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Burning Rock Dx

Burning Rock Biotech Limited

BNR US Equity

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Our value-building blocks

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

New Businesses

Large market potential

At pipeline or early commercial stage

Early Detection

Asymptomatic population

MRD

Early-stage oncology patients

Biopharma

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

Common Infrastructure

Accelerating growth of new businesses

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

Base Business

Commercial stage

Therapy Selection

Late-stage oncology patients

Summary of recent progress

Early detection

2022 commercialization on track

- Contracting completed with a small number of pilot hospitals
- Focus on 1) customer education in preparation for commercial roll-out and 2) contracting additional hospitals

Pipeline development progressing well

- 9-cancer product development **reading out in 1H2022**, with potential to demonstrate performance improvement vs. the 6-cancer test
- 6-cancer test interventional study for the intend-to-use population to launch in 2022, paving way for a future registrational trial

MRD

Product development on track for 2022 launch

- Lung-cancer data **read-out in 1H2022**

Therapy selection

Continued leadership, particularly in the in-hospital segment

- **+37% YoY** in-hospital testing kit volume growth during 3Q21 despite Covid hit in Aug

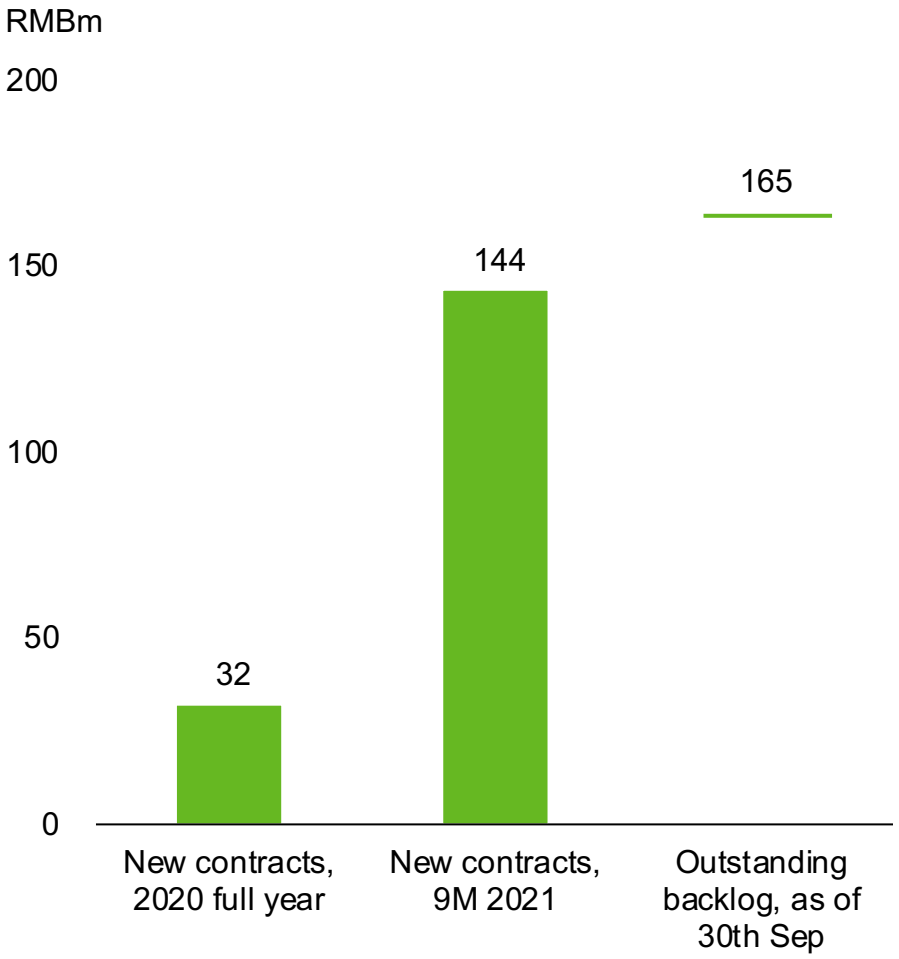
Biopharma

Strong growth, expansion outside of China

- New contract value reached RMB144m during 9M21, **4.5x vs. 2020 full-year**
- Multiple pharma projects contracted for our California lab

Pharma collaboration – our first step of global expansion

Newly contracted pharma projects



New, strong demand

- New rules for CDx[1] requirement from NMPA
- Innovative Chinese pharma going global
- MNCs seeking reliable global NGS CDx partners that can operate in China

Burning Rock advantages

- CLIA-certified and CAP-accredited labs in Guangzhou and California
- Global registration capability, with NMPA and FDA experience. Recent addition of Dr. Sharon Liang as VP of Regulatory Affairs (US and Europe) and Quality Assurance with extensive FDA experience[2]
- Comprehensive product line covering tissue and liquid modalities, with strong product performance

Notes

[1] Companion diagnostics, associated with a targeted drug's pivotal study and regulatory approval

[2] Dr. Sharon Liang is a human genetics expert with nearly two decades of experience in molecular cancer diagnostic medical device product development and regulatory in academia, government and industry. She was the US FDA committee member for the US President's Precision Medicine Initiative (PMI) Project, leading Bioinformatics group. She led and contributed to the development of many molecular diagnostic devices approved by the FDA, including the first NGS sequencer, first NGS Oncopanel, first NGS tumor profiling assay, first Direct-to-Consumer test, first microarray genetic tests, and companion diagnostics. Before joining Burning Rock, Dr. Liang worked at GRAIL, a cancer early detection diagnostic company, primarily responsible for regulatory strategy and execution

Product pipeline

Broad portfolio with key products demonstrating globally competitive data
2022 seeing 3 new product launches, and 9-cancer early detection data read-out

	Product	Status	Key data
Asymptomatic	6-cancer early detection **Commercialization starting 2022**	Product dev. complete; Multi-center case-control validation studies complete; IU population interventional studies under planning	*ESMO Asia* mini-oral presentation[1]
	9-cancer early detection	Product dev. ongoing; Multi-center case-control validation studies recruiting	First read-out in 1H2022
	22-cancer early detection	Product dev. ongoing; Multi-center case-control validation studies recruiting	First read-out in 2024
Early-stage oncology patients	MRD[2] for solid tumors **Commercialization starting 2022**	Product dev. complete; Lung cancer validation study ongoing; Validation in colon, esophageal, etc. under planning	Lung cancer read-out in 1H2022
	DetermaRx* **Commercialization starting 2022**	Tech transfer ongoing	*Lancet* (incl. validation cohort of 1006 Chinese patients)[3]
Late-stage oncology patients	4-gene test for NSCLC#	Product dev. complete; Pivotal study complete; NMPA approved	**First** NMPA approved NGS-panel in China
	Expanded NSCLC panel	Product dev. complete; Pivotal study complete; Under NMPA review process	
	OncoCompass™ ctDNA#	Product dev. complete; Pivotal study to be launched in 2H21; In leading position for NMPA approval process[4]	SEQC2: *Nature Biotechnology*[5]
	OncoScreen™ CGP[6] tissue#	Product dev. complete; Pivotal study to be launched in 2H21; Among leading players for NMPA approval process	SEQC2: *Genome Biology*[7]
	myChoice HRD Plus*	Tech transfer complete; Pharma studies first-patient-in 2H21	GIS score: FDA approved algorithm

Notes:
Commercialized product * In-licensed product
[1] "Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq)", ESMO Asia Virtual Congress 2020, Nov 2020
[2] Molecular residual disease test for solid tumors
[3] "A practical molecular assay to predict survival in resected non- squamous, non-small-cell lung cancer: development and international validation studies". Lancet, March 2012
[4] Typing test passed in Oct 2020
[5] "Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology", Nature Biotechnology, Apr 2021
[6] Comprehensive genomic profiling
[7] "Cross-oncopanel study reveals high sensitivity and accuracy with overall analytical performance depending on genomic regions", Genome Biology, Apr 2021

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Early detection

Burning Rock's early detection technology

Globally competitive technology and multi-cancer validation progress

Competitive technology

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

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

Validation on independent multi-site case-control cohorts , with prospective interventional trial on intended use population under planning

VIRTUAL 2020 ESMO ASIA

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

Product development since 2016

1 of 2 companies globally with high specificity (>98%) and tissue-of-origin detection capability

Proof-of-concept
2016 – 2019

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

3-cancer
2017 – 2020

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

Product development complete. Entering commercialization 2022

6-cancer
2018 – Nov 2020

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

Product development in progress

9-cancer
2019 – Ongoing

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

22-cancer[3]
2020 – Ongoing

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

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

Clinical programs on track

9-cancer first read-out expected in 1H2022

Only company in China with 10,000-subject or larger early-detection clinical studies launched

	Assay development	Proof-of-concept	Model training via large-scale case-control study	Intend-to-use population validation (Feasibility for registration trial)
6-cancer	Completed		Completed *THUNDER study*[1]	Specificity holding well in EAP[2]. Interventional study under planning
9-cancer	Completed	***PROMISE*** study *2,035 participants* Reading-out 1H2022		***PREDICT*** *study* *14,026 participants* First read-out around end of 2022
22-cancer[3]	Ongoing	Under planning		***PRESCIENT*** *study* *11,879 participants* First read-out by 2024

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

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

Principal Investigator: Prof. Jia Fan

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

PRESCIENT

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

Principal Investigators

Prof. Jie He

Prof. Jie Wang

Head of the Dept. of Medicine, CHCAMS

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

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

Leadership in multi-cancer early detection

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

	Challenge	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

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MRD

Clinical utilities of MRD in solid tumors

1) Risk stratification post resection (adjuvant therapy), 2) relapse monitoring, 3) therapy response monitoring

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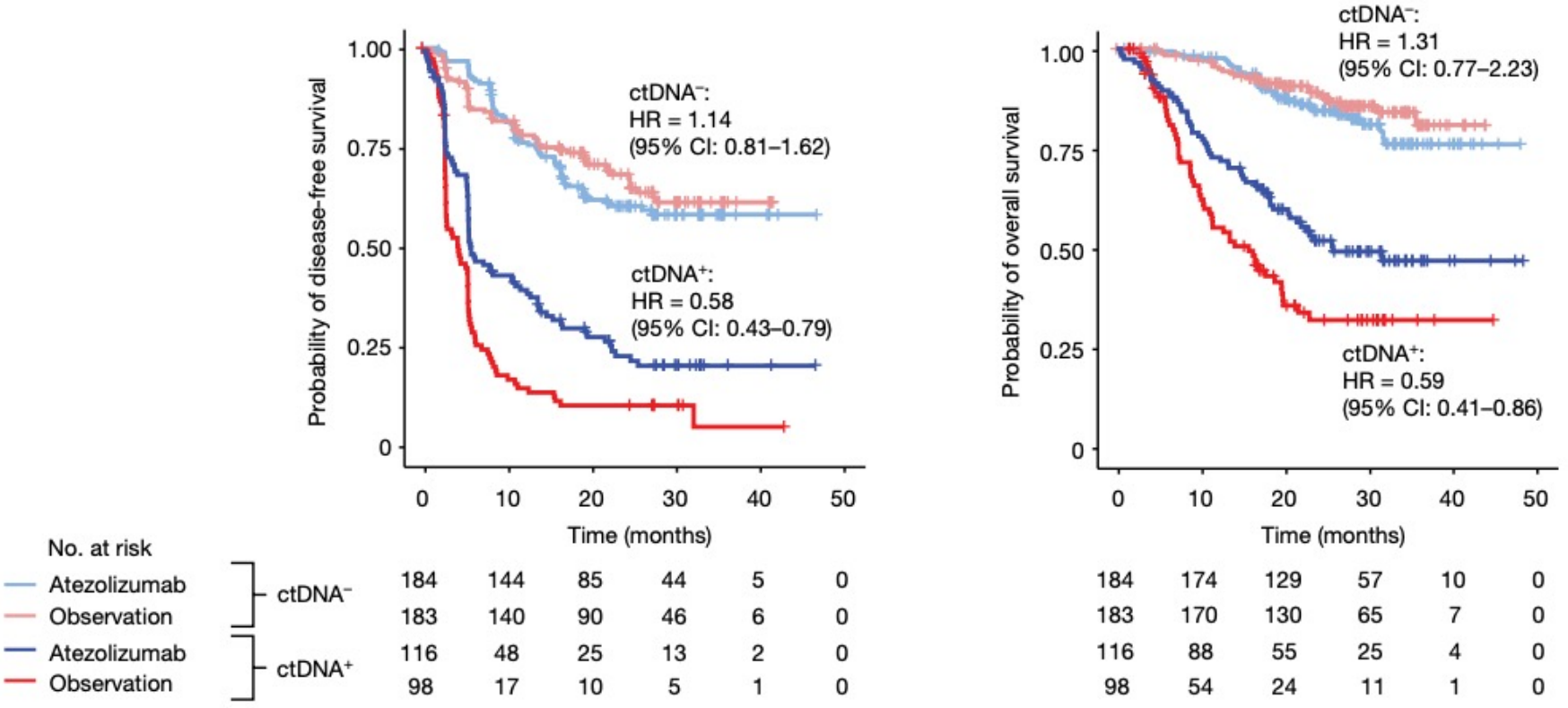
Article | Published: 16 June 2021

ctDNA guiding adjuvant immunotherapy in urothelial carcinoma

Thomas Powles ✉, Zoe June Assaf [ ], Sanjeev Mariathasan ✉

Minimally invasive approaches to detect residual disease after surgery are needed to identify patients with cancer who are at risk for metastatic relapse. Circulating tumour DNA (ctDNA) holds promise as a biomarker for molecular residual disease and relapse[1]. We evaluated outcomes in 581 patients who had undergone surgery and were evaluable for ctDNA from a randomized phase III trial of adjuvant atezolizumab versus observation in operable urothelial cancer. This trial did not reach its efficacy end point in the intention-to-treat population. Here we show that ctDNA testing at the start of therapy (cycle 1 day 1) identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm hazard ratio = 6.3 (95% confidence interval: 4.45–8.92); $P < 0.0001$). Notably, patients who were positive for ctDNA had improved disease-free survival and overall survival in the atezolizumab arm versus the observation arm (disease-free survival hazard ratio = 0.58 (95% confidence interval:



MRD product pipelines

Tumor-agnostic and tumor-informed products under parallel development

	Assay and Model Development	Analytical Validation	Clinical Validation (Prognosis and Surveillance)	Product Launch
Tumor-informed	Completed Personalized assay: brPROPHET Target limit-of-detection (LOD): 4E-5		Lung read-out: 1H2022, Colon / Esophageal / Gastric read-out: 2022 Interventional studies under planning	1H2022
Tumor-agnostic	Completed Mutation-based: high-spec + low-sens Methylation-based: high-sens + low-spec		Mutation-based complete (lung/colon) Methylation-based ongoing	

Recent Trends in MRD Recognition and Adoption in China

- MRD recommended for relapse-risk prediction for early-stage NSCLC patients by the 2021 *Chinese Lung Cancer Clinician Consensus*
- MRD technology is required to demonstrate an LOD lower than 2E-4
- Some clinicians and pharma companies are exploring MRD-driven patient-selection or dose/treatment-plus/minus adjuvant therapy studies
- Most NGS companies only offer mutation panel-based liquid biopsy assays, with sub-optimal sensitivity for MRD utility

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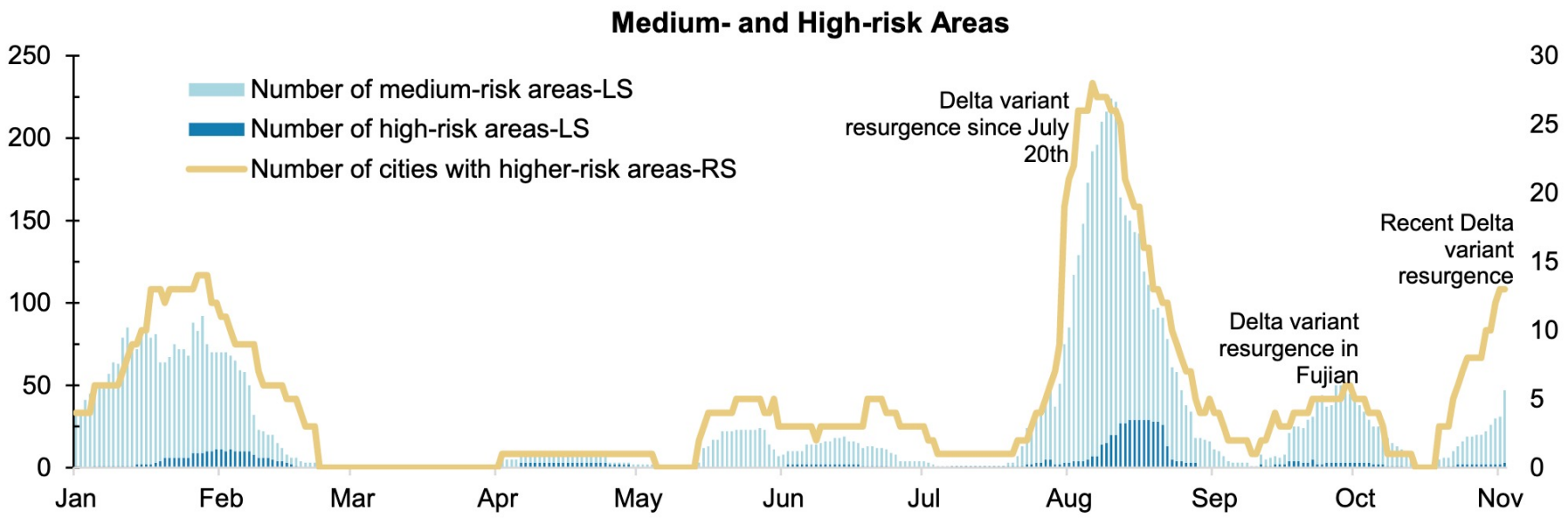
Financials

Travel restrictions impacting volumes due to ‘zero-case’ approach in China

August saw significant impact from a delta-variant resurgence

Currently in the middle of another wave as of 16th November

Number of cities affected[1]



Examples of Covid impact

- School closures in Beijing, Shanghai; suspension of all out-bound travel in Shijiazhuang (Jan)
- Quarantine of residents, school closures in Guangzhou (May)
- Cancellation of trains, flights to Beijing; no hotel booking permitted for travelers from higher-risk cities in Beijing (Aug)

Note:

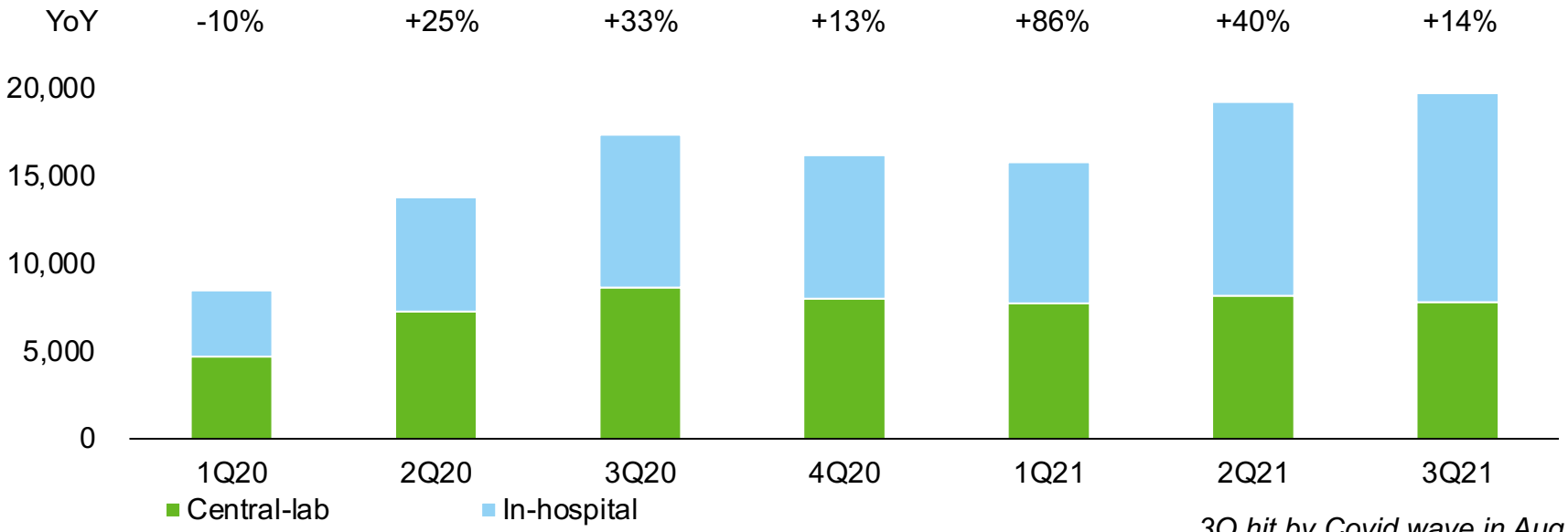
[1] Daily designations by the National Health Commission, where medium and high-risk districts within a city were called out.
Residents from high-risk districts are typically placed with quarantine requirements.
Residents from medium-risk districts face travel restrictions and quarantine requirements as specified by local and designation cities.

Accelerated transition towards in-hospital during 2021

Industry-leading overall volume growth, +38% during 9M21

In-hospital volume contribution reaching above 50% since 2Q21

Therapy selection volumes[1]



3Q hit by Covid wave in Aug

YoY growth resumed in Sep and Oct

In-hospital our strategic focus

We see in-hospital as the future for late-stage patient testing business

- ✓ Testing performed within hospital, patient paying to the hospital, conforming to typical norm in China
- ✓ Sticky, institutionalized relationship with the hospital
- ✓ Stronger competitive differentiation with product performance playing a larger role
- X Lower unit price per test vs. central-lab model, leading to lower blended ASP while we transition towards more in-hospital

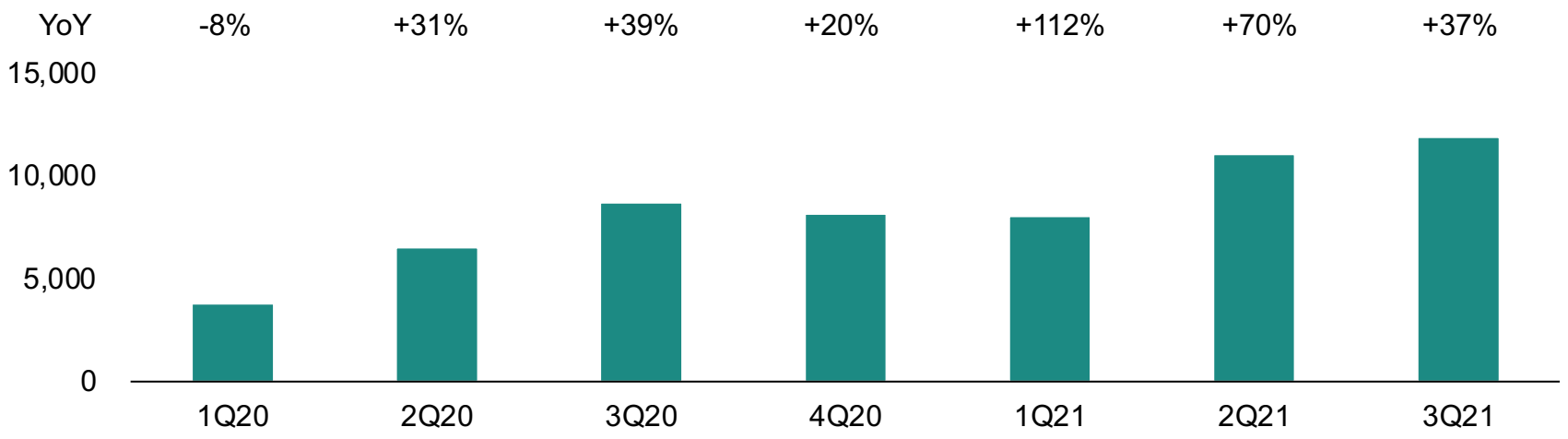
Notes:

[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

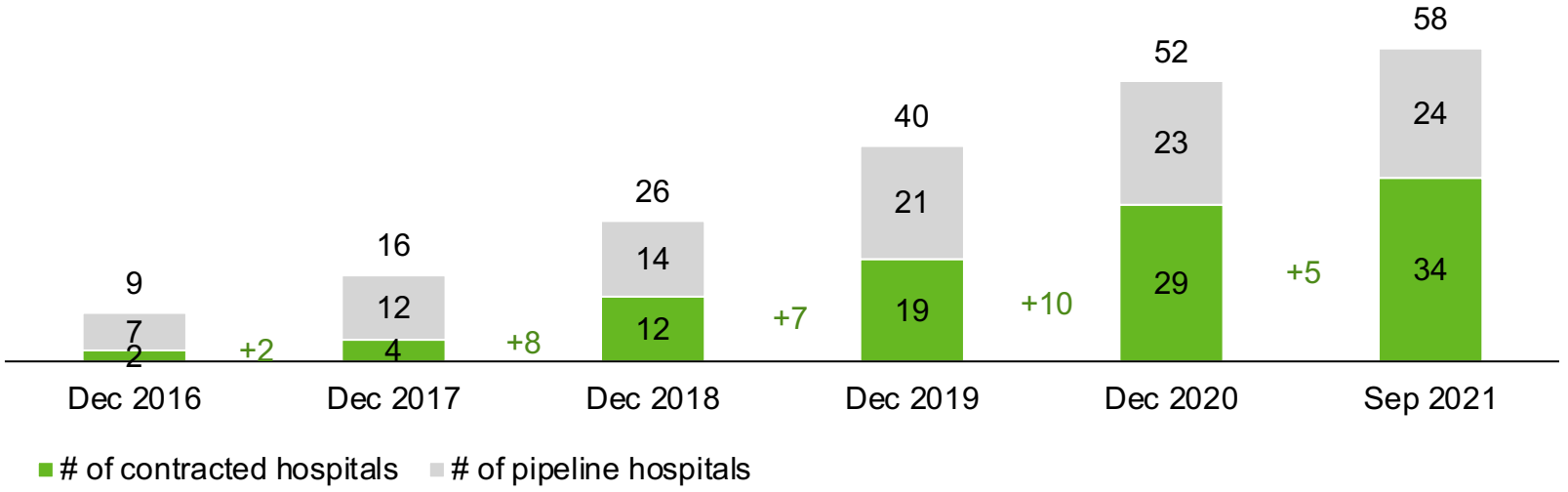
In-hospital segment

Dominant market share, industry-leading growth rate
Resilient volumes in 3Q despite Covid impact

Number of testing kits shipped to partner hospitals[1]



Number of partner hospitals



Notes:
[1] Excludes kits for validation, training and other purposes
In-hospital primarily through direct-sales model

Central-lab segment

Subject to Covid fluctuations and LDT regulatory uncertainty in China

Central-lab volumes

	2018	2019	2020	1Q20	2Q20	3Q20	4Q20	1Q21	2Q21	3Q21
# of ordering hospitals	263	335	312	232	284	289	294	303	300	287
# of ordering physicians	1,135	1,632	1,318	810	1,175	1,194	1,114	1,082	1,013	920
# of patients tested[1]	15,821	23,075	25,262	4,680	7,252	8,644	7,989	7,716	8,155	7,808
YoY	*67%*	*46%*	*9%*	*-12%*	*20%*	*28%*	*5%*	*65%*	*12%*	*-10%*
QoQ					*55%*	*19%*	*-8%*	*-3%*	*6%*	*-4%*

LDT regulation

- Lack of clear regulations historically, resulting in low entry-barrier and low-quality competition
- Increasing regulatory focus, *Regulations on the Supervision and Administration of Medical Devices*[2] (effective Jun 2021) provides clear space for LDT where there is no approved IVD product, within qualified medical institutions. Currently pending implementation rules, with drafting led by NMPA. NMPA rule-making a key further step towards regulating the NGS testing industry, establishing clear entry barrier

Note:

[1] A patient who took multiple tests in different quarters of a given year is counted only once for that year

[2] "医疗器械管理条例", 第五十三条 对国内尚无同品种产品上市的体外诊断试剂，符合条件的医疗机构根据本单位的临床需要，可以自行研制，在执业医师指导下在本单位内使用。具体管理办法由国务院药品监督管理部门会同国务院卫生主管部门制定

Financials

Strong volume growth (+38% in 9M21) but transient impact on blended ASP during transition to in-hospital 3Q21 impacted by Covid surge in August

RMB millions	2019	2020	*18 YoY*	*19 YoY*	*20 YoY*	1Q20	2Q20	3Q20	4Q20	1Q21	2Q21	*3Q21*	*3Q21 YoY*	*3Q21 QoQ*	2021 Guide
Revenue	**381.7**	**429.9**	***88%***	***83%***	***13%***	**67.3**	**107.0**	**123.9**	**131.7**	**106.6**	**127.3**	**126.6**	***2%***	***-1%***	Around **500**
Central lab	276.3	297.3	*83%*	*71%*	*8%*	46.1	74.6	89.9	86.7	74.6	80.0	78.8	*-12%*	*-2%*	
In-hospital[1]	87.7	117.9	*209%*	*164%*	*34%*	17.1	27.6	31.7	41.5	29.0	40.5	43.7	*38%*	*8%*	
Pharma	17.7	14.7	*15%*	*25%*	*(17%)*	4.1	4.8	2.3	3.6	3.1	6.8	4.1	*79%*	*-40%*	
Gross profit	**273.3**	**313.9**	***88%***	***102%***	***15%***	**44.8**	**78.4**	**91.6**	**99.2**	**76.9**	**90.2**	**91.6**	***0%***	***2%***	
Total opex	**442.4**	**726.3**	***54%***	***49%***	***64%***	**104.1**	**151.4**	**216.2**	**254.6**	**248.8**	**292.3**	**262.7**	***22%***	***-10%***	
R&D[2]	147.5	214.1	*114%*	*43%*	*45%*	37.9	45.9	58.7	71.6	55.0	87.2	79.2	*35%*	*-9%*	
S&M[2]	152.0	165.1	*52%*	*49%*	*9%*	29.6	37.5	43.9	54.2	52.5	65.2	74.7	*70%*	*15%*	
G&A[2]	120.8	174.6	*18%*	*40%*	*44%*	32.6	40.6	44.9	56.5	56.9	56.8	55.5	*24%*	*-2%*	
SBC[3]	22.1	172.5				4.0	27.4	68.7	72.3	84.4	83.0	53.3			
Operating profit	(169.1)	(412.4)				(59.3)	(73.0)	(124.6)	(155.4)	(171.9)	(202.0)	(171.1)			
GP margin	**71.6%**	**73.0%**				**66.5%**	**73.3%**	**73.9%**	**75.3%**	**72.2%**	**70.9%**	**72.3%**			
Opex / revenue	116%	169%				155%	142%	175%	193%	233%	230%	208%			
S&M / revenue	40%	39%				44%	36%	36%	43%	52%	53%	61%			

Notes:

[1] Within in-hospital segment, over 95% revenues are kit revenues, which are recurring in nature; the remaining are instrument revenues. In-hospital primarily through direct-sales model

[2] Excluding share based compensation (SBC)

[3] Share based compensation

Summary outlook and catalysts

	Growth driver	Catalyst	Metrics
Near-term	• Therapy selection volume growth through in-hospital taking share, out-growing industry		• IVD kit volume • New hospital add backlog
Medium-term	• Early detection commercialization in 2022		• Product revenues
	• MRD launch in 2022	• Data read-out in 2022	
	• Biopharma, international growth ex. China	• Additional wins of global studies	• Project backlog
Long-term	• Early detection product upgrade	• 9-cancer test first read-out in 2022, 22-cancer in 2024	
	• Early detection product regulatory approval	• Launch of large validation study	
	• Therapy selection IVD entry barrier	• NMPA approvals of OncoCompass™ ctDNA and OncoScreen™ CGP[6] tissue panels	

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Appendix 1

Early detection

ESMO Asia mini-oral presentation, Nov 2020

Overview of training and validation sets

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

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

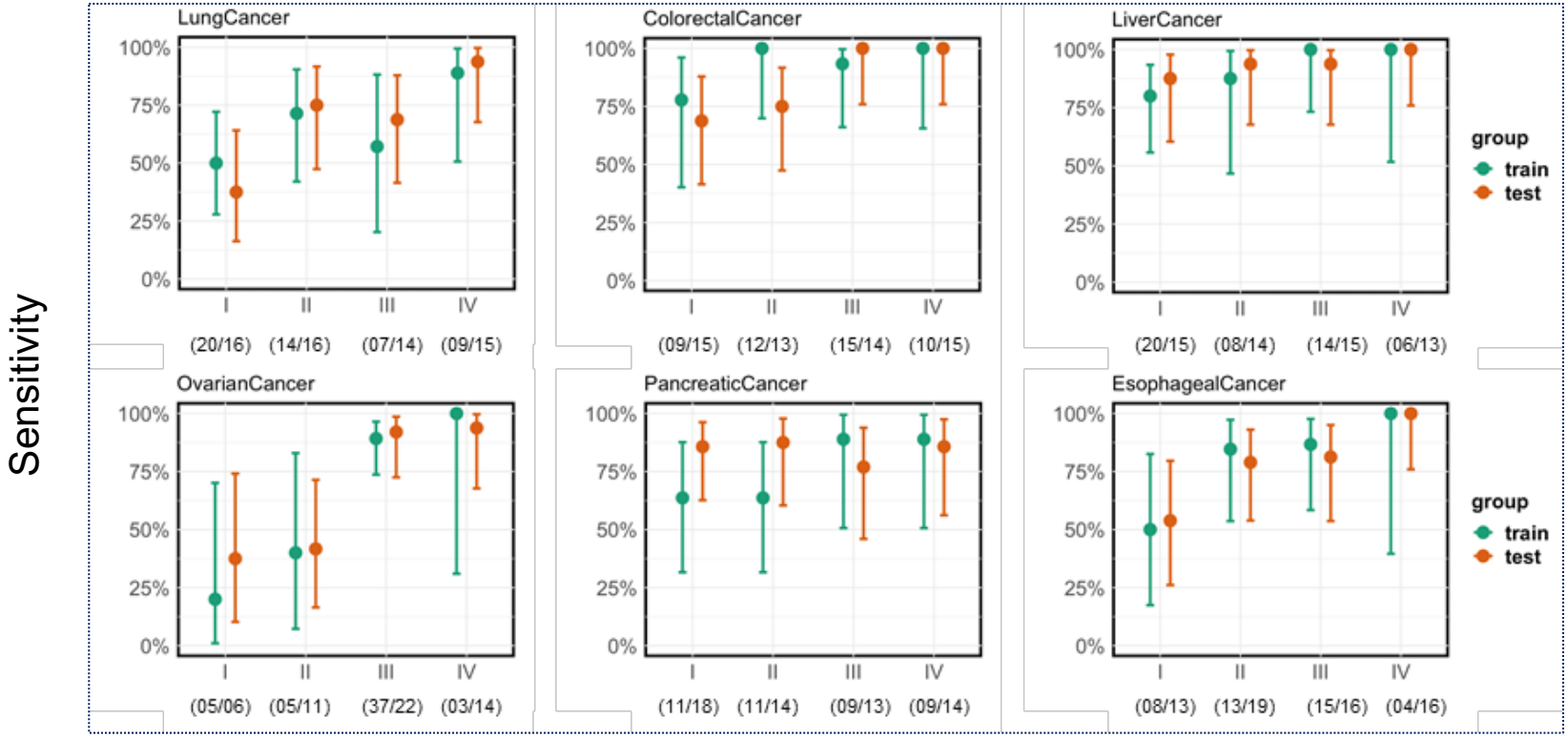
1. Similar age distribution between cases and controls, and between training set and validation set
2. Balanced sample size among different stages and cancer types

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

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

ESMO Asia mini-oral presentation, Nov 2020

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



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

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

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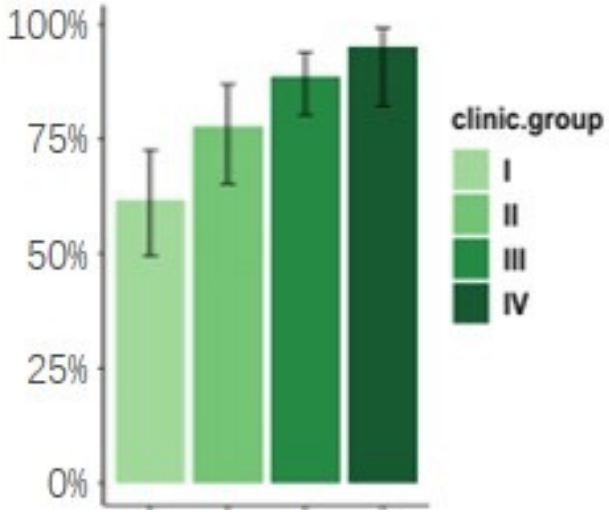
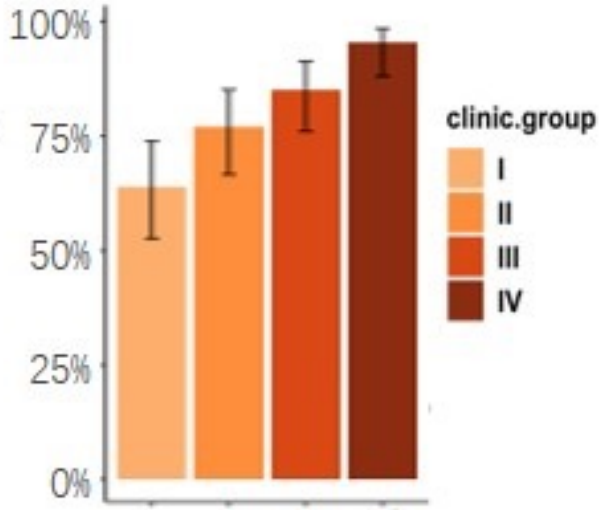
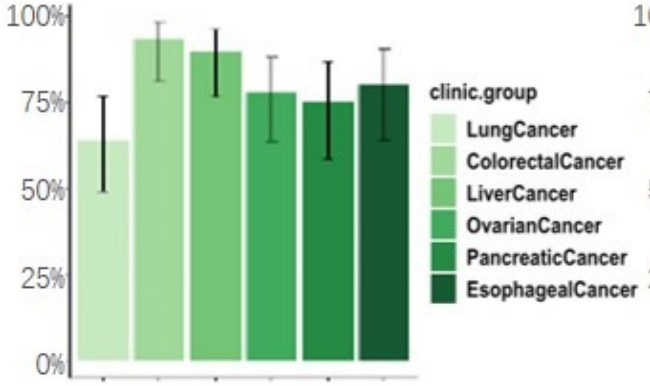


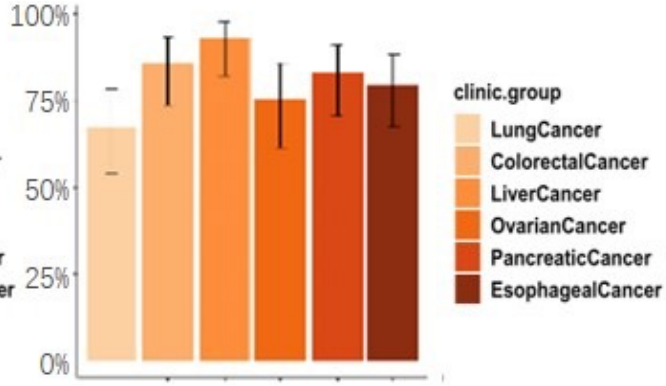
Training



Validation



Training

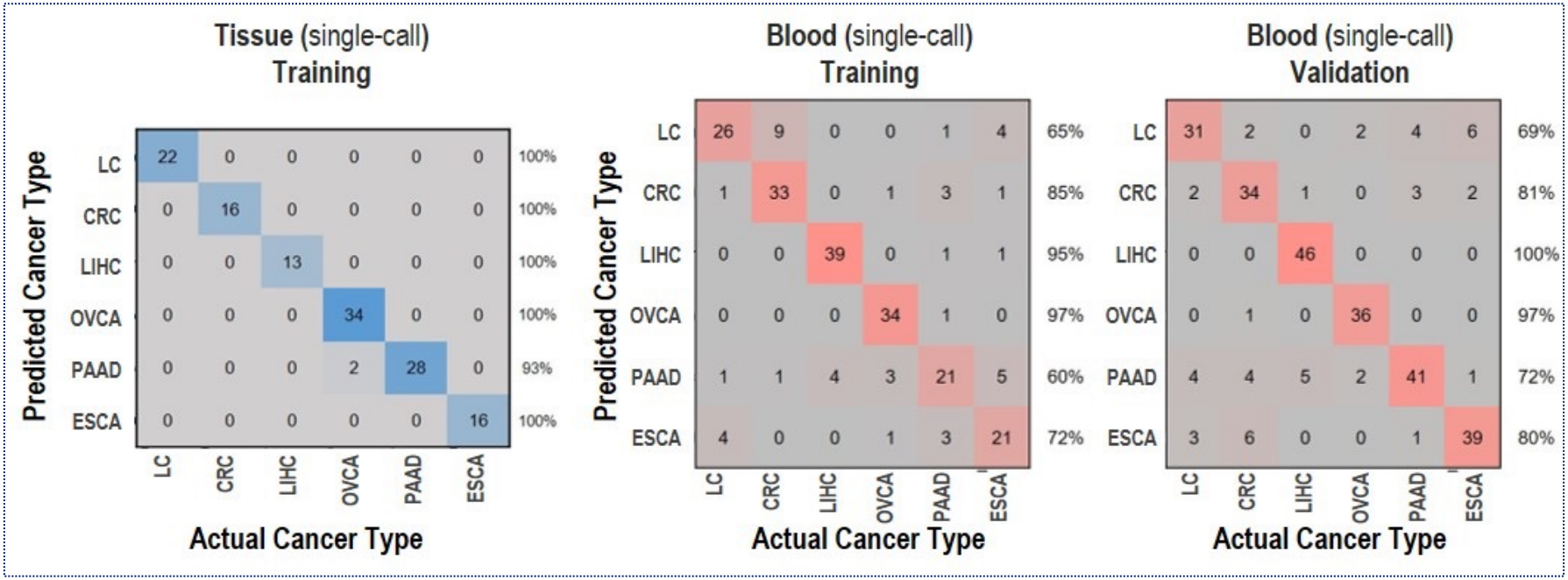


Validation

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

ESMO Asia mini-oral presentation, Nov 2020

Our test predicts the tissue of origin with high accuracy



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

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

ESMO Asia mini-oral presentation, Nov 2020

6-cancer test sensitivity by cancer type and stage

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

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

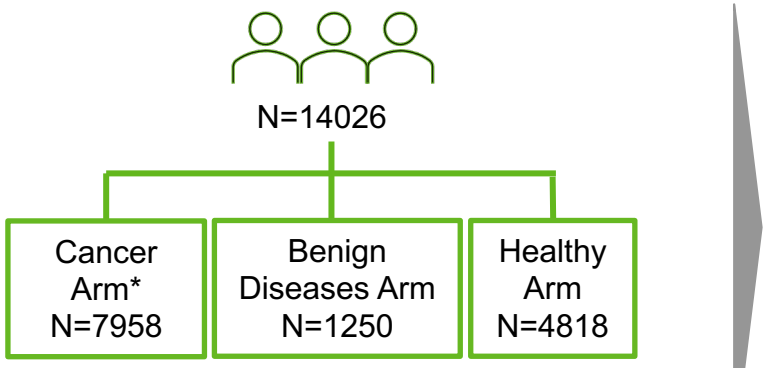
Source: Qiang Gao et al., LBA3 Early detection and localization of multiple cancers using a blood-based methylation assay (Elsa-seq), ESMO Asia Virtual Congress 2020, Nov 2020

The PREDICT study (NCT04817306)

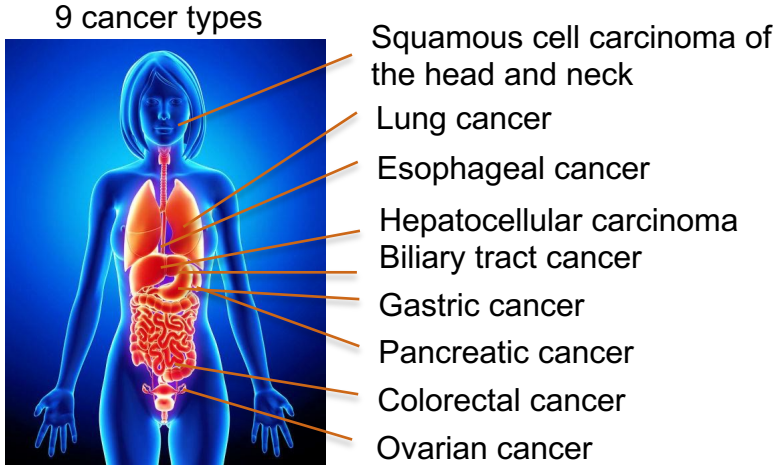
Study design

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

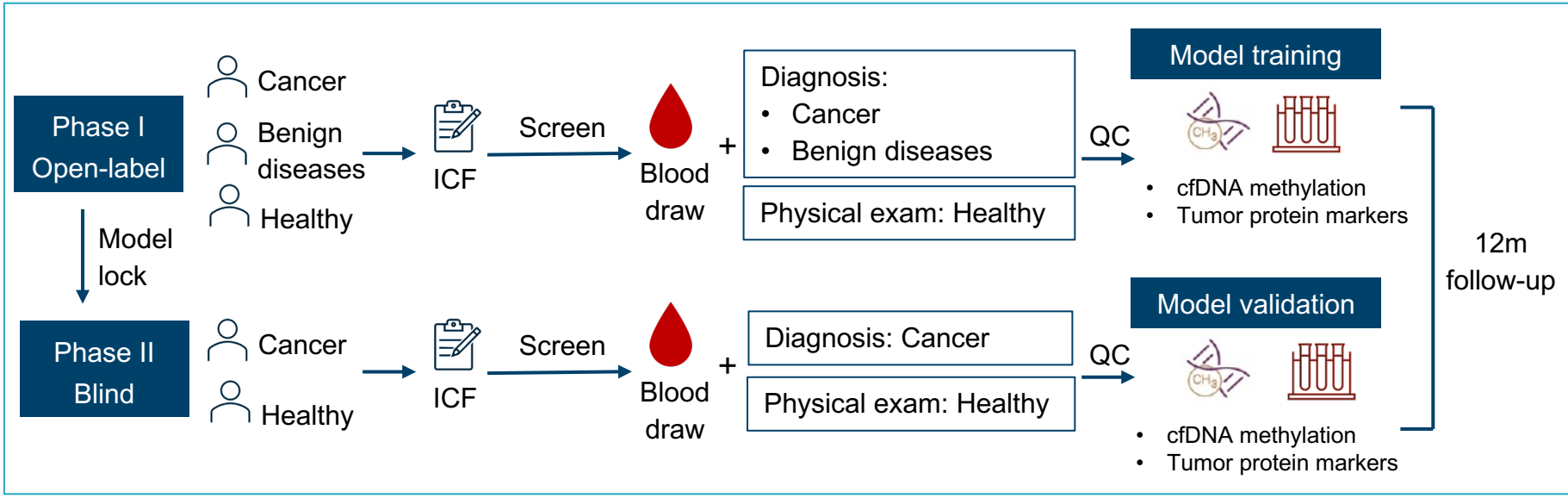
Participants



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



Study Design



The PREDICT study (NCT04817306)
Objectives and timeline

Objectives

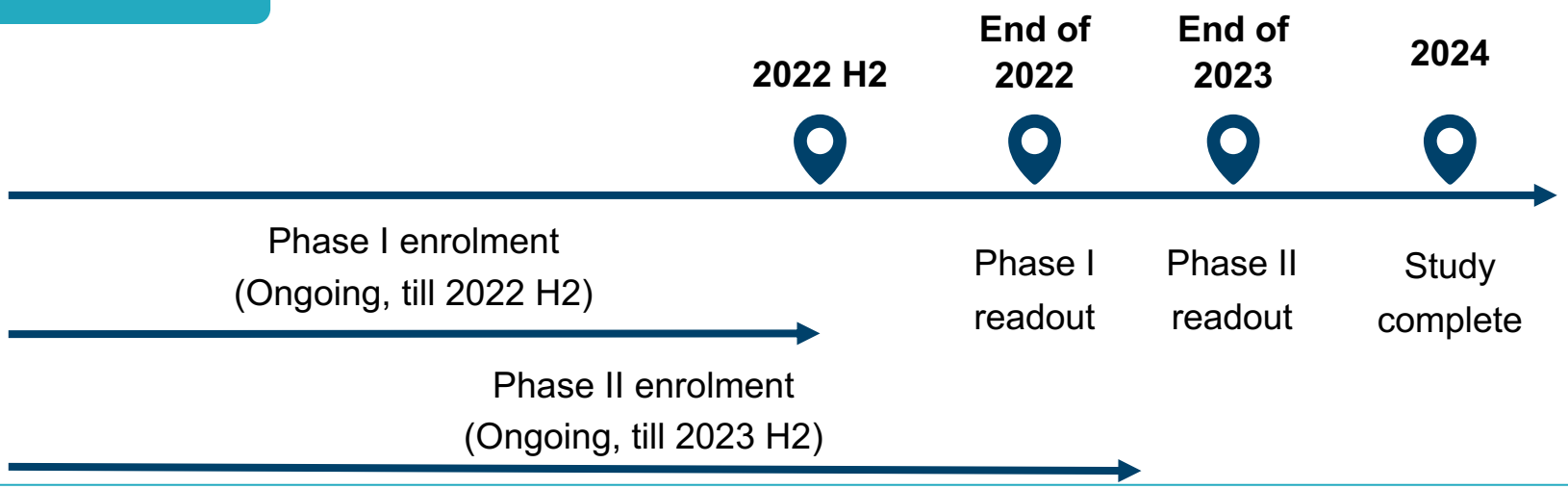
Primary objective:

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

Key secondary objectives:

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

Timeline



Note: TOO, tissue of origin

The PREDICT study (NCT04817306)

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

The PRESCIENT study (NCT04822792)

Study design

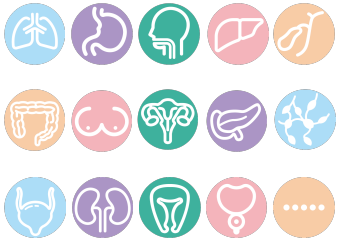
PRESCIENT is a *prospective, multi-center, case-control, observational* study aimed to train and validate the performance of a multi-omics model in the detection of 22 cancers

Participants

N=11879

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

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



22 cancer types

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

Study Design

Cancer
Benign diseases
Healthy

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

- cfDNA methylation
- Tumor protein markers
- Other omics biomarkers

The PRESCIENT study (NCT04822792)
Objectives and timeline

Objectives

Primary objective

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

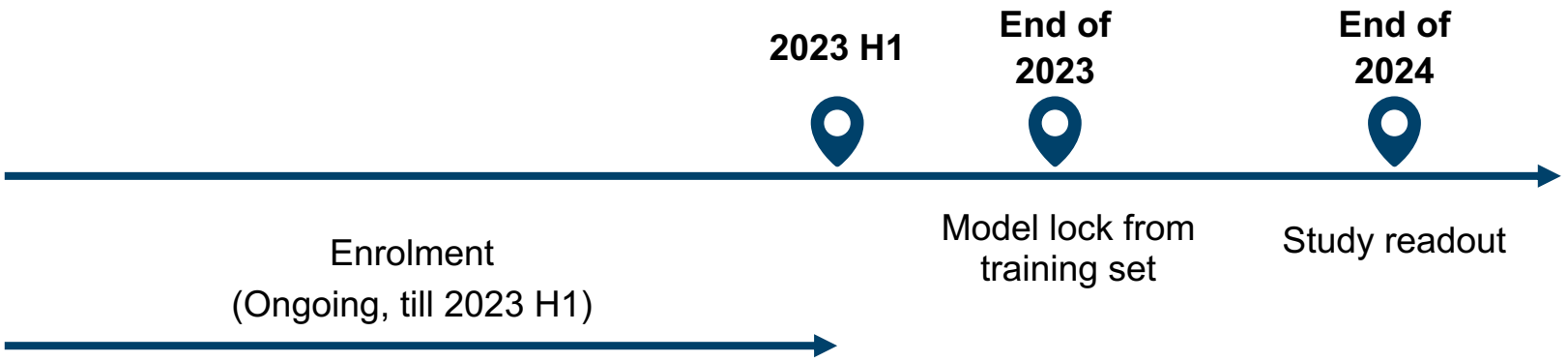
Secondary objective

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

Exploratory objective:

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

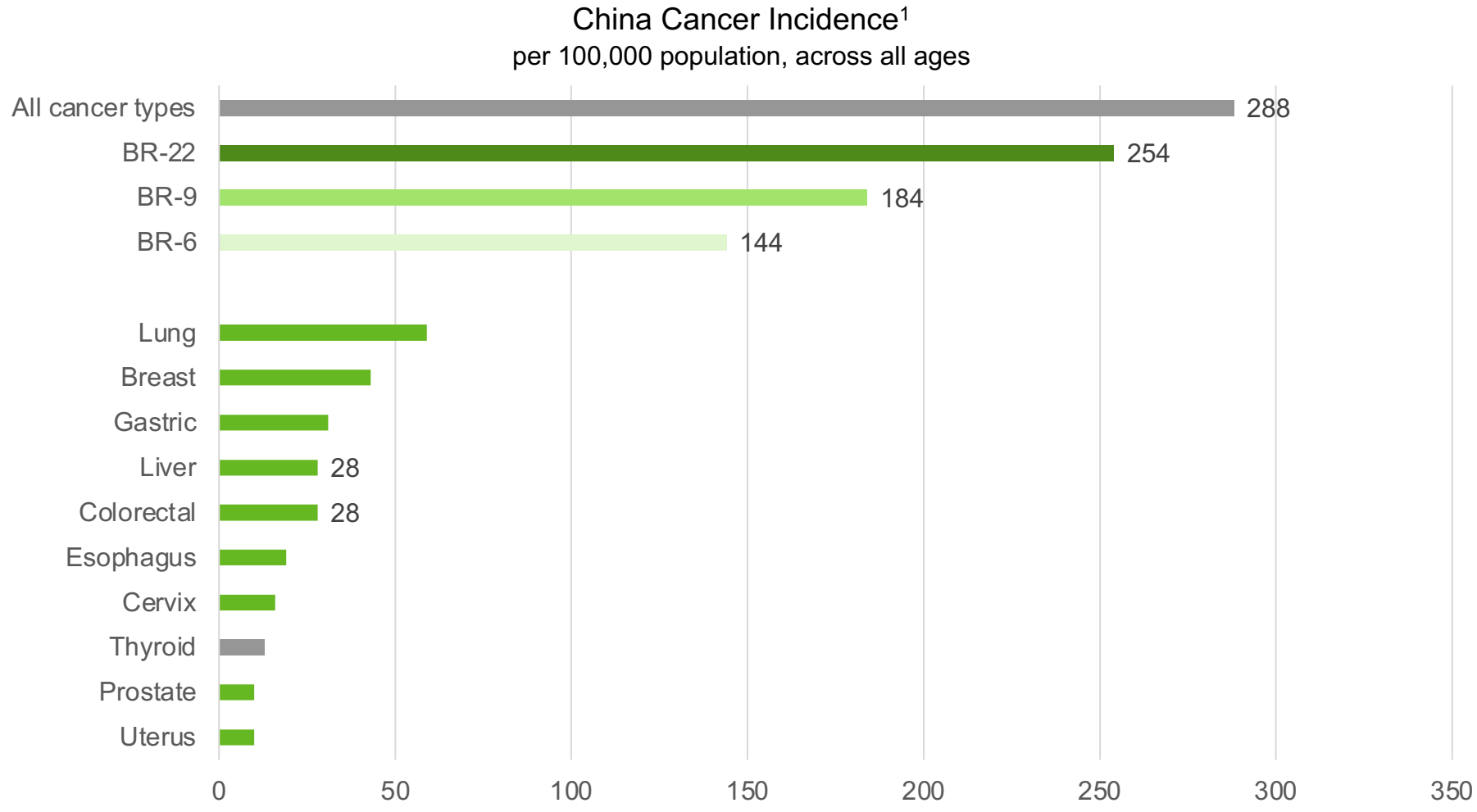
Timeline



Note: TOO, tissue of origin

Multi vs. single cancer early detection

Multiple times larger TAM



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

Notes:

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

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

Multi vs. single cancer early detection in China

Significantly higher technology barrier

Single-cancer test

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

Multi-cancer test

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

燃石医学
Burning Rock Dx

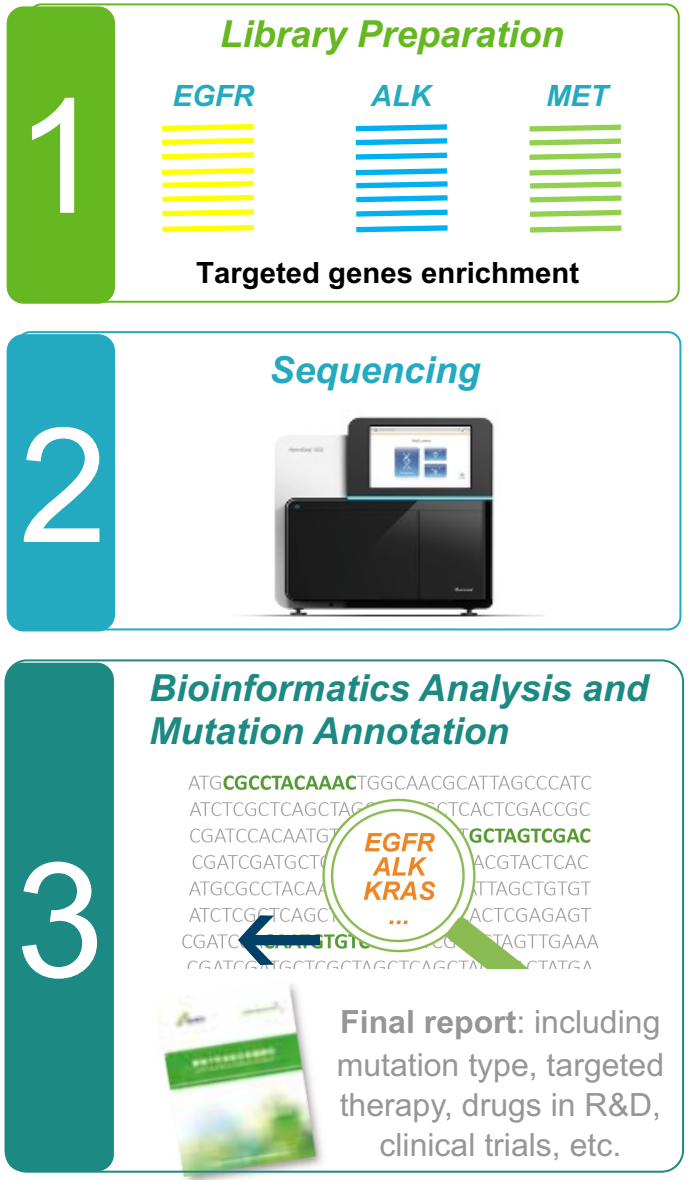
Appendix 2

Therapy selection

NGS testing

Diagnostics companies focus on steps 1 and 3

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



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

Demonstrated in high-impact analytical validation study

SEQC2 Study Overview

MAQC/SEQC Consortium Projects – An Overview

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


Guidance for Industry
Pharmacogenomic Data Submissions — Companion Guidance

Issues and Study Objectives

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

of ctDNA

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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

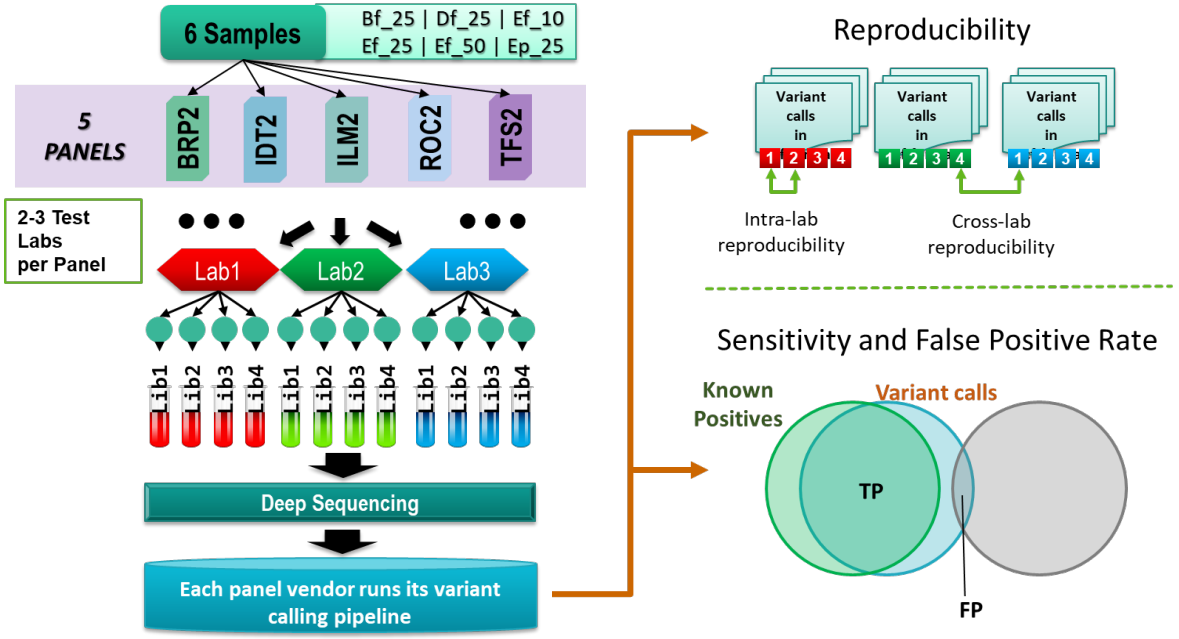
TFS2

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

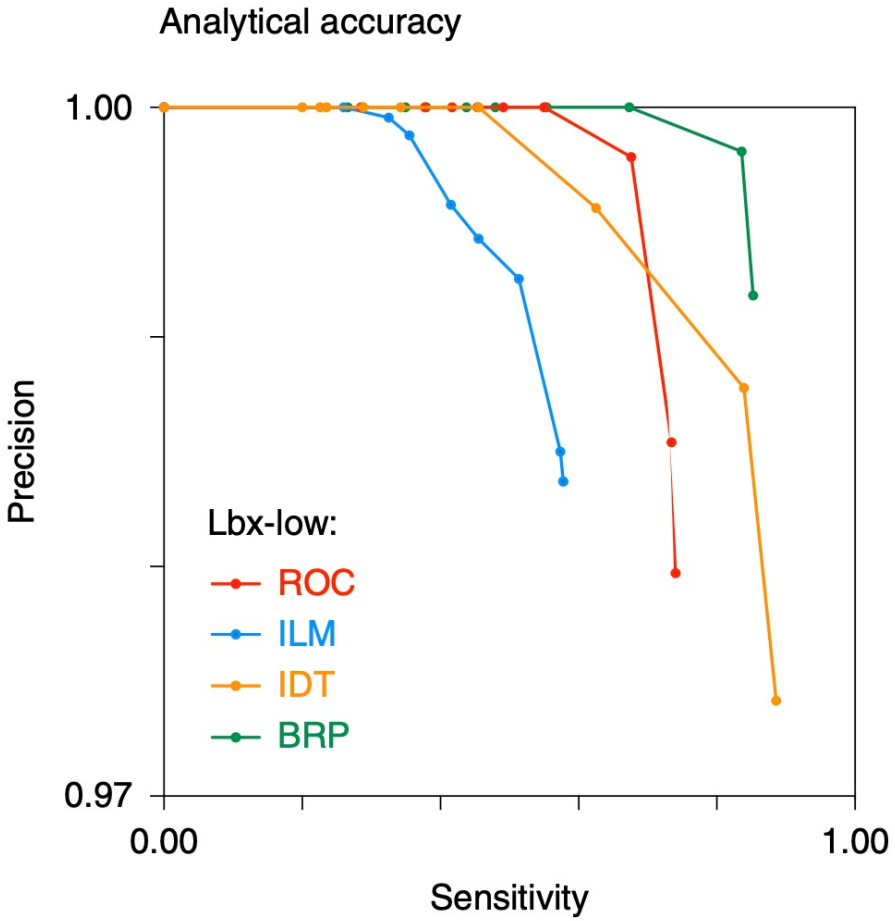
Participating assays and study design

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



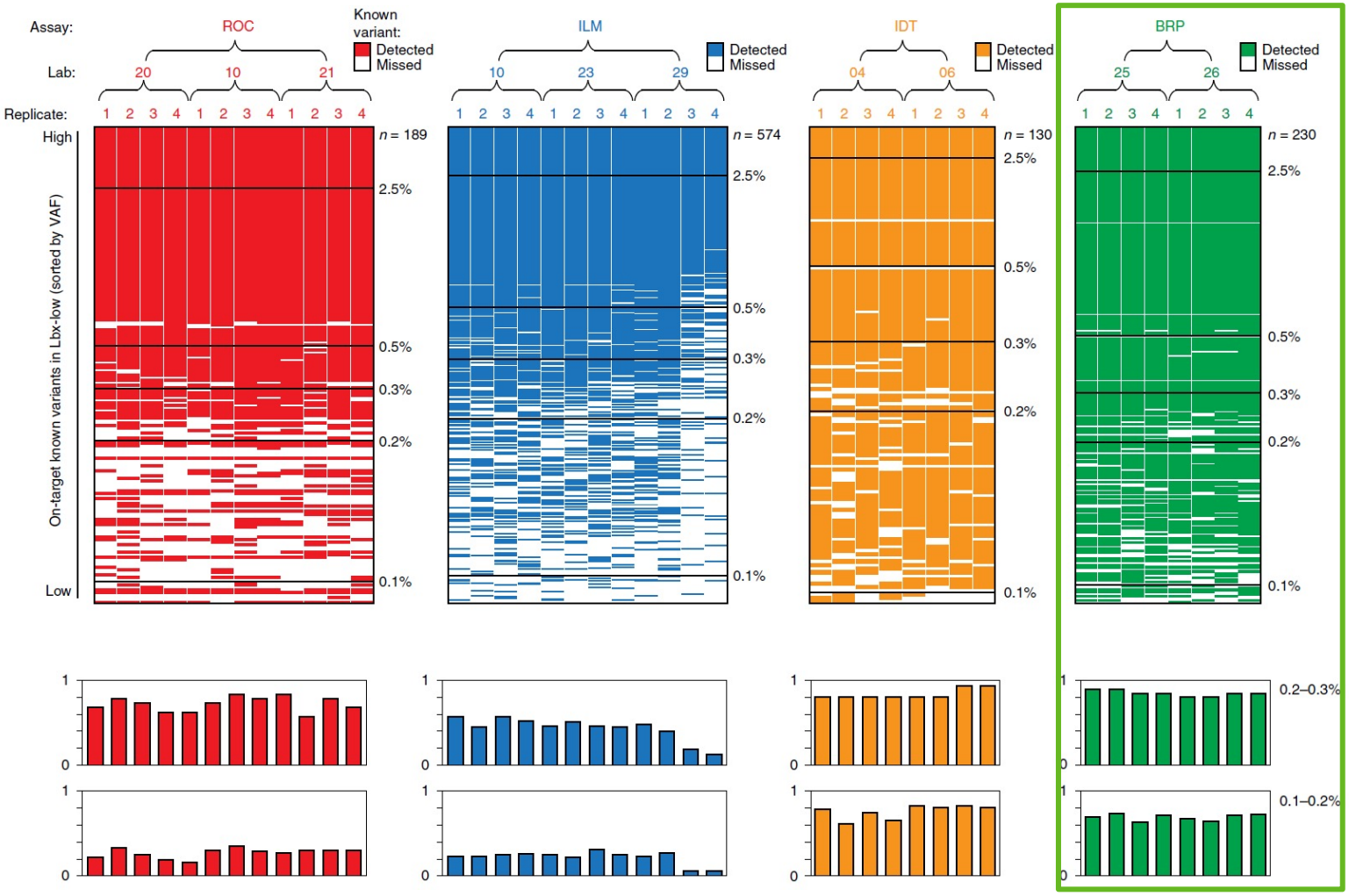
Assay	Known negatives (kb)	FPs per replicate (mean [range])	FP-rate (FP / kb) at specified VAF threshold > 0%	> 0.1%	> 0.5%
ROC	47.1	2.91 [1-6]	0.061	0.044	0.000
ILM	133	5.25 [2-10]	0.039	0.039	0.008
IDT	39.3	2.75 [0-6]	0.070	0.057	0.000
BRP	53.4	1.65 [0-5]	0.030	0.007	0.000

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