03	200 (0.10%)	0.02	2,300 (0.41%)	0.31
63- and 65-year-olds	16,100 (10.9%)	600 (0.12%)	0.03	400 (0.24%)	0.03	5,200 (0.93%)	0.32
<i>Extending the screening interval</i>							
28 months	12,600 (8.6%)	-200 (-0.04%)	-0.01	-200 (-0.12%)	-0.02	600 (0.11%)	0.05
30 months	19,000 (12.9%)	-200 (-0.03%)	-0.01	-300 (-0.19%)	-0.02	900 (0.16%)	0.05
32 months	18,500 (12.5%)	-200 (-0.05%)	-0.01	-500 (-0.27%)	-0.03	1,200 (0.21%)	0.06
34 months	18,000 (12.2%)	-200 (-0.05%)	-0.01	-600 (-0.35%)	-0.03	1,100 (0.20%)	0.06
36 months	16,200 (11.0%)	400 (0.08%)	0.02	-100 (-0.08%)	-0.01	5,300 (0.95%)	0.32

*3-month disruption in the first half of 2020 due to the COVID-19 pandemic. Simulated three different strategies for the total target population: 1) increasing the FIT cut-off, 2) skipping one screening for specific screening ages, and 3) extending the screening interval.*

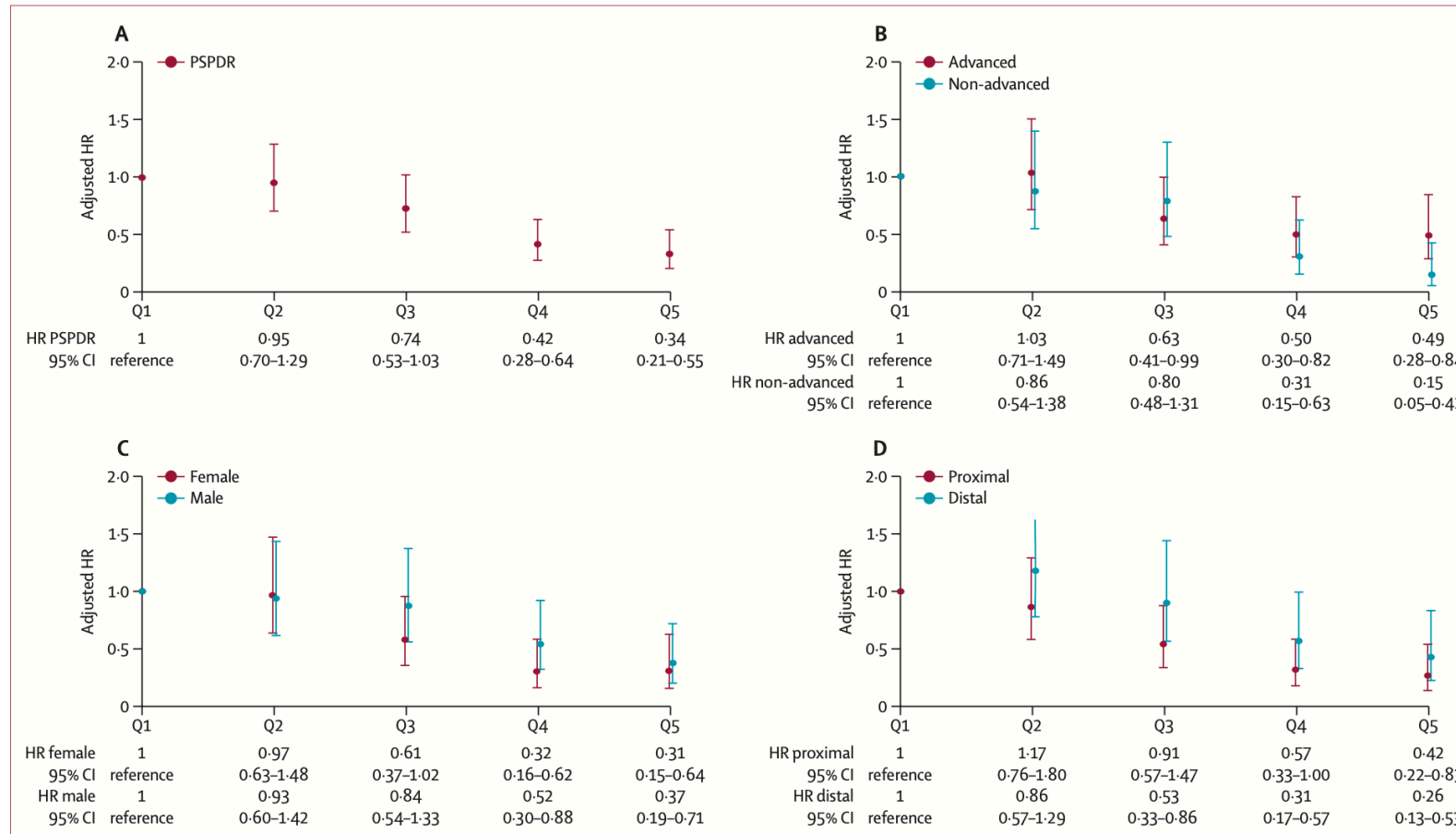
# Adenoma Detection Rate

**Table 2.** Adenoma Detection Rate and Risk of an Interval Colorectal Cancer among All Patients.

Adenoma Detection Rate	Interval Cancer  <i>no. of cases</i>	Hazard Ratio (95% CI)*	Unadjusted Risk  <i>no. of cases/ 10,000 person-yr</i>
Continuous rate	712	0.97 (0.96–0.98)	7.7
Rate quintile			
Quintile 1: 7.35–19.05%	186	1.00 (reference)	9.8
Quintile 2: 19.06–23.85%	144	0.93 (0.70–1.23)	8.6
Quintile 3: 23.86–28.40%	139	0.85 (0.68–1.06)	8.0
Quintile 4: 28.41–33.50%	167	0.70 (0.54–0.91)	7.0
Quintile 5: 33.51–52.51%	76	0.52 (0.39–0.69)	4.8

# Serrated polyp detection and risk of interval post-colonoscopy colorectal cancer: a population-based study

David E F W M van Toledo\*, Joep E G Ijspeert\*, Patrick M M Bossuyt, Arne G C Bleijenberg, Monique E van Leerdam, Manon van der Vlugt, Iris Lansdorp-Vogelaar, Manon C W Spaander, Evelien Dekker



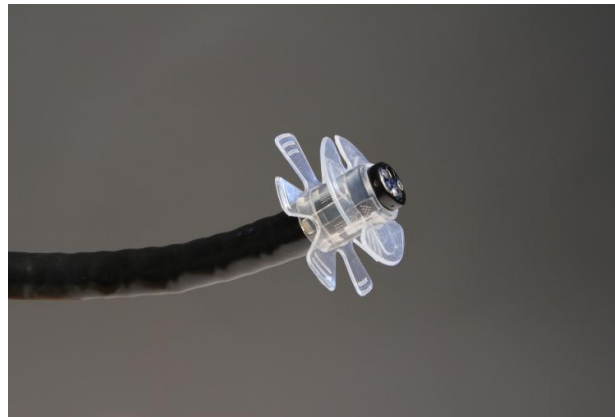
**Figure 2: Adjusted HRs for interval post-colonoscopy colorectal cancer according to quintile of PSPDR, overall (A), stratified by cancer stage (B), stratified by sex (C), and stratified by location (D)**  
HRs were adjusted for sex and age (except for C), and random effect was applied to adjust for correlation within endoscopists. Proximal indicates located proximal to the descending colon, including the splenic flexure; distal indicates located distal to the splenic flexure. HR=hazard ratio. PSPDR=proximal serrated polyp detection rate.

# Distal Attachment Devices

Endocuff vision



Endoring

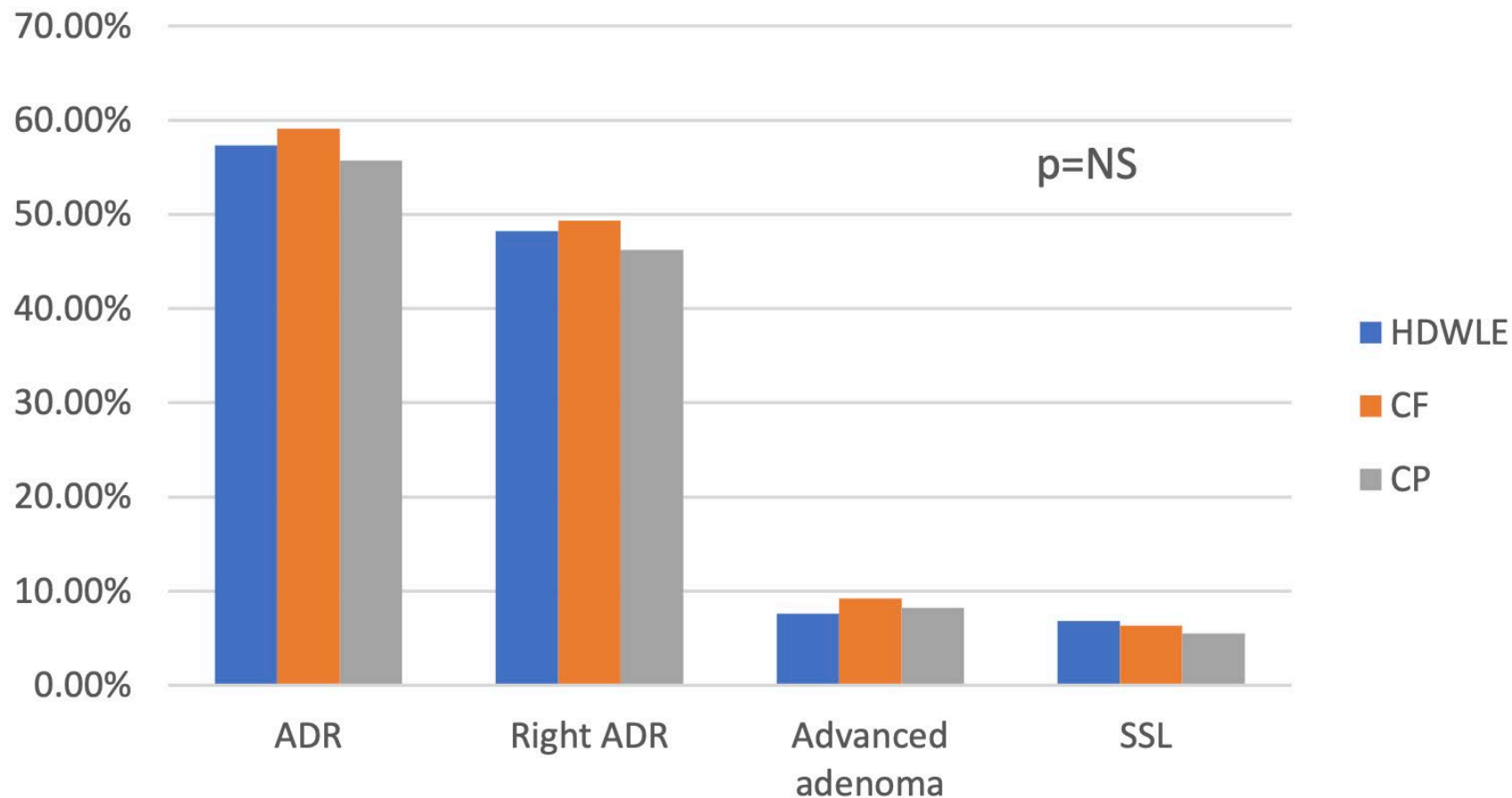


Distal Cap

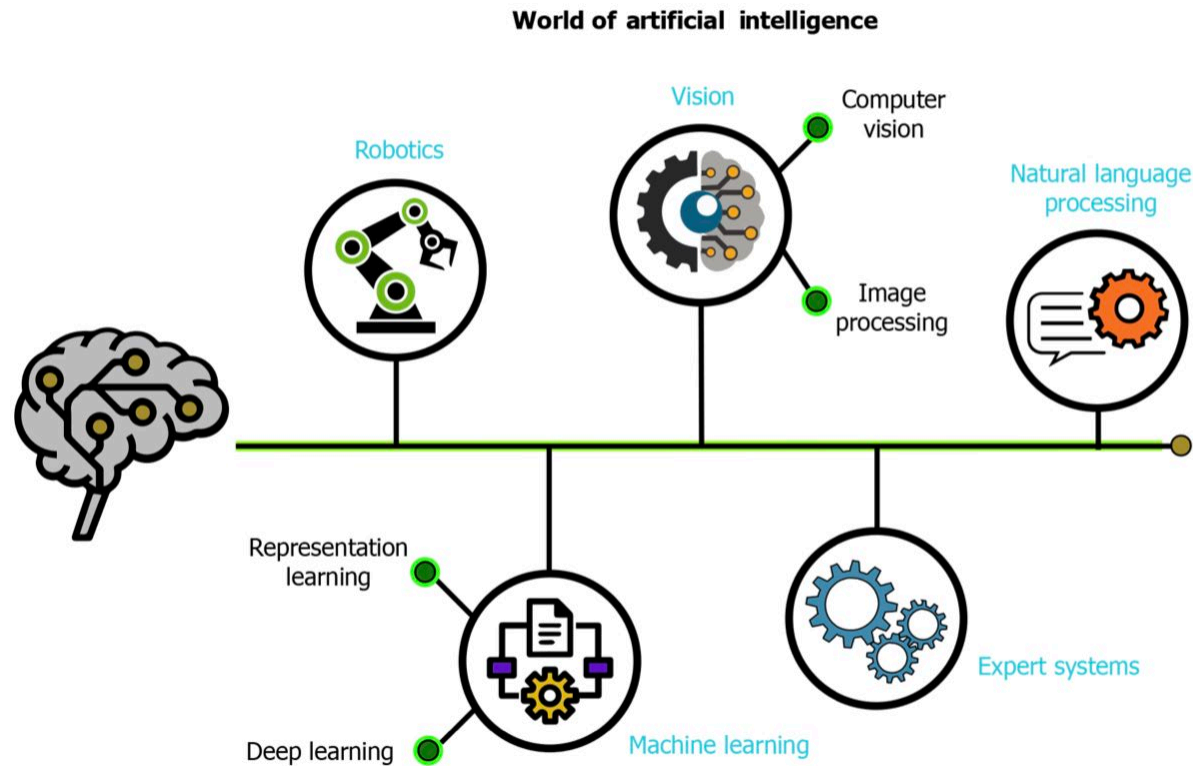


<https://www.youtube.com/watch?v=OmKWE1LAjD0>

Comparison of overall ADR, right ADR, advanced adenoma detection, and sessile serrated lesion detection rates among 3 groups.

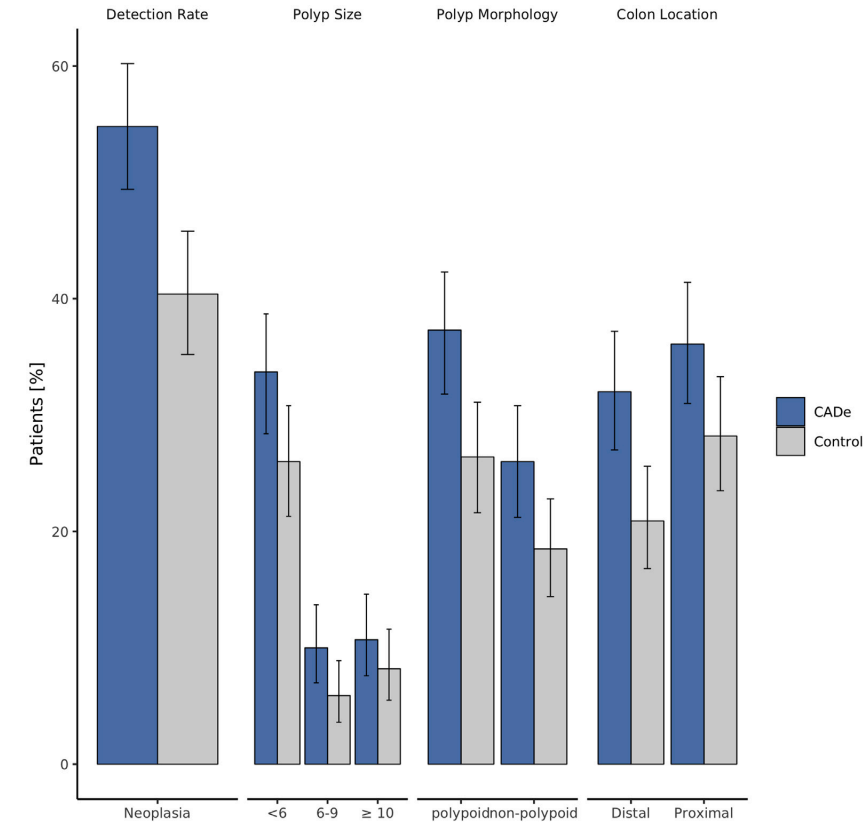
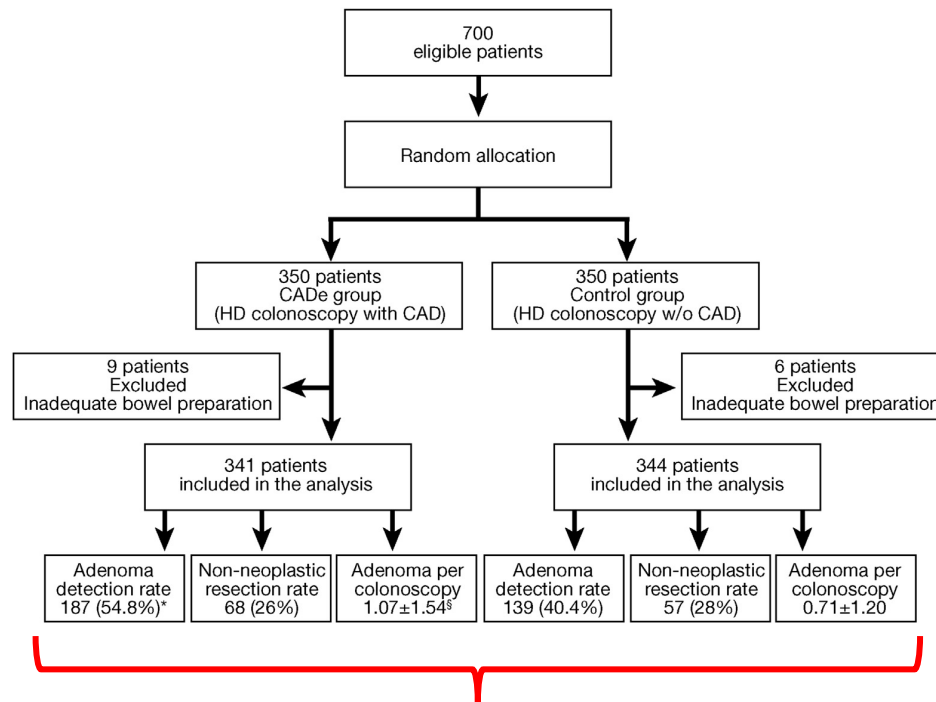


Artificial intelligence: a set of fields that are combining to improve tasks that involve human cognitive functions such as learning, reasoning and self-correction.





# Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial



# Real-Time Computer-Aided Detection of Colorectal Neoplasia During Colonoscopy A Systematic Review and Meta-analysis

Figure 2. Forest plot: ADR.

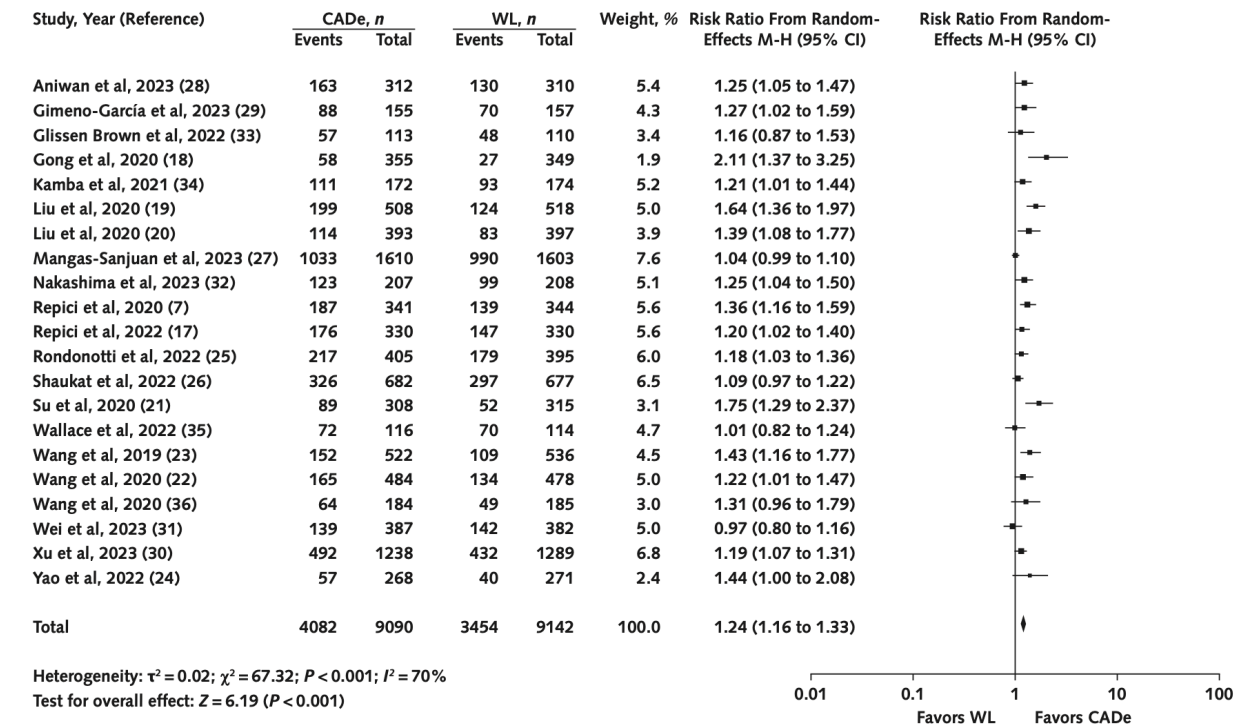
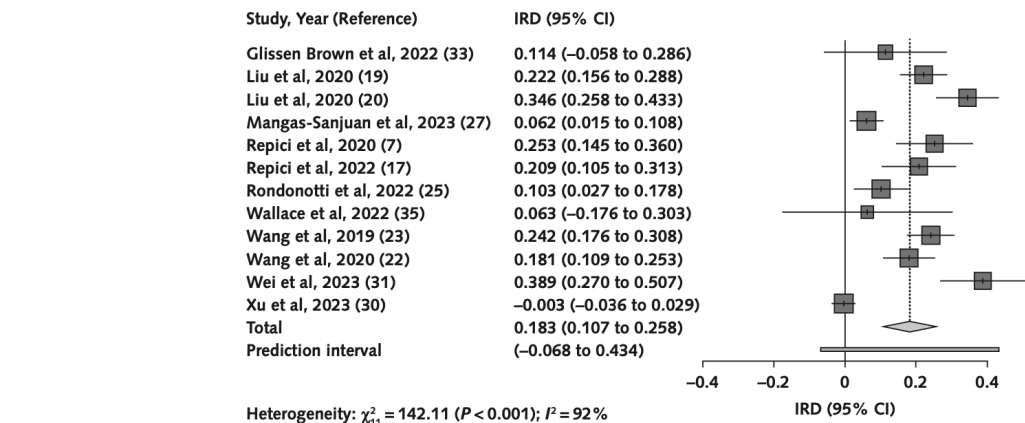
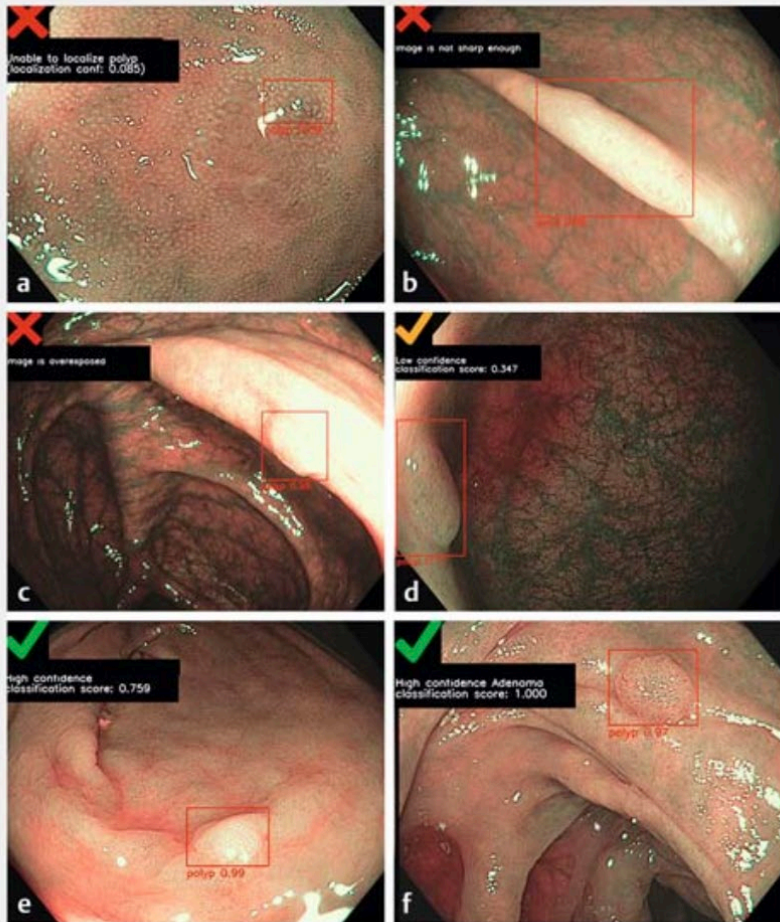


Figure 4. Forest plot: nonneoplastic lesions per colonoscopy.



«The use of CADe for polyp detection during colonoscopy results in increased detection of adenomas but not advanced adenomas and in higher rates of unnecessary removal of nonneoplastic polyps».

# Computer-aided diagnosis for optical diagnosis of diminutive colorectal polyps including sessile serrated lesions: a real-time comparison with screening endoscopists



► **Table 2** Diagnostic performance of the computer-aided diagnosis system and endoscopists in differentiating diminutive colorectal polyps.

	Overall		Only high-confidence predictions	
	CADx (n=423)	Endoscopists (n=423)	CADx (n=422)	Endoscopists (n=367)
Per polyp subtype accuracy <sup>1</sup>	73.1 (68.6–77.2)	76.1 (71.8–80.1)	73.2 (68.7–77.4)	79.8 (75.4–83.8)
Adenoma vs. nonadenoma (i. e. serrated), % (95%CI)				
▪ Accuracy	77.8 (73.3–81.7)	82.7 (78.8–86.2)	78.0 (73.7–81.8)	85.0 (80.9–88.5)
▪ Sensitivity	90.3 (87.0–93.7)	87.3 (83.6–91.1)	90.3 (87.0–93.7)	89.9 (86.2–93.5)
▪ Specificity	47.2 (38.3–56.0)	71.5 (63.6–79.5)	47.5 (38.7–56.4)	72.3 (63.6–81.0)
▪ PPV	80.6 (76.4–84.9)	88.2 (84.6–91.9)	80.9 (76.7–85.1)	89.5 (85.8–93.2)
▪ NPV	66.7 (56.8–76.6)	69.8 (61.8–77.9)	66.7 (56.8–76.6)	73.0 (64.3–81.7)
SSL vs. non-SSL, % (95%CI)				
▪ Accuracy	88.9 (85.5–91.7)	88.8 (85.2–91.9)	88.9 (85.5–91.7)	88.8 (85.2–91.9)
▪ Sensitivity	17.1 (5.6–28.6)	58.5 (43.5–73.6)	17.1 (5.6–28.6)	67.7 (50.6–82.8)
▪ Specificity	96.6 (94.8–98.4)	89.5 (86.5–92.6)	96.6 (94.8–98.4)	91.0 (88.0–94.1)
▪ PPV	35.0 (14.1–55.9)	37.5 (25.6–49.4)	35.0 (14.1–55.9)	42.3 (28.9–55.7)
▪ NPV	91.6 (88.9–94.3)	95.3 (93.0–97.5)	91.5 (88.8–94.3)	96.5 (94.5–98.5)

CADx, computer-aided diagnosis; PPV, positive predictive value; NPV, negative predictive value; SSL, sessile serrated lesion.

<sup>1</sup> For the calculation of the per polyp subtype accuracy adenomas, SSLs and hyperplastic polyps were considered as different histological subtypes.

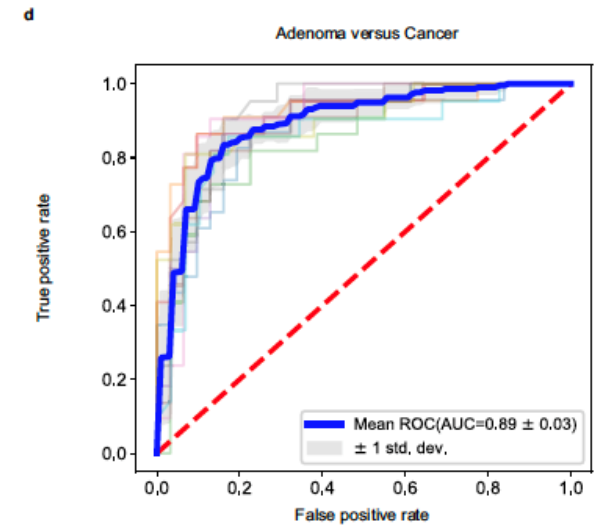
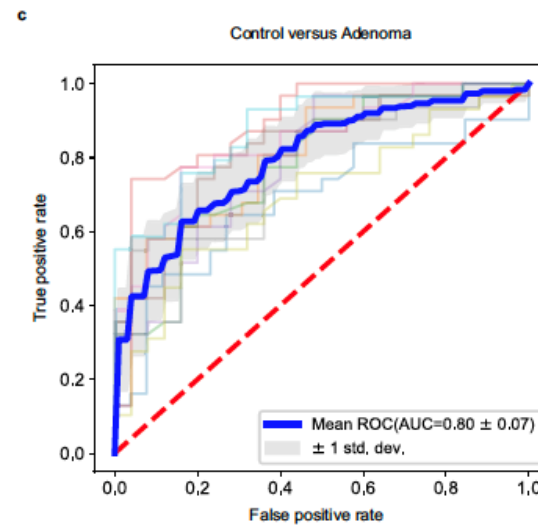
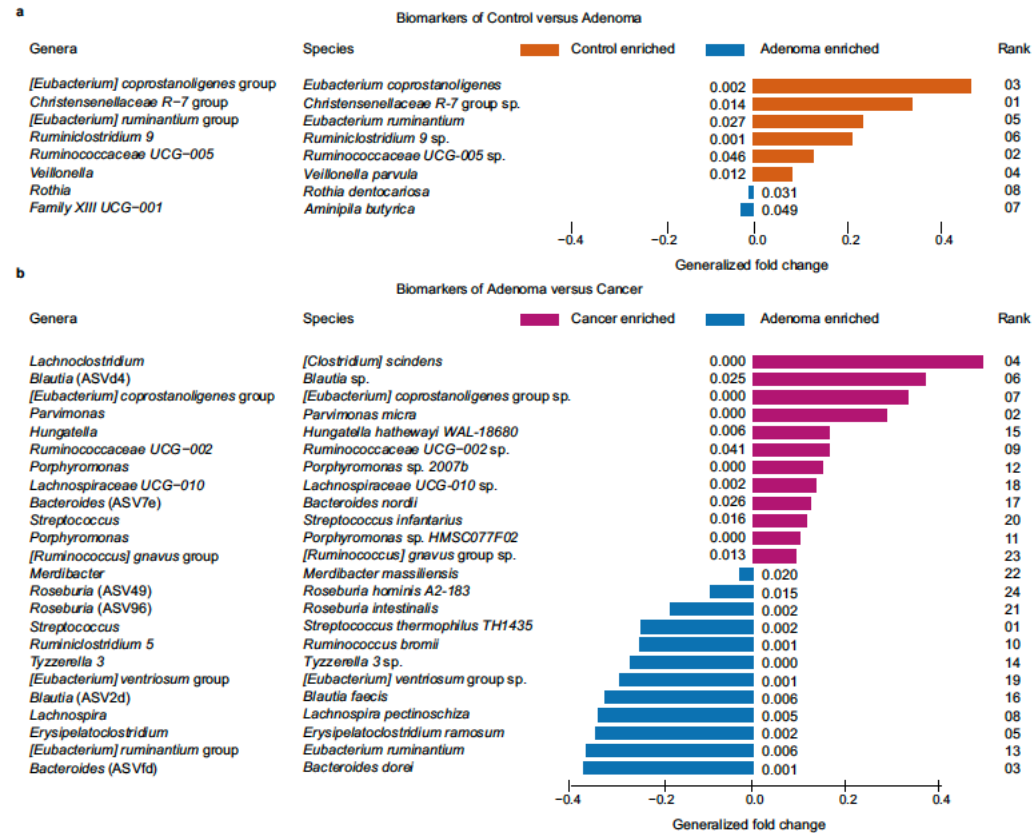
# Cologuard vs FIT

**Table 1.** Sensitivity and Specificity of the Multitarget Stool DNA Test and the Fecal Immunochemical Test (FIT) for the Most Advanced Findings on Colonoscopy.

Most Advanced Finding	Colonoscopy (N = 9989)	Multitarget DNA Test (N = 9989)		FIT (N = 9989)	
		Positive Results	Sensitivity (95% CI)	Positive Results	Sensitivity (95% CI)
	<i>no.</i>	<i>no.</i>	%	<i>no.</i>	%
Colorectal cancer					
Any	65	60	92.3 (83.0–97.5)	48	73.8 (61.5–84.0)
Stage I to III*	60	56	93.3 (83.8–98.2)	44	73.3 (60.3–83.9)
Colorectal cancer and high-grade dysplasia	104	87	83.7 (75.1–90.2)	66	63.5 (53.5–72.7)
Advanced precancerous lesions†	757	321	42.4 (38.9–46.0)	180	23.8 (20.8–27.0)
Nonadvanced adenoma	2893	498	17.2 (15.9–18.6)	220	7.6 (6.7–8.6)
			Specificity (95% CI)		Specificity (95% CI)
All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy	9167	1231	86.6 (85.9–87.2)	472	94.9 (94.4–95.3)
Negative results on colonoscopy	4457	455	89.8 (88.9–90.7)	162	96.4 (95.8–96.9)

- Sensitivity of MT-sDNA test exceeded that of FIT
- FIT slightly more specific

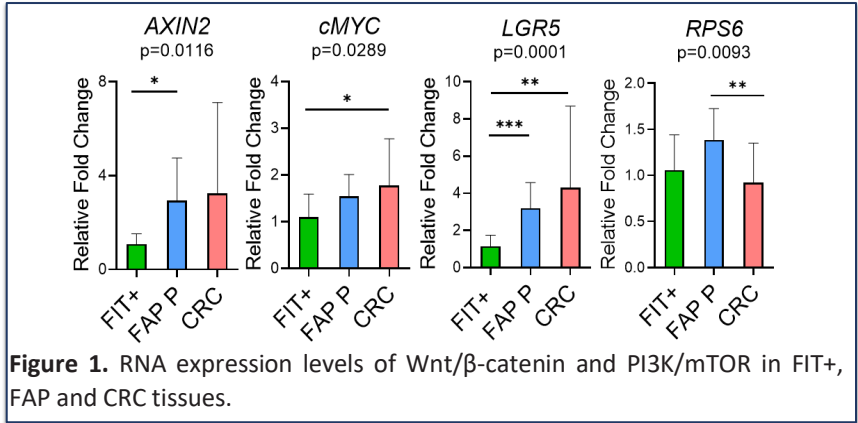
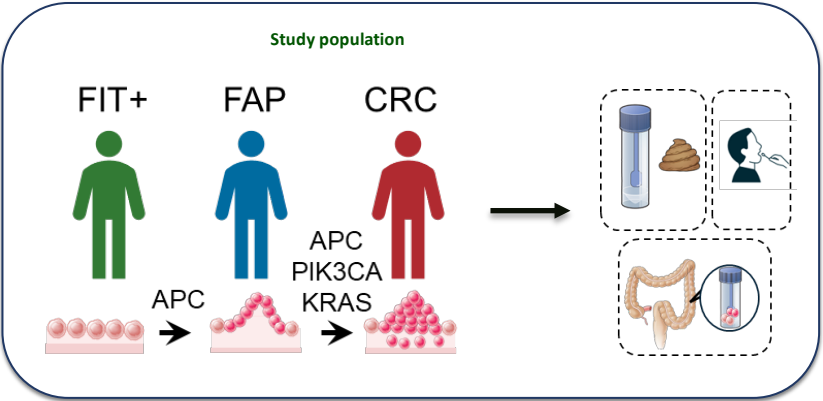
# Microbial markers across populations in early detection of colorectal cancer



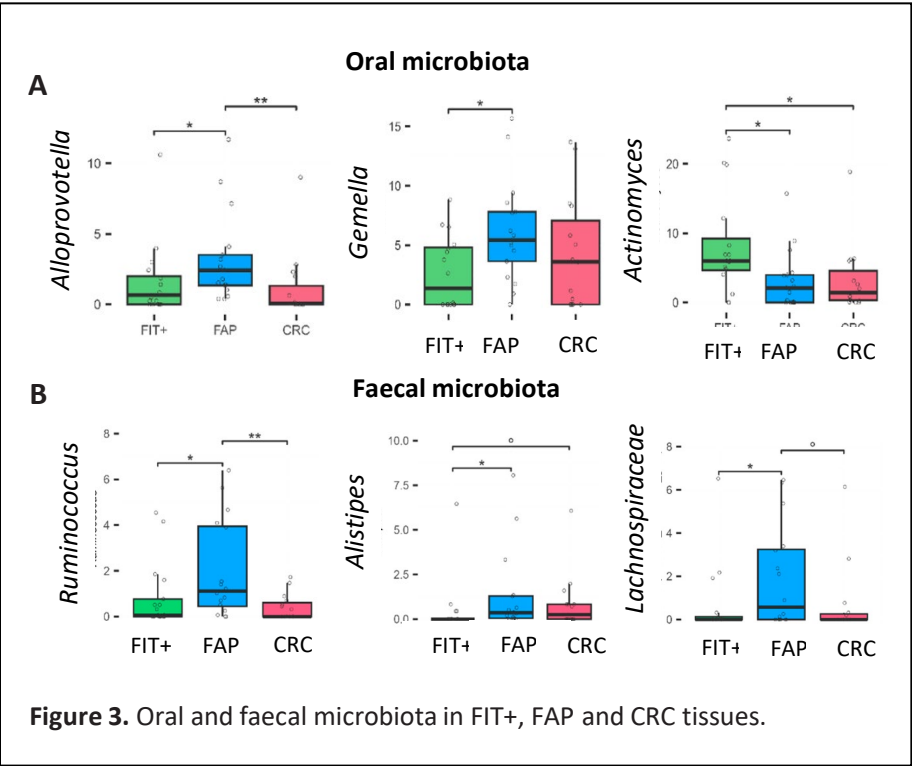


# A multitarget framework for WNT signalling-driven colorectal cancer prevention and early detection

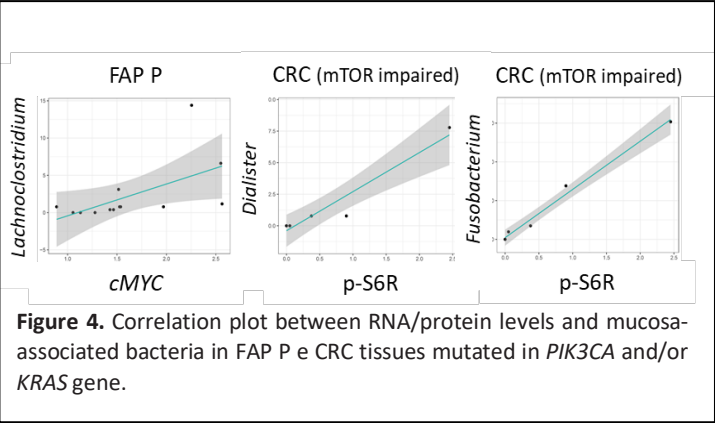
The aim of the study was to identify potential targets for the prevention and early detection of CRC in the setting of Wnt/ $\beta$ -catenin disruption.



**Figure 1.** RNA expression levels of Wnt/ $\beta$ -catenin and PI3K/mTOR in FIT+, FAP and CRC tissues.

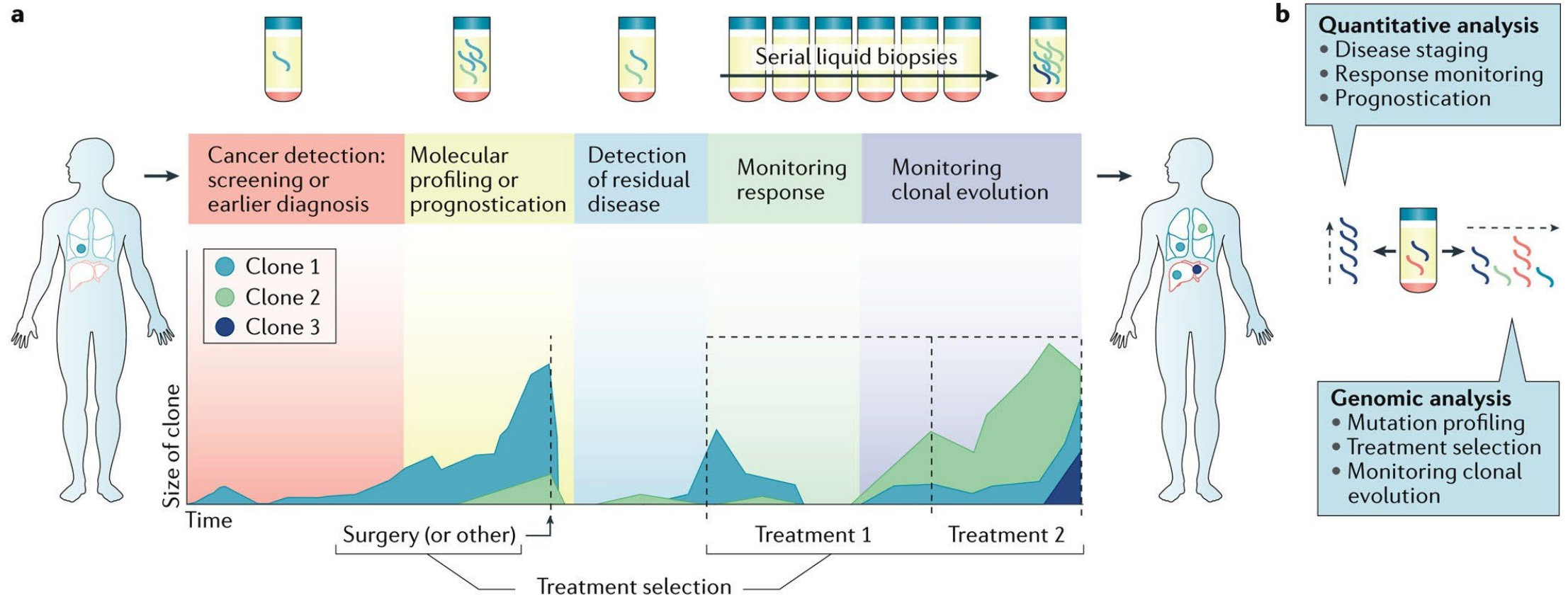


**Figure 3.** Oral and faecal microbiota in FIT+, FAP and CRC tissues.

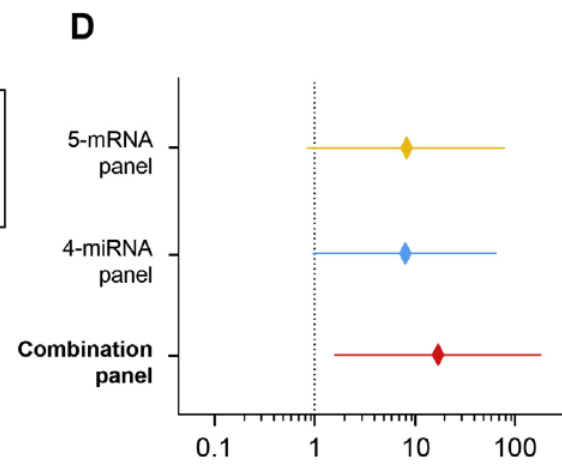
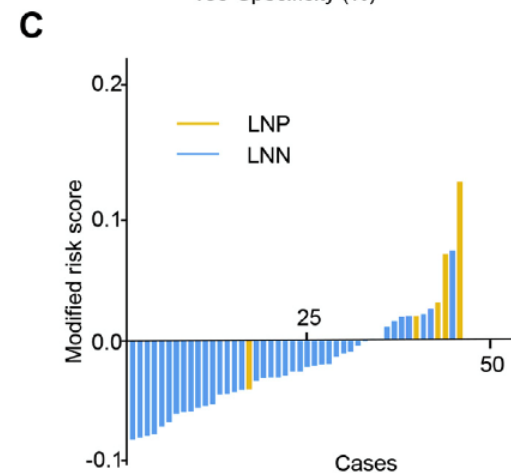
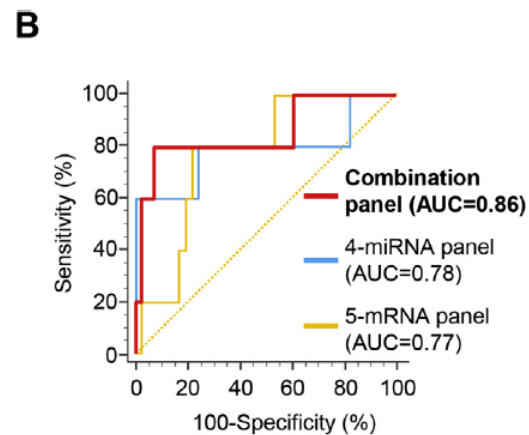
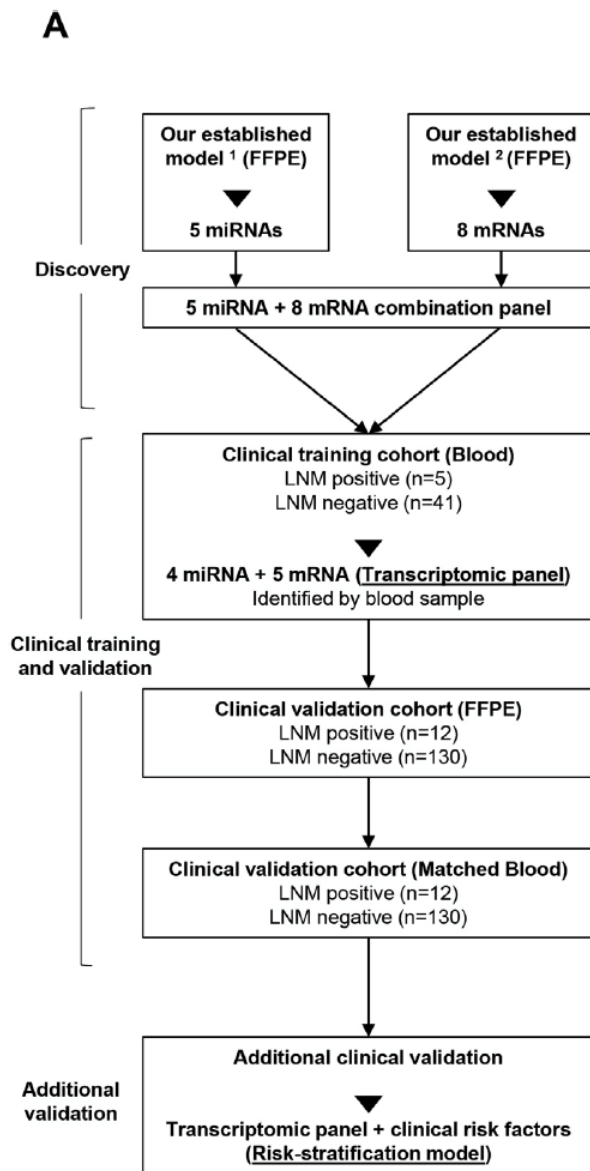


**Figure 4.** Correlation plot between RNA/protein levels and mucosa-associated bacteria in FAP and CRC tissues mutated in *PIK3CA* and/or *KRAS* gene.

# Liquid Biopsy and Colorectal Cancer



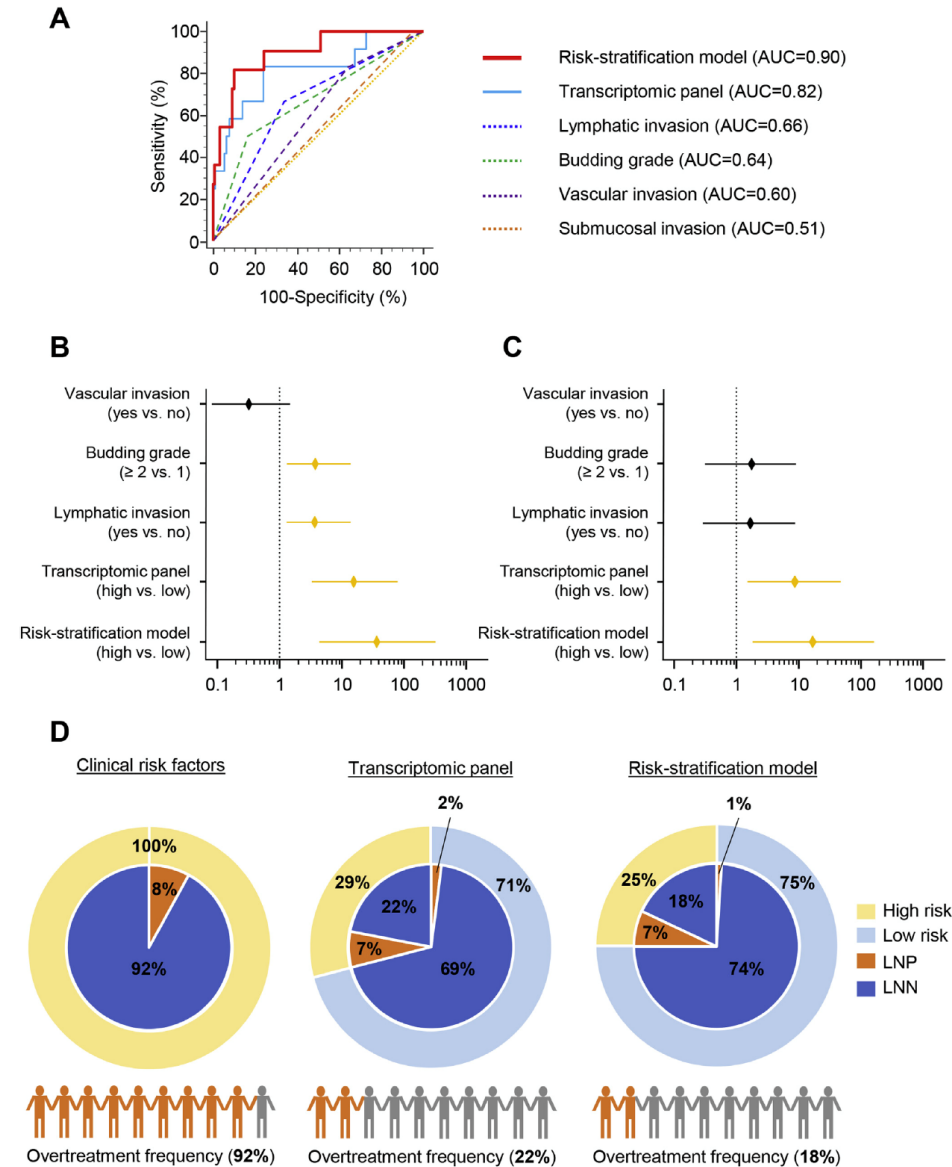
Nature Reviews | **Cancer**

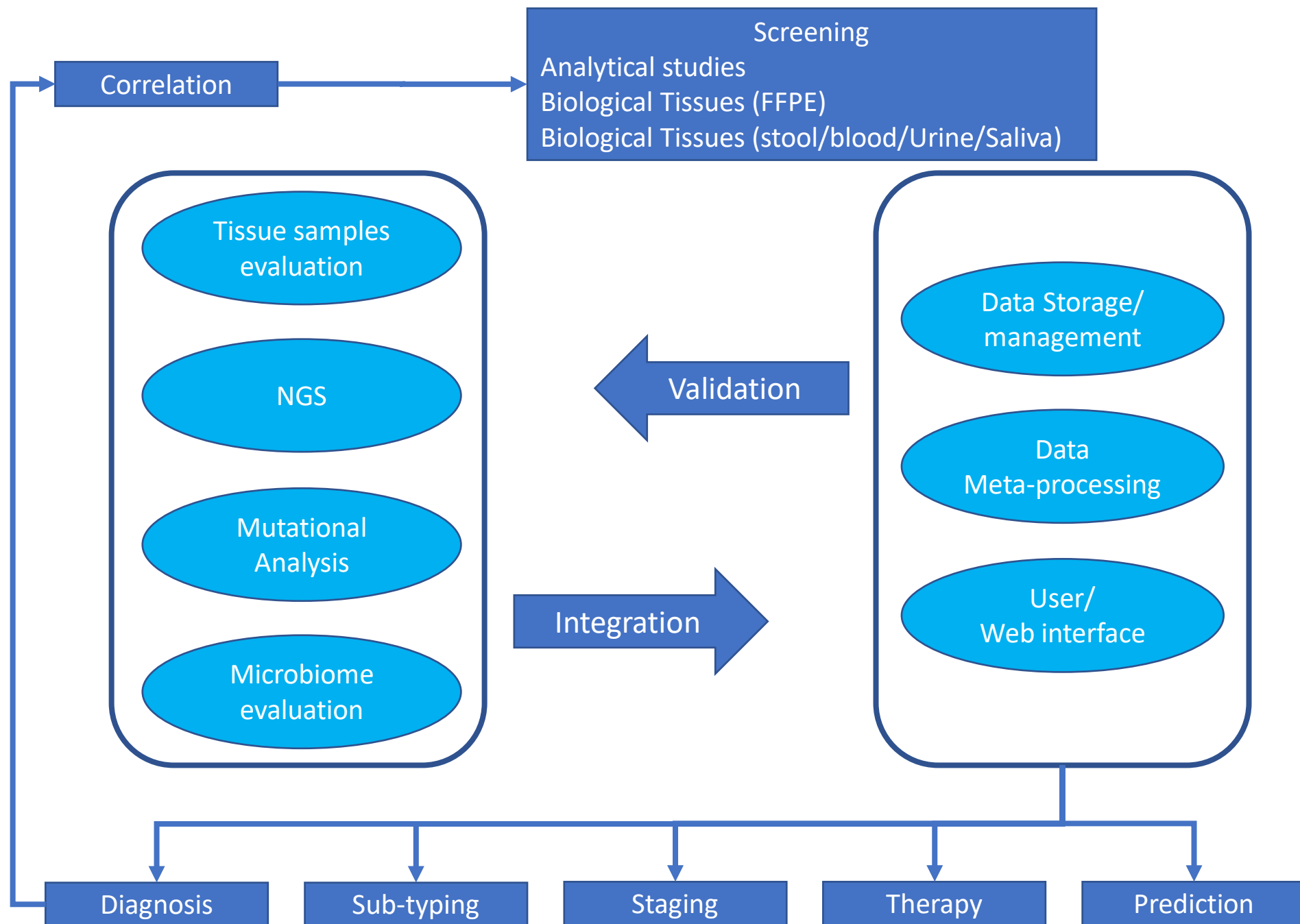


# Liquid biopsy for pT1 risk stratification

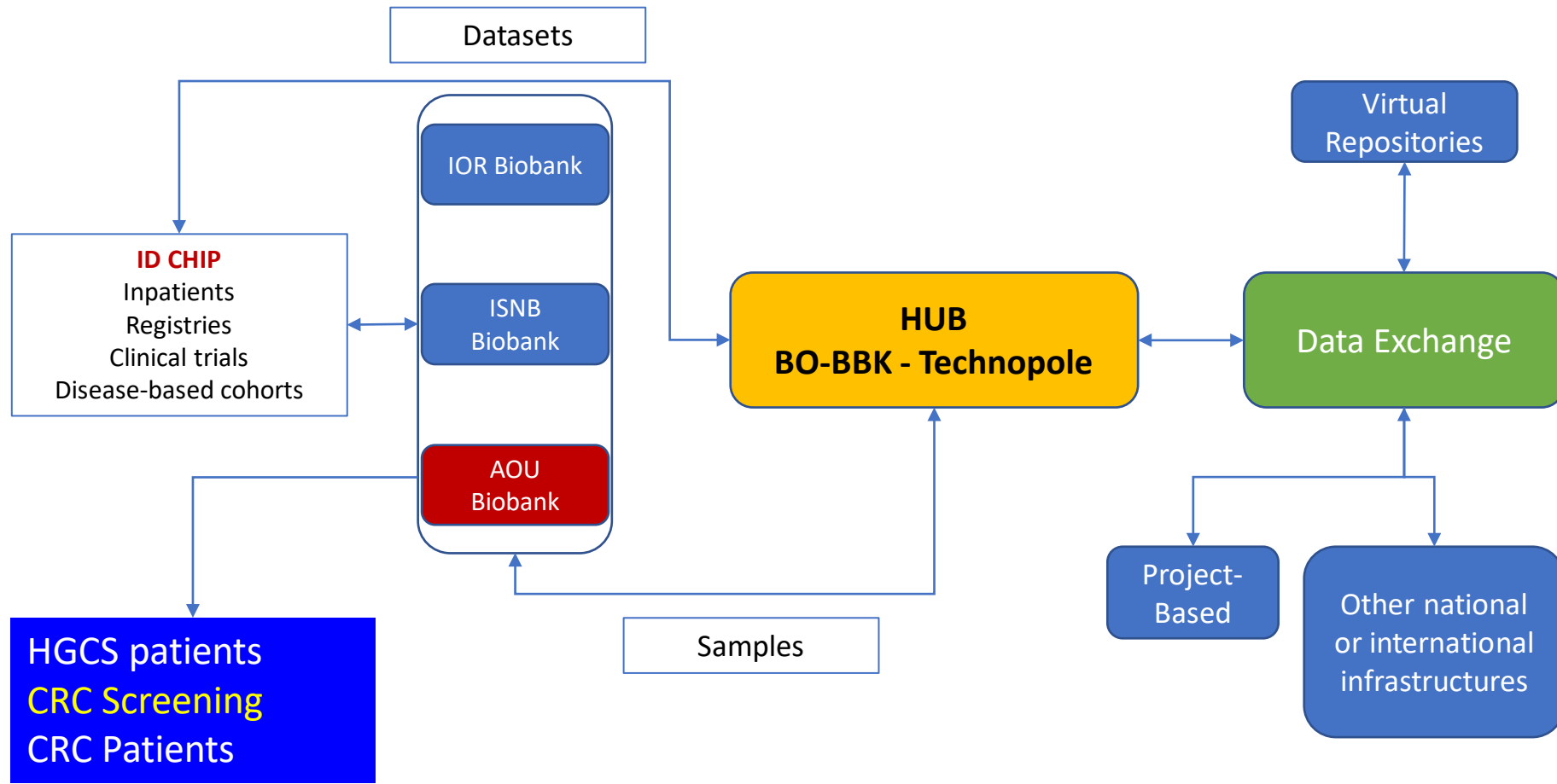


# Liquid biopsy for pT1 risk stratification





# Biobank at IRCCS AOU Bologna



# Conclusions

- CRC screening is a research platform that over the years has continuously led to understanding the epidemiology, the natural history and the pathogenesis of the disease
- There are still important gaps that need to be filled such as true prevalence of hereditary syndromes within the general population, new and improved screening tests, best and quality measures
- Using the CRC screening as research platform will lead to preventing and treating the disease more efficiently