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gruppo italiano screening colorettale

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XVII CONGRESSO NAZIONALE 2024

"LIQUID BIOPSY" E "MOLECULAR TOOLS" PER LA DIAGNOSTICA DELLO SCREENING CRC: FATTIBILITÀ *VS* ASPETTATIVE

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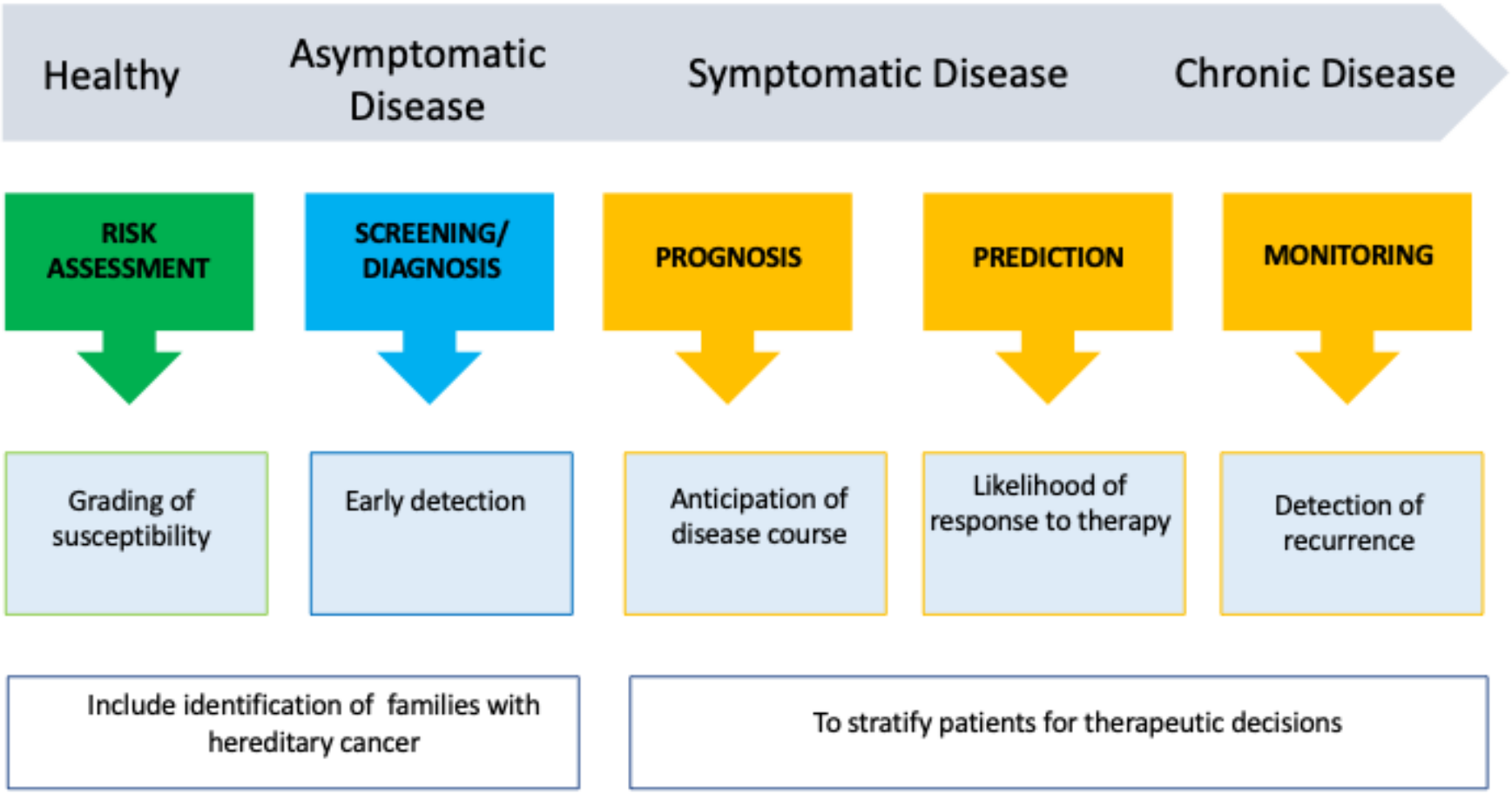
What are CRC molecular subtypes used for?

Clinical contexts

- Diagnosis ⇒ molecular subtypes, linked to:

- Outcome
  - Prognostication
  - Prediction

Translational efforts apply to different clinical scenarios



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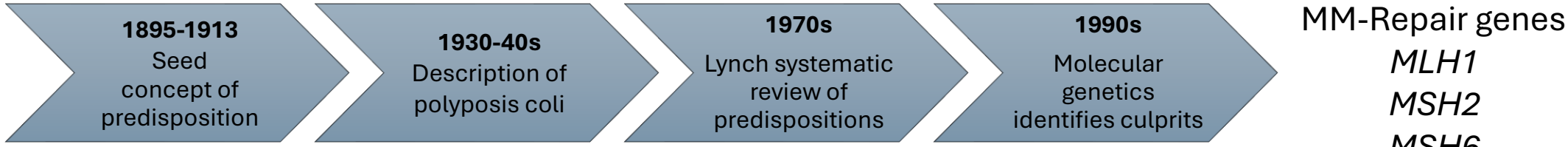
All clinical scenarios contributed to the scientific development of CRC molecular genetics

Scenario	Field / application
• Susceptibility	inherited predispositions
• Early detection	molecular stool tests – recently, blood
• Prognosis	different behavior (e.g. MSI *vs* MSS), ctDNA
• Prediction/monitoring:	*KRAS* mutations in liquid biopsies
	ctDNA

Developmental pathway of molecular genetics in GI oncology: the contribution of inherited predispositions



Colorectal cancer risk levels

Risk category	Level of CRC risk, %	Risk factors
Very high	>20	Personal or family history of a hereditary CRC syndrome (eg, adenomatous polyposis syndromes, Lynch syndrome, and hamartomatous polyposis syndromes) Serrated polyposis syndrome
High	10–20	Family history of 1 or more first-degree relative with CRC younger than 60 y or 2 first-degree relatives at any age Personal history of AA or advanced serrated polyp Inflammatory bowel disease
Average risk	4	No symptoms and no factor above

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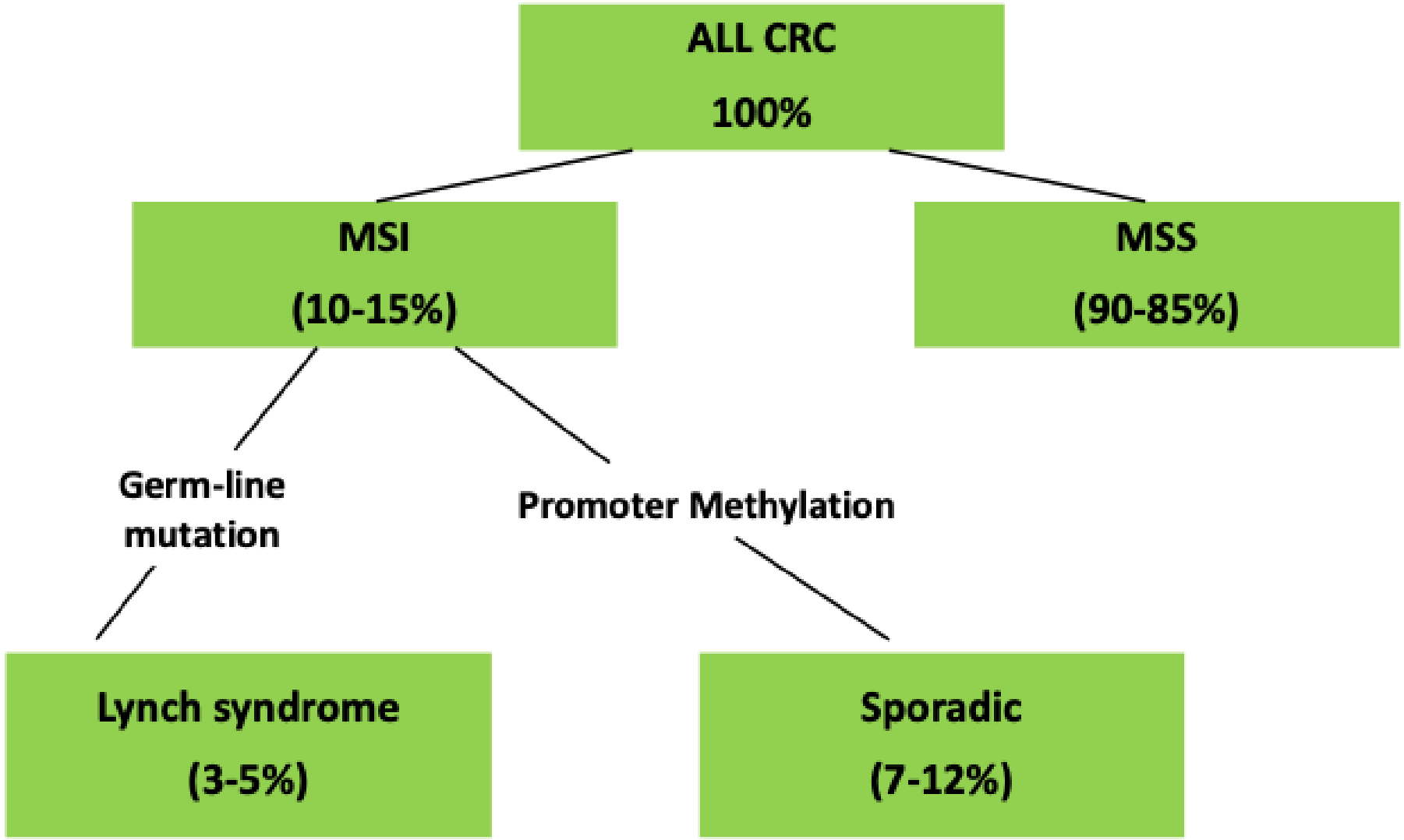
Carriers of inherited predispositions do not undergo screening

Molecular phenotypes of CRC – evolution over time

CRC understanding, time-laps

- Early 90s': oncogene activation (e.g. *KRAS*) + tumor suppressor silencing (e.g. *APC*, *TP53*)
- Mid 90s': Microsatellite instability (MSI) vs Chromosomal instability (CIN, or MS-Stable)
- Early 2000s': CpG Methylator phenotype
- NGS evolution: Consensus Molecular Subtypes (CMS 1-4; mRNA expression patterns)

Prevalence of MSI CRC subclasses



De La Chapelle, JCO 2010

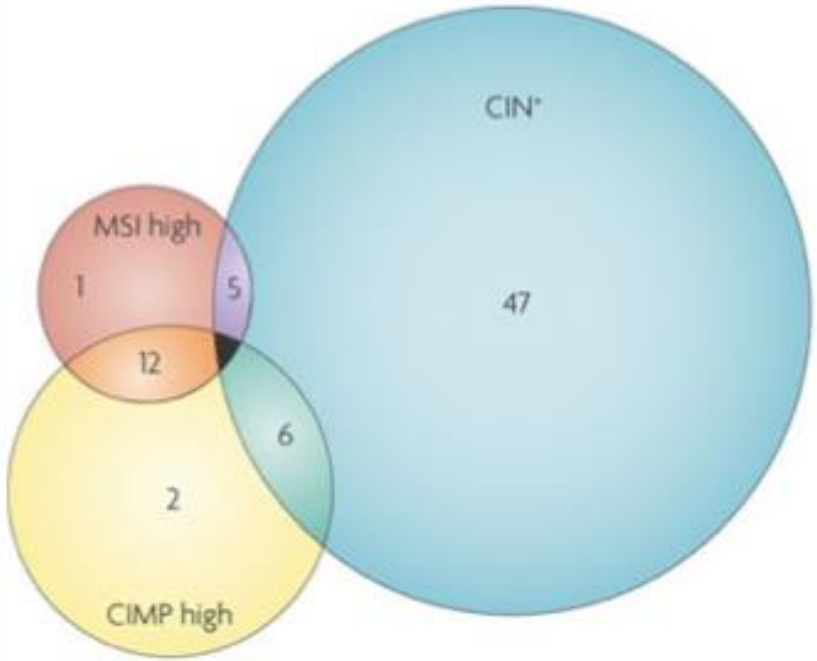
Molecular phenotypes of CRC – scenario in the 2010s

CpG Island methylator phenotype (CIMP): a distinct CRC pathway which may lead to MSI

A. Patterns of Genomic Instability in CRC

Types of Instability and Syndrome	Type of Defect	Genes Involved
• Chromosomal Instability (CIN)	Somatic	LOH at *APC* *p53* *SMAD4*
• DNA MMR defects (MSI)		
HNPCC	Germ-line	*MLH1 MSH2 MSH6*
Sporadic MSI cancer	Somatic	MLH1
• CpG island methylator phenotype (CIMP)	Somatic	*MLH1 MINT1 MINT2 MINT3*
• Base excison repair defect	Germ-line	*MYH*

B. Frequency & Association of Different Patterns



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Evolving impact of molecular genetics on CRC

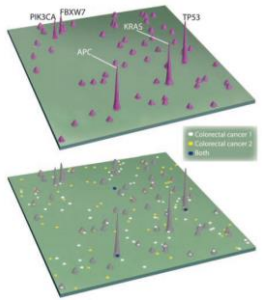
➢**Descriptive era**

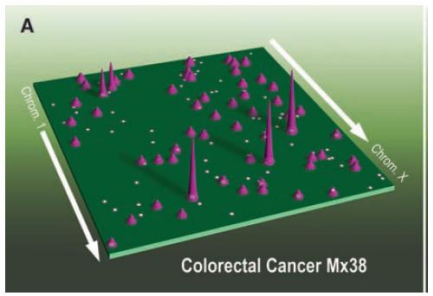
1. Inherited predispositions, ↑ risk and disease behavior
2. Somatic mutational signature → relevance of specific mutations
3. “Landscape” perspective = NGS breakthrough

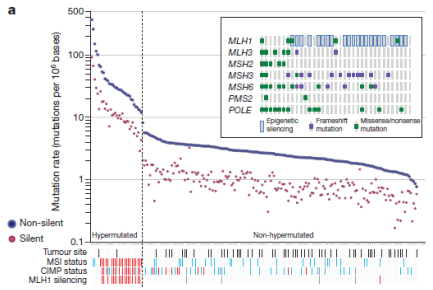
   → similarities/differences (*mountain & hills*; *driver & passengers*)

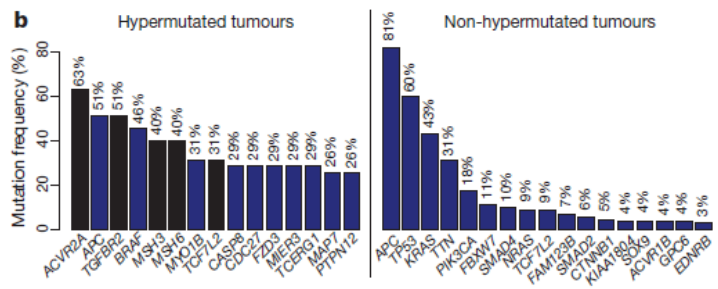
➢**Actionability era**

1. Mutational patterns as determinants of drug responsiveness
   the anti EGRF story → *RAS* mutations and siblings
2. Landscape-oriented search for actionable mutations



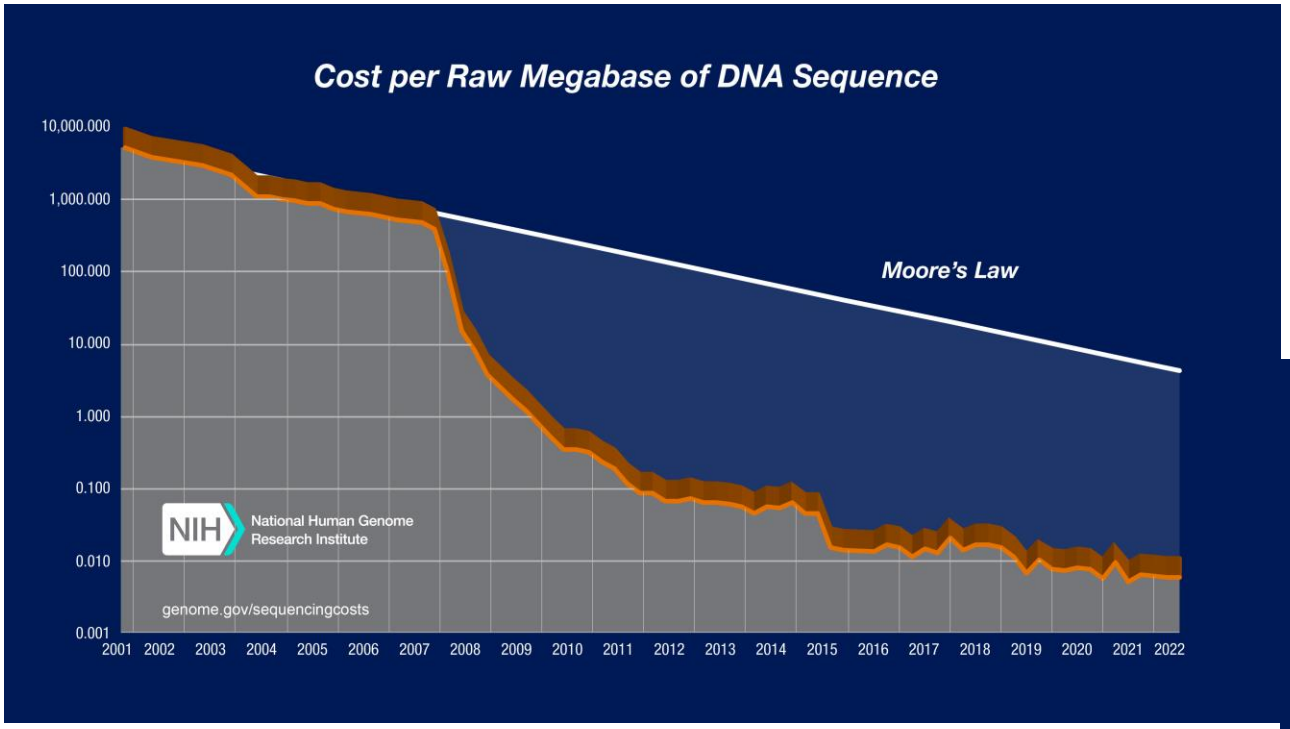




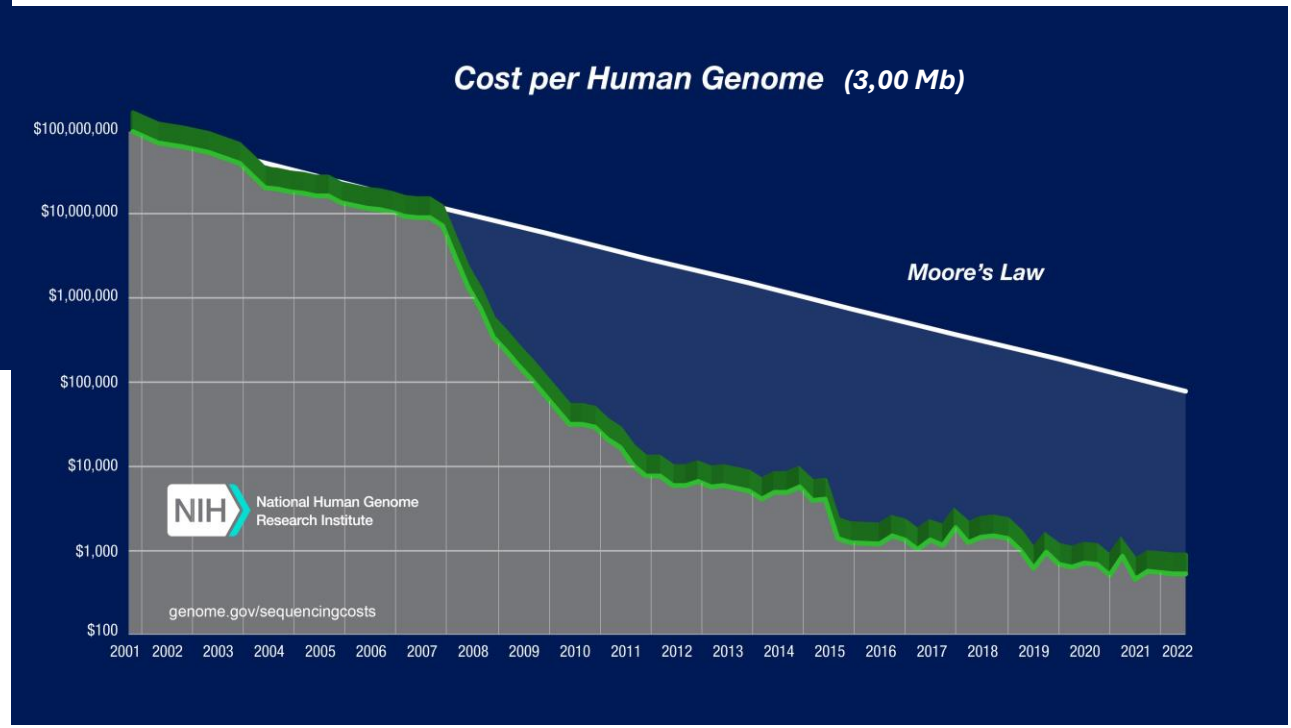


DNA Sequencing Technologies and costs over time

«From analogic to digital»



Moore's Law, describes a long-term trend in the computer hardware industry that involves the doubling of 'compute power' every two years. Technology improvements that 'keep up' with Moore's Law are widely regarded to be doing exceedingly well.

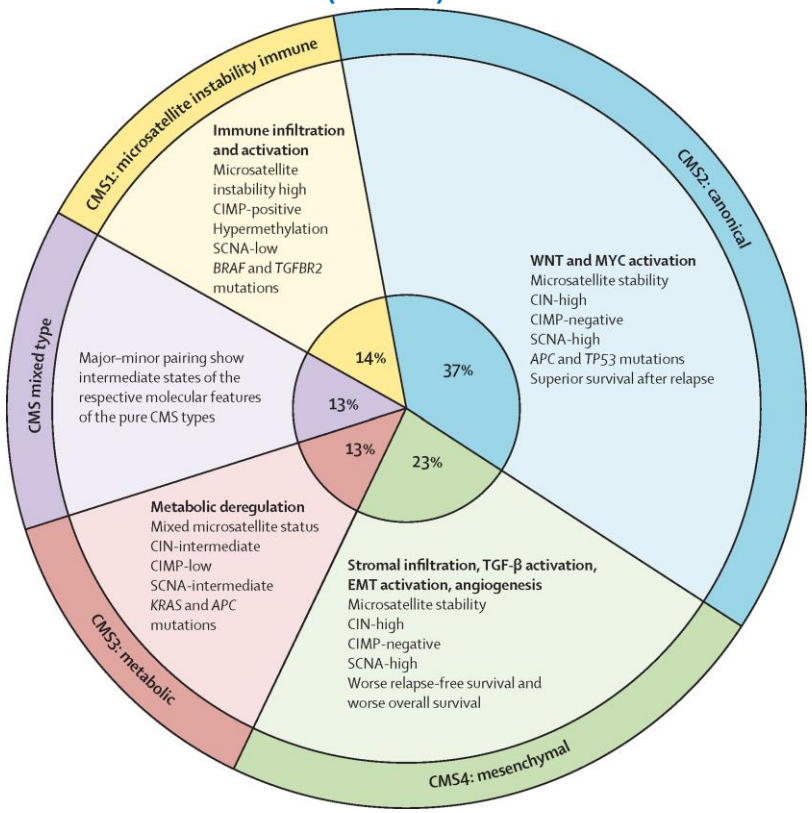


2001 - 2007: first generation – Sanger
Since 2008: second generation or «next» NGS

National Human Genome Research Institute (NHGRI)
Costs by 2022

CRC: molecular world and screening universe. Competition or communication?

Consensus Molecular Subtypes (CMS)



Lancet, 2024

Table 2. Recommended Noninvasive Colorectal Cancer Screening Test Characteristics

	Sensitivity, % (95% CI)		Specificity, % (95% CI)	
Test accuracy	CRC	AA	CRC	AA
FIT[16]				
≤10 μg/g	80 (76–83)	31 (27–35)	91 (89–93)	NR
>10 to ≤20 μg/g	69 (63–75)	21 (18–25)	94 (93–96)	NR
>20 to ≤30 μg/g	73 (62–81)	18 (13–23)	96 (95–97)	NR
FIT[17]				
10 μg/g	91 (84–95)	40 (33–47)	90 (86–93)	90 (87–93)
20 μg/g	75 (61–86)	25 (20–31)	95 (92–96)	95 (93–96)
Pivotal trial[18]				
FIT (20 μg/g)	74 (61–84)	24 (21–27)	95 (94–95)	NR
MTsDNA	92 (83–97)	42 (39–46)	87 (86–87)	NR
Septin 9[22]	48 (32–64)	11 (7–16)	91.5 (90–93)	NR

NR, not recommended.

Gastroenterology, 2022

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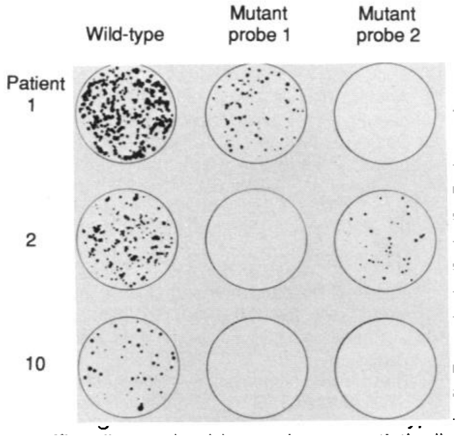
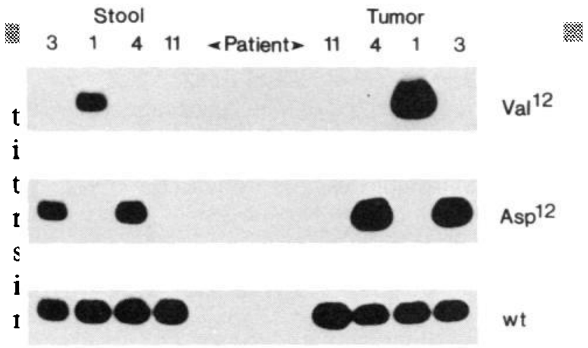
(Early) diagnosis: the beginning of the "molecular competition"

Proof of concept

12. S. A. Karl, B. W. Bowen, J. C. Avise, *Genetics*, in press.
13. Locations and sample sizes for American oysters in the present study are as follows: MA, Woods Hole, MA (*n* = 35); SC, Charleston, SC (23); GA, Cumberland Island, GA (33); FL1, New Smyrna Beach, FL (30); FL2, Stuart, FL (29); FL3, Port Charlotte, FL (29); FL4, Panacea, FL (39); FL5, Carabelle River, FL (18); and LA, Grand Isle, LA (41). Living oysters were collected and placed on wet ice for transportation to the laboratory. Total cell DNA was extracted from mantle-gonad tissue by homogenizing in 50 mM tris-HCl (pH 8.0), 100 mM EDTA, and 100 mM NaCl followed by one cycle of phenol, phenol-chloroform, and chloroform extraction. RNA was removed by ribonuclease A digestion for 3 hours followed by a repeat of the organic extractions described above. We precipitated DNA by adjusting the aqueous fraction to a final concentration of 300 mM sodium acetate and 70% ethanol; it was then vacuum-dried and resuspended in 1 × TE (10 mM tris-HCl, pH 8.0, 1

terns were visualized with shortwave ultraviolet light. Polymorphisms were indicated by the gain or loss of fragments in the restriction profiles.
16. To eliminate the possibility that our nuclear loci mistakenly may have represented mtDNA polymorphisms, we probed a Southern (DNA) blot of the amplified scnDNA products with purified oyster mtDNA. No bands appeared in the autoradiogram except in control lanes. The hypothesis of mtDNA contamination is further discounted by the nature of the scnDNA polymorphisms themselves, which involved diploid genotypes with general conformance to Hardy-Weinberg expected genotypic frequencies. This result further supports the idea that the loci are inherited in a Mendelian fashion. In addition, all pairwise comparisons of the four loci show insignificant deviations from gametic equilibrium [B. S. Weir and C. C. Cockerham, in *Mathematical Evolutionary Theory*, M. E. Feldman, Ed. (Princeton Univ. Press, Princeton, NJ, 1989), pp. 86–110].
17. D. W. Garton, R. K. Koehn, T. M. Scott, *Genetics*





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tract. Furthermore, it contains numerous degradative enzymes derived from cells, food, and bacteria. It was therefore unclear whether mutant genes from tumor cells could survive in this hostile environment and be detectable in clinical specimens.

To investigate this possibility, we examined stools from individuals with CR tumors for mutations of K-*ras* at codons 12 or 13, which occur commonly in these neoplasms (*8–12*). We first analyzed tumors from 24 patients for the presence of K-*ras* gene mu-

most reproducible procedure was used (*18*). Approximately 100 mg of stool frozen at −80°C was diluted with 300 μl of lysis buffer [500 mM tris, 16 mM EDTA, 10 mM NaCl (pH 9.0)], and particulates and most bacteria were removed by centrifugation. Proteins were digested with proteinase K and extracted with phenol and chloroform. After ethanol precipitation, the DNA was further purified by binding to glass beads. From 0.5 to 5.0 μg of DNA was typically obtained. The first exon of K-*ras* was then

Detection rate: 8/9 *RAS* mutated, 88.9%
0 false positive

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Fecal DNA versus Fecal Occult Blood for CRC Screening in an average risk population

Table 2. Most Advanced Finding at Colonoscopy and Results of the Fecal DNA Panel and Occult-Blood Test in the Analyzed Subgroup.*

Most Advanced Finding at Colonoscopy	Group That Could Be Evaluated (N=4404)	Analyzed Subgroup (N=2507)†	Positive Fecal DNA Panel		Positive Occult-Blood Test	
	no.		*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Adenocarcinoma	31	31	16/31	51.6 (34.8–68.0)	4/31	12.9 (5.1–28.9)
TNM stage I	15	15	8/15	53.3 (30.1–75.2)	1/15	6.7 (1.2–29.8)
TNM stage II	8	8	5/8	62.5 (30.6–86.3)	2/8	25.0 (7.1–59.1)
TNM stage III	8	8	3/8	37.5 (13.7–69.4)	1/8	12.5 (2.2–47.1)
TNM stage IV	0	0	0		0	
Adenocarcinoma + high-grade dysplasia	72	71	29/71	40.8 (30.2–52.5)	10/71	14.1 (7.8–24.6)
Advanced adenoma	426	403	61/403	15.1 (12.0–19.0)	43/403	10.7 (8.0–14.1)
High-grade dysplasia	41	40	13/40	32.5 (20.1–48.0)	6/40	15.0 (7.1–29.1)
Villous adenoma	139	133	24/133	18.0 (12.4–25.4)	13/133	9.8 (5.8–16.0)
Tubular adenoma ≥1 cm	230	214	23/214	10.7 (7.3–15.6)	22/214	10.3 (6.9–15.1)
Unspecified	16	16	1/16	6.2 (1.1–28.3)	2/16	12.5 (3.5–36.0)
Minor polyps‡	1627	648	49/648	7.6 (5.8–9.9)	31/648	4.8 (3.4–6.7)
Tubular adenoma <1 cm	762	286	23/286	8.0 (5.9–12.7)	15/286	5.2 (3.5–9.2)
Hyperplastic	633	276	17/276	6.2 (3.9–9.6)	10/276	3.6 (2.0–6.5)
Unspecified	232	86	9/86	10.5 (5.6–18.7)	4/86	4.6 (1.8–11.4)
No polyps on colonoscopy§	2318	1423	79/1423	5.6 (4.5–6.9)⇨94.6	68/1423	4.8 (3.9–5.8)⇨95.2

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Imperiale TF, *NEJM*, 2004

Fecal DNA versus Fecal Occult Blood for Colorectal-Cancer Screening in an average risk population

Table 3. Most Advanced Finding at Colonoscopy and Positivity of Individual Fecal DNA Tests.

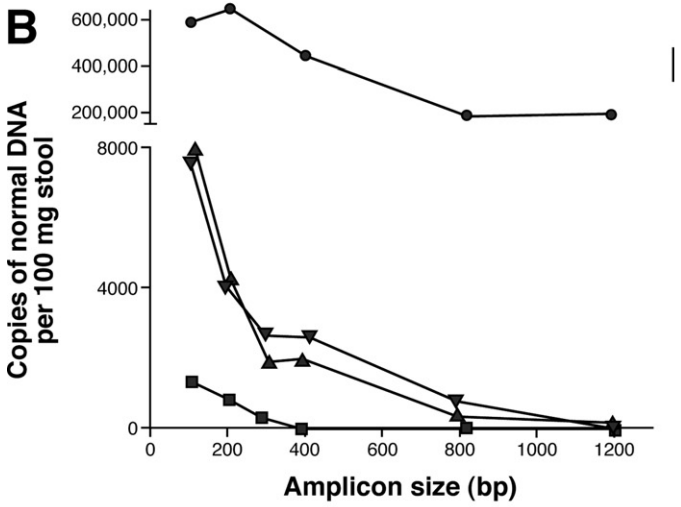
Most Advanced Finding at Colonoscopy	Total No.	Positive Fecal DNA					
		Overall	K-*ras*	*p53*	*APC*	BAT-26*	Long DNA†
		number (percent)					
Adenocarcinoma	31	16 (51.6)	5 (16.1)	8 (25.8)	9 (29.0)	2 (6.5)	1 (3.2)
Advanced adenoma	403	61 (15.1)	18 (4.5)	11 (2.7)	27 (6.7)	5 (1.2)	8 (2.0)
High-grade dysplasia	40	13 (32.5)	5 (12.5)	2 (5.0)	3 (7.5)	0	5 (12.5)
Other	363	48 (13.2)	13 (3.6)	9 (2.5)	24 (6.6)	5 (1.4)	3 (0.6)
Minor polyps	648	49 (7.6)	19 (2.9)	5 (0.8)	16 (2.5)	4 (0.6)	8 (1.2)
No polyps on colonoscopy	1423	79 (5.6)	22 (1.5)	16 (1.1)	11 (0.8)	16 (1.1)	18 (1.3)

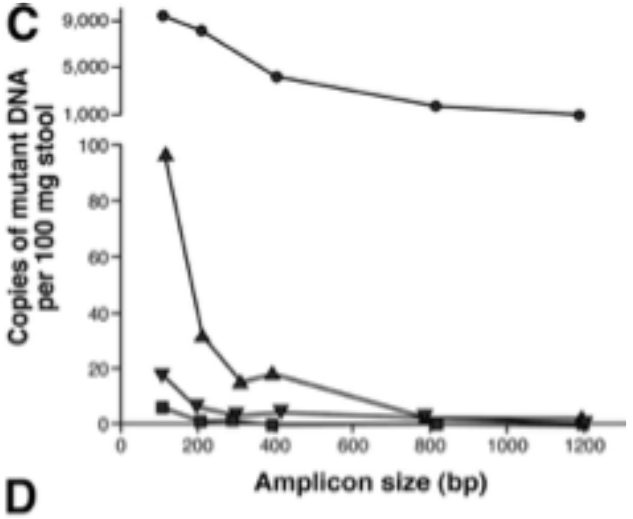
* BAT-26 is a microsatellite-instability marker.
† A marker of long DNA is thought to reflect disordered apoptosis of cancer cells sloughed into the colonic lumen.

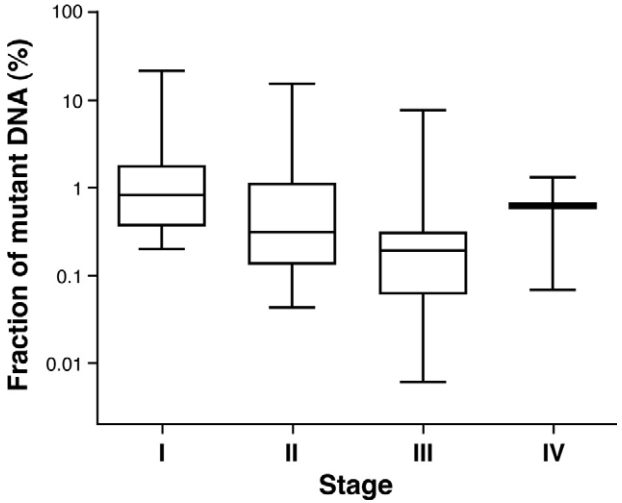
Imperiale TF, *NEJM*, 2004

Analysis of mutations in DNA isolated from plasma and stool of CRC patients

Paired specimens	Number	Positive	Yield
Stool	25	23	92%
Plasma	16	8	50%







Dihel F, *Gastroenterology*, 2008

Next-Generation stool DNA test accurately detects CRC and large adenomas

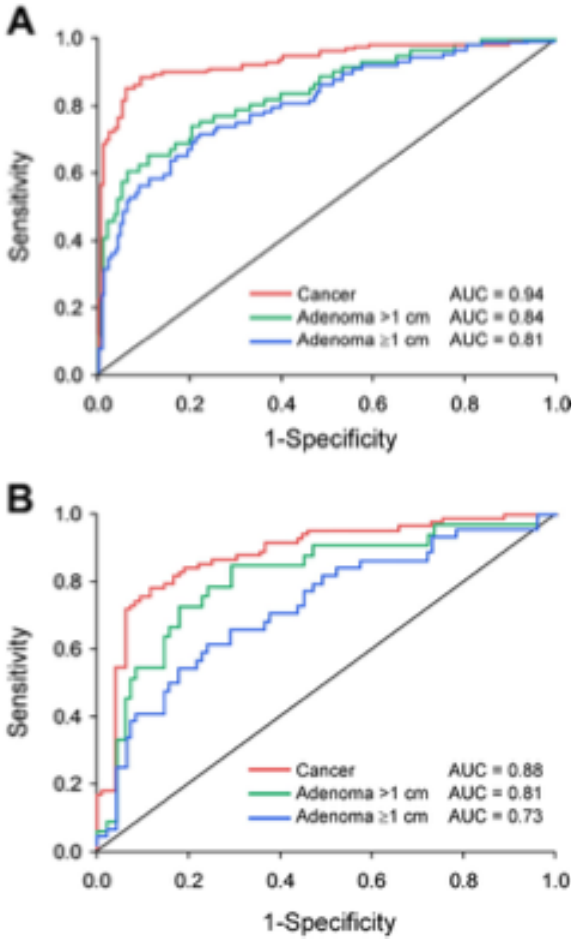
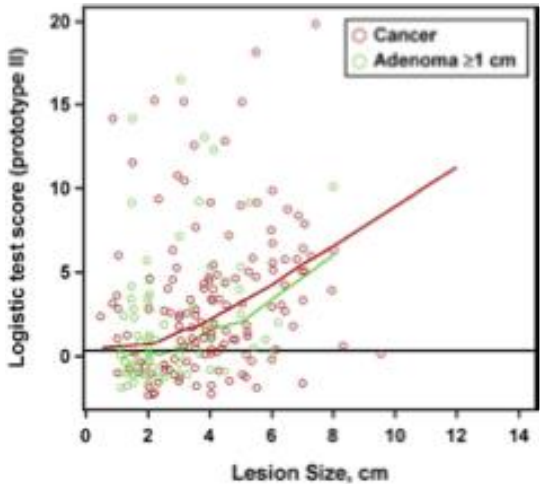


Table 2. Neoplasm Detection Rates by a Next-Generation Stool DNA Test[a]

	Sensitivity, % (95% CI)	Observed specificity, % (95% CI)
Training set		
Cancer	89 (83–93)	90 (85–94)
Adenoma		
Size >1 cm	62 (49–74)	90 (85–94)
Size ≥1 cm	56 (45–67)	90 (85–94)
Test set		
Cancer	78 (68–86)	85 (77–92)
Adenoma		
Size >1 cm	64 (45–80)	85 (77–92)
Size ≥1 cm	48 (31–66)	85 (77–92)
Combined		
Cancer	85 (80–89)	89 (85–92)
Adenoma		
Size >1 cm	63 (52–73)	89 (85–92)
Size ≥1 cm	53 (45–62)	89 (85–92)



Investigation

- 52 CRC
- 133 advanced adenoma
- 293 ctrls

Random assignemnt

- 2/3 trainin set
- 1/3 test set

sDNA test detects

- 4 methylated genes*
- mutant *KRAS**
- also quantifies hemoglobin

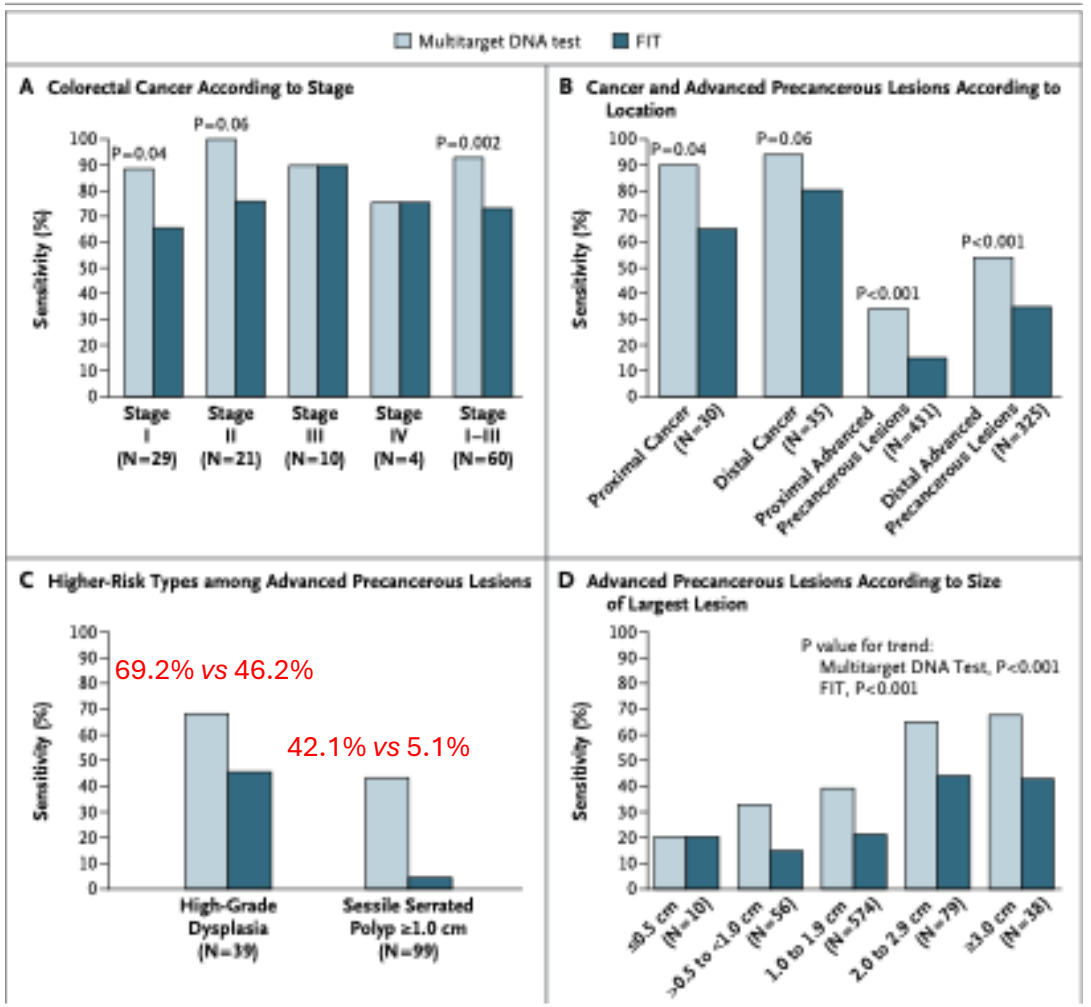
*by quantitative, allele-specific, real-time target and signal amplification

Ahlqist, *Gastroenterology*, 2012

Multitarget stool DNA testing for CRC screening

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)
	no.	no.	%	no.	%
Colorectal cancer					
Any	65	60	92.3 (83.0–97.5)	48	73.8 (61.5–84.0)
Stage I to III[a]	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)



Imperiale TF, *NEJM*, 2014

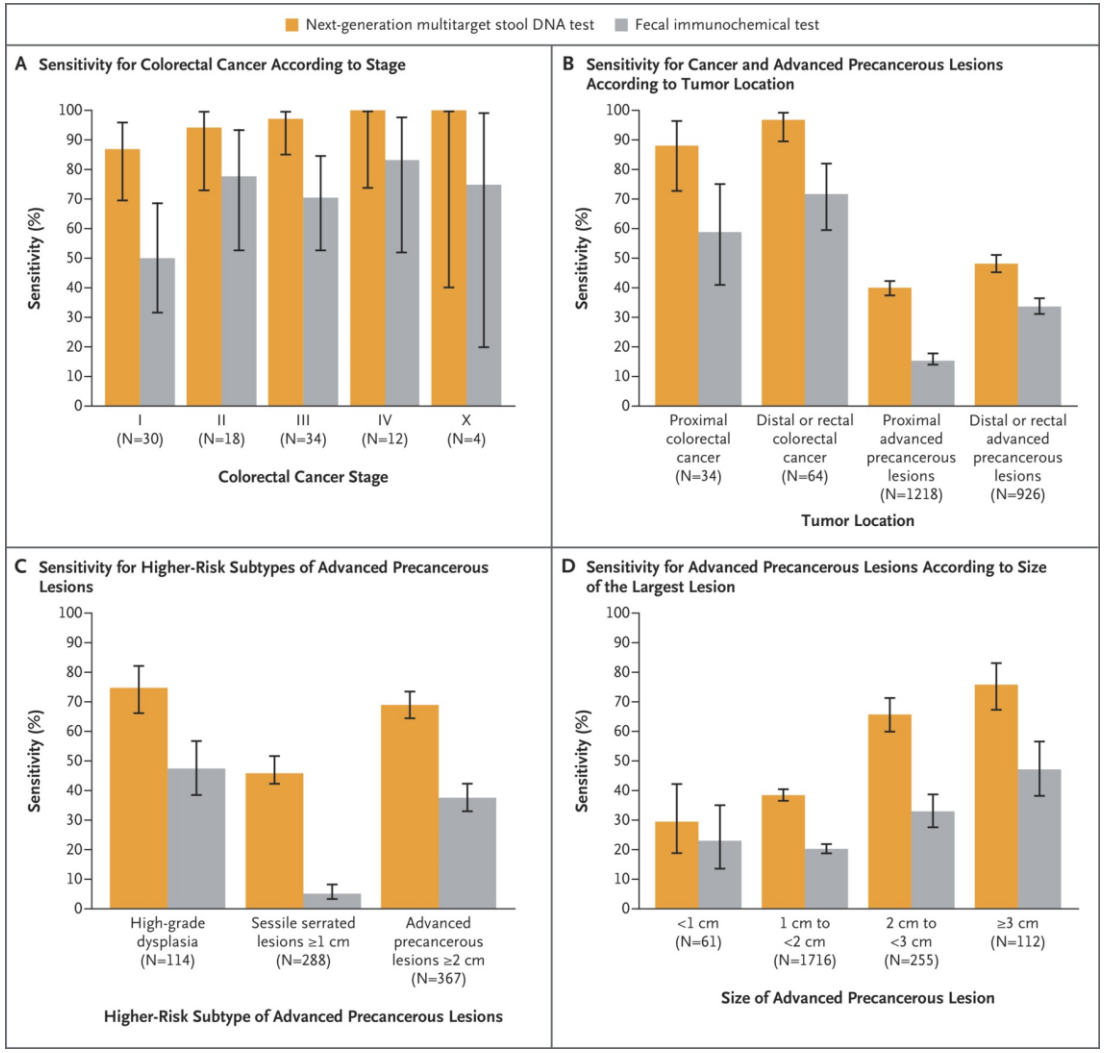
Sensitivity and specificity of the next-generation multitarget stool DNA test and the commercial FIT

Table 1. Sensitivity and Specificity of the Next-Generation Multitarget Stool DNA Test and the Commercial FIT.*

Variable	Colonoscopy (N=20,176)	Next-Generation Multitarget Stool DNA Test (N=20,176)		FIT (N=20,176)	
	No. of Participants	No. of Results	Assessment (95% CI)	No. of Results	Assessment (95% CI)
			%		%
Sensitivity					
Colorectal cancer					
Any	98	92	93.9 (87.1–97.7)†	66	67.3 (57.1–76.5)
Stage I, II, or III‡	82	76	92.7 (84.8–97.3)	53	64.6 (53.3–74.9)
Advanced precancerous lesions	2,144	931	43.4 (41.3–45.6)†	500	23.3 (21.5–25.2)
High-grade dysplasia	114	85	74.6 (65.6–82.3)	54	47.4 (37.9–56.9)
Specificity					
Advanced neoplasia§	17,934	16,245	90.6 (90.1–91.0)	16,997	94.8 (94.4–95.1)¶
Nonneoplastic findings or negative colonoscopy‖	10,961	10,156	92.7 (92.2–93.1)	10,492	95.7 (95.3–96.1)
Negative colonoscopy**	7,510	7,012	93.4 (92.8–93.9)	7,207	96.0 (95.5–96.4)

Primary aim: improve specificity.

- It appears unlikely that adding "test on test" would ⇧ specificity
- More likely adding molecular markers to FIT would ⇧ sensitivity



The NEW ENGLAND JOURNAL of MEDICINE

Imperiale TF, 2004

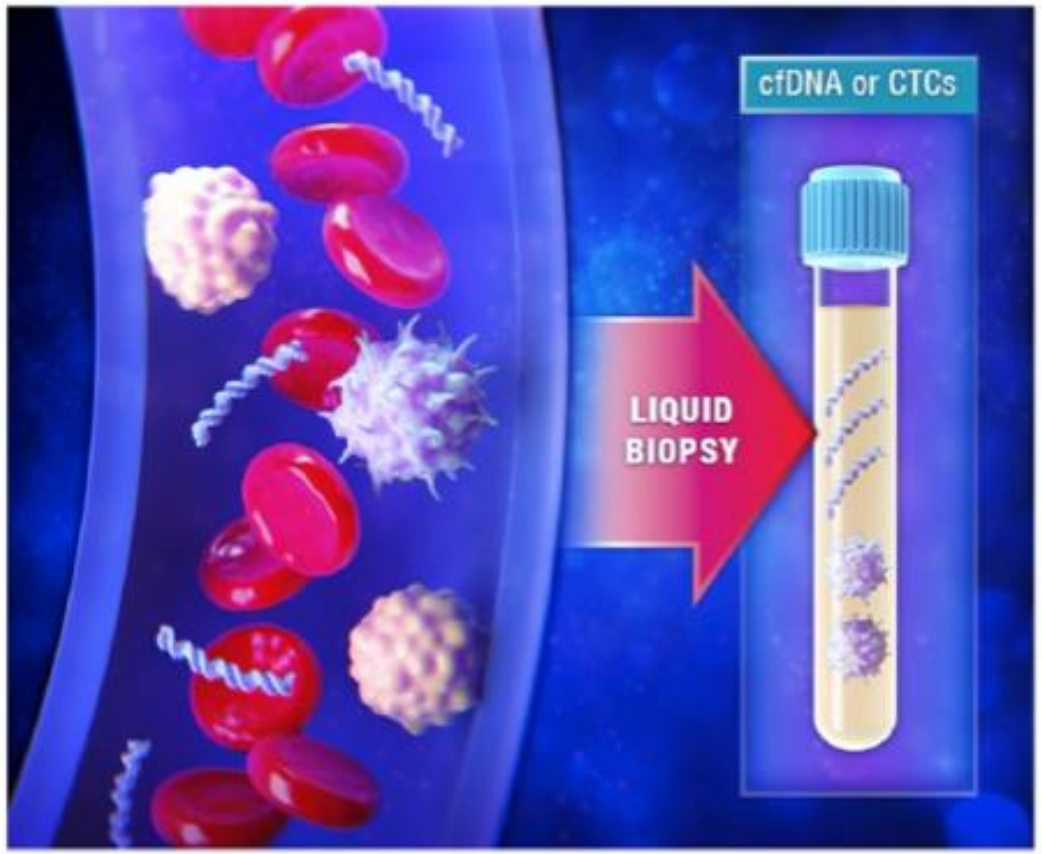
Commentaries to the papers by Imperiale

- Adaption of the cutoff value to yield specificity similar to that reported for the MTs DNA test by Imperiale et al. (86.6%) resulted in very similar sensitivities for both tests (i.e., 86.7%) Brenner H, *NEJM, 2014*
- A commercial FIT can achieve similar diagnostic results to the newer stool DNA test. Lowering the positivity threshold of a high-quality FIT may be a much more economical way to increase sensitivity. Seum T, *JAMA Int Med*, 2024

		Study		
		BLUE-C[a]	BLITZ	
Metric	Outcome	NG-MSDT	FIT[c] (cutoff 11.7 µg/g)[d]	FIT[c] (cutoff 10 µg/g)[d]
Sensitivity (95% CI)	CRC, any stage	93.9 (87.1-97.7)	94.7 (85.4-98.9)	96.5 (87.9-99.6)
	CRC, stage I-III	92.7 (84.8-97.3)	93.8 (82.8-98.7)	95.8 (85.7-99.5)
	Advanced precancerous lesion	43.4 (41.3-45.6)	38.3 (34.8-41.9)	41.5 (38.0-45.1)
	Any advanced neoplasm	45.6 (43.6-47.7)	42.3 (38.9-45.8)	45.4 (41.9-48.9)
Specificity (95% CI)	No advanced neoplasm	90.6 (90.1-91.0)	90.6 (89.8-91.3)	89.0 (88.2-89.8)

Sceanarios driving liquid biopsy development

Exploiting liquid biopsy in clinical practice



The Claims

DIAGNOSIS:
Genotyping cfDNA in the blood to determine the tumor profile

RESPONSE AND FOLLOW UP:
Analysis of cfDNA and CTC for real time monitoring of response to treatment

TUMOR EVOLUTION:
Emergence of molecular alterations associated with resistance to therapy

MINIMAL RESIDUAL DISEASE:
The presence of cfDNA or CTC in the circulation indicates that the disease is still present

Disease Monitoring

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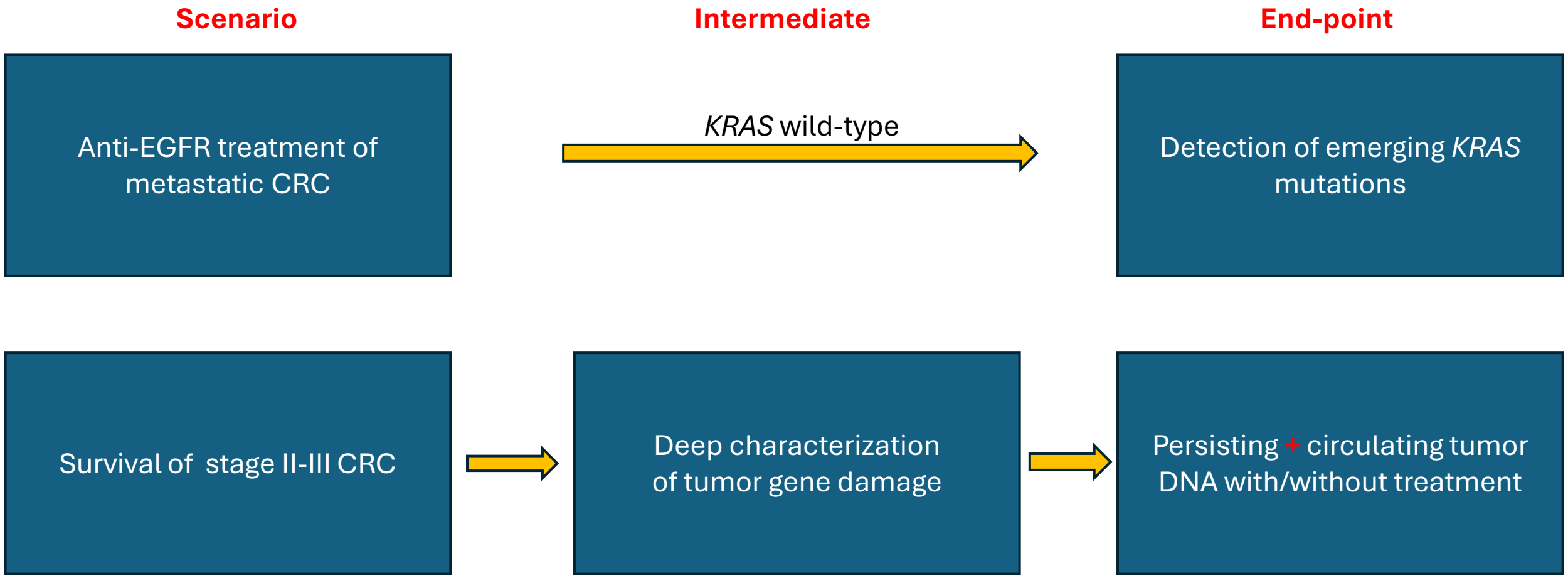
Rationales for liquid biopsies in driving or monitoring treatments



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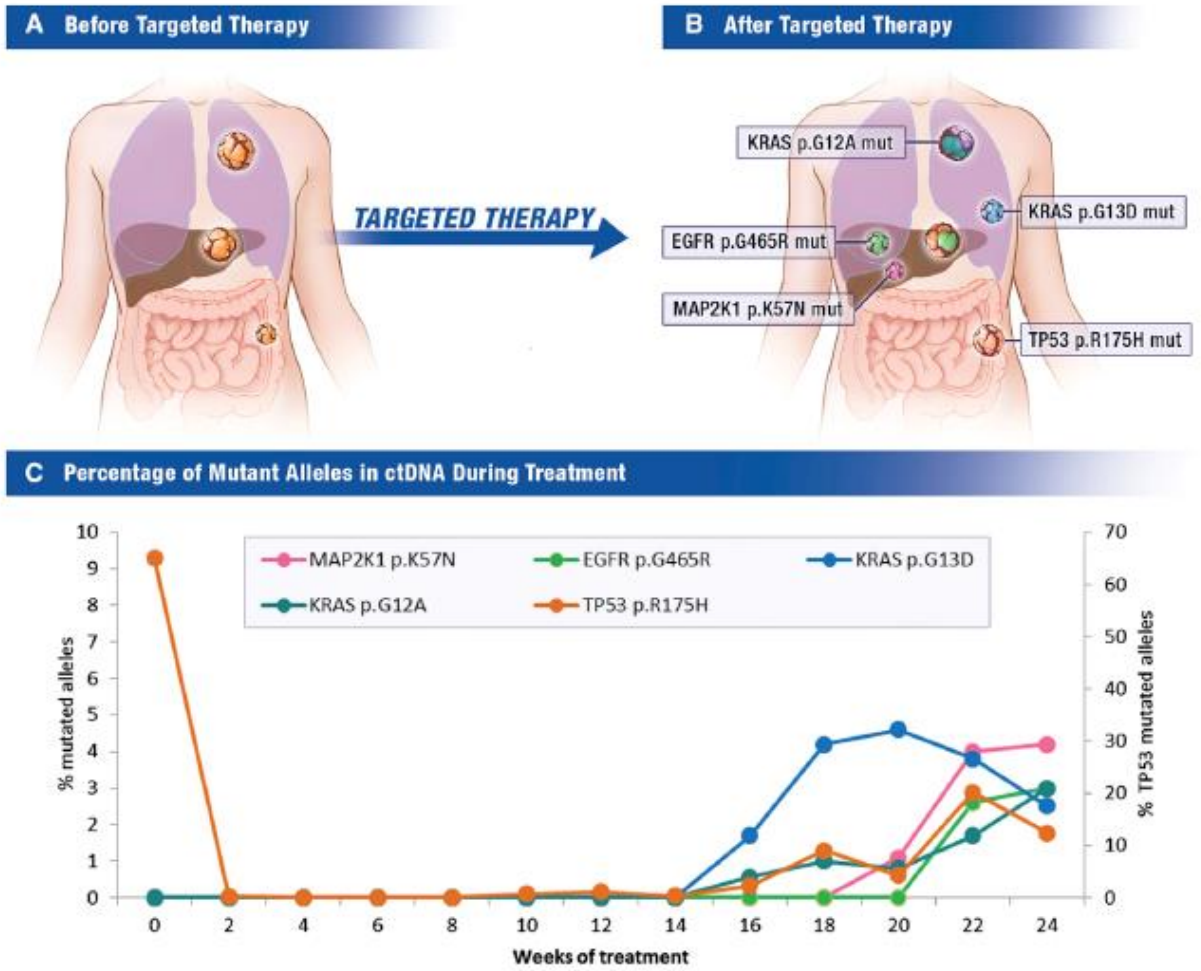
Emergence/selection of mutant alleles during pharmacological treatment



Bardelli A, *Cancer Cell*, 2017

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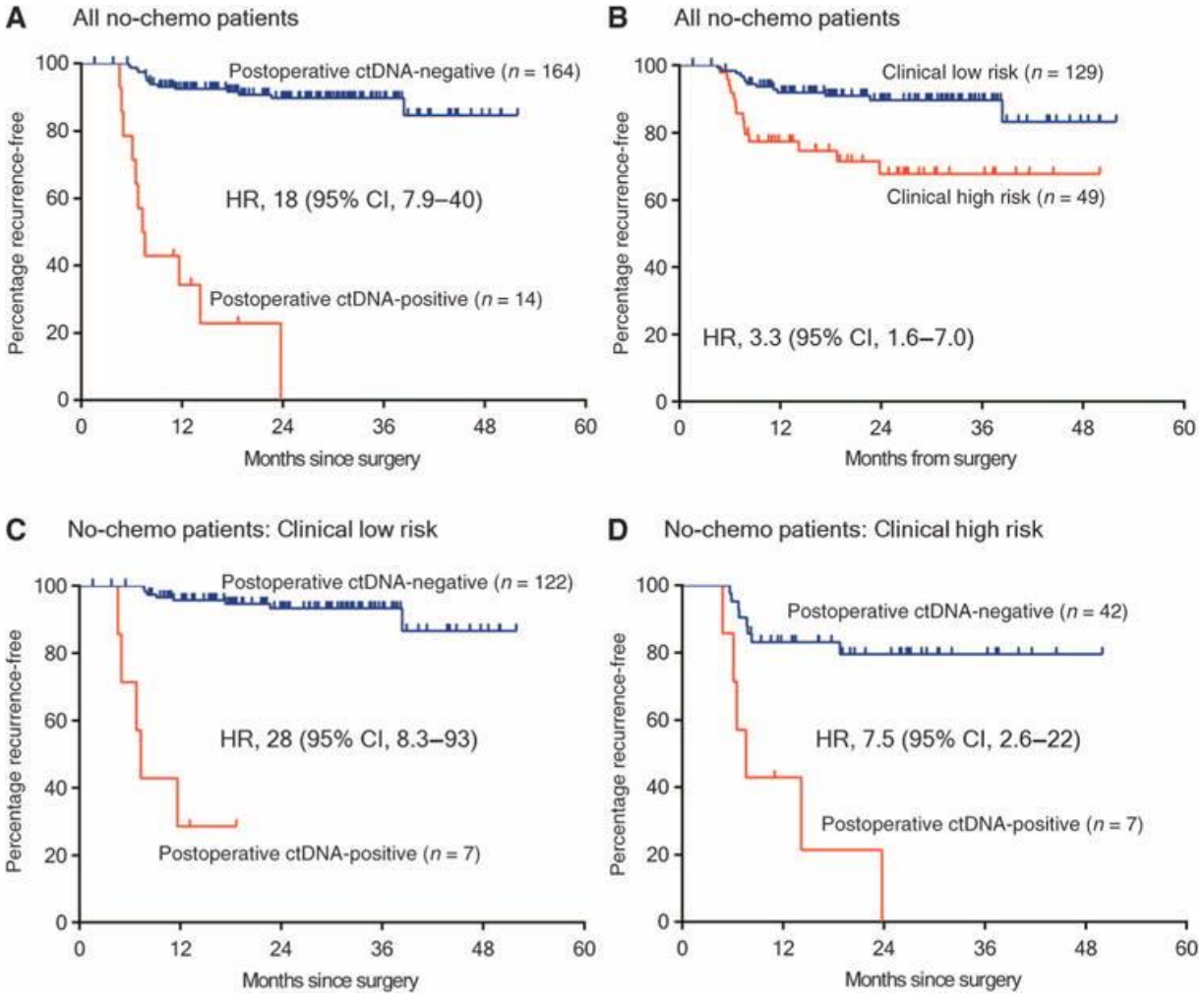
Liquid biopsy and and postoperative disease progression in stage II by circulating tumor DNA (ctDNA)



Total, 230 pts, no adjuvant therapy, 178

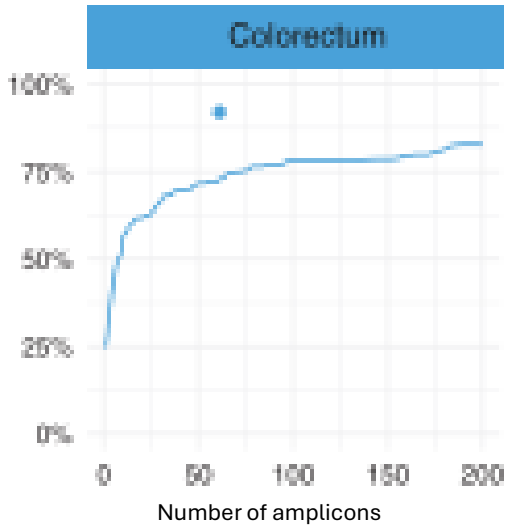
ctDNA +, 14 (7.9%) -> 11 (79%) recurred
ctDNA - , 164 (92.1%) -> 16 (9.8%) recurred

In patients treated with chemotherapy,
the presence of ctDNA was also associated
with an inferior recurrence-free survival
(HR, 11; 95% CI, 1.8 to 68; P = 0.001

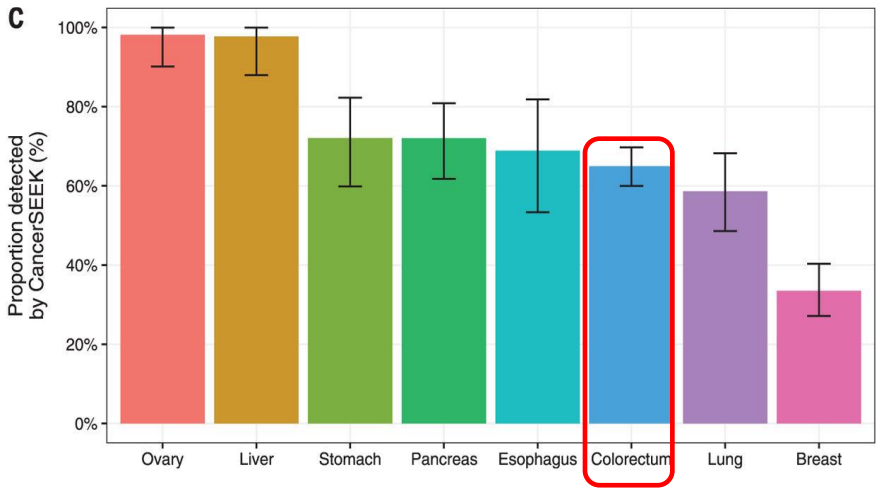
Tie J, *Sci Transl Med*, 2016

Detection and localization of surgically resectable cancers with a multi-analyte blood test (CancerSEEK)

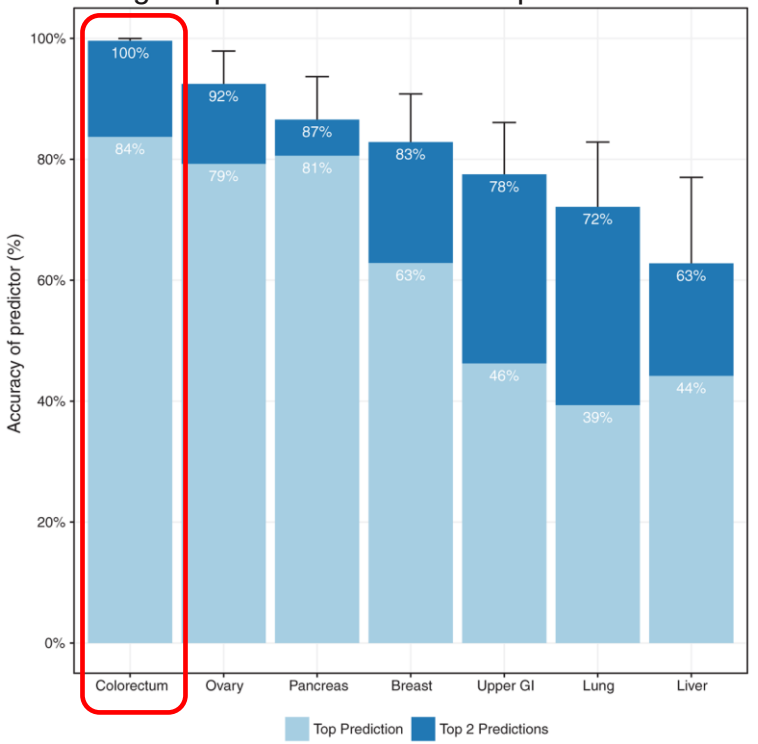
Ultradeep sequencing + protein biomarkers



Sensitivity of CancerSEEK by tumor type



Identification of cancer type by supervised machine learning for patients classified as positive.



Cohen JD, *Science, 2018*

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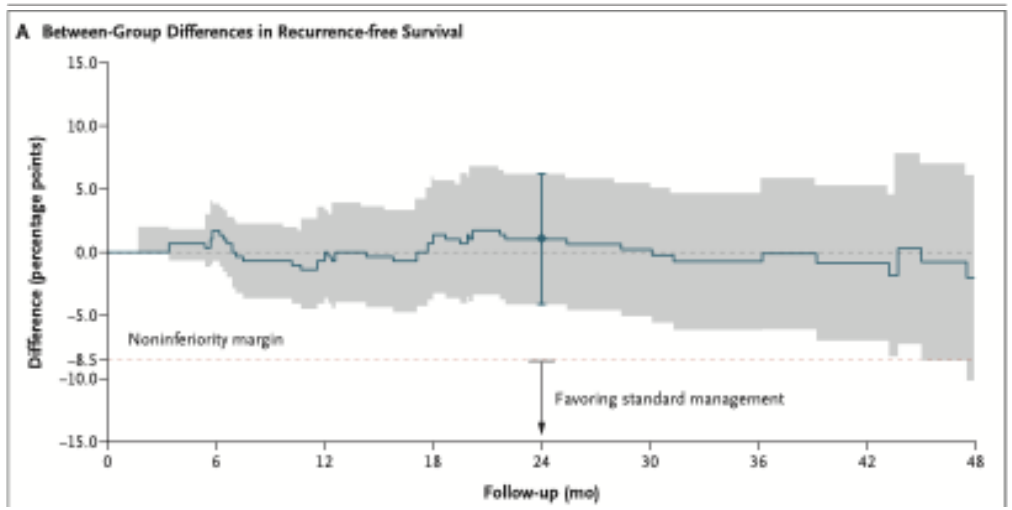
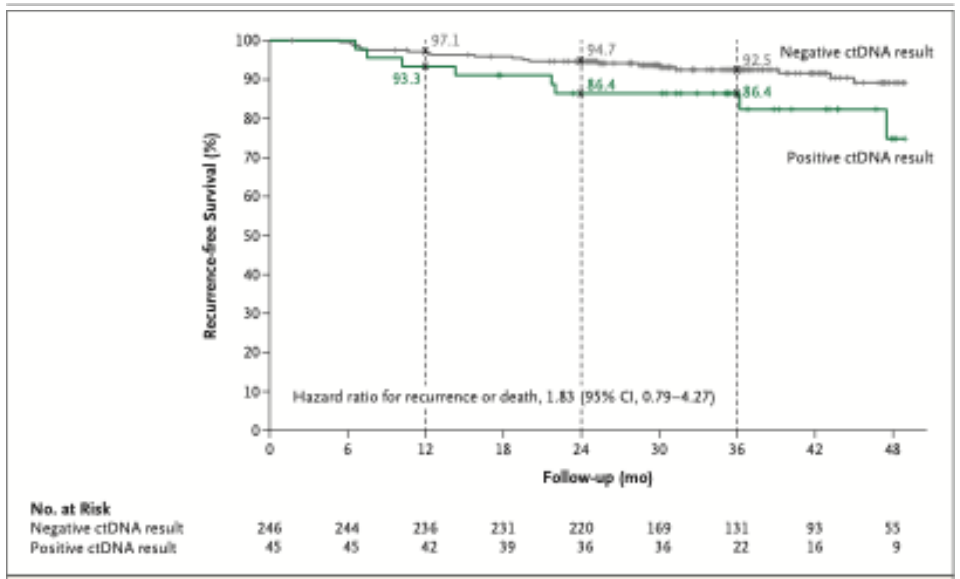
Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer





455 patients

302, ctDNA guided management
153, standard management

Chemo: 15% in ctDNA management
28% in standard
RR 1.82 (95%CI, 1.25-2.65)

3-year recurrence-free survival, 86.4% among ctDNA+ patients who received adjuvant chemotherapy and 92.5% among ctDNA-negative patients who did not.

Tie J, *NEJM*, 2022

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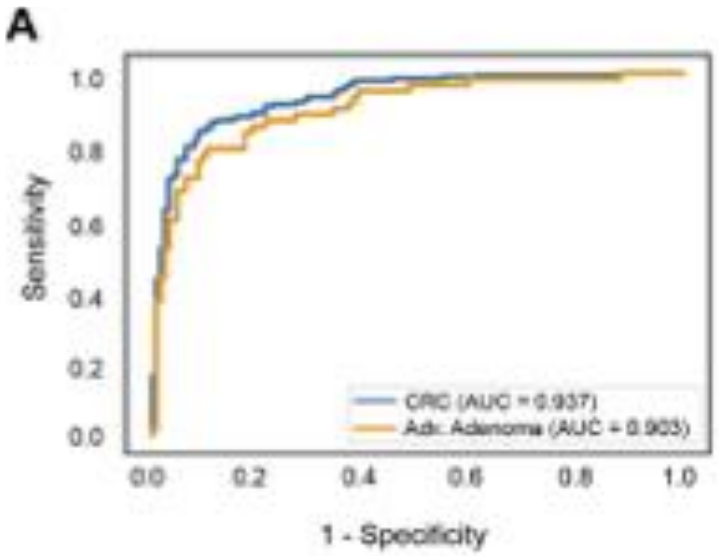
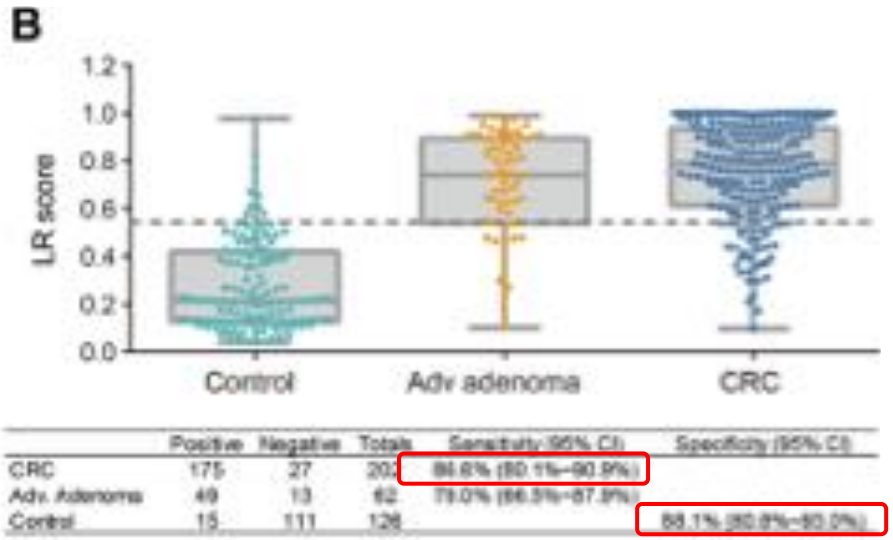
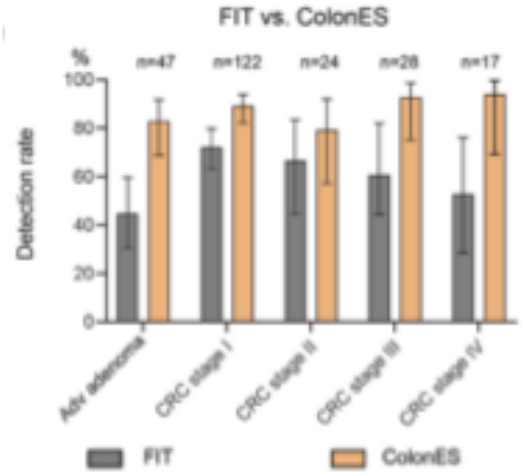
Early detection and prognosis prediction for CRCby circulating tumour DNA methylation haplotypes: a multicentre cohort study

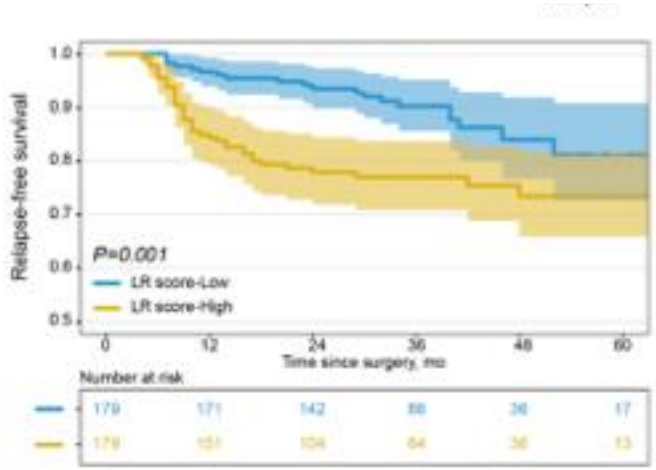


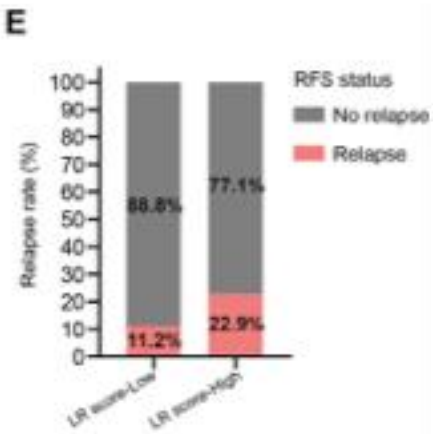


590 CRC patients
182 advanced adenoma patients
366 healthy controls



& prognostication⇨





Mo, *Lancet, 2023*

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A Cell-free DNA Blood-Based Test for CRC Screening

Table 2. Sensitivity and Specificity of the Cell-free DNA (cfDNA) Blood-Based Test for the Most Advanced Findings on Colonoscopy.*

Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	*no.*	%
Colorectal cancer			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
			Specificity (95% CI)
Nonadvanced adenomas, nonneoplastic findings, and negative colonoscopy	6680	698	89.6 (88.8–90.3)
Nonneoplastic findings and negative colonoscopy	4514	457	89.9 (89.0–90.7)

* Excluded were 10 stage IV and 7 pathologically confirmed, incompletely staged colorectal cancers.
† Advanced precancerous lesions include advanced adenomas and sessile serrated lesions at least 10 mm in the largest dimension.

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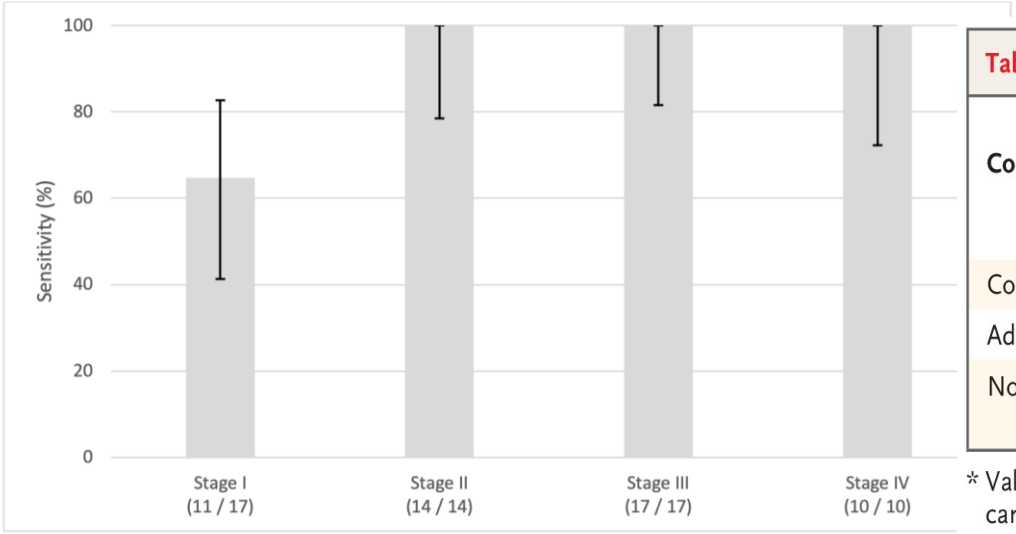
The NEW ENGLAND JOURNAL of MEDICINE

Chung DC, 2024

A Cell-free DNA Blood-Based Test for CRC Screening



Pathology confirmed, incompletely staged cancers not shown (N = 7)

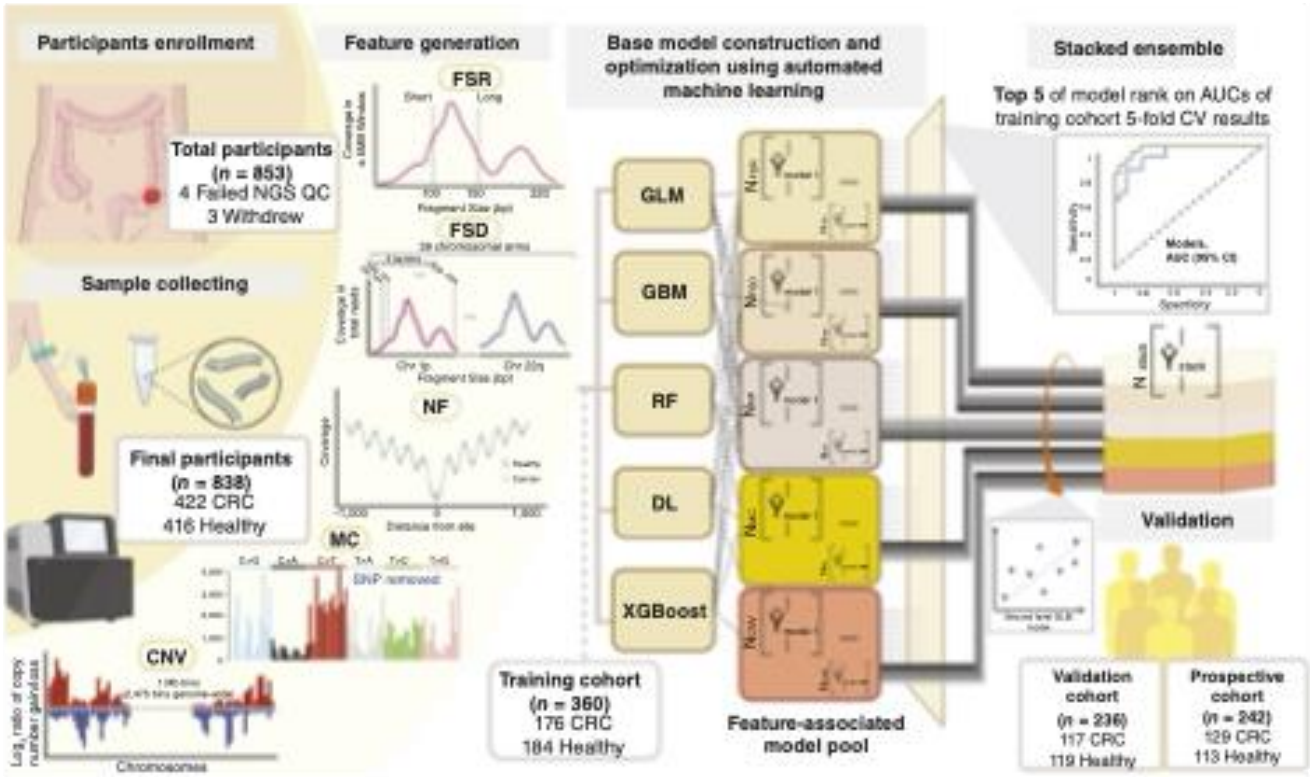
Table 3. Expected Diagnostic Yield in a Theoretical Screening Population of 100,000 Average-Risk Persons.*

Colonoscopy Finding	Persons with Finding	Positive cfDNA Blood-Based Test (N=11,049)		Negative cfDNA Blood-Based Test (N=88,951)	
	no.	*no.*	%	*no.*	%
Colorectal cancer	420	349	3.16	71	0.08
Advanced precancerous lesions	10,800	1423	12.88	9,377	10.54
Nonadvanced neoplasia or negative colonoscopy	88,780	9277	83.96	79,503	89.38

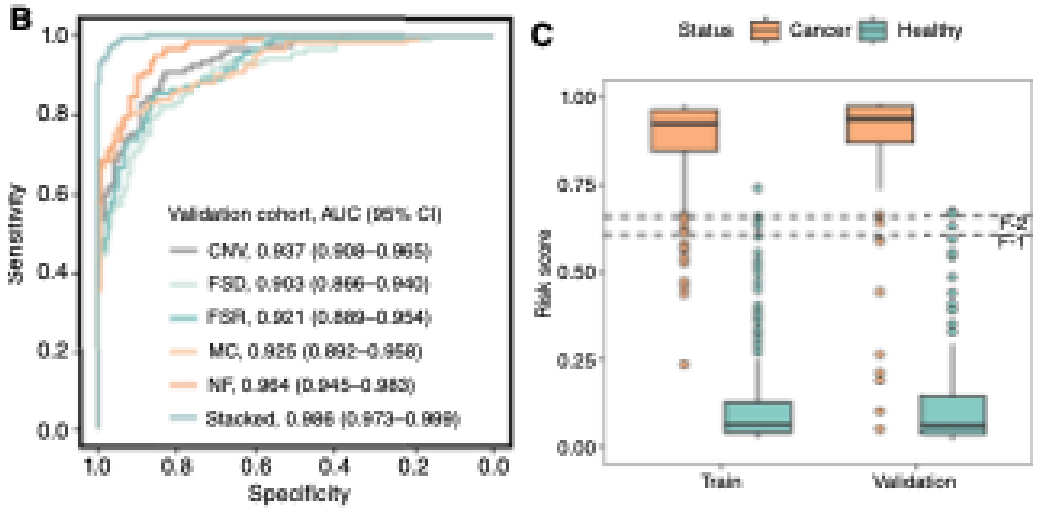
* Values were derived from study data extrapolated to a theoretical population of 100,000 patients with the observed prevalence of colorectal cancer of 0.42% and prevalence of advanced precancerous neoplasia of 10.84% in the ECLIPSE study.

Sensitivity : all stages, 89.7%. Stage I only, 64.7%

Multidimensional fragmentomics enables early and accurate detection of CRC



	Sensitivity	Specificity
Validation	95.8%	98.0%
Prospective	91.5%	95.6%



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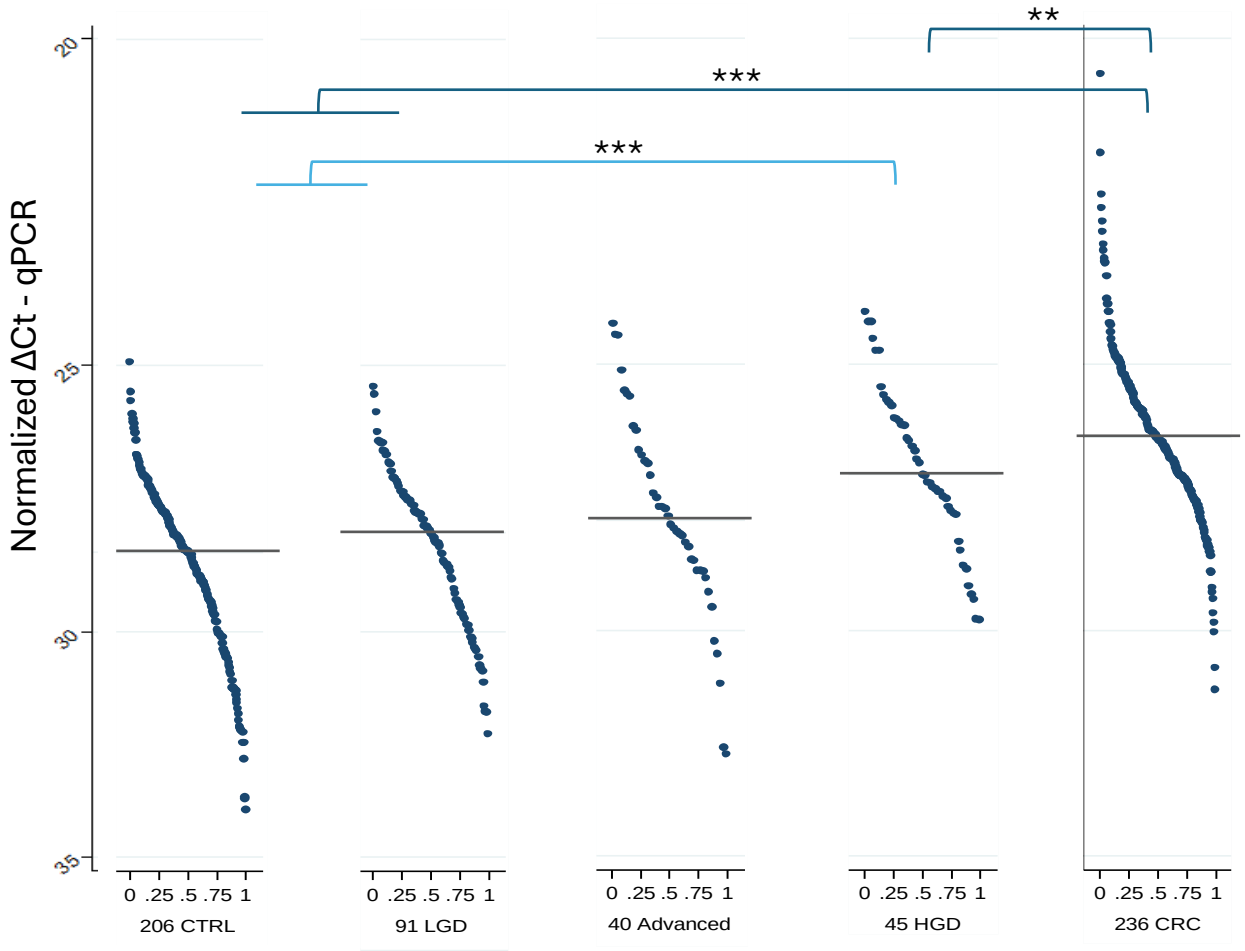
Cao, *Cancer Res, 2024*

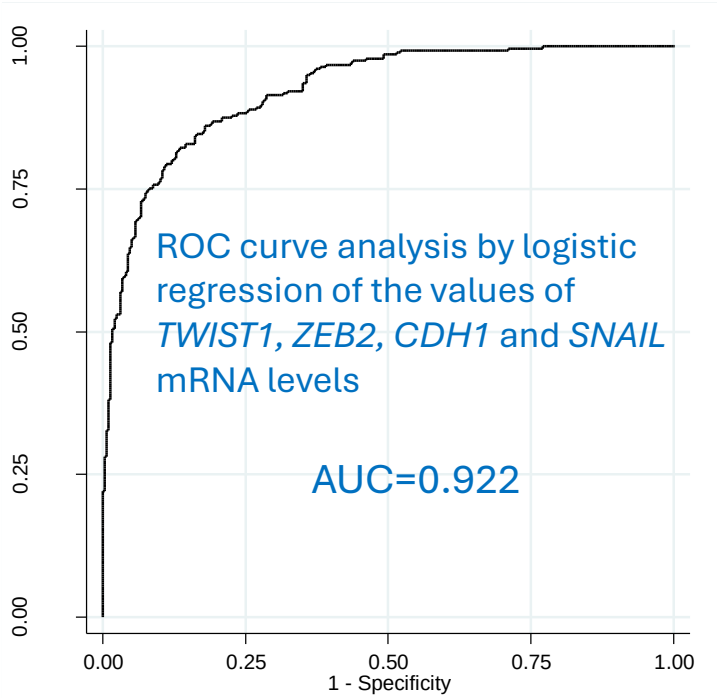
Ascertainment of CRC by a liquid biopsy assessing Epitelial to Mesenchymal Transition factors mRNA levels in blood

Levels of *TWIST1* mRNA in the blood, all patient classes *vs* controls



***, p-value<0.0001
**, p-value<0.05

—— = Median ΔCt



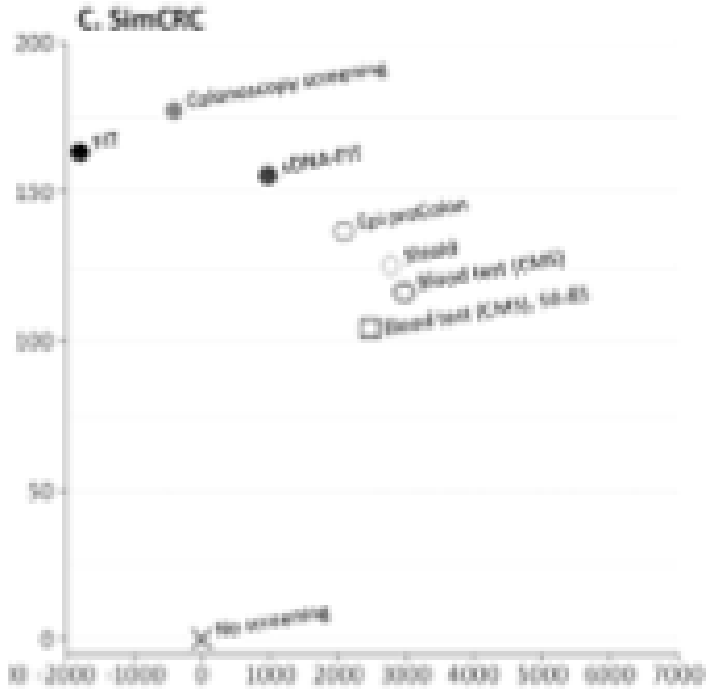
	Detection	Sens	Spec
CRC	205/236	86.9%	89.6%
HGD	28/45	62.2%	
AA	16/40	40.0%	

Greco L, *manuscript in preparation*

Effectiveness and Cost-Effectiveness of CRC Screening With a Blood Test That Meets the Centers for Medicare & Medicaid Services Coverage Decision

Table 1. Screening Test Characteristics Used in the Analysis

Screening test	1 – specificity	Sensitivity[a] by size of the most advanced lesion: Adenomas 1 to <6 mm	Adenomas 6 to <10 mm	Adenomas ≥10 mm	CRC	Source
FIT	0.036		0.076[b]	0.238[c]	0.738	15
sDNA-FIT	0.09		0.15[b]	0.42[c]	0.94	15
Blood test (CMS)	0.1	0.1[d]	0.1[d]	0.1[d]	0.74	9
Colonoscopy	0.1325[e]	0.69	0.81	0.91	0.91	16,17
Sensitivity analysis						
FIT	0.036		0.076[b]	0.238[c]	80%[f]	15,26
Blood test (Epi proColon)	0.196	0.2[d]	0.2[d]	0.204	0.702	22,23
Blood test (Shield)	0.1	0.1[d]	0.1[d]	0.13	0.83	24
Blood test (CMS)	0.1	0.1[d]	0.1[d]	0.1[d]	80%[f]	9,26



Net cost per 1,000 45 yr-olds

Even with higher screening uptake, triennial blood-based screening, with the CMS-specified minimum performance sensitivity of 74% and specificity of 90%, was not projected to be cost-effective compared with established strategies for CRC screening.

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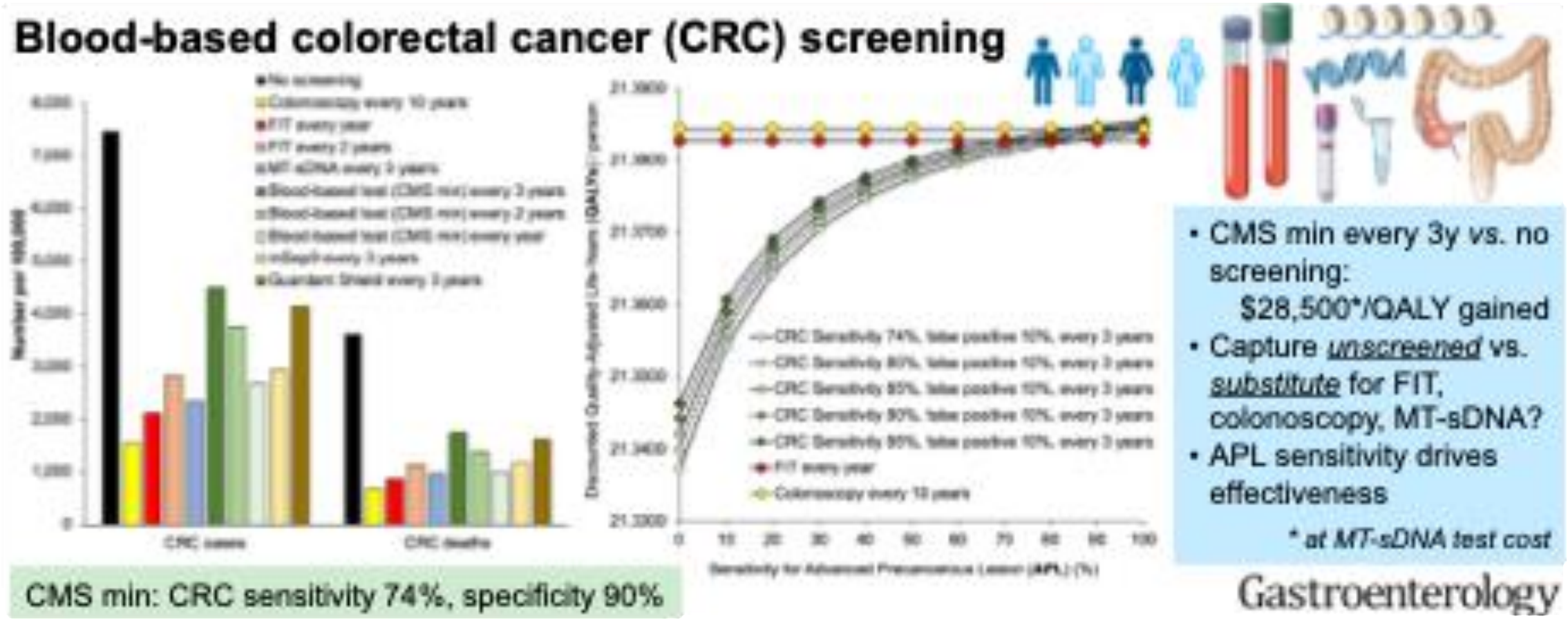
Van den Putelaar, *Gastroenterology*, 2024

Molecular competition as of now



Ladabaun U, *Gastroenterology*, 2024

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AGA commentary offers reality check on blood-based CRC screening

- A blood test for CRC that meets minimal CMS criteria for sensitivity and performed every three years would likely result in better outcomes than no screening.
- Because blood tests for CRC are predicted to be less effective and more costly than currently established screening programs, they cannot be recommended to replace established effective screening methods
- Potential benchmarks that industry might use to assess an effective blood test for CRC going forward would be sensitivity for stage I-III CRC of >90%, with sensitivity for advanced adenomas of > 40-50%.

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Diagnosis added to the clinical scenarios of CRC molecular genetics

Feasibility	Expectations
Molecular tests in the digital era allow CRC (early) detection in • blood • stool ➢ Yet, fingerprinting of precursor lesions=unsatisfactory	Translation from diagnosis to screening requires • specificity implementation • cost reduction • proper assessment of the timing of test administration (*interval cancers?*)

What are dreaming of ?