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Liquid Biopsy in der Krebsfrüherkennung

Elke Holinski-Feder

2024

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Genetische Veränderungen auf dem Weg zur Tumorzelle
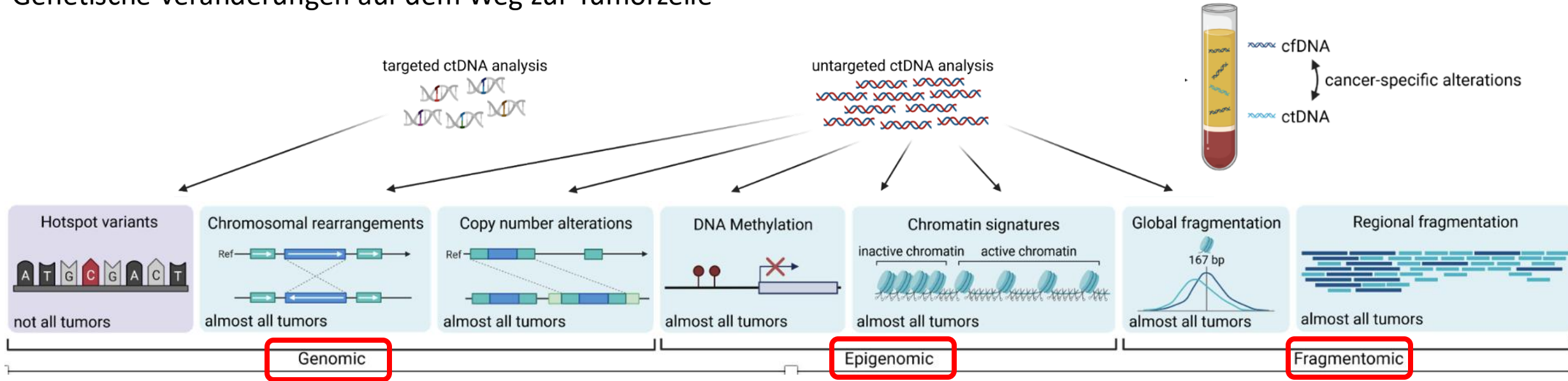
SNV
Spezifische
Driver -
Varianten

SV
Struktur-
Varianten
Dosisneutral
Translokationen
Inversionen

CNV
Deletionen
Duplikationen
von dosis-
sensitiven
Genen

Methylation
An- und Ab-
schalten von
Genen durch
Methylierung
von
Promoter-
regionen

Chromatin-
Veränderungen
Zugänglichkeit
von regulatorischen
Sequenzen
An- und Abschalten
Von Genen

Fragmentierung
Global über das gesamte Genom
Regional in spezifischen Bereichen
Mit tumorrelevanten Genen

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

Daniel C Chung [1], Darrell M Gray 2nd [1], Harminder Singh [1], Rachel B Issaka [1], Victoria M Raymond [1], Craig Eagle [1], Sylvia Hu [1], Darya I Chudova [1], AmirAli Talasaz [1], Joel K Greenson [1], Frank A Sinicrope [1], Samir Gupta [1], William M Grady [1]

Affiliations + expand

PMID: 38477985   DOI: 10.1056/NEJMoa2304714

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

Guardant Health

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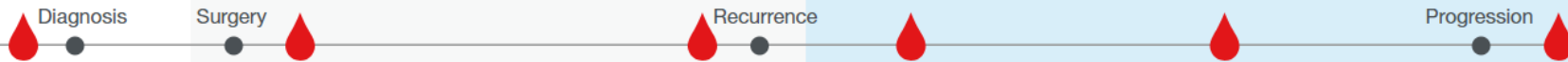**SCREENING AND EARLY DETECTION***

EARLY-STAGE CANCER*
Residual disease detection and recurrence surveillance (commercially available since 2021[3])

ADVANCED CANCER*
Treatment selection and optimization (commercially available since 2014[3,4†])

Patient Timeline[‡]

Diagnosis | Surgery | Recurrence | Progression

shield™

GUARDANT**REVEAL**

FDA APPROVED
GUARDANT360CDx

GUARDANT360Response

GUARDANT360™

GUARDANT360TissueNext™

200,000 patients tested & 260+ peer-reviewed publications[3]

— Laboratory-developed test
— FDA-approved test

ECLIPSE STUDY
A registrational study validated Shield for CRC screening in over 10,000 average-risk patients.[3,5]

National Cancer Institute and National Comprehensive Cancer Network cancer centers use Guardant Health's existing blood-based tests to inform treatment decisions for patients with early- and late-stage cancer[3]

Varianten, Fragmentierung, Methylierung
Keine Preisangaben

Varianten NGS-Panel , Methylierung
3500 Dollar

Varianten NGS-Panel
5000 Dollar

A multimodal approach for accurate and early detection of colorectal cancer

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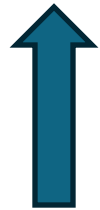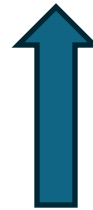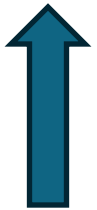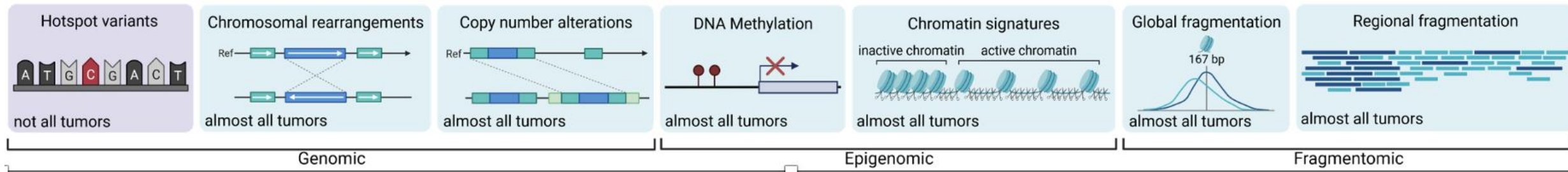
Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	no.	%
Colorectal cancer			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
			Specificity (95% CI)
Nonadvanced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

Stage I – III Sensitivity: 81%[#]

Sensitivity (%)

- Localized — Stage I/II: 72%
- Regional — Stage III: 100%
- Distant — Stage IV: 100%
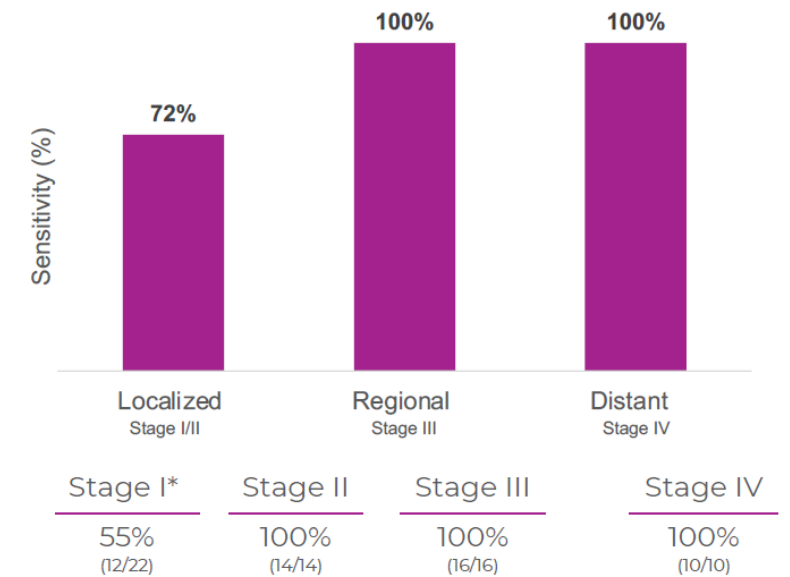
Stage I*	Stage II	Stage III	Stage IV
55% (12/22)	100% (14/14)	100% (16/16)	100% (10/10)

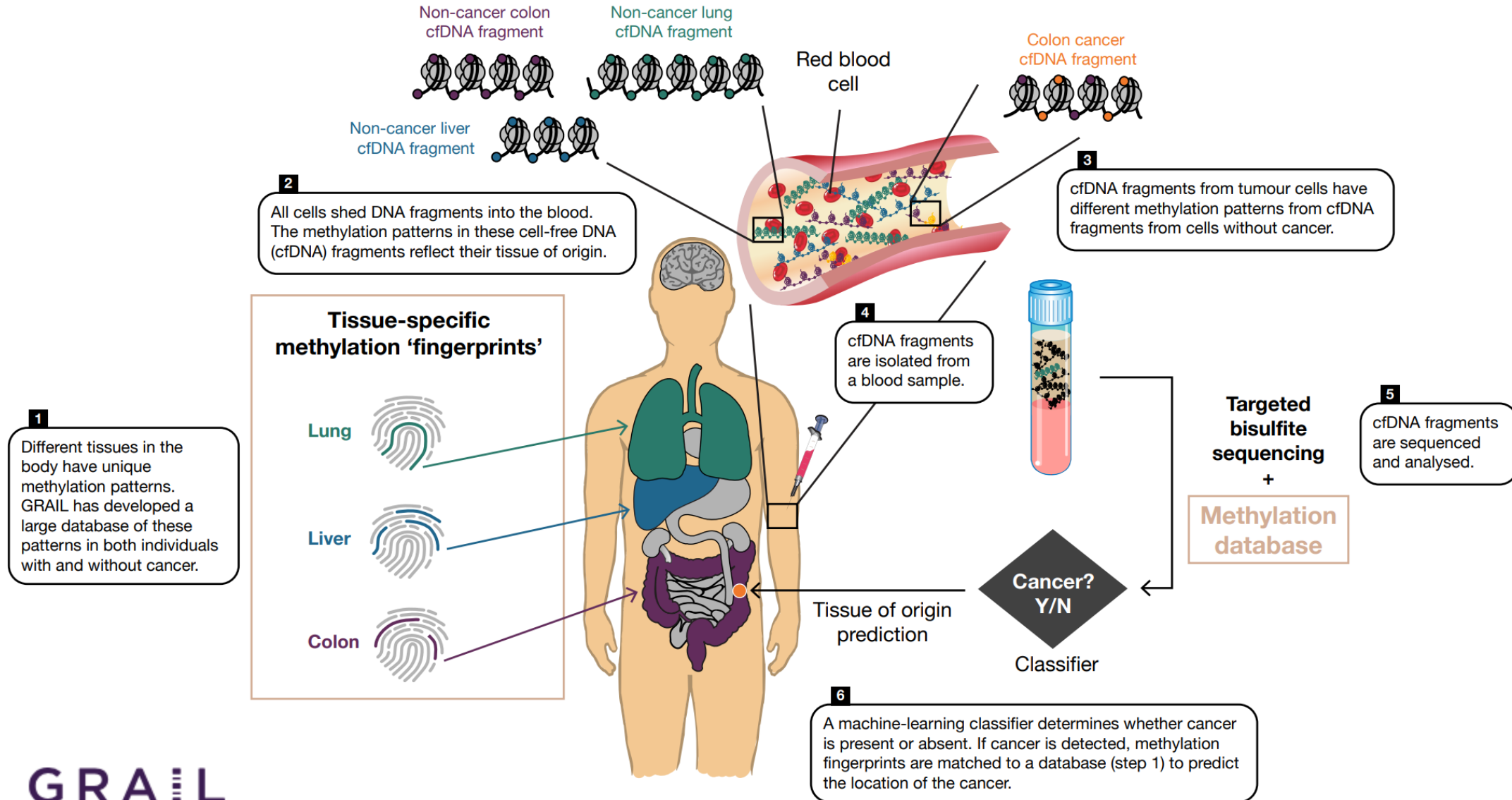*Assumes 5 incompletely staged malignant polyps are Stage I disease (1/5 detected)

Guardant Health Shield:
- screening black box,
- vermutlich nicht gemomweit,
- binäres Ergebnis, ctDNA da oder nicht da

Proben müssen in die USA geschickt werden, IGEL

Vermutlich regionale Sequenzierung

What else?

- Grail Illumina = Methylierungsmuster
- EPINUC = Modifikation von Nukleosomen
- LIFE-CNA = LIquid biopsy Fragmentation, Epigenetic signature and Copy Number Alteration

Galleri multi-cancer early detection test
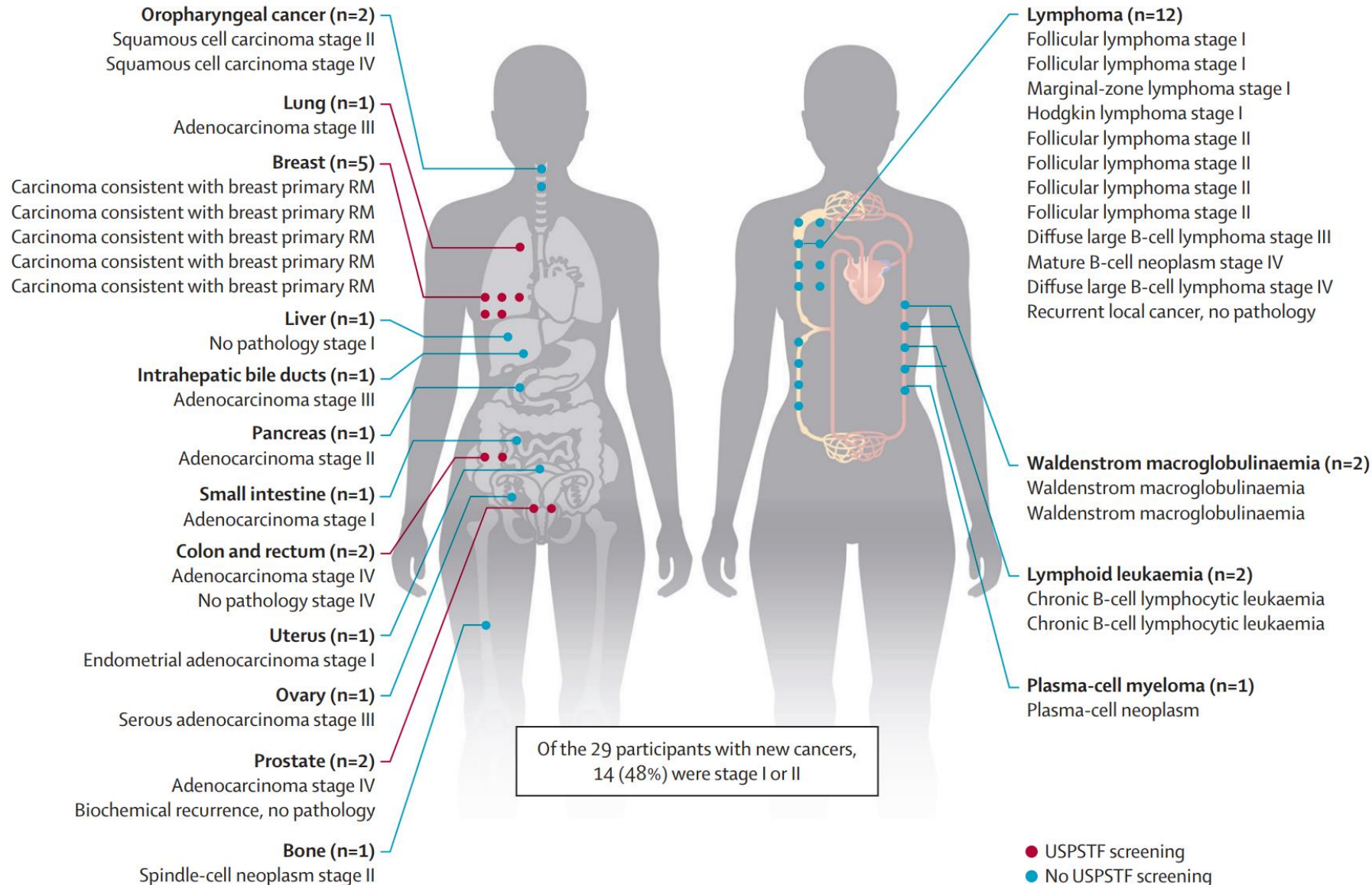
|	Age ≥50 years with additional cancer risk (n=3681)	Age ≥50 years without additional cancer risk (n=2940)	Total (n=6621)
Resolution			
All	56 (1·5%)	36 (1·2%)	92 (1.4%)
True positive	24 (0·7%)	11 (0·4%)	35 (0·5%)
False positive	32 (0·9%)	25 (0·9%)	57 (0·9%)
Positive predictive value	24/56; 43% (30·8–55·9)	11/36; 31% (18·0–46·9)	35/92; 38% (28·8–48·3)
Negative predictive value	3449/3502; 98·5% (98·0–98·8)	2786/2819; 98·8% (98·4–99·2)	6235/6321; 98·6% (98·3–98·9)
Specificity	3449/3480; 99·1% (98·7–99·4)	2786/2810; 99·1% (98·7–99·4)	6235/6290; 99·1% (98·9–99·3)
Yield rate	24/3681; 0·65% (0·41–0·92)	11/2940; 0·37% (0·17–0·61)	35/6621; 0·53% (0·36–0·71)
Number needed to screen	3681/24; 153 (108–245)	2940/11; 267 (163–588)	6621/35; 189 (141–276)
Predicted origin accuracy*			
First CSO correct	20/23; 87% (67·9–95·5)	9/11; 82% (52·3–94·9)	29/34; 85% (69·9–93·6)
First or second CSO correct	23/23; 100% (85·7–100)	10/11; 91% (62·3–99·5)	33/34; 97% (85·1–99·8)

Data are n (%), n/N, or % (95% CI). CSO=cancer signal origin. *Excludes one participant with indeterminate CSO from the true-positive set.

Oropharyngeal cancer (n=2)
Squamous cell carcinoma stage II
Squamous cell carcinoma stage IV

Lung (n=1)
Adenocarcinoma stage III

Breast (n=5)
Carcinoma consistent with breast primary RM
Carcinoma consistent with breast primary RM
Carcinoma consistent with breast primary RM
Carcinoma consistent with breast primary RM
Carcinoma consistent with breast primary RM

Liver (n=1)
No pathology stage I

Intrahepatic bile ducts (n=1)
Adenocarcinoma stage III

Pancreas (n=1)
Adenocarcinoma stage II

Small intestine (n=1)
Adenocarcinoma stage I

Colon and rectum (n=2)
Adenocarcinoma stage IV
No pathology stage IV

Uterus (n=1)
Endometrial adenocarcinoma stage I

Ovary (n=1)
Serous adenocarcinoma stage III

Prostate (n=2)
Adenocarcinoma stage IV
Biochemical recurrence, no pathology

Bone (n=1)
Spindle-cell neoplasm stage II

Lymphoma (n=12)
Follicular lymphoma stage I
Follicular lymphoma stage I
Marginal-zone lymphoma stage I
Hodgkin lymphoma stage I
Follicular lymphoma stage II
Follicular lymphoma stage II
Follicular lymphoma stage II
Follicular lymphoma stage II
Diffuse large B-cell lymphoma stage III
Mature B-cell neoplasm stage IV
Diffuse large B-cell lymphoma stage IV
Recurrent local cancer, no pathology

Waldenstrom macroglobulinaemia (n=2)
Waldenstrom macroglobulinaemia
Waldenstrom macroglobulinaemia

Lymphoid leukaemia (n=2)
Chronic B-cell lymphocytic leukaemia
Chronic B-cell lymphocytic leukaemia

Plasma-cell myeloma (n=1)
Plasma-cell neoplasm

Of the 29 participants with new cancers,
14 (48%) were stage I or II

● USPSTF screening
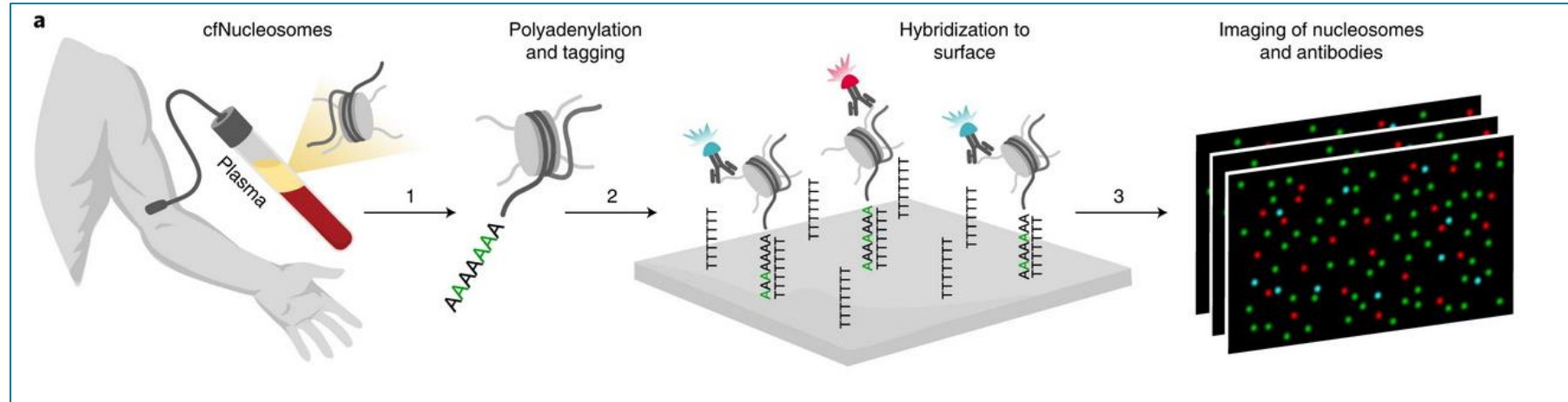● No USPSTF screening

Analysis of circulating tumor DNA - LIFE-CNA - CRC

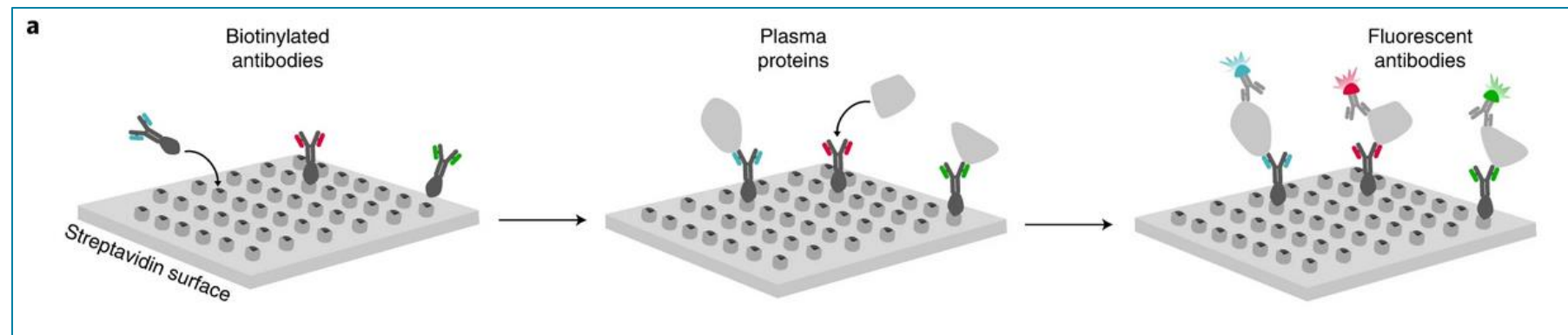*LIFE-CNA = LIquid biopsy Fragmentation, Epigenetic signature and Copy Number Alteration analysis*
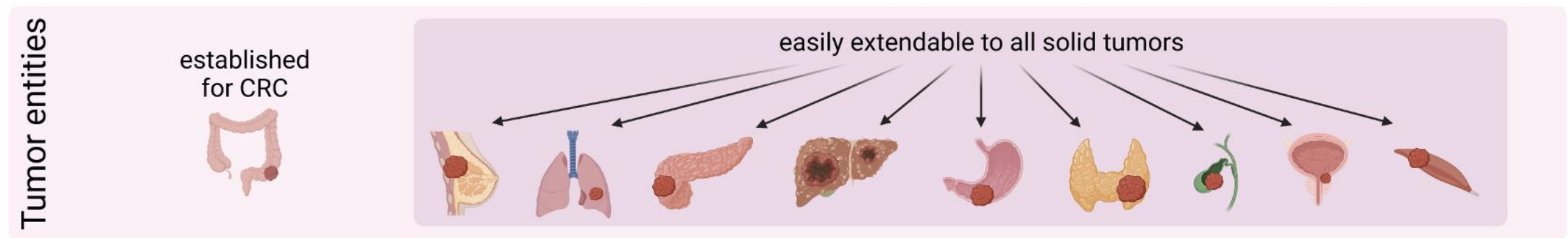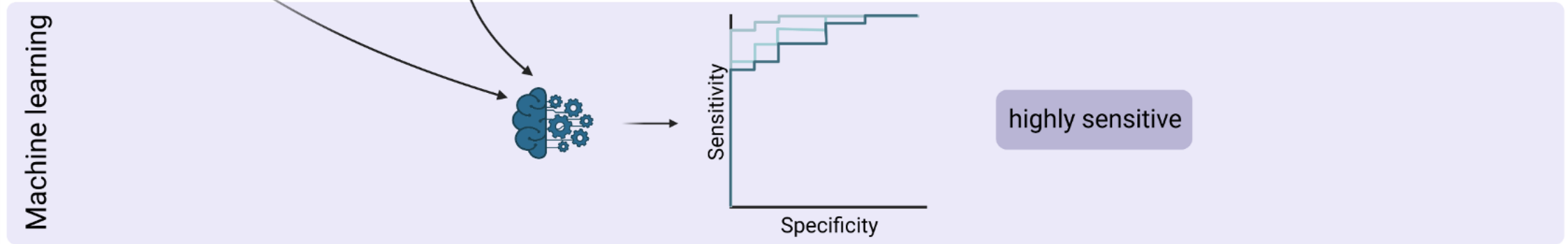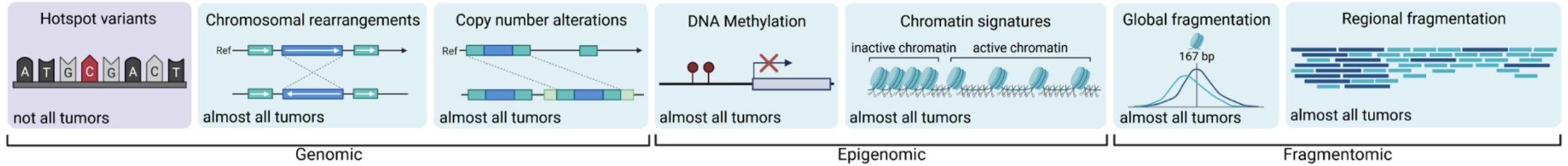
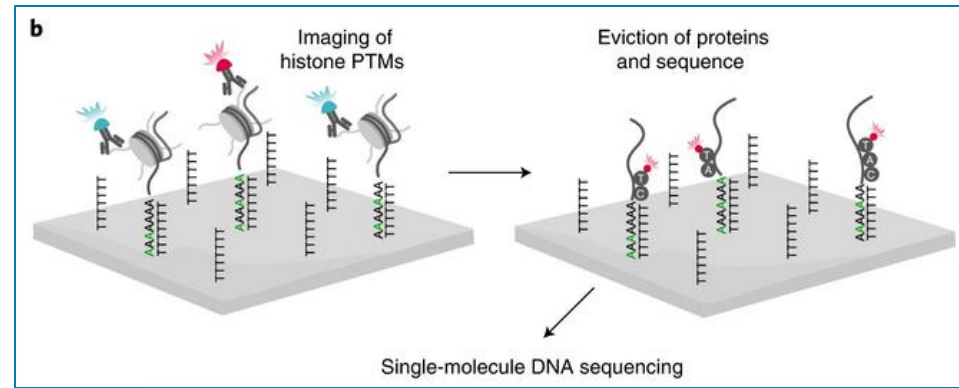# EPINUC - Detection of single nucleosomes and PTMs from plasma
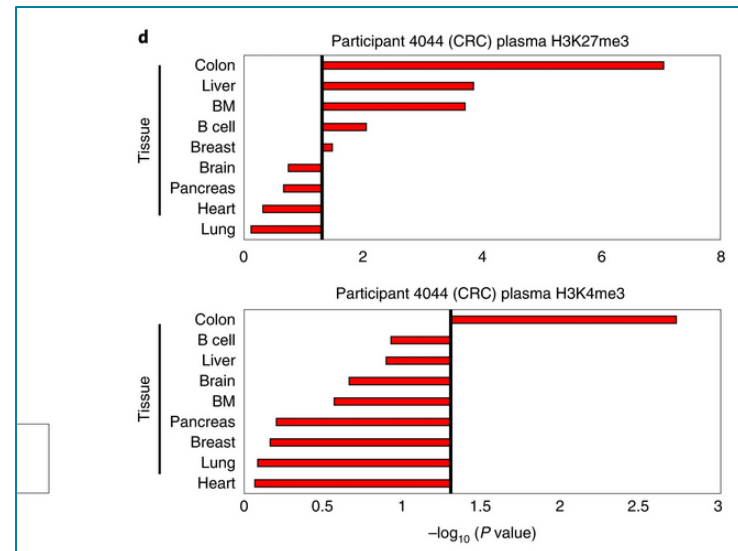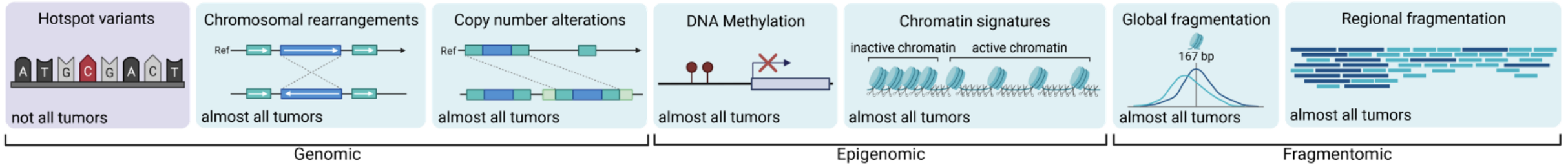
cf Nucleosomes +PTMs

multiplexed protein biomarkers

EPINUC-Seq

Proof of principle
→ sequences map to regions specific in tissue of origin

Analysis of circulating tumor DNA - LIFE-CNA - CRC

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LIFE-CNA = LIquid biopsy Fragmentation, Epigenetic signature and Copy Number Alteration analysis

RESEARCH   **Open Access**

Somatic copy number alteration and fragmentation analysis in circulating tumor DNA for cancer screening and treatment monitoring in colorectal cancer patients

Ariane Hallermayr[1,2,3], Tobias Wohlfrom[1], Verena Steinke-Lange[1,4], Anna Benet-Pagès[1,5], Florentine Scharf[1], Ellen Heitzer[6,7,8], Ulrich Mansmann[3], Christopher Haberl[9], Maike de Wit[10,11], Holger Vogelsang[12], Markus Rentsch[13,14], Elke Holinski-Feder[1,4] and Julia M. A. Pickl[1,4*]
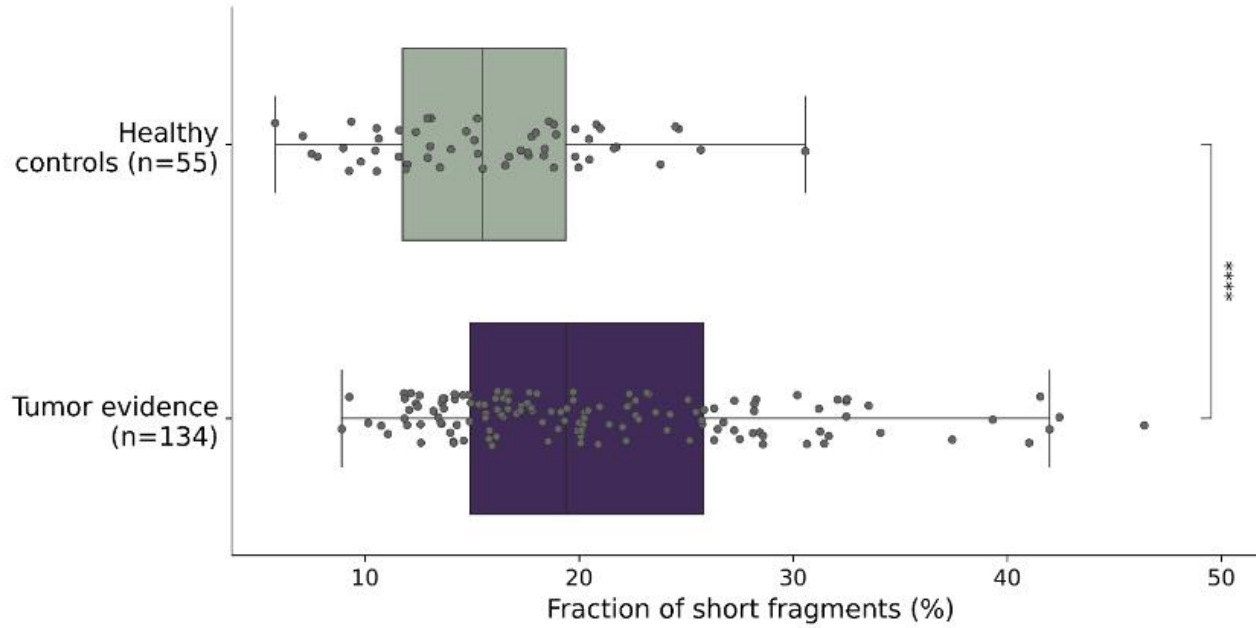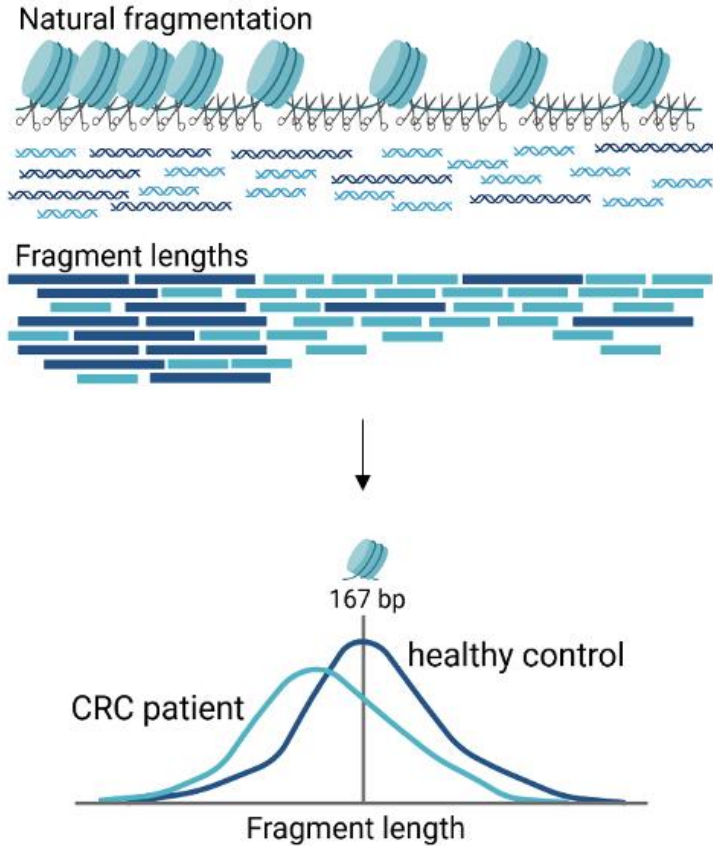
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ctDNA detection at diagnosis:

16 patients

Localized CRC (UICC I-III)

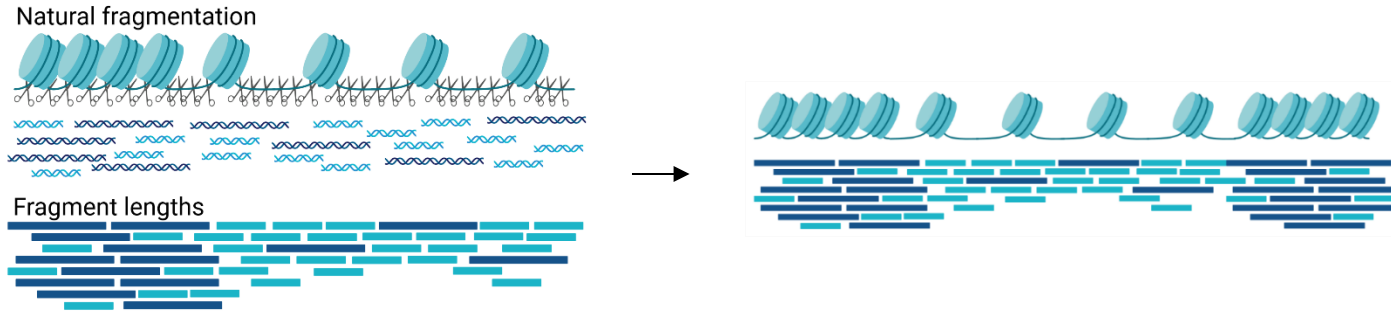LIFE-CNA   81% LIFE-CNA + ML: 93%

Metastatic CRC (UICC IV)

LIFE-CNA   94% LIFE-CNA + ML: 94%

created with BioRender.com

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Higher fraction of short fragments (90 to 150 bp) in CRC patients compared to healthy controls

Hallermayr et al. *J Hematol Oncol*. 2022

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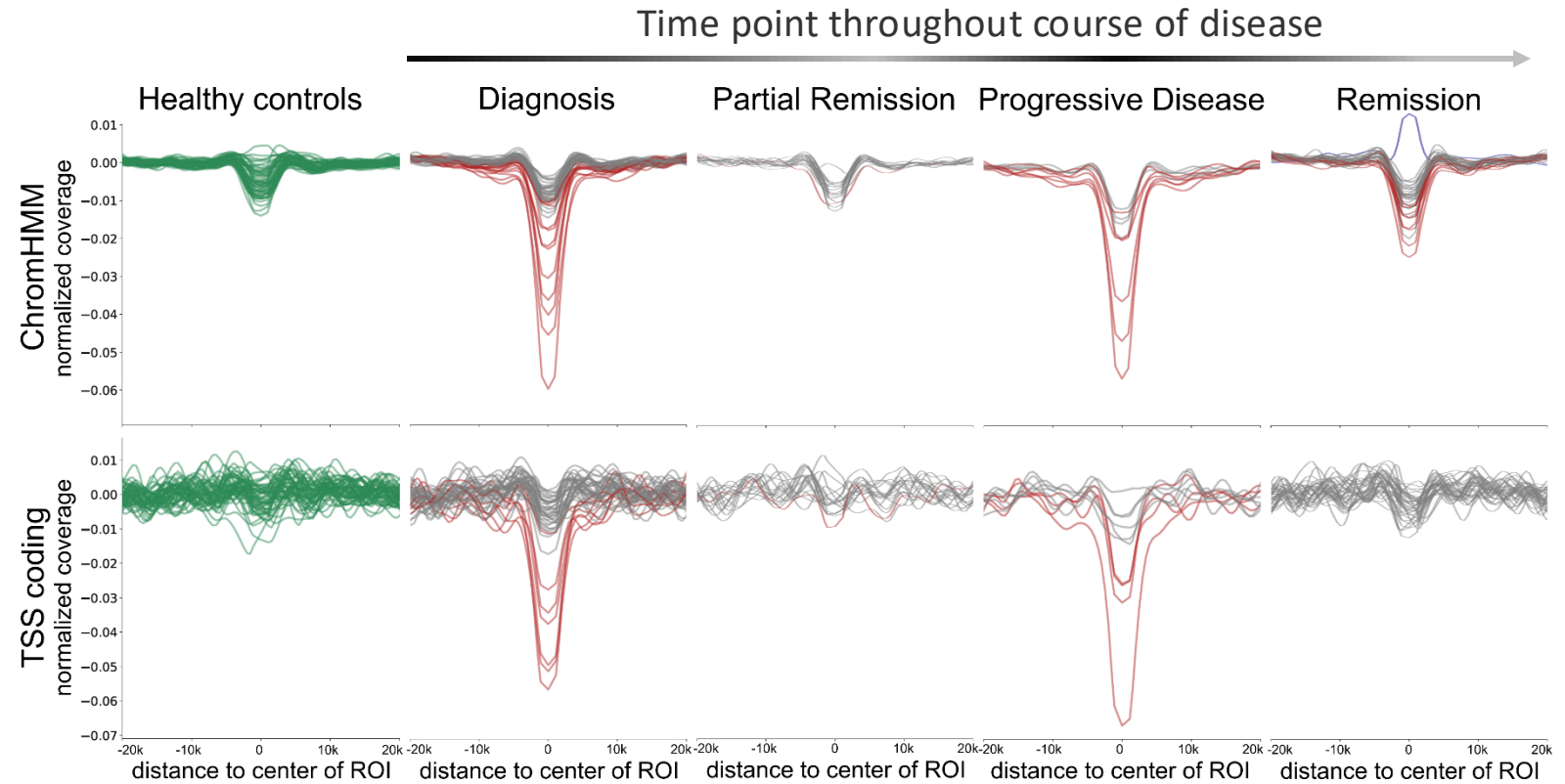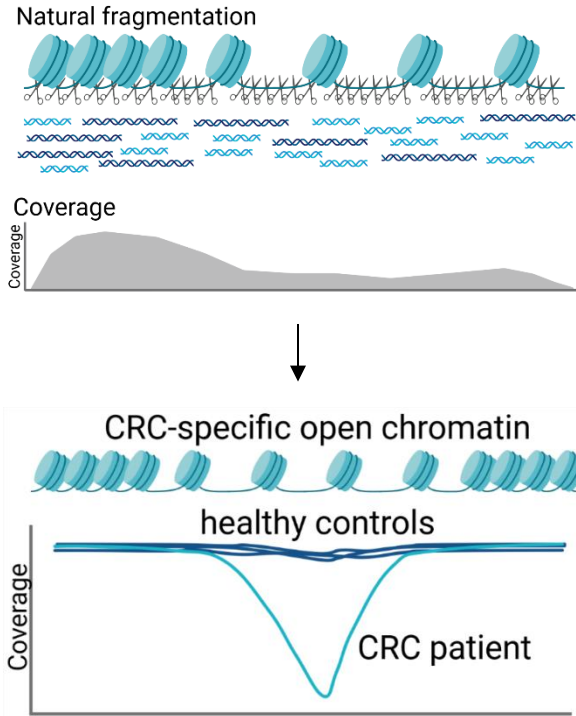Medizinisch Genetisches Zentrum

Natural fragmentation

Fragment lengths

Significant differences in S/L ratio between healthy controls and CRC patient samples with tumor evidence

CRC specific fragmentation profile

shorter
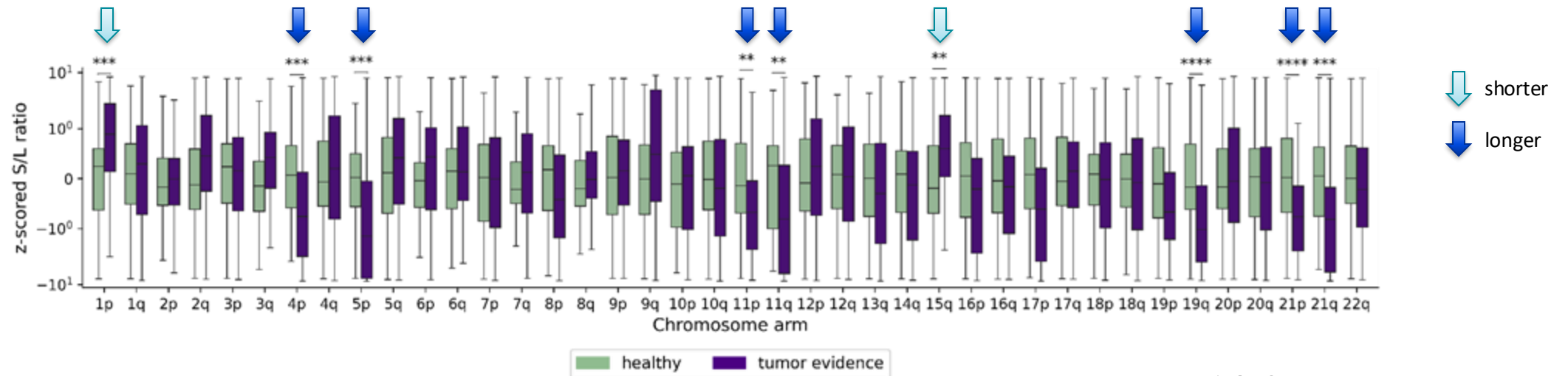
longer

$$S/L\text{-ratio} = \frac{90 - 150\ bp\ fragments}{151 - 220\ bp\ fragments}$$

Hallermayr et al. *J Hematol Oncol*. 2022

CRC specific chromatin signatures

Natural fragmentation

Coverage

CRC-specific open chromatin

healthy controls

CRC patient

Time point throughout course of disease

Healthy controls | Diagnosis | Partial Remission | Progressive Disease | Remission

ChromHMM normalized coverage

TSS coding normalized coverage

distance to center of ROI

— healthy controls
— no difference to controls
— significantly stronger coverage drop
— significantly weaker coverage drop

Detection of ctDNA based on active chromatin in samples with clinically evident tumor burden

TSS = transcriptional start sites
ChromHMM = chromatin-state discovery and characterization tool

Hallermayr et al. *J Hematol Oncol*. 2022

Early detection of precancerous lesion is difficult

Early detection and disease monitorin of cancer is feasable in the near future

Available now

Guardant Health

- Guardant 360 Tumor advanced cancer: diagnosis and monitoring
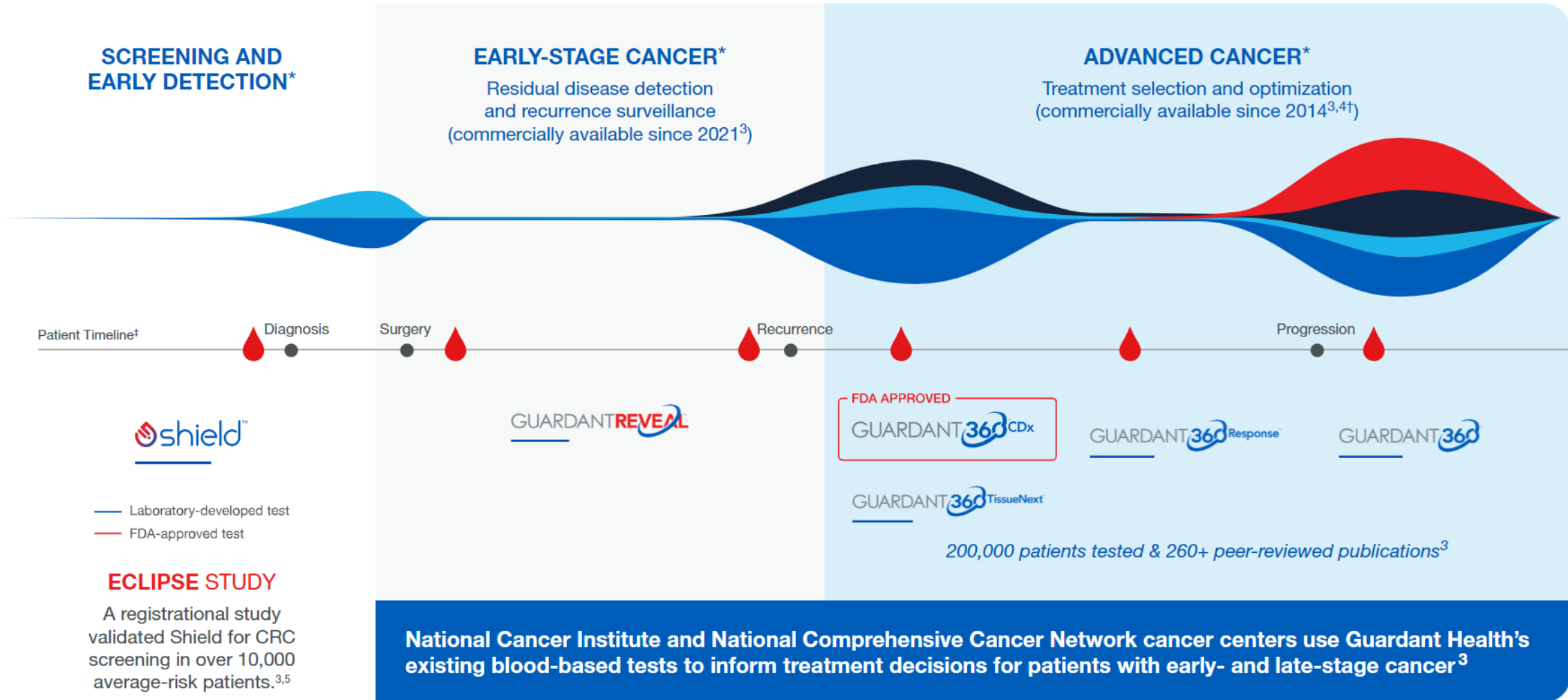- Guardant Reveal early stage cancer: diagnosis and monitoring

Under develpment

- Guardant Shield screening and early detection
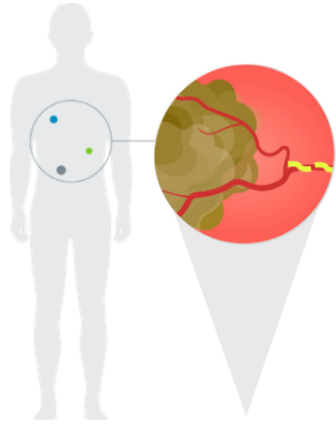- Grail screening and early detection
- LIFE-CNA

Text

Text

Varianten, Fragmentierung, Methylierung
Keine Preisangaben

Varianten NGS-Panel , Methylierung
3500 Dollar

Varianten NGS-Panel
5000 Dollar