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## Novel stool and blood tests – CRC vs advanced adenoma detection

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# Overview

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- Technology and bioanalytes of emerging CRC screening tests
- Novel CRC screening tests
  - Stool based
  - Blood based
- Performance of these tests
- Future directions

# ctDNA and sDNA/sRNA test technology

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- sDNA based assay
  - methylated *LASS4, LRRC4, PPP2R5C, ZDHHC1*
  - fecal hemoglobin (ELISA)
- sRNA based assay
  - ACY1, AREG, CDH1, EGLN2, KRAS, SMAD4, TNFRSF10B*
  - FIT
  - smoking status
- ctDNA based assay
  - ctDNA: mutations, methylated DNA, chromatin fragments
  - ctDNA + proteins
- The ctDNA tests depend on AI informed patterns for CRC.

# Novel and Emerging CRC screening tests

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- ctDNA test (Shield test, Guardant Health)
- ctDNA and protein test (Freenome)
  
- MT-sRNA test (Colosense, Geneoscopy)
- MT-sDNA test (Cologuard, Exact Sciences)

# ctDNA CRC screening test (Shield test)

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

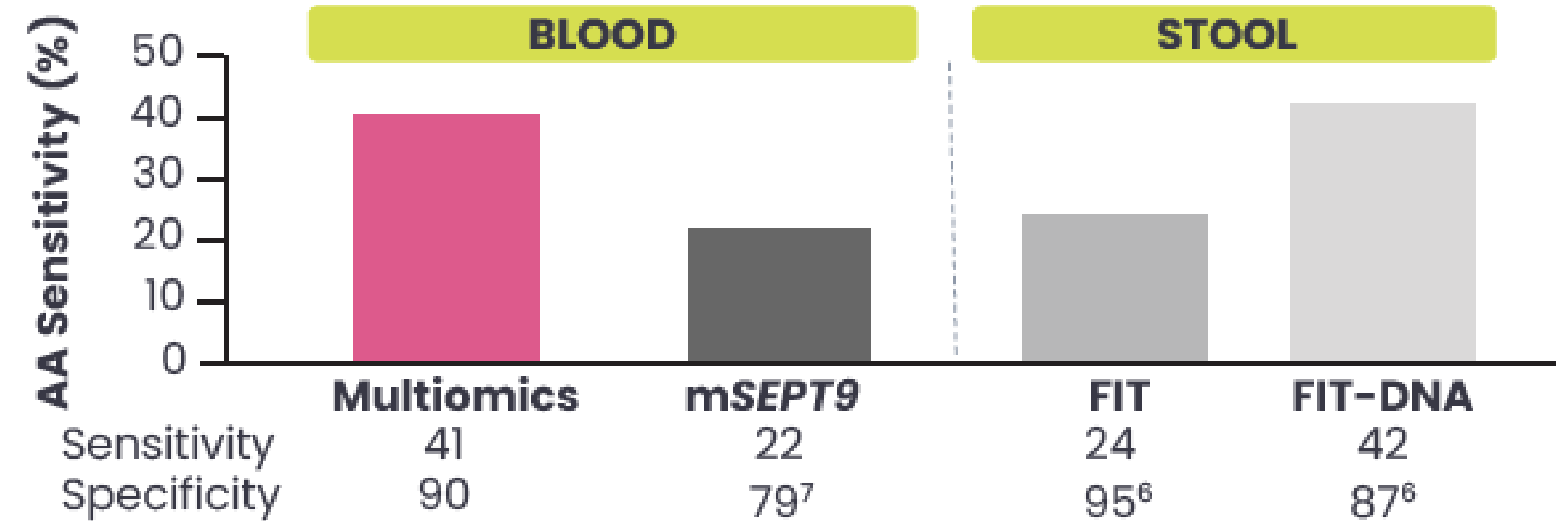
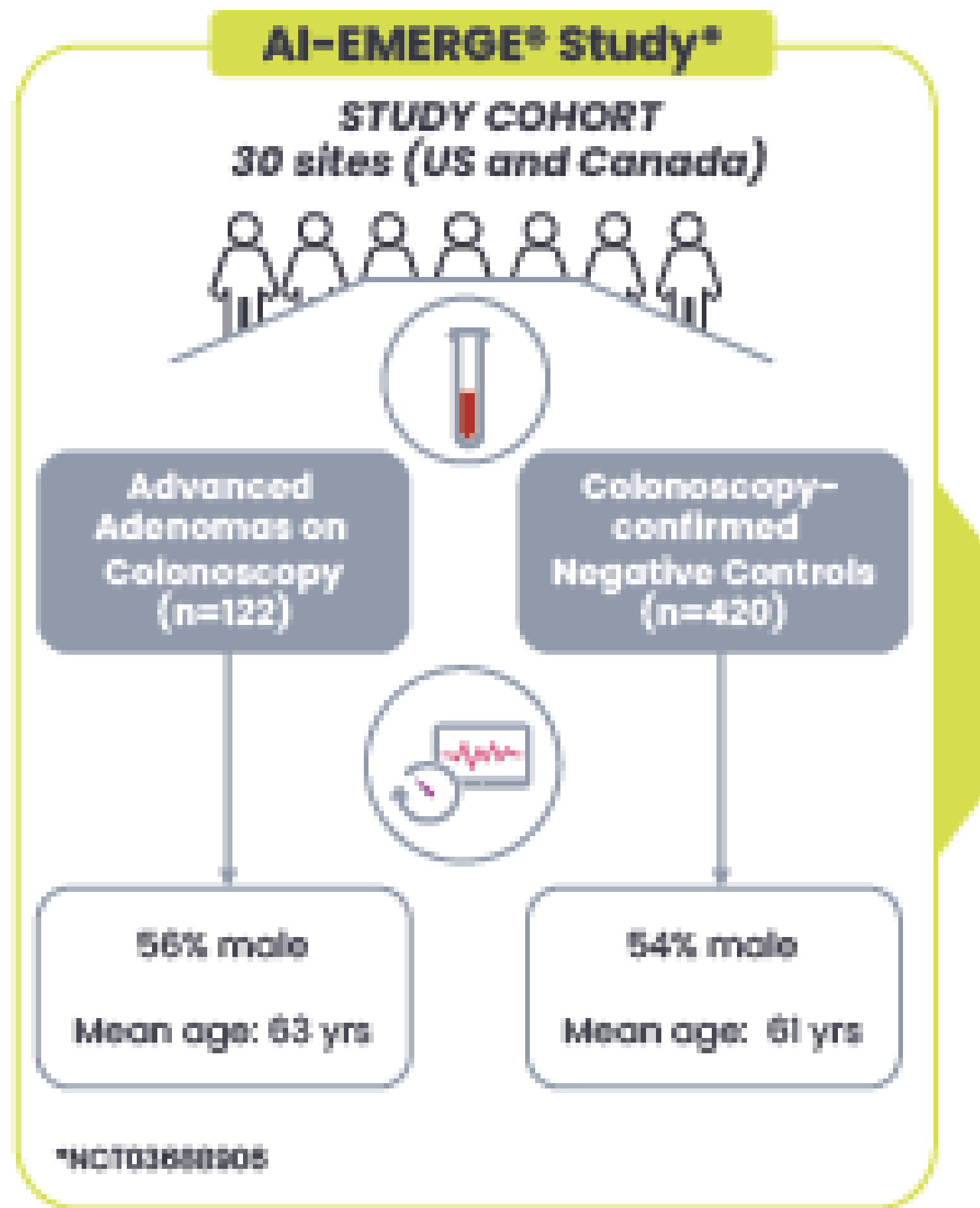
Variable	Most Advanced Finding on Colonoscopy <i>no.</i>	cfDNA Blood-Based Test	
		Positive Test <i>no.</i>	Sensitivity (95% CI) %
<b>Colorectal cancer</b>			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
<b>Specificity (95% CI)</b>			
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)

HGD 23%

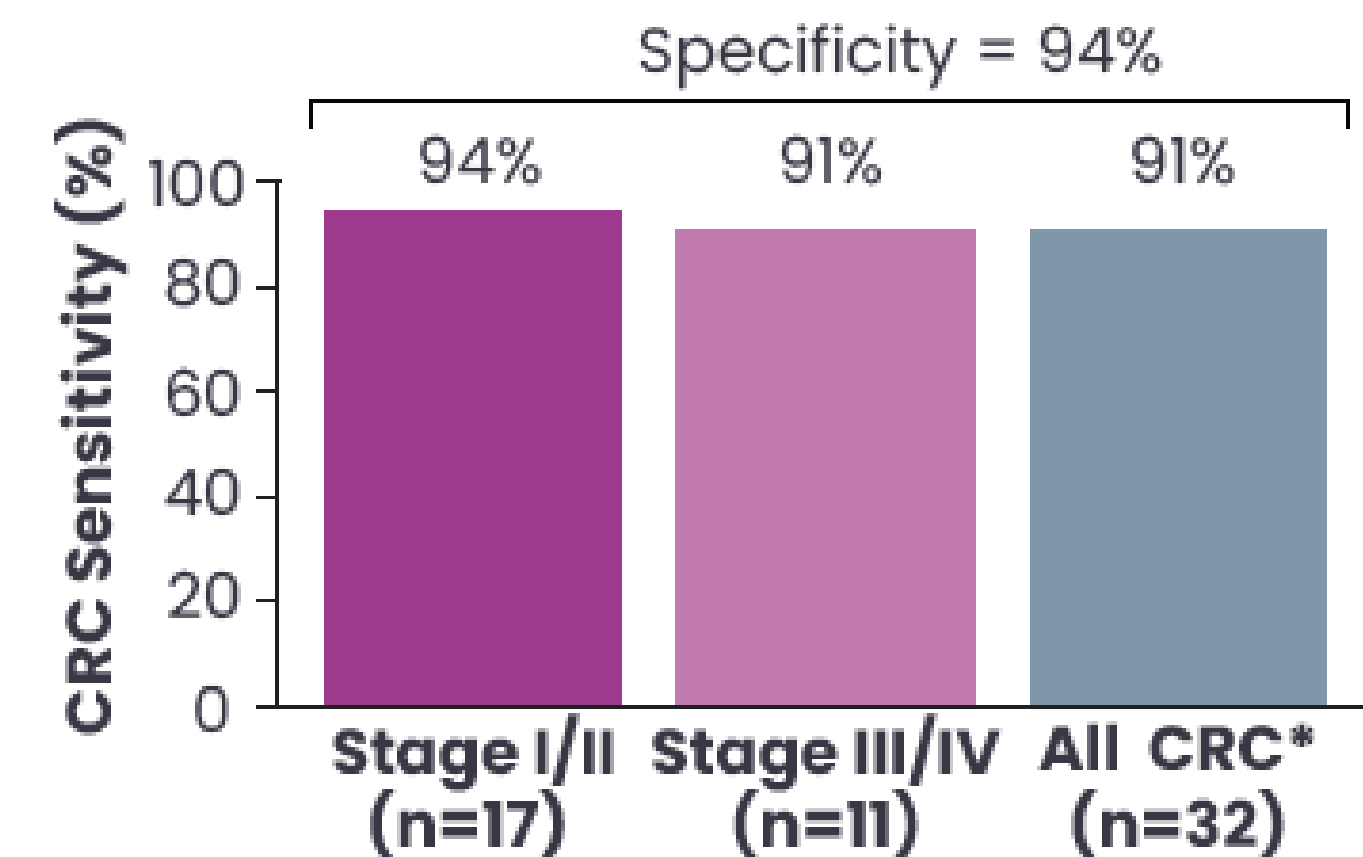
\* Excluded were 10 stage IV and 7 pathologically confirmed, incompletely staged colorectal cancers.

† Advanced precancerous lesions include advanced adenomas and sessile serrated lesions at least 10 mm in the largest dimension.

# ctDNA+ protein blood CRC screening test (Freenome)



AA sensitivity was greater than mSEPT9, the only blood test for CRC screening currently available  
AA sensitivity was much higher than FIT and comparable to FIT-DNA



# ctDNA+ protein blood CRC screening test (Freenome)

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- Overall Results from PREEMPT trial
- CRC sensitivity: 79.2%  
(Stage I: 57.1%, Stage II: 100%, Stage III: 82.4%, Stage IV: 100%)
- CRC specificity: 91.5% (for non-advanced colorectal neoplasia).
- Advanced adenoma (AA) sensitivity: 12.5% sensitivity in detecting advanced adenomas (AA)
- If protein markers added: AA sensitivity 16.4%, CRC sensitivity 80.5%
- AA with high-grade dysplasia (aka stage 0) sensitivity: 29%
- All endpoints were powered at 96%

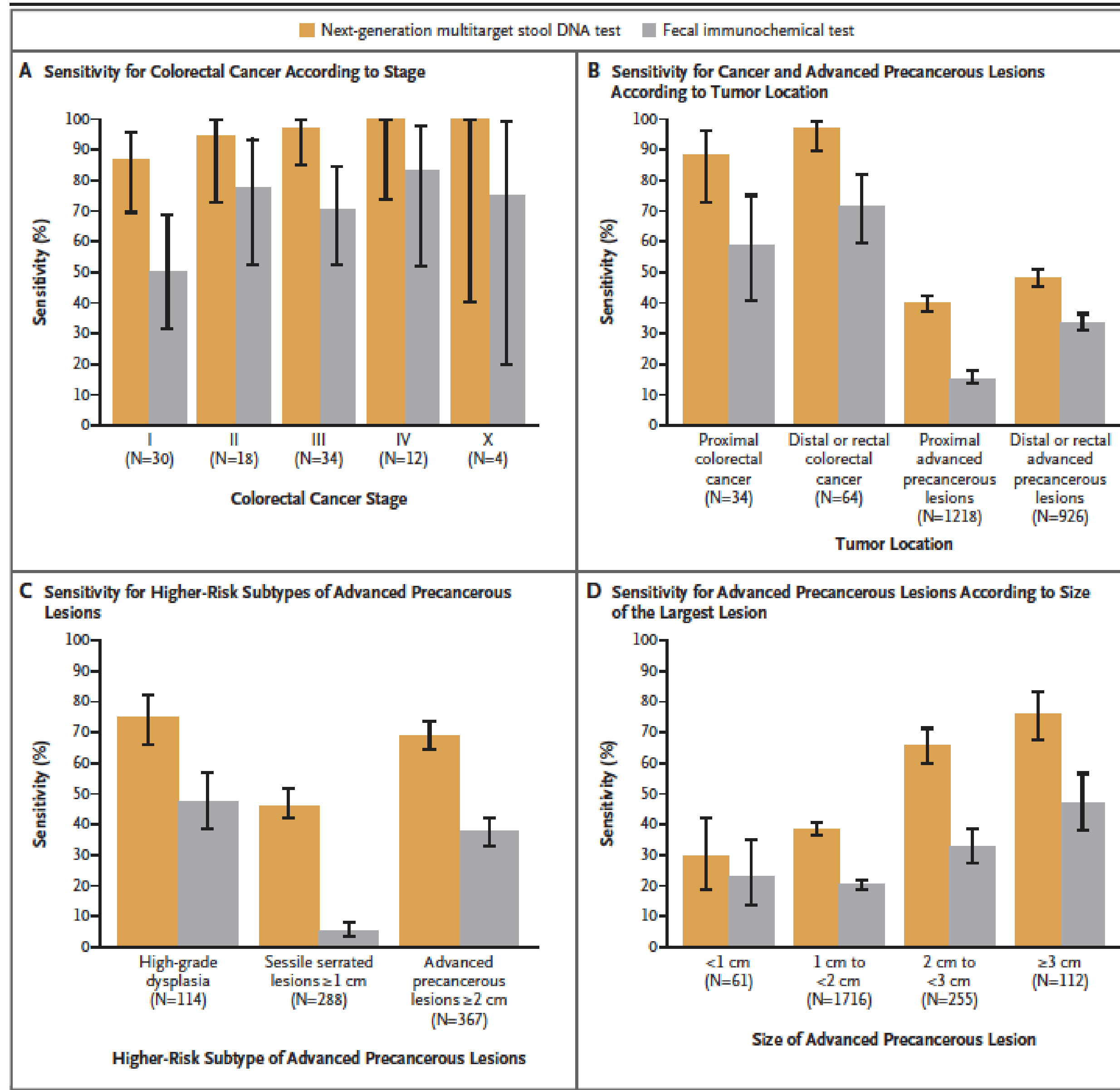
# MT-sDNA CRC screening test (Cologuard, Exact Sciences)

**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)  %
<b>Sensitivity</b>					
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)
<b>Specificity</b>					
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)



# MT-sDNA CRC screening test (Cologuard)



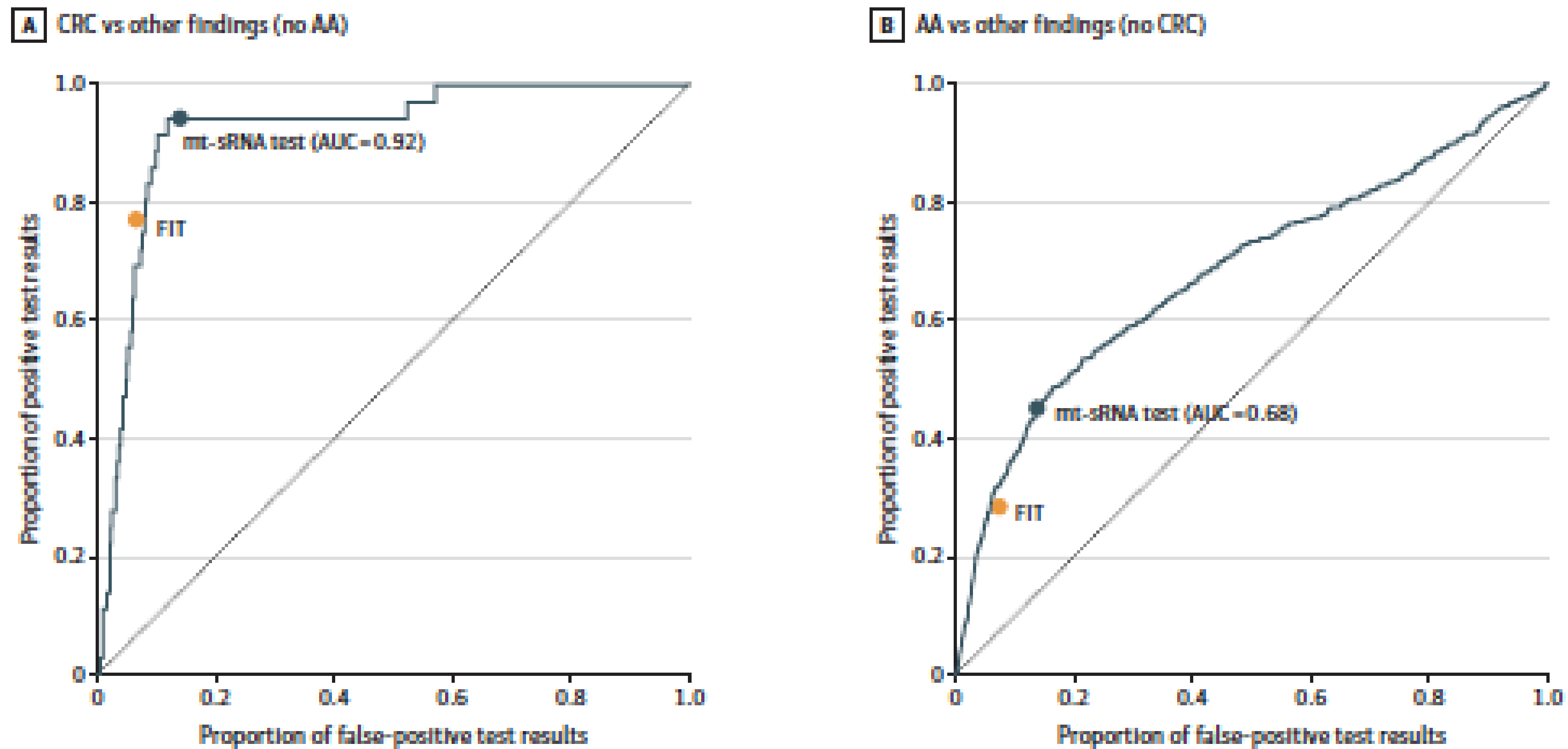
# MT-sRNA CRC screening test (Colosense, Geneoscopy)

**Table 2. Sensitivity and Specificity of the Multitarget Stool RNA (mt-sRNA) Test and Fecal Immunochemical Test (FIT)**

Outcome	mt-sRNA test (RNA and FIT)		Fecal Immunochemical test (FIT)	
	No./total No.	Sensitivity (95% CI), %	No./total No.	Sensitivity (95% CI), %
<b>Colorectal cancer (CRC)</b>	34/36	94.4 (81-99)	28/36	77.8 (61-90)
Stage I	14/14	100 (77-100)	10/14	71.4 (42-92)
Stage II	10/12	83.3 (52-98)	9/12	75.0 (43-95)
Stage III	9/9	100 (66-100)	8/9	88.9 (52-100)
Stage IV				
Unknown	1/1	100 (0-100)	1/1	100 (0-100)
<b>Advanced adenomas</b>	278/606	45.9 (42-50)	175/606	28.9 (25-33)
HGD or ≥10 adenomas (any size)	30/46	65.2 (50-79)	22/46	47.8 (33-63)
TVA (any size)	78/164	47.6 (40-55)	53/164	32.3 (25-40)
TSA or TA ≥10 mm	170/396	42.9 (38-48)	100/396	25.3 (21-31)

# MT-sRNA CRC screening test (Colosense)

Figure 2. Sensitivity and Specificity of the Multitarget Stool RNA (mt-sRNA) Test and the Fecal Immunochemical Test (FIT) for Index Lesions Observed on Colonoscopy



The mt-sRNA test receiver operating characteristic area under the curve (AUC) evaluated colorectal cancer (CRC) and advanced adenoma (AA) findings compared with all other findings (medium-risk adenomas, low-risk adenomas, and no findings).

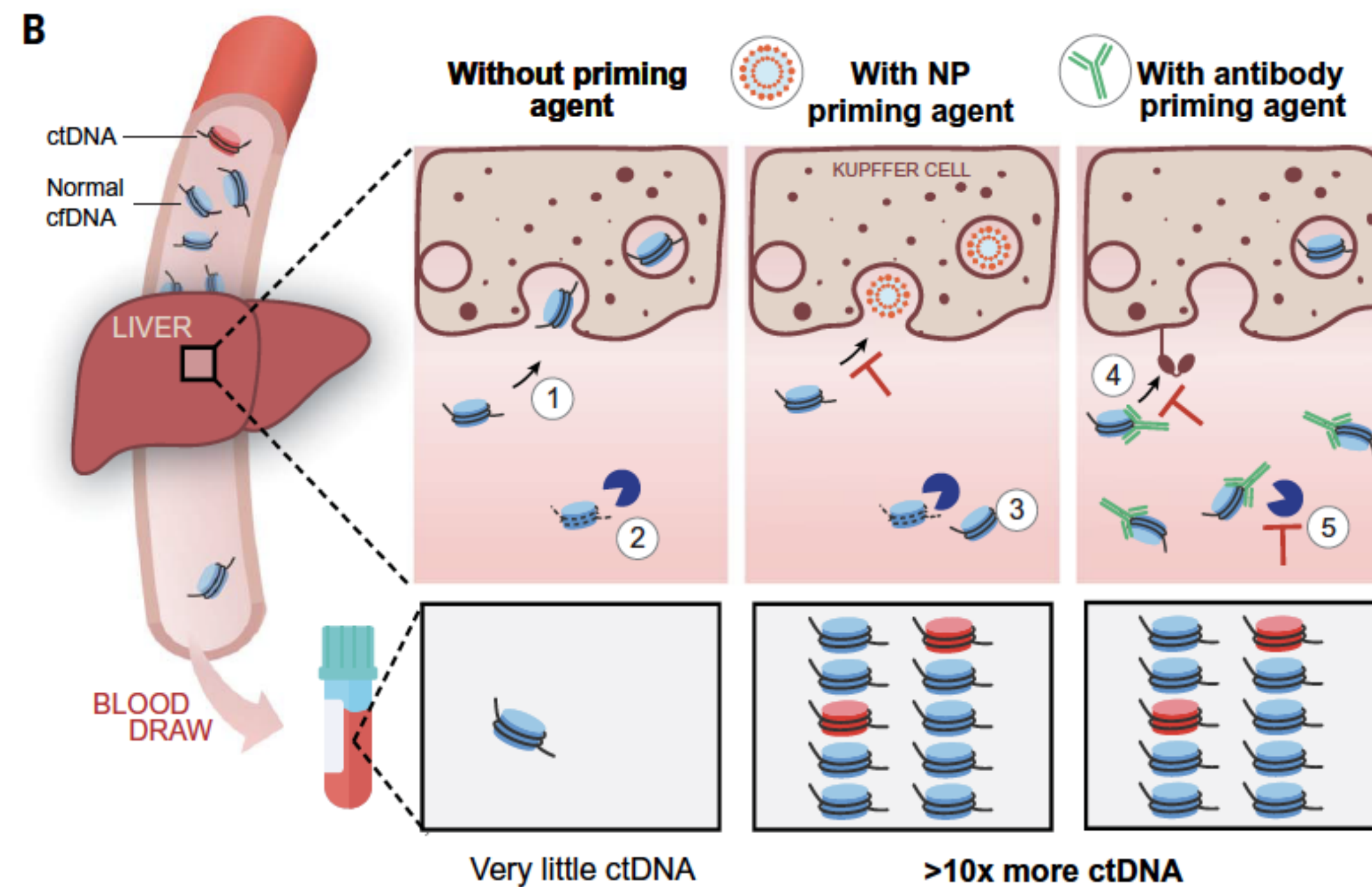
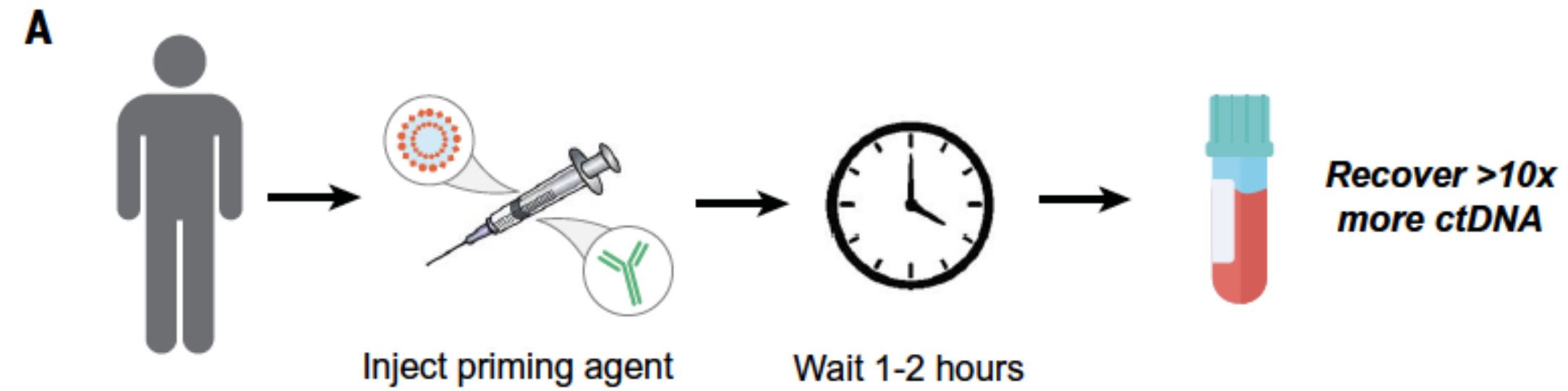
# Conclusions

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- Stool based tests
  - Current performance: CRC >90%, AA>40/45%
  - Is this the limit of performance?
  - Is this good enough?
- Blood based tests
  - Current performance: CRC >80%, AA>12%
  - Is this the limit of performance?
- Future directions
  - Other bioanalytes: autoantibodies
  - Improved technology: bioanalyte capture or detection

# Future Directions

- Bioanalyte capture: Improve cfDNA recovery





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