燃石医学
Burning Rock Dx

Burning Rock Biotech Limited

4Q2021 results presentation

BNR US Equity

22 Mar 2022

Disclaimer

This presentation has been prepared by Burning Rock Biotech Limited (the "Company") solely for information purpose and has not been independently verified. No representations, warranties or undertakings, express or implied, are made by the Company or any of its affiliates, advisers, or representatives as to, and no reliance should be placed upon, the accuracy, fairness, completeness or correctness of the information or opinions presented or contained in this presentation. None of the Company or any of its affiliates, advisers or representatives accept any responsibility whatsoever (in negligence or otherwise) for any loss howsoever arising from any information presented or contained in this presentation or otherwise arising in connection with the presentation. The information presented or contained in this presentation is subject to change without notice and its accuracy is not guaranteed.

Certain statements in this presentation, and other statements that the Company may make, are forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended. These statements reflect the Company's intent, beliefs or current expectations about the future. These statements can be recognized by the use of words such as "expects," "plans," "will," "estimates," "projects," "intends," "anticipates," "believes," "confident" or words of similar meaning. These forward-looking statements are not guarantees of future performance and are based on a number of assumptions about the Company's operations and other factors, many of which are beyond the Company's control, and accordingly, actual results may differ materially from these forward-looking statements. The Company or any of its affiliates, advisers or representatives has no obligation and does not undertake to revise forward-looking statements to reflect future events or circumstances.

This presentation does not constitute an offer to sell or issue or an invitation to purchase or subscribe for any securities of the Company for sale in the United States or anywhere else. No part of this presentation shall form the basis of or be relied upon in connection with any contract or commitment whatsoever.

THE INFORMATION CONTAINED IN THIS DOCUMENT IS BEING GIVEN SOLELY FOR YOUR INFORMATION AND ONLY FOR YOUR USE IN CONNECTION WITH THIS PRESENTATION. THE INFORMATION CONTAINED HEREIN MAY NOT BE COPIED, REPRODUCED, REDISTRIBUTED, OR OTHERWISE DISCLOSED, IN WHOLE OR IN PART, TO ANY OTHER PERSON IN ANY MANNER. ANY FORWARDING, DISTRIBUTION OR REPRODUCTION OF THIS PRESENTATION IN WHOLE OR IN PART IS UNAUTHORIZED.

By viewing, accessing or participating in this presentation, participants hereby acknowledge and agree to keep the contents of this presentation and these materials confidential. Participants agree not to remove these materials, or any materials provided in connection herewith, from the conference room where such documents are provided. Participants agree further not to photograph, copy or otherwise reproduce this presentation in any form or pass on this presentation to any other person for any purpose, during the presentation or while in the conference room. Participants must return this presentation and all other materials provided in connection herewith to the Company upon completion of the presentation. By viewing, accessing or participating in this presentation, participants agree to be bound by the foregoing limitations. Any failure to comply with these restrictions may constitute a violation of applicable securities laws.

Our value-building blocks

Extending leadership of NGS-based precision oncology from late-stage patients to earlier stages, driving the next phase of growth

New Businesses

Large market potential

At pipeline or early commercial stage

Early Detection

Asymptomatic population

MRD

Early-stage oncology patients

Biopharma

Global CDx partner for pivotal trials of targeted drugs. Pharma R&D

Common Infrastructure

Accelerating growth of new businesses

- Strong brand to support new product launches & attract talent
- Broad industry network and synergy across different business units
- Large volumes supporting lower cost & faster innovation

Base Business

Commercial stage

Therapy Selection

Late-stage oncology patients

Recap of 2021 and recent progress

Therapy selection

- Achieved 38% volume growth year-on-year, reaching 70k+ units (central-lab and in-hospital combined) during 2021, out-growing industry
- Strong market share gain through in-hospital strategy; in-hospital volume growth of 63% in 2021
- 18% revenues growth to RMB508m, slightly above revised guidance of RMB500m[1]
- Achieved NMPA approval of our second NGS kit[2]

MRD

- Completed product development, based on a personalized approach
- First datasets (NSCLC[3] and CRC[4] post-operative prognosis) reading out at AACR
- Commercial launch in March 2022

Biopharma

- Fast build-up of backlog projects. Contract value of RMB183m signed during 2021, 5.7x vs. 2020

Early detection

- Clinical – 9-cancer test development on track. First large cohort (PROMISE study, c. 2,000 participants) completed enrollment and reading out in 2022

Notes:
[1] ˜Lower unit price in in-hospital channel vs. central-lab dragged blended ASP
[2] Details in our announcement on 15th Mar 2022, Burning Rock Secures Second NGS Kit Approval from the NMPA
[3] Non-small cell lung cancer
[4] Colorectal cancer

2022 outlook

Therapy selection

- New product launches to expand into additional indications[1]
- Continued drive towards in-hospital testing, with accelerating number of newly contracted hospitals, and volume ramp of existing hospitals
- Accelerated revenue growth vs. 2021 (initial 2022 revenue guidance of RMB620m, +22%)
- Efficiency improvement, with selling expenses as % of revenues to shrink vs. 2021

MRD

- Commercial ramp-up
- Additional studies with additional cancer types under planning

Biopharma

- Continued build-up of project backlog
- Higher contribution to overall revenues vs. 2021

Early detection

- Clinical – First intended-use population multi-cancer interventional study in China (PREVENT study) to launch in 2022
- Commercial – driving increased product contracting with hospital health check-up departments

Notes:
[1] DetermaRx for early stage lung cancer, myChoice HRD Plus as a gold-standard for HRD score

NMPA approved NGS panels

NMPA approved testing kit by major NGS-focused companies[1]

	First NMPA-approved kit	Second NMPA-approved kit
燃石医学 Burning Rock Dx	EGFR, ALK, BRAF, KRAS Approved in Jul **2018** First approved NGS kit in China	EGFR, KRAS, MET, ERBB2, BRAF, PIK3CA, ALK, ROS1, RET Approved in Mar **2022**
Novogene 诺禾	EGFR, KRAS, BRAF, PIK3CA, ALK, ROS1 Approved in Aug **2018**	
Geneseeq 世和	EGFR, ALK, ROS1, BRAF, KRAS, ERBB2 Approved in Sep **2018**	
BGI 华大	EGFR, KRAS, ALK Approved in Aug **2019**	
Gene+ 吉因加	EGFR, KRAS, ALK Approved in Dec **2019**	
Genetron 泛生子	EGFR, KRAS, BRAF, ERBB2, PIK3CA, ALK, ROS1, MET Approved in Feb **2020**	
Genecast 臻和	KRAS, NRAS, BRAF, PIK3CA Approved in Mar **2021**	
3DMed 思路迪		

Highlights on our second NMPA-approved kit

- Only 30ng DNA input required, applicable to small tissue samples
- First NMPA approved NGS kit with CNV[2] mutation type, with MET exon14 skipping

Notes:
[1] Major NGS-focused companies listed. The list is not exhaustive. A total of 13 kits have been approved by the NMPA as of the date of this presentation
[2] Copy number variation

燃石医学
Burning Rock Dx

Early detection

Product development since 2016

Demonstrated high specificity (>98%) and tissue-of-origin detection capability

Proof-of-concept
2016 – 2019

- Proof of concept on our methylation based, machine learning aided technology platform
- Results published on *Nature Biomedical Engineering*, "Ultrasensitive detection of circulating tumour DNA via deep methylation sequencing aided by machine learning"

3-cancer
2017 – 2020

- Lung, Colorectal Cancer (CRC), Hepatocellular Carcinoma (HCC)
- Results released at AACR Special Conference on Liquid Biopsy, Jan 2020
- 95.1% specificity and 80.8% sensitivity[1]

Product development complete. Entering commercialization 2022

6-cancer
2018 – Nov 2020

- Lung, CRC, HCC, Ovarian, Pancreatic, Esophageal
- Results released at ESMO Asia, Nov 2020
- 98.3% specificity and 80.6% sensitivity[2]
- Tissue-of-origin (TOO) result in 98.6% cases; accuracy 81.0%

Product development in progress

9-cancer
2019 – Ongoing

- Additional cancer types: Gastric, Biliary Tract, Head & Neck
- Ongoing PROMISE study and PREDICT study

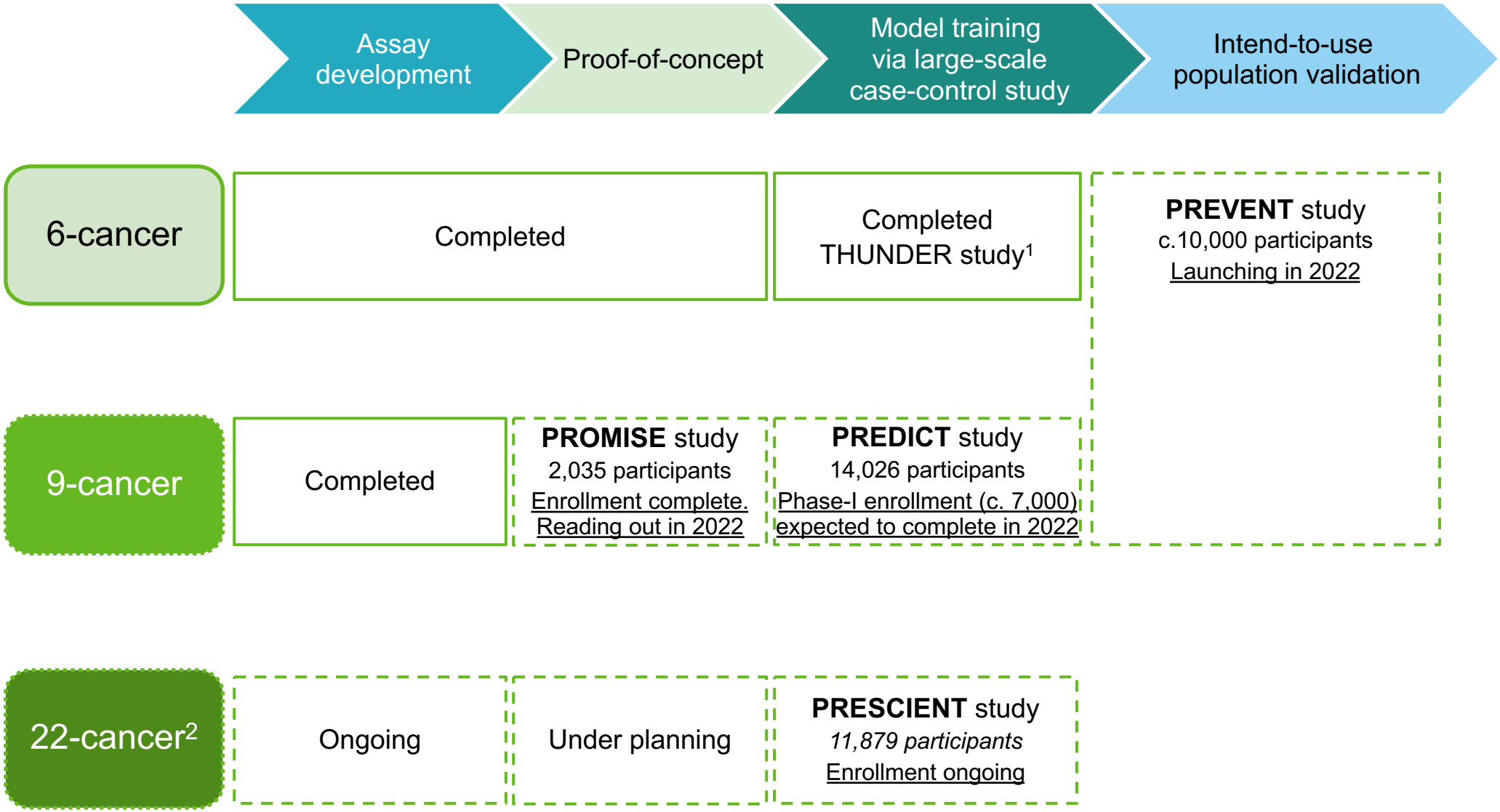
22-cancer[3]
2020 – Ongoing

- BR-22 covers 88% of China's cancer incidence
- Ongoing PRESCIENT study

Notes:
[1] Training and validation cohorts combined, 490 cancer samples, 226 control samples. Sample size is aggregated through a series of case-control studies. 95.1% specificity (95% CI 91.2-97.4) and 80.8% sensitivity (95% CI 77.0-84.1)
[2] Validation cohort, 351 cancer samples, 288 control samples. Sample size is aggregated through a series of case-control studies. 98.3% specificity (95% CI 95.8-99.4) and 80.6% sensitivity (95% CI 76.0-84.6). Further details in Appendix 1.
[3] Final number of cancer types subject to development progress

Clinical programs

9-cancer first read-out expected in 2022



Notes:
[1] THUNDER series of studies. Latest results presented at ESMO Asia, Nov 2020
[2] Final number of cancer types subject to development progress

Burning Rock's early detection technology

Globally competitive technology with multi-cancer validation

Competitive technology

Methylation + machine learning to overcome challenges of low ctDNA abundance and TOO, leading to feasibility for multi-cancer early detection

Multi-cancer validation data

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-021-00746-5

Check for updates

Ultrasensitive detection of circulating tumour DNA via deep methylation sequencing aided by machine learning

VIRTUAL 2020 ESMO ASIA

Early detection and localization of multiple cancers using a blood-based methylation assay (ELSA-seq)

← AACR Annual Meeting 2022 Itinerary Planner Home

Session OPO.CL11.01 - Biomarkers

5116 - Analytical performance of ELSA-seq, a blood-based test for early detection of multiple cancers

Session OPO.CL11.01 - Biomarkers

5109 - Development of cfDNA reference standards for methylation-sequencing tests

Data read-out on analytical performance of ELSA-seq

← AACR Annual Meeting 2022 Itinerary Planner Home

Session OPO.CL11.01 - Biomarkers

5116 - Analytical performance of ELSA-seq, a blood-based test for early detection of multiple cancers

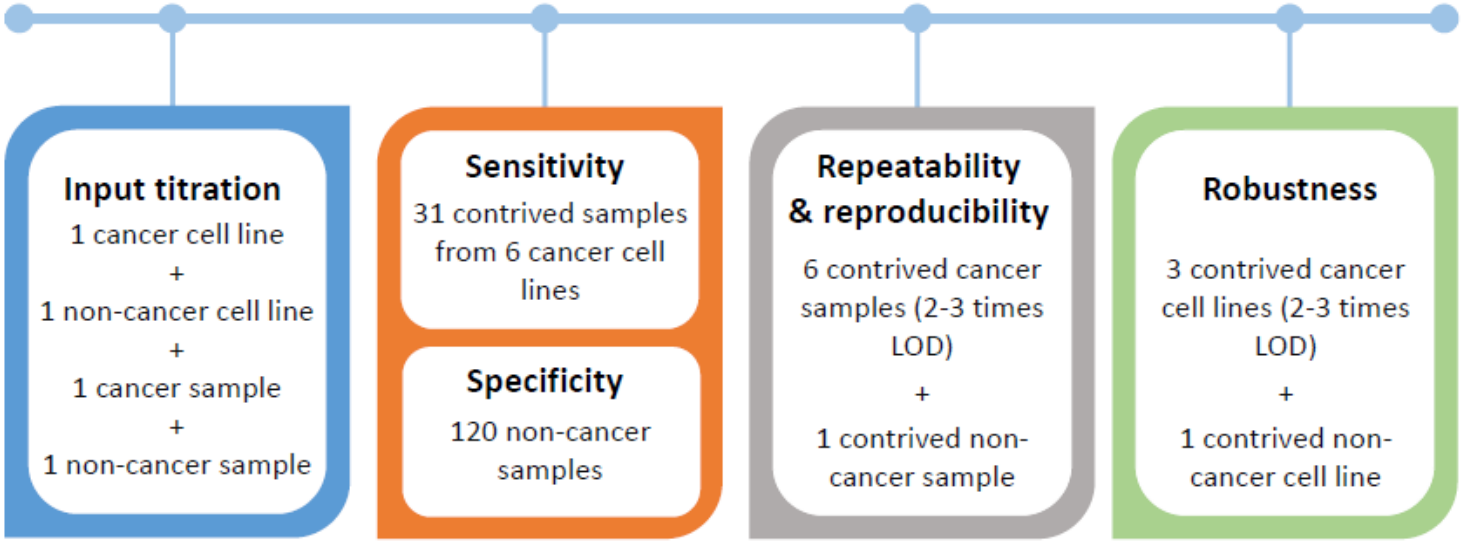


Figure 1: Analytical validation of the Multi-Cancer Detection Blood Test (MCDBT). Input titration, analytical sensitivity, specificity, repeatability, reproducibility, and robustness were assessed for two models (MCDBT-1 and MCDBT-2), which show different likelihood ratios for updating the chance of an individual suffering from cancer.

Full analytical validation study was conducted on ELSA-seq. LoD was demonstrated to be between 0.02% and 0.11% across different cancer types.

Leadership in multi-cancer early detection

First-in-class, high entry-barrier, multi-year effort

	Challenges	BNR position
1 Technology	**Low amount of cancer signal** in the circulating bloodstream, much more challenging vs. tissue	**Proprietary chemistry and algorithm** • On par with global leader, competitive sensitivity in earlier stages for certain cancers • Multi-year lead vs. China peers (most showing liver-cancer and colon-cancer data only)
2 Clinical	**Large, multi-year studies required** from case-control to intend-to-use population, from observational to interventional (e.g. CCGA study: 15,254 participants, 8,584 with cancer, 6,670 without cancer)	**Sponsorship from top physicians** • Catching up with global leader, to improve specificity and tissue-of-origin performance through large clinical studies • Multi-year lead in China as the only company with studies over 10,000+ subject scale launched
3 Regulatory	**First-in-class in nature** with no established regulatory pathway	**Leading regulatory capability in China** • Exploring possible pathway, leveraging experience through the country's first NGS kit approval by the NMPA
4 Commercial	**Unprecedented product**	**Multi-pronged approach** • Initially working with hospital health check-up departments, leveraging synergy from in-hospital therapy selection business

Leadership from top-tier principal investigators key to clinical success

Also drives increasing recognition on multi-cancer early detection among clinicians

PREDICT

- Leading site: Shanghai Zhongshan Hospital
  - One of China's largest comprehensive academic hospitals
  - Performs c.104,000 operations and serves c.169,000 inpatients and over 4,236,000 outpatients on an annual basis[1]
  - Ranked top 5 in the 2019 China's general hospital rankings[2]
- Other sites include but not limited to
  - Ruijin Hospital
  - Shanghai Jiaotong University School of Medicine
  - Fudan University Shanghai Cancer Center

Principal Investigator: Prof. Jia Fan

- Fellow of the Chinese Academy of Sciences
- President of Shanghai Zhongshan Hospital

PRESCIENT

- Leading site: Cancer Hospital of the Chinese Academy of Medical Sciences[3]
  - The first and top cancer-specialist hospital in China
  - The National Clinical Center for Cancer Research, the National Center for Quality Control on Standardized Cancer Treatment and Diagnosis, the National Clinical Center for Drug Research
- Other sites include but not limited to
  - Beijing Cancer Hospital
  - Jilin Cancer Hospital
  - Hubei General Hospital

Principal Investigators

Prof. Jie He

Prof. Jie Wang

Head of the Dept. of Medicine, CHCAMS

- Fellow of the Chinese Academy of Sciences
- President of CHCAMS

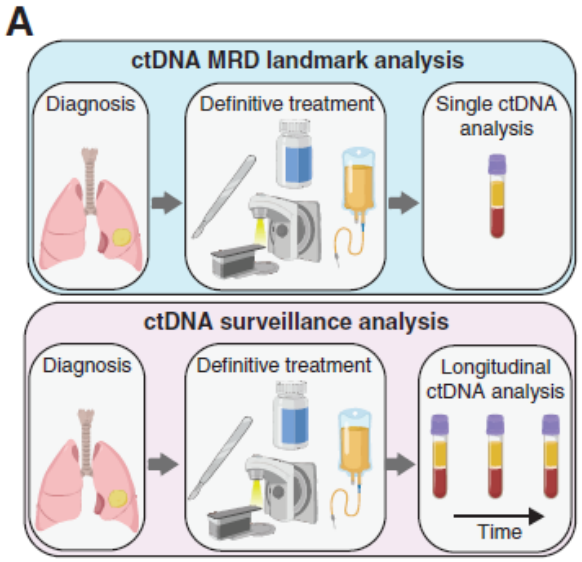
Notes:
[1] Based on 2018 statistics
[2] http://rank.cn-healthcare.com/rank/general-best
[3] CHCAMS

燃石医学
Burning Rock Dx

MRD

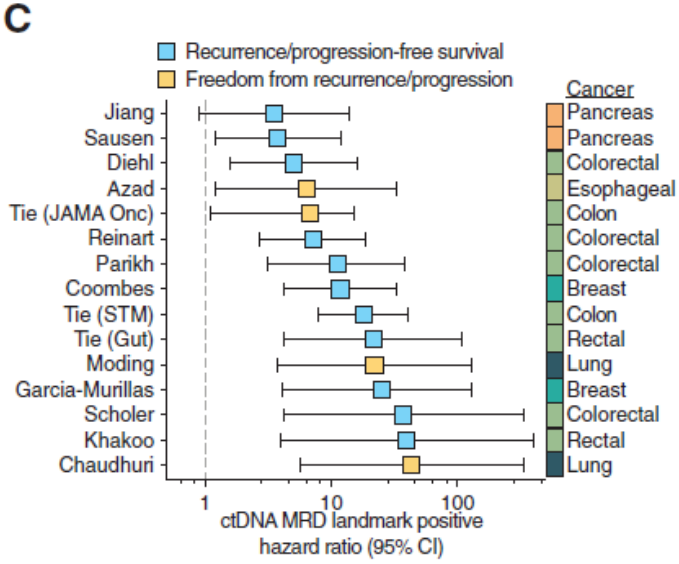
Clinical utilities of MRD in solid tumors

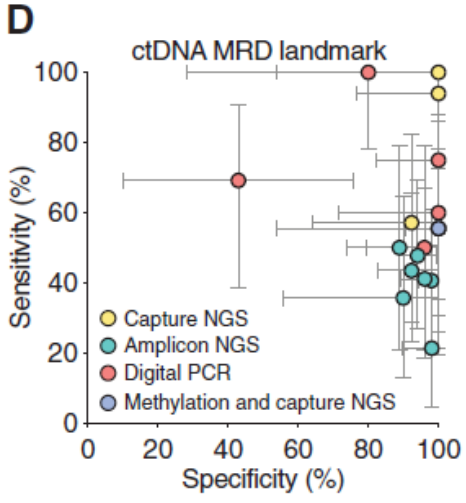
1) risk stratification and regimen selection (landmark analysis), 2) relapse monitoring (surveillance analysis)

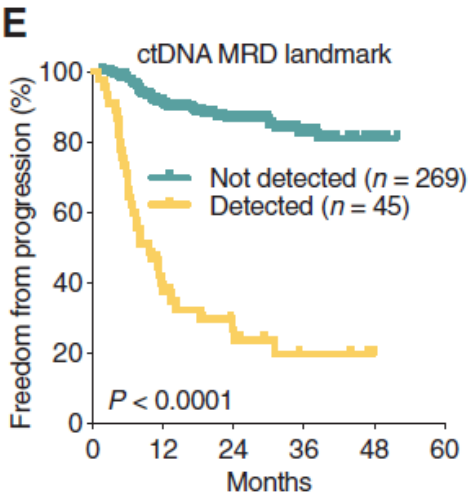


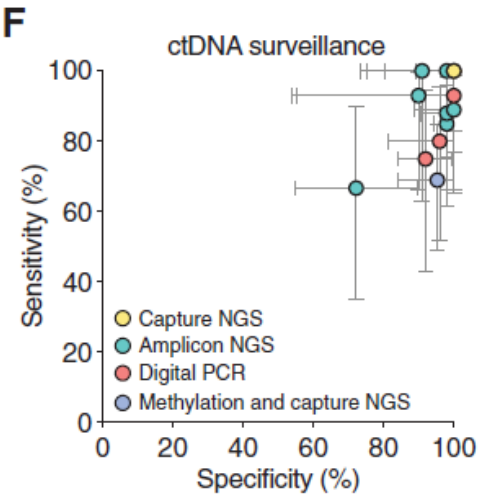
B

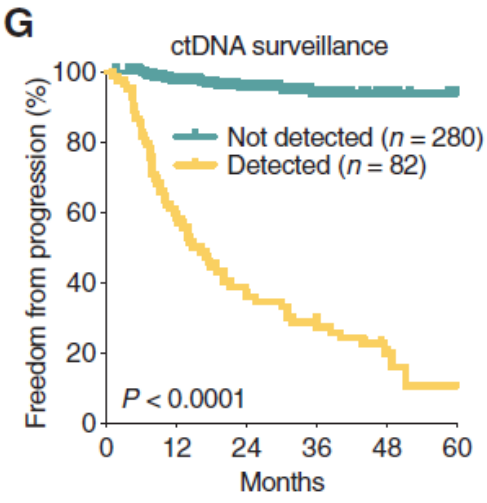
Cancer	Reference	# Patients	Analysis Landmark	Analysis Surveillance
Lung	Peng (111)	48	Yes	Yes
Lung	Chaudhuri (62)	37	Yes	Yes
Lung	Abbosh (31)	24	Yes	Yes
Lung	Moding (90)	12	Yes	No
Breast	Garcia-murillas (113)	101	No	Yes
Breast	Coombes (34)	49	Yes	Yes
Breast	Garcia-murillas (27)	43	Yes	Yes
Breast	Olsson (112)	20	No	Yes
Colon	Tie (91)	178	Yes	Yes
Rectal	Tie (89)	159	Yes	No
Colorectal	Reinert (36)	94	Yes	Yes
Colon	Tie (92)	88	Yes	No
Colorectal	Parikh (52)	72	Yes	Yes
Colon	Wang (114)	40	No	Yes
Colorectal	Schøler (28)	26	Yes	Yes
Rectal	Khakoo (109)	23	Yes	No
Colorectal	Diehl (107)	20	Yes	No
Esophageal	Azad (65)	20	Yes	No
Pancreas	Jiang (110)	27	Yes	No
Pancreas	Sausen (108)	20	Yes	No
Bladder	Christensen (35)	66	Yes	Yes
	Total	**1167**	**18**	**13**









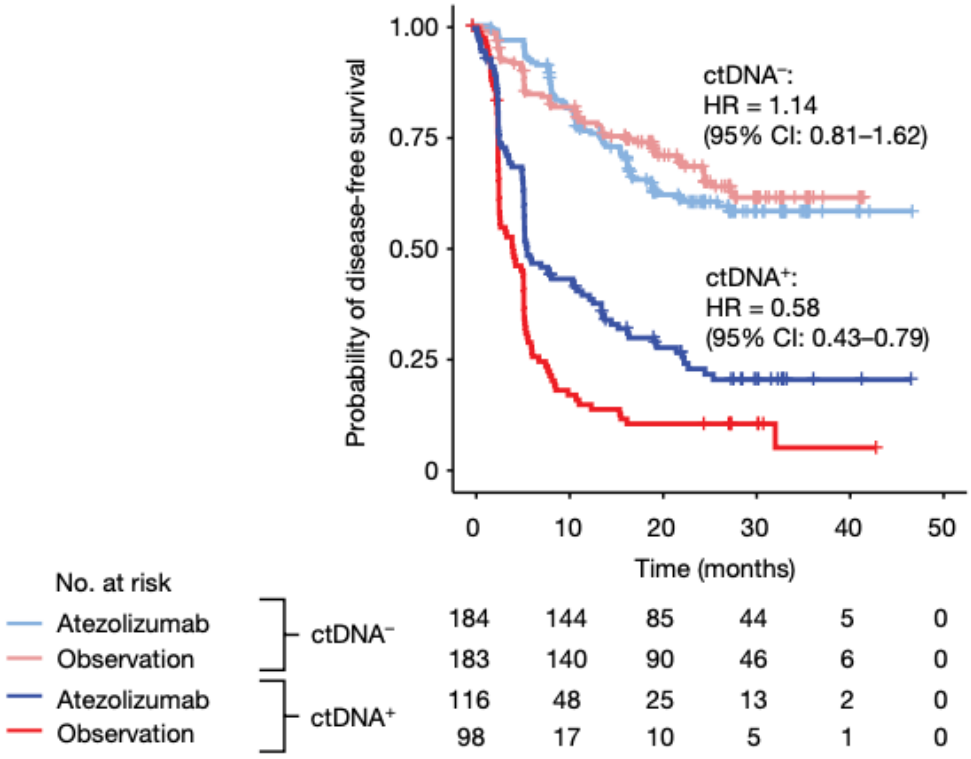


Cancer Discov. 2021 Nov 16. doi: 10.1158/2159-8290.CD-21-0634

Clinical utilities of MRD in solid tumors

1) risk stratification and regimen selection (landmark analysis), 2) relapse monitoring (surveillance analysis)

IMvigor010 – MRD demonstrating CDx potential



Nature. 2021 Jun 16. doi: 10.1038/s41586-021-03642-9.

Chinese oncologists developing consensus on MRD applications in solid tumors, e.g. lung cancer

第18届中国肺癌高峰论坛
——肺癌分子(微小)残留病灶(MRD)的检测和临床应用共识

共识一：MRD的概念

- 肺癌分子残留病变，指的是经过治疗后，传统影像学(包括PET/CT)或实验室方法不能发现，但通过液体活检发现的癌来源分子异常，代表着肺癌的持续存在和临床进展可能；
- 肺癌分子异常：指的是在外周血可稳定检测出丰度≥0.02%的ctDNA，包括肺癌驱动基因或其他的Ⅰ/Ⅱ类基因变异。

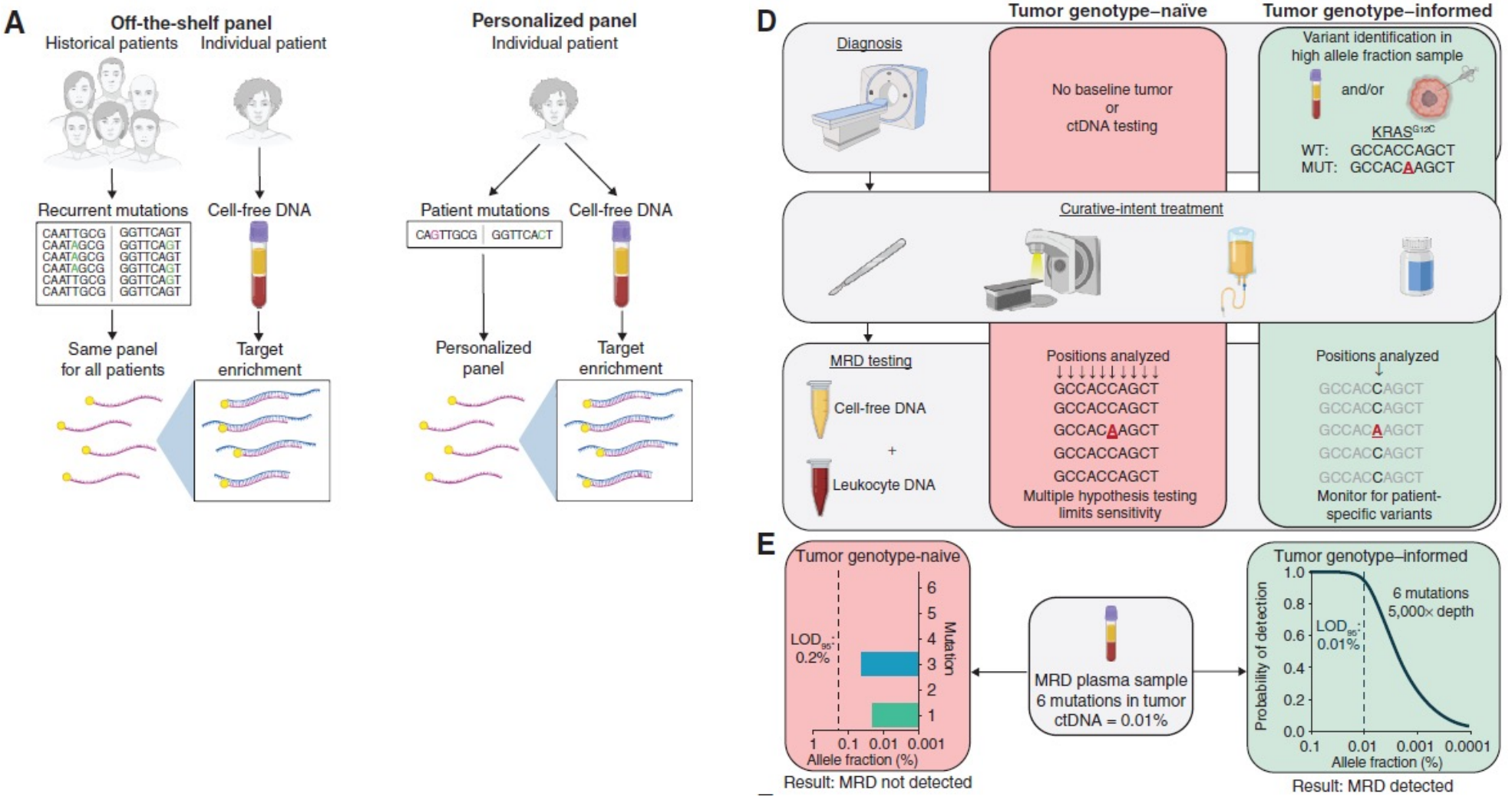
共识二：MRD检测的基本技术要求

- MRD检测的基本技术，包括Tumor-informed assays(个体化定制)和 Tumor agnostic assays(NGS panel和多组学技术)，目前均处在探索阶段，需要前瞻性研究确定其敏感性、特异性和预测价值；
- 采用二代测序技术(NGS)，所选的多基因 panel中必须覆盖患者Ⅰ/Ⅱ类基因变异，基本技术标准是可稳定检出丰度≥0.02%的ctDNA；
- 驱动基因阳性的非小细胞肺癌，MRD的分子panel应包括该驱动基因；
- MRD评估报告中必须包括cfDNA丰度， ctDNA丰度，所检测基因VAF值；
- 需要建立针对免疫治疗的MRD标准。

Chinese lung cancer consensus on MRD detection and clinical application, 2021

Clinical utilities of MRD in solid tumors

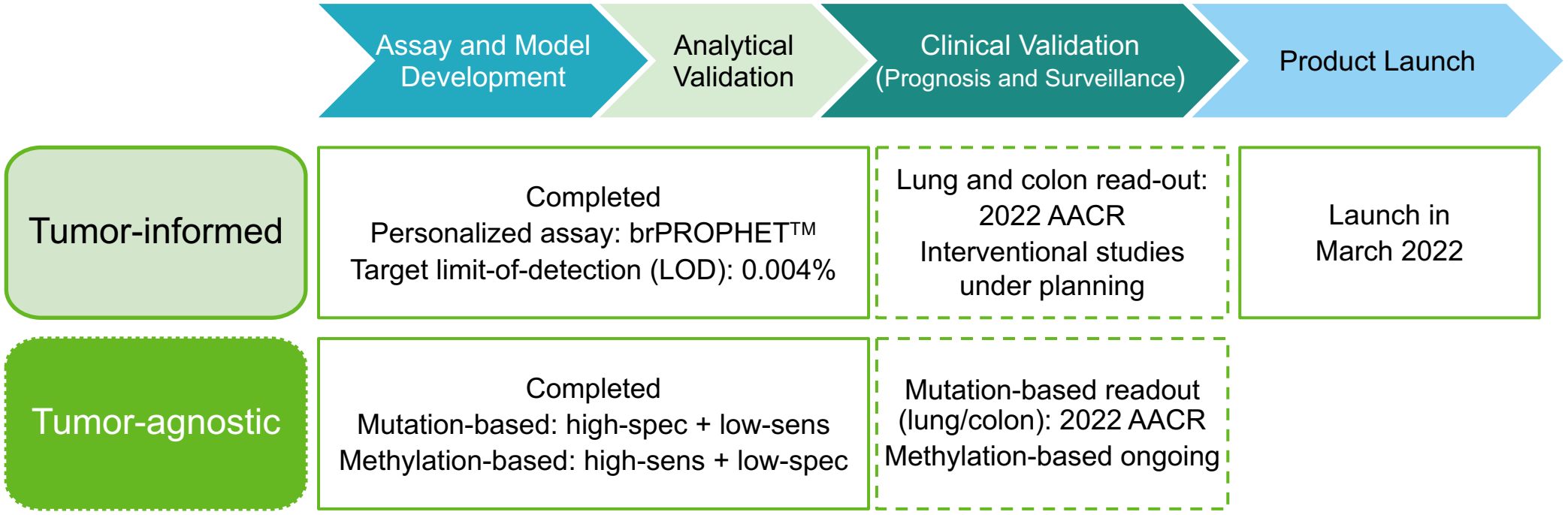
Fixed panel vs. personalized panel approaches



Cancer Discov. 2021 Nov 16. doi: 10.1158/2159-8290.CD-21-0634

MRD product pipelines

Personalized approach (brPROPHET™) demonstrating stronger performance, esp. in early stage patients



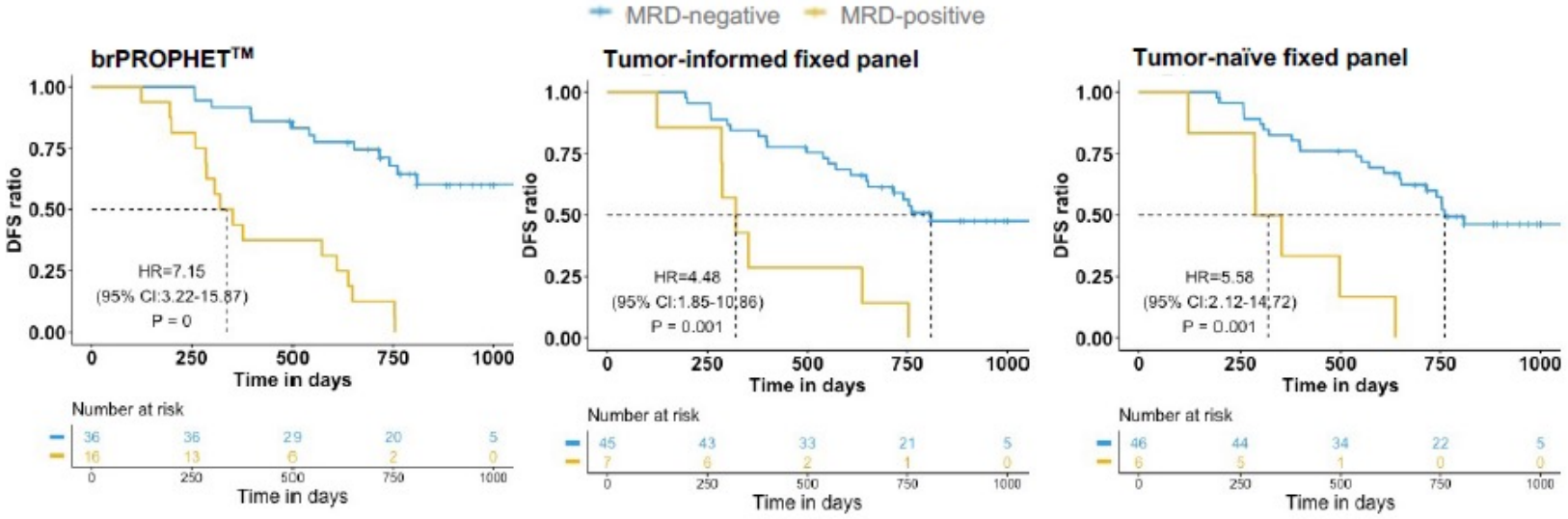
Recent trends on MRD clinical adoption in China

- MRD recommended for relapse-risk prediction for early-stage NSCLC patients by the 2021 *Chinese Lung Cancer Clinician Consensus*
- MRD technology is required to demonstrate an LOD lower than 0.02%
- Some clinicians and pharma companies are exploring MRD-driven patient-selection or treatment-plus/minus adjuvant therapy studies
- Most NGS companies only offer mutation panel-based liquid biopsy assays, with sub-optimal sensitivity for MRD utility

MRD clinical validation data readout
NSCLC

Session OPO.PR02.01 - Clinical Prevention, Early Detection, and Interception

5916 - Tumor-informed patient-specific panel outperforms tumor-naïve and tumor-informed fixed panel for circulating tumor DNA (ctDNA)-based postoperative monitoring of non-small cell lung cancer (NSCLC)



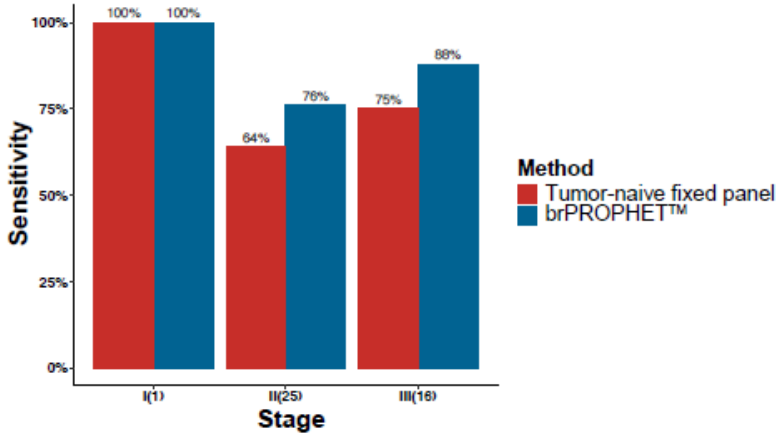
Three-year prognostication with brPROPHET™ assay at B+C time-points yielded higher sensitivity (59% vs 26% vs 22%), negative predictive value (66% vs 51% vs 50%), and hazard ratio (7.15, 95%CI [3.2-15.9] vs 4.48 [1.9-10.9] vs 5.58 [2.1-14.7]) as compared with tumor-informed and tumor-naïve fixed panel assays.

In the full MEDAL cohort, MRD- patients assessed by brPROPHET™ achieved a 12-month recurrence-free rate > 95% (unpublished data)

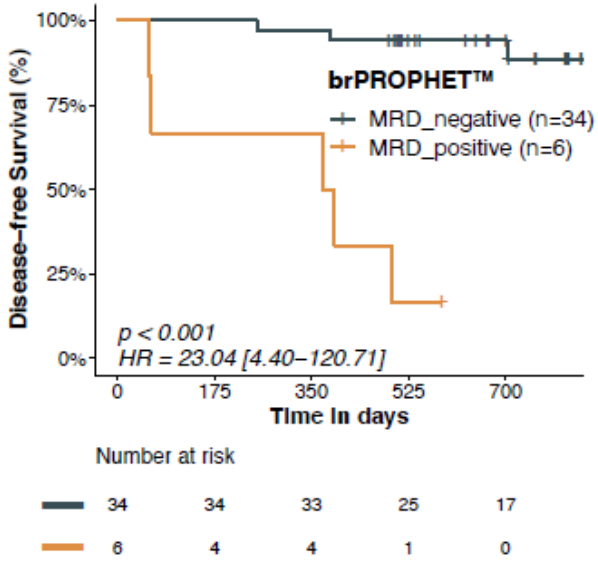
MRD clinical validation data readout
CRC

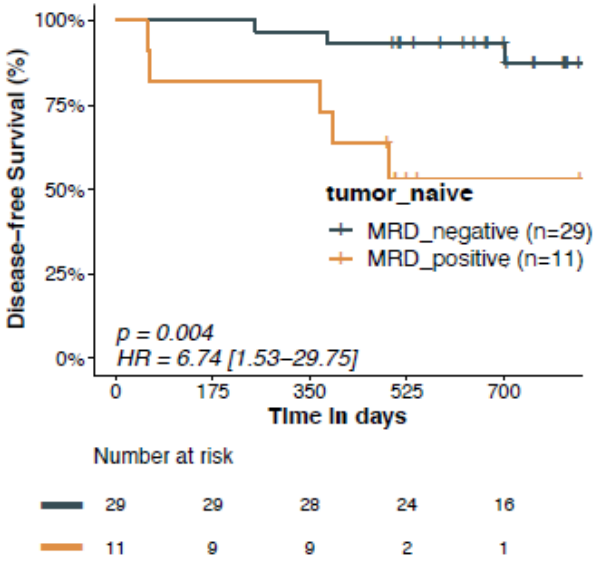
Session OPO.PR02.01 - Clinical Prevention, Early Detection, and Interception

5917 - Patient-specific tumor-informed circulating tumor DNA (ctDNA) analysis for postoperative monitoring of patients with stages I-III colorectal cancer (CRC)



brPROPHET™ demonstrated superior sensitivity and specificity to fixed panel in pre-operative ctDNA detection and post-operative MRD calling among relapsed patients



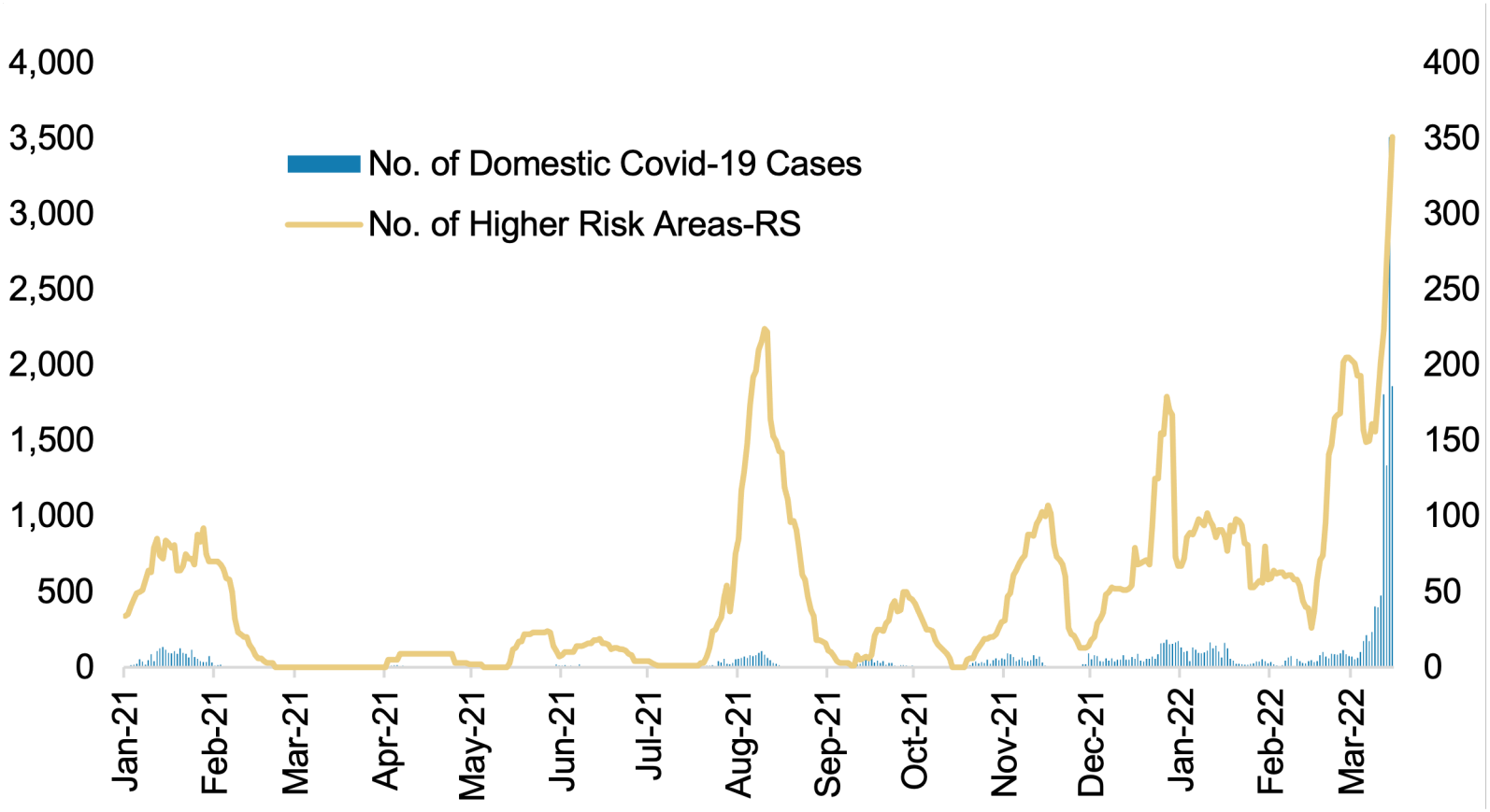


燃石医学
Burning Rock Dx

Financials

Latest Covid impact

Omicron wave spreading in China; much larger impact due to higher transmissions



Worst wave of outbreaks observed since the nation-wide lockdown in 2020

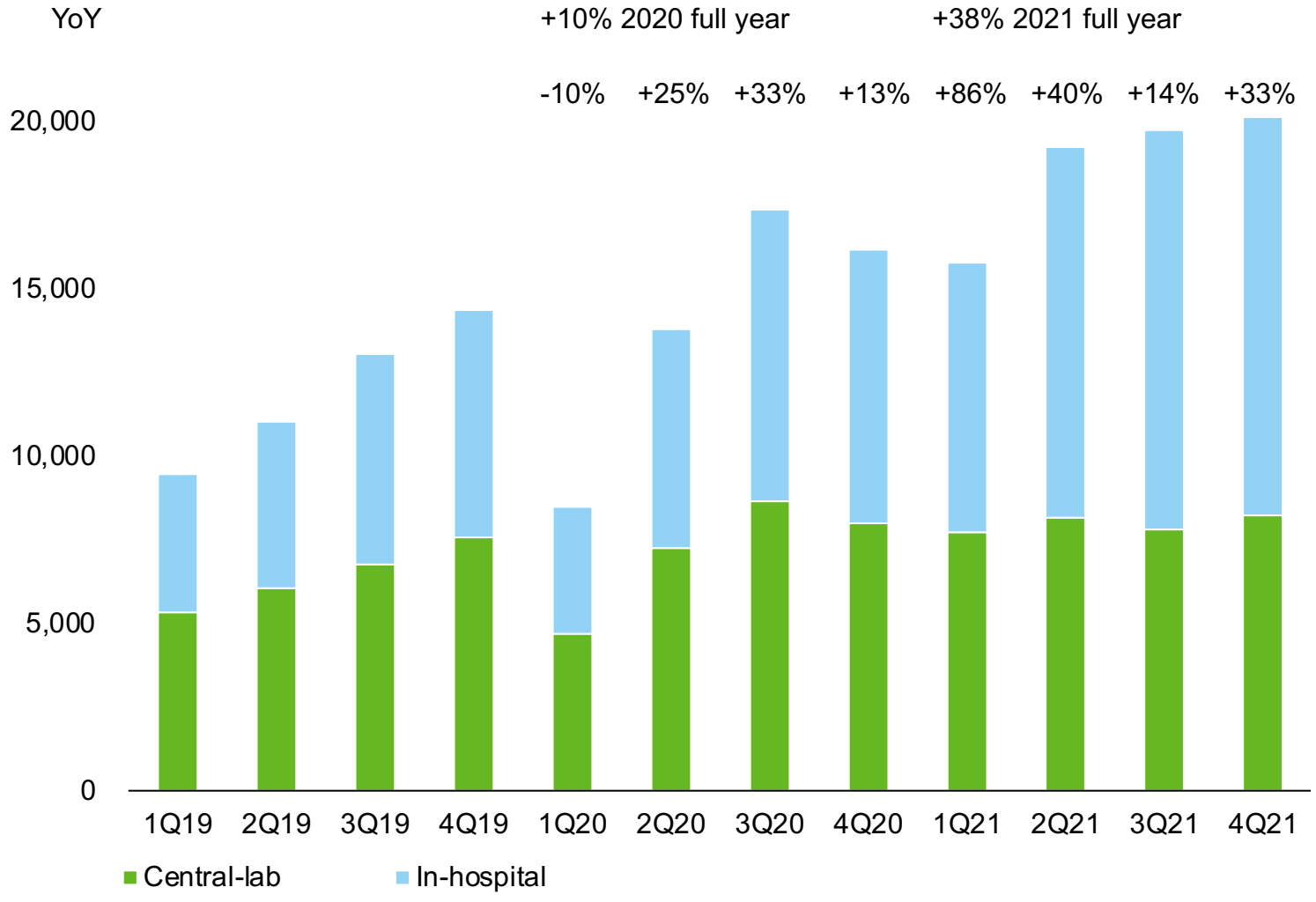
- Shanghai school closures, semi-lockdown (Mar 2022)
- Shenzhen lockdown (Mar 2022)
- Changchun lockdown (Mar 2022)
- Jilin province lockdown (Mar 2022)

Continued in-hospital strength and improved central-lab driving growth uplift

4Q21 growth turned better than 3Q21, Jan-Feb 2022 (pre Covid lockdowns in Mar) even better than 4Q21

Central-lab volume growth turned positive in 4Q21, and grew better Jan-Feb 2022, on the back of new products

Volumes by channel[1]



Jan-Feb 2022 +56%

- Central-lab +11%
- In-hospital + high d.d.[2]

Notes:

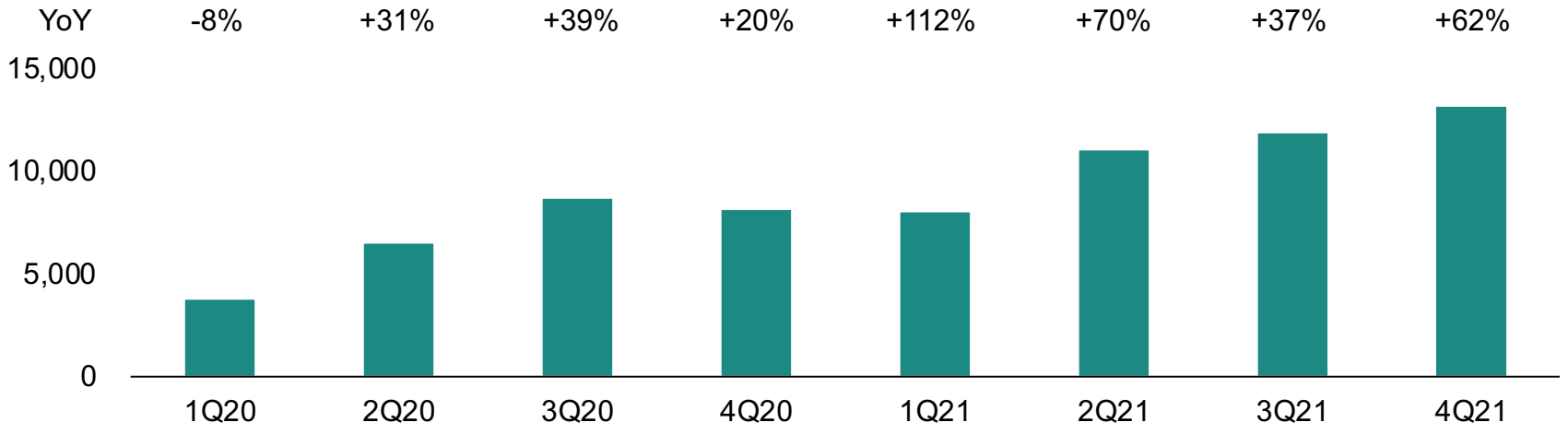
[1] Central-lab (LDT) volumes represented by the number of patients tested. In-hospital (IVD) volumes represented by the number of testing kits shipped to partner hospitals

[2] Double digits

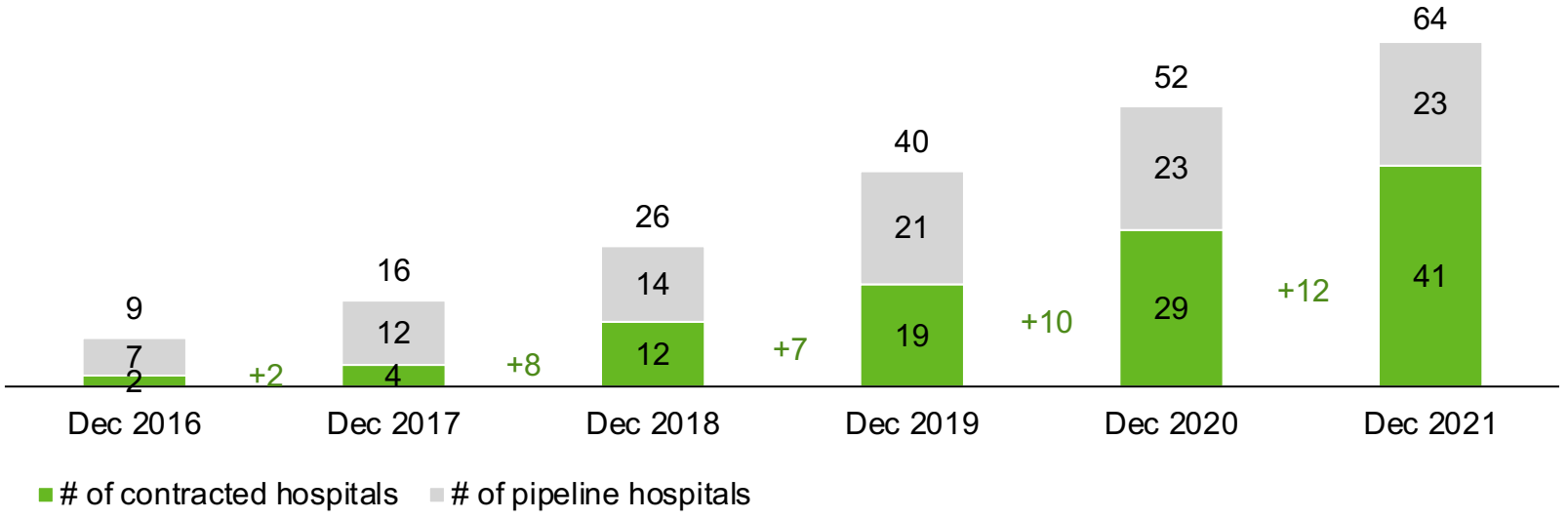
In-hospital segment

Accelerated rate of penetrating into additional hospitals during 2021

Number of testing kits shipped to partner hospitals[1]



Number of partner hospitals



Notes:

[1] Excludes kits for validation, training and other purposes

In-hospital primarily through direct-sales model

Financials

RMB millions	2020	2021	*19 YoY*	*20 YoY*	*21 YoY*	1Q20	2Q20	3Q20	4Q20	1Q21	2Q21	*3Q21*	4Q21	*4Q21 YoY*	*4Q21 QoQ*	2022 Guide
Revenue	**429.9**	**507.9**	***83%***	***13%***	***18%***	**67.3**	**107.0**	**123.9**	**131.7**	**106.6**	**127.3**	**126.6**	**147.3**	***12%***	***16%***	**620**
Central lab	297.3	319.4	*71%*	*8%*	*7%*	46.1	74.6	89.9	86.7	74.6	80.0	78.8	86.0	*-1%*	*9%*	
In-hospital[1]	117.9	165.1	*164%*	*34%*	*40%*	17.1	27.6	31.7	41.5	29.0	40.5	43.7	51.9	*25%*	*19%*	
Pharma	14.7	23.4	*25%*	*(17%)*	*59%*	4.1	4.8	2.3	3.6	3.1	6.8	4.1	9.4	*165%*	*132%*	
Gross profit	**313.9**	**364.1**	***102%***	***15%***	***16%***	**44.8**	**78.4**	**91.6**	**99.2**	**76.9**	**90.2**	**91.6**	**105.4**	***6%***	***15%***	
Total opex	**726.3**	**1,161.2**	***49%***	***64%***	***60%***	**104.1**	**151.4**	**216.2**	**254.6**	**248.8**	**292.3**	**262.7**	**357.5**	***41%***	***36%***	
R&D[2]	214.1	338.2	*43%*	*45%*	*57%*	37.9	45.9	58.7	71.6	55.0	87.2	79.2	116.7	*63%*	*47%*	
S&M[2]	165.1	293.6	*49%*	*9%*	*75%*	29.6	37.5	43.9	54.2	52.5	65.2	74.7	101.1	*87%*	*35%*	
G&A[2]	174.6	248.6	*40%*	*44%*	*39%*	32.6	40.6	44.9	56.5	56.9	56.8	55.5	79.5	*41%*	*43%*	
SBC[3]	172.5	280.8				4.0	27.4	68.7	72.3	84.4	83.0	53.3	60.2			
Operating profit	**(412.4)**	**(797.1)**				**(59.3)**	**(73.0)**	**(124.6)**	**(155.4)**	**(171.9)**	**(202.0)**	**(171.1)**	**(252.1)**			
GP margin	**73.0%**	**71.7%**				**66.5%**	**73.3%**	**73.9%**	**75.3%**	**72.2%**	**70.9%**	**72.3%**	**71.5%**			
Opex / revenue	169%	229%				155%	142%	175%	193%	233%	230%	208%	243%			
S&M / revenue	39%	60%				44%	36%	36%	43%	52%	53%	61%	70%			

Notes:
[1] Within in-hospital segment, over 95% revenues are kit revenues, which are recurring in nature; the remaining are instrument revenues. In-hospital primarily through direct-sales model
[2] Excluding share based compensation (SBC)
[3] Share based compensation

燃石医学
Burning Rock Dx

Appendix 1

Early detection

ESMO Asia mini-oral presentation, Nov 2020

Overview of training and validation sets

Training	Control	Cancer	LC	CRC	LIHC	OVCA	PAAD	ESCA
total	195	274	50	46	48	50	40	40
age, mean+/-SD	53+/-6	57+/-8	60+/-6	60+/-8	55+/-8	50+/-8	59+/-7	57+/-6
age, min/max	40/72	40/75	47/74	44/75	43/72	40/73	42/71	45/70
sex, female, n (%)	128 (70)	110 (40)	16 (32)	21 (46)	4 (8)	50 (100)	14 (35)	5 (13)
clinical stage, n (%)								
I		73 (27)	20 (40)	9 (20)	20 (41)	5 (10)	11 (27)	8 (20)
II		63 (23)	14 (28)	12 (26)	8 (17)	5 (10)	11 (27)	13 (33)
III		97 (35)	7 (14)	15 (32)	14 (29)	37 (74)	9 (23)	15 (37)
IV		41 (15)	9 (18)	10 (22)	6 (13)	3 (6)	9 (23)	4 (10)

Validation	Control	Cancer	LC	CRC	LIHC	OVCA	PAAD	ESCA
total	288	351	61	57	57	53	59	64
age, mean+/-SD	54+/-6	59+/-8	62+/-7	61+/-9	54+/-8	54+/-7	61+/-9	62+/-6
age, min/max	40/74	40/75	45/74	44/75	40/73	42/68	40/74	46/74
sex, female, n (%)	171 (59)	146 (42)	22 (36)	21 (37)	9 (16)	53 (100)	19 (32)	22 (34)
clinical stage, n (%)								
I		83 (23)	16 (26)	15 (26)	15 (26)	6 (11)	18 (30)	13 (20)
II		87 (25)	16 (26)	13 (23)	14 (25)	11 (21)	14 (24)	19 (30)
III		94 (27)	14 (23)	14 (25)	15 (26)	22 (42)	13 (22)	16 (25)
IV		87 (25)	15 (25)	15 (26)	13 (23)	14 (26)	14 (24)	16 (25)

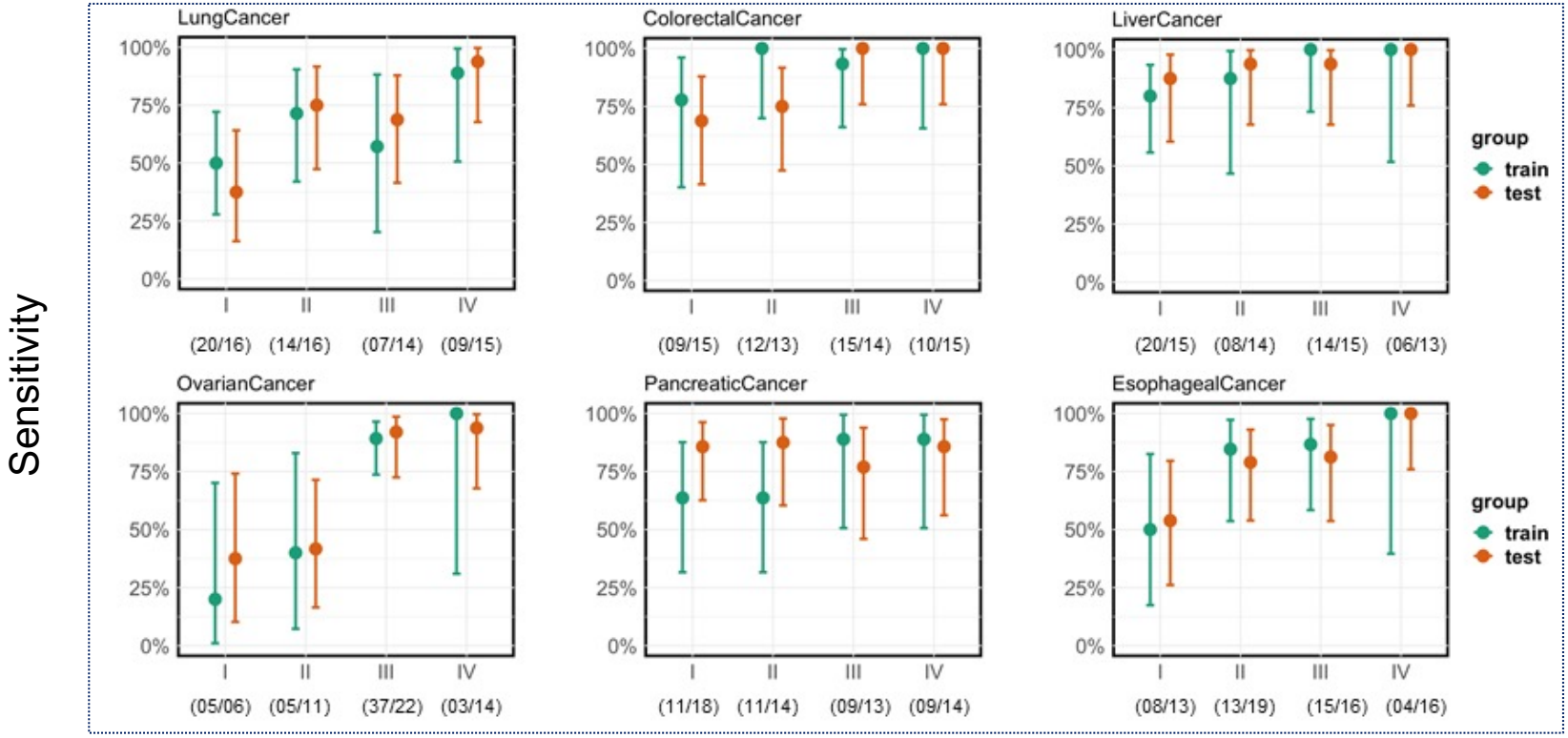
1. Similar age distribution between cases and controls, and between training set and validation set
2. Balanced sample size among different stages and cancer types

Note: Sample size numbers are aggregated through a series of case-control studies

Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

ESMO Asia mini-oral presentation, Nov 2020

Our test detects cancers at an early stage with high specificity and high sensitivity

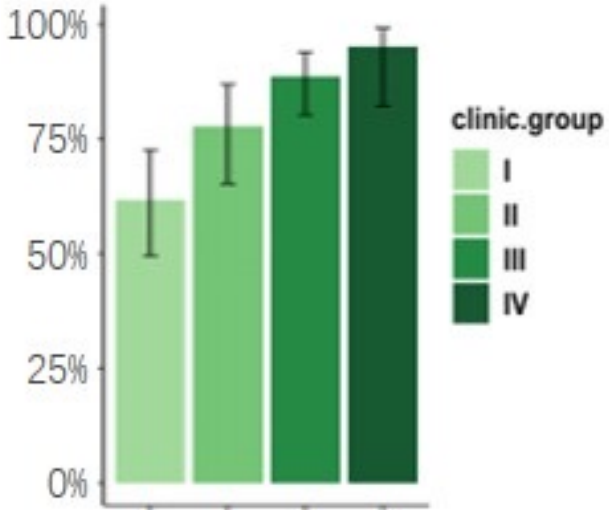


- The specificity was **99.5%** (95%CI: 96.7-100%; training) and **98.3%** (95%CI: 95.8-99.4%; validation)
- The sensitivity was **79.9%** (95%CI: 74.6-84.4%; training) and **80.6%** (95%CI: 76.0-84.4%; validation)

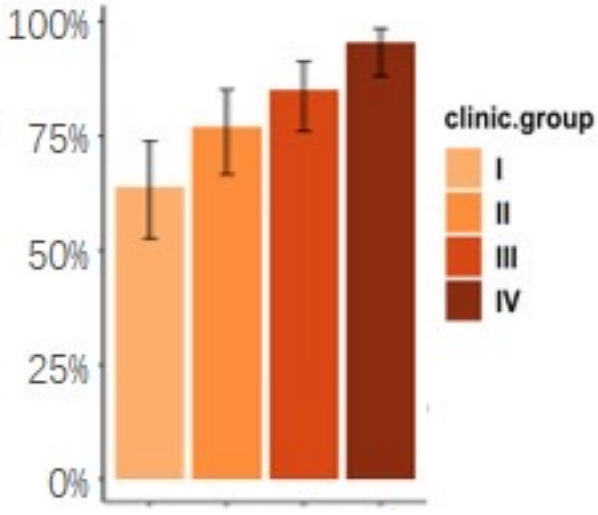
Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

ESMO Asia mini-oral presentation, Nov 2020

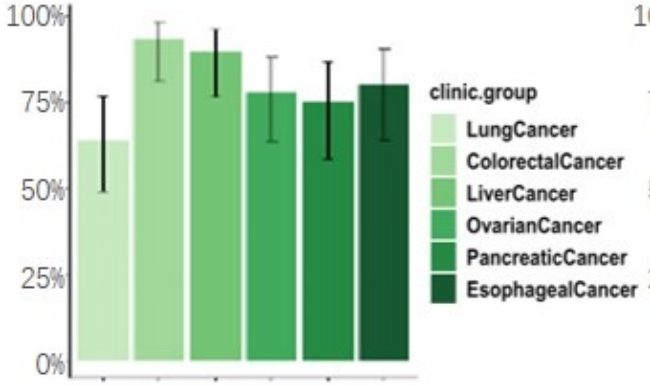
Our test detects cancers at an early stage with high specificity and high sensitivity



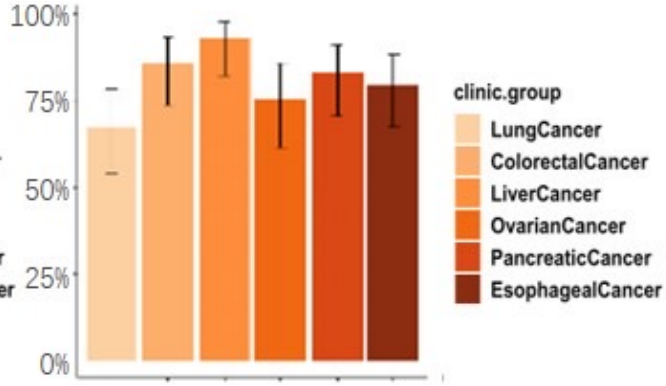
Training



Validation



Training

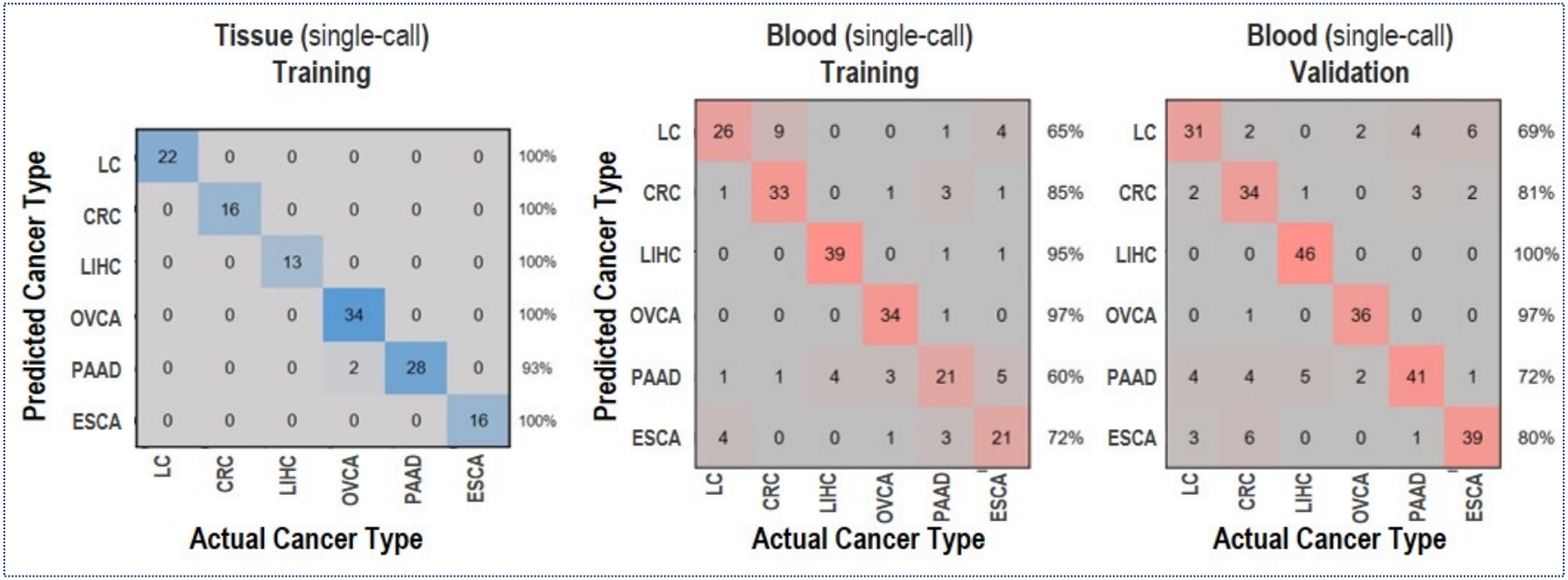


Validation

Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

ESMO Asia mini-oral presentation, Nov 2020

Our test predicts the tissue of origin with high accuracy



- The classifier was able to distinguish different cancer tissue samples with exceptional accuracy **(129/131).**
- **98.6%** of detected cancer blood samples were assigned an organ-source in both training and validation sets:
  - For single organ calls, the predictive accuracy was **79%** (training) and **82%** (validation);
  - For top-two organ calls, the predictive accuracy was **89%** (training) and **87%** (validation).

Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

ESMO Asia mini-oral presentation, Nov 2020

6-cancer test sensitivity by cancer type and stage

Sensitivity and Specificity - Correct#/Total# (%)

Cancer	Group	I	II	III	IV	Overall
Lung	Train	10/20 (50.0)	10/14 (71.4)	4/7 (57.1)	8/9 (88.9)	32/50 (64.0)
	Test	6/16 (37.5)	12/16 (75.0)	9/14 (64.3)	14/15 (93.3)	41/61 (67.2)
Colorectal	Train	7/9 (77.8)	12/12 (100.0)	14/15 (93.3)	10/10 (100.0)	43/46 (93.5)
	Test	10/15 (66.7)	10/13 (76.9)	14/14 (100.0)	15/15 (100.0)	49/57 (86.0)
Liver	Train	16/20 (80.0)	7/8 (87.5)	14/14 (100.0)	6/6 (100.0)	43/48 (89.6)
	Test	13/15 (86.7)	13/14 (92.9)	14/15 (93.3)	13/13 (100.0)	53/57 (93.0)
Ovarian	Train	1/5 (20.0)	2/5 (40.0)	33/37 (89.2)	3/3 (100.0)	39/50 (78.0)
	Test	2/6 (33.3)	5/11 (45.5)	20/22 (90.9)	13/14 (92.9)	40/53 (75.5)
Pancreatic	Train	7/11 (63.6)	7/11 (63.6)	8/9 (88.9)	8/9 (88.9)	30/40 (75.0)
	Test	15/18 (83.3)	12/14 (85.7)	10/13 (76.9)	12/14 (85.7)	49/59 (83.1)
Esophageal	Train	4/8 (50.0)	11/13 (84.6)	13/15 (86.7)	4/4 (100.0)	32/40 (80.0)
	Test	7/13 (53.8)	15/19 (78.9)	13/16 (81.3)	16/16 (100.0)	51/64 (79.7)
Sensitivity	Train					219/274 (79.9)
	Test					283/351 (80.6)
Specificity	Train					194/195 (99.5)
	Test					283/288 (98.3)

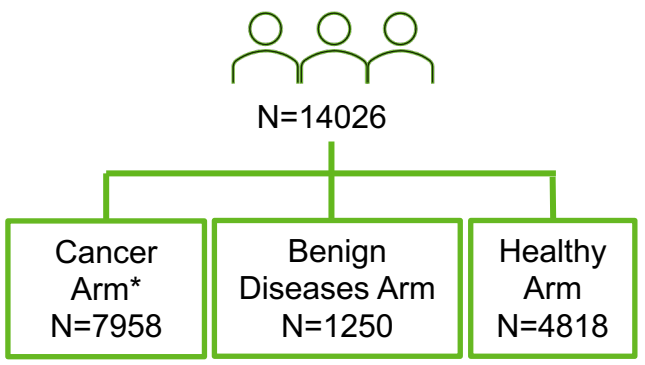
Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

The PREDICT study (NCT04817306)

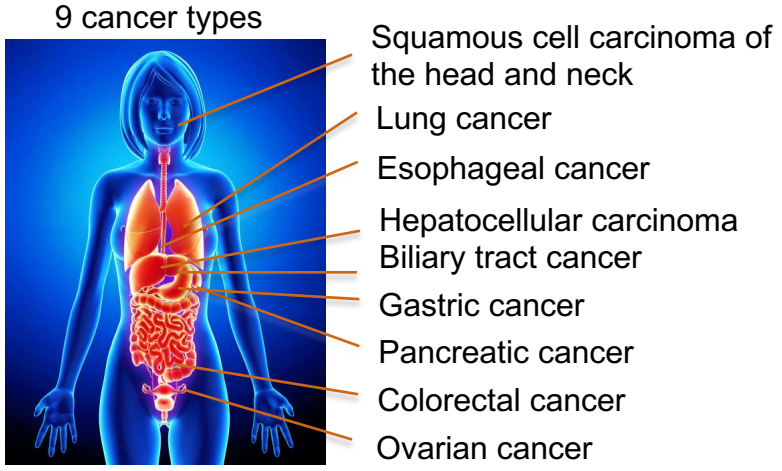
Study design

PREDICT is a *prospective, multi-center, case-control, observational* study for the detection of 9 cancer types through a cell-free DNA (cfDNA) methylation based, machine learning aided model

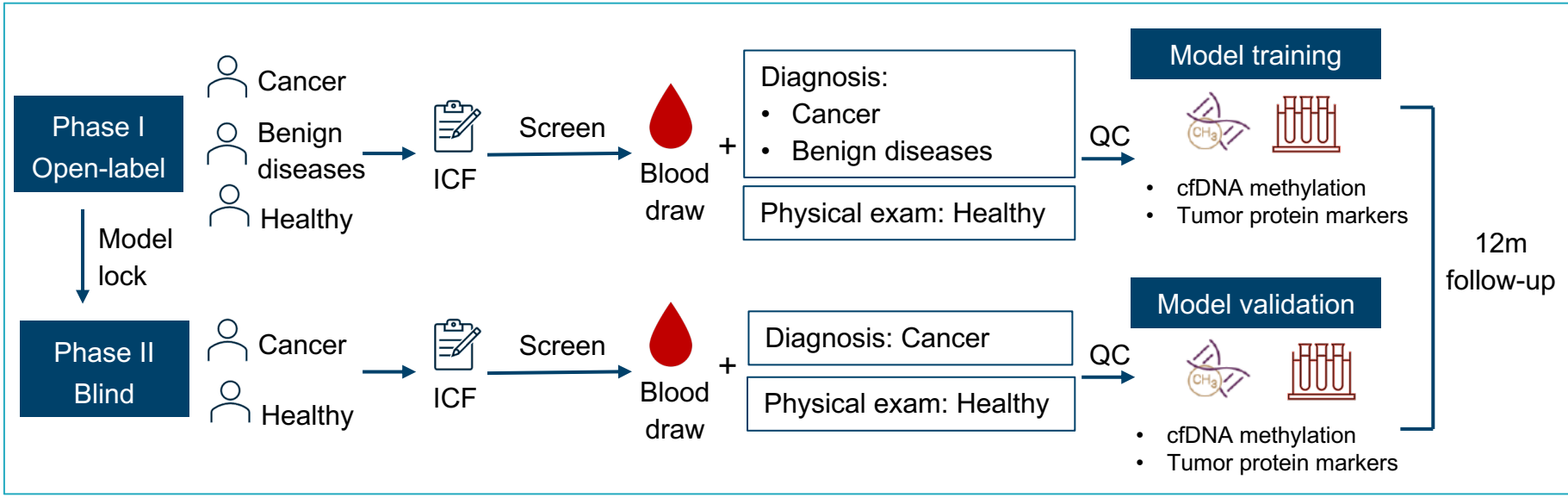
Participants



* Stages I-III represent more than 75% of the cancer participants



Study Design



The PREDICT study (NCT04817306)
Objectives and timeline

Objectives

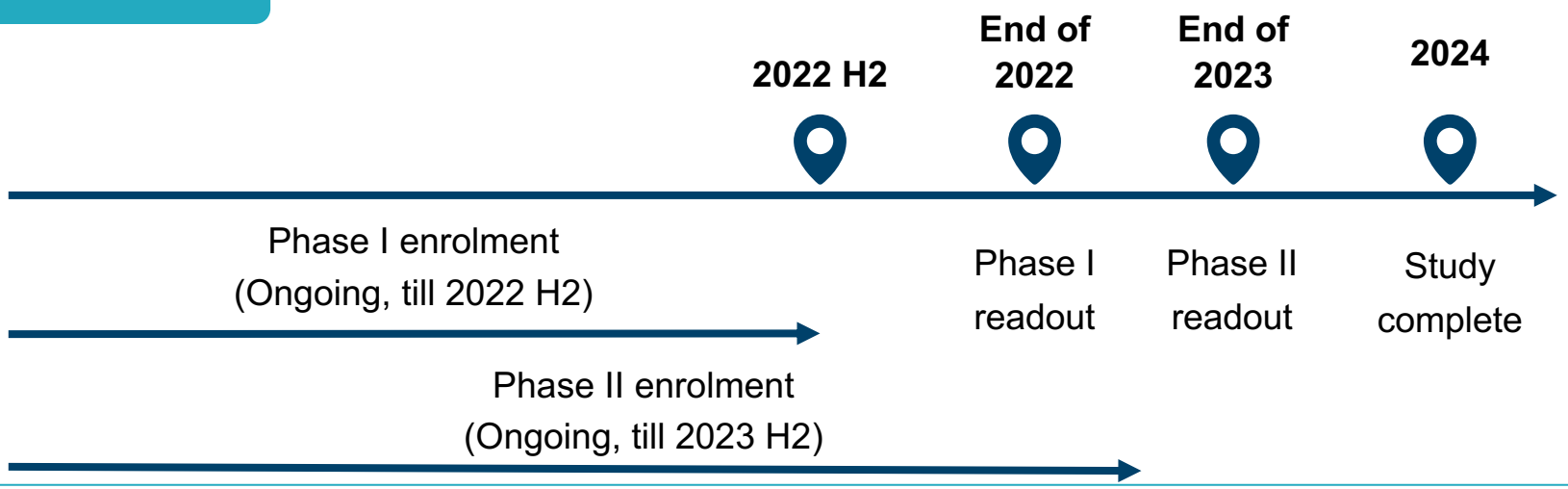
Primary objective:

- To train and validate the *sensitivity, specificity and TOO accuracy* of a cfDNA methylation-based model for early detection of 9 types of cancers

Key secondary objectives:

- To evaluate the sensitivity, specificity and TOO accuracy of a cfDNA methylation-based model in various *types and stages of cancers*
- To evaluate the sensitivity, specificity and TOO accuracy of a cfDNA methylation-based model *combined with other biomarkers*
- To evaluate the *positive predictive value* of a cfDNA methylation-based model among asymptomatic "cancer-free" individuals within a 12-month follow up period

Timeline



Note: TOO, tissue of origin

The PREDICT study (NCT04817306)

National Oncology Conference on Standardized Diagnosis and Treatment, Beijing, 14th-16th May 2021

The PRESCIENT study (NCT04822792)

Study design

PRESCIENT is a *prospective, multi-center, case-control, observational* study aimed to train and validate the performance of a multi-omics model in the detection of 22 cancers

Participants

N=11879

- Cancer Arm* N=9078
- Benign Diseases Arm N=1571
- Healthy Arm N=1230

* Stages I-III represent more than 75% of the cancer participants

22 cancer types

- Lung
- Stomach
- Esophagus
- Liver
- Biliary tract
- Colorectal
- Breast
- Cervix
- Pancreas
- Lymphoma
- Bladder
- Hematology
- Kidney
- Uterus
- Nasopharyngeal
- Prostate
- Ovary
- Head and neck
- Sarcoma
- Thorax
- Melanoma
- Testis

Study Design

Cancer
Benign diseases
Healthy

→ ICF → Screen → Blood draw + Diagnosis: Cancer, Benign diseases; Physical exam: Healthy → QC → Model training and validation

- cfDNA methylation
- Tumor protein markers
- Other omics biomarkers

The PRESCIENT study (NCT04822792)
Objectives and timeline

Objectives

Primary objective

- To train and validate the *sensitivity, specificity and TOO accuracy* of a cfDNA methylation-based model combined with tumor protein markers for early detection of 22 types of cancers

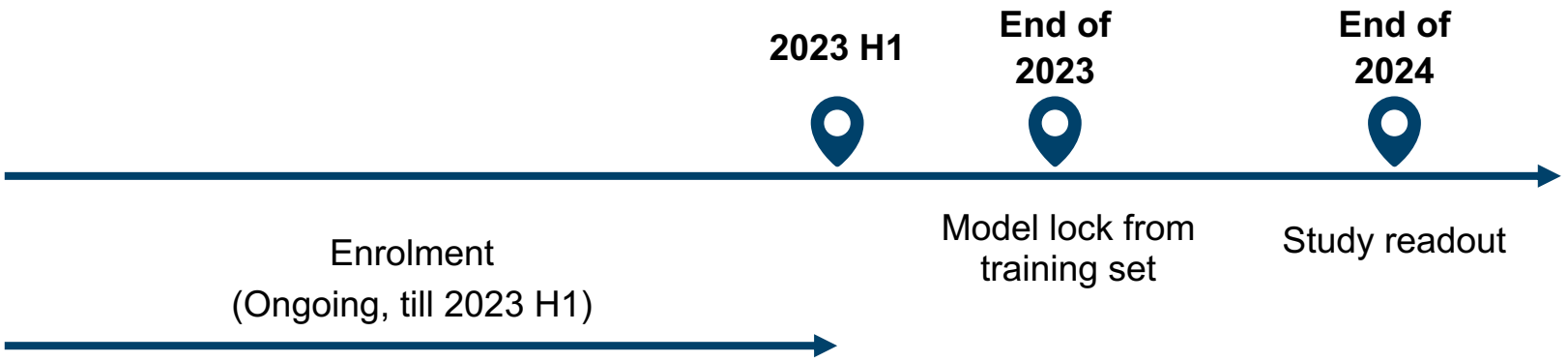
Secondary objective

- To evaluate the sensitivity and specificity of a cfDNA methylation-based model combined with tumor protein markers in early detection of 22 types of cancers *in different stages*

Exploratory objective:

- To evaluate the sensitivity and specificity of *other genetic/epigenetic biomarkers combined with a cfDNA methylation-based model and tumor protein markers* in early detection of cancers

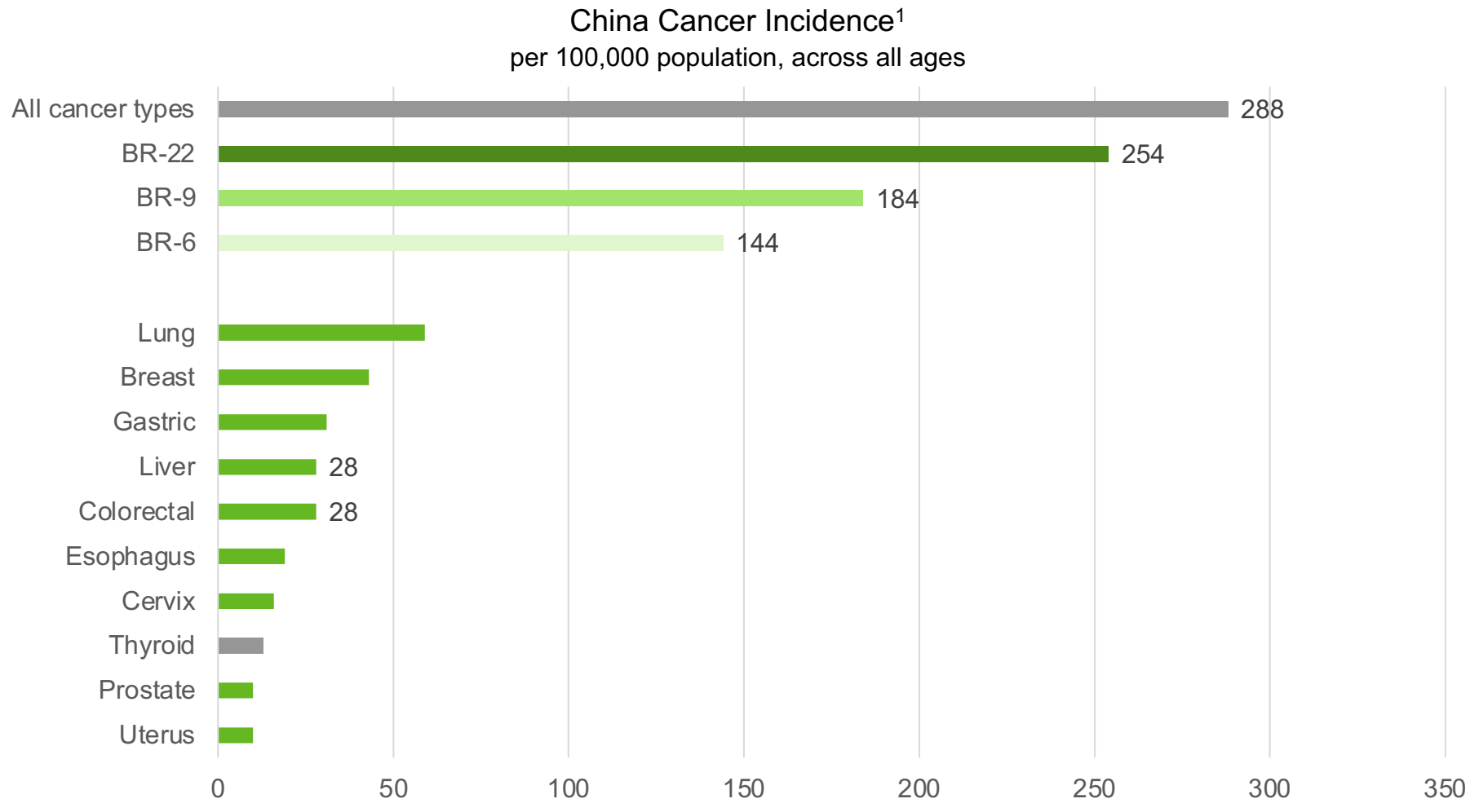
Timeline



Note: TOO, tissue of origin

Multi vs. single cancer early detection

Multiple times larger TAM



BR-22 covers 88% of China's cancer incidence[2]

Notes:

[1] Incidence data per "2018 China cancer registry annual report ", J He et al., ISBN 978-7-117-28585-8

[2] Final number of cancer types subject to development progress

Multi vs. single cancer early detection in China

Significantly higher technology barrier

Single-cancer test

- Established technology, typically PCR based, with readily available products
  - US – First FDA approved product in 2014 (first submission in 2012)
  - China – NMPA approved products (class-III, including tissue and blood-based) in 2017, 2018, 2019, 2020, 2021, etc
- Small panel, low cost
- Relatively simple genomic data analytics

Multi-cancer test

- Biologically, blood-based tests are multi-cancer in nature
- Highly complex technology with product risk
  - Globally, only a small number of innovators have locked-down products going under intended-use validation
- Data as a key factor for development and validation
  - Evolving dataset leads to continuous product improvement and greater validation
- Unprecedented commercial potential
  - Possibility to fundamentally shift oncology landscape from late-stage therapeutics to earlier stage intervention

燃石医学
Burning Rock Dx

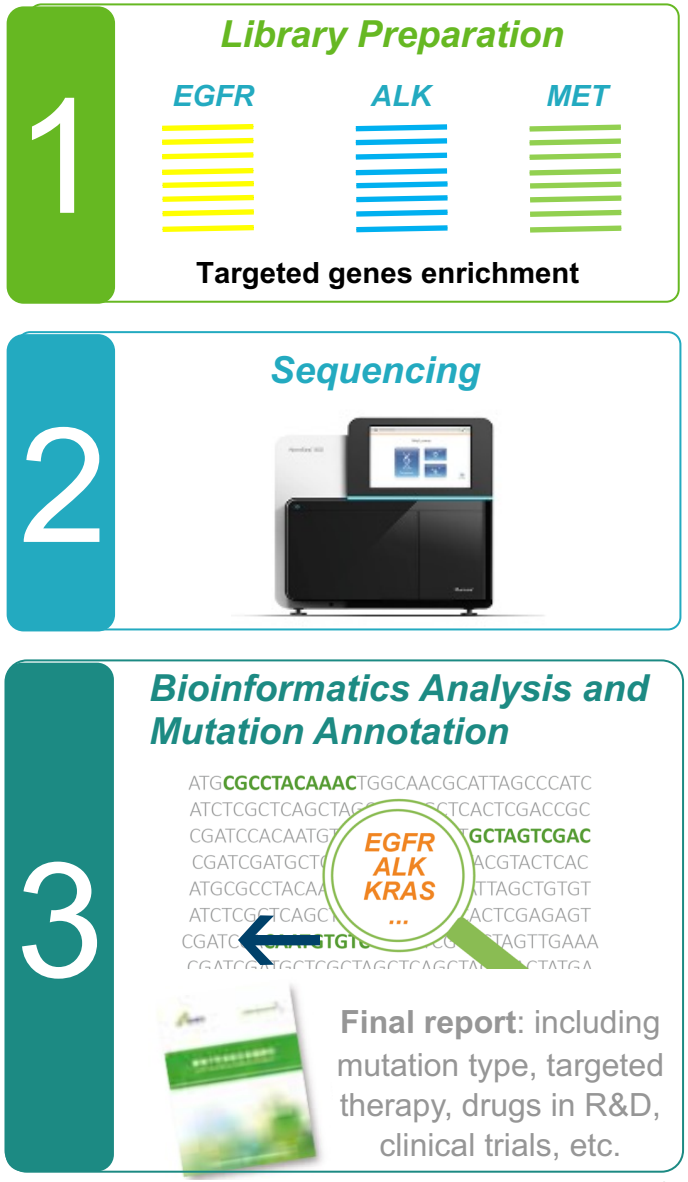
Appendix 2

Therapy selection

NGS testing

Diagnostics companies focus on steps 1 and 3

	NGS
Throughput	**High**-throughput
Efficiency	**Parallel** testing
Cost	**Low-cost** per biomarker
Biomarker Profiling	**Comprehensive** profiling & **superior** accuracy
Fit for Liquid Sample	**Liquid availability**



Leading liquid-biopsy product in China, with globally competitive performance

Demonstrated in high-impact analytical validation study

SEQC2 Study Overview

MAQC/SEQC Consortium Projects – An Overview

- An FDA-led community-wide consortium effort to assess technical performance and application of emerging technologies (e.g., genomics).


Guidance for Industry
Pharmacogenomic Data Submissions — Companion Guidance

Issues and Study Objectives

- FDA approved several NGS tests with sensitivity for AF ~5%
- Hundreds lab developed tests (LDT): sensitivity ~ 2-10%
- FDA approved ctDNA tests with sensitivity for AF ~0.3%

of ctDNA

ance across

al for
tion !!!

nature biotechnology
ARTICLES
https://doi.org/10.1038/s41587-021-00857-z
Check for updates

Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology

Liquid Biopsy

- False positive rate estimate through Known Negatives
- All of them by VAF ranges:
  - 0.1 - 0.5%, 0.5 - 2.5%, >2.5%
  - Finer VAF ranges for sensitivity: 0.1 - 0.2%, 0.2 - 0.3%, 0.3 - 0.5%
- Evaluate the impact of DNA input amount
  - Three levels of input for Ef: 10ng, 25ng, 50ng
- Evaluate the impact of synthetic plasma (DNA extraction)
  - Qubit HS calibration and quantification
  - Calculate extraction yield

➢ Enzymatic fragmentation ➢ better ligation efficiency

➢ Gel-based size selection (160bp-180bp) to mimic cfDNA

➢ 1ng/ul to mimic concentration after DNA extraction from plasma

➢ Ep: 40ng/ml Ef in synthetic plasma

25 | Ef_10
50 | Ep_25

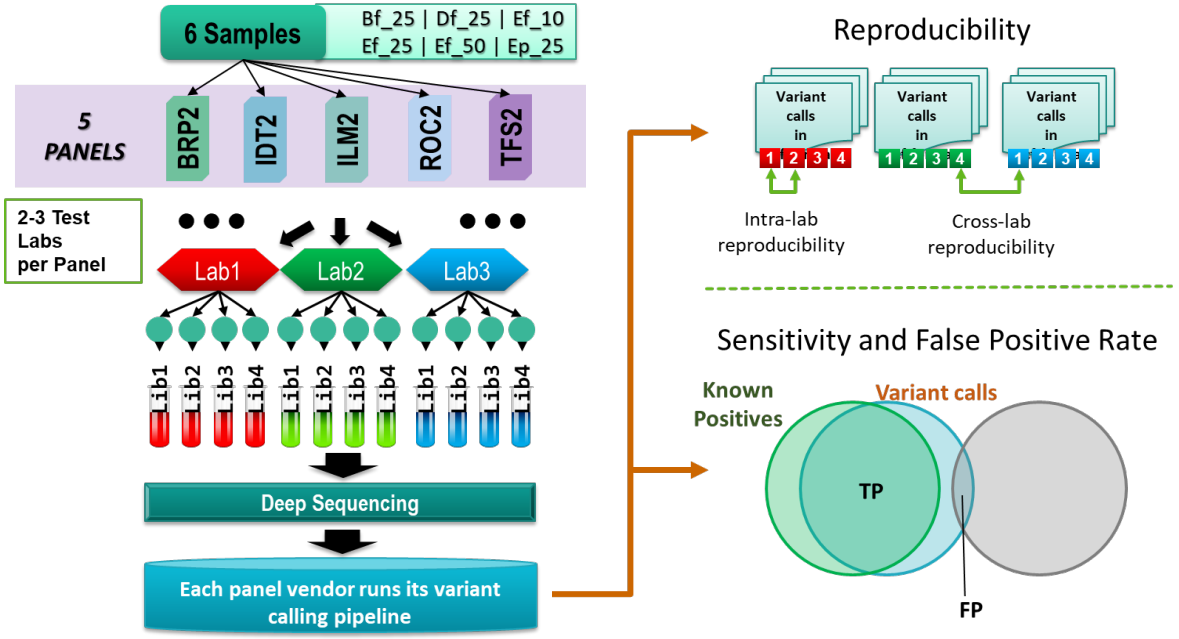
TFS2

BRP2: Burning Rock Dx LungPlasma v4
IDT2: IDT xGen Non-Small Cell Lung Cancer
ILM2: Illumina TruSight 170 with UMI
ROC2: Roche AVENIO ctDNA Expanded Kit
TFS2: Thermo Fisher Oncomine Lung cfDNA Assay

Source:
Slides from "Establishing the analytical validity of circulating tumor DNA sequencing for precision oncology", 5th Annual Liquid Biopsy for Precision Oncology Summit, Feb 2021
Further information in Appendix 2

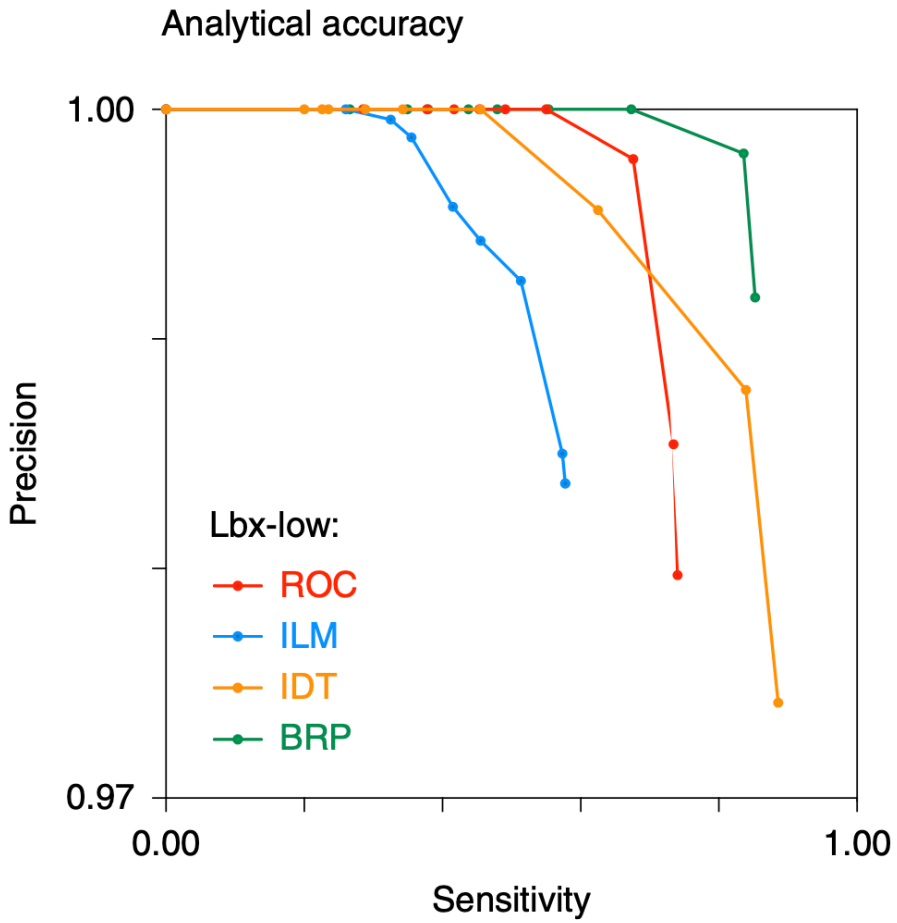
Participating assays and study design

Name	Vendor	ctDNA assay	Sequencing platform	Target genes	Reportable region (kb)	Coding (kb)	CTR (kb)	Negatives (× 1,000)	Variants
ROC	Roche Sequencing Solutions	AVENIO ctDNA (Expanded Kit)	Illumina NextSeq	77	161.7	140.2	103.8	47.1	189
ILM	Illumina	TruSight Tumor 170 + UMI	Illumina NovaSeq	154	501.0	390.1	338.4	133.0	574
IDT	Integrated DNA Technologies	xGen Non-small Cell Lung Cancer	Illumina NovaSeq	24	110.1	93.2	76.5	39.3	130
BRP	Burning Rock Biotech	Lung Plasma v4	Illumina NovaSeq	168	226.9	148.5	125.1	53.4	229
TFS	Thermo Fisher Scientific	Oncomine Lung cfDNA assay	Ion Torrent S5 XL	11	1.9	1.6	1.3	0.8	5



Source:
"Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology", Nature Biotechnology, Apr 2021

Overall analytical accuracy and specificity



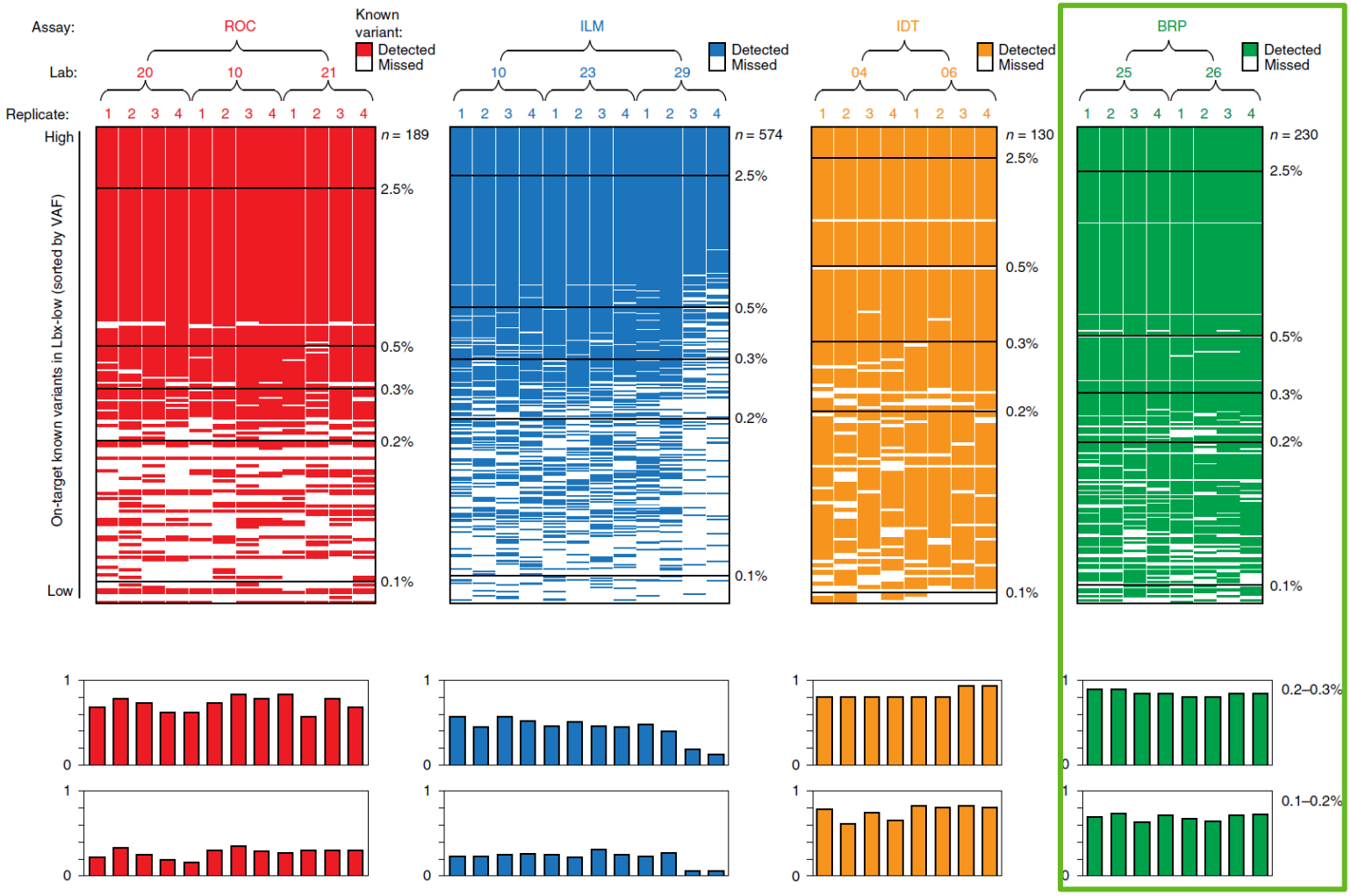
Assay	Known negatives (kb)	FPs per replicate (mean [range])	FP-rate (FP / kb) at specified VAF threshold > 0%	> 0.1%	> 0.5%
ROC	47.1	2.91 [1-6]	0.061	0.044	0.000
ILM	133	5.25 [2-10]	0.039	0.039	0.008
IDT	39.3	2.75 [0-6]	0.070	0.057	0.000
BRP	53.4	1.65 [0-5]	0.030	0.007	0.000

The analytical accuracy was measured by **Precision-Sensitivity** plot (25ng LBx-Low)
The false positive rates were computed by FP/kb region.
Once different VAF threshold increases, FP rates dropped further.

"To compare the accuracy of the participating ctDNA assays, we generated precision recall curves, ranking known variants and FPs according to their observed VAFs. **For Lbx-low samples at 25ng input, BRP was the most accurate assay, with roughly equivalent sensitivity but superior precision to IDT** (Fig. 4b and Supplementary Fig. 4c). "

Source:
"Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology", Nature Biotechnology, Apr 2021

Performance – Sensitivity



- LBx-low (25 ng input) replicates in each participating assay in different expected VAF bin.

"**The most sensitive assays (IDT and BRP) achieved sensitivity greater than 0.90 for variants with 0.3–0.5% VAF**; however, no assays reached this mark for variants with 0.2–0.3% or 0.1–0.2% VAF (Fig. 4a)."

"The performance characteristics of the assays evaluated here were broadly similar to what has been reported by several ctDNA sequencing providers (based on internal testing) that did not participate in this study. During validation of the Guardant360 CDx hybrid capture assay, variants were detected with high sensitivity (~94%) at VAF ≥ 0.4%, declining to ~64% among variants with VAF ranging from 0.05% to 0.25%." FoundationACT showed ~99% sensitivity for SNVs with VAF > 0.5%, ~95% for 0.25%–0.5% VAF and ~70% for 0.125–0.25% VAF."

Source:
"Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology", Nature Biotechnology, Apr 2021