

第30回 抗悪性腫瘍薬開発フォーラム

世界・アジアをリードする日本からの臨床開発～3密（産官学&知行果）を目指して～』

第二部 世界におけるアジアのリーズナブルなポジショニング

ゲノムを含むデータ連携について～研究者の目線から～ スクラム・ジャパンの歩みからの展望

From 'MAY BE' to 'MUST BE'

吉野 孝之

国立がん研究センター東病院 消化管内科 科長

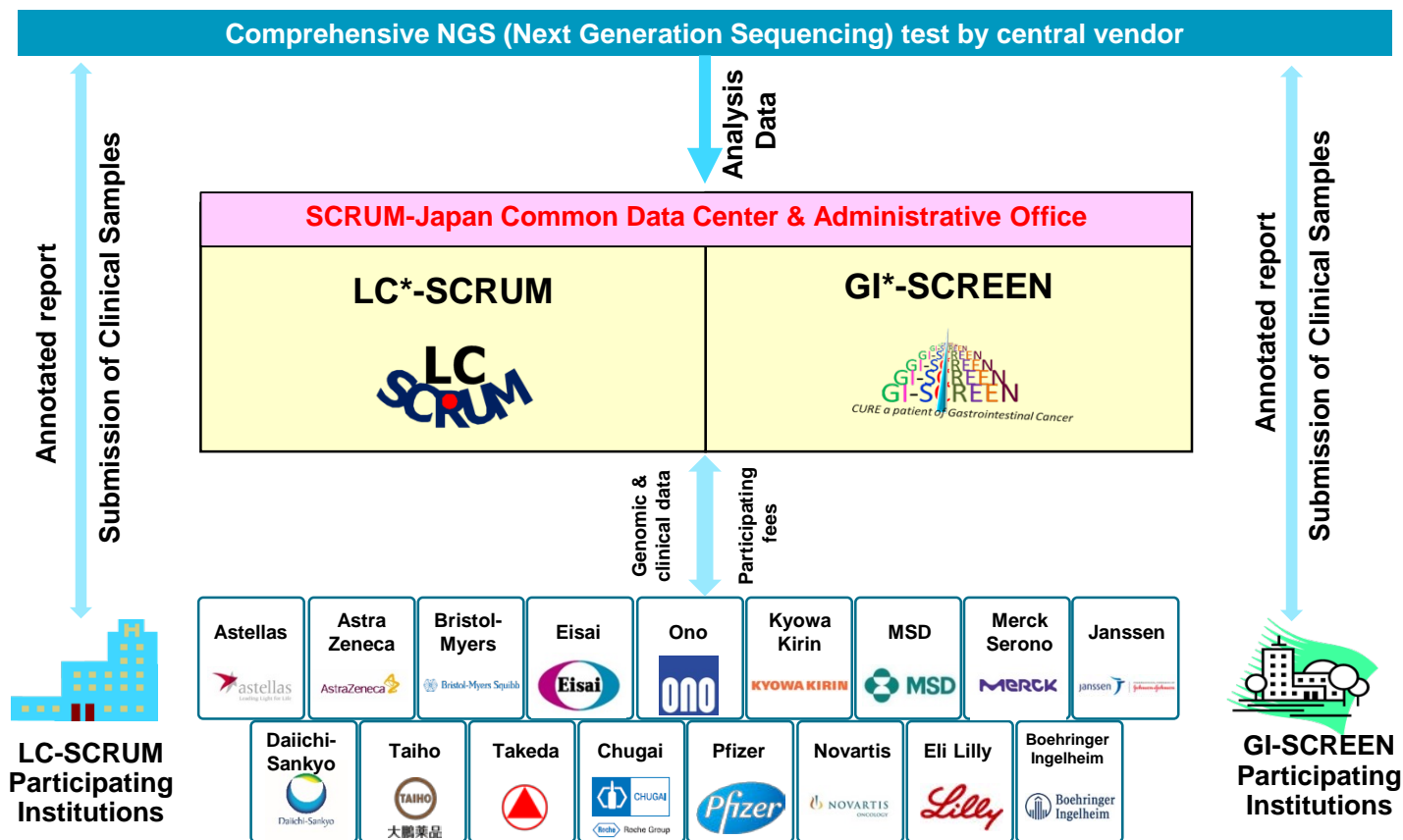


Feb 13th, 2021

Agenda

- **PAST to Present: Achievement of the SCRUM-Japan**
 - **Tissue NGS* Screening (SCR) and stratified clinical trials**
 - **Data Base (DB)**
 - **Liquid Bx SCR and stratified clinical trials**
 - **International Collaboration**
- **TODAY: Ongoing innovative projects**
 - **Liquid Bx & Microbiome (MB)**
 - **Artificial intelligence /Machine Learning (AI/ML)**
 - **CIRCULATE-Japan (C-J) and Early Detection (COSMOS)**
- **TOMORROW: Translating Multi-Omics into Clinical Utility**

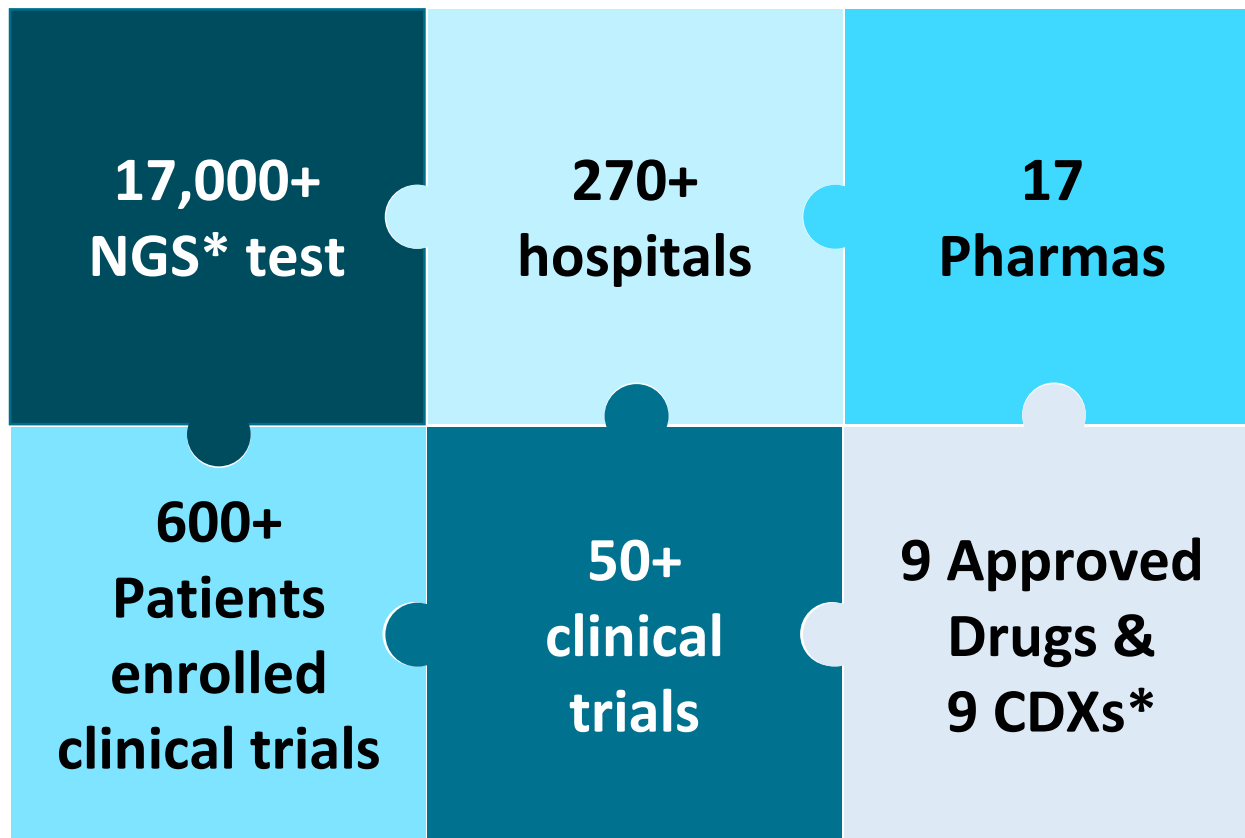
SCRUM-Japan Project Since 2015



Accomplishment of SCRUM-Japan so far

On-time clinico-pathologic-genome data sharing with academia & Pharmas

As of July 2020



GI-SCREEN
GI-SCREEN
GI-SCREEN
CURE a patient of Gastrointestinal Cancer

MONSTAR

**LC
SCRUM**

Co-PIs, Takayuki Yoshino (GI-SCREEN) and Koichi Goto (LC-SCRUM)

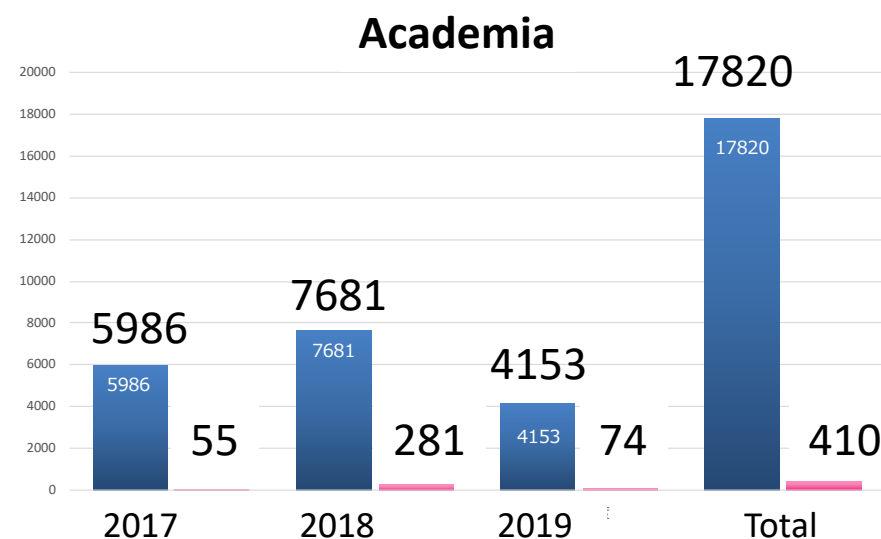
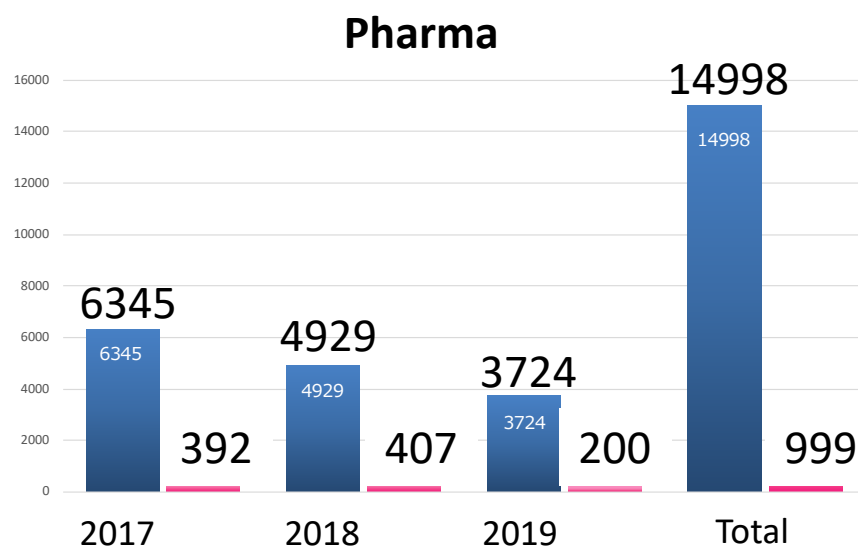
**Notes;*
NGS, Next Generation
Sequencing; CDX, companion
diagnostic test



Update on Yoshino T, et al. Oral presentation at Google Cloud Next '19 in San Francisco
https://www.youtube.com/watch?v=iO4x1aJw_Jc

Comparison of key elements between NCI-MATCH and SCRUM-Japan

	NCI-MATCH (US)	SCRUM-Japan
funding	Public grant	Public grant/industry budget
Starting year	2015	2015
NGS panel	commercial (OCP/OCA)	commercial (OCP/OCA)
Study type	IIT	IIT+SIT
Study enrollment from the screening platform	Closed	Open platform
No. of studies	40	56 (incl. 20 IIT)
Target tumors	All solid tumors	All solid tumors
No. of enrollment(11/2018)	6,000	17,000+
Rate for study enrollment	5%	3%
No. of completed studies	11	29
No. of agents approved	1	9
Clinical/genome data sharing	none	66 acad. ctrs. and 17 industries
Liquid biopsy screening	Not yet	Ongoing
Regulatory-grade registry	Not yet	Ongoing
Microbiome	Not yet	Ongoing

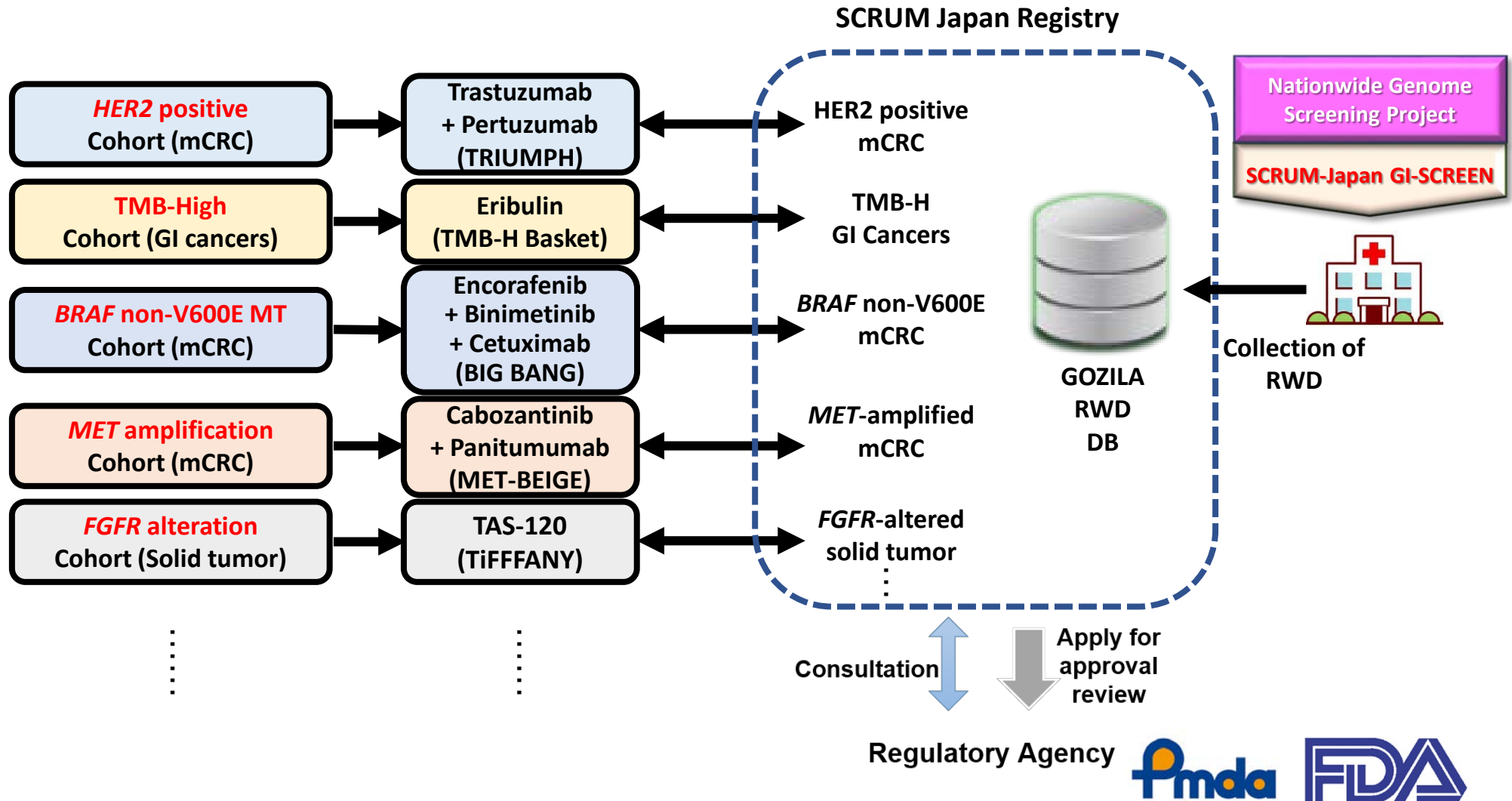
On-time clinico-pathologic-genome data sharing; Number of accesses/number of data downloads



 No. Assesses
 No. DLs

Utilization of Real World Data

Comparison of Endpoints in Each Sub-study with Data in SCRUM Japan Registry



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SCRUM-Japan ctDNA Screening Platform

As of Dec 2020



GOZILA

N= 3572

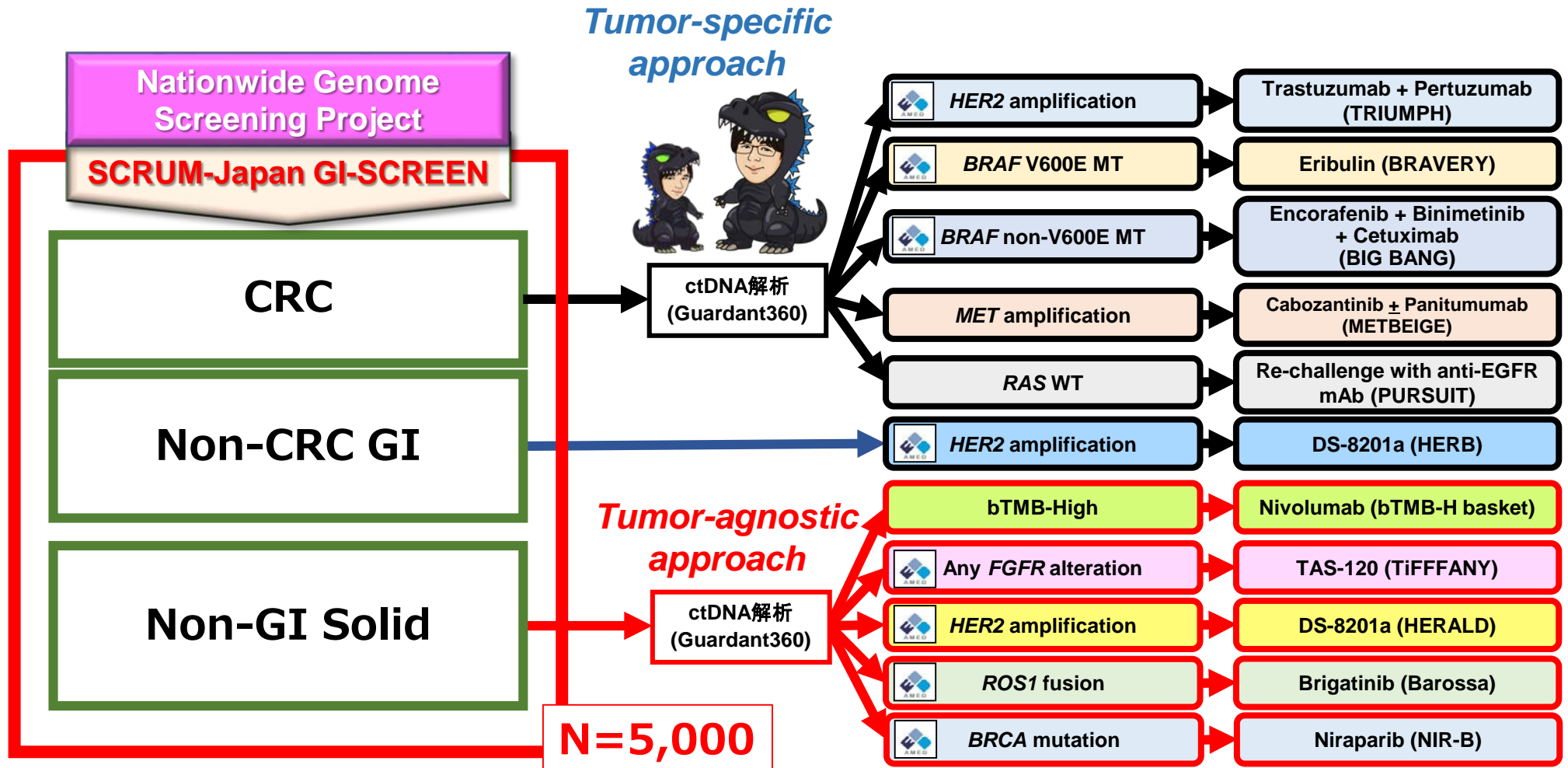
Stage IV GI Cancers mainly
Since Jan 2018

MONSTAR

N= 1237

Stage IV solid tumors
Since July 2019

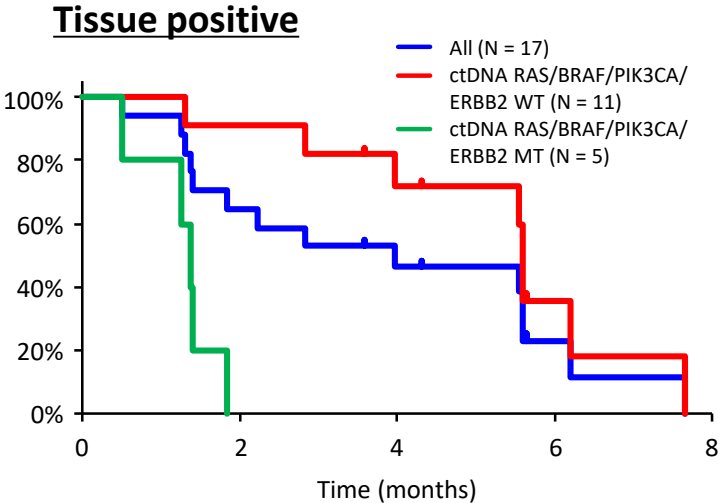
Ongoing Clinical Trials





TRIUMPH; PROGRESSION-FREE SURVIVAL WITH TRASTUZUMAB AND PERTUZUMAB

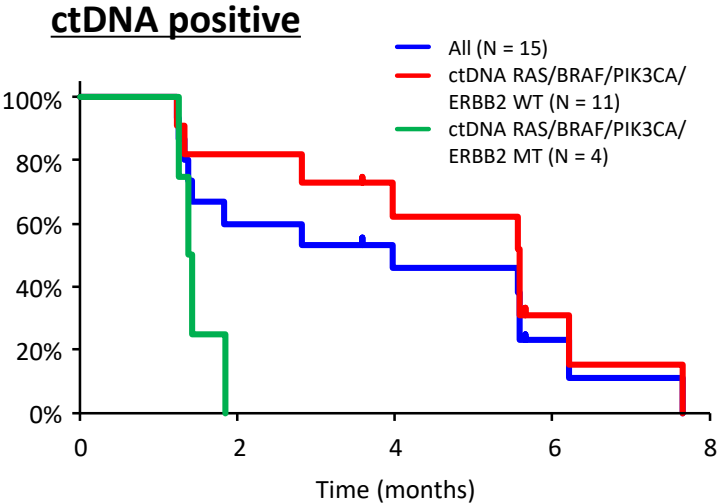
Liquid Bx SCR



No. at Risk				
All*				
17	11	7	2	0
Quadruple WT				
11	10	7	2	0
Any MT				
5	0	0	0	0

* Including one patient without a ctDNA result

	Median PFS, months (95% CI)
All	4.0 (1.4-5.6)
ctDNA RAS/BRAF/PIK3CA/ERBB2 WT	5.6 (2.8-7.7)
ctDNA RAS/BRAF/PIK3CA/ERBB2 MT	1.4 (0.5-1.8)



No. at Risk				
All				
15	9	6	2	0
Quadruple WT				
11	9	6	2	0
Any MT				
4	0	0	0	0

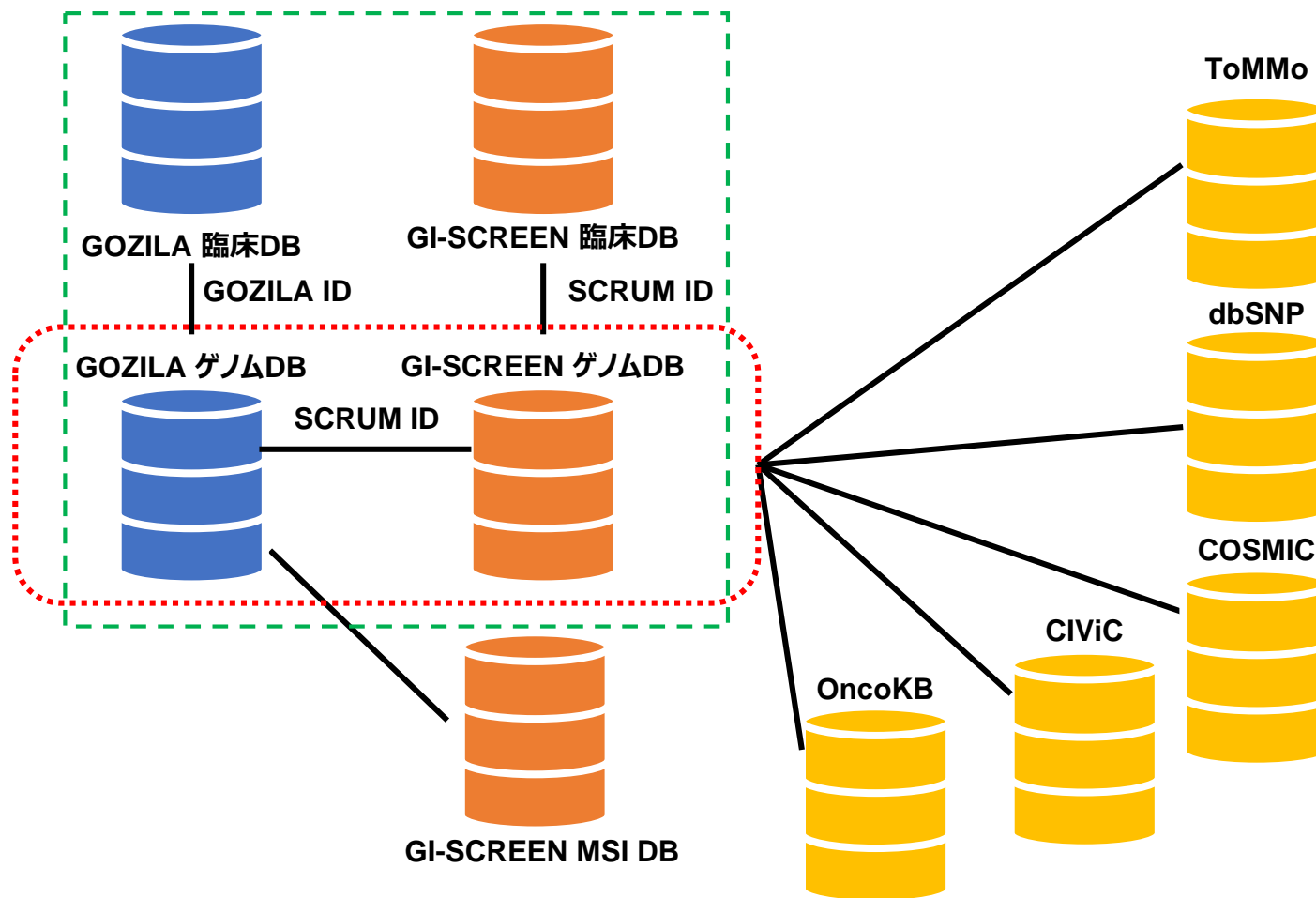
	Median PFS, months (95% CI)
All	4.0 (1.3-5.6)
ctDNA RAS/BRAF/PIK3CA/ERBB2 WT	5.6 (1.3-6.2)
ctDNA RAS/BRAF/PIK3CA/ERBB2 MT	1.4 (1.2-1.8)



Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies

Yoshiaki Nakamura^{1,2,33}, Hiroya Taniguchi^{1,2,33}, Masafumi Ikeda³, Hideaki Bando⁴, Ken Kato^{5,6}, Chigusa Morizane⁷, Taito Esaki⁸, Yoshito Komatsu⁹, Yasuyuki Kawamoto⁹, Naoki Takahashi¹⁰, Makoto Ueno¹¹, Yoshinori Kagawa¹², Tomohiro Nishina¹³, Takeshi Kato¹⁴, Yoshiyuki Yamamoto¹⁵, Junji Furuse¹⁶, Tadamichi Denda¹⁷, Hisato Kawakami¹⁸, Eiji Oki¹⁹, Takako Nakajima²⁰, Naohiro Nishida²¹, Kensei Yamaguchi²², Hisateru Yasui²³, Masahiro Goto²⁴, Nobuhisa Matsuhashi²⁵, Koushiro Ohtsubo²⁶, Kentaro Yamazaki²⁷, Akihito Tsuji²⁸, Wataru Okamoto^{2,29}, Katsuya Tsuchihara^{2,30}, Takeharu Yamanaka³¹, Izumi Miki², Yasutoshi Sakamoto², Hiroko Ichiki², Masayuki Hata², Riu Yamashita³⁰, Atsushi Ohtsu¹, Justin I. Odegaard³² and Takayuki Yoshino¹✉

GI-SCREENとGOZILA等のDBs

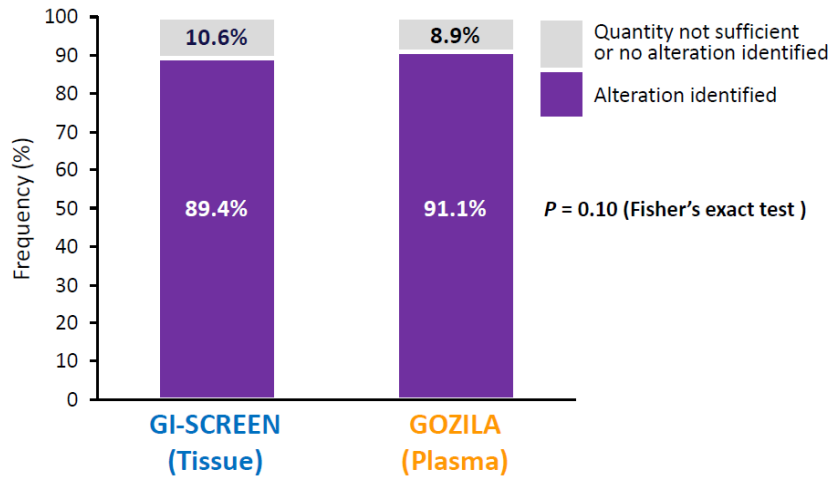


DB間の横断検索を可能としている

Utility of Circulating Tumor DNA Sequencing in Advanced Gastrointestinal Cancer: SCRUM-Japan GI-SCREEN & GOZILA Studies.

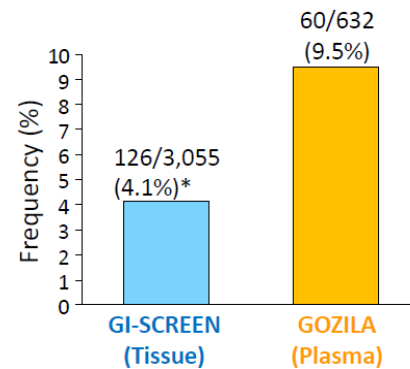


Tissue and Plasma Genotyping Demonstrate Similar Success Rates



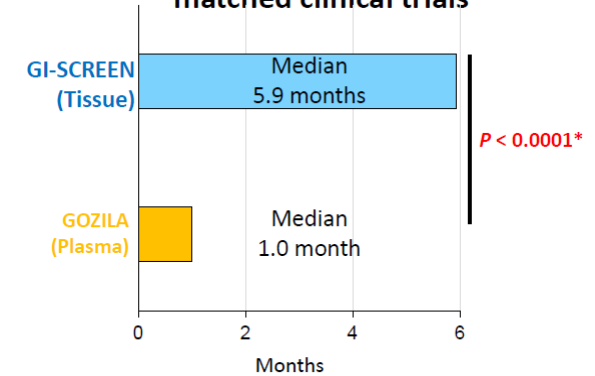
Trial enrollment rate in patients with actionable alterations

$P < 0.0001$ (Fisher's exact test)



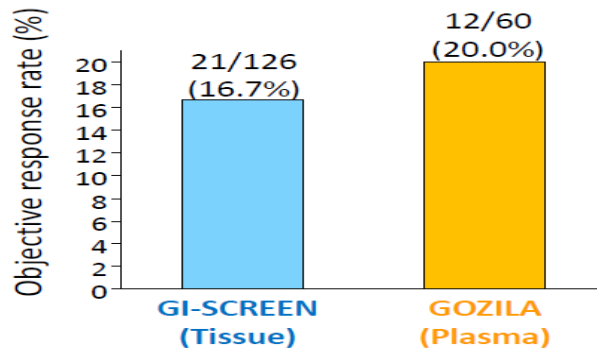
*Twenty-six patients were overlapped.

Interval between enrollment to genotyping studies and matched clinical trials

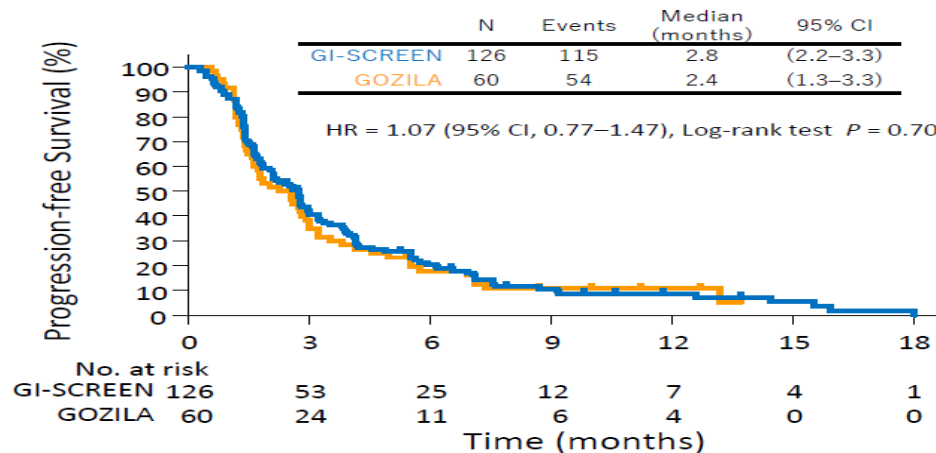


Objective response rate

$P = 0.69$ (Fisher's exact test)

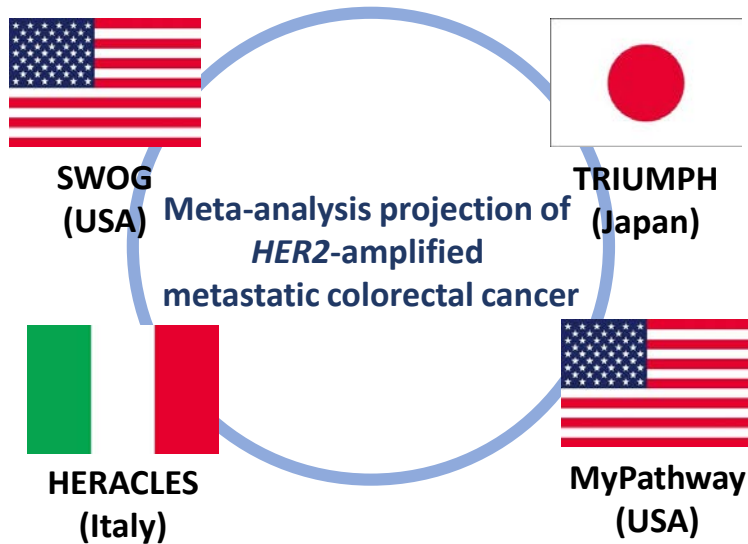


Progression-free survival

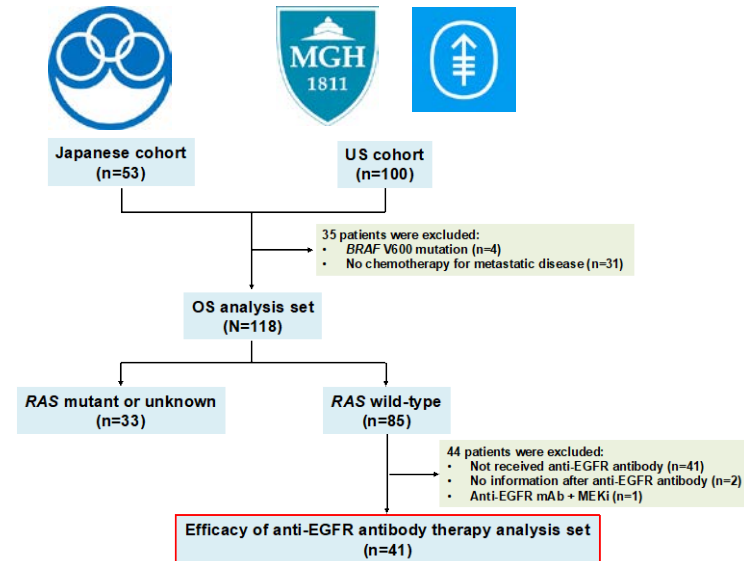


Global Collaboration

International collaboration for HER2 positive colorectal cancer



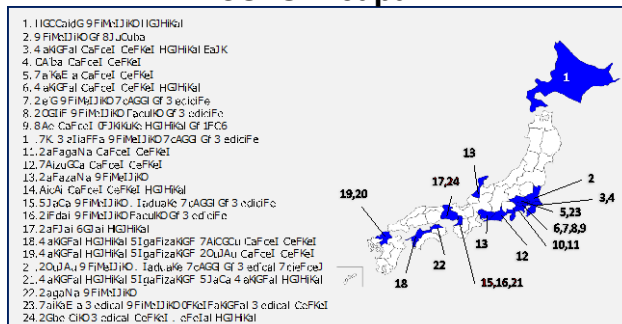
International collaboration for *BRAF* non-V600E mutation



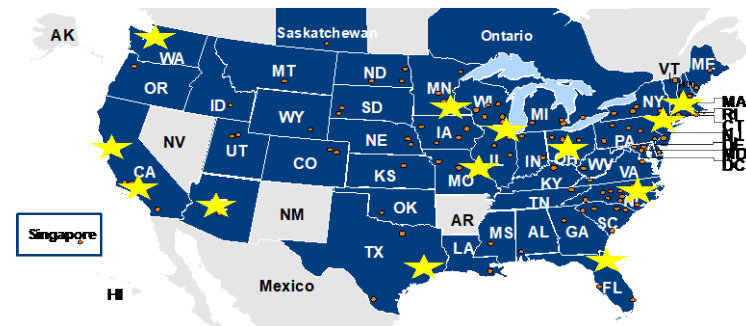
Yaeger R, Kotani D,....., Yoshino T, et al. *Clin Cancer Res*. 2019 *in press*

Collaboration for ctDNA-guided umbrella/basket trials

SCRUM-Japan



ACCRU



Global Collaboration led by ours (representative example)

Unification of International Diagnostic Criteria

International Harmonization of Provisional Diagnostic Criteria for *ERBB2*-Amplified Metastatic Colorectal Cancer Allowing for Screening by Next-Generation Sequencing Panel

Satoshi Fujii, MD, PhD¹; Anthony M. Magliocco, MD, FRCPC, FCAP²; Jihun Kim, MD, PhD³; Wataru Okamoto, MD, PhD⁴; Jeong Eun Kim, MD, PhD⁵; Kentaro Sawada, MD, PhD⁶; Yoshiaki Nakamura, MD, PhD⁶; Scott Kopetz, MD, PhD⁷; Woong-Yang Park, MD, PhD⁸; Katsuya Tsuchihara, MD, PhD⁹; Tae Won Kim, MD, PhD¹⁰; Kanwal Raghav, MD, MBBS⁷; and Takayuki Yoshino, MD, PhD⁶

Fujii S, Yoshino T. *JCO Precision Oncology*, 2020

World's First Guideline for Tumor-agnostic Precision Oncology in Advanced Solid Cancer

JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions

T. Yoshino^{1*}, G. Pentheroudakis², S. Mishima¹, M. J. Overman³, K.-H. Yeh⁴, E. Baba⁵, Y. Naito⁶, F. Calvo⁷, A. Saxena⁸, L.-T. Chen⁹, M. Takeda¹⁰, A. Cervantes¹¹, H. Taniguchi¹, K. Yoshida¹², Y. Kodera¹³, Y. Kitagawa¹⁴, J. Tabernero¹⁵, H. Burris¹⁶ & J.-Y. Douillard¹⁷

Yoshino T, *Ann Oncol*. 2020

新たな臓器横断的ゲノム診療の選択肢の可能性

SPECIAL ARTICLE

JSCO-ESMO-ASCO-JSMO-TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or NTRK fusions

ANNALS OF
ONCOLOGY
driving innovation in oncology

The percentage of patients with a high TMB was much higher than for either MSI or known/likely NTRK rearrangements in adult tumours (as high as 54.60% in skin tumours, 6.32% overall in 212 704 adult profiles) but was low in pediatric patients (maximum 2.25% in gliomas, 0.91% overall in 4382 pediatric profiles).

Note; high TMB (denied as >20 mutations/Mb) in solid tumours from adult (age >18 years) and paediatric (age <18 years) patients.

FDA Approves Pembrolizumab for TMB-High Tumors

June 17th 2020
OncLive Staff



Related Topics ▾

The FDA has approved pembrolizumab (Keytruda) to treat adult and pediatric patients with unresectable or metastatic solid tumors that are tissue tumor mutational burden–high (≥ 10 mutations/megabase) and have progressed following prior therapy and who have no satisfactory alternative treatment options.





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The 3rd-stage MONSTAR-SCREEN

	SCRUM-Japan GI-SCREEN	SCRUM-Japan MONSTAR-SCREEN
Period	～2019 Mar	July 2019 ～ Mar 2021
Number	6,391 patients (CRC 3439、non-CRC 2952)	2,000 patients
Field	GI cancers	GI, breast, skin, head and neck, Gynecological, urological
Aims	Promoting new drugs/devices Creating large-scale database Screening for clinical trials 	Promoting new drugs/devices Promoting translational research Screening for clinical trials targeting resistant mechanisms 

GI cancers ⇒ All solid tumors

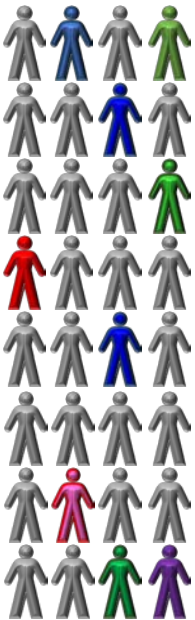
Screening system ⇒ Monitoring system

Platform of translational research to develop new drugs



Nationwide Genome Screening Project
SCRUM-Japan
MONSTAR-SCREEN

全固形がん
(肺がん除く)



NGS解析*

SCRUM-Japan MONSTAR-SCREEN

Main Target N=2000を平均2回測定



薬物療法未治療の患者 (4)
(大腸癌・胃癌・乳癌・黒色腫に限定)
N = 500 (10%が治験対象と想定)



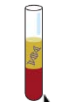
特定の遺伝子異常が同定された患者 (1)
N = 500 (30%が治験対象と想定)



免疫療法を含む治療を受ける患者 (5)
N = 500 (10%が治験対象と想定)



分子標的薬治療に伴うClonal Evolution
の可能性がある患者 (3)
例: mCRCの抗EGFR抗体治療後
N = 500 (20%が治験対象と想定)



N=350の臨床
試験登録を目標

F1L

Microbiome
(6)

臨床情報+

+SCRUM-Japan内で収集する臨床情報・治療効果等をより詳細に収集(現在の前向きレジストリの収集項目を踏襲)

個別研究

Target E

Clinical Trial E

Target F

Clinical Trial F

Target G**

Clinical Trial G

経時的な評価

Targetはあるが、治験不適格・治験不参加患者

自然史の追跡

16S rRNA-seq



Registryの促進および経時的な評価による科学的な裏づけ (2)

Consultation

Regulatory Agency



** Clonal Evolutionに伴うTarget。Clonal Evolutionに対する臨床開発を意味する。

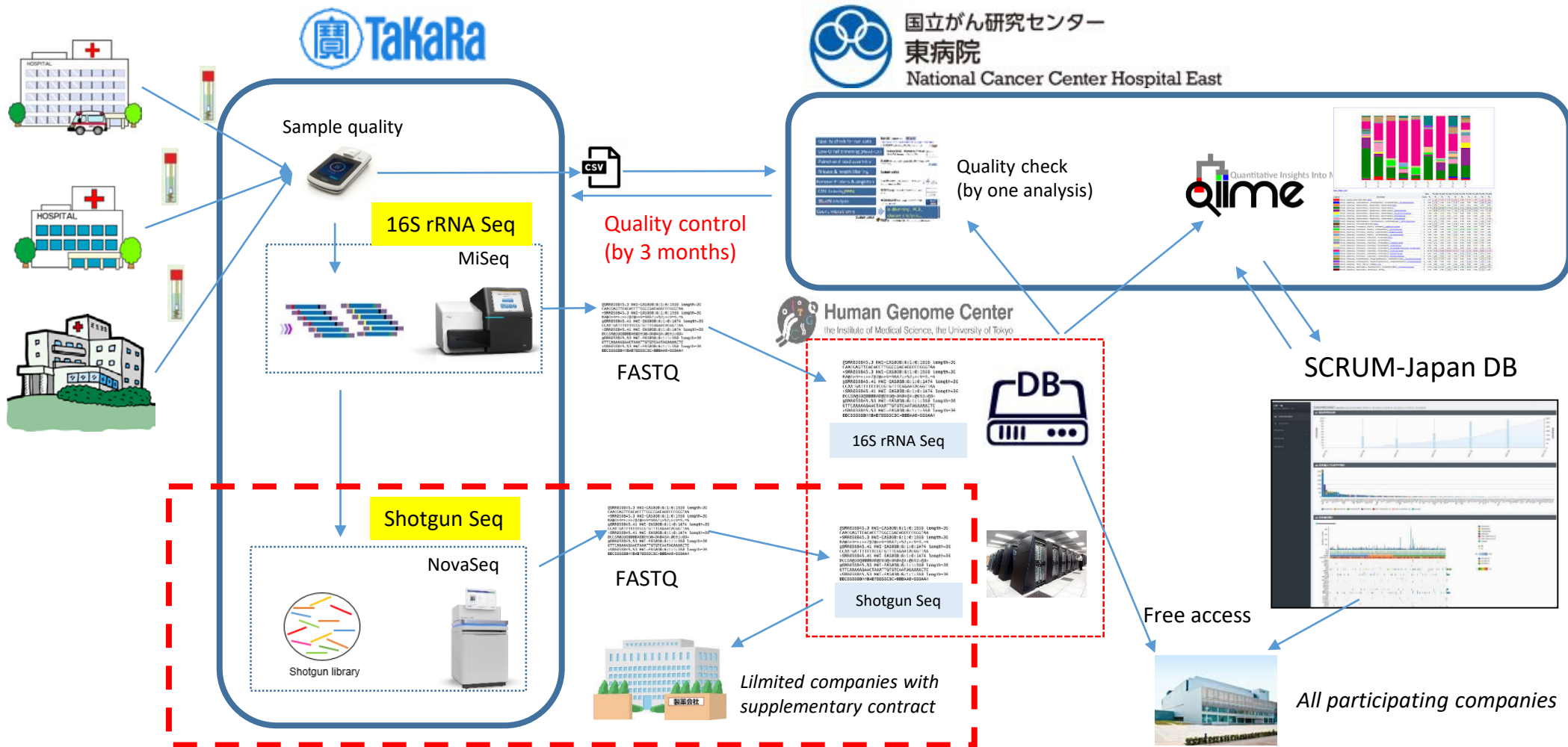
F1L

*FoundationOneやNCCオンコパネルなどの組織NGS解析結果も収集(VCF File)

腫瘍組織のNGS解析結果を収集
比較によるClonal Evolutionの全体像の把握とカタログ化 (3)

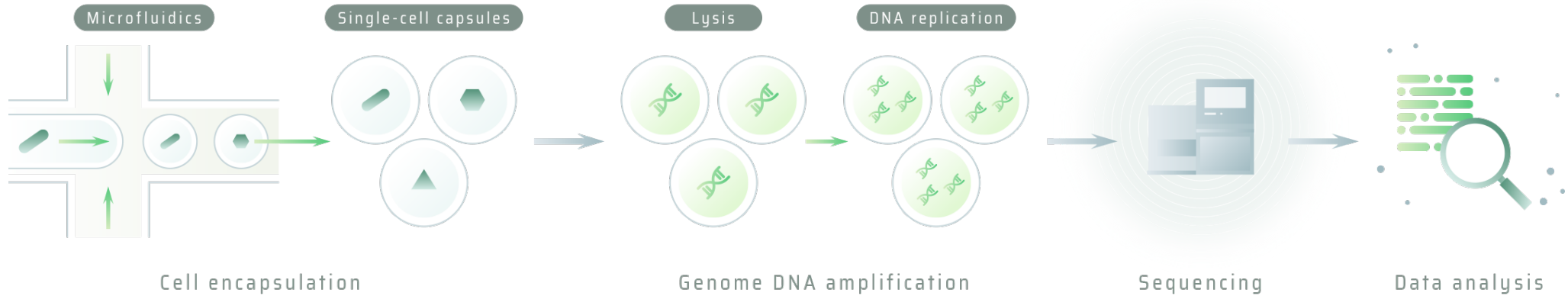
SCRUM-Japan参加企業との共同研究範囲

Microbiome analysis



We adopt both 16S rRNA and shotgun Seq

Single cell genome analysis



This is a Novel technology for bacterial genome analysis

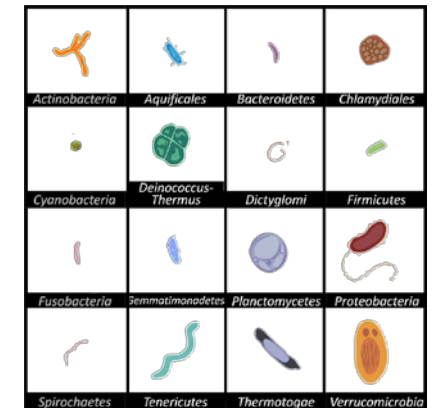
This method can analyze individual bacterial whole genome without contamination.

Conventional metagenome analysis



- Feature of the whole image
- Miscellaneous information
- Abstract understanding

Single cell metagenome analysis



- Feature of individual bacteria
- Organized information
- Essential understanding

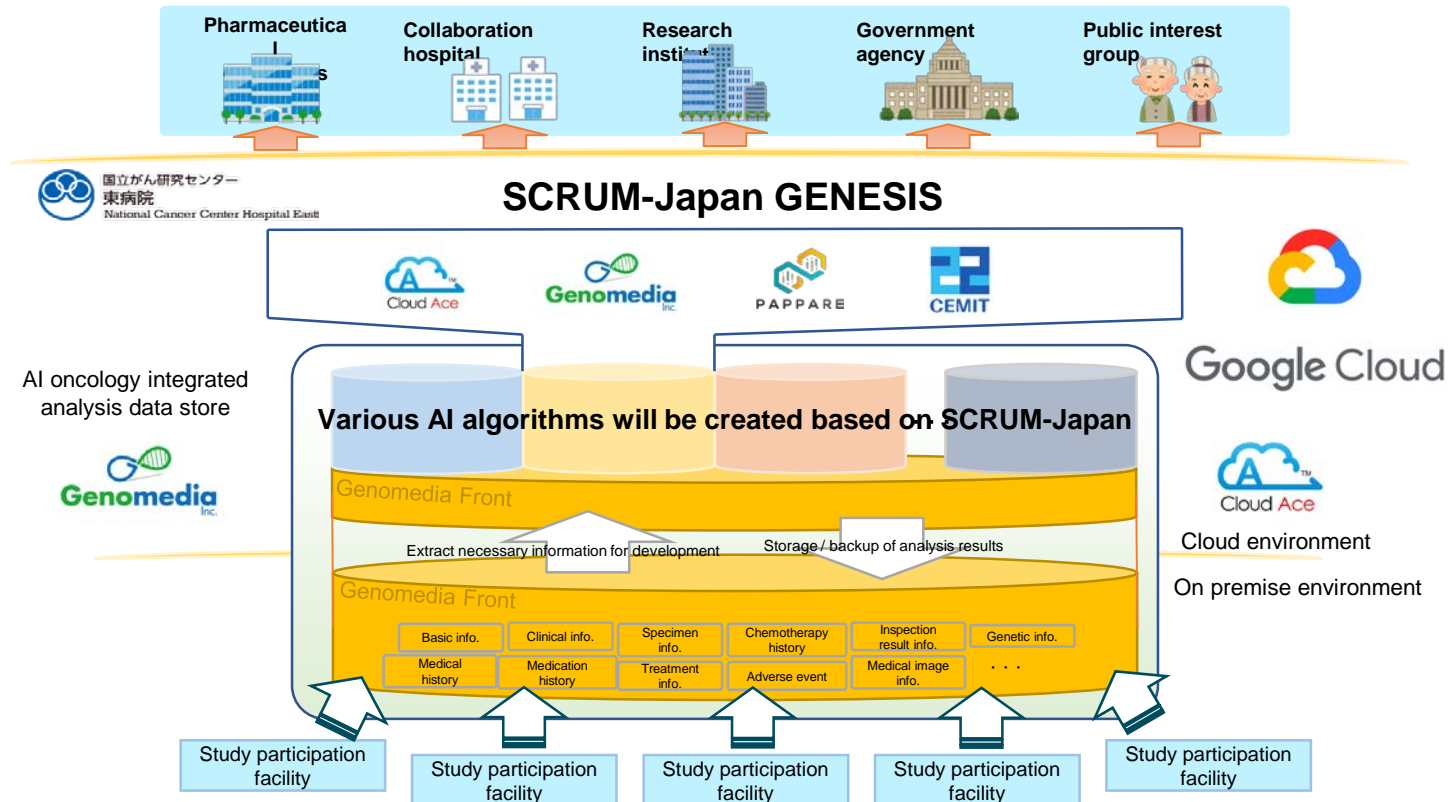


Differences Among Each Microbiome Analyses

	16S rRNA analysis	Shotgun metagenome analysis	Single cell genome analysis
purpose	bacterial species component data	Whole genome sequencing	Functional analysis in individual bacteria
Target	16S rRNA gene	Collection of whole genome fragment	All genome of individual bacteria
Read length	400 bases	Several million ~ several ten million bases	Several 100 million ~ several billion bases per cell
Bacterial component	○	○	○
Functional gene component	×	○	○
Linkage of bacteria and function	×	△	○
Discrimination of strain	×	×	○

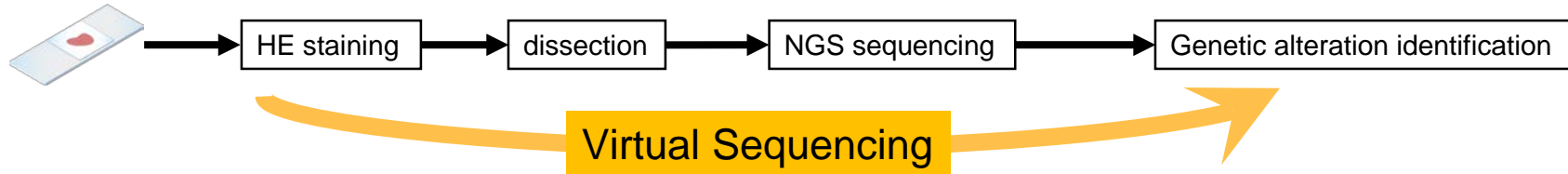
We plan these analyses in this study (about 200 cases)

SCRUM-Japan GENESIS Project

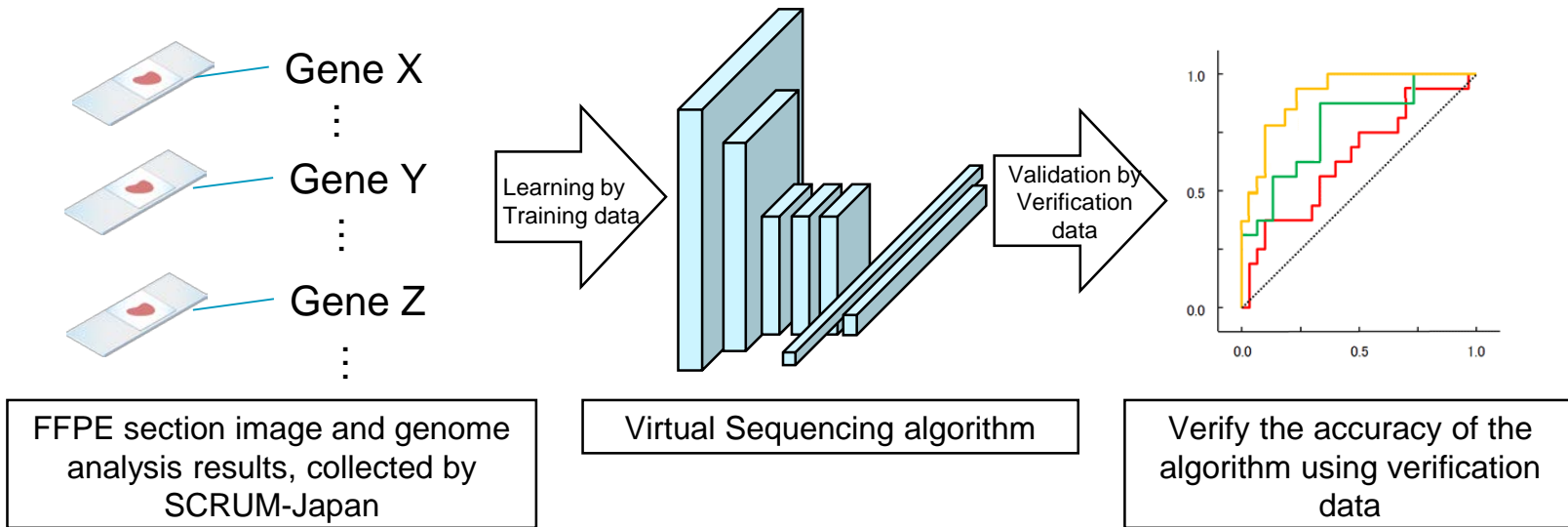


SCRUM-Japan GENESIS Virtual Sequencing Project

Virtual Sequencing VSQ



Development of prompt & accurate genome alteration estimation method using AI image processing

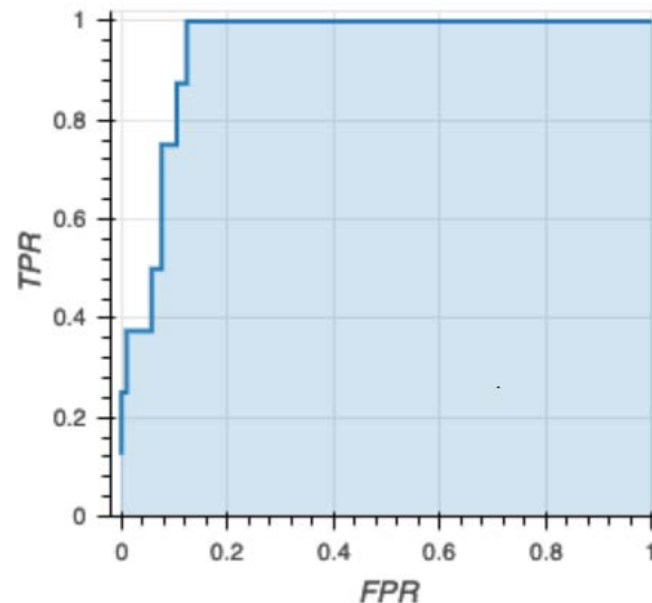


Preliminary result for gene X

Virtual Sequencing VSQ



AUC 0.94 in ROC*



*Gene X positive prediction for whole slide images under prespecified conditions.

Only a previous study⁺ showed an AUC from 0.640 to 0.856 to predict for 10 genes in patients with lung cancer.

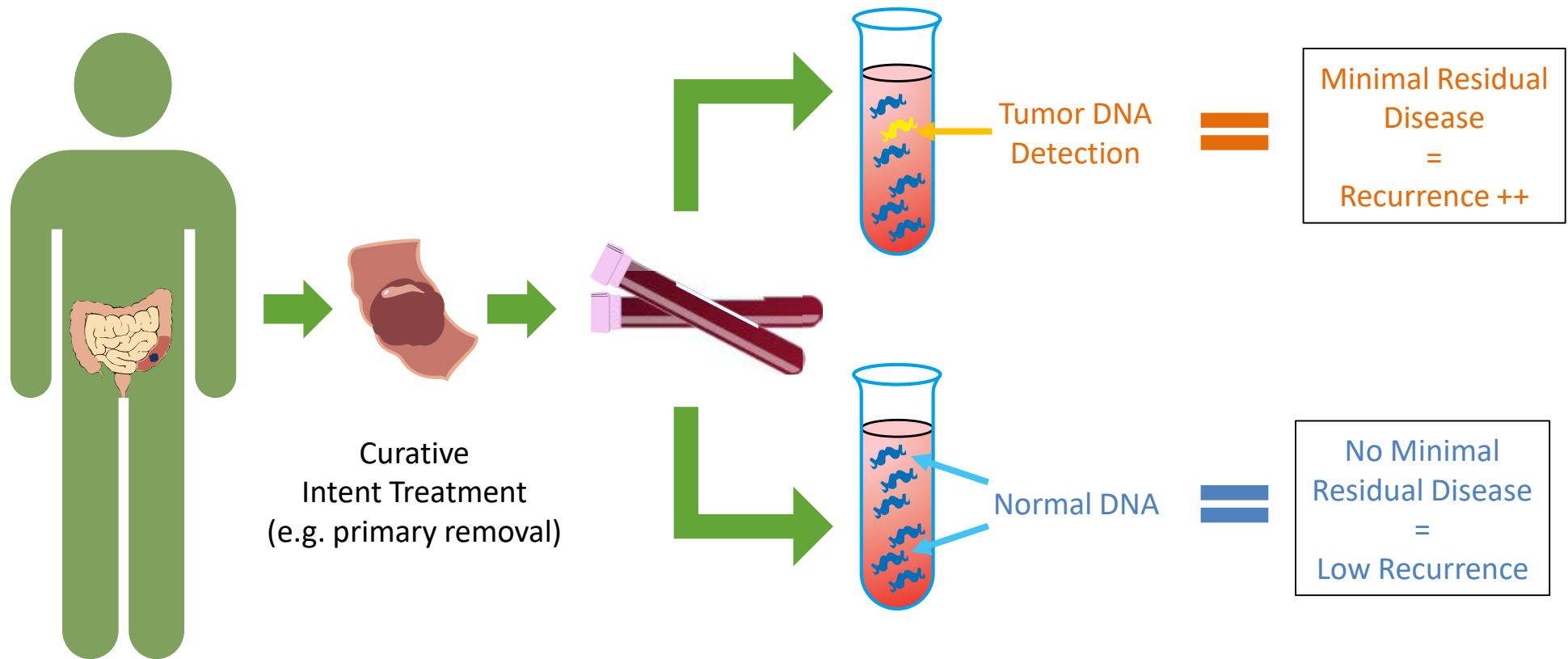
⁺Coudray N, et al. *Nature Med.* 2018

Yoshino T, et al. Oral presentation at Google Cloud Next '19
https://www.youtube.com/watch?v=iO4x1aJw_Jc

Agenda

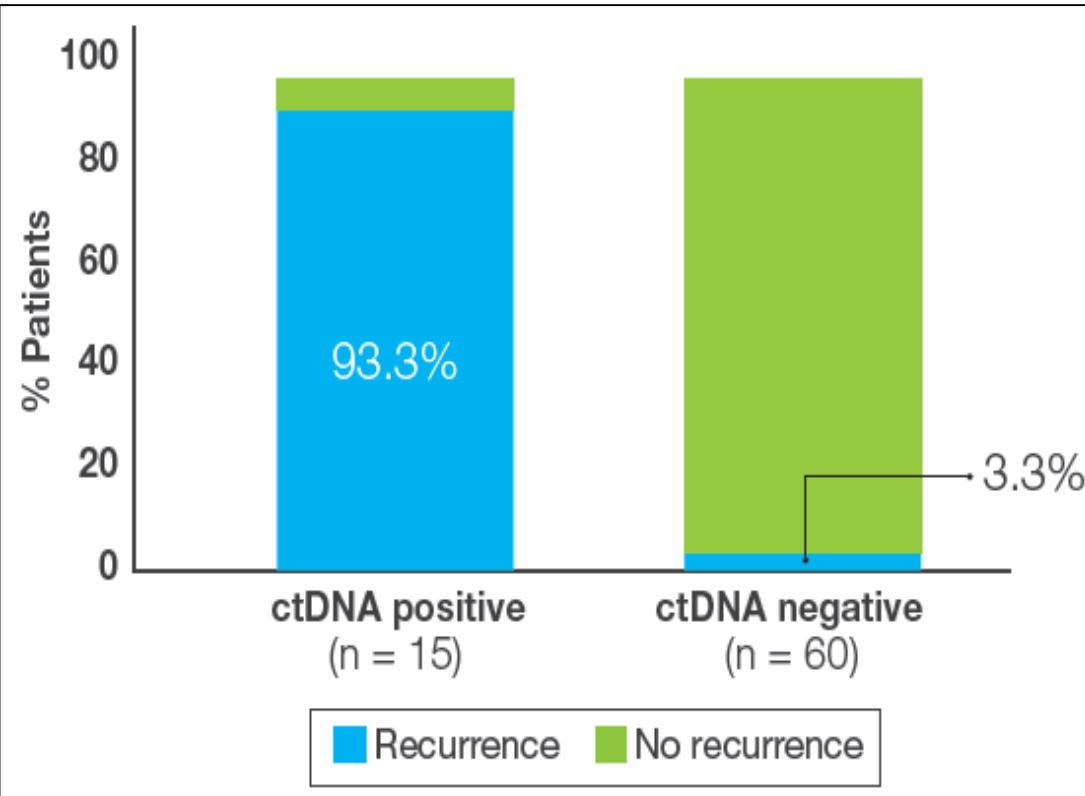
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Recurrence Risk Assessment: ctDNA Detecting Minimal Residual Disease (MRD)



Tie J, et al.: ASCO-GI 2019 #GI19.

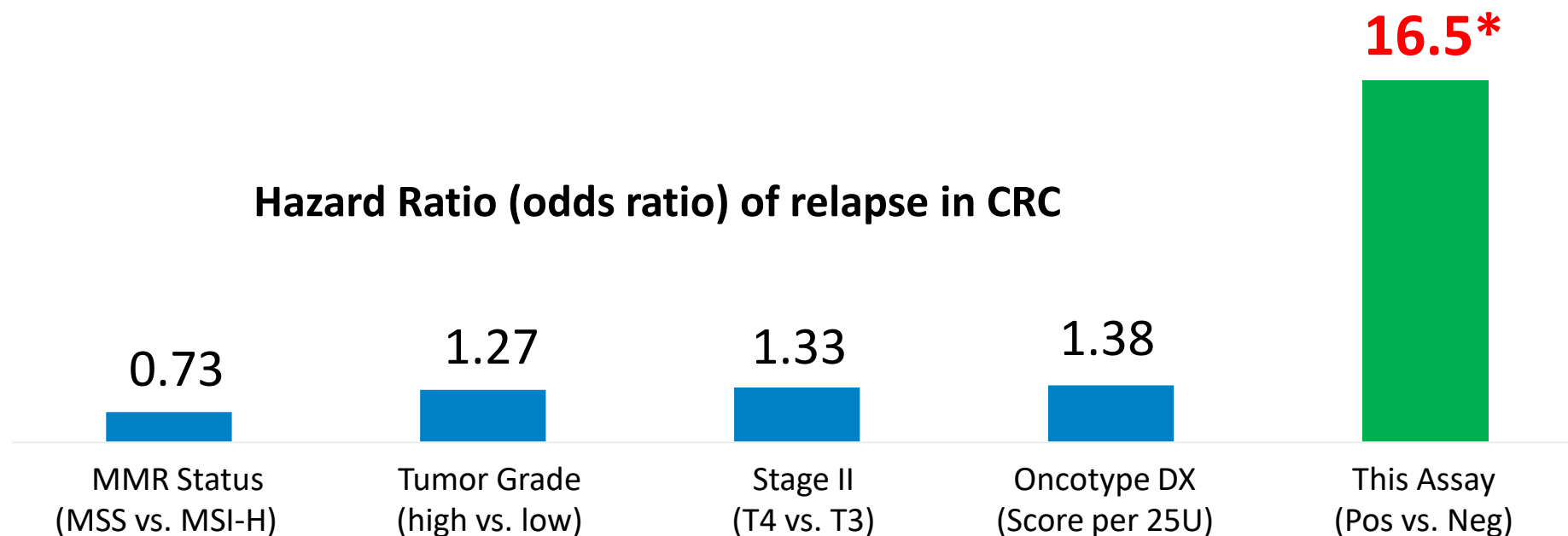
Stratification by Post-operative ctDNA Status



Signatera

Stage I-III CRC, n = 130

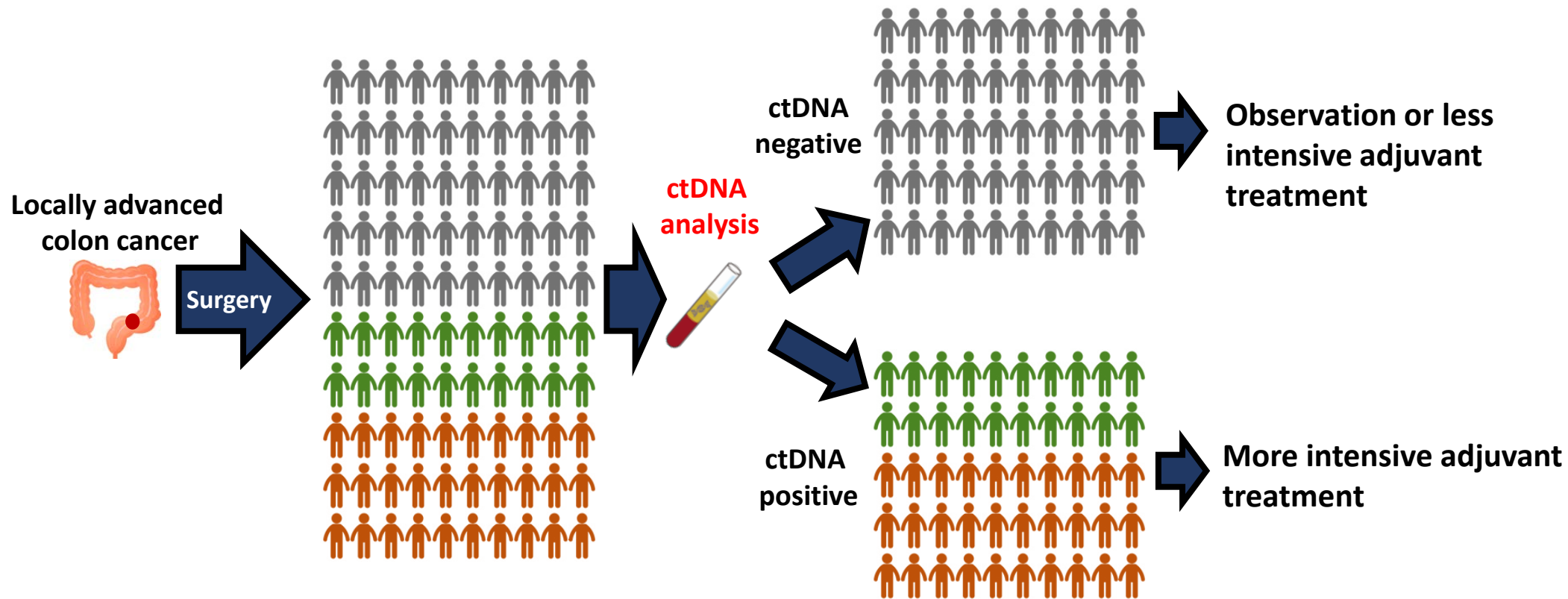
Cross-comparison of Predictivity



本アッセイによる根治手術後の再発予測能は、既知の再発予測マーカーよりはるかに優れている。

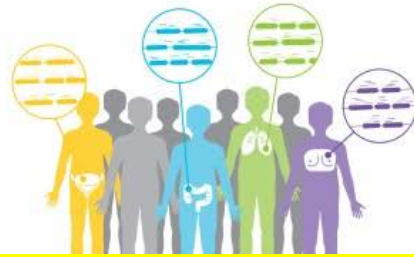
*Tarazona N, et al. Abst #4009 ASCO 2020

Ideal Precision Medicine for Resected Colon Cancer



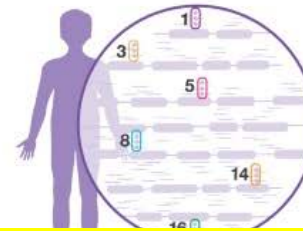
アッセイ紹介

Personalized and Tumor-Informed Methodology Means Each Patient Gets Custom-Built Assay



全エクソーム解析（正常部および癌部）

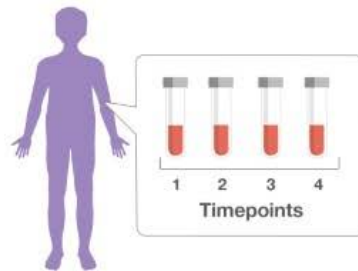
- 1 Analyze sequencing of tumor tissue and matched normal blood at initial timepoint



患者毎にカスタムパネルを作製

- 2 Select individual-specific, clonal, somatic variants and design custom primers for each patient

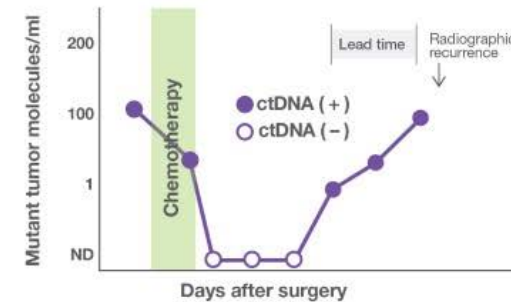
Can detect as few as 1 genomic tumor equivalent in 10 ml of blood (VAF = 0.01%)



- 3 Obtain whole blood samples at longitudinal timepoints (eg, every 3 months)



- 4 Cell-free DNA extraction and patient-specific multiplex PCR followed by NGS



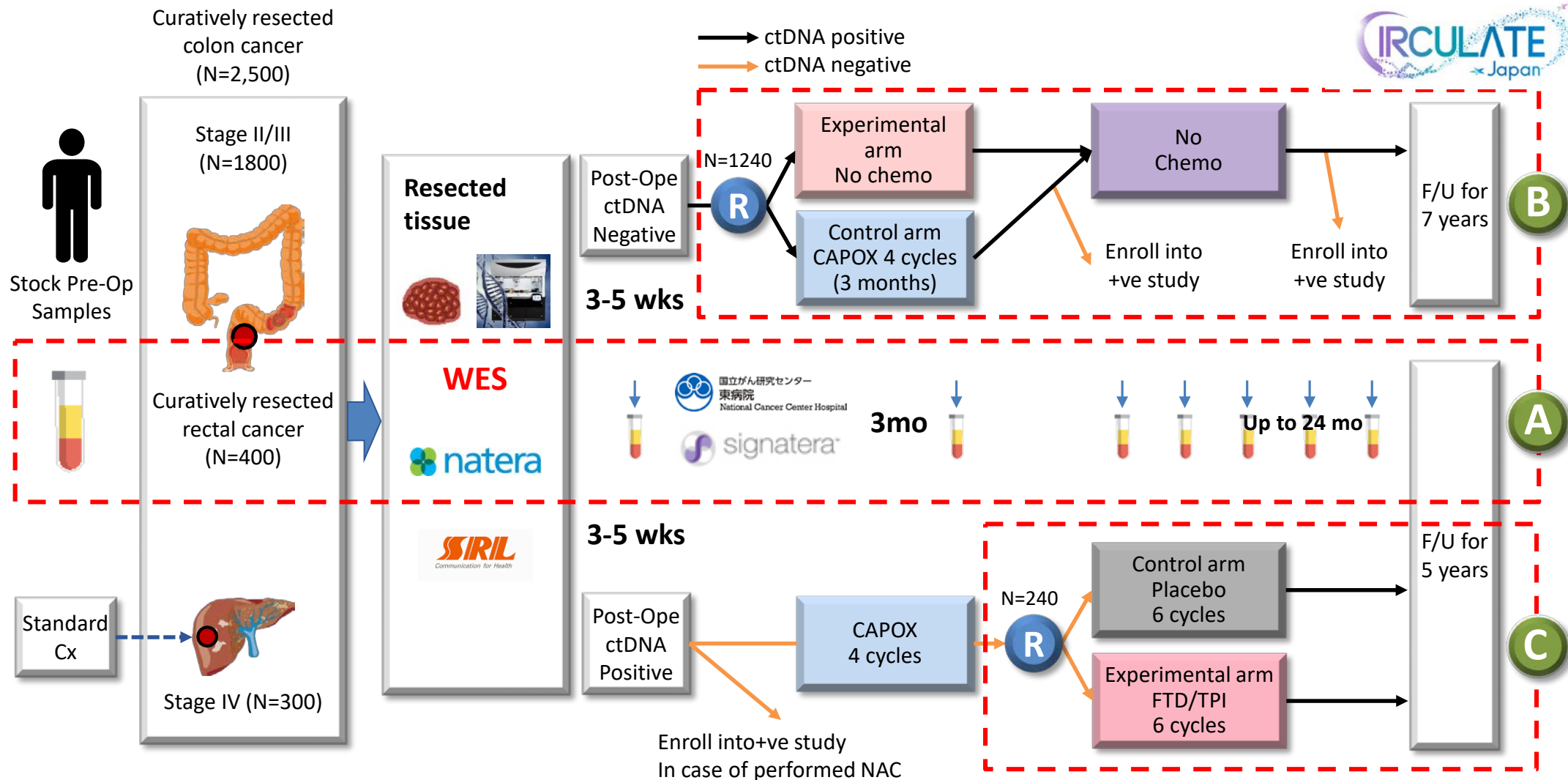
- 5 Analyze ultra-deep NGS data in plasma to detect presence of ctDNA

カスタムパネルによるモニタリング

ctDNA陽転化による再発の早期同定

CIRCULATE JAPAN Overall Architecture

Incl. Taiwan



New Horizon for Early Detection by ctDNA Analysis



Colorectal cancer screening
✓ Fecal occult blood test



Gastric cancer screening
✓ Stomach X-ray
✓ Gastroendoscopy



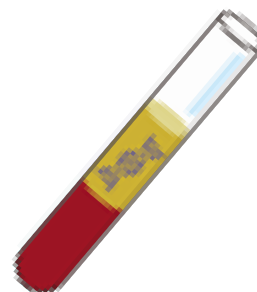
Lung cancer screening
✓ Chest X-ray
✓ Sputum cytology



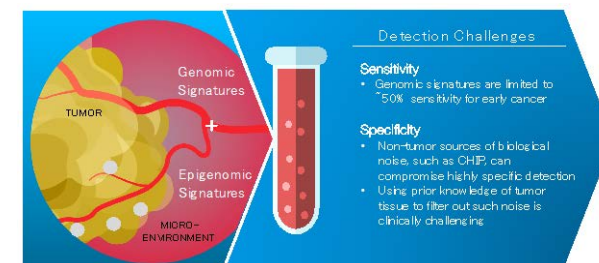
Cervical cancer screening
✓ Cervical cytology



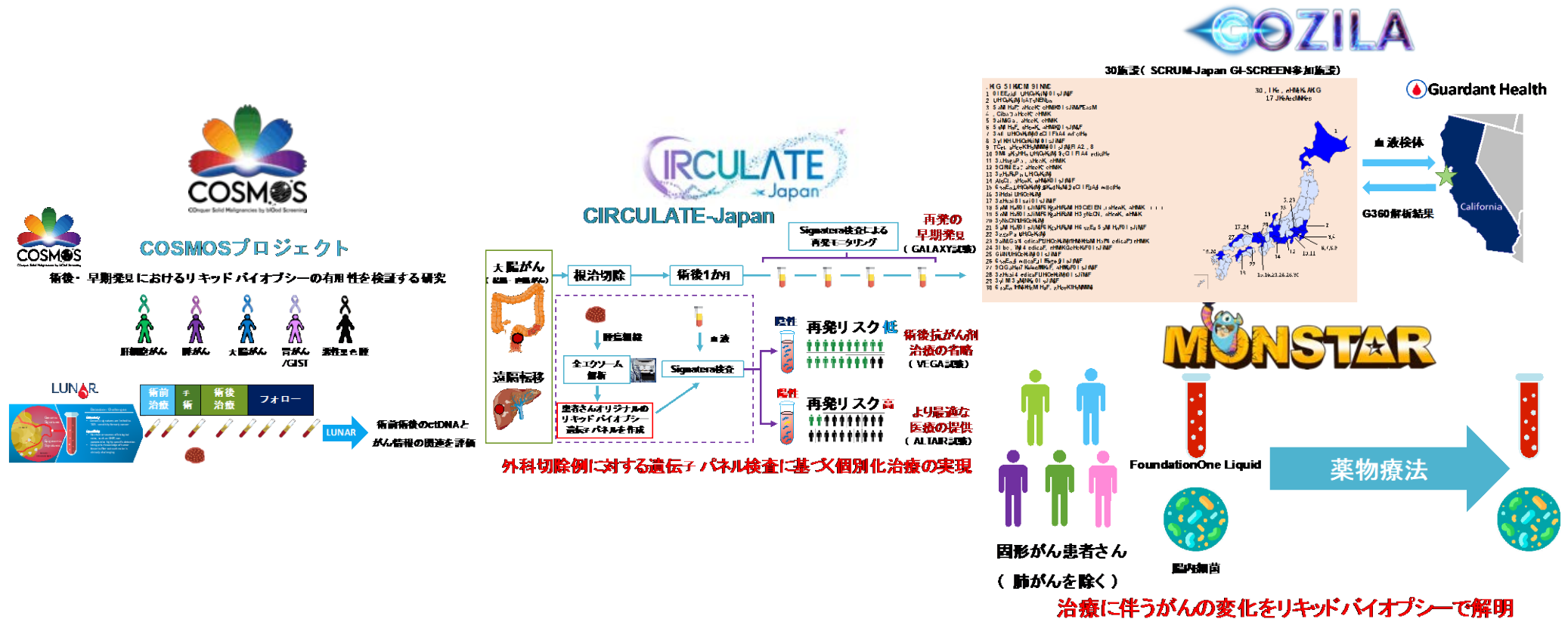
Breast cancer screening
✓ Mammography



All cancer type
✓ **ctDNA analysis**



我々が行っているリキッドバイオプシー研究



早期発見

術後リスク評価

進行がんのがんゲノム医療

Agenda

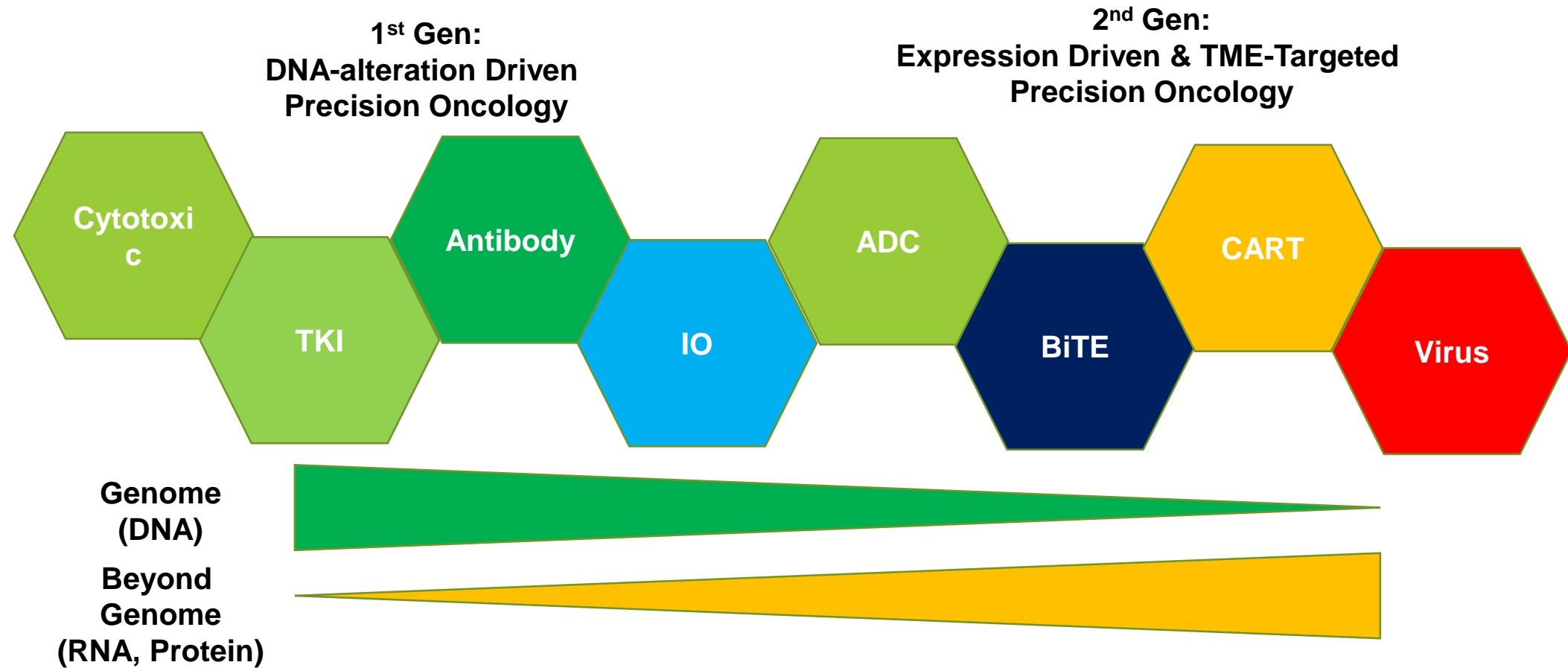
- **PAST to Present: Achievement of the SCRUM-Japan**
 - Tissue NGS* Screening (SCR) and stratified clinical trials
 - Data Base (DB)
 - Liquid Bx SCR and stratified clinical trials
 - International Collaboration
- **TODAY: Ongoing innovative projects**
 - Liquid Bx & Microbiome (MB)
 - Artificial intelligence /Machine Learning (AI/ML)
 - CIRCULATE-Japan (C-J)
- **TOMORROW: Translating Multi-Omics into Clinical Utility**

Hypothesis

- ✓ AI-driven multi-omics analysis reveals what is actually happening in tissues & cells as well as tumor micro-environment.
Clarify More Molecular Blueprint
- ✓ AI-driven multi-omics analysis identify candidate multidimensional biomarkers.
Beyond Single Biomarkers

From Genomics to Multi-Omics with AI

Development of Anti-cancer Drugs



MONSTAR SCREEN-2 (Main Part)

From Genomics to Multi-Omics with AI



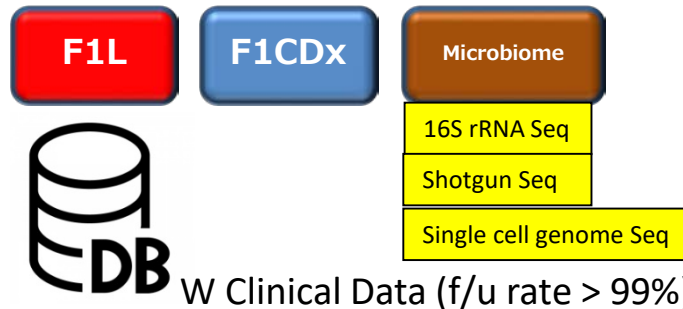
Since April 2021 during 3 years

Pan-cancer excl. lung cancer (N = 2,000)
Pre- and post-treatment



- ✓ 1st line or Subsequent line with intent for trial enrollment
- ✓ PS 0 or 1

- | | |
|-----------------|-----------------|
| ■ Colorectal | ■ Gynecological |
| ■ Gastric | ■ Urological |
| ■ Pancreatic | ■ H&N |
| ■ Biliary tract | ■ Melanoma |
| ■ Breast | ■ Others |



Tumor
tissue

Pan-cancer excl. lung cancer (N = 2,750)
AI Predictor, Database access



Clinical Data



DNA

WES
(SNV, CNV, Fusion,
HRD, TMB, SNP,
Pathogen)



RNA

WTS
(Fusion,
Signature [i.e. CMS])

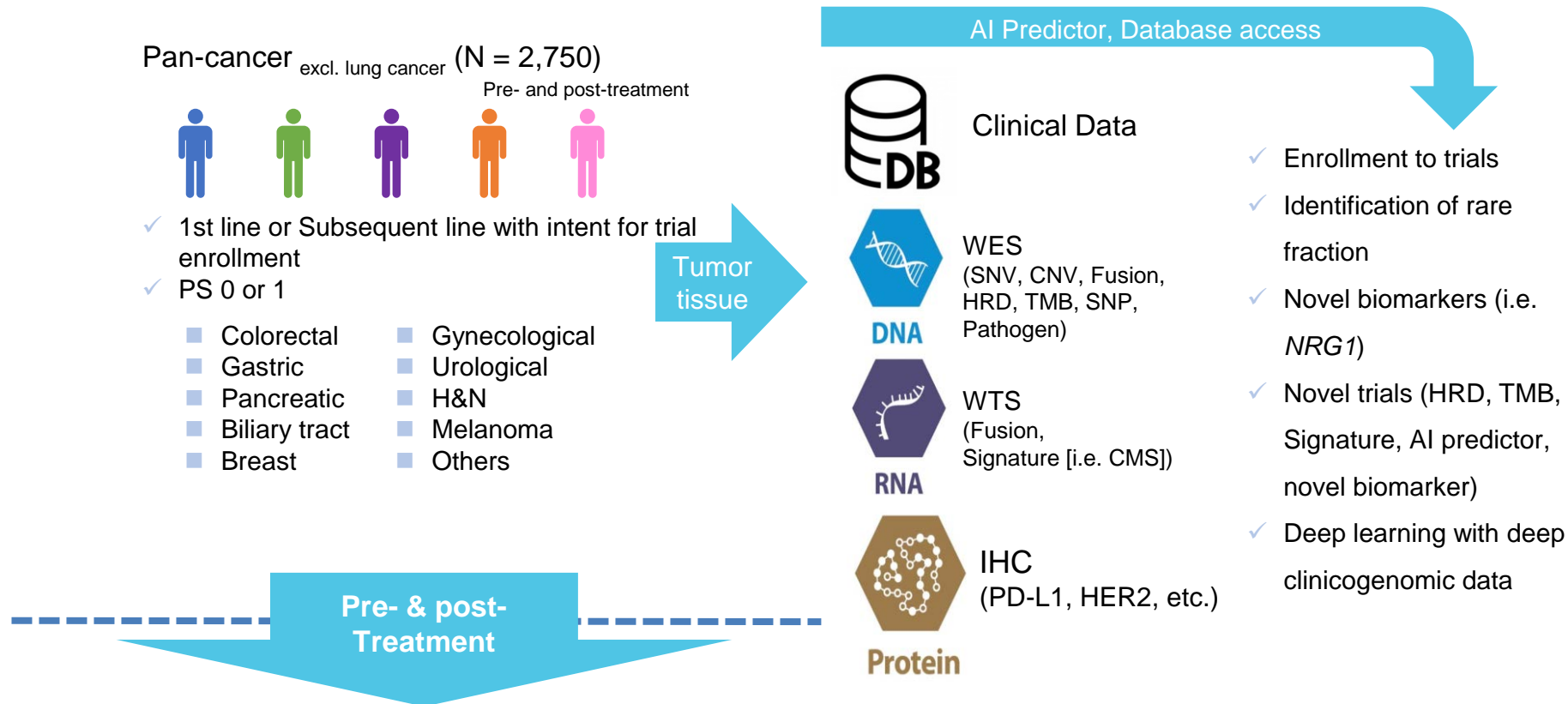


Protein

IHC
(PD-L1, HER2, etc.)

- ✓ Enrollment to trials
- ✓ Identification of rare fraction
- ✓ Novel biomarkers (i.e. *NRG1*)
- ✓ Novel trials (HRD, TMB, Signature, AI predictor, novel biomarker)
- ✓ Deep learning with deep clinicogenomic data

MONSTAR SCREEN-2 (Sub Part)



Pan-cancer excl. lung cancer (N = 2,500 X twice)

- ✓ **Whole-exome/transcriptome circulating tumor NA (nucleic acid) analysis**

Beyond Genomics



Summary - From 'MAY BE' to 'MUST BE' -

Metastatic Disease

- Clinical utility for analyzing ctDNA in GI cancers & international collaborations are actively ongoing. We established ctDNA analysis likely to enable more GI cancer patients to enroll clinical trials without compromising efficacy.

MRD & Early detection

- Beyond cancer patient selection for targeted therapy, the potential of ctDNA analysis may expand the utility to patient stratification for adjuvant chemotherapy and early detection.

Beyond Genomics

- We will investigate clinical utility for analyzing multi-omics incl. ctNA in all solid tumors in the near future, that is, evoking the paradigm shift from genomics to multi-omics with AI toward the digital medicine.