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思勤

真理至上，以人为本
seek and you will find

A panel of Seven Protein tumor Markers for Effective and Affordable Multi-cancer Early Detection by Artificial Intelligence

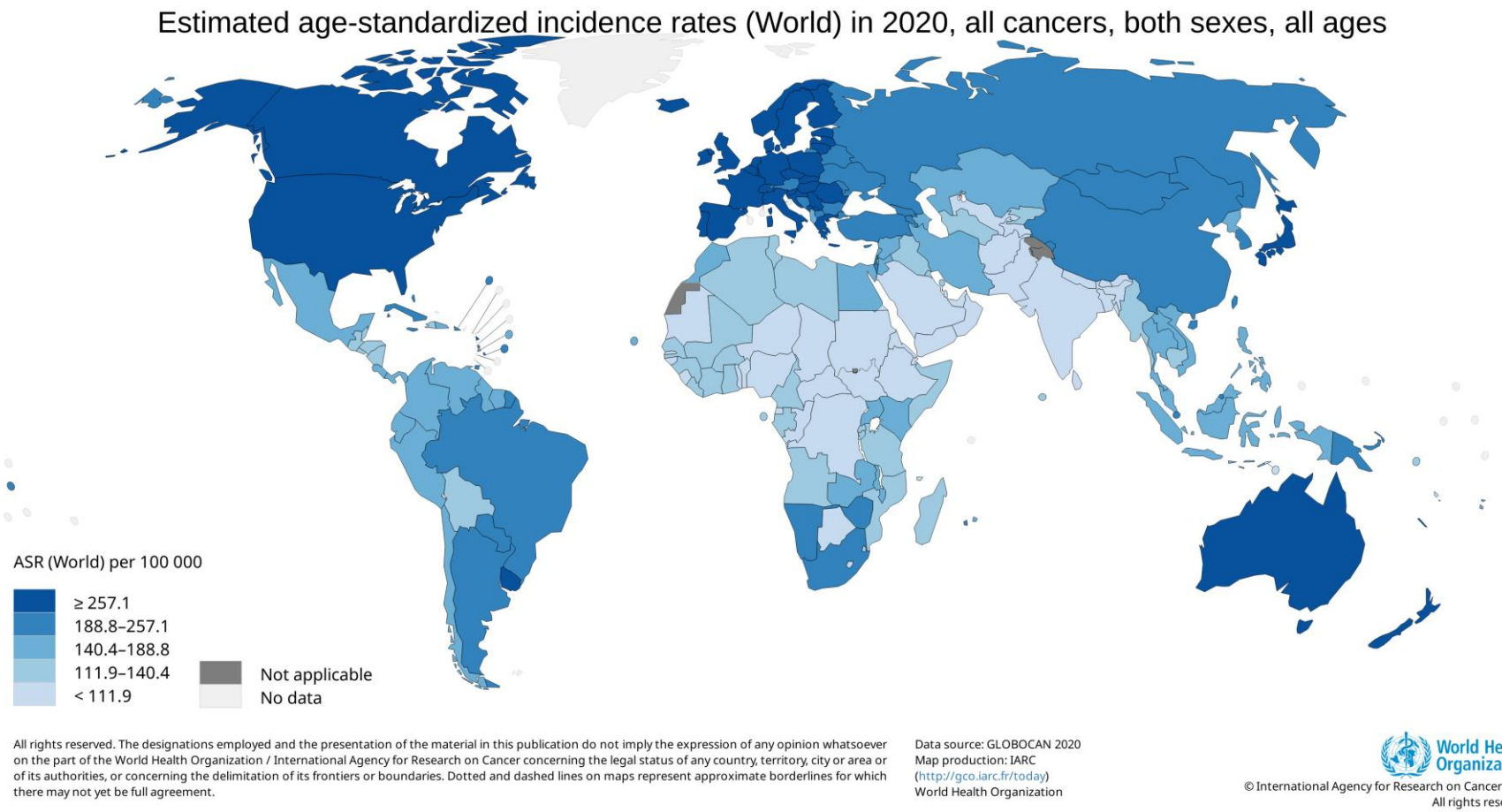
Dao-Ling Huang, PhD

Inspire2Live & SeekIn

Cancer is An Important Public Health Issue Worldwide

New cancer cases
19.3 million

Cancer deaths
10.0 million



Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J Clin 2021; 71: 209–49.

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Multi-cancer Early Detection (MCED) - Detecting Cancer Early When It Is Still Curable

"Many patients in Africa are diagnosed with advanced cancers and do not complete their care. There are several reasons for this, cost being the main one: patients frequently must pay out of pocket to access care, incurring expenses that can be financially catastrophic. Poor referral systems that may not support timely pathways to care or adequate treatment, palliative or supportive services".[1]

The World Health Organization (WHO) recommends implementation of early cancer detection and prevention programs at the primary care level, but most early detection tests are too complex and/or too costly for community-based care, particularly in medically underserved areas.[2]

The future cancer detection for global access

- Detect many cancer types instead of one at a time
- Remotely accessible
- Very easy to scale up
- Cost-effective (LMICs version: $20)

1. https://www.afro.who.int/news/where-does-cancer-care-stand-africa-today
2. https://www.aacrmeetingnews.org/news/international-physician-scientists-address-global-cancer-burden/?utm_source=aacr-news-email&utm_medium=email&utm_campaign=aacr-post-1-email-int&utm_content=button&utm_medium=email&utm_campaign=AACR%20Meeting%20News%20-%20Post%20Issue%201%20-%20April%2027%20%20INT&utm_content=AACR%20Meeting%20News%20-%20Post%20Issue%201%20-%20April%2027%20-%20INT+CID_4503e21cf41aa7c375f838078ecb4ec9&utm_source=aacr_news_email&utm_term=Read%20More

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Proof of Concept Study

Detection of asymptomatic cancers by shallow genome sequencing and 8 protein markers (AFP, CA125, CA15-3, CA19-9, CA72-4, CEA, CYFRA 21-1 and NSE)

Genetics inMedicine

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nature > genetics in medicine > articles > article

Article | Published: 12 April 2019

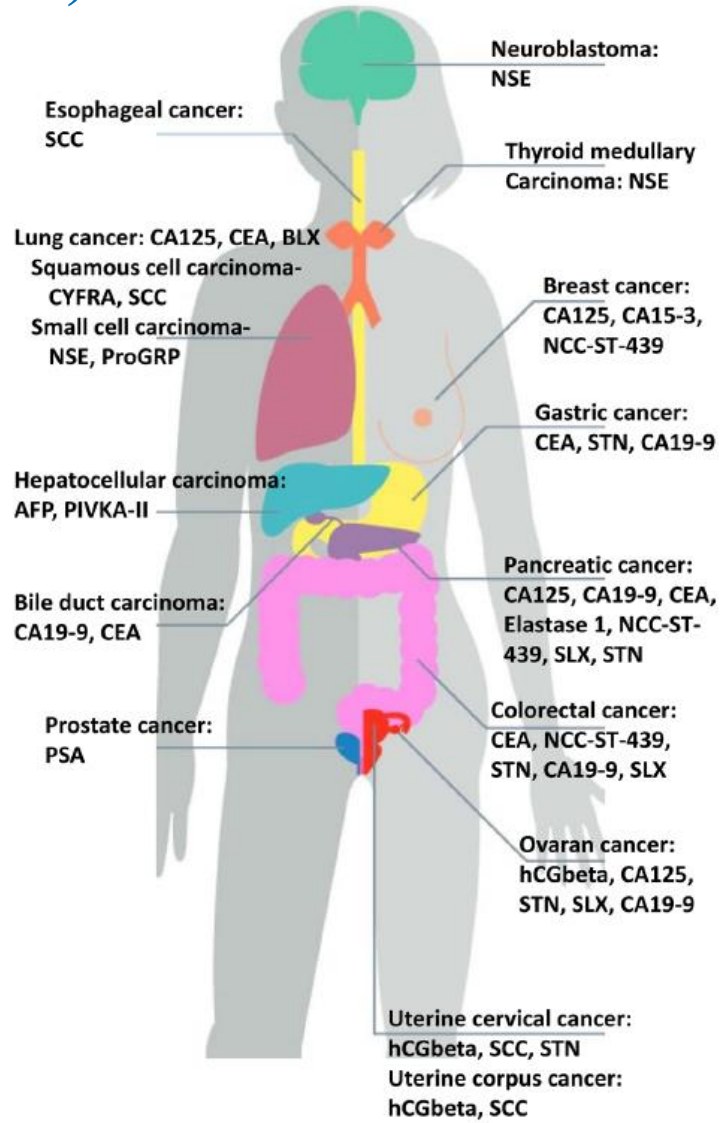
Identifying occult maternal malignancies from 1.93 million pregnant women undergoing noninvasive prenatal screening tests

Xing Ji MD, Jia Li PhD, ... Mao Mao MD, PhD + Show authors

Genetics in Medicine **21**, 2293–2302 (2019) | Cite this article

Clinical Applications of Protein Tumor Markers (PTMs)

Screening → Diagnosis → Prognosis → Monitor treatment → Detect recurrence



1. Bates SE. Clinical applications of serum tumor markers. Ann Intern Med. 1991 Oct 15;115(8):623-38.
2. Mizuno, T., Goto, T., Shimojo, K. and Watanabe, N. (2021) Clinical Utility of Tumor Markers. Open Journal of Pathology. 2021; 11, 38-57.

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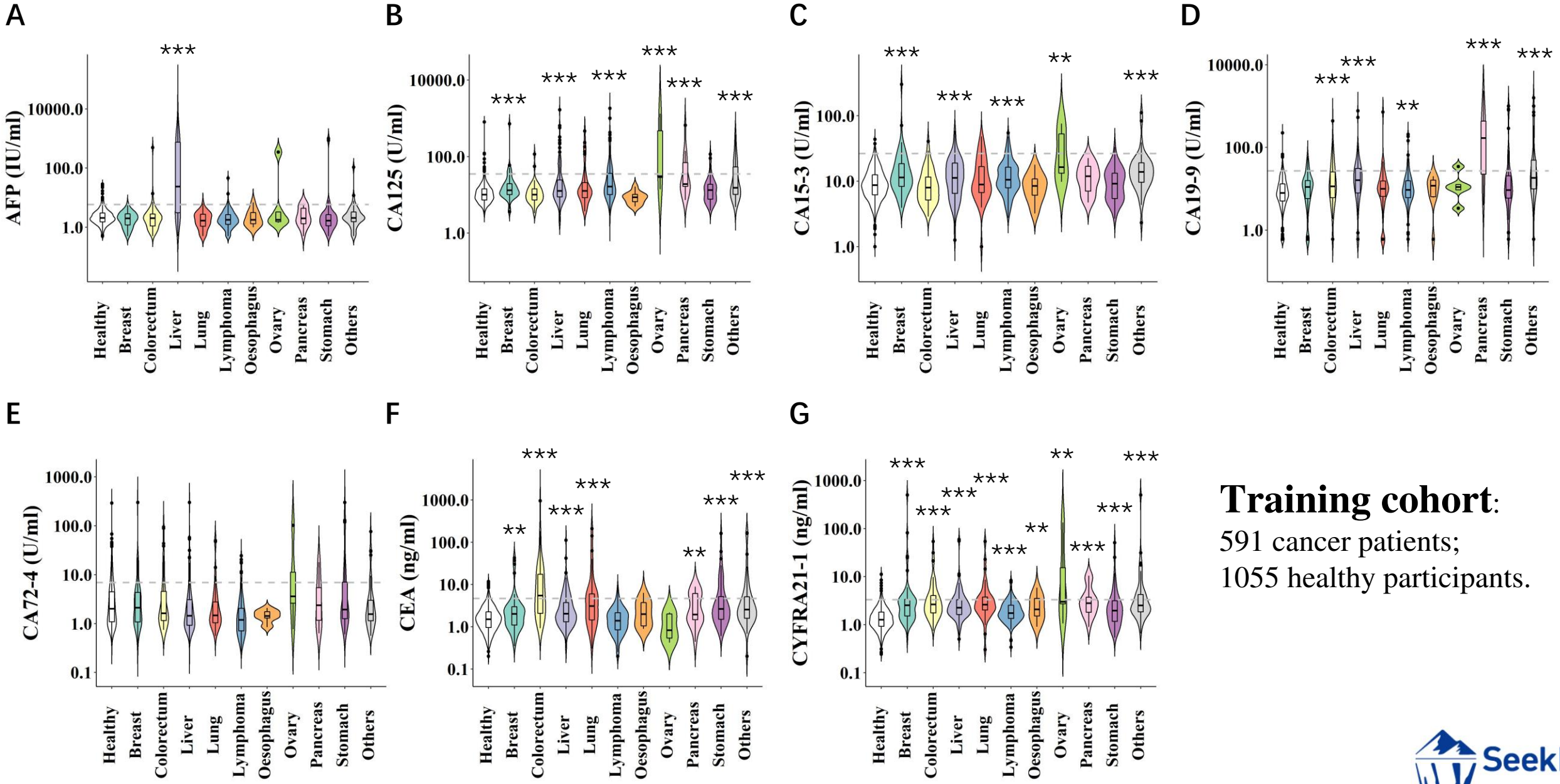
Quantification of PTMs in Different Cancer Types



Training cohort:
591 cancer patients;
1055 healthy participants.

7 PTMs: AFP, CA125, CA15-3, CA19-9, CA72-4, CEA, and CYFRA 21-1

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Roche’s Full-line Electrochemiluminescence Immunoassay (ECLI) Analyzers

Instrument picture				
Instrument model	**cobas e411**	**cobas e601**	**cobas e602**	**cobas e801**
Detection speed	86 tests/h	170 tests/h	170 tests/h	300 tests/h
Sample throughput	30 sample positions	150 sample positions	300 sample positions	300 sample positions
Reagent throughput	18 reagent positions	25 reagent positions	25 reagent positions	48 reagent positions

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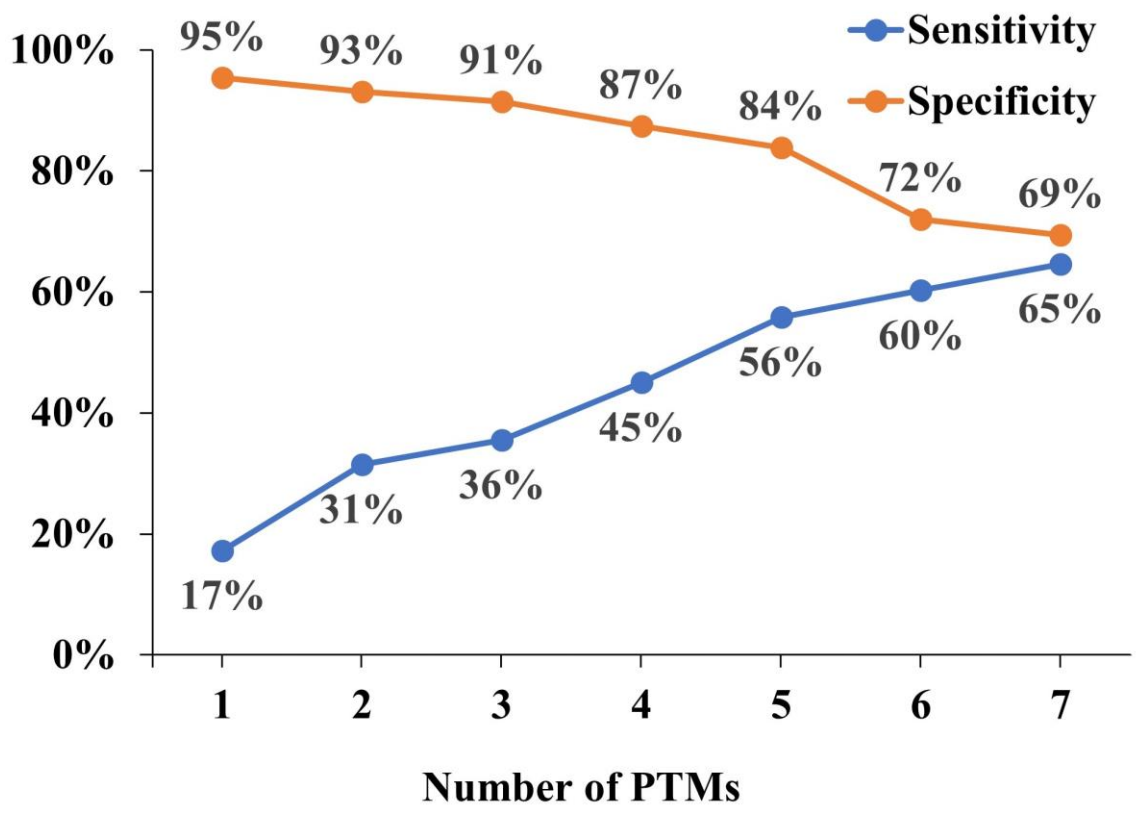
Performance of Conventional Clinical Method in Training Cohort

	Cancer	Non-cancer
Predict cancer*	382	323
Predict non-cancer	209	732
Sensitivity (95% CI)	**64·6% (60·6%, 68·5%)**	
Specificity (95% CI)	**69·4% (66·5%, 72·2%)**	
PPV (95% CI)	54·2% (50·4%, 57·9%)	
NPV (95% CI)	77·8% (75·0%, 80·4%)	

*Subjects with at least one of the markers included in the panel showing values above the cut-off point were considered as being positive. PPV, positive predictive value. NPV, negative predictive value.



The false positive rate accumulates as the number of markers increases

Luan, Y., Zhong, GL., Li, SY., Wu, W., Liu, SQ., Zhu, DD., Feng, YM., Zhang, YX., Duan, CH., and Mao, M. A panel of seven protein tumour markers for effective and affordable multi-cancer early detection by artificial intelligence:

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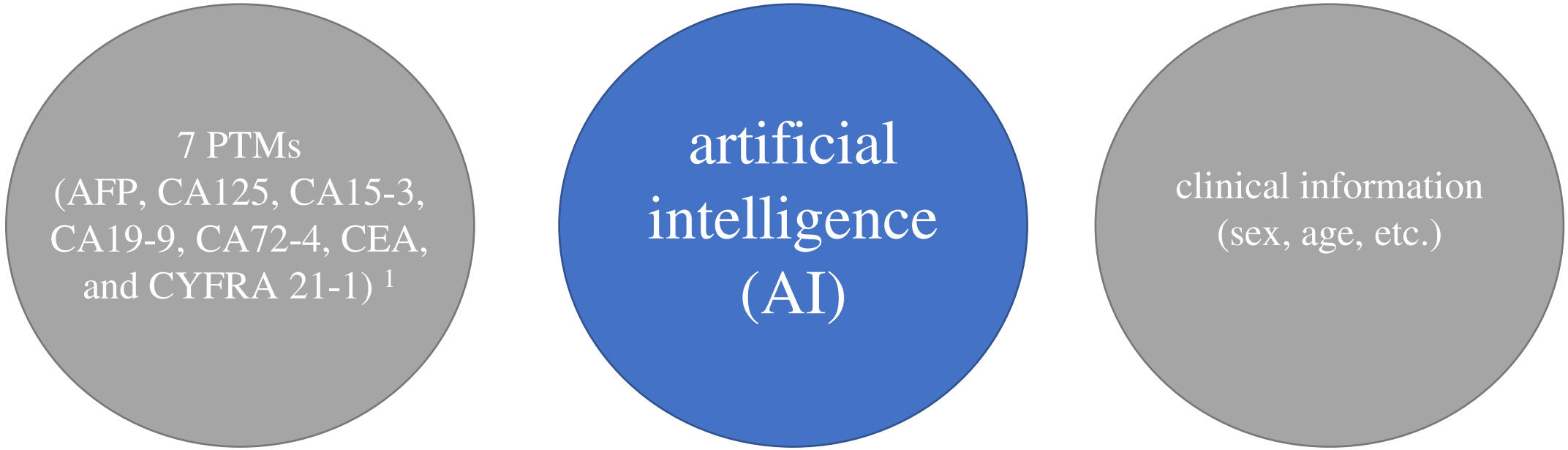
AI-powered MCED Test - OncoSeek



PTM: Protein Tumor Markers

1. Ji X, Li J, Huang Y, et al. Identifying occult maternal malignancies from 1.93 million pregnant women undergoing noninvasive prenatal screening tests. Genetics in Medicine 2019; 21: 2293–302.

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The Performance of OncoSeek Was Validated in a Large Study

	Training cohort	Independent validation cohort 1	Independent validation cohort 2*	Independent validation cohort 3
Sample origin	SeekIn/China	SYSMH/China	JHUSM/USA	BGI/China
Sample type	Plasma	Serum	Plasma	Plasma
Platform	Roche cobas e411	Roche cobas e601	Bio-Rad Bio-Plex 200	GBI ELISA
Sample size	Cancer (n = 591) Non-cancer (n = 1055)	Cancer (n = 363) Non-cancer (n = 5556)	Cancer (n = 1005) Non-cancer (n = 812)	Cancer (n = 34) Non-cancer (n = 416)

Breast **Colorectum** **Liver** **Lung** **Lymphoma** **Oesophagus** **Ovary** **Pancreas** **Stomach**

SYSMH: Sun Yat-sen Memorial Hospital, Sun Yat-sen University
JHUSM: Johns Hopkins University School of Medicine.
*Cohen, et al. Science. 2018 Feb 23;359(6378):926-930.

Luan, Y., Zhong, GL., Li, SY., Wu, W., Liu, SQ., Zhu, DD., Feng, YM., Zhang, YX., Duan, CH., and Mao, M. A panel of seven protein tumour markers for effective and affordable multi-cancer early detection by artificial intelligence: a large-scale and multicentre case–control study, eClinicalMedicine 2023;61: 102041

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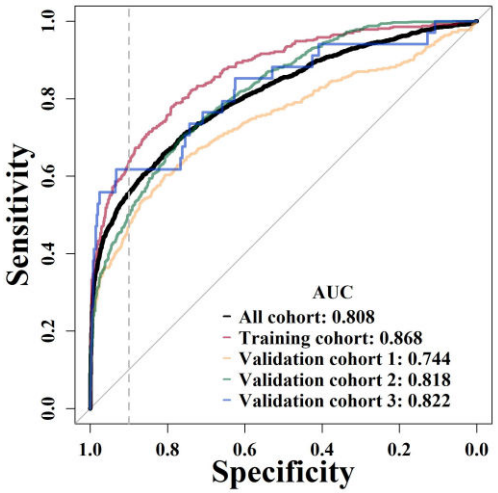
The Data Strongly Proved the Robustness of the OncoSeek Test



	Training cohort (SeekIn/China)		Independent validation cohort 1 (SYSMH/China)		Independent validation cohort 2 (JHUSM/USA)		Independent validation cohort 3 (BGI/China)	
	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Predict cancer	344	105	141	332	527	90	19	21
Predict non-cancer	247	950	222	5224	478	722	15	395
Sensitivity (95% CI)	58·2% (54·1%, 62·2%)		38·8% (33·8%, 44·1%)		52·4% (49·3%, 55·6%)		55·9% (37·9%, 72·8%)	
Specificity (95% CI)	90·0% (88·1%, 91·8%)		94·0% (93·4%, 94·6%)		88·9% (86·6%, 91·0%)		95·0% (92·4%, 96·8%)	
PPV (95% CI)	76·6% (72·4%, 80·5%)		29·8% (25·7%, 34·2%)		85·4% (82·4%, 88·1%)		47·5% (31·5%, 63·9%)	
NPV (95% CI)	79·4% (77·0%, 81·6%)		95·9% (95·4%, 96·4%)		60·2% (57·3%, 63·0%)		96·3% (94·0%, 97·9%)	

SYSMH: Sun Yat-sen Memorial Hospital, Sun Yat-sen University. JHUSM: Johns Hopkins University School of Medicine.
PPV: positive predictive value. NPV: negative predictive value.

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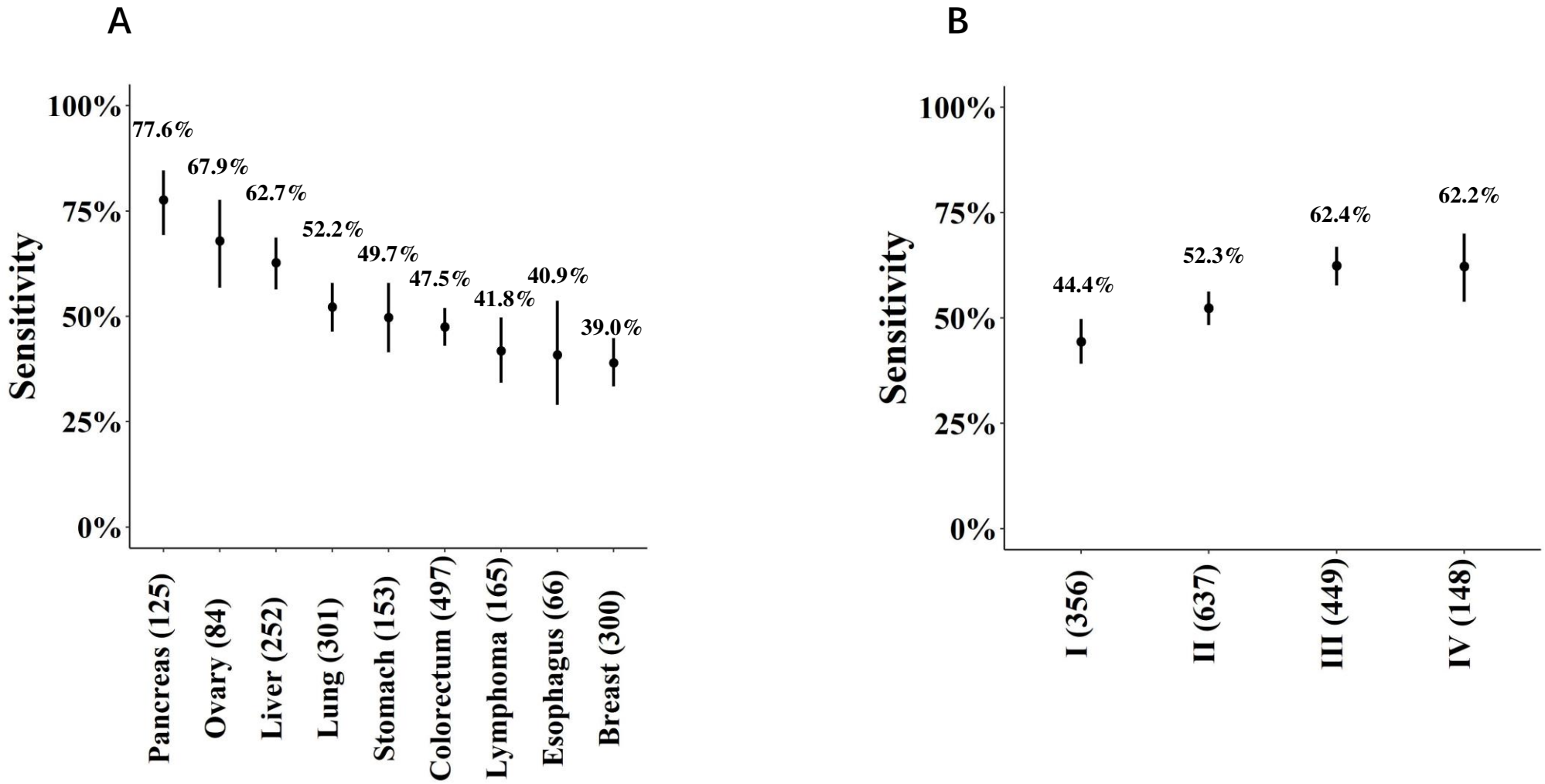
The Performance of OncoSeek Test in Different Cancer Types and Stages



Luan, Y., Zhong, GL., Li, SY., Wu, W., Liu, SQ., Zhu, DD., Feng, YM., Zhang, YX., Duan, CH., and Mao, M. A panel of seven protein tumour markers for effective and affordable multi-cancer early detection by artificial intelligence: a

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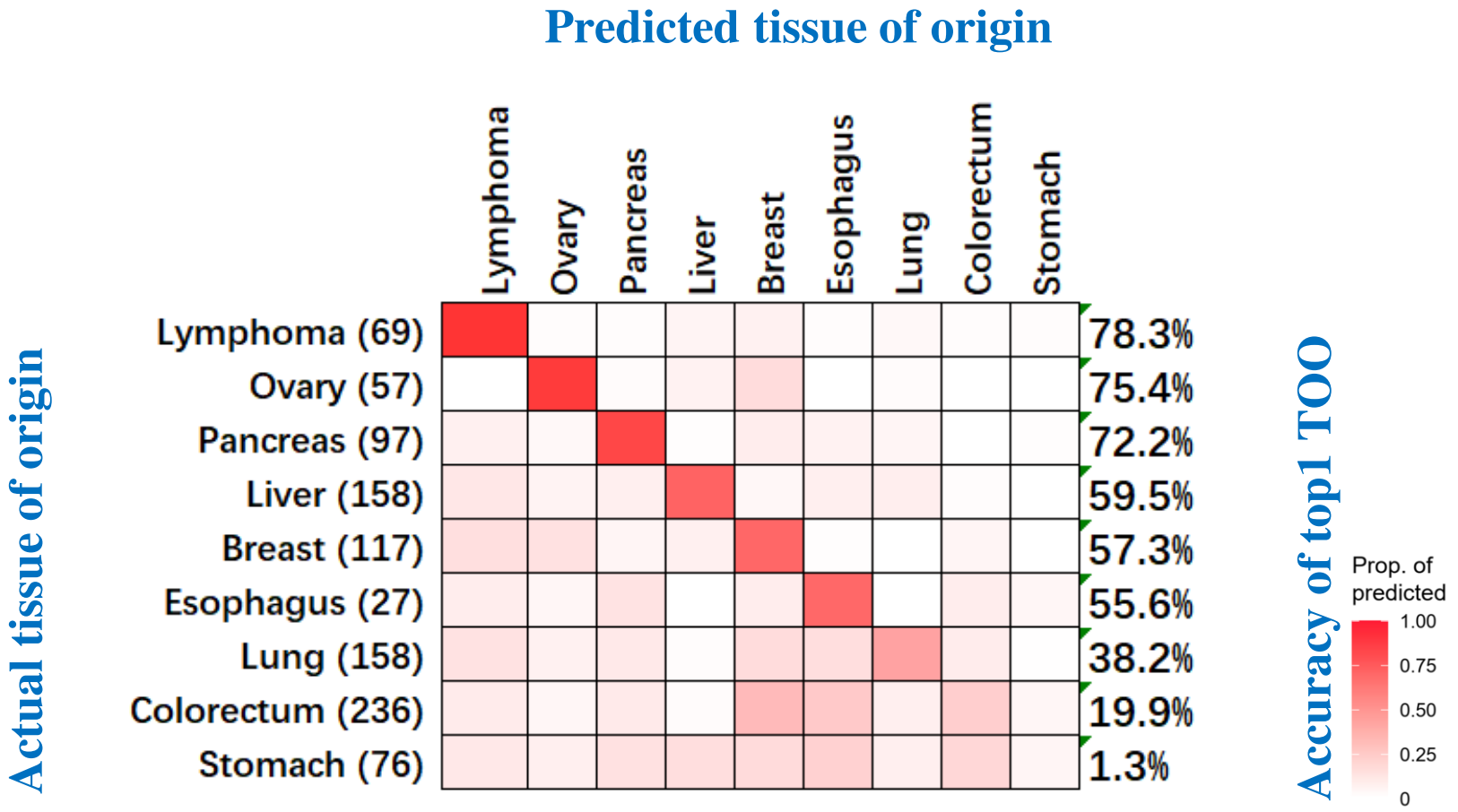
Tissue of Origin (TOO) Accuracy by Individual Cancer Type



The overall accuracy of the top two most possible organ systems in the true positives was **65.4%**, which could assist the clinical diagnostic workup.

Luan, Y., Zhong, GL., Li, SY., Wu, W., Liu, SQ., Zhu, DD., Feng, YM., Zhang, YX., Duan, CH., and Mao, M. A panel of seven protein tumour markers for effective and affordable multi-cancer early detection by artificial intelligence:

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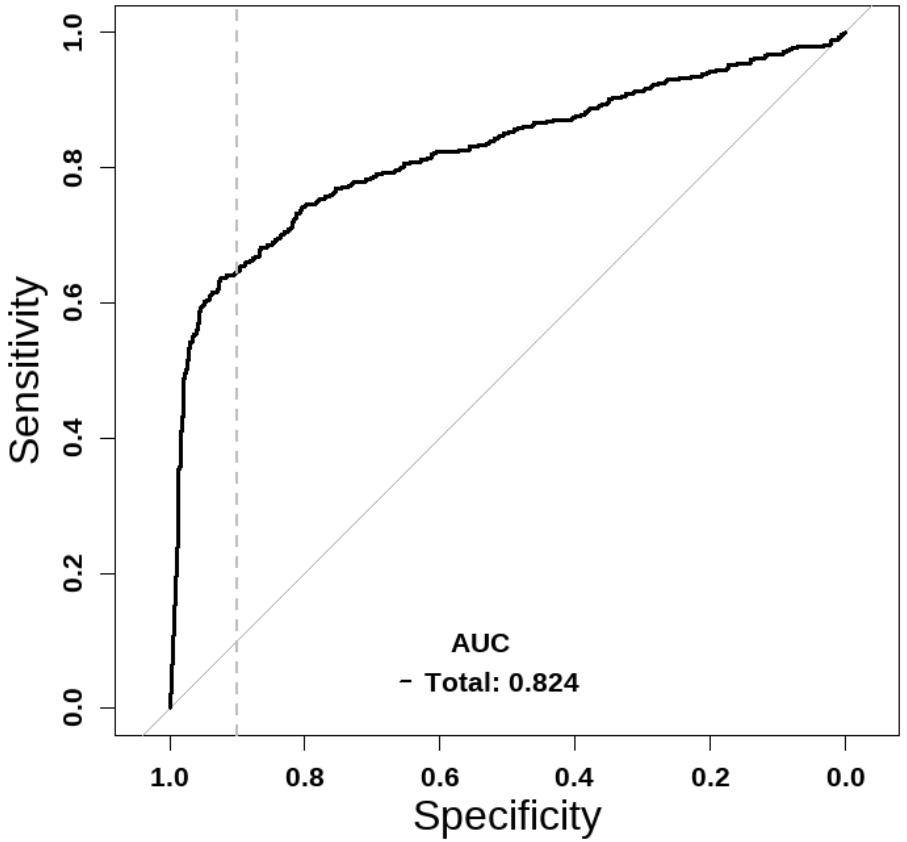
Independent Validation 4 From Henan Cancer Hospital (n=1350)

Early diagnosis:
We retrospectively reviewed 613 samples from Henan Cancer Hospital, collecting PTMs from patients with clinical symptoms who required further confirmation through biopsy or surgery. Given the limited number of cases diagnosed as non-cancer (108), we augmented the non-cancer group by including 737 non-cancer patients from the health check center at the same hospital.



	validation 4 (HNCH/China)	
	Cancer	Non-cancer
Predict cancer	369	159
Predict non-cancer	136	686
Sensitivity (95% CI)	73.1% (69.0%, 76.9%)	
Specificity (95% CI)	81.2% (78.4%, 83.8%)	
PPV (95% CI)	69.9% (65.8%, 73.8%)	
NPV (95% CI)	83.5% (80.7%, 85.9%)	

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Independent Validation Cohort 5 From Brazil (n=59)

Real world evaluation from Brazilian clinician	Total #	Predict negative	Predict Positive	
		Low Risk	Medium Risk	High Risk
Cancer patients without cancer-related treatment	2	1	1	
Cancer patients with recent treatment and cancer residue	4			4
Cancer patients with recent treatment and no cancer residue	3	3		
Patients with a cancer history, having undergone radical surgery and completed all treatments over two years ago (Non-cancer)	11	10	1	
Non-cancer individuals without a history of cancer	39	35	4	

Sensitivity: 5/6 = 83.3%
Specificity: 48/53 = 90.6%

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OncoSeek Workflow

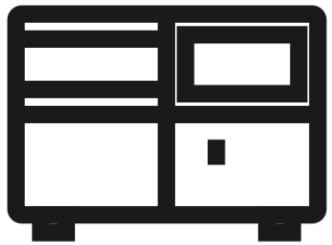
1. Sample collection

Collect a tube of blood

2. Transportation

Mail to central lab

3. PTM quantification



Quantify by ECLI

4. Data analysis

POC & TOO by AI

$20

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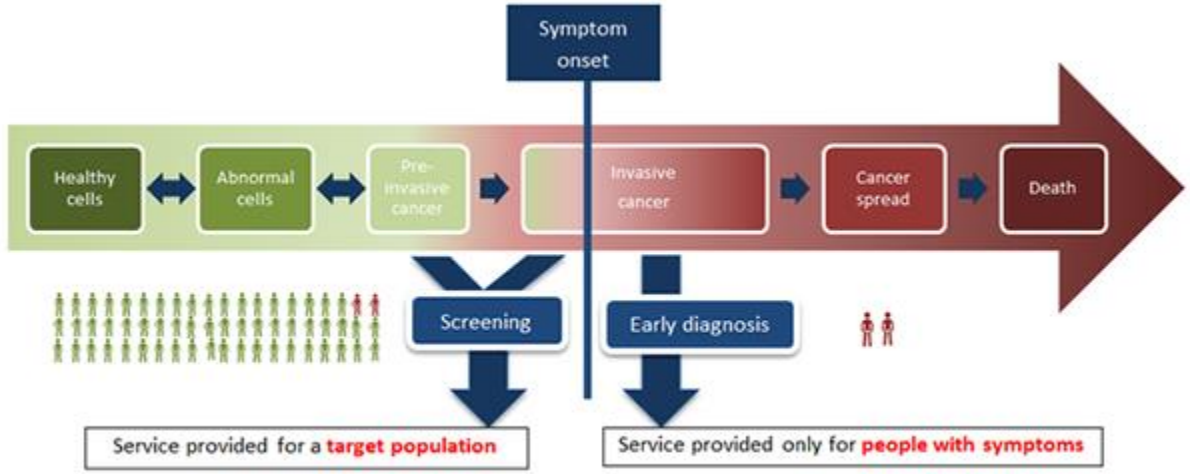
Three Applications



Screening

Screening applies tests to a population who do not have signs or symptoms of a cancer and who are at average risk for it. OncoSeek conducts risk screening for nine high prevalent cancers among individuals and identifies high-risk individuals. By closely monitoring them, cancer can be detected in a curable stage. (52% sensitivity/93% specificity)

Early diagnosis

Early diagnosis is a critical public health strategy in all settings due to the improved outcomes by treatment at as the earliest stage as possible. In the early stages, surgery and radiotherapy are often successful. OncoSeek is proven to detect cancer from people with symptoms and trace the TOO efficiently, helping patients reduce the time to diagnose and enable them take appropriate treatment as early as possible. (66% sensitivity/81% specificity)

Reducing false-positives

With the support of AI algorithms, OncoSeek has reduced false-positive rate nearly 7-fold for the general population undergoing annual physical checks, effectively addressing the issue of high false-positive rates associated with tumor marker panels. This ensures accurate and reliable testing results for individuals undergoing annual physical checks. (false positive rate 46% -> 7%)

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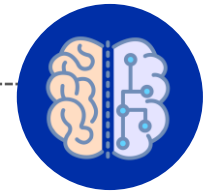
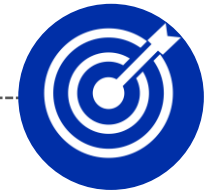
Conclusions

1.  OncoSeek is a blood test and empowered by artificial intelligence algorithm for multi-cancer early detection.

2.  This test showed high specificity and sufficient sensitivity as an MCED test.

3.  The high accuracy of tissue of origin of this test could help direct the diagnostic workup.

4.  This test is affordable ($20) and accessible requiring nothing more than a blood draw at the screening sites, which makes it acceptable and sustainable in LMICs.

5.  The next step is to conduct a large-scale prospective study of OncoSeek and to explore the clinical utility of this test.

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Pan-cancer products

思康宁®

SeekIn Care®

Pan-cancer early detection

SeekIn Cure™

思康安®

Pan-cancer Recurrence monitoring

SeekInClarity™

Pan-cancer Treatment Response monitoring

思康明®

Indicated subjects:	Healthy population	Post-op patients of radical resection	Late-stage patients
Launch date:	Nov. 2018	May 2019	Aug. 2020

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Product – SeekInCare®

思康宁®
SeekInCare®

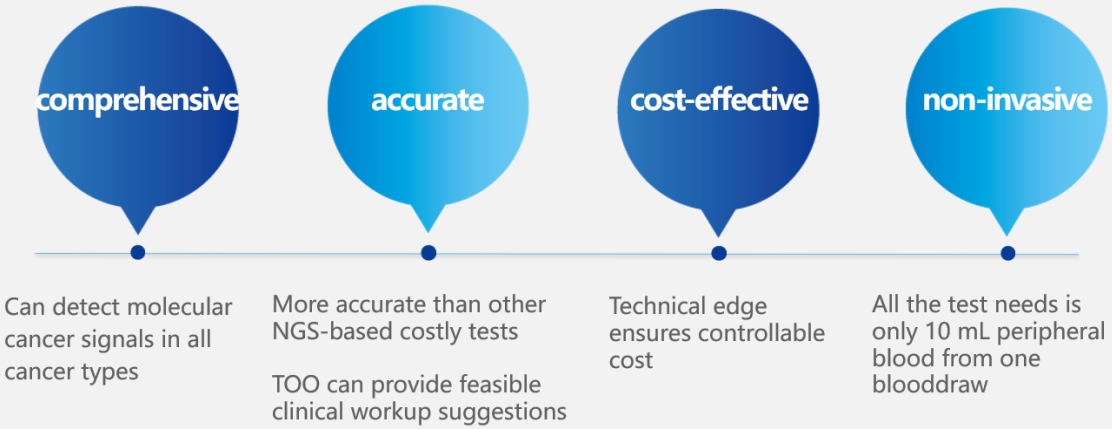
the first-in-class blood-based pan-cancer early detection test

CE Marking

A panoramic view of cancer genomics landscape + protein markers

Big data + AI

A blood-based test generating CRS and locating TOO



" An inborn pan-cancer early detection test"

Methodology paper: Meng Z, et al. Non-invasive detection of hepatocellular carcinoma with circulating tumor DNA features and AFP. J Mol Diagn. 2021 Sep;23(9):1174-1184.

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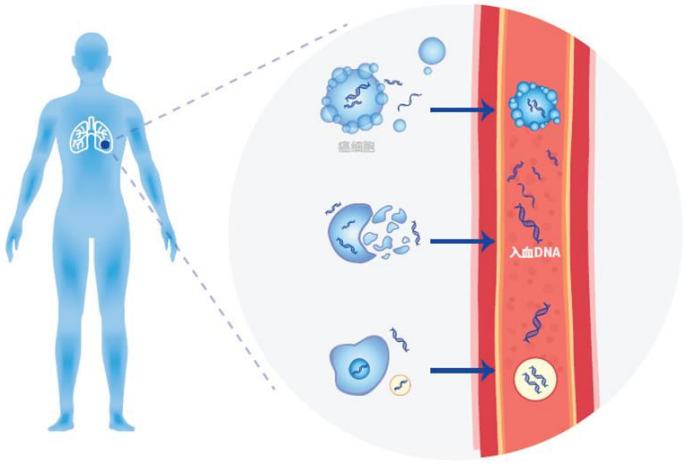
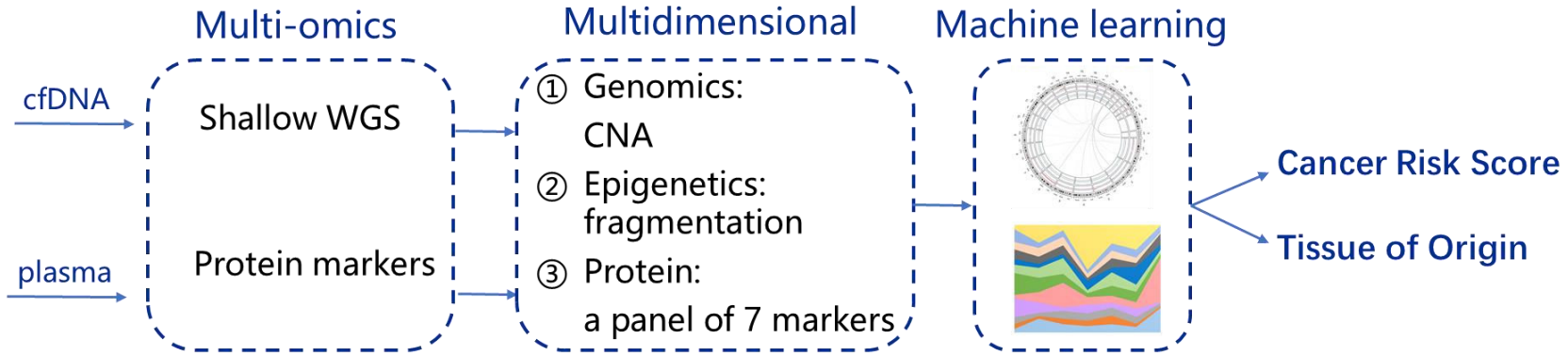
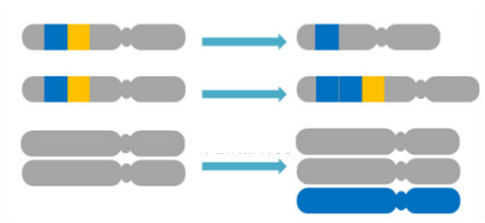
Technical edge



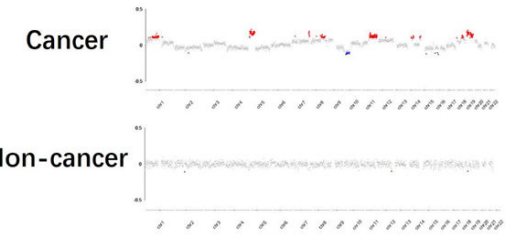


We capture the cancer genomic landscape via a panoramic view by shallow WGS. Thus cancer hallmarks such as CNA and fragment size in conjunction with protein biomarkers can be utilized to refine the MCRS model.

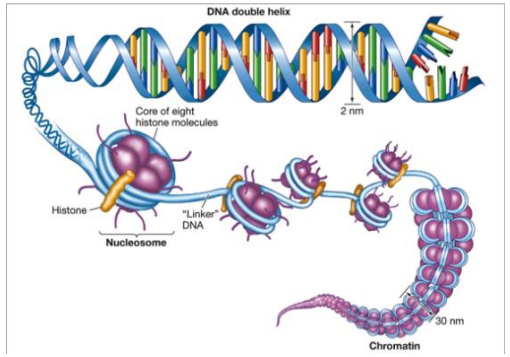
① Copy number aberration (CNA)

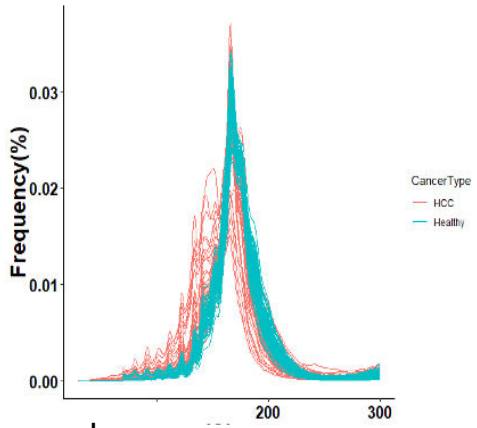


CNA analysis from cfDNA sWGS



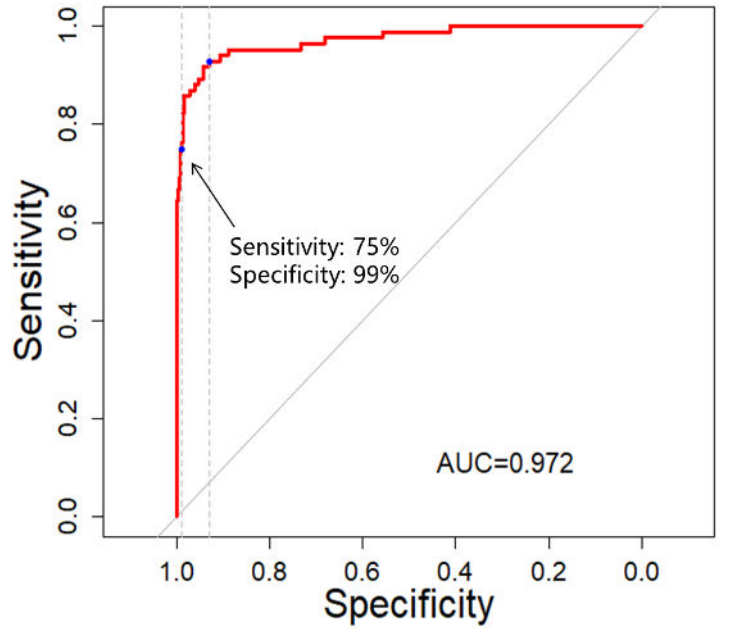
② Fragmentation





③ Protein markers

AFP, CEA, CA199, CA125, CA153, CA211, CA724



Case-control validation studies

Company	Method	Cancer	Normal	Cancer Types	Sensitivity (%)	Specificity (%)	TOO (%)
GRAIL[4]	cfDNA methylation panel	2823	1254	>50	51.5	99.5	TOP1: 89
Exact Sciences[5]	Mutation panel (plasma + WBC) + methylation panel + REALSeqS + Proteins	566	566	15	61.0	98.2	No
SeekIn[3]	sWGS + 7 proteins	617	584	27	65.5	97.9	TOP1: 70 TOP2: 85

1. Klein, E. A., et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Annals of Oncology, 32(9), 11. (2021).
2. Douville, C., et al. Multi-cancer early detection through evaluation of aneuploidy, methylation, mutation, and protein biomarkers in plasma. Poster at ESMO 2022
3. Mao M., et al. Integrating multi-omics features for blood-based pan cancer early detection. Poster at The 2022 Early Detection of Cancer Conference in Portland

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Prospective/real world studies

Study	# of cases	# of test positive	# of cancers	# of cancers identified by test	# of false positive cases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	# of SOS*	Follow-up (median month)	Cancer Types
DETECT-A[6]	10006	134	96	26	108	27.1	98.9	19.4	99.3	24	>12	10
PATHFINDER[7]	6621	92	121	35	57	28.9	99.1	38.0	98.6	48	>12	16
SeekInRW	1203	52	10	6	46	60.0	96.1	11.5	99.7	-	24.8	5

*Cancer identified by clinical standard of screening (SOS)

1. Lennon, A. M., et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science, 369(6499), eabb9601. (2020).
2. Schrag, D. PATHFINDER: A Prospective Study of a Multi-Cancer Early Detection Blood Test. Oral presentation at ESMO 2022.

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SeekInCare vs OncoSeek

	SeekInCare	OncoSeek
Method	sWGS + 7 PTMs	7 PTMs
Cancer	616	1993
Normal	898	7839
Cancer types	27	20
Sensitivity (%)	66%	52%
Specificity (%)	98%	93%
TOO (%)	85%	65%
Cost	$ 185	$ 25