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Burning Rock Dx

Burning Rock Biotech Limited

4Q2022 results

Nasdaq and LSE: BNR

28 Mar 2023

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Our value-building blocks

Extending leadership in NGS-based precision oncology from late-stage to earlier stage patients

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

2022 review

Corporate

- Completed profitability-driven organizational optimization
- Delivered strong YoY growth during Covid-light quarters (Q1 revenues +27%, Q3 revenues +22%)
- Completed listing on the London Stock Exchange, offering an alternative listing venue in addition to Nasdaq[1]

Therapy selection

- +11% YoY volume growth despite Covid challenges, driven by in-hospital channel (+23% volume growth in 2022, Q1 +83%, Q3 +24%)
- 9-gene panel approved by NMPA, our second NMPA-approved product

MRD

- Publication of initial read-out on lung and colorectal cancers at AACR 2022, and on colorectal and pancreatic cancers at ASCO GI 2023
- Commercially launched in March

Biopharma

- Continued back-log build-up, new contract value +43% to RMB263m in 2022
- +212% revenue growth on strong back-log execution

Early detection

- FDA breakthrough device designation granted
- Thunder study for 6-cancer test development submission and publication on Annals of Oncology
- Promise study (2,035 subjects, 9-cancer test development) completed and read-out, Predict and Prescient studies (c.17,000[2] subjects, 22-cancer test development) ongoing, Prevent (12,500 subjects, validation) study launched

Notes:
[1] Shares are fungible between the London Stock Exchange and Nasdaq, offering continued trading and listing.
ADR delisting risk removed for now.
"Accordingly, until such time as the PCAOB issues any new determination, there are no issuers at risk of having their securities subject to a trading prohibition under the HFCAA." (http://www.sec.gov/hfcaa)
[2] Total number of subjects for Predict and Prescient studies.

2023 outlook

Corporate

Goal #1, profitability

- Achieve adjusted profitability breakeven excluding R&D during a 2023 quarter (defined as Non-GAAP gross profit – SG&A expenses)

Goal #2, profitable growth

- 20% revenue growth in 2023

Goal #3, further our lead in multi-cancer early detection as the #1 in China and a top player globally

- R&D spend focused on early detection clinical studies

Therapy selection

- Improve sales productivity
- Drive growth via in-hospital channel

MRD

- Roll-out to additional hospitals
- Execute interventional studies to build further clinical evidence

Biopharma

- Continue profitable growth

Early detection

- Validate 6-cancer test (Prevent study), interim read-out expected in 2H23
- Develop 22-cancer test (Predict and Prescient studies)
- Establish regulatory pathways with the FDA and NMPA
- Commercialization pilot at select public hospitals

Cash position

3 years runway based on existing cash balance

Sufficient cash to fund early detection product development and all existing clinical studies

RMBm	2021	2022	2023E[1]	2024E[1]
Operating cash outflow[2]	478	457		
Capex[3]	213	75		
Sum	691	532	c.400	c.200
Cash balance[4]		925		

Estimate assumptions

- Cash spend to focus on early detection clinical studies, the bulk of which will run through 2023 and drop off in 2024
- Commercial business to breakeven during 2023 (no further upside assumed in 2024 estimate)

Notes:
[1] Based on management's current estimate and subject to change
[2] Net cash used in operating activities
[3] Purchase and prepayment of property and equipment and intangible assets, issuance of convertible loan, out of investing cashflows
[4] Consists of Cash and cash equivalents of approximately RMB905m and restricted cash of approximately RMB20m as of the end of 2022

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Early detection

Burning Rock's early detection technology

Competitive technology

Methylation + machine learning to overcome challenges of low ctDNA abundance

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

Multi-cancer validation data

ELSEVIER

Annals of Oncology

Available online 26 February 2023

In Press, Journal Pre-proof What's this?

Original Article

Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies

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

ESMO 2022

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

Regulatory breakthrough

FDA breakthrough device designation granted

Product development roadmap

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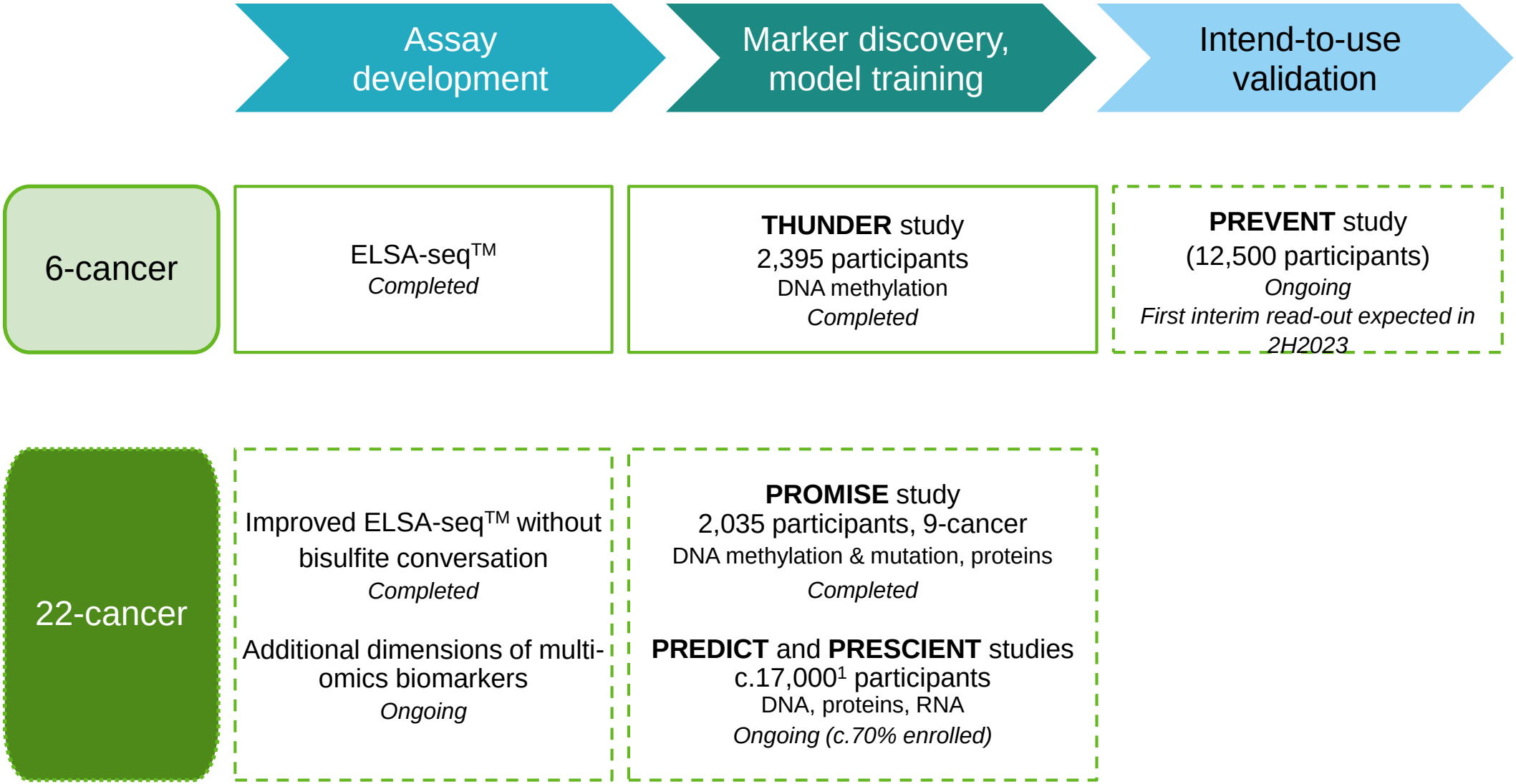
22-cancer
2019 – Ongoing

- Covering 88% of China’s cancer incidence
- PROMISE study (N=2,035) completed, improved performance vs. 6-cancer test
- PREDICT and PRESCIENT studies ongoing

Clinical programs

One of the largest datasets globally, prospectively enrolled, across large number of cancer types / stages



Note：

[1] Total number of subjects for Predict and Prescient studies.

Running the largest clinical programs in China supported by top physicians

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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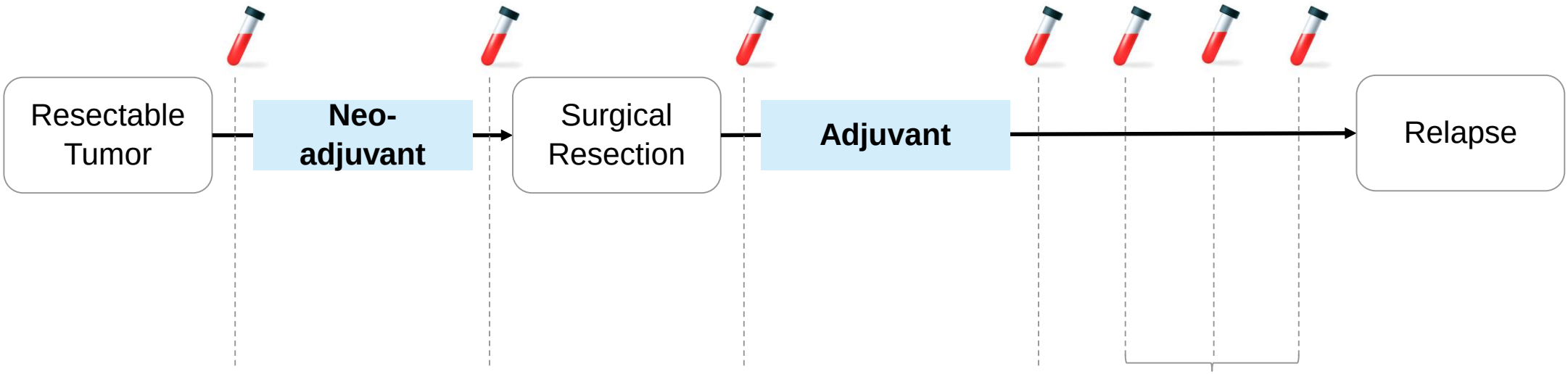
Minimal Residual Disease (MRD)

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

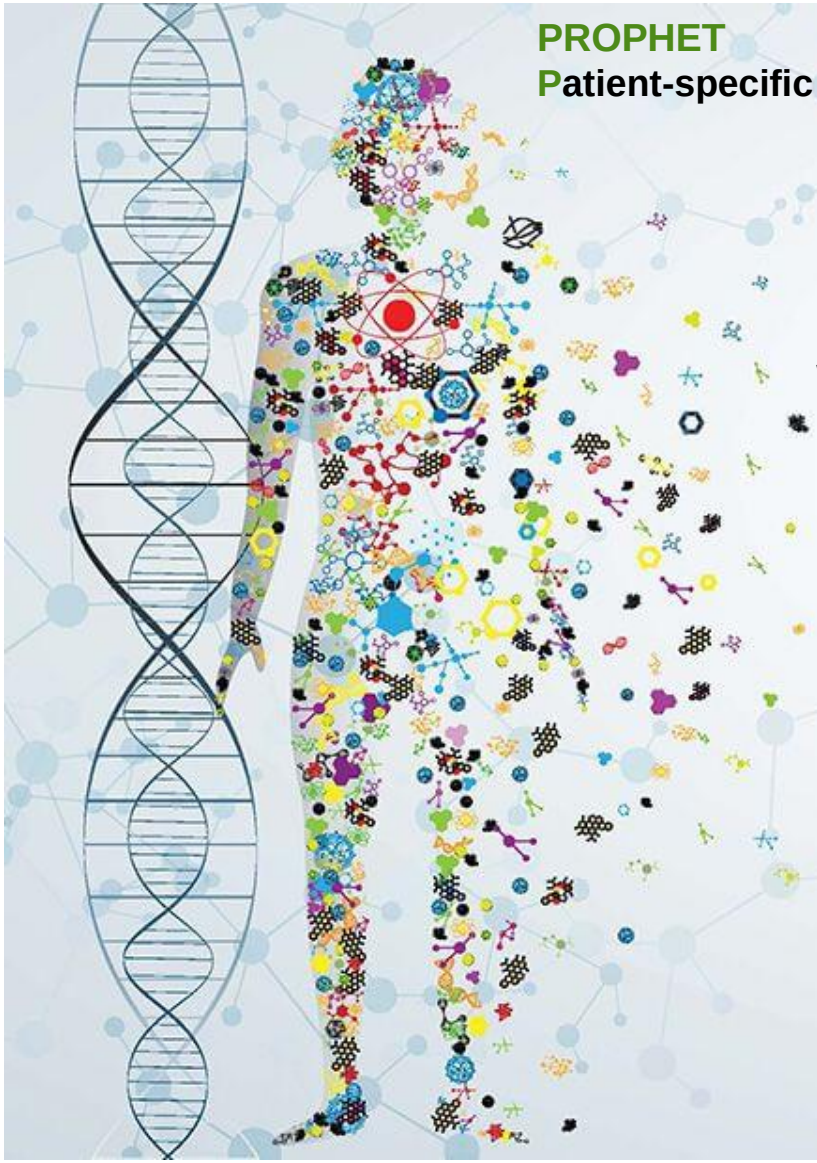
Identify "cured" patients

Predict relapse

Nice-to-have prognosis

Actionable diagnosis that drives treatment choice

brPROPHET™ – Burning Rock's MRD solution



PROPHET
Patient-specific pROgnostic and Potential tHErapeutic marker Tracking

Whole Exome Sequencing Tumor Profiling with add-on region for SV detection

SNV/SV/CNV/MSI/HLA/Therapy Selection

Personalized Panel

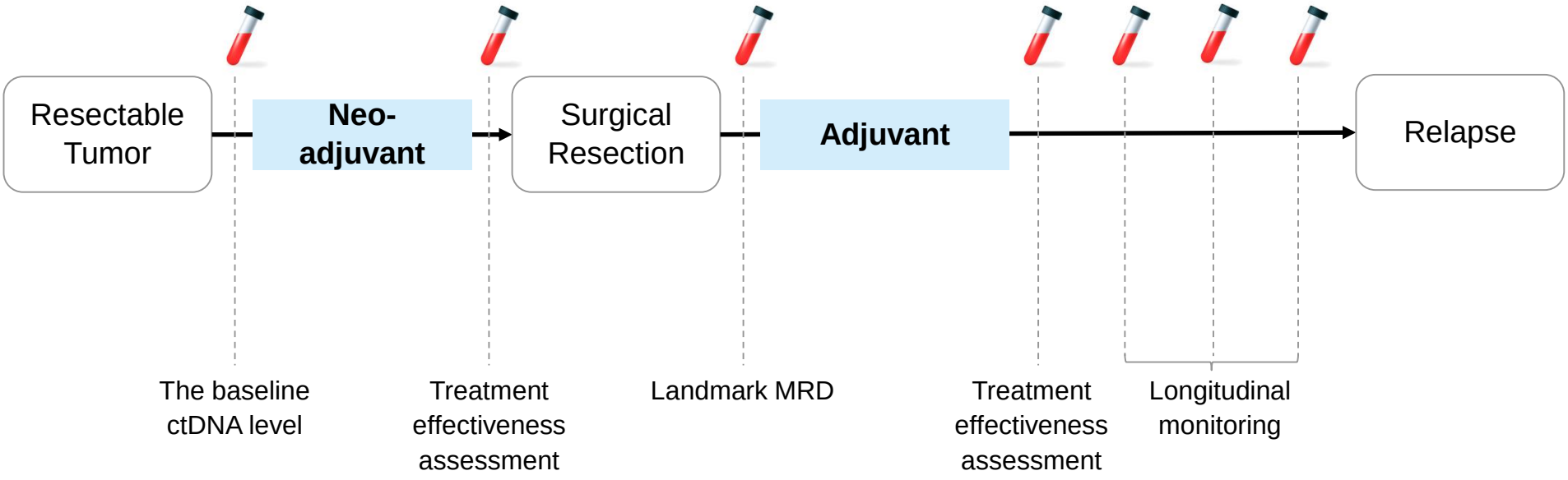
Intelligent selection of 50 tracking sites

brPROPHET MRD Assay

100,000x Raw Depth/UMI error correction/Tumor Fraction Estimation

Burning Rock's MRD publications

Covers adjuvant and relapse settings in lung, colorectal, pancreatic cancers



Non-small-cell lung cancer	Baseline, landmark and longitudinal monitoring timepoints completed AACR 2022 Abstract 5916, AACR 2023 Abstract 1039	
Colorectal cancer	Baseline and landmark timepoints AACR 2022 Abstract 5917, ASCO GI 2023 Abstract 213	Longitudinal monitoring ongoing
Pancreatic cancer	Baseline, landmark and longitudinal monitoring timepoints completed ASCO GI 2023 Abstract 744	

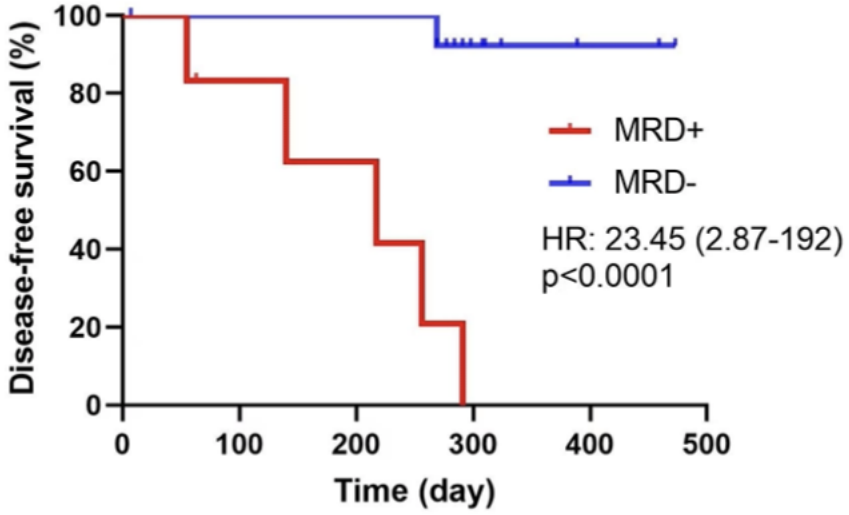
Data publication at ASCO GI (Jan 2023)

First dataset on pancreatic cancer, demonstrating strong MRD utility

Table 1: ctDNA detection at serial timepoints

	Baseline (Day 0)	Timepoint A (Day 7)	Timepoint B (Day 30)	Timepoint C (During AT)	Follow-ups
Positive	20	2	1	2	4
Negative	0	16	9	12	5
Positive Rate	**100%**	**11.1%**	**10%**	**14.3%**	**44.4%**

Figure 1: Longitudinal MRD detection is associated with shorter disease-free survival



Patients: A total of 20 patients (stage I/II 10 [50.0%] / 9 [45.0%]) were analyzed. 13 (65.0%) patients were treated with adjuvant therapy (AT) after surgery.
Samples: Tumor tissue samples were collected at the surgery. Plasma samples collected at baseline (n=20), landmark 7-day (n=18) and 1-month (n=10), and longitudinal points (n=23) were analyzed. Patients were followed for a median of 302 days.

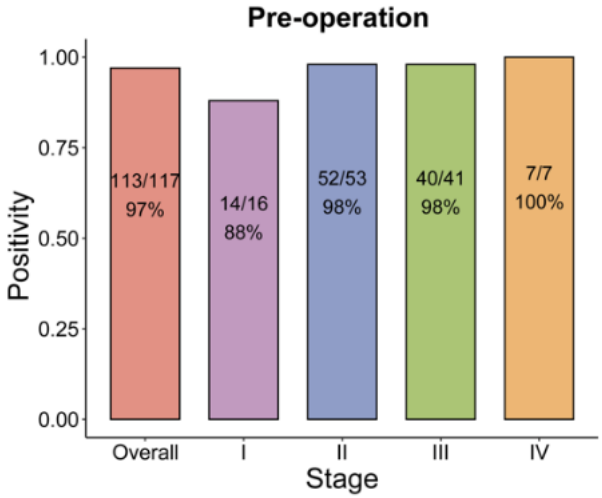
Source: Wang et al., Patient-specific tumor-informed circulating tumor DNA (ctDNA) assay predicts cancer recurrence in patients with resected pancreatic cancer, ASCO GI 2023

Data publication at ASCO GI (Jan 2023)

Second dataset on colorectal cancer, demonstrating power of personalized MRD test

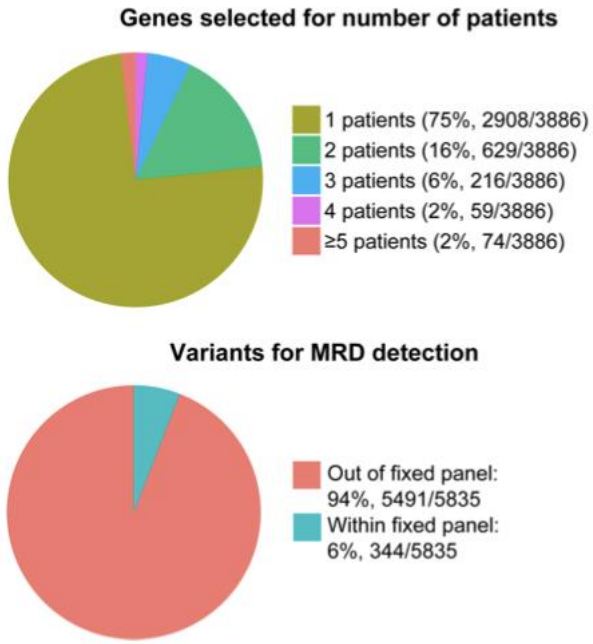
brPROPHET™ has high detection sensitivity

Preoperative ctDNA was detected in 97% (113/117) of the patients with 88% (14/16), 98% (52/53), 98% (40/41), and 100% (7/7) in stage I, II, III and IV, respectively



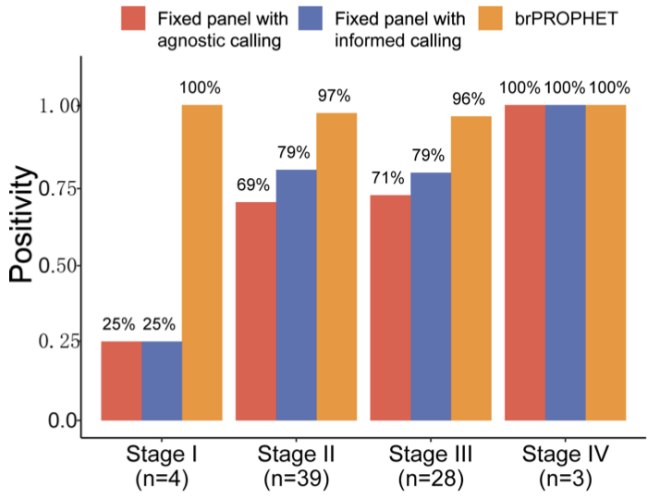
Most mutation variants fall outside of fixed panels

Only 6% of designed variants were included in the fixed panel. 75% of genes selected for panel design were private to a specific patient.



brPROPHET™ significantly out-performs fixed panels

Preoperative ctDNA was detected in 97% (113/117) of the patients with 88% (14/16), 98% (52/53), 98% (40/41), and 100% (7/7) in stage I, II, III and IV, respectively



Patients: A total of 117 patients (stage II/III 53 [45.3%] / 41 [35.0%]) who received surgery were analyzed. A subset of 74 patients were analyzed for comparisons of different methods.
Samples: Tumor tissue samples were collected at the surgery. Plasma samples collected at baseline, landmark 7-day and 1-month, and longitudinal points were analyzed.

Source: Cao et al., Patient-specific tumor-informed circulating tumor DNA analysis for molecular residual disease detection in surgical patients with stages I-IV colorectal cancer, ASCO GI 2023

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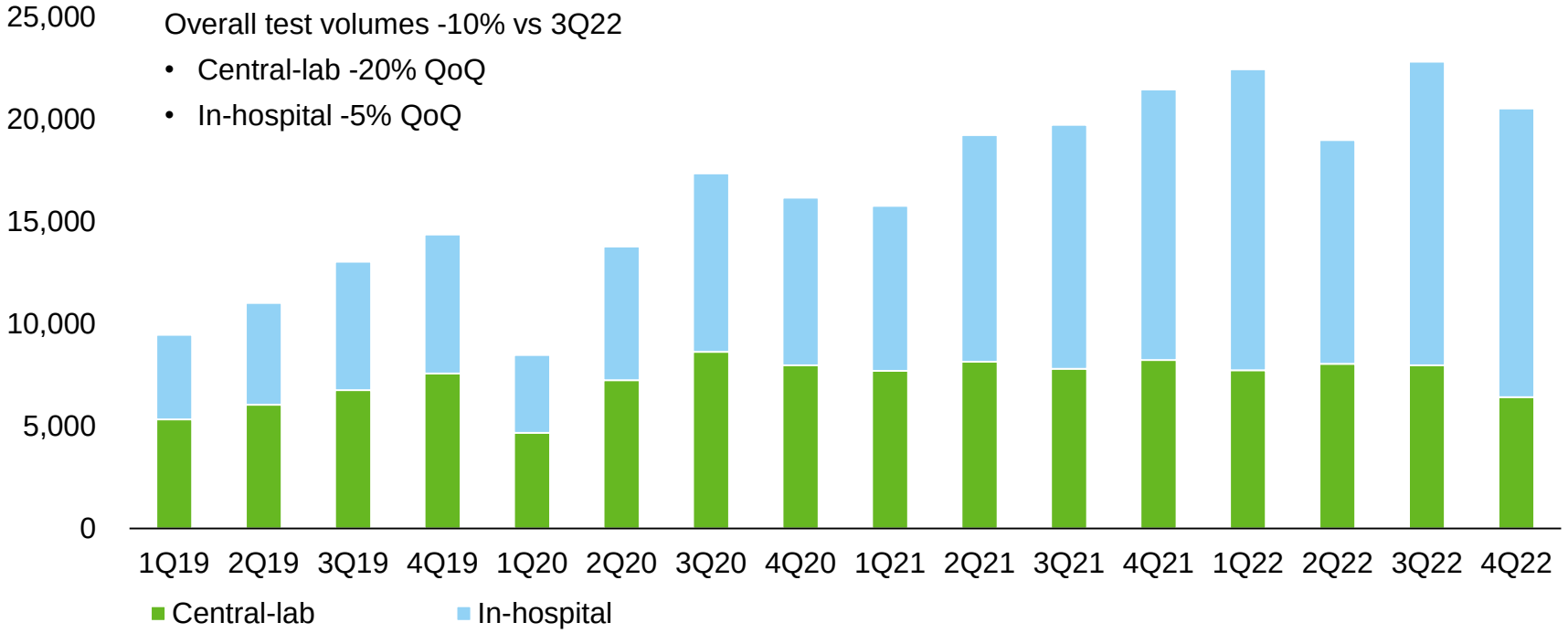
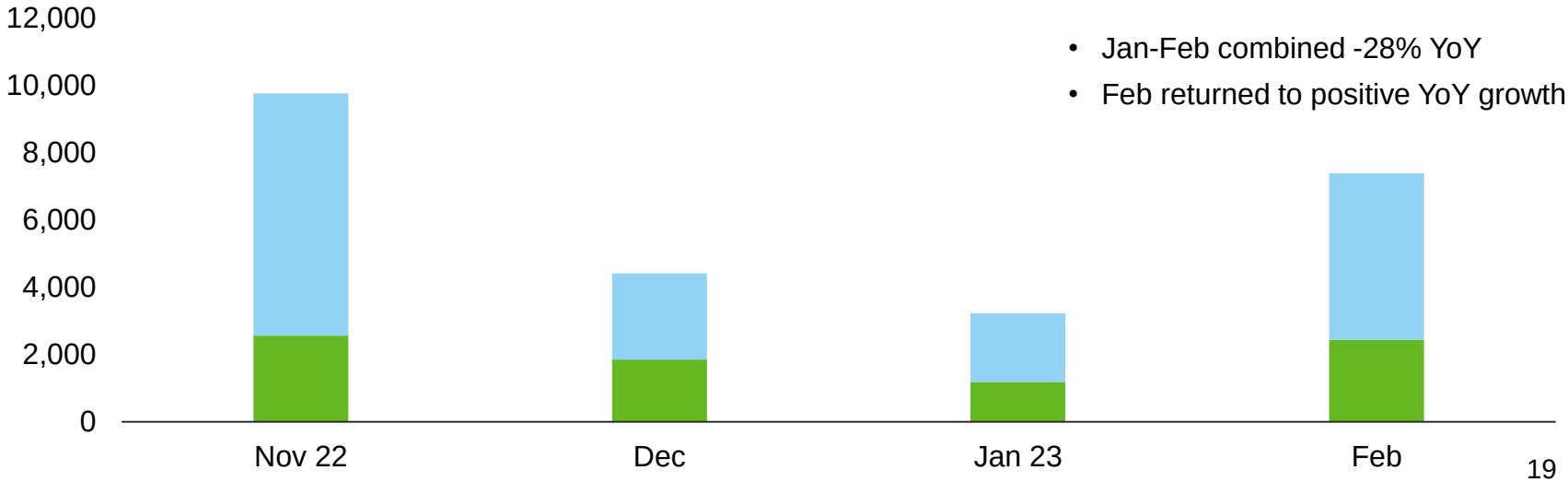
Financials

Quarterly volumes

Volumes by channel[1]





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

Financials

RMB0.93bn / USD134m cash and investments on balance as of December 31, 2022

RMB millions	2021	2022	*19 YoY*	*20 YoY*	*21 YoY*	*22 YoY*	1Q22	2Q22	3Q22	4Q22	*4Q22 YoY*	*4Q22 QoQ*	2023 Guide
Revenue	**507.9**	**563.1**	**83%**	**13%**	**18%**	**11%**	**135.5**	**130.8**	**154.6**	**142.2**	**-3%**	**-8%**	**+20%**
Central lab	319.4	314.8	71%	8%	7%	-1%	74.2	78.6	90.0	72.0	-16%	-20%	
In-hospital[1]	165.1	175.3	164%	34%	40%	6%	49.0	34.2	49.6	42.5	-18%	-14%	
Pharma	23.4	73.0	25%	-17%	59%	212%	12.3	18.0	15.0	27.7	195%	85%	
Non-GAAP Gross profit[2]	**368.2**	**411.0**		**14%**	**16%**	**12%**	**92.7**	**90.9**	**117.0**	**110.4**	**3%**	**-6%**	
Total opex	**1,161.2**	**1,360.5**	**49%**	**64%**	**60%**	**17%**	**350.4**	**348.1**	**343.3**	**318.7**	**-11%**	**-7%**	
R&D[3]	324.1	344.4					100.9	77.7	88.7	77.1	-32%	-13%	
S&M[3]	283.4	350.6					84.6	100.3	85.4	80.3	-19%	-6%	
G&A[3]	228.8	250.5					61.2	74.8	68.4	46.1	-37%	-33%	
SBC	280.8	325.1					79.8	76.7	77.4	91.2			
D&A	44.1	89.9					23.9	18.6	23.4	24.0			
Non-GAAP GP - SG&A	**(144.0)**	**(190.1)**					**(53.1)**	**(84.2)**	**(36.8)**	**(16.0)**			
Operating profit	**(797.1)**	**(980.3)**					**(262.8)**	**(265.5)**	**(234.6)**	**(217.4)**			
Net operating cash flows	**(477.9)**	**(456.9)**					**(144.4)**	**(109.3)**	**(135.5)**	**(67.7)**			
Non-GAAP GP margin[2]	72.5%	73.0%					68.4%	69.5%	75.7%	77.6%			
Opex[3] / revenue	165%	168%					182%	193%	157%	143%			
S&M[3] / revenue	56%	62%					62%	77%	55%	56%			

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

Product Development Roadmap

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)

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2018 – 2020
CE Mark, FDA BDD

- Lung, CRC, HCC, Ovarian, Pancreatic, Esophageal
- THUNDER study (N=2,385) completed, 98.9% specificity and 69.1% sensitivity, top-2 predicted origin accuracy of 91.7% (independent validation cohort)
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2019 – Ongoing

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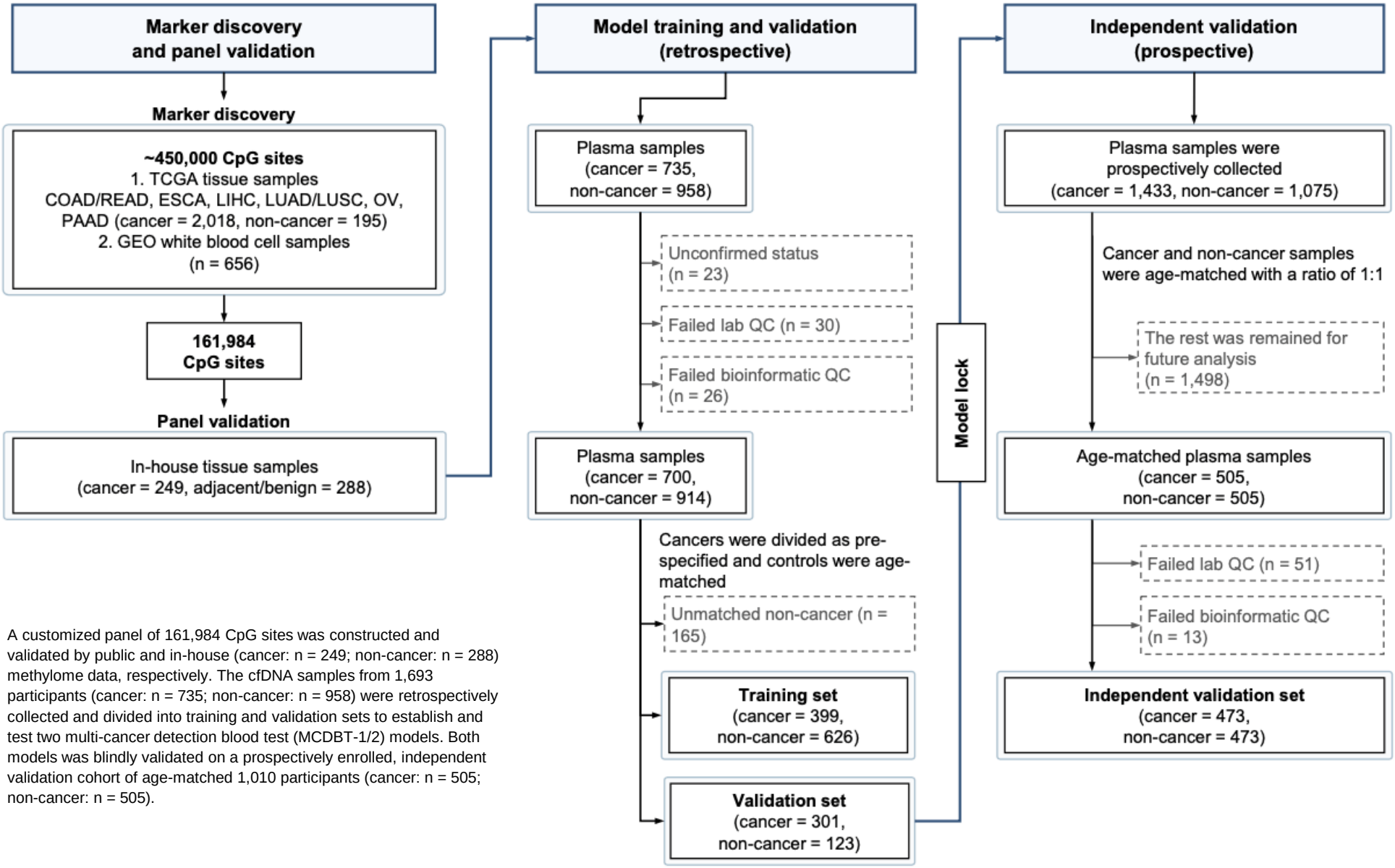
6-cancer test marker discovery and model training

The THUNDER study, 2395 participants



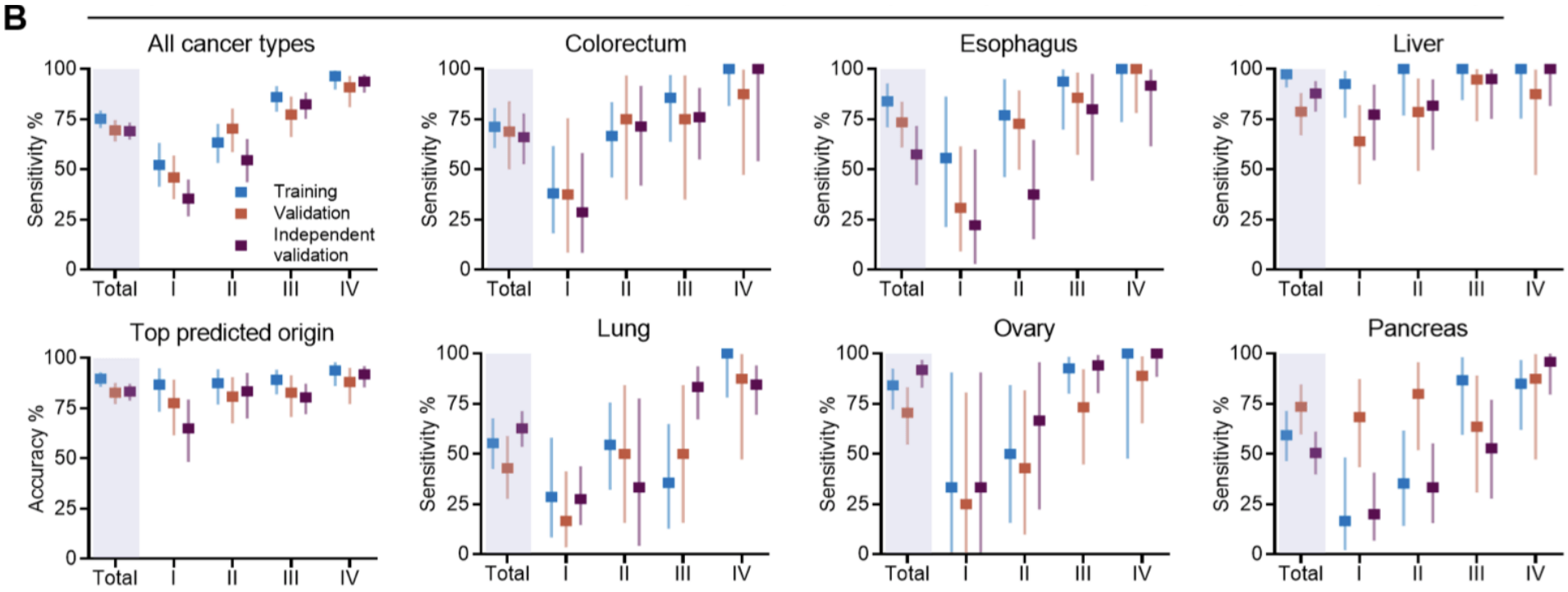
A customized panel of 161,984 CpG sites was constructed and validated by public and in-house (cancer: n = 249; non-cancer: n = 288) methylome data, respectively. The cfDNA samples from 1,693 participants (cancer: n = 735; non-cancer: n = 958) were retrospectively collected and divided into training and 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).

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

6-cancer test, detection-of-cancer performance in case-control cohorts

The THUNDER study

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.



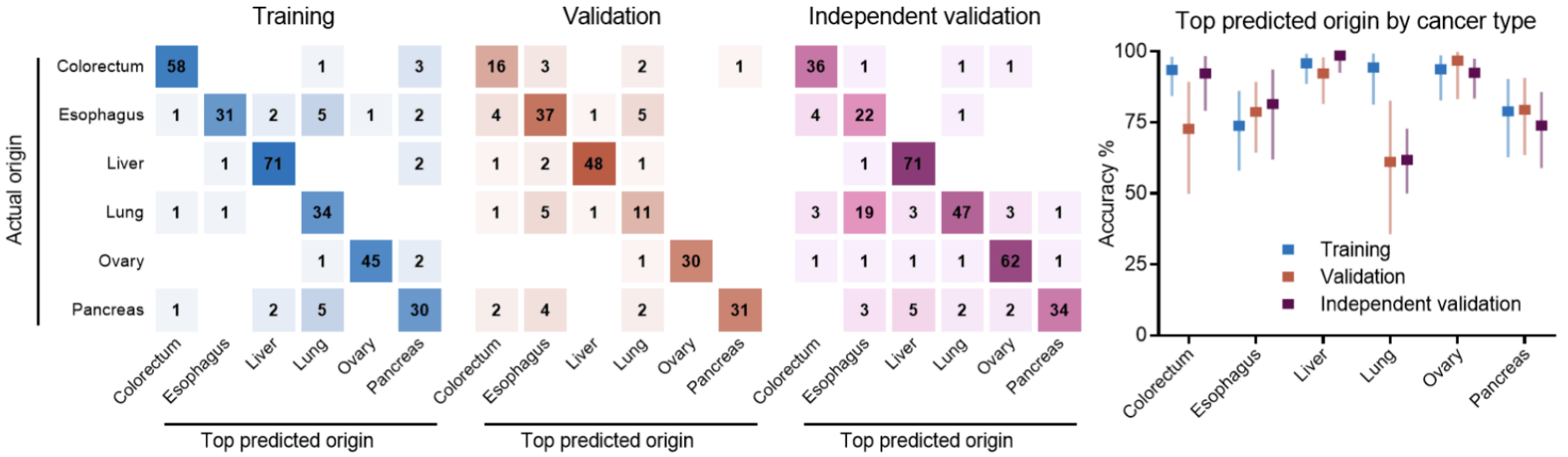
Data set	Specificity (%)	Sensitivity (%)	Accuracy of top predicted origin (%)	Accuracy of top two predicted origins (%)
Training set	99.7 (98.9-100.0)	75.2 (70.6-79.4)	89.7 (85.7-92.9)	94.7 (91.5-96.9)
Validation set	100.0 (97.0-100.0)	69.4 (63.9-74.6)	82.8 (77.0-87.6)	89.4 (84.5-93.3)
Independent validation set	**98.9 (97.6-99.7)**	**69.1 (64.8-73.3)**	**83.2 (78.7-87.1)**	**91.7 (88.2-94.5)**

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

6-cancer test, top-predicted-origin performance in case-control cohorts

The THUNDER study

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.



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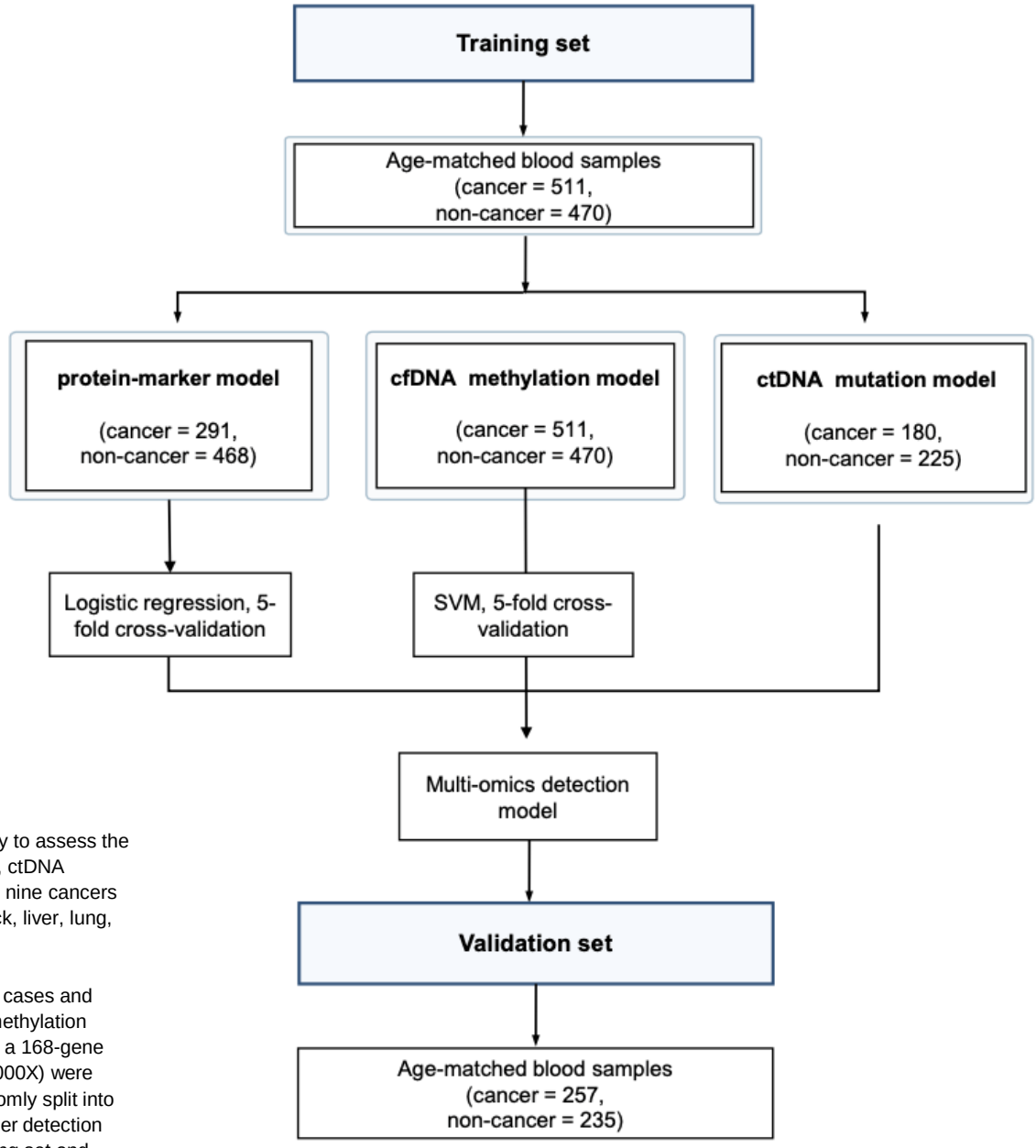
9-cancer test, multi-omics model

The PROMISE study



PROMISE is a prospective multicenter case-control study to assess the performance of multi-omics including cfDNA methylation, ctDNA mutation and protein biomarkers in the early detection of nine cancers in the biliary tract, colorectum, esophagus, head and neck, liver, lung, ovary, pancreas and stomach.

Blood samples were prospectively collected from cancer cases and non-cancer controls. A targeted cell-free DNA (cfDNA) methylation panel of ~490,000 CpG sites (1,000X) by ELSA-seq and a 168-gene mutation panel (35,000X, matched white blood cells:10,000X) were sequenced. Age-matched cases and controls were randomly split into training (n = 981) and test sets (n = 492). The multi-cancer detection blood test (MCDBT) models were developed in the training set and then validated in the test set.

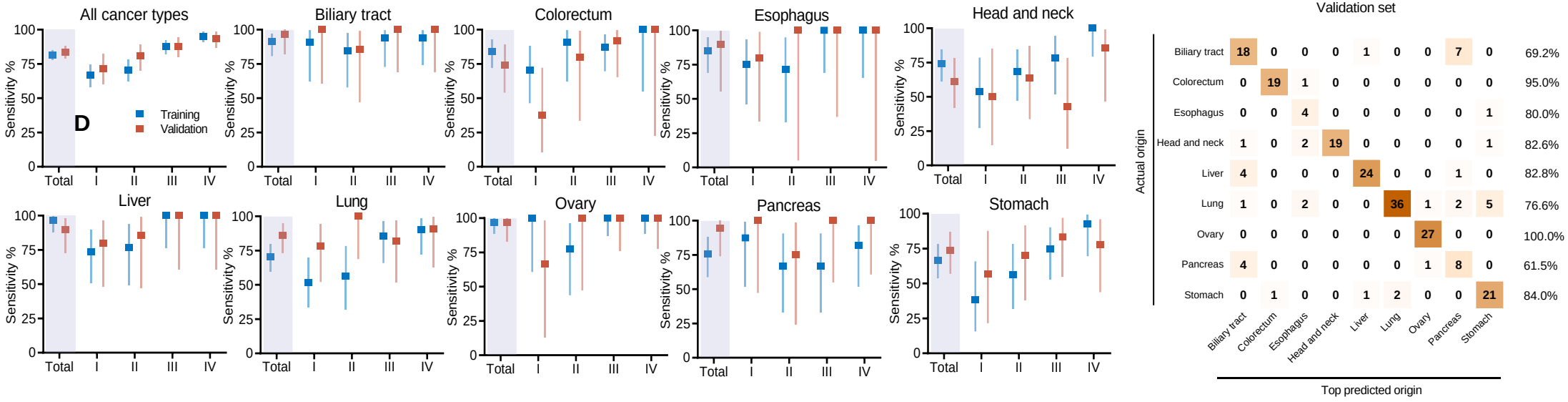
Source: Gao et al., a multi-cancer early detection model based on liquid biopsy of multi-omics biomarkers, ESMO 2022

9-cancer test multi-omics model performance

The PROMISE study

	Cancer (n)	Non-cancer (n)	Specificity (%)	Sensitivity (%)	Accuracy of top predicted origin (%)
Training	470	511	97.9% (96.1%-99.0%)	81.7% (78.1%-84.9%)	86.6% (83.0%-90.0%)
Validation	257	235	98.3% (96.6%-99.4%)	83.7% (79.0%-88.0%)	81.9% (76.0%-87.0%)

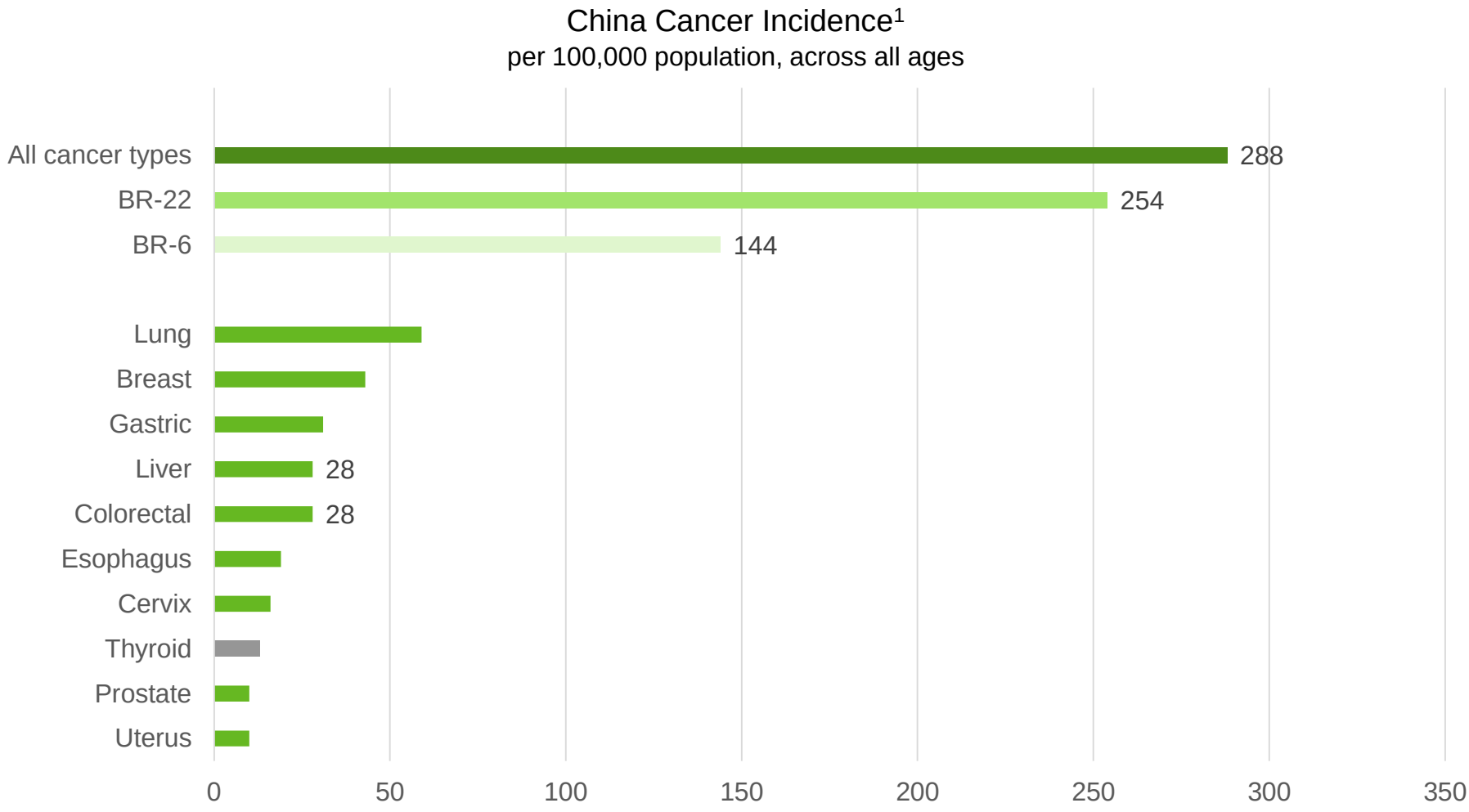
	Multi-omics	Methylation	Mutation	Protein
Specificity (95% CI)	98.3% (96.6%–99.4%)	99.1% (97.3%–99.8%)	99.6% (97.9%–100.0%)	99.6% (98.7%–100.0%)
Sensitivity (95% CI)	83.7% (78.6%–88.0%)	79.0% (73.5%–83.8%)	49.4% (41.9%–57.0%)	47.8% (40.8%–54.9%)



- PROMISE demonstrated 83.7% sensitivity and 98.3% specificity for 9 cancers
- Methylation contributed >90% of the total sensitivity, while protein and mutation collectively provided <10% additional positive detections

Source: Gao et al., a multi-cancer early detection model based on liquid biopsy of multi-omics biomarkers, ESMO 2022

Burning Rock's 22-cancer test covers 88% of China's cancer incidence



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

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 that has launched studies with over 10,000+ subjects
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 hospitals' health check-up departments, leveraging synergy from in-hospital therapy selection business

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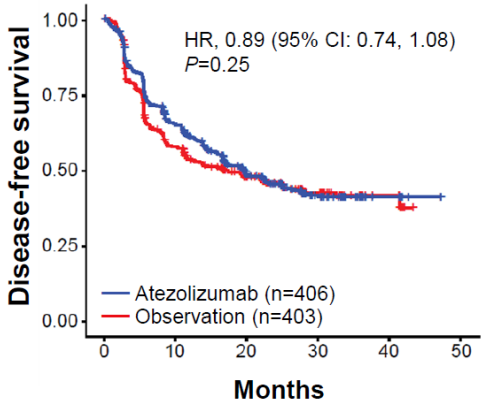
Appendix 2

MRD

How do MRD studies advance utility

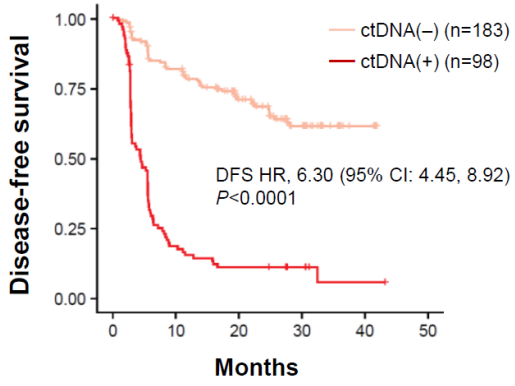
Example 1: IMvigor010, enrich the high-risk group and "tune-up" adjuvant treatment

ITT

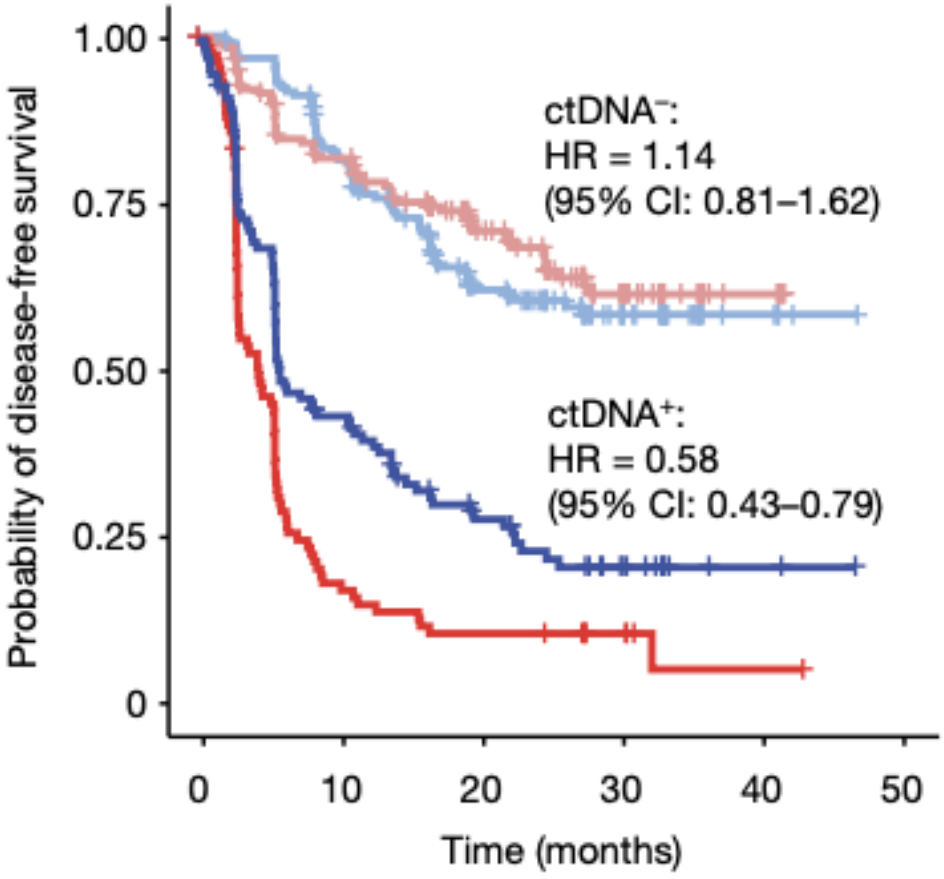


Atezo, MIUC Adjuvant Therapy
"All comers" demonstrated NO efficacy
TMB/PD-L1 showed NO prediction

Observation arm



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

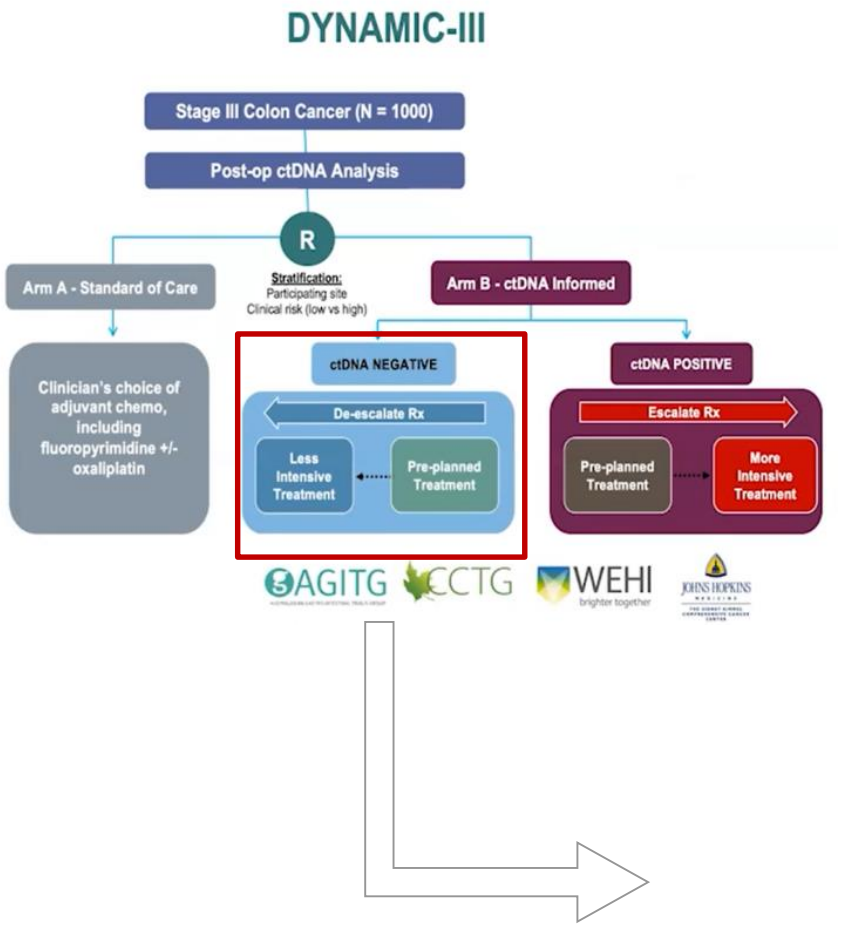


Indeed, only baseline MRD+ pts showed benefit

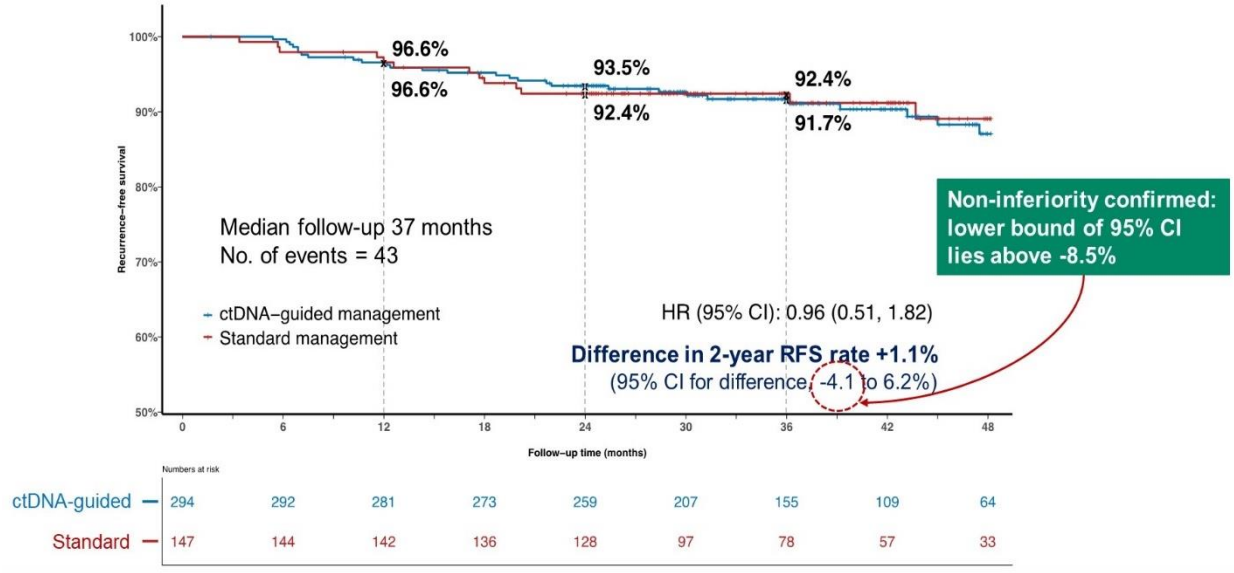
Nature. 2021 Jun 16. doi: 10.1038/s41586-021-03642-9.

How do MRD studies advance utility

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

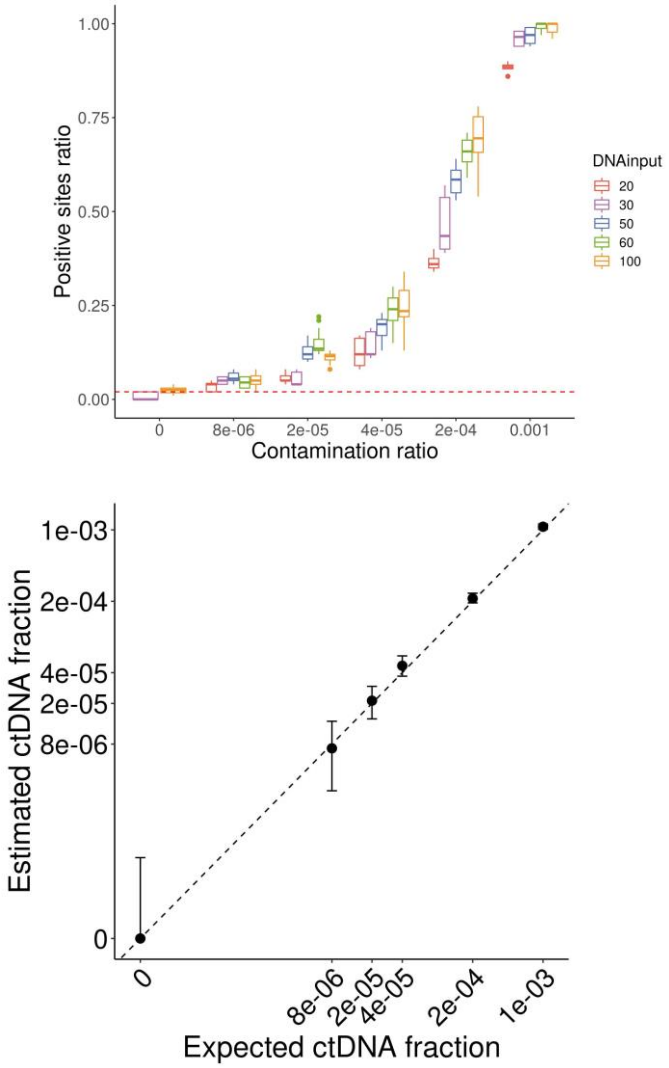


ctDNA-guided vs standard

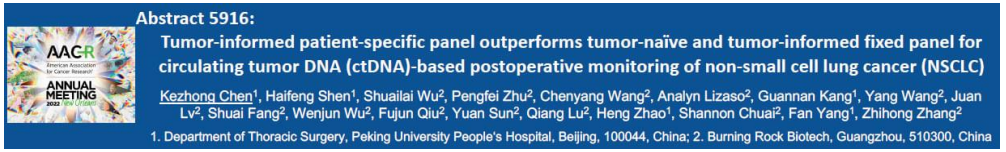


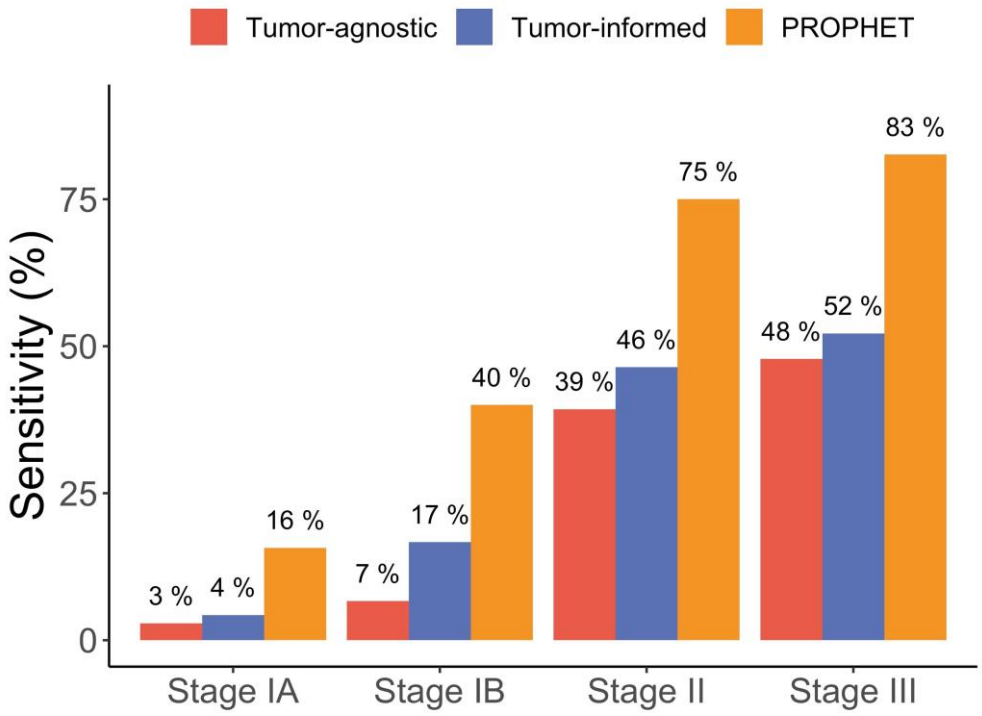
The ctDNA-guided MRD- group had fewer patients with adjuvant chemotherapy than the standard group (15% vs. 29%) with non-inferiority of 3-year RFS (92.4% vs 91.7%)

brPROPHET™ – Advantages of Personalized Panel



brPROPHET achieves great detection accuracy and quantitative precision at ctDNA fraction of $4x10^{-5}$

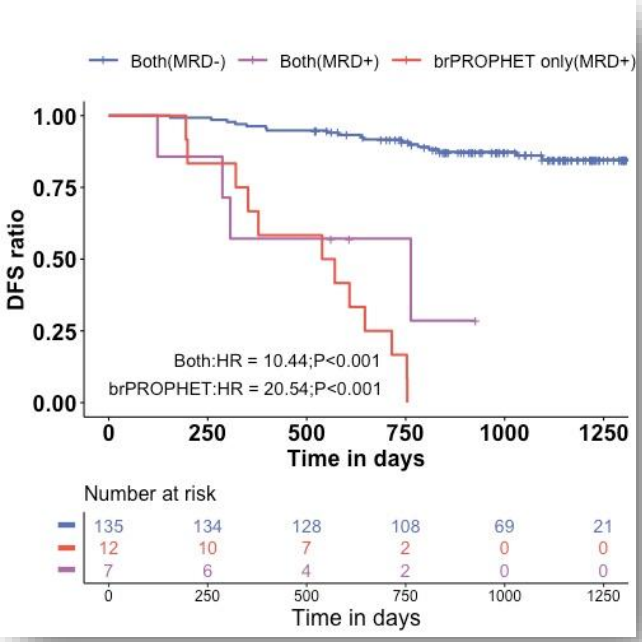


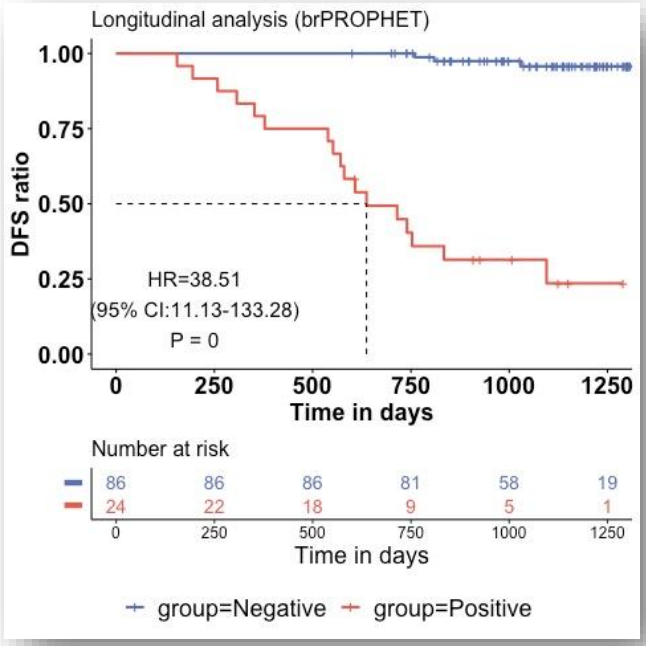


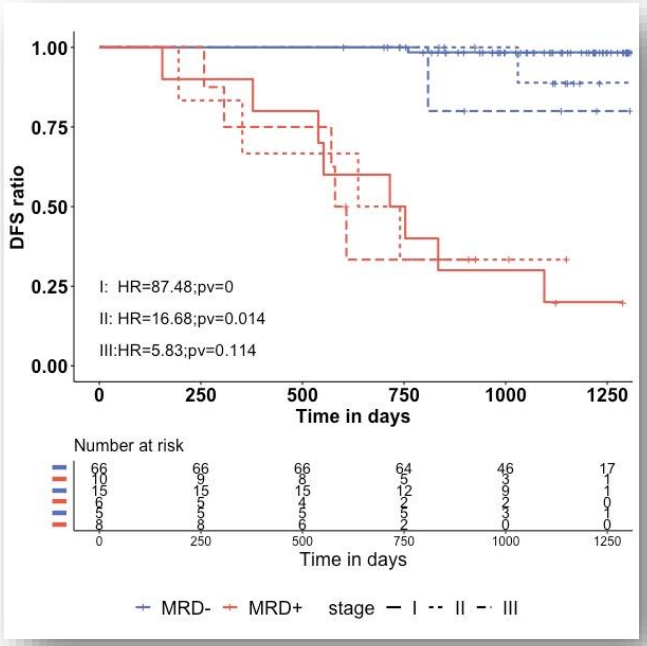
brPROPHET shows greater sensitivity than fixed-panel methods among NSCLC pre-operative ctDNA samples

MRD clinical validation data readout

NSCLC – MEDAL study





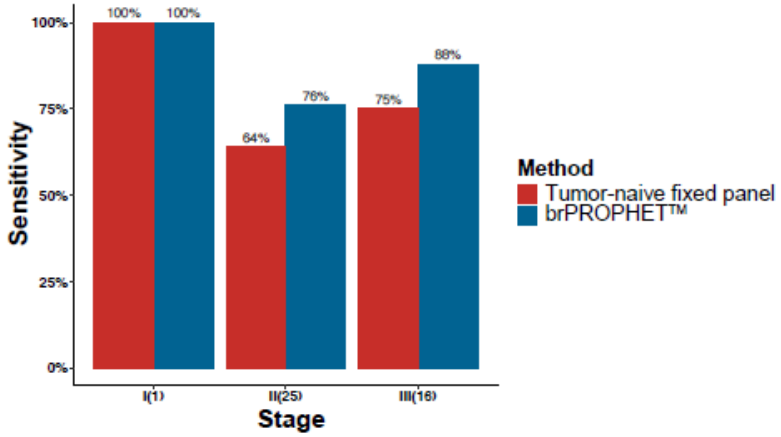


- *brPROPHET identified 2.7 times more true high-risk patients than the fixed panel approach at the landmark time point*
- *Longitudinally MRD negative patients has near-perfect prognosis with median of 3-year follow-up*
- *The prognosis differentiation holds true for patients with different clinical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

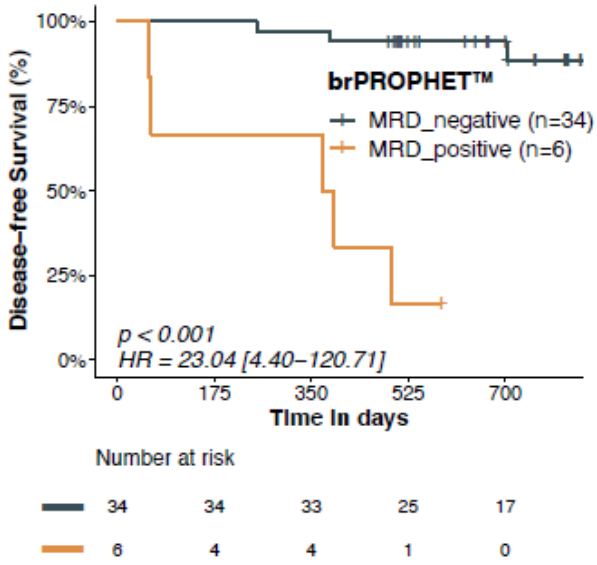
MRD clinical validation data readout
CRC

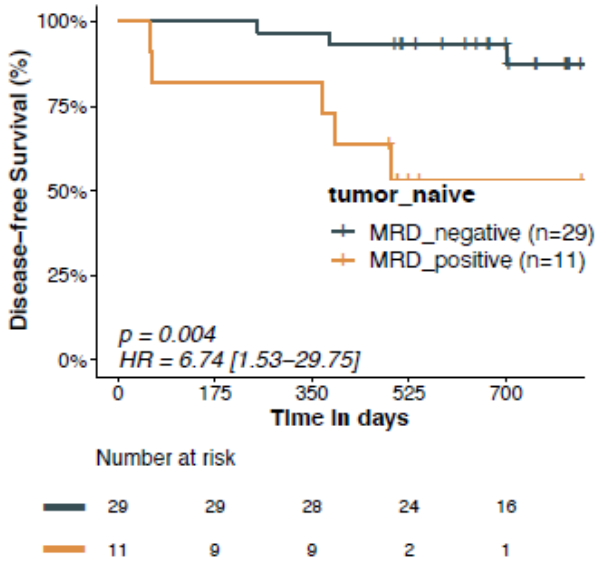
Session OPO.PR02.01 - Clinical Prevention, Early Detection, and Interception

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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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

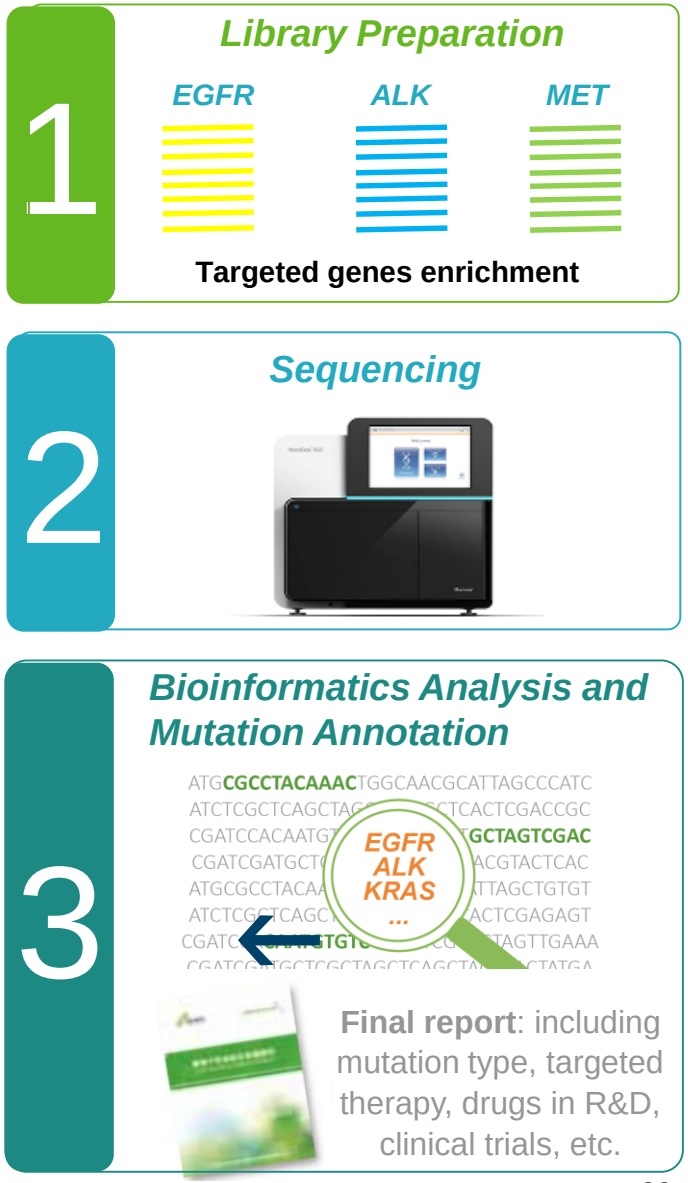
- Only 30ng DNA input required, applicable to small tissue samples
- First NMPA approved NGS kit with CNV[2] mutation type, with MET exon14 skipping

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).

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

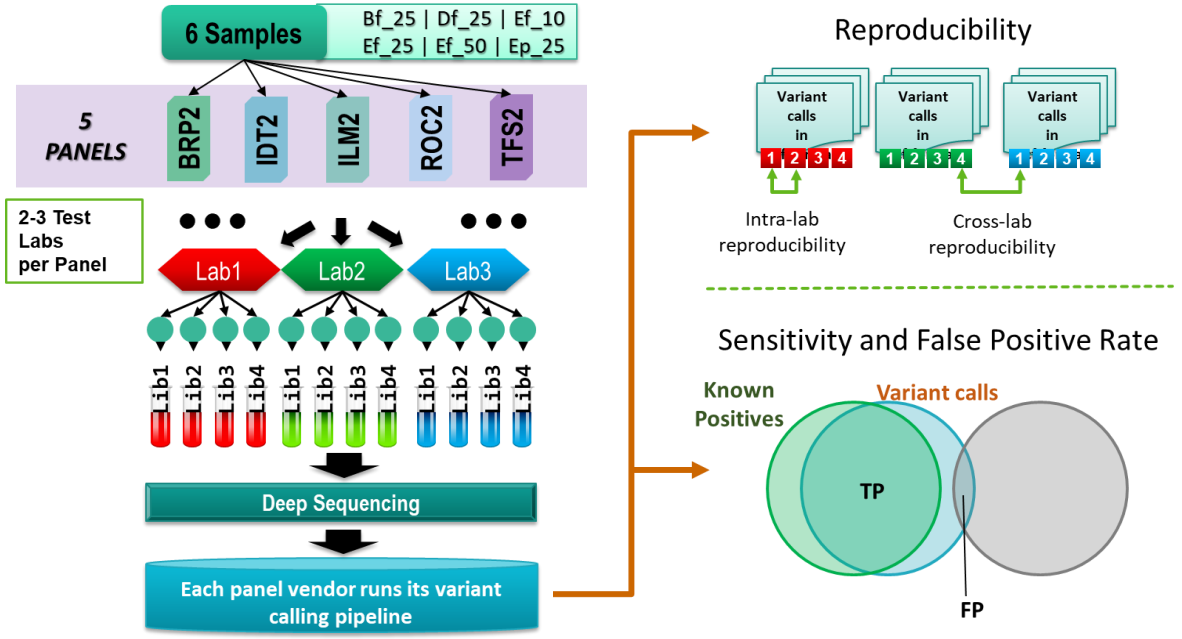
TFS2

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

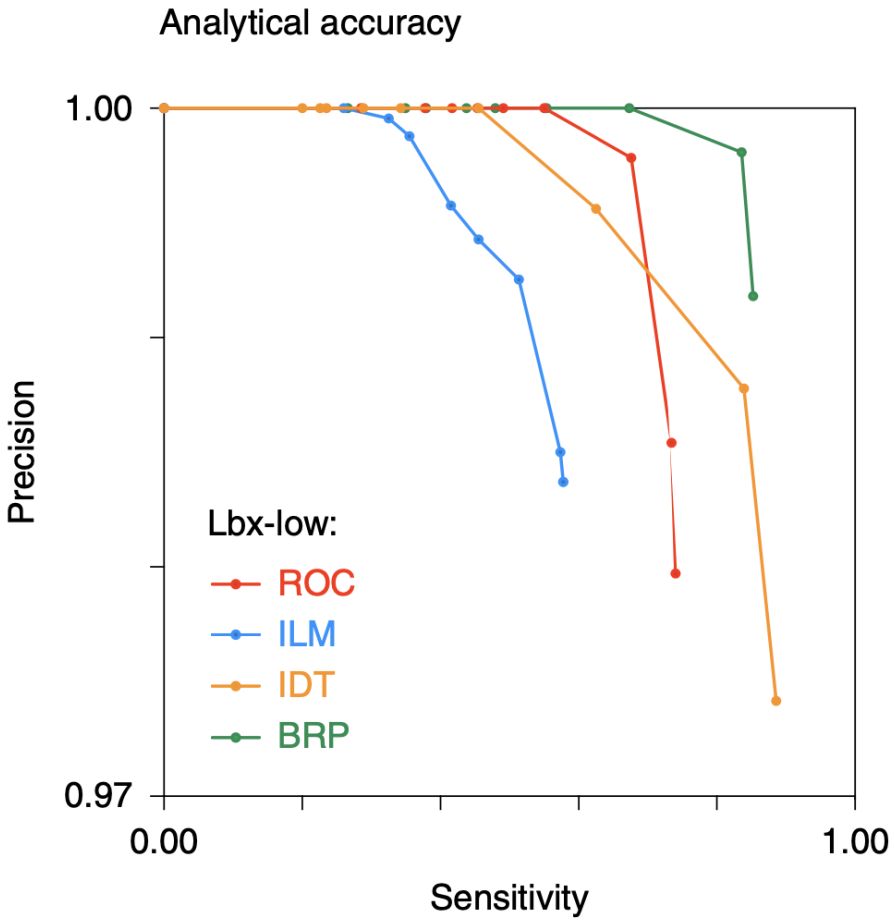
Participating assays and study design

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



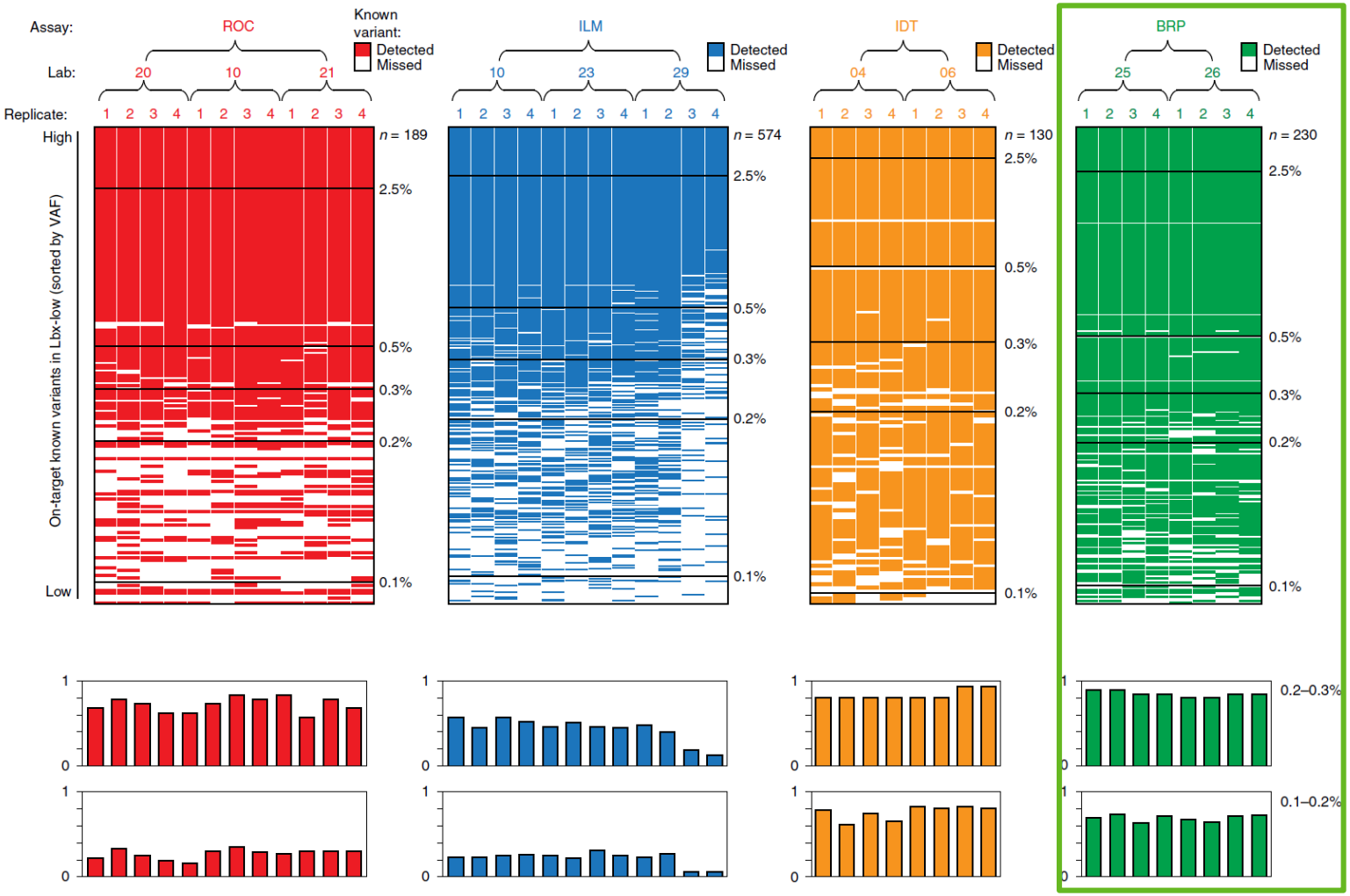
Assay	Known negatives (kb)	FPs per replicate (mean [range])	FP-rate (FP / kb) at specified VAF threshold > 0%	> 0.1%	> 0.5%
ROC	47.1	2.91 [1-6]	0.061	0.044	0.000
ILM	133	5.25 [2-10]	0.039	0.039	0.008
IDT	39.3	2.75 [0-6]	0.070	0.057	0.000
BRP	53.4	1.65 [0-5]	0.030	0.007	0.000

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