燃石医学
Burning Rock Dx

# Burning Rock Biotech Limited

## 1Q2023 results

Nasdaq and LSE: BNR

30 May 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

# 2023 goals and outlook

**Corporate**

Goal #1, profitability

- Achieve adjusted profitability breakeven excluding R&D during a 2023 quarter (defined as Non-GAAP gross profit *minus* 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 of personalized brPROPHET™ test to additional hospitals
- Execute interventional studies to build further clinical evidence

**Biopharma**

- Continue profitable growth

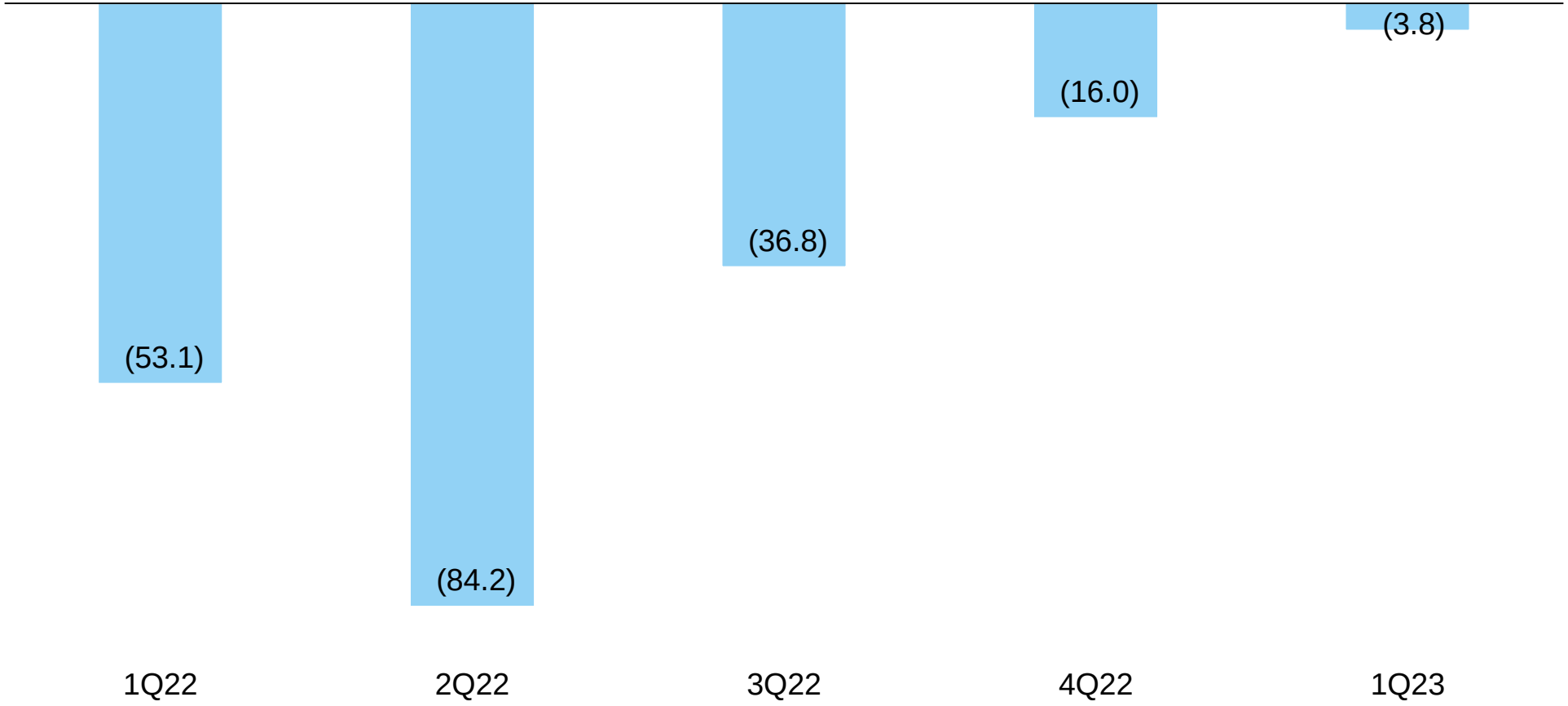
**Early detection**

- 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 selected public hospitals

# 1Q2023 executing on track towards breakeven

## Defined as Non-GAAP gross profit *minus* SG&A

Non-GAAP gross profit *minus* SG&A* (RMB millions)




Notes:

* Non-GAAP gross profit, which is defined as gross profit excluding depreciation and amortization (D&A). Non-GAAP SG&A excludes share based compensation (SBC) and D&A.

# 1Q2023 progress

**Corporate**

- Execution towards profitability well underway
  Non-GAAP gross profit *minus* SG&A expenses -RMB3.8m in 1Q23
- On track to achieve breakeven on the above metric at some quarter in 2023

**Therapy selection**

- Rebound in 1Q led by in-hospital strength, with double-digit volume growth in March, turning Jan and Feb combined negative growth into positive growth for 1Q
- Sales efficiency continues to improve. Non-GAAP selling expenses as % of revenues dropped to 42% in 1Q23, vs. 62% in 1Q22

**MRD**

- Continued commercial traction with physicians and hospitals
- Additional data releases on lung and other cancer types at AACR and the upcoming ASCO

**Biopharma**

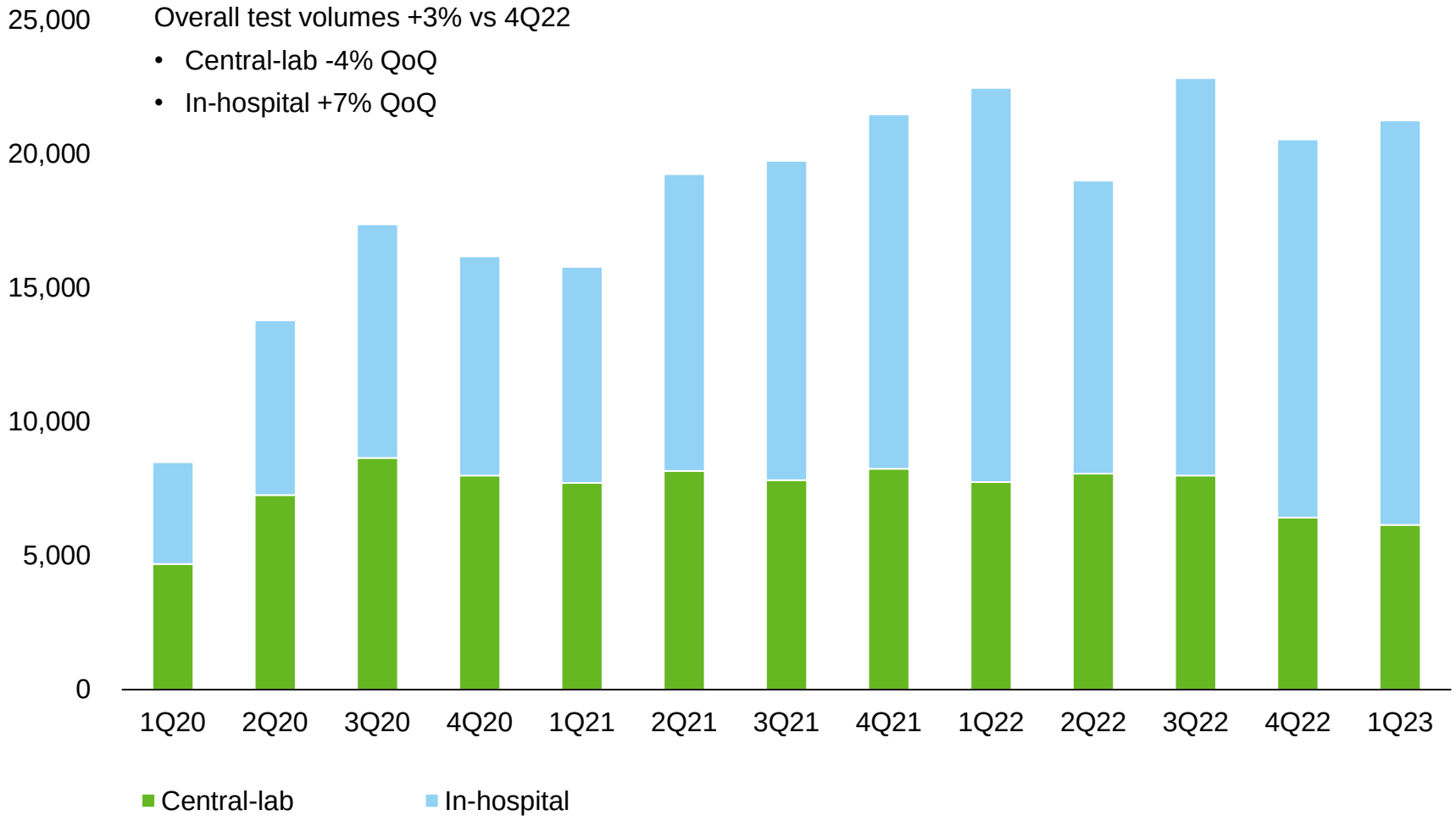
- Growing backlog. Contract value of new projects +27% YoY in 1Q23
- Triple digit revenue growth YoY in 1Q23

**Early detection**

- Clinical studies on track
- Ongoing dialogues with regulatory bodies, with US FDA (breakthrough device designation granted) and with China's NMPA

# 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

| RMB millions | 2021 | 2022 | 19 YoY | 20 YoY | 21 YoY | 22 YoY | 1Q22 | 2Q22 | 3Q22 | 4Q22 | 1Q23 | 1Q23 YoY | 1Q23 QoQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Revenue** | **507.9** | **563.1** | **83%** | **13%** | **18%** | **11%** | **135.5** | **130.8** | **154.6** | **142.2** | **142.6** | **5%** | **0%** |
| Central lab | 319.4 | 314.8 | 71% | 8% | 7% | -1% | 74.2 | 78.6 | 90.0 | 72.0 | 61.8 | -17% | -14% |
| In-hospital[1] | 165.1 | 175.3 | 164% | 34% | 40% | 6% | 49.0 | 34.2 | 49.6 | 42.5 | 51.6 | 5% | 21% |
| Pharma | 23.4 | 73.0 | 25% | -17% | 59% | 212% | 12.3 | 18.0 | 15.0 | 27.7 | 29.2 | 137% | 5% |
| | | | | | | | | | | | | | |
| **Non-GAAP Gross profit[2]** | **368.2** | **411.0** | | **14%** | **16%** | **12%** | **92.7** | **90.9** | **117.0** | **110.4** | **107.9** | **16%** | **-2%** |
| | | | | | | | | | | | | | |
| **Total opex** | **1,161.2** | **1,360.5** | **49%** | **64%** | **60%** | **17%** | **350.4** | **348.1** | **343.3** | **318.7** | **287.2** | **-18%** | **-10%** |
| R&D[3] | 324.1 | 344.4 | | | | | 100.9 | 77.7 | 88.7 | 77.1 | 74.0 | -27% | -4% |
| S&M[3] | 283.4 | 350.6 | | | | | 84.6 | 100.3 | 85.4 | 80.3 | 60.5 | -28% | -25% |
| G&A[3] | 228.8 | 250.5 | | | | | 61.2 | 74.8 | 68.4 | 46.1 | 51.2 | -16% | 11% |
| SBC | 280.8 | 325.1 | | | | | 79.8 | 76.7 | 77.4 | 91.2 | 77.8 | | |
| D&A | 44.1 | 89.9 | | | | | 23.9 | 18.6 | 23.4 | 24.0 | 23.7 | | |
| **Non-GAAP GP - SG&A** | **(144.0)** | **(190.1)** | | | | | **(53.1)** | **(84.2)** | **(36.8)** | **(16.0)** | **(3.8)** | | |
| **Operating profit** | **(797.1)** | **(980.3)** | | | | | **(262.8)** | **(265.5)** | **(234.6)** | **(217.4)** | **(188.5)** | | |
| **Net operating cash flows** | **(477.9)** | **(456.9)** | | | | | **(144.4)** | **(109.3)** | **(135.5)** | **(67.7)** | **(113.1)** | | |
| | | | | | | | | | | | | | |
| Non-GAAP GP margin[2] | 72.5% | 73.0% | | | | | 68.4% | 69.5% | 75.7% | 77.6% | 75.7% | | |
| Opex[3] / revenue | 165% | 168% | | | | | 182% | 193% | 157% | 143% | 130% | | |
| S&M[3] / revenue | 56% | 62% | | | | | 62% | 77% | 55% | 56% | 42% | | |

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)

# Cash position

## 3 years runway based on existing cash balance

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

| RMBm | 2022 | 1Q2023 | 2023E[1] | 2024E[1] |
|---|---|---|---|---|
| Operating cash outflow[2] | 457 | 113 | | |
| Capex[3] | 75 | 4 | | |
| Sum | 532 | 117 | c.400 | c.200 |
| Cash balance at period-end[4] | 925 | 803 | | |

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 RMB793m and restricted cash of approximately RMB10m as of the end of 1Q2023

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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

**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)

**6-cancer**
2018 – 2020

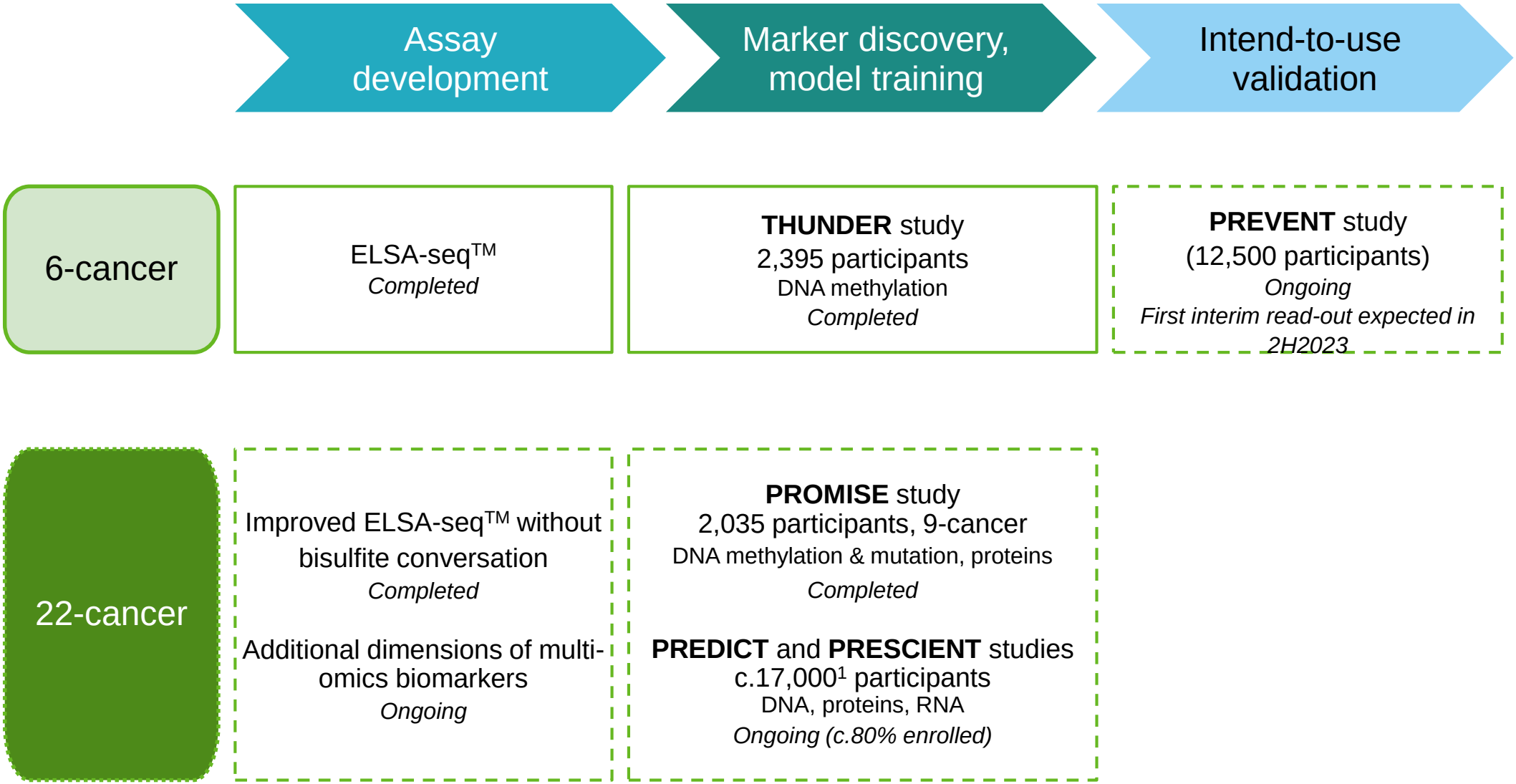
- Lung, CRC, HCC, Ovarian, Pancreatic, Esophageal
- THUNDER study (N=2,385) completed, 98.9% specificity and 69.1% sensitivity, top-2 predicted origin accuracy of 91.7% (independent validation cohort)
- PREVENT study (prospective and interventional, IU population) ongoing

**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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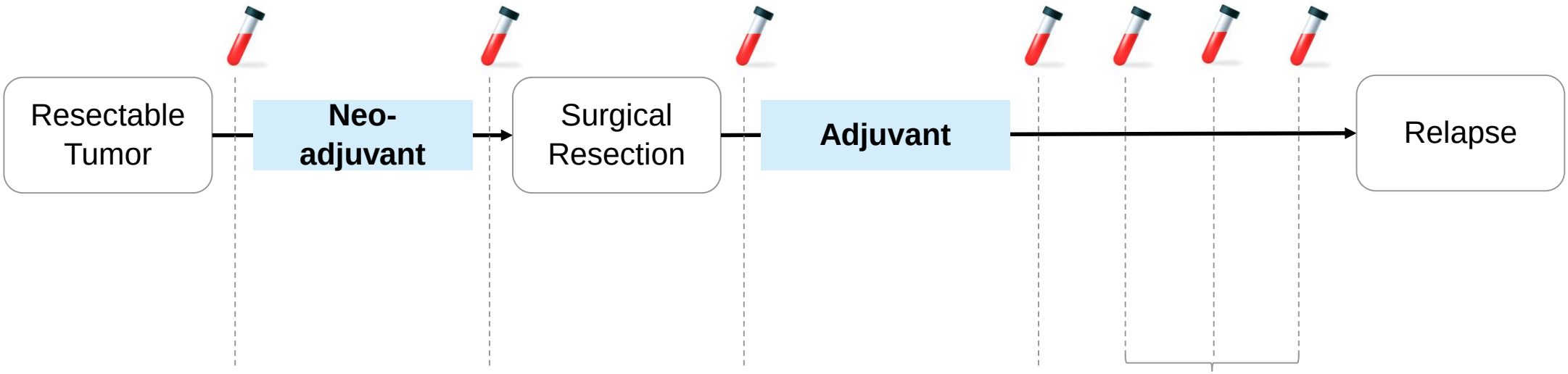
# Minimal Residual Disease (MRD)

# 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**

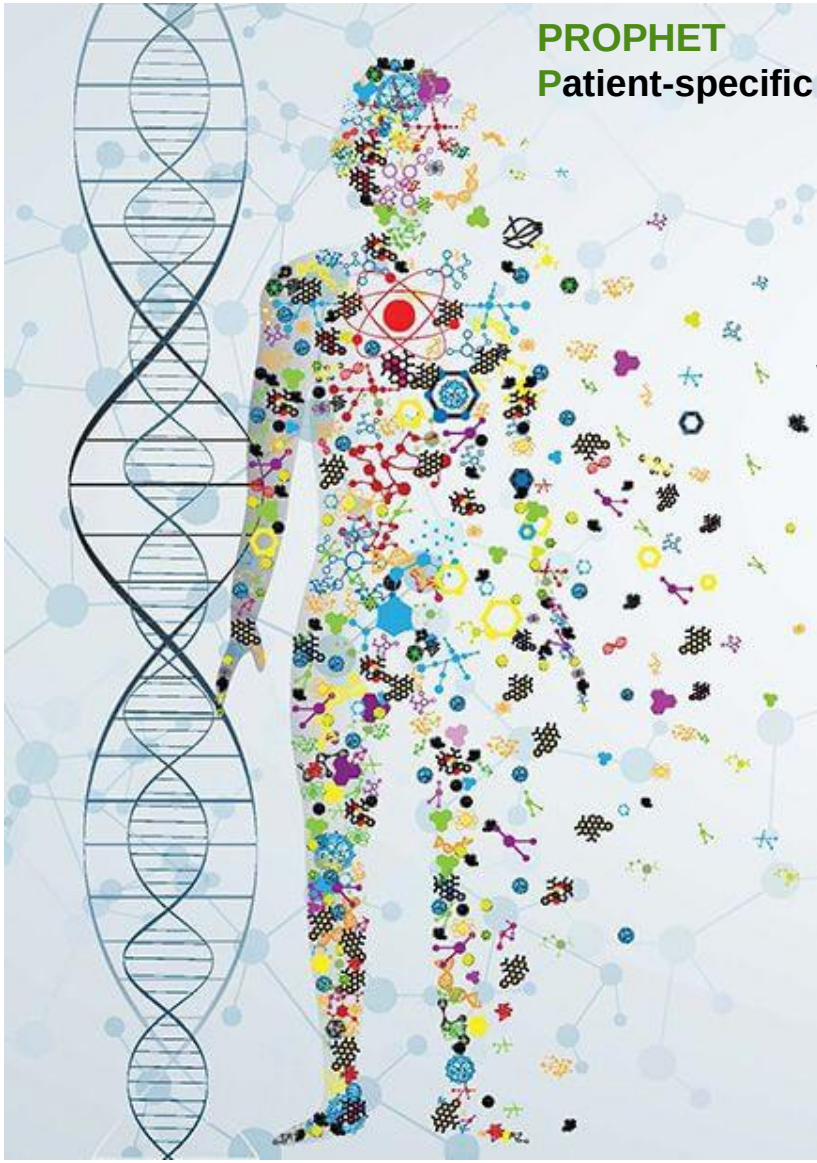
**Identify "cured" patients**

**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

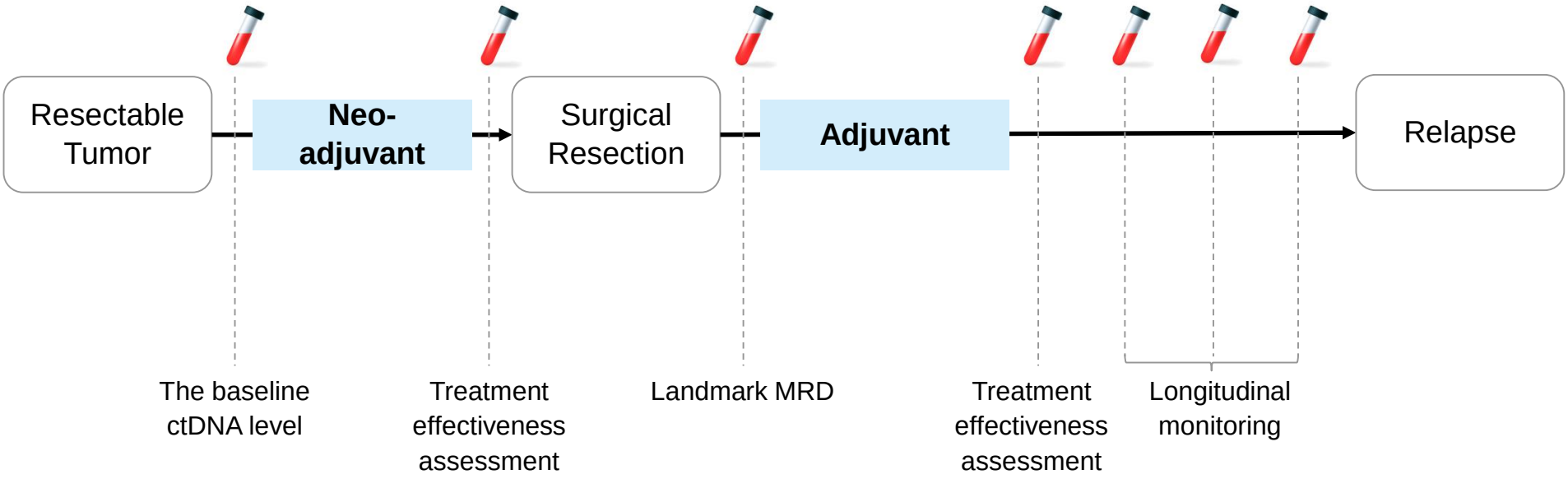
Intelligent selection of 50 tracking sites

## brPROPHET MRD Assay

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

# Burning Rock's MRD clinical publications

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




| | | |
|---|---|---|
| Non-small-cell lung cancer | Baseline, landmark and longitudinal monitoring timepoints completed<br>AACR 2022 Abstract 5916, AACR 2023 Abstract 1039 | |
| Colorectal cancer | Baseline and landmark timepoints<br>AACR 2022 Abstract 5917, ASCO GI 2023 Abstract 213 | Longitudinal monitoring ongoing |
| Gastric cancer | Baseline and landmark timepoints<br>AACR 2023 Abstract 6682 | |
| Pancreatic cancer | Baseline, landmark and longitudinal monitoring timepoints completed<br>ASCO GI 2023 Abstract 744 | |
| Biliary tract cancer | Baseline and landmark timepoints<br>AACR 2023 Abstract 6682 | |

# Individualized tumor-informed ctDNA analysis for postoperative monitoring of non-small cell lung cancer (NSCLC) – the MEDAL study

**Individualized tumor-informed circulating tumor DNA (ctDNA) analysis for postoperative monitoring of non-small cell lung cancer (NSCLC) - the MEDAL study**

Kezhong Chen[1], Chenyang Wang[2], Haifeng Shen[1], Xi Li[2], Yichen Jin[1], Shuailai Wu[2], Fujun Qiu[2], Qiang Lu[2], Di Peng[2], Shuai Fang[2], Bing Li[2], Juan Lv[2], Jinlei Song[2], Yang Wang[2], Shannon Chuai[2], Zhihong Zhang[2]

1. Thoracic oncology institute and Department of thoracic surgery, Peking University People's Hospital, Beijing, 100044, China;
2. Burning Rock Biotech, Guangzhou, 510300, China

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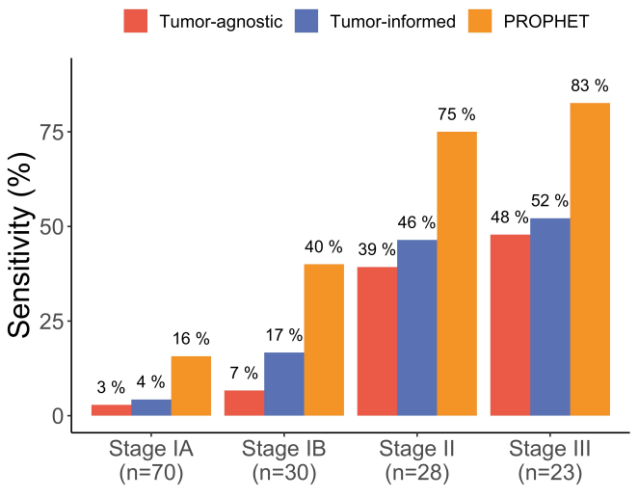
AACR American Association for Cancer Research ANNUAL MEETING 2023

APRIL 14-19 • #AACR23

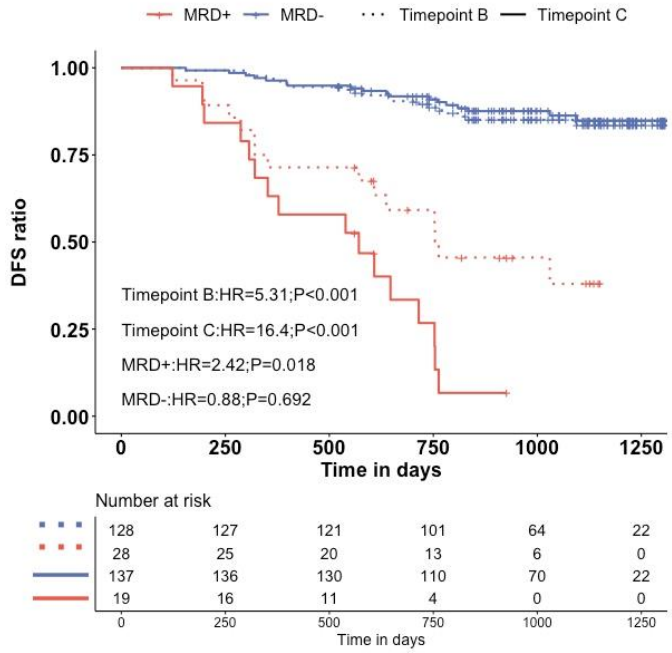
## Personalized assay significantly out-performs fixed panels

**3a** Sensitivity of pre-operative plasma from patients with different clinical stages by three MRD assays



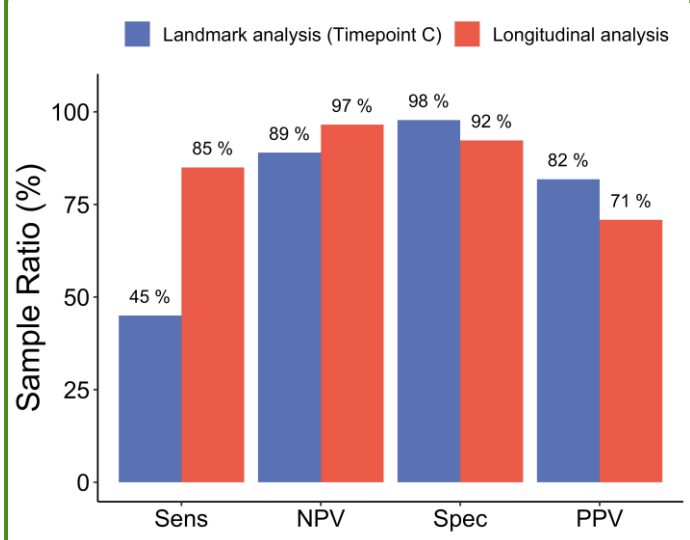

## Post-operative prognostic at landmark timepoint

**4a** Landmark MRD status showed a significant association with DFS




## Longitudinal analysis with follow-up timepoints

**5a** Sensitivity, NPV, specificity, and PPV for recurrence prediction. Landmark (timepoint C) and longitudinal analysis




Notes

#Timepoint B and C refer to 3-day and 30-day past surgery

Source: Chen et al., Individualized tumor-informed circulating tumor DNA (ctDNA) analysis for postoperative monitoring of non-small cell lung cancer (NSCLC) - the MEDAL study , AACR 2023

# Gastric cancer cohort publication at AACR 2023

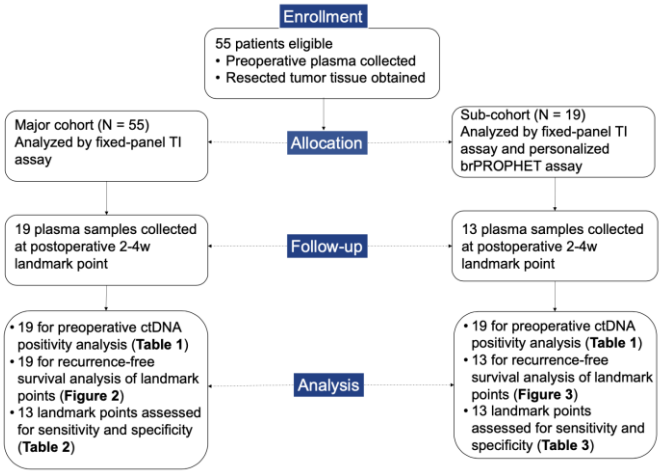
## Circulating tumor DNA - based molecular residual disease predicts relapse in patients with resectable gastric cancer

Pei Xue[1], Yanfei Shao[1], Xueliang Zhou[1], Haiyan Li[2], Yang Wang[2], Chenyang Wang[2], Hao Zhang[2], Bing Li[2], Shuo Shi[2], Haiwei Du[2], Jing Sun[1]
1. Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China
2. Burning Rock Biotech, Guangzhou, China

2023 AACR
#1037

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

### Study cohort




### Personalized assay significantly out-performs fixed panels

The ctDNA+ rate of preoperative samples detected by fixed panel and personalized brPROPHET™ assays

| ctDNA⁺ rate | Stage I | Stage II | Stage III | Overall |
|---|---|---|---|---|
| Fixed panel | 0% (0/4) | 0% (0/3) | 58.3% (7/12) | 36.8% (7/19) |
| brPROPHET | 100% (4/4) | 66.7% (2/3) | 91.7% (11/12) | 89.5% (17/19) |

### Postoperative prognosis

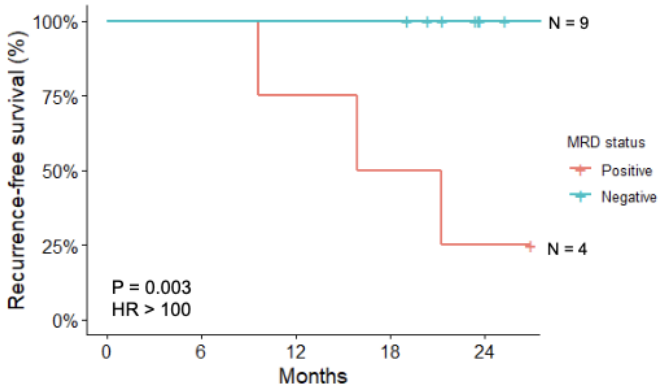



**Table 3. The performance of MRD status detected by brPROPHET in predicting tumor recurrence.**

| MRD status | Tumor recurrence | | |
|---|---|---|---|
| | + | - | |
| + | 3 | 1 | PPV=75% |
| - | 0 | 9 | NPV=100% |
| | Sensitivity=100% | Specificity=90% | |

PPV, positive predictive value; NPV, negative predictive value.



Source: Xue et al., Circulating tumor DNA based molecular residual disease predicts relapse in patients with resectable gastric cancer, #1037 AACR 2023

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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"

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2017 – 2020

- Lung, Colorectal Cancer (CRC), Hepatocellular Carcinoma (HCC)

**6-cancer**
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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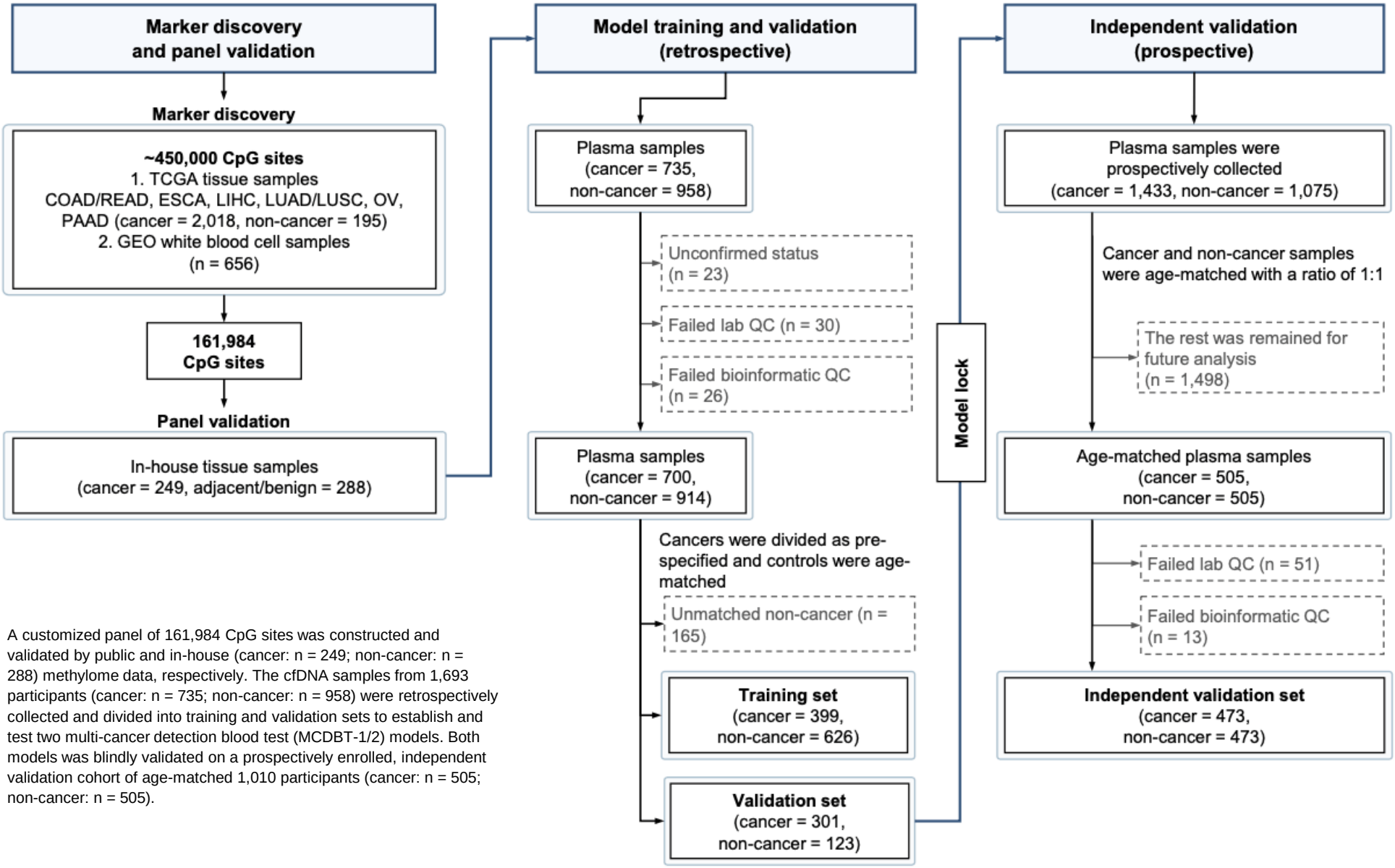
# 6-cancer test marker discovery and model training

## 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).

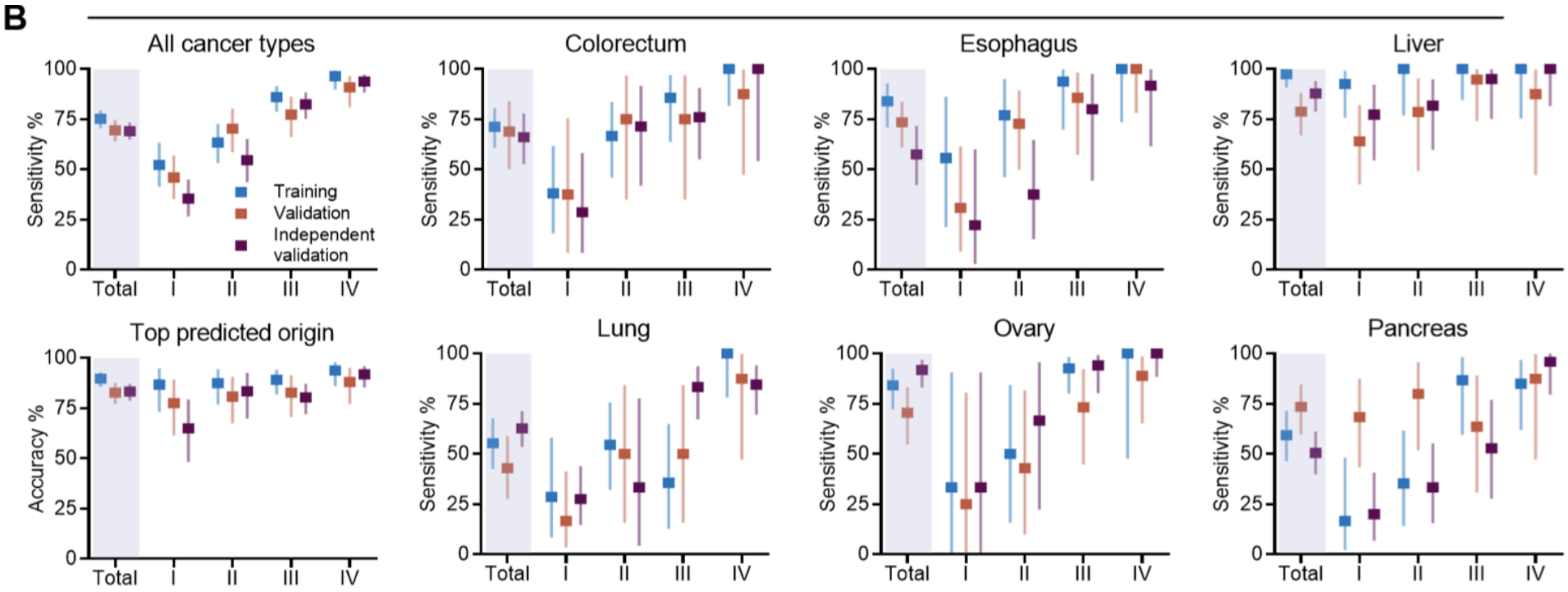


Source: Gao et al., Unintrusive multi-cancer detection by circulating cell-free DNA methylation sequencing (THUNDER): development and independent validation studies, ASCO 2022

# 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.



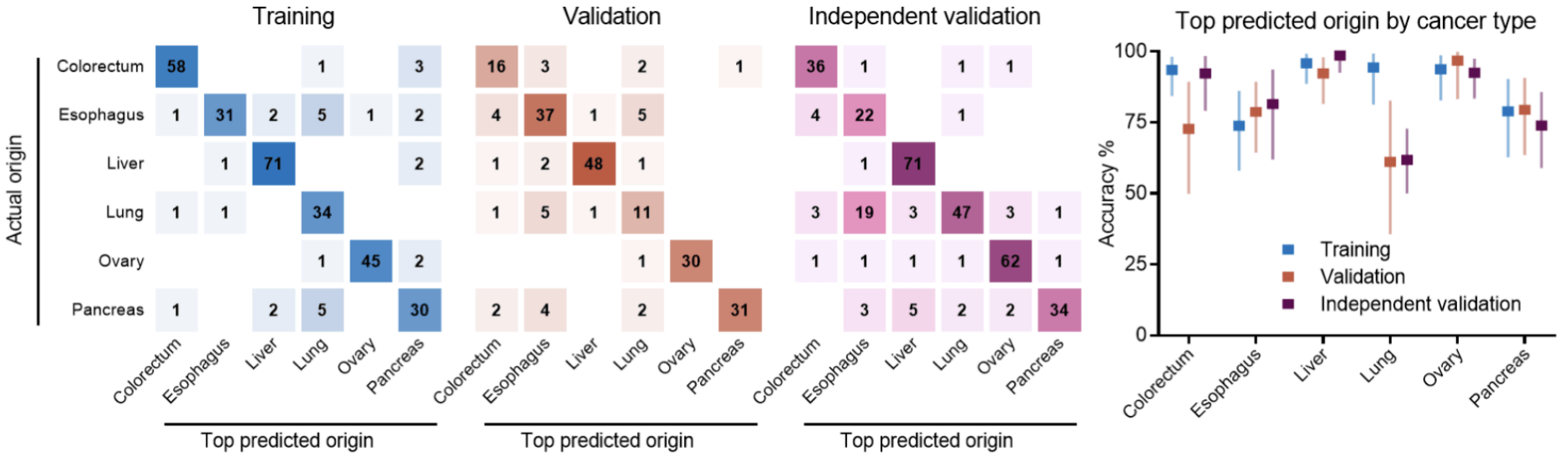

| Data set | Specificity (%) | Sensitivity (%) | Accuracy of top predicted origin (%) | Accuracy of top two predicted origins (%) |
|---|---|---|---|---|
| Training set | 99.7 (98.9-100.0) | 75.2 (70.6-79.4) | 89.7 (85.7-92.9) | 94.7 (91.5-96.9) |
| Validation set | 100.0 (97.0-100.0) | 69.4 (63.9-74.6) | 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.




| 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

# 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)

**6-cancer**
2018 – 2020
**CE Mark, FDA BDD**

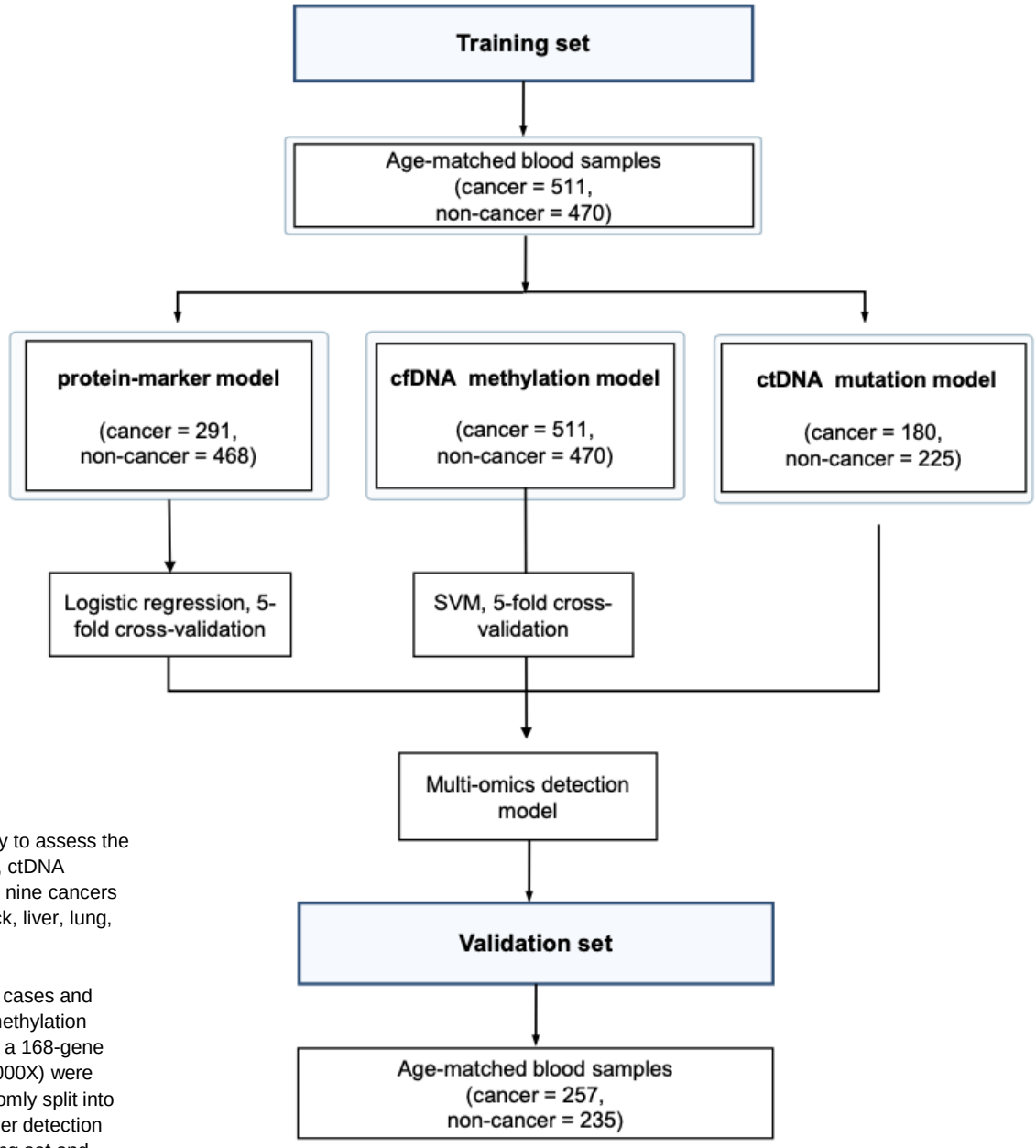
- Lung, CRC, HCC, Ovarian, Pancreatic, Esophageal
- THUNDER study (N=2,385) completed, 98.9% specificity and 69.1% sensitivity, top-2 predicted origin accuracy of 91.7% (independent validation cohort)
- PREVENT study (prospective and interventional, IU population) ongoing

**22-cancer**
2019 – 2022

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

# 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.

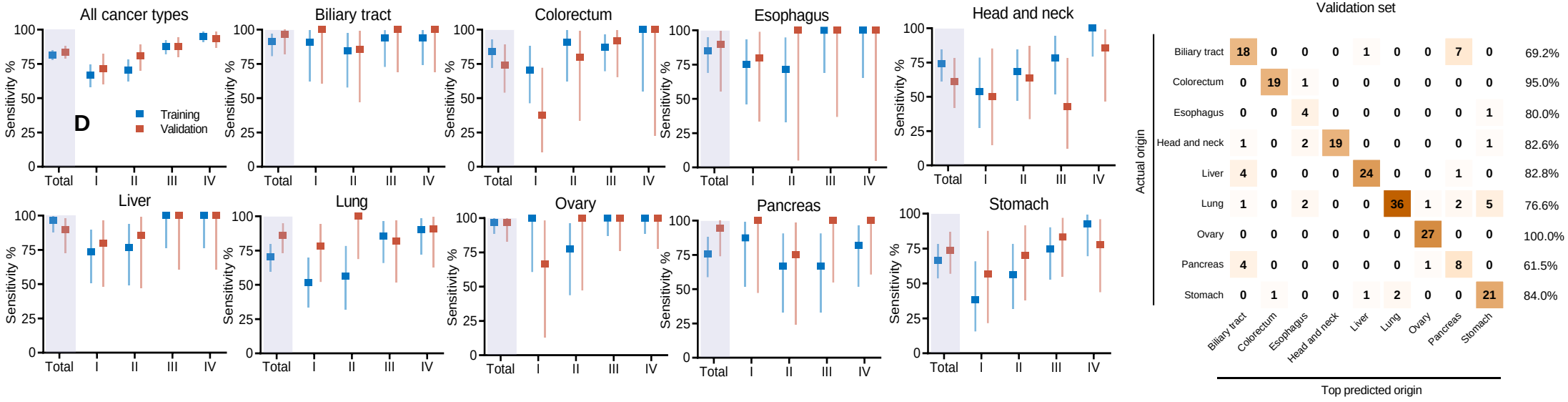
Source: Gao et al., a multi-cancer early detection model based on liquid biopsy of multi-omics biomarkers, ESMO 2022

# 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%) |

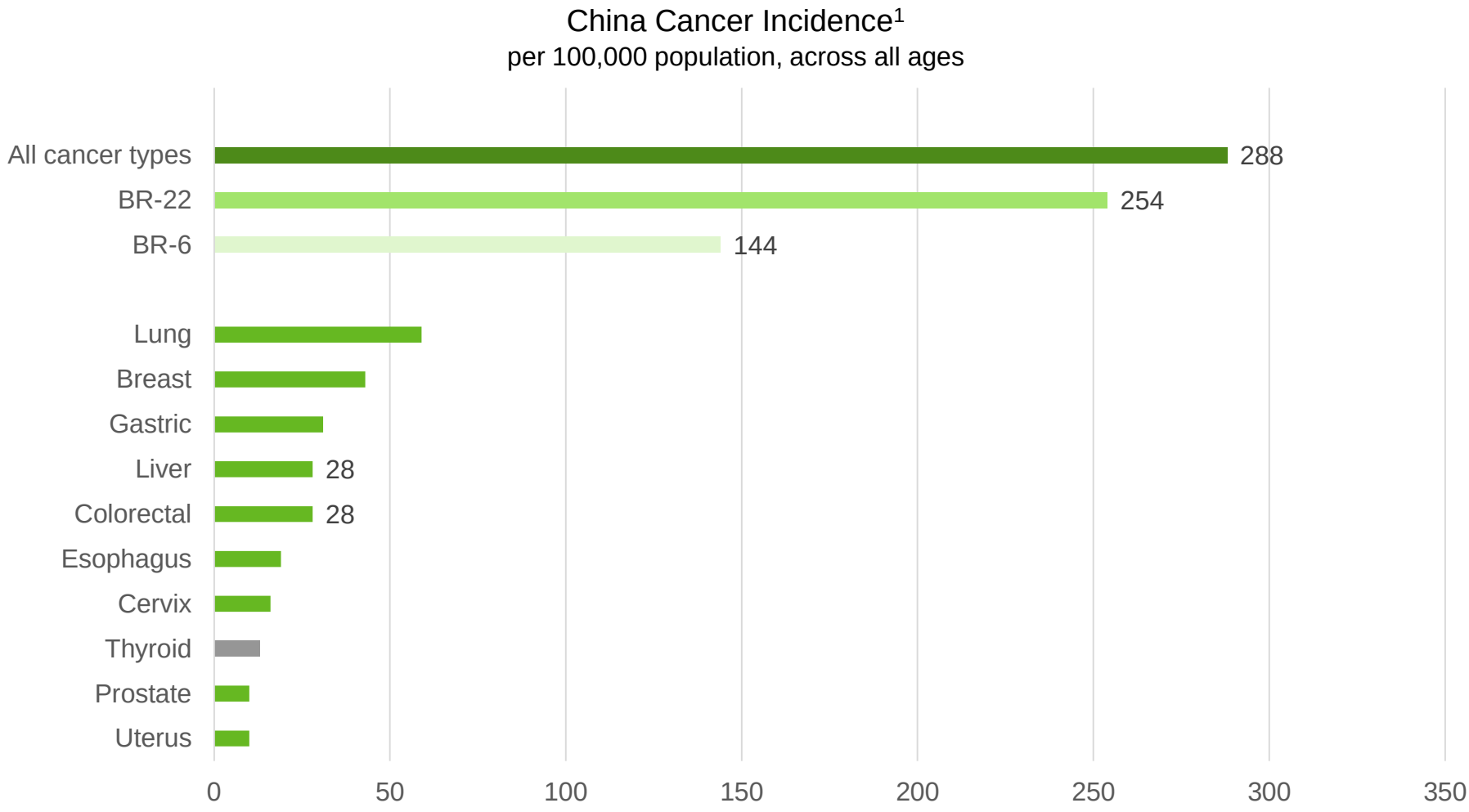



- PROMISE demonstrated 83.7% sensitivity and 98.3% specificity for 9 cancers
- Methylation contributed >90% of the total sensitivity, while protein and mutation collectively provided <10% additional positive detections



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**<br>in the circulating bloodstream, much more challenging vs. tissue | **Proprietary chemistry and algorithm**<br>• On par with global leader, competitive sensitivity in earlier stages for certain cancers<br>• Multi-year lead vs. China peers (most showing liver-cancer and colon-cancer data only) |
| 2 Clinical | **Large, multi-year studies required**<br>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**<br>• Catching up with global leader, to improve specificity and tissue-of-origin performance through large clinical studies<br>• 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**<br>with no established regulatory pathway | **Leading regulatory capability in China**<br>• Exploring possible pathway, leveraging experience through the country's first NGS kit approval by the NMPA |
| 4 Commercial | **Unprecedented product** | **Multi-pronged approach**<br>• Initially working with hospitals' health check-up departments, leveraging synergy from in-hospital therapy selection business |

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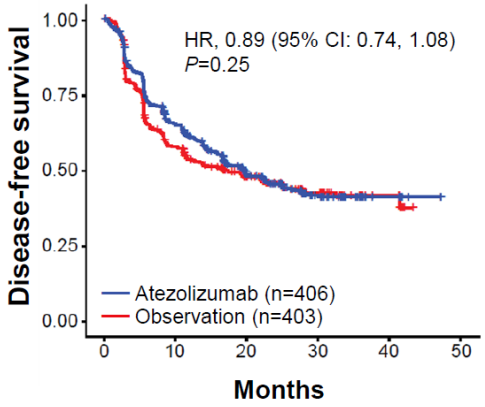
# Appendix 2

MRD

# How do MRD studies advance utility

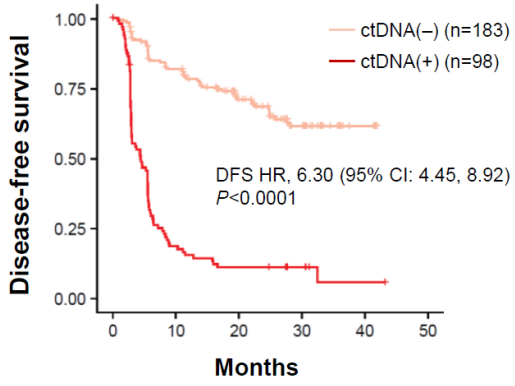
*Example 1: IMvigor010, enrich the high-risk group and "tune-up" adjuvant treatment*

**ITT**

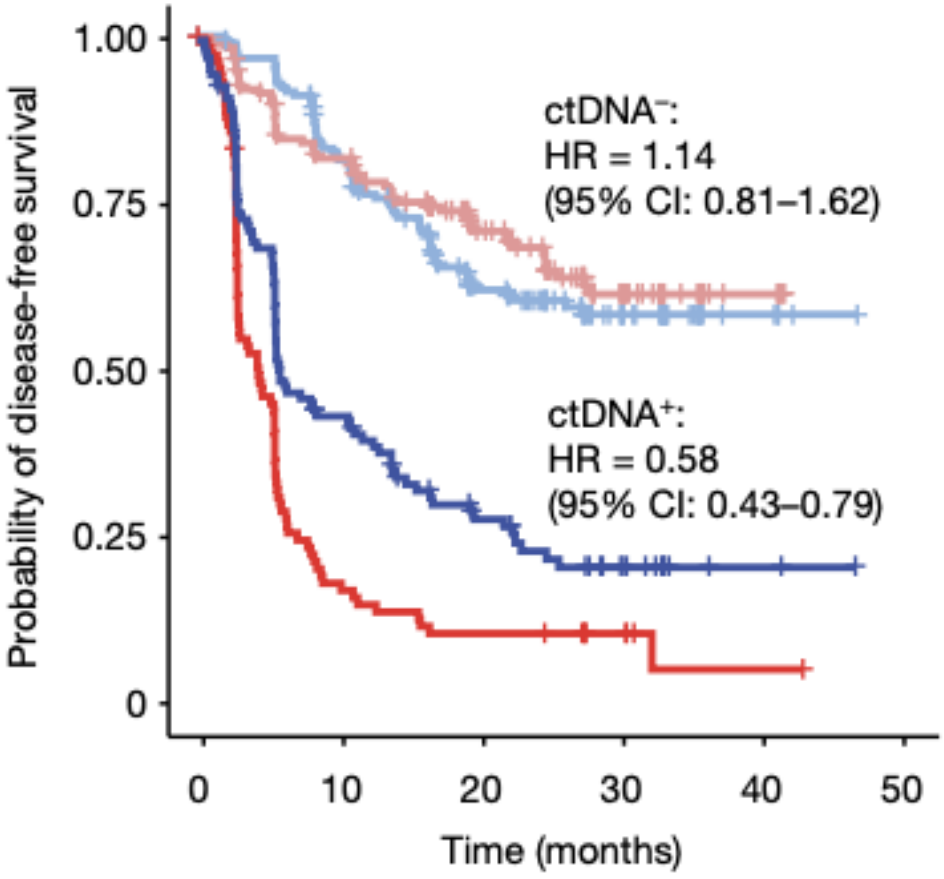



**Atezo, MIUC Adjuvant Therapy**
**"All comers" demonstrated NO efficacy**
**TMB/PD-L1 showed NO prediction**

**Observation arm**




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

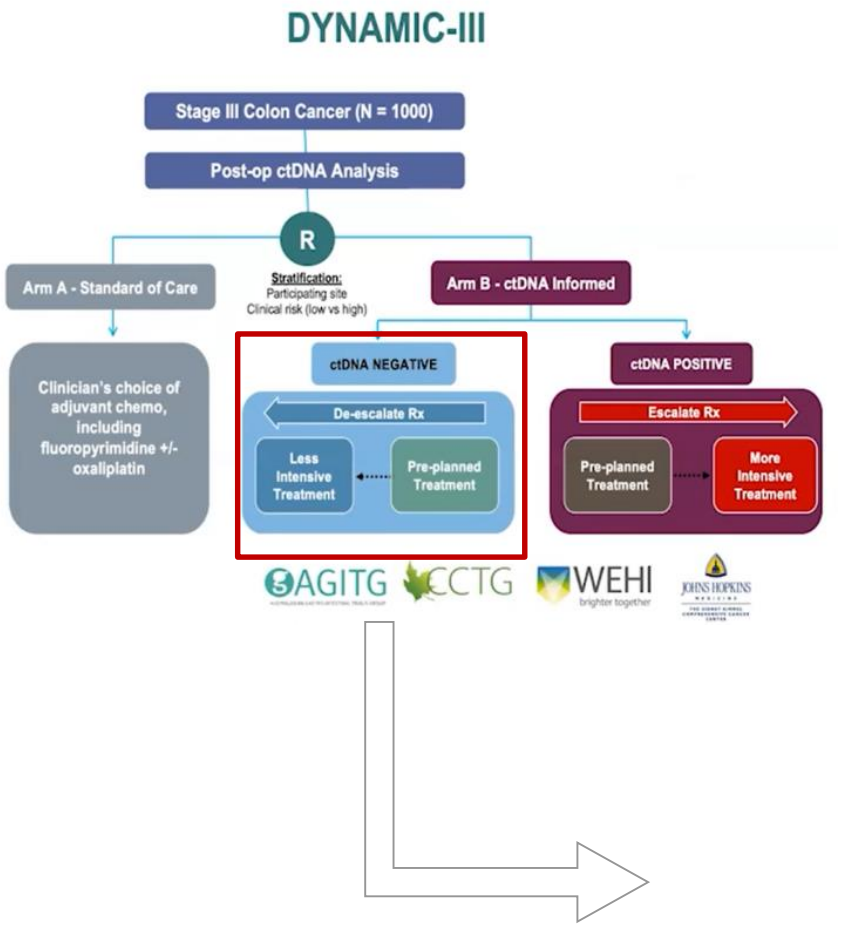



**Indeed, only baseline MRD+ pts showed benefit**

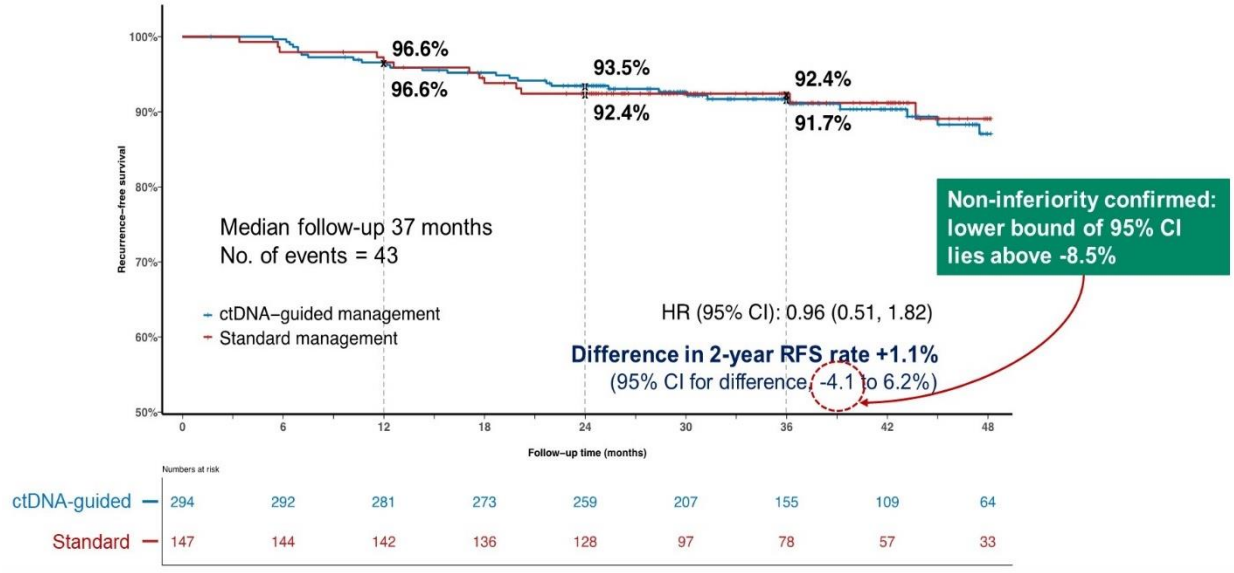
Nature. 2021 Jun 16. doi: 10.1038/s41586-021-03642-9.

# How do MRD studies advance utility

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




## ctDNA-guided vs standard

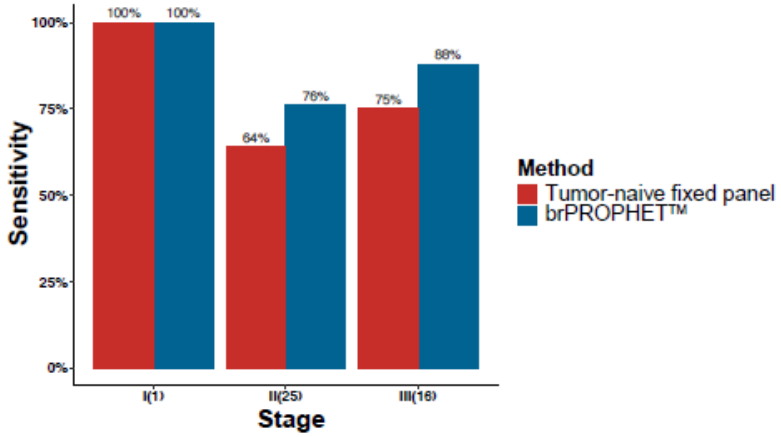



The ctDNA-guided MRD- group had fewer patients with adjuvant chemotherapy than the standard group (15% vs. 29%) with non-inferiority of 3-year RFS (92.4% vs 91.7%)

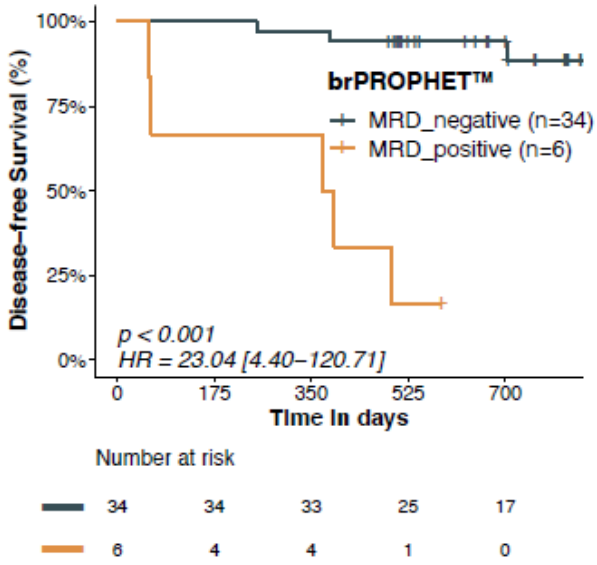
# Colorectal cancer cohort publication at AACR 2022

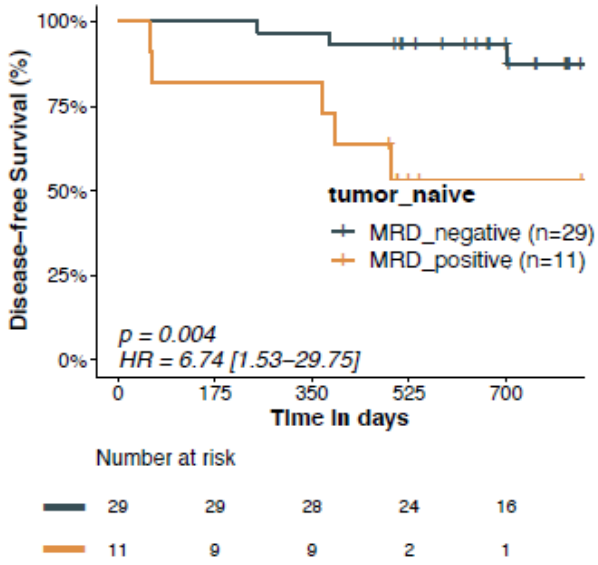
**Session OPO.PR02.01 - Clinical Prevention, Early Detection, and Interception**

## 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*

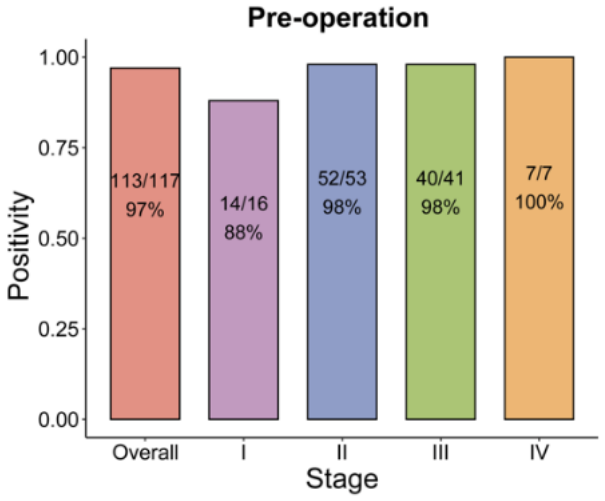


# Second colorectal cancer cohort publication at ASCO GI 2023

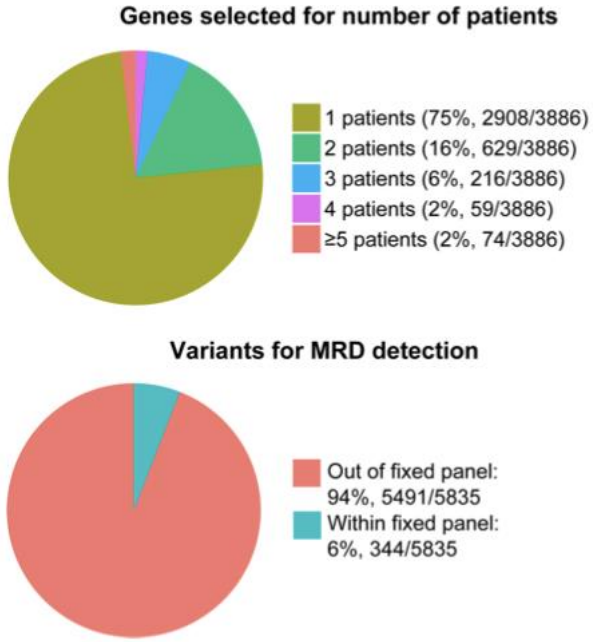
**brPROPHET™ has high detection sensitivity**

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



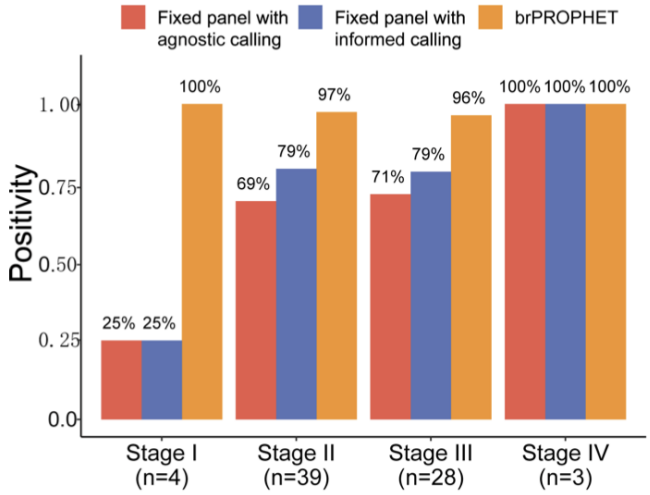

**Most mutation variants fall outside of fixed panels**

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.



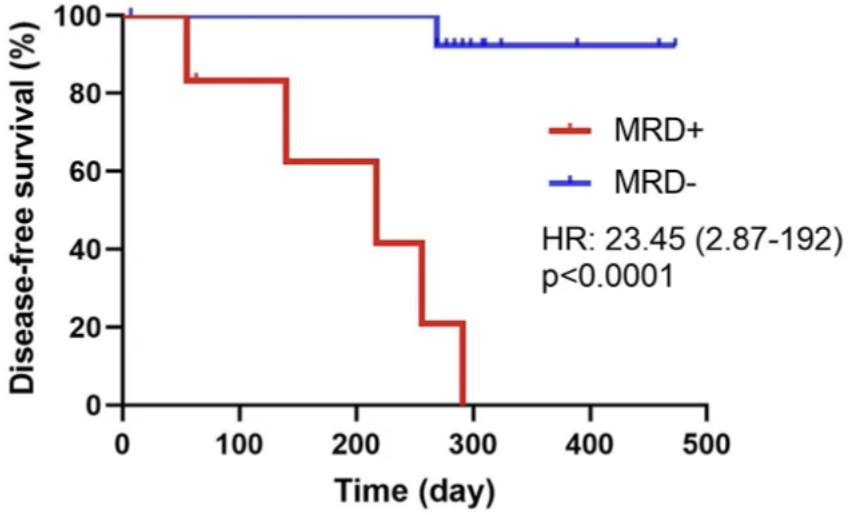
Source: Cao et al., Patient-specific tumor-informed circulating tumor DNA analysis for molecular residual disease detection in surgical patients with stages I-IV colorectal cancer, ASCO GI 2023

# Pancreatic cancer cohort publication at ASCO GI 2023

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

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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<br>Approved in Jul **2018**<br>First approved NGS kit in China | EGFR, KRAS, MET, ERBB2, BRAF, PIK3CA, ALK, ROS1, RET<br>Approved in Mar **2022** |
| Novogene<br>诺禾 | EGFR, KRAS, BRAF, PIK3CA, ALK, ROS1<br>Approved in Aug **2018** | |
| Geneseeq<br>世和 | EGFR, ALK, ROS1, BRAF, KRAS, ERBB2<br>Approved in Sep **2018** | |
| BGI<br>华大 | EGFR, KRAS, ALK<br>Approved in Aug **2019** | |
| Gene+<br>吉因加 | EGFR, KRAS, ALK<br>Approved in Dec **2019** | |
| Genetron<br>泛生子 | EGFR, KRAS, BRAF, ERBB2, PIK3CA, ALK, ROS1, MET<br>Approved in Feb **2020** | |
| Genecast<br>臻和 | KRAS, NRAS, BRAF, PIK3CA<br>Approved in Mar **2021** | |
| 3DMed<br>思路迪 | | |

Highlights on our second NMPA-approved kit

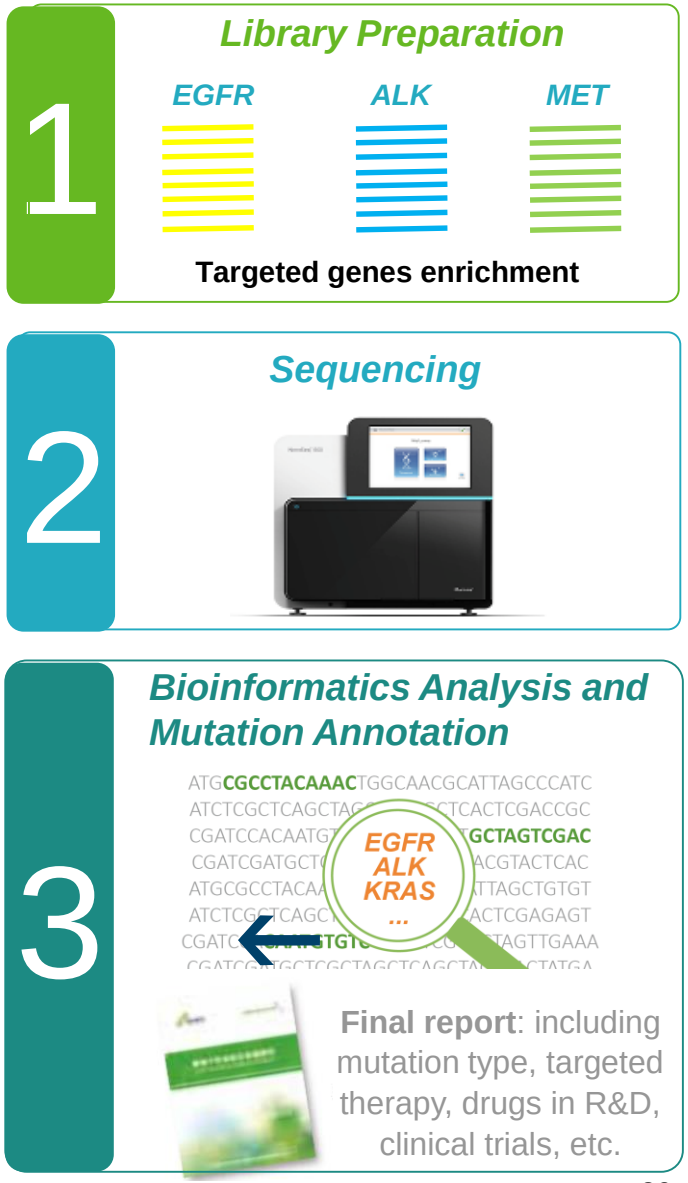
- Only 30ng DNA input required, applicable to small tissue samples
- First NMPA approved NGS kit with CNV[2] mutation type, with MET exon14 skipping

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

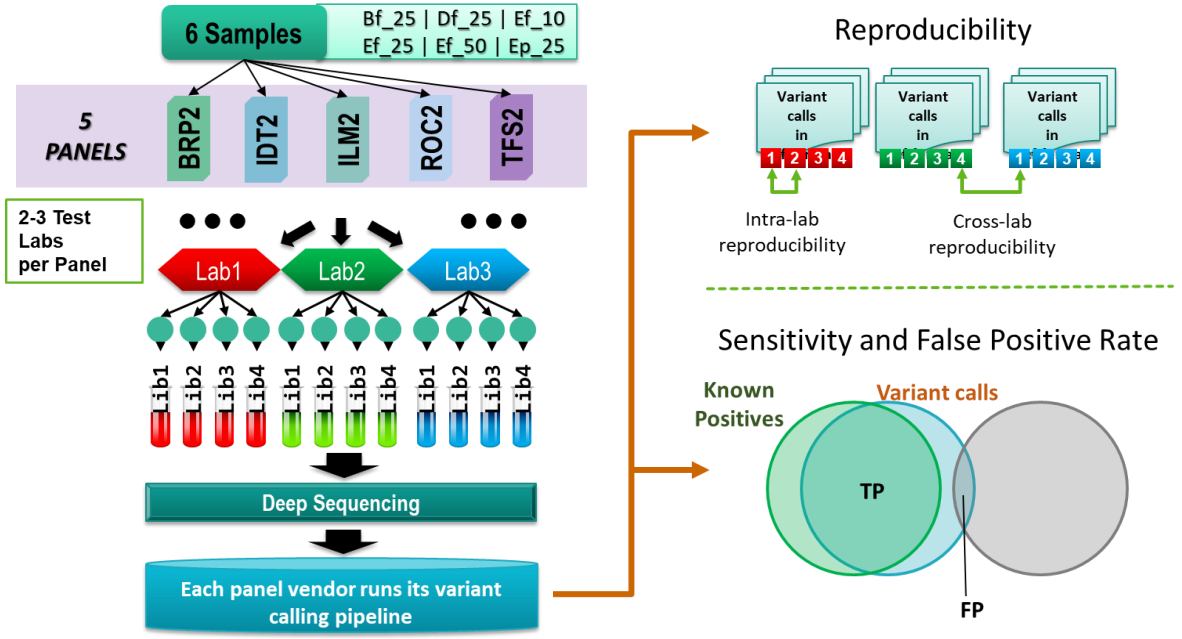
TFS2

| |
|---|
| **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

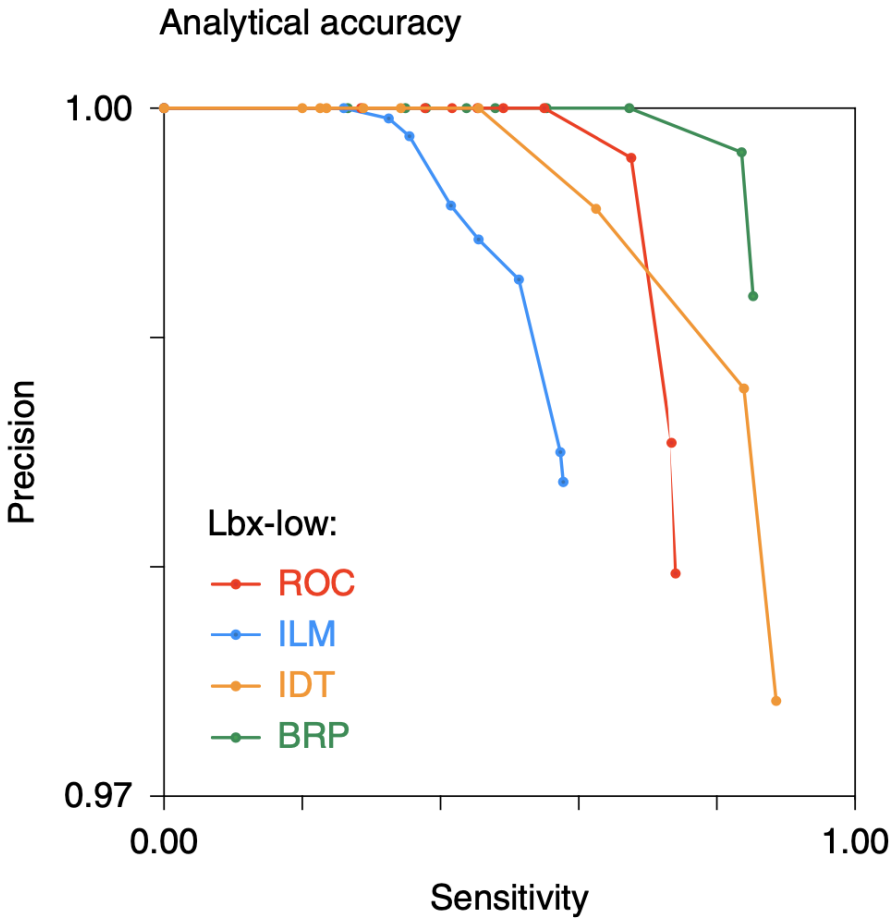
| Name | Vendor | ctDNA assay | Sequencing platform | Target genes | Reportable region (kb) | Coding (kb) | CTR (kb) | Negatives (× 1,000) | Variants |
|---|---|---|---|---|---|---|---|---|---|
| ROC | Roche Sequencing Solutions | AVENIO ctDNA (Expanded Kit) | Illumina NextSeq | 77 | 161.7 | 140.2 | 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 |

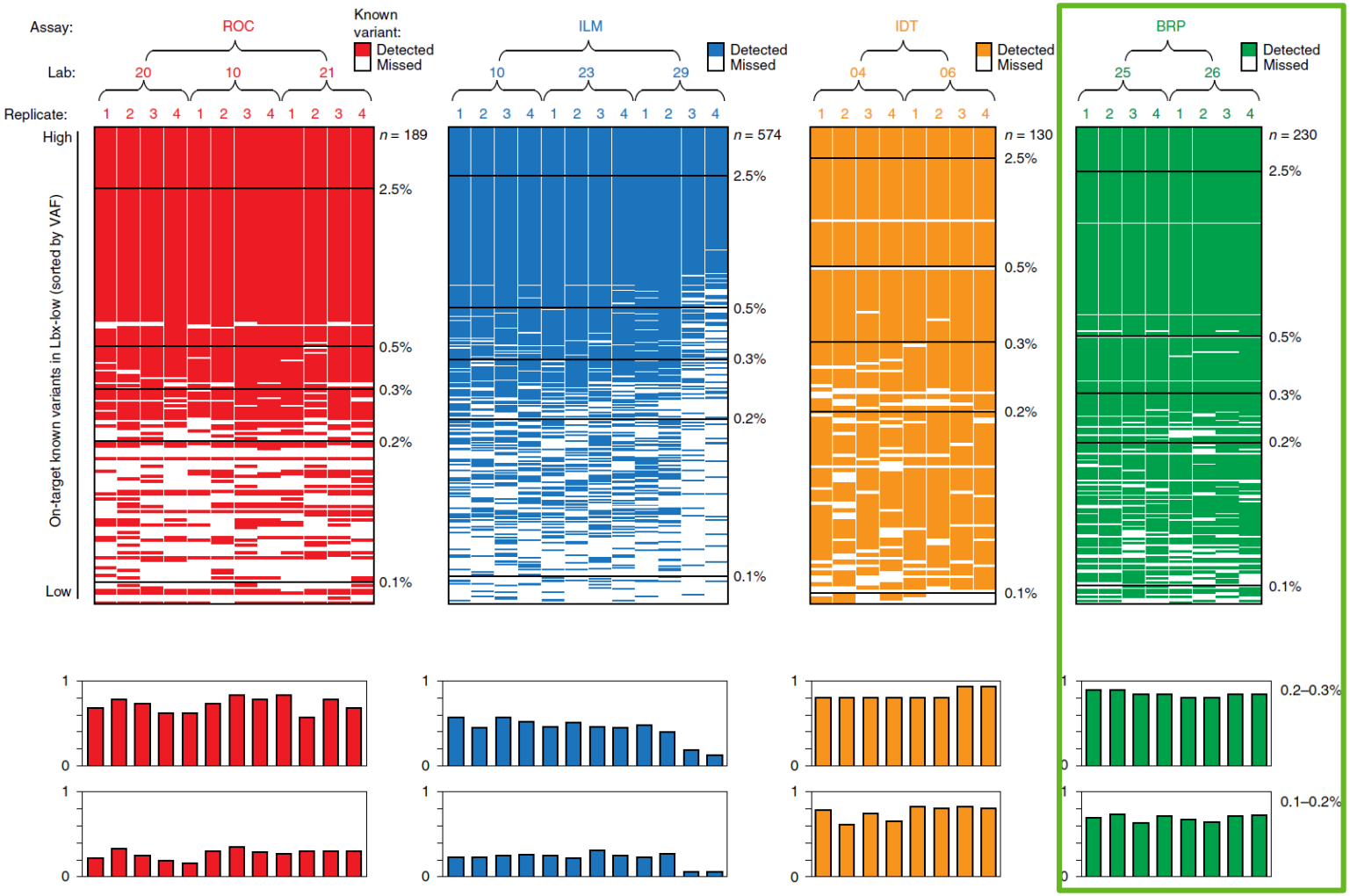
The analytical accuracy was measured by **Precision-Sensitivity** plot (25ng LBx-Low)
The false positive rates were computed by FP/kb region.
Once different VAF threshold increases, FP rates dropped further.

"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