燃石医学
Burning Rock Dx

Burning Rock Biotech Limited

2Q2022 results

BNR US Equity

31 Aug 2022

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Our value-building blocks

Extending leadership in NGS-based precision oncology from late-stage to earlier stage patients, opening up addressable market

New Businesses

Large market potential

At early commercial phase

Early Detection

Asymptomatic population

MRD[1]

Early-stage oncology patients

Biopharma

Global CDx[2] 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

Developed Business

Commercial phase

Therapy Selection

Late-stage oncology patients

Notes:
[1] Minimal residual disease of solid tumors
[2] Companion diagnostics

Objectives by segment

Continued topline growth with higher operating efficiency and reduced cash spend

Therapy selection

- Positive operating profitability in 2023

  Through accelerated transition towards the profitable in-hospital channel and reduced opex in central-lab

MRD

- Multi-year, high double digit revenue growth, driving next leg of growth

  Greenfield category, no gold standard from older technologies (e.g. PCR)

  Indication expansion from NSCLC[1] to CRC[2], breast and other cancer types via additional clinical studies

  Higher product entry barrier of *personalized* MRD test vs. *fixed-panel* products in therapy selection

Biopharma

- High double digit growth

  Continued build-up of project backlog, leveraging Burning Rock's strength in quality and product performance

  Already profitable due to high sales efficiency

Early detection

- Product – more cancer types, better performance

  Incorporate additional signal sources, enrich machine-learning model through large (over 10k+ subjects) studies

- Regulatory – establish approval pathway

  Dialogues with the NMPA and additional clinical studies to translate clear unmet need to proof of clinical utility

- Commercial – build first wave of seed customers

  Working with a few large hospitals to build blood-based multi-cancer early detection into health check-up routines

Notes:
[1] Non-small cell lung cancer
[2] Colorectal cancer

Recent progress

+3% YoY revenue growth in 2Q despite severe Covid impact, driven by in-hospital growth outside of Covid impacted regions, MRD contribution and pharma revenues

Therapy selection

- Continued execution of growth via in-hospital – severe Covid impact in Shanghai and Beijing, but other regions combined grew +60% YoY in 2Q (by test volume)
- Team and opex optimization

MRD

- Strong commercial ramp post launch in Mar 2022, following data read-out on NSCLC[1] and CRC[2] at AACR
- Work underway to launch 2 interventional studies in 2022. Full MEDAL study data on NSCLC[1] expected to be released in 4Q22

Biopharma

- Revenue grew by triple digit YoY to RMB18m, contributing to 14% of overall revenues (up from 5% in 2Q21)
- Strong backlog build, with newly contracted project value +49% YoY to RMB158m during 7M22

Early detection

- Data release – PROMISE study (2,035 participants) for 9-cancer test completed, reading out at ESMO in Sep
- Clinical programs – PREVENT study launched (12,500 participants), China's first multi-cancer prospective interventional study

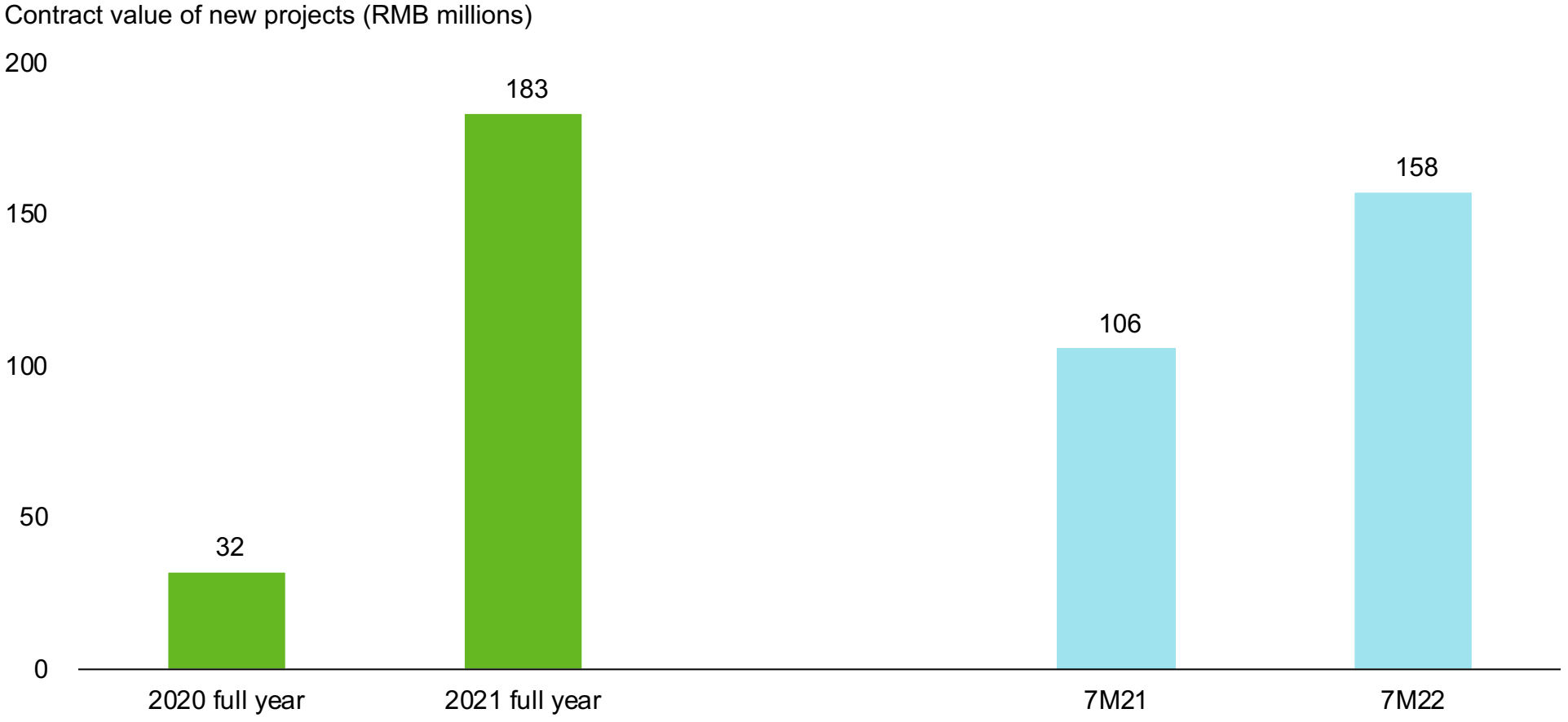
Notes:
[1] Non-small cell lung cancer
[2] Colorectal cancer

Biopharma services

Rapid backlog build-up continues

1H22 pharma revenues +207% YoY (to RMB18m, contributing to 14% of overall revenues)

Newly contracted pharma projects



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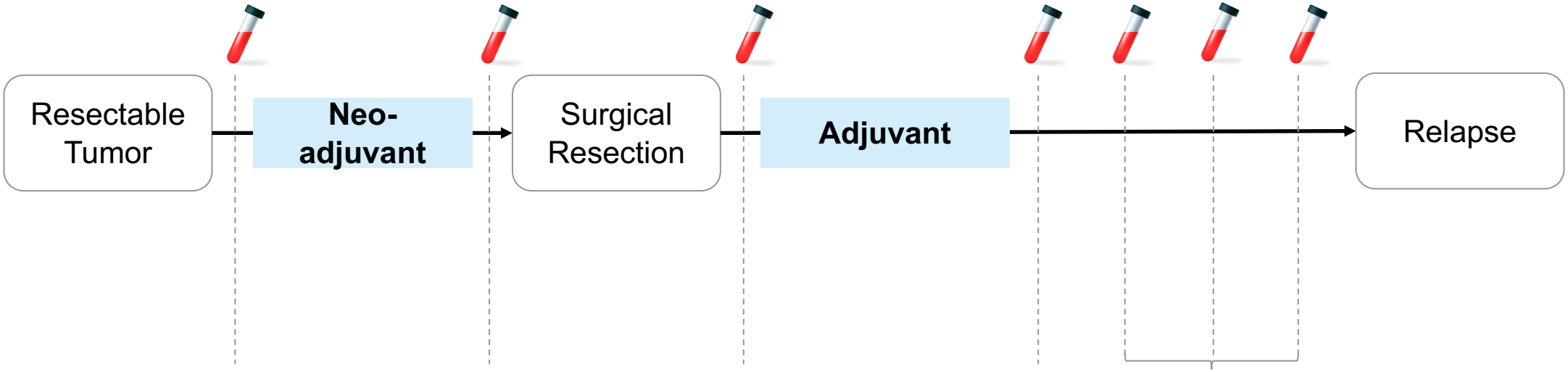
MRD

MRD test plays a role at multiple timepoints throughout the treatment journey



Good vs. poor prognosis

Whether and how to perform surgery

Good vs. poor prognosis

Identify low-risk patients and "tune-down" adjuvant treatment

Identify high-risk patients and "tune-up" treatment

Good vs. poor prognosis

Identify "cured" patients

Predict relapse

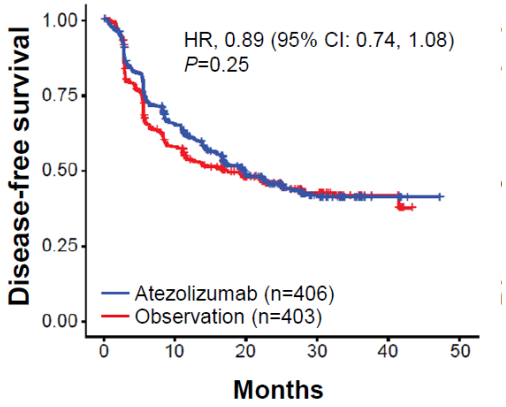
Nice-to-have prognosis

Actionable diagnosis that drives treatment choice

How do MRD studies advance utility

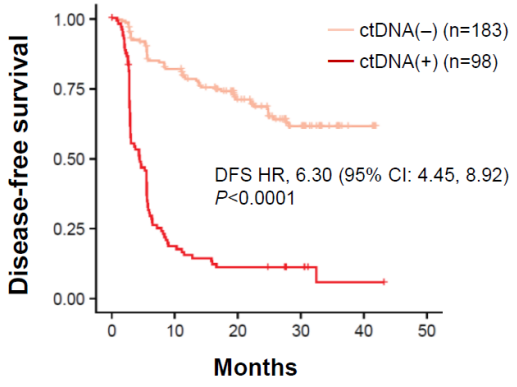
Example 1: IMvigor010, enrich the high-risk group and "tune-up" adjuvant treatment

ITT

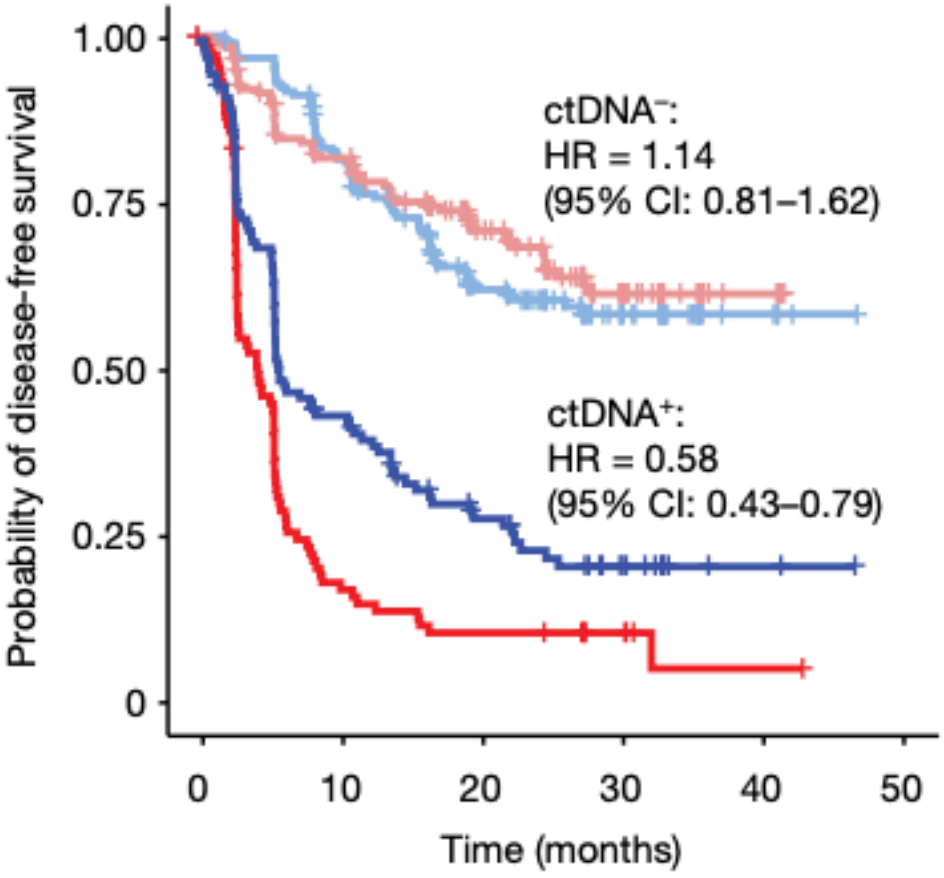


Atezo, MIUC Adjuvant Therapy
"All comers" demonstrated NO efficacy
TMB/PD-L1 showed NO prediction

Observation arm



Landmark MRD+ pts (39%) had worse prognosis
Maybe only those patients can benefit?

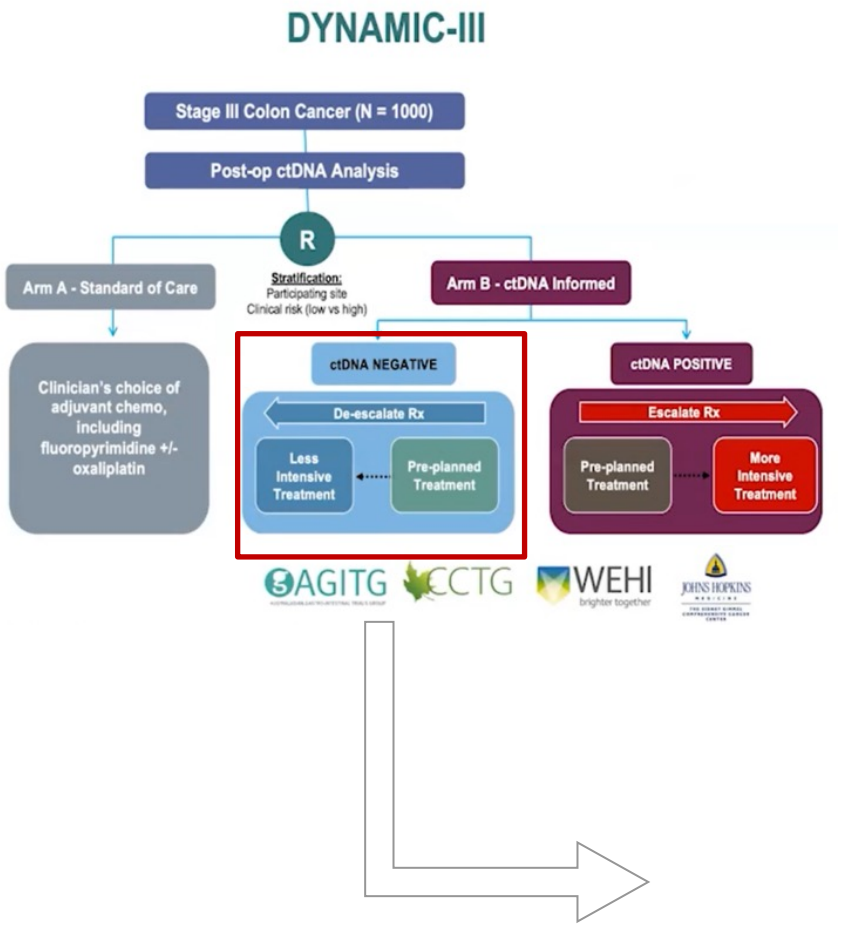


Indeed, only baseline MRD+ pts showed benefit

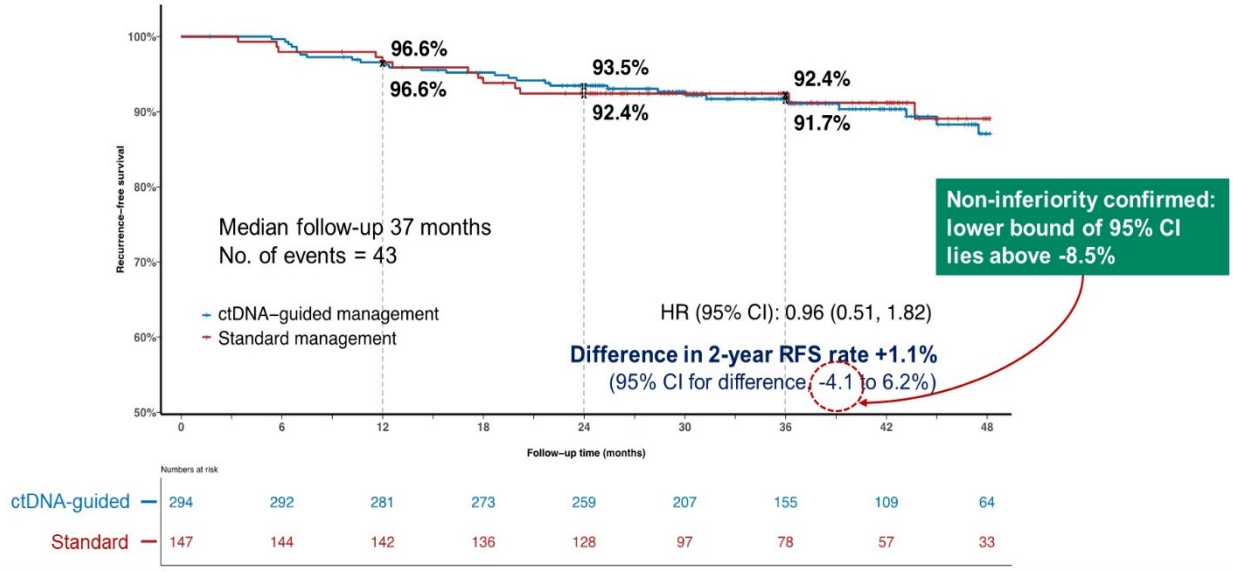
Nature. 2021 Jun 16. doi: 10.1038/s41586-021-03642-9.

How do MRD studies advance utility

Example 2: Dynamic, identify low-risk patients and "tune-down" adjuvant treatment



ctDNA-guided vs standard



The ctDNA-guided MRD- group had fewer patients with adjuvant chemotherapy than the standard group (15% vs. 29%) with non-inferiority of 3-year RFS (92.4% vs 91.7%)

MRD clinical adoption through physician consensus

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

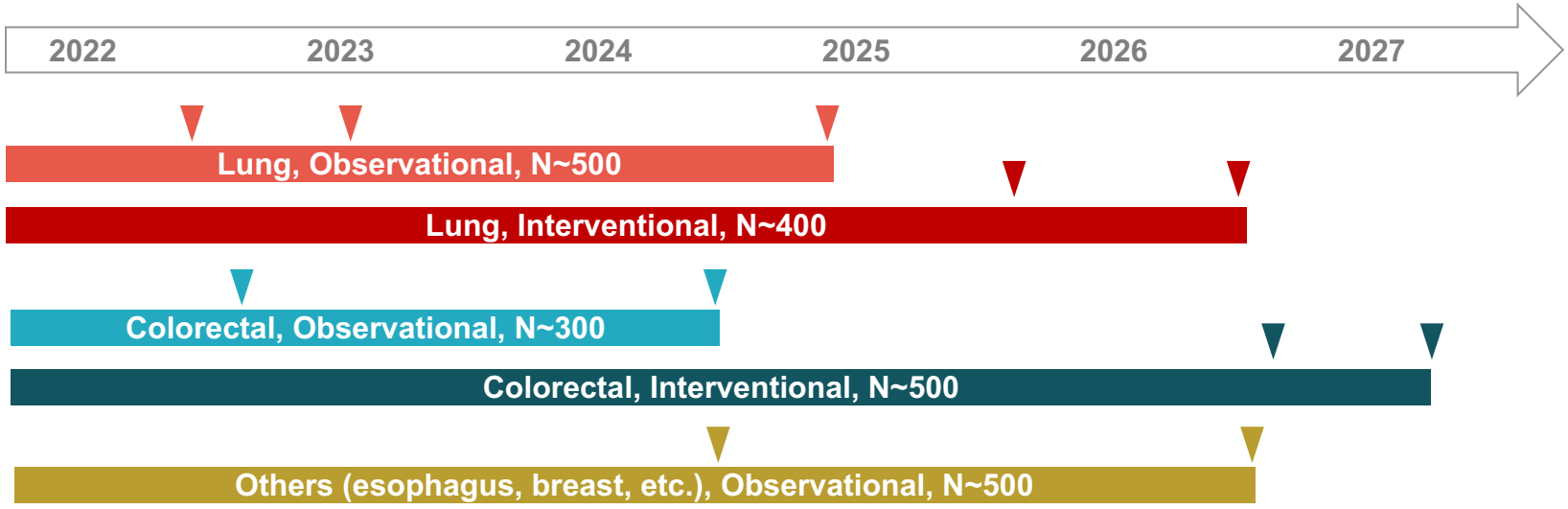
- MRD检测的基本技术，包括Tumor-informed assays(个体化定制)和 Tumor agnostic assays(NGS panel和多组学技术)，目前均处在探索阶段，需要前瞻性研究确定其敏感性、特异性和预测价值；
- 采用二代测序技术(NGS)，所选的多基因 panel中必须覆盖患者Ⅰ/Ⅱ类基因变异，基本技术标准是可稳定检出丰度≥0.02%的ctDNA；
- 驱动基因阳性的非小细胞肺癌，MRD的分子panel应包括该驱动基因；
- MRD评估报告中必须包括cfDNA丰度， ctDNA丰度，所检测基因VAF值；
- 需要建立针对免疫治疗的MRD标准。

Burning Rock development plans

Personalized approach (brPROPHET™) demonstrating strong analytical performance
Additional clinical studies to expand indications

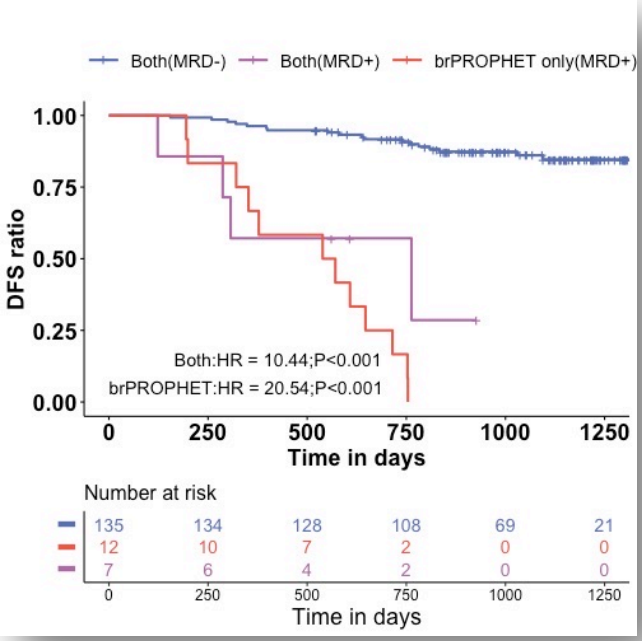
	Assay and Model Development	Analytical Validation	Clinical Validation (Prognosis and Surveillance)	Product Launch
Product development and initial clinical read-out	Completed Personalized assay: brPROPHET™ Target limit-of-detection (LOD): 0.004%	Lung and colon data read-out at 2022 AACR	Commercially launched in March 2022	

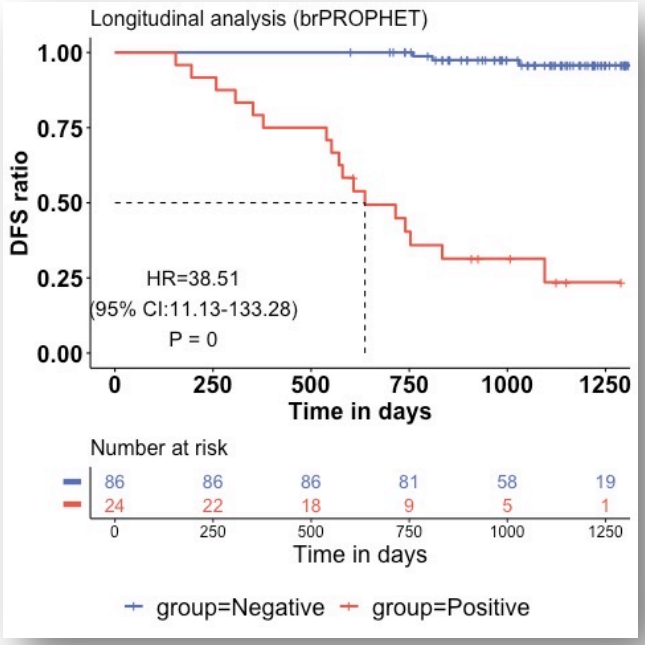
Additional clinical programs for indication expansion

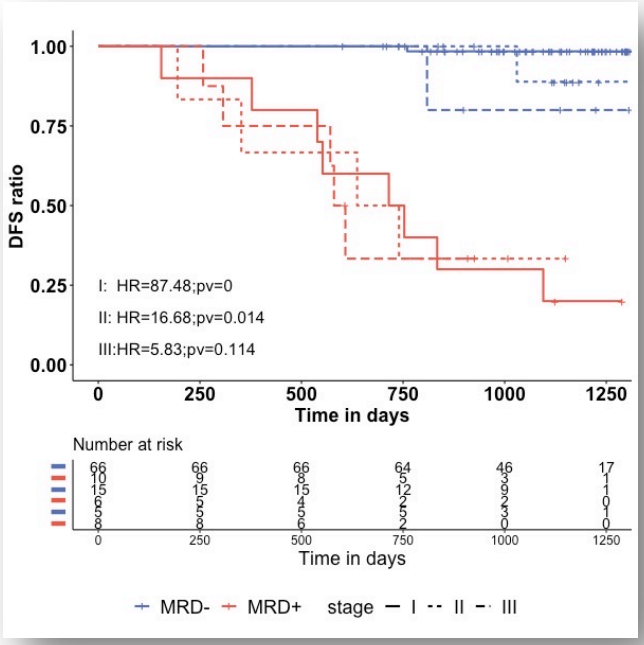


MRD clinical validation data readout

NSCLC – MEDAL study





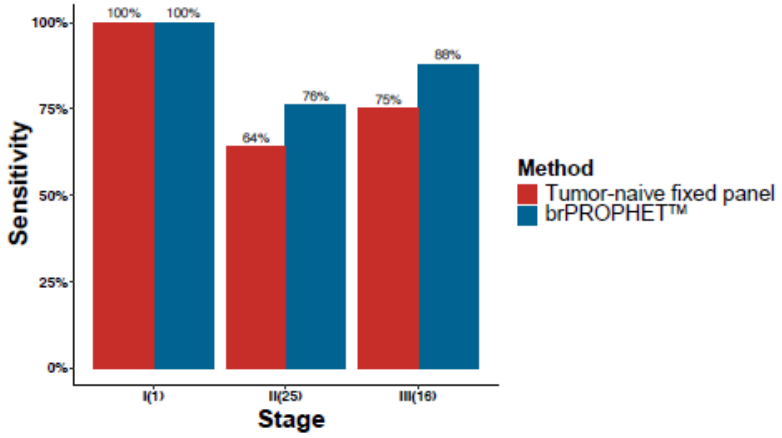


- *brPROPHET identified 2.7 times more true high-risk patients than the fixed panel approach at the landmark time point*
- *Longitudinally MRD negative patients has near-perfect prognosis with median of 3-year follow-up*
- *The prognosis differentiation holds true for patients with different clinical stage*

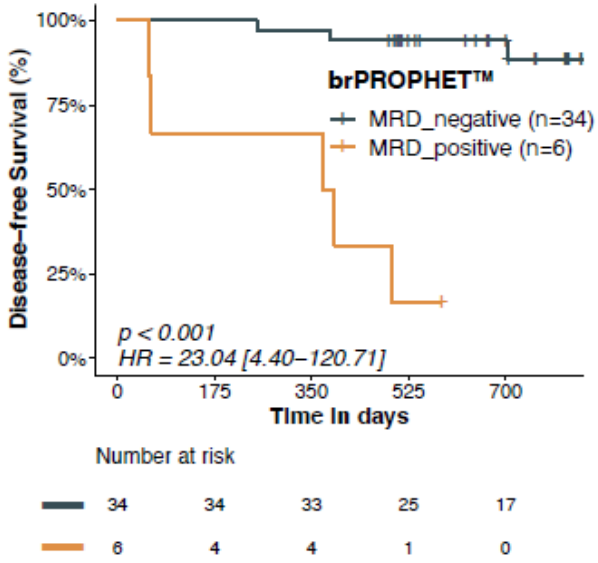
MRD clinical validation data readout
CRC

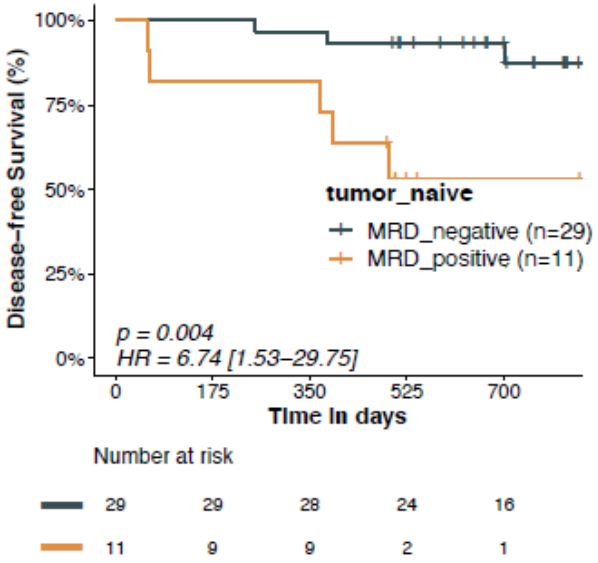
Session OPO.PR02.01 - Clinical Prevention, Early Detection, and Interception

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





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Early detection

Product development since 2016

Demonstrated high specificity 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)
- 95.1% specificity and 80.8% sensitivity[1]

Product development complete

6-cancer
2018 – Nov 2020

- Lung, CRC, HCC, Ovarian, Pancreatic, Esophageal
- 98.9% specificity and 69.1% sensitivity[2]

Product development in progress

9-cancer
2019 – Ongoing

- Additional cancer types: Gastric, Biliary Tract, Head & Neck
- PROMISE study concluded, reading out at ESMO in Sep 2022
- Ongoing PREDICT study

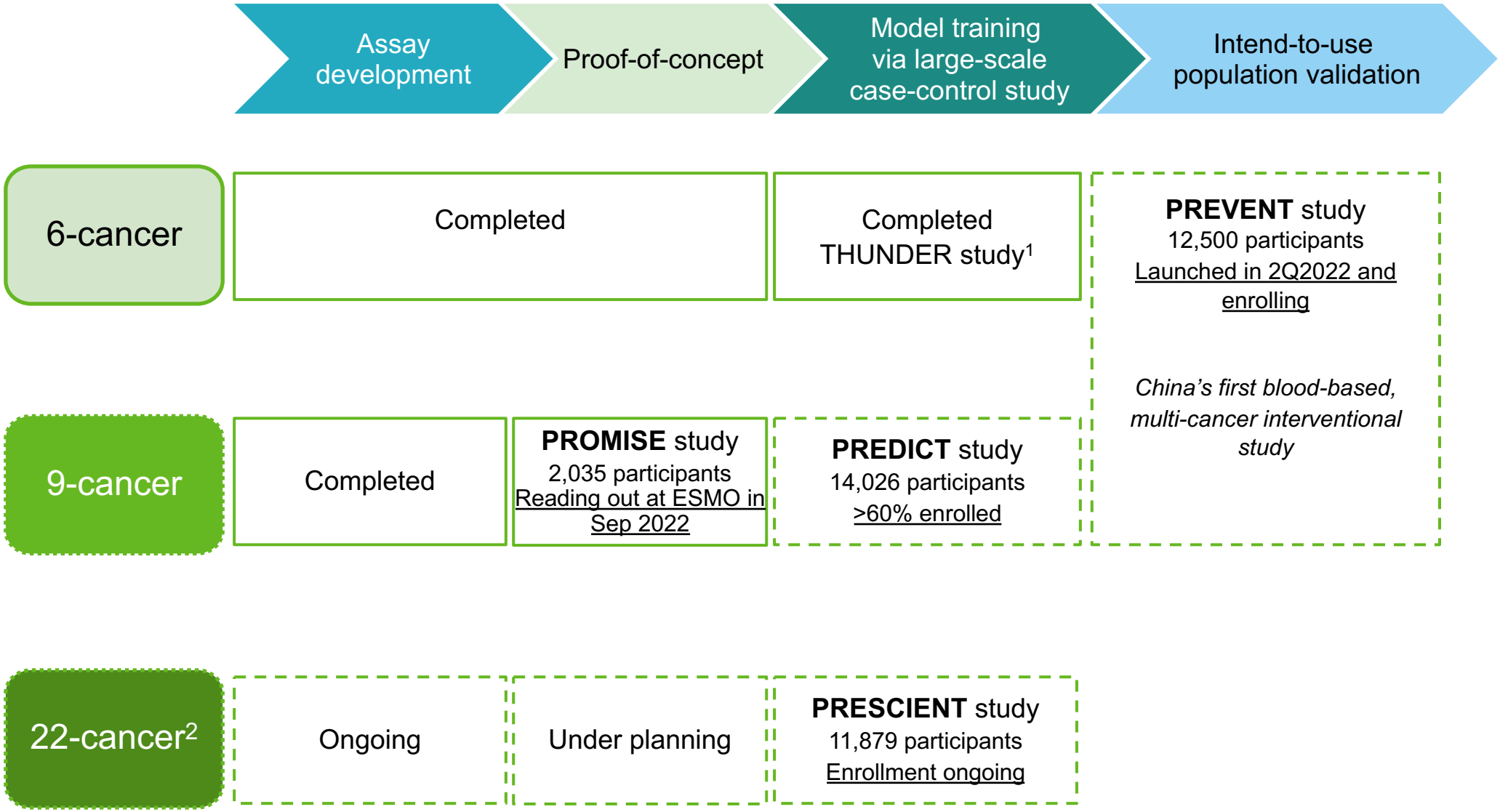
22-cancer[3]
2020 – Ongoing

- 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] Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies, ASCO 2022. Further details in Appendix 1.
[3] Final number of cancer types subject to development progress

Clinical programs

9-cancer development first read-out in Sep (PROMISE study)
China's first interventional study for multi-cancer launched in 2Q (PREVENT study)



Notes:
[1] THUNDER series of studies. Latest results presented at ASCO 2022, Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies
[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, leading to feasibility of 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 2022

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

ASCO 2022

Clinical validation of a multicancer detection blood test by circulating cell-free DNA (cfDNA) methylation sequencing: The THUNDER study.

ESMO 2022

The performance of a multi-cancer early detection model based on liquid biopsy of multi-omics biomarkers: A proof of concept study (PROMISE study)

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]

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

Principal Investigators

Prof. Jie He

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

Prof. Jie Wang

- Head of the Dept. of Medicine, CHCAMS

PREVENT

Principal Investigator: Prof. Weiming Li

- President of West China Hospital

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

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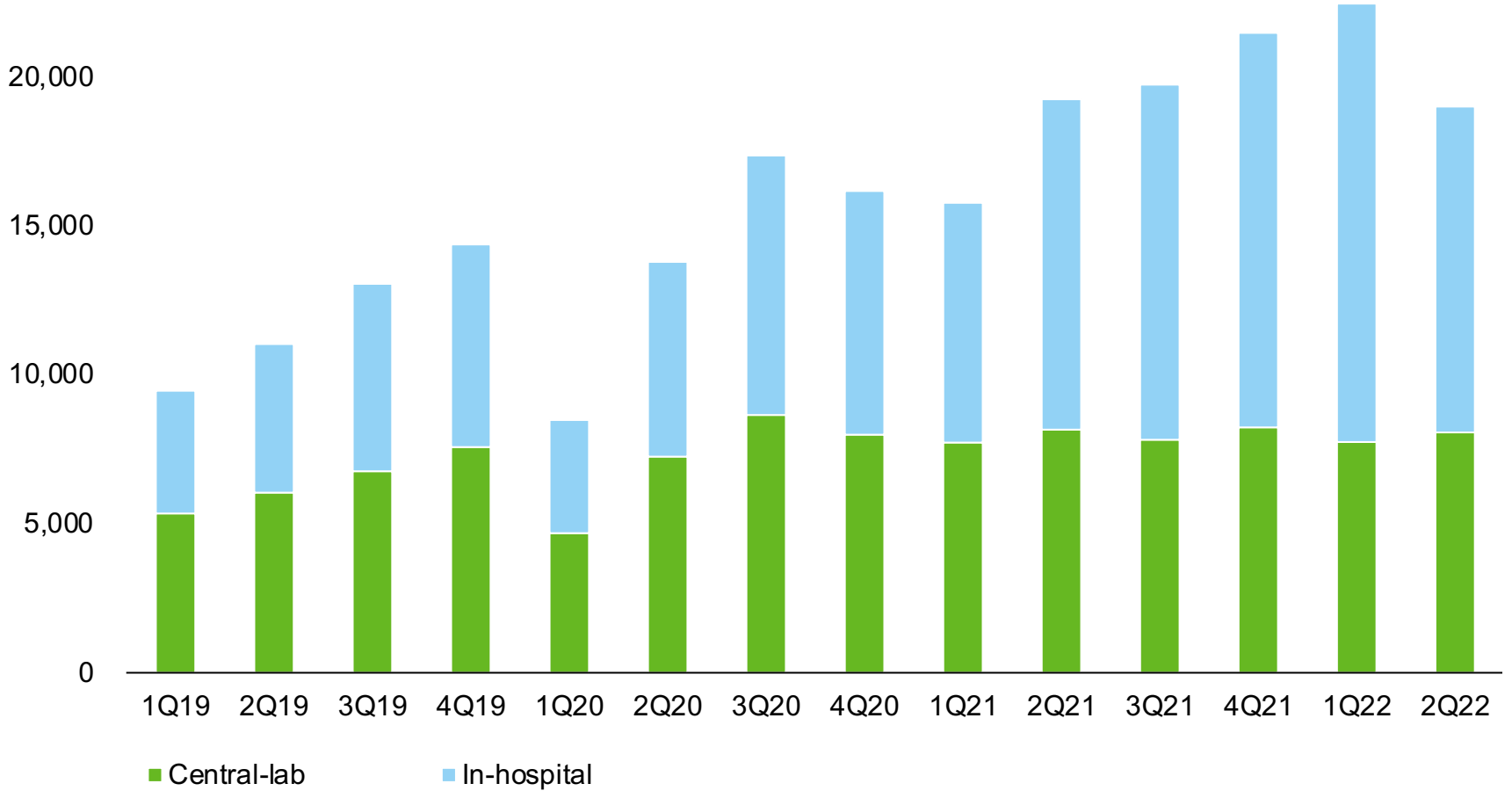
Financials

In-hospital and MRD driving growth uplift, but patient volumes negatively impacted by Covid related restrictions

Volumes by channel[1]

Overall test volumes -1.3% YoY in 2Q

- Better than peer volume performance indicates share gain
- Central-lab -1.2%, with MRD launch partially offsetting Covid impact
- In-hospital -1.4%, dragged by Shanghai and Beijing Covid impact (-49%), but other regions grew strong (+60%)



Notes:

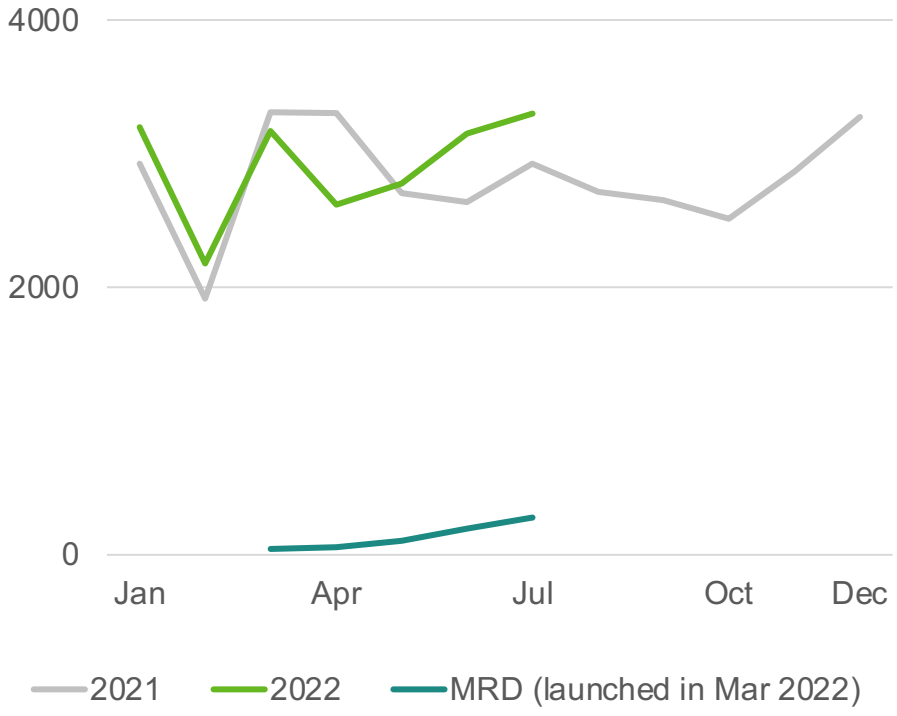
[1] Central-lab (LDT) volumes represented by the number of patients tested. In-hospital (IVD) volumes represented by the number of testing kits shipped to partner hospitals

Latest trends

Continued secular growth of in-hospital penetration and MRD, despite Covid disruptions
Overall volume growth turned from -11% in Jun to +6% in Jul

Central-lab volumes
Jul +13% YoY, improved vs. 2Q's -1%, driven by MRD

In-hospital volumes
Shanghai, Beijing not yet fully recovered from Covid, strong growth in other regions



Volume growth YoY	Jan 2022	Feb	Mar	Apr	May	Jun	Jul
All regions	+149%	+95%	+36%	+60%	-11%	-28%	+0.2%
Shanghai and Beijing	+147%	+60%	+35%	+43%	-68%	-79%	-25%
Other regions	+152%	+154%	+37%	+78%	+56%	+51%	+41%

Notes:
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
MRD – minimal residual disease testing

Financials

Opex to trend down over time

RMB1.15bn / USD172m cash and investments on balance as of Jun 2022

RMB millions	2021	*19 YoY*	*20 YoY*	*21 YoY*	1Q21	2Q21	*3Q21*	4Q21	1Q22	2Q22	*2Q22 YoY*	*2Q22 QoQ*	2022 Guide
Revenue	**507.9**	**83%**	**13%**	**18%**	**106.6**	**127.3**	**126.6**	**147.3**	**135.5**	**130.8**	**3%**	**-3%**	**620**
Central lab	319.4	71%	8%	7%	74.6	80.0	78.8	86.0	74.2	78.6	-2%	6%	
In-hospital[1]	165.1	164%	34%	40%	29.0	40.5	43.7	51.9	49.0	34.2	-16%	-30%	
Pharma	23.4	25%	(17%)	59%	3.1	6.8	4.1	9.4	12.3	18.0	165%	46%	
Non-GAAP Gross profit[2]	**368.2**				**77.1**	**90.7**	**93.0**	**107.4**	**92.7**	**90.9**	**0%**	**-2%**	
Total opex	**1,161.2**	**49%**	**64%**	**60%**	**248.8**	**292.3**	**262.7**	**357.5**	**350.4**	**348.1**	**19%**	**-1%**	
R&D[3]	324.1				52.7	84.3	73.5	113.6	100.9	77.7	-8%	-23%	
S&M[3]	283.4				50.0	62.7	72.1	98.6	84.6	100.3	60%	19%	
G&A[3]	228.8				52.6	51.1	51.7	73.4	61.2	74.8	46%	22%	
SBC	280.8				84.4	83.0	53.3	60.2	79.8	76.7			
D&A	44.1				9.1	11.2	12.1	11.7	23.9	18.6			
Operating profit	**(797.1)**				**(171.9)**	**(202.0)**	**(171.1)**	**(252.1)**	**(262.8)**	**(265.5)**			
Net operating cash flows	**(477.9)**				**(113.1)**	**(119.0)**	**(133.4)**	**(112.3)**	**(144.4)**	**(109.3)**			
Non-GAAP GP margin[2]	72.5%				72.4%	71.2%	73.4%	72.9%	68.4%	69.5%			
Opex[3] / revenue	165%				146%	156%	156%	194%	182%	193%			
S&M[3] / revenue	56%				47%	49%	57%	67%	62%	77%			

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] Non-GAAP gross margin, which is defined as gross margin excluding depreciation and amortization (D&A)

[3] Excluding share based compensation (SBC) and depreciation and amortization (D&A)

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Appendix 1

Early detection

AACR 2022

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

- **Analytical sensitivity.** The limit of detection with 95% probability (LOD_{95}) was established using 5ng DNA, the lowest claimed input amounts. Two models were assessed with a fixed training specificity at 95% (MCDBT-1) and 99% (MCDBT-2), respectively. Among six tested cancer types, the LOD_{95} was estimated down to 0.02% with respect to VAF.

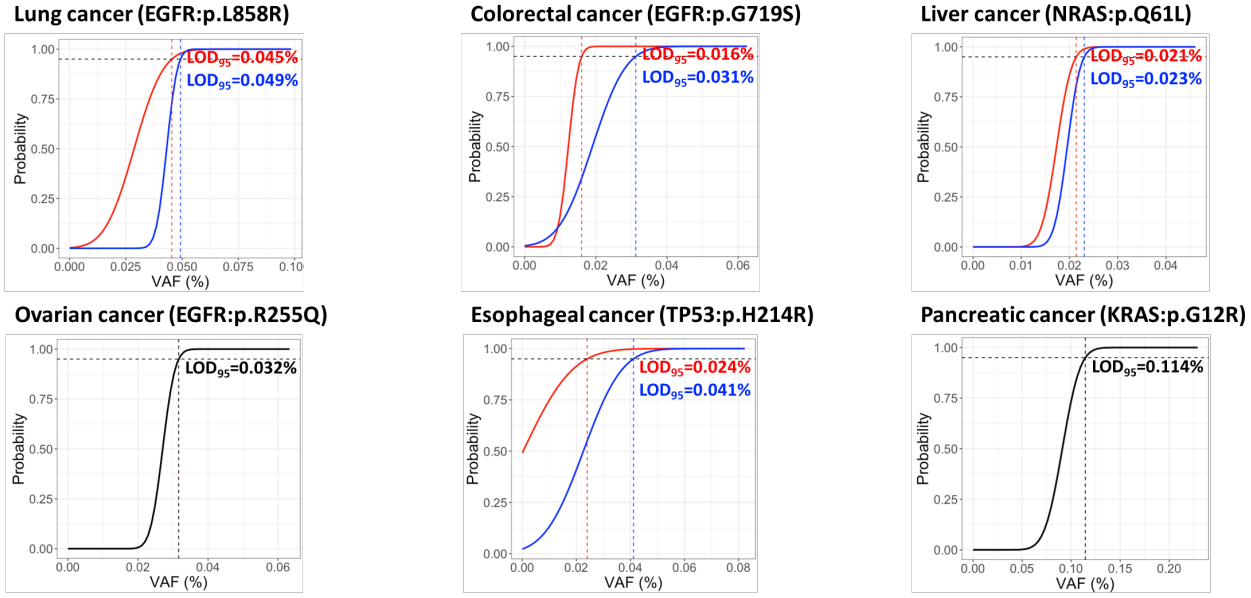


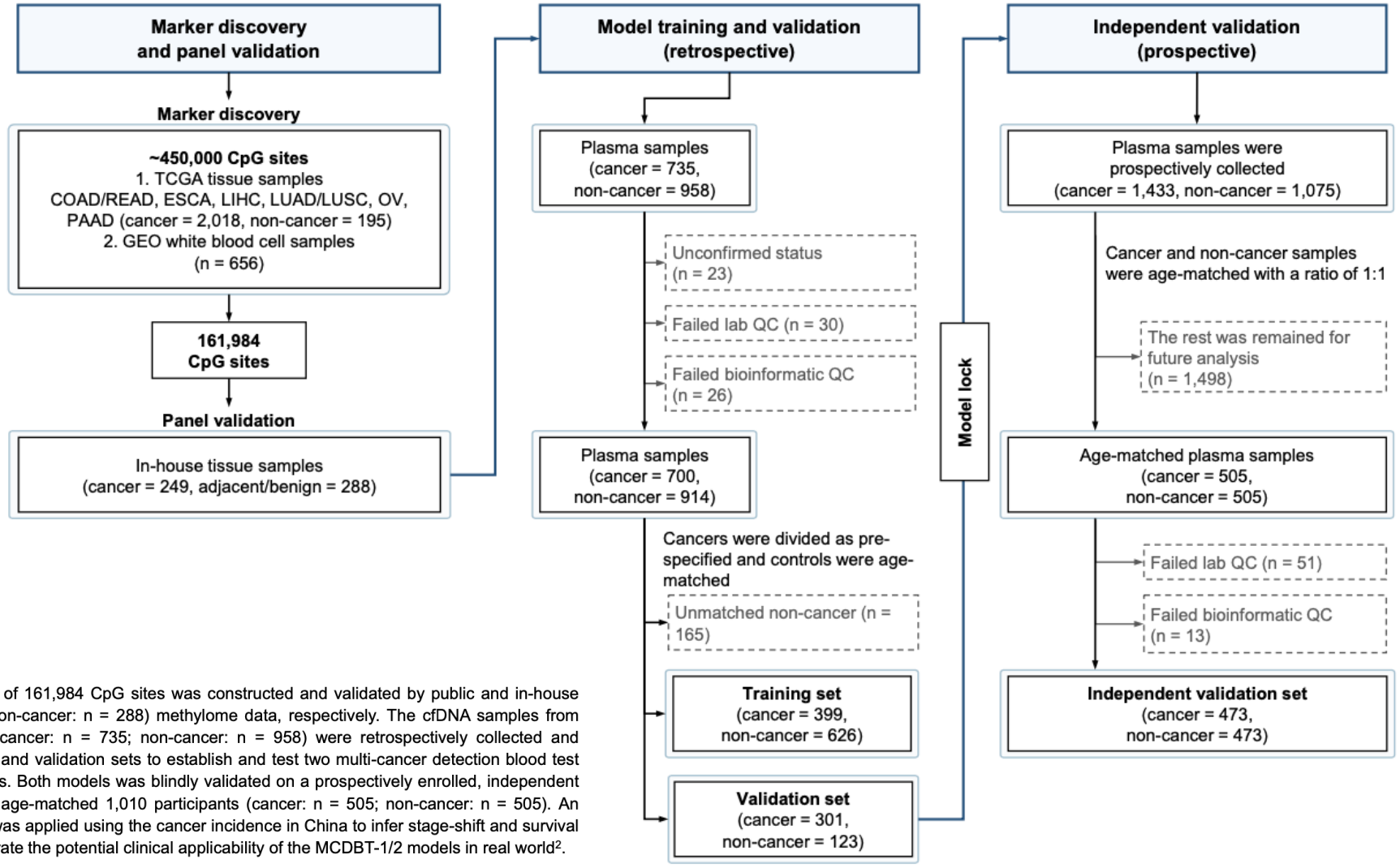
Figure 3: The LOD_{95} for 6 cancer types using two prediction models. Probit fit of DOC accuracy versus VAF using cell line dilution series. The red and blue curves represent MCDBT-1 and MCDBT-2 results, respectively. The black curves indicate the same results obtained by both models. The dotted lines indicate the LOD_{95} for each model.

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

ASCO 2022 – Thunder study read-out of the 6-cancer test

Cohort

Fig 1. Flow chart.



A customized panel of 161,984 CpG sites was constructed and validated by public and in-house (cancer: n = 249; non-cancer: n = 288) methylome data, respectively. The cfDNA samples from 1,693 participants (cancer: n = 735; non-cancer: n = 958) were retrospectively collected and divided into training and validation sets to establish and test two multi-cancer detection blood test (MCDBT-1/2) models. Both models was blindly validated on a prospectively enrolled, independent validation cohort of age-matched 1,010 participants (cancer: n = 505; non-cancer: n = 505). An interception model was applied using the cancer incidence in China to infer stage-shift and survival benefits to demonstrate the potential clinical applicability of the MCDBT-1/2 models in real world[2].

Source: Gao et al., Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies, ASCO 2022

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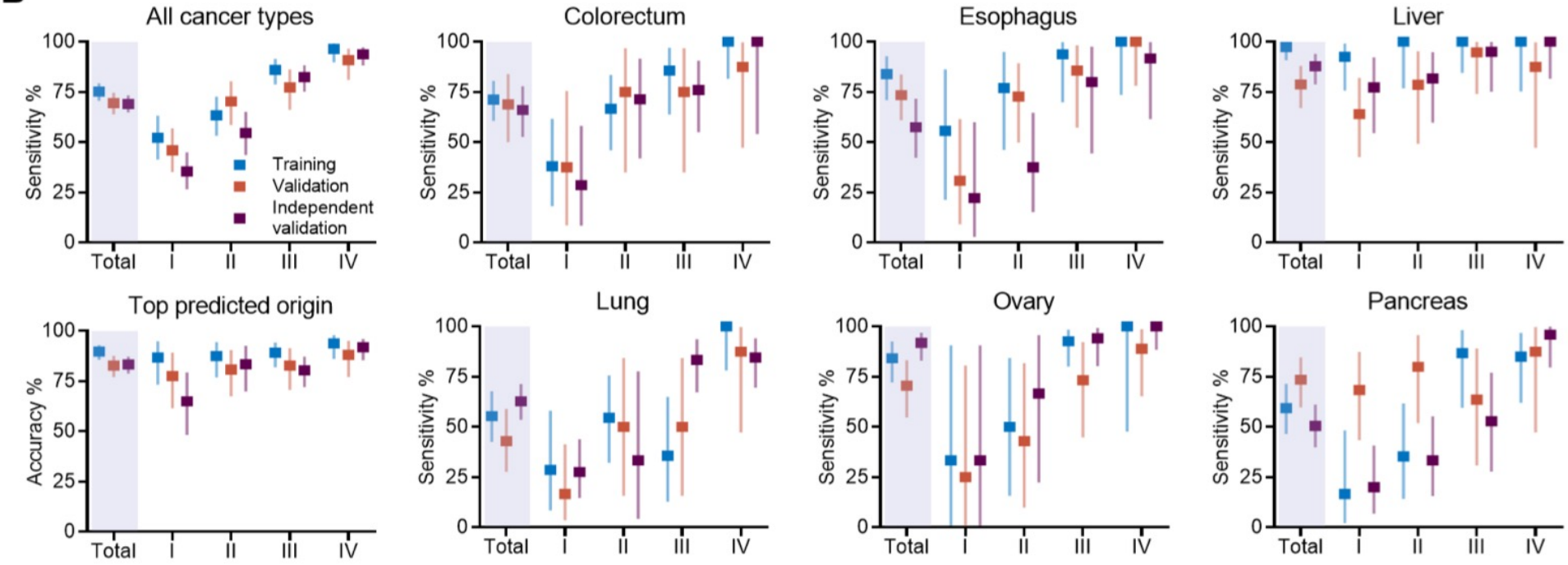
Clinical performance on cancer detection

Fig 3. Performance of the MCDBT-1/2 models. A. Sensitivity, specificity, accuracy of top predicted origin, and accuracy of top two predicted origins. **B**. The overall sensitivity, accuracy of top predicted origin, and sensitivity stratified by cancer types reported by tumor stage.

A

			MCDBT-1		MCDBT-2	
	Cancer (n)	Non-cancer (n)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
Training	399	626	99.7 (98.9-100.0)	75.2 (70.6-79.4)	98.9 (97.7-99.5)	79.9 (75.7-83.8)
Validation	301	123	100.0 (97.0-100.0)	69.4 (63.9-74.6)	98.4 (94.2-99.8)	76.7 (71.6-81.4)
Independent validation	473	473	98.9 (97.6-99.7)	69.1 (64.8-73.3)	95.1 (92.8-96.9)	75.1 (71.9-79.8)

B

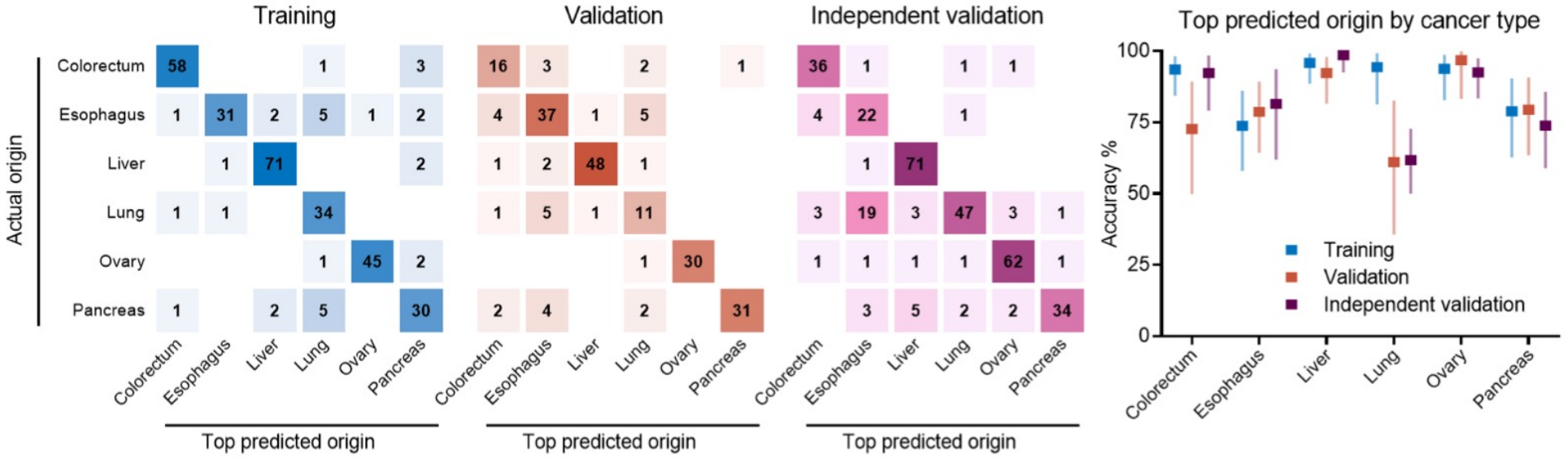


Source: Gao et al., Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies, ASCO 2022

ASCO 2022 – Thunder study read-out of the 6-cancer test

Clinical performance on tissue of origin

Fig 4. Top predicted origin for the MCBDT-1 model. Confusion matrices representing the predicted origin in the training, the validation, and the independent validation sets.



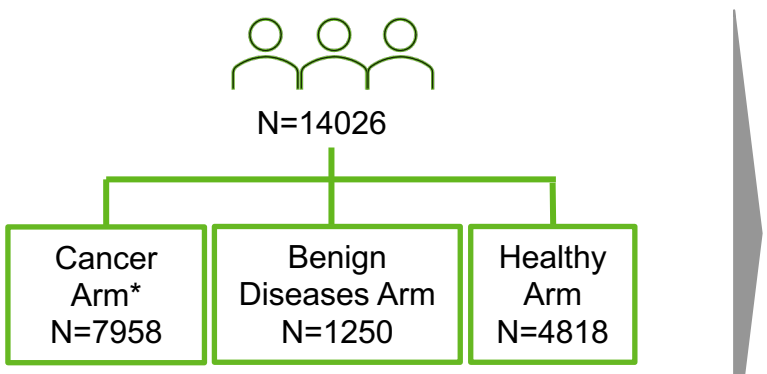
Source: Gao et al., Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies, ASCO 2022

The PREDICT study (NCT04817306)

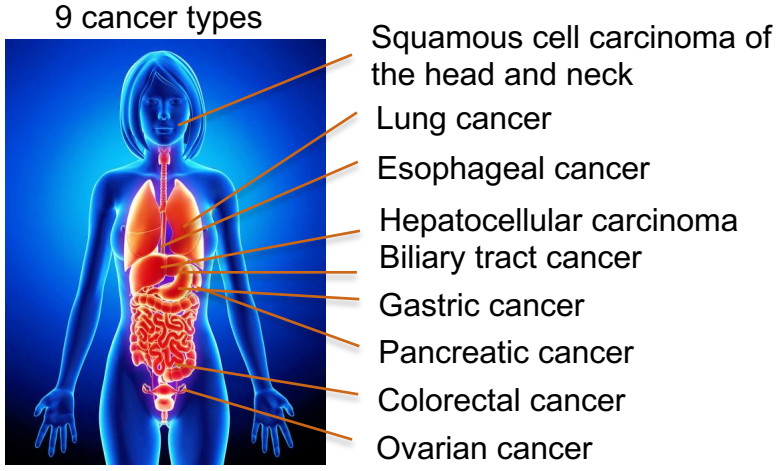
Study design

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

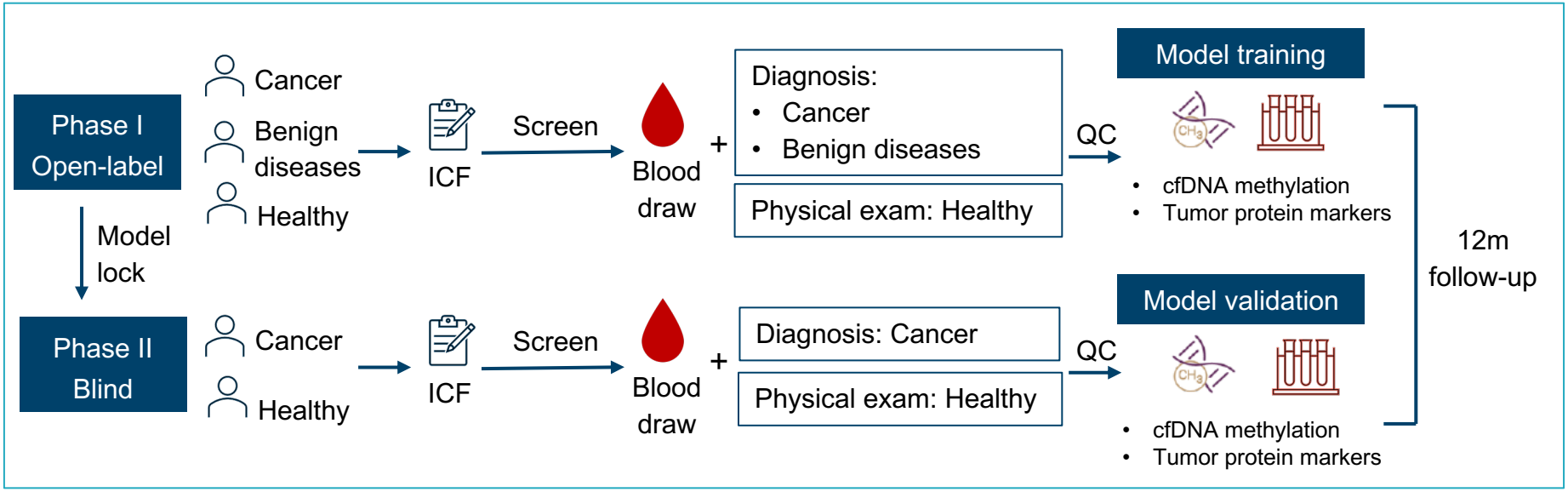
Participants



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



Study Design



The PREDICT study (NCT04817306)

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

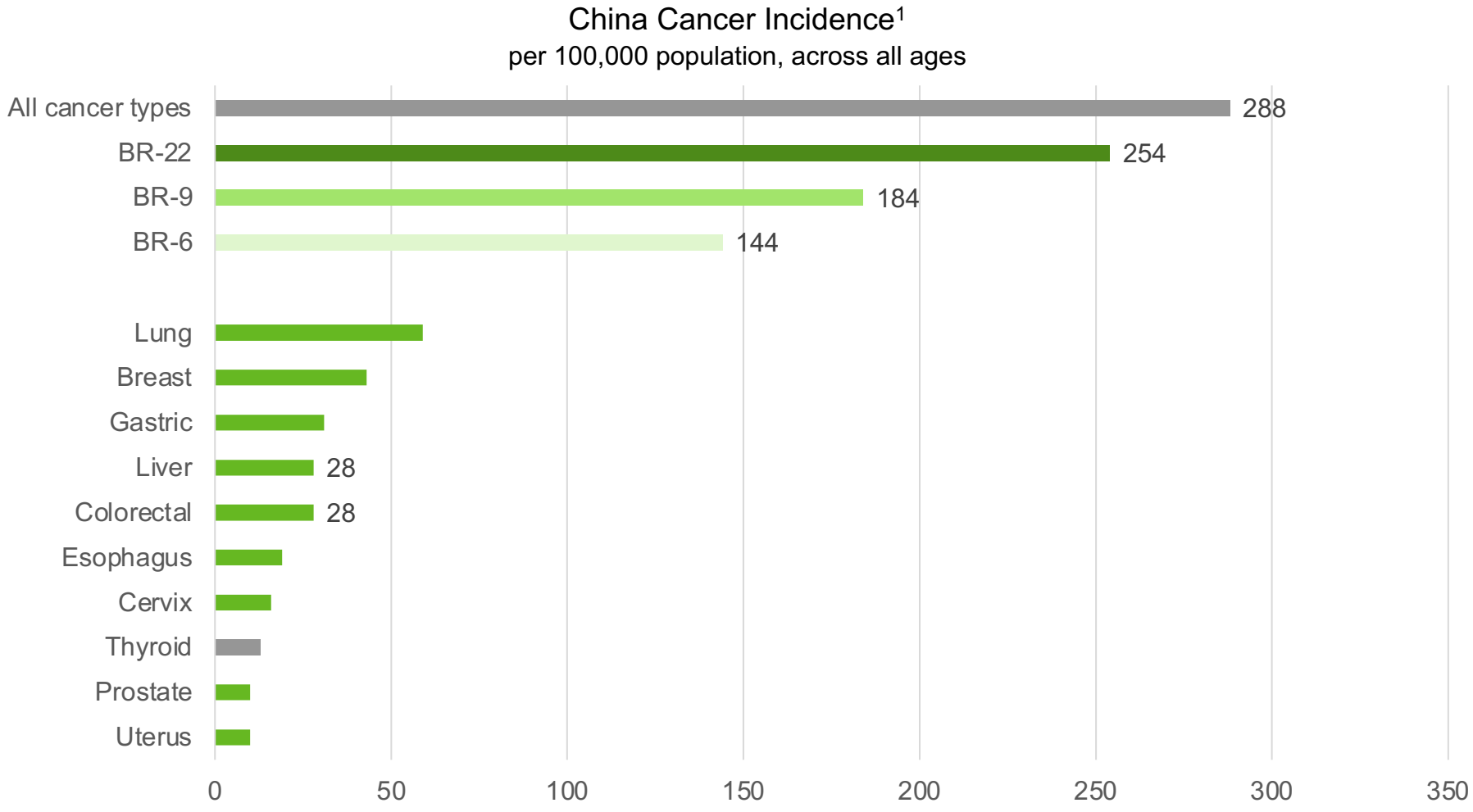
Cancer
Benign diseases
Healthy

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

- cfDNA methylation
- Tumor protein markers
- Other omics biomarkers

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

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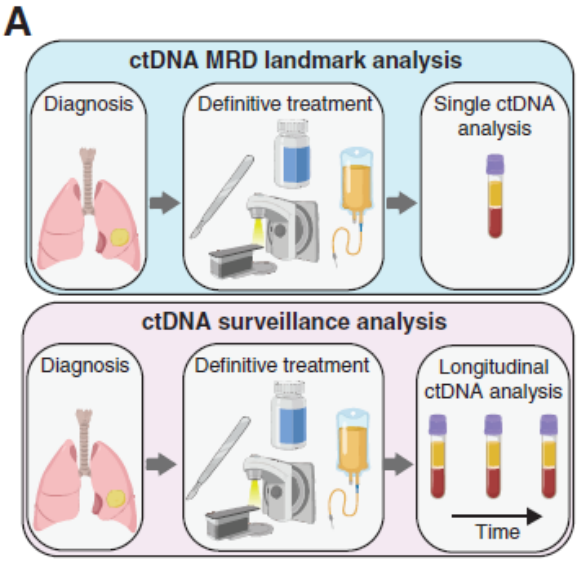
Appendix 2

MRD

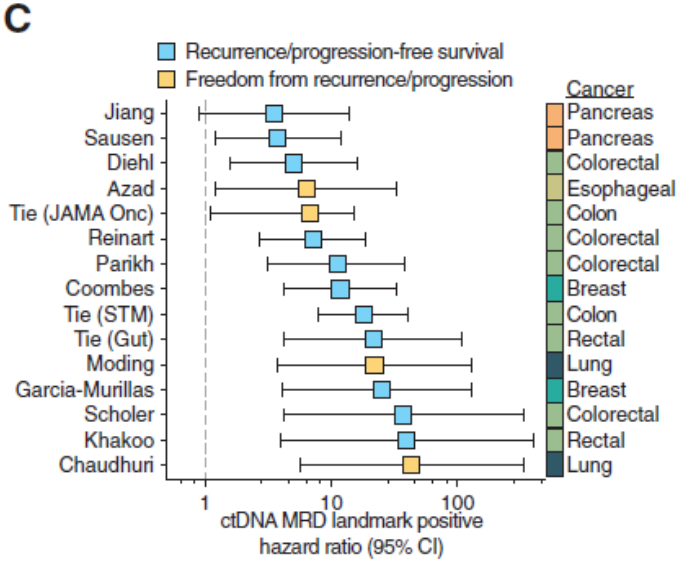
Clinical utilities of MRD in solid tumors

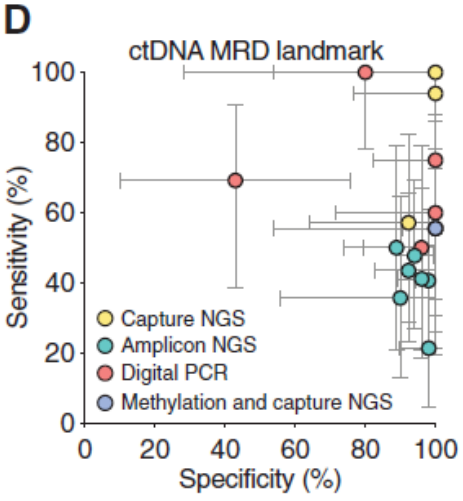
1) risk stratification and regimen selection (landmark analysis), 2) relapse monitoring (surveillance analysis)

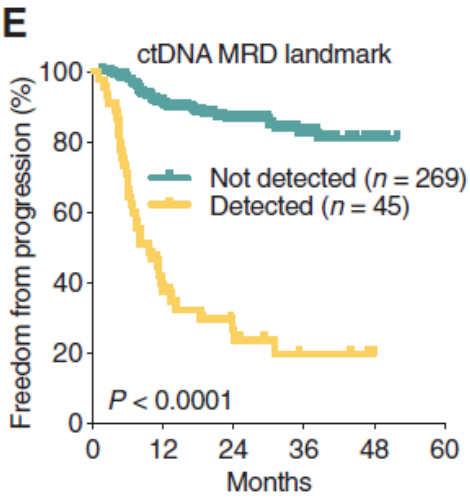


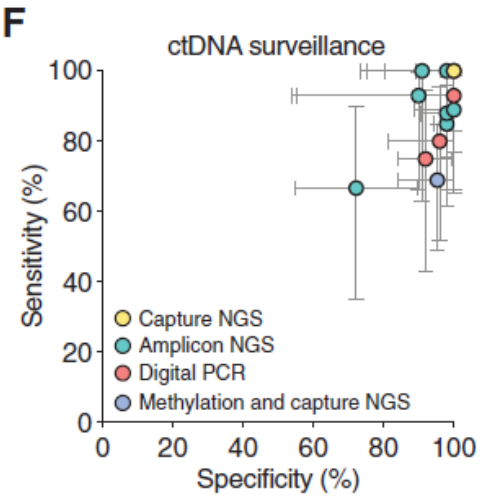
B

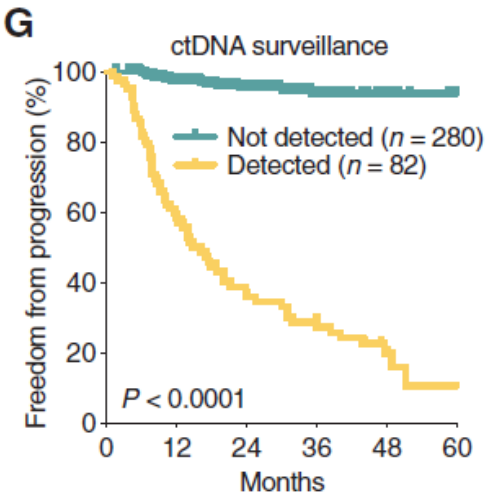
Cancer	Reference	# Patients	Analysis: Landmark	Analysis: Surveillance
Lung	Peng (111)	48	Yes	Yes
Lung	Chaudhuri (62)	37	Yes	Yes
Lung	Abbosh (31)	24	Yes	Yes
Lung	Moding (90)	12	Yes	No
Breast	Garcia-murillas (113)	101	No	Yes
Breast	Coombes (34)	49	Yes	Yes
Breast	Garcia-murillas (27)	43	Yes	Yes
Breast	Olsson (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**







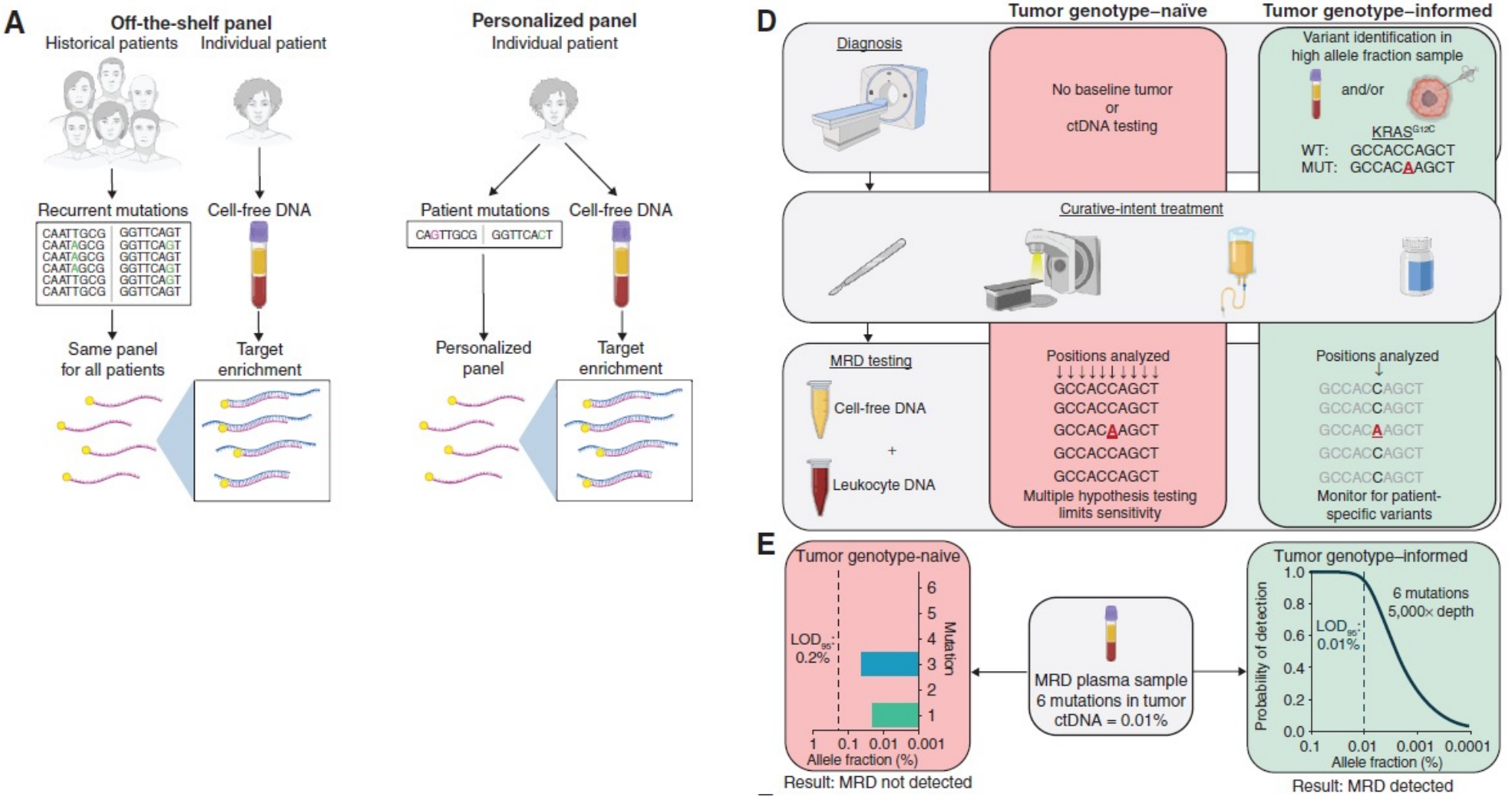




Cancer Discov. 2021 Nov 16. doi: 10.1158/2159-8290.CD-21-0634

Clinical utilities of MRD in solid tumors

Fixed panel vs. personalized panel approaches



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

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Appendix 3

Therapy selection

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

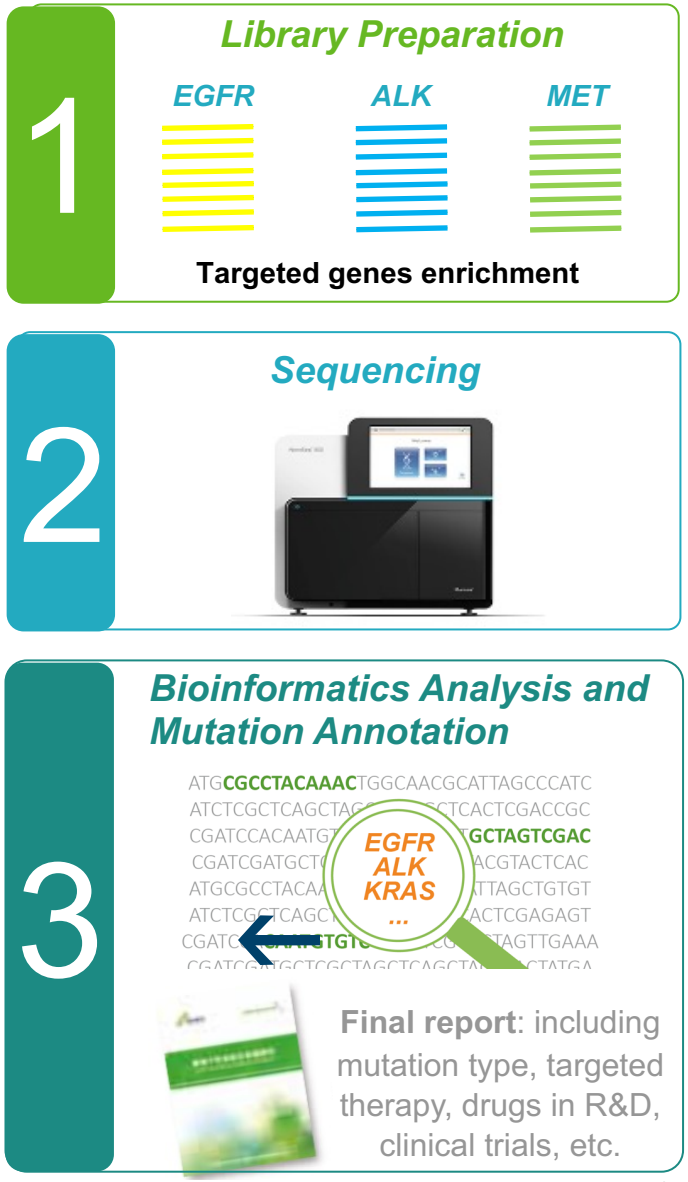
- Only 30ng DNA input required, applicable to small tissue samples
- First NMPA approved NGS kit with CNV[2] mutation type, with MET exon14 skipping

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

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%

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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

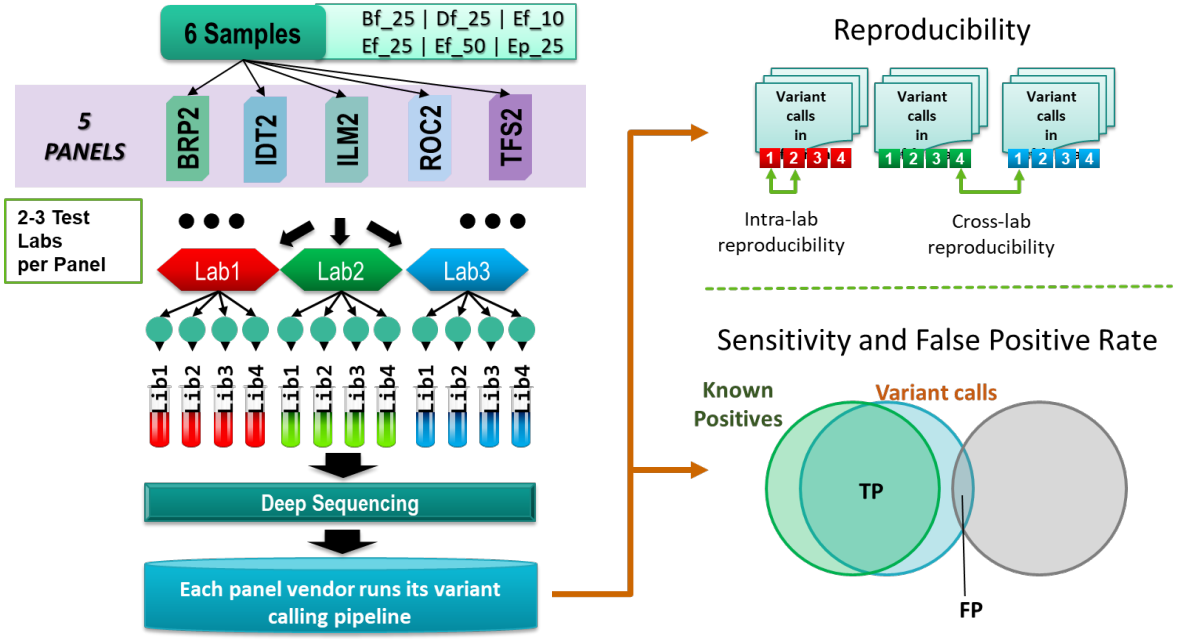
TFS2

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

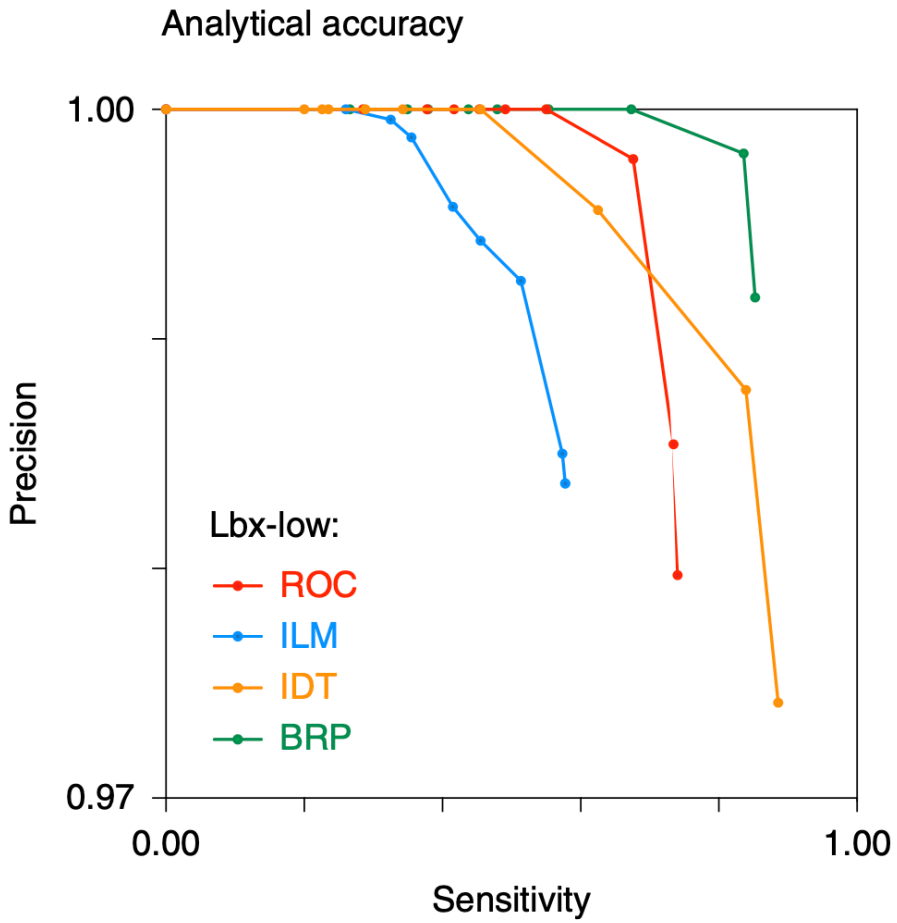
Participating assays and study design

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



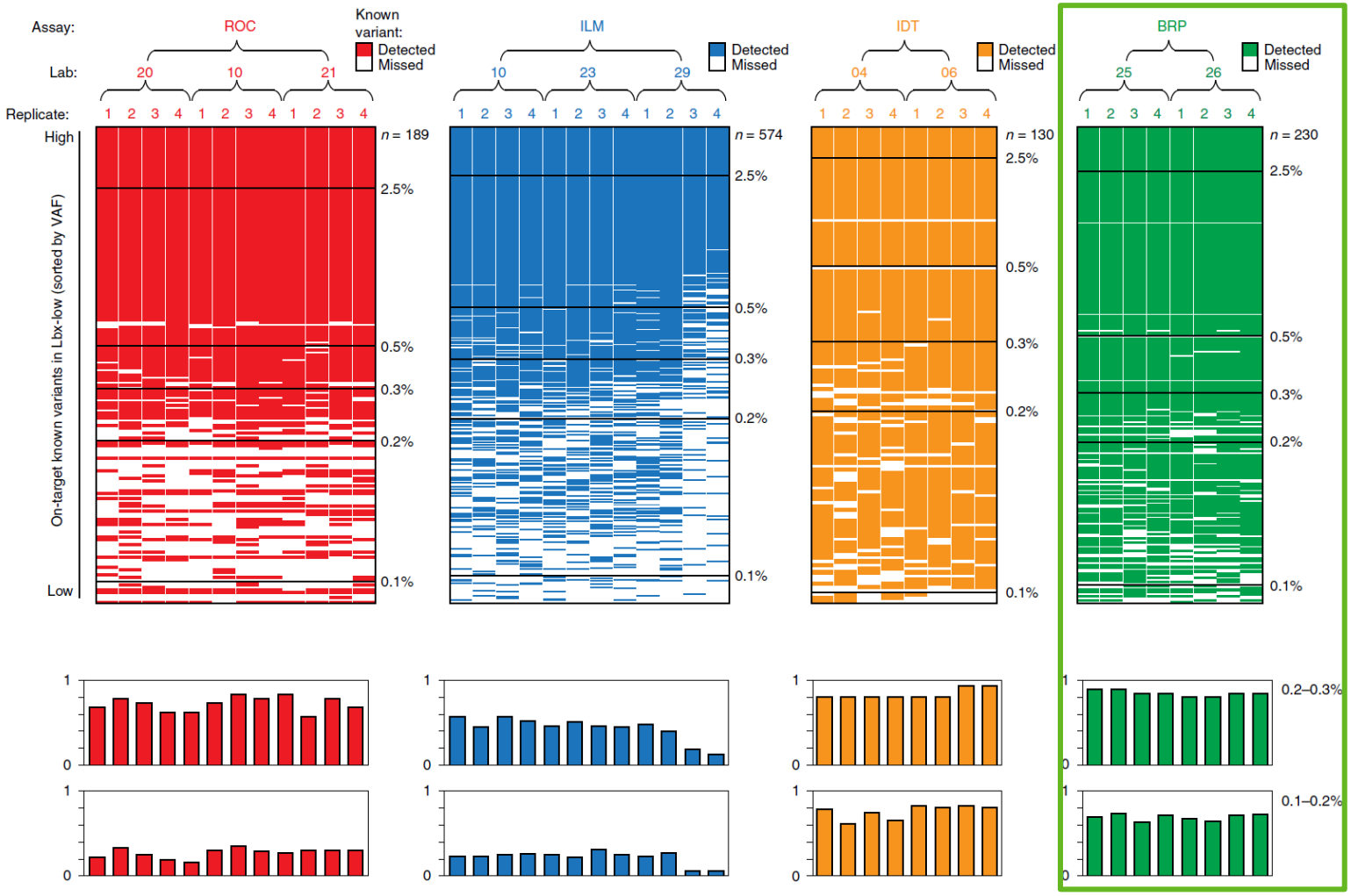
Assay	Known negatives (kb)	FPs per replicate (mean [range])	FP-rate (FP / kb) at specified VAF threshold > 0%	> 0.1%	> 0.5%
ROC	47.1	2.91 [1-6]	0.061	0.044	0.000
ILM	133	5.25 [2-10]	0.039	0.039	0.008
IDT	39.3	2.75 [0-6]	0.070	0.057	0.000
BRP	53.4	1.65 [0-5]	0.030	0.007	0.000

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