



2021年6月12日

第28回抗悪性腫瘍薬開発フォーラム

リキッドバイオプシーによる がんゲノム医療時代の幕開け

中村能章

国立がん研究センター東病院

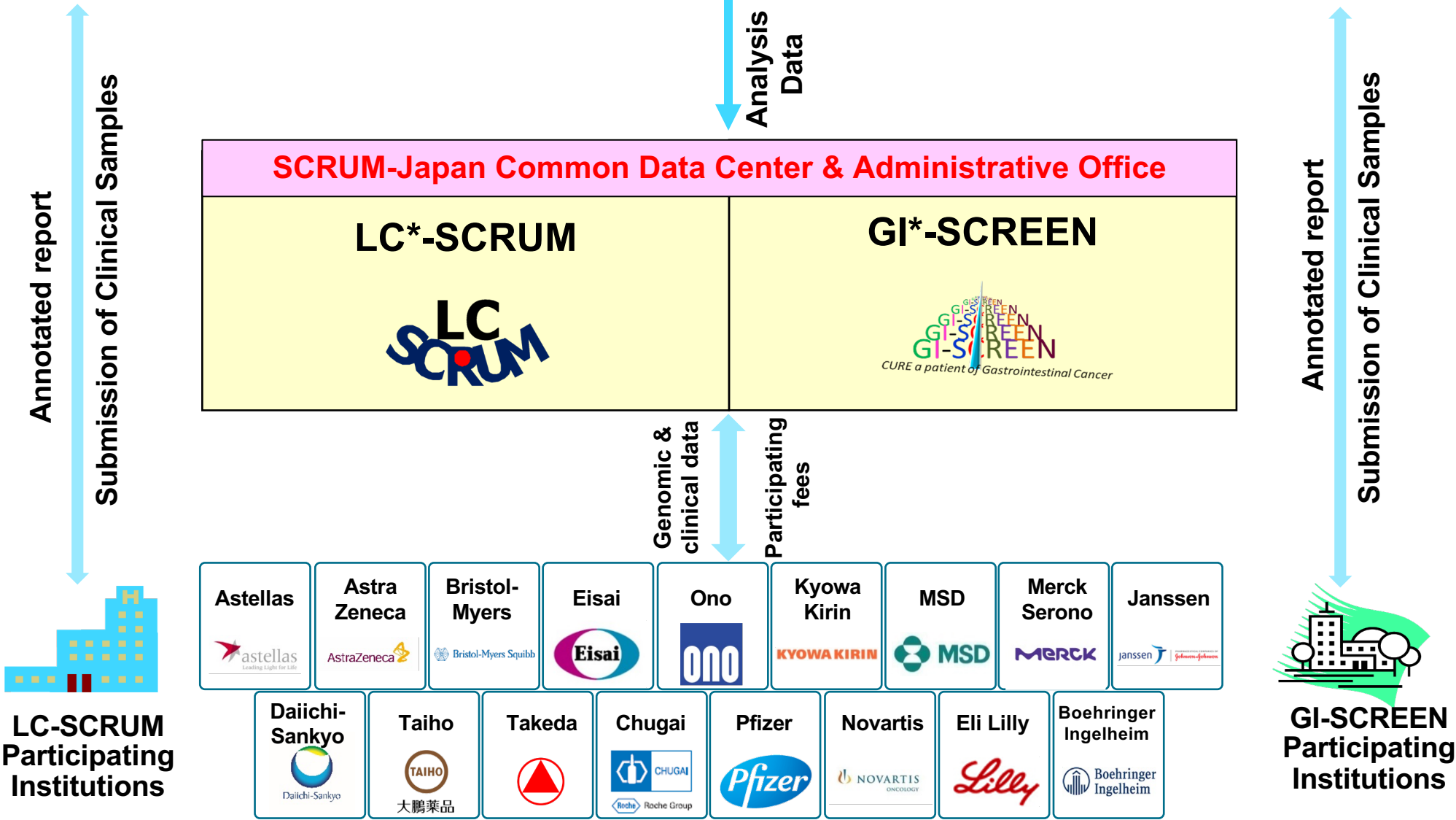
臨床研究支援部門トランスレーショナルリサーチ推進部トランスレーショナルリサーチ支援室

／消化管内科



SCRUM-Japan Project Since 2015

Comprehensive NGS (Next Generation Sequencing) test by central vendor



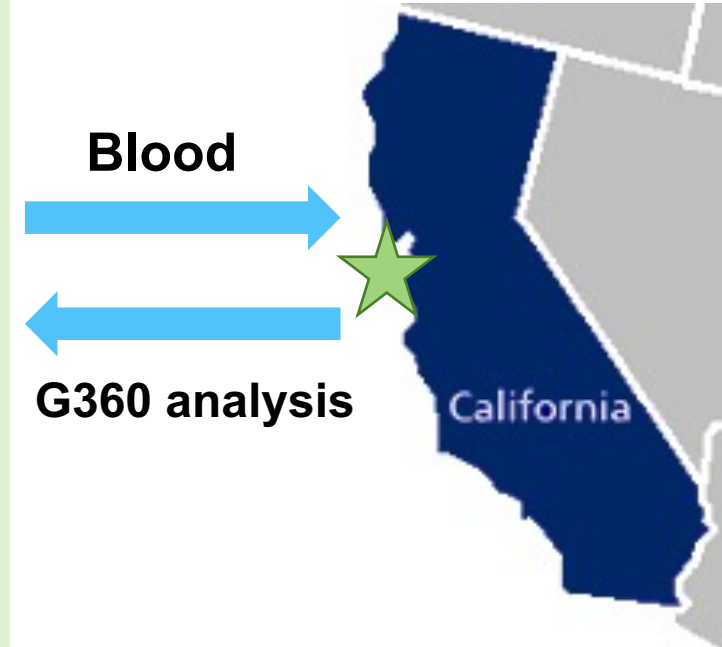
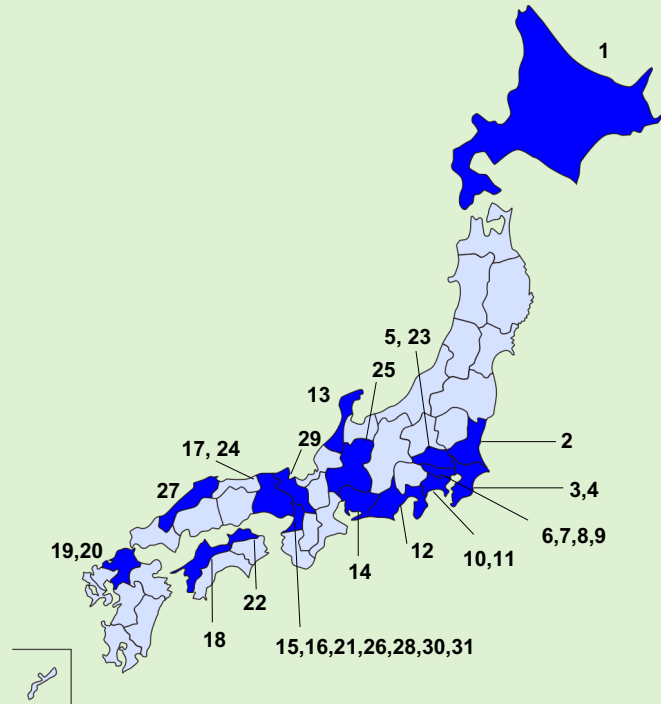
GOZILA Nationwide ctDNA Screening Project



From North to South

1. Hokkaido University Hospital
2. University of Tsukuba
3. National Cancer Center Hospital East
4. Chiba Cancer Center
5. Saitama Cancer Center
6. National Cancer Center Hospital
7. Keio University School of Medicine
8. Kyorin University Hospital
9. The Cancer Institute Hospital of JFCR
10. St.Marianna University School of Medicine
11. Kanagawa Cancer Center
12. Shizuoka Cancer Center
13. Kanazawa University
14. Aichi Cancer Center Hospital
15. Osaka University Graduate School of Medicine
16. Kindai University
17. Kansai Rosai Hospital
18. National Hospital Organization Shikoku Cancer Center
19. National Hospital Organization Kyushu Cancer Center
20. Kyushu University
21. National Hospital Organization Osaka National Hospital
22. Kagawa University
23. Saitama Medical University International Medical Center
24. Kobe City Medical Center General Hospital
25. Gifu University Hospital
26. Osaka Medical College Hospital
27. Shimane Prefectural Central Hospital
28. Kansai Medical University Hospital
29. Kyoto Katsura Hospital
30. Osaka International Cancer Institute
31. Osaka General Medical Center

31 Core Centers from 17 prefectures



- Launched on Jan, 2018
- All GI cancers
- Sample size: 5000
- 4069 pts enrolled by Apr 2021

ctDNA解析の利点

- Turnaround timeが短く患者の治療適応の判断が速やかに可能
- Heterogeneityを評価することが可能

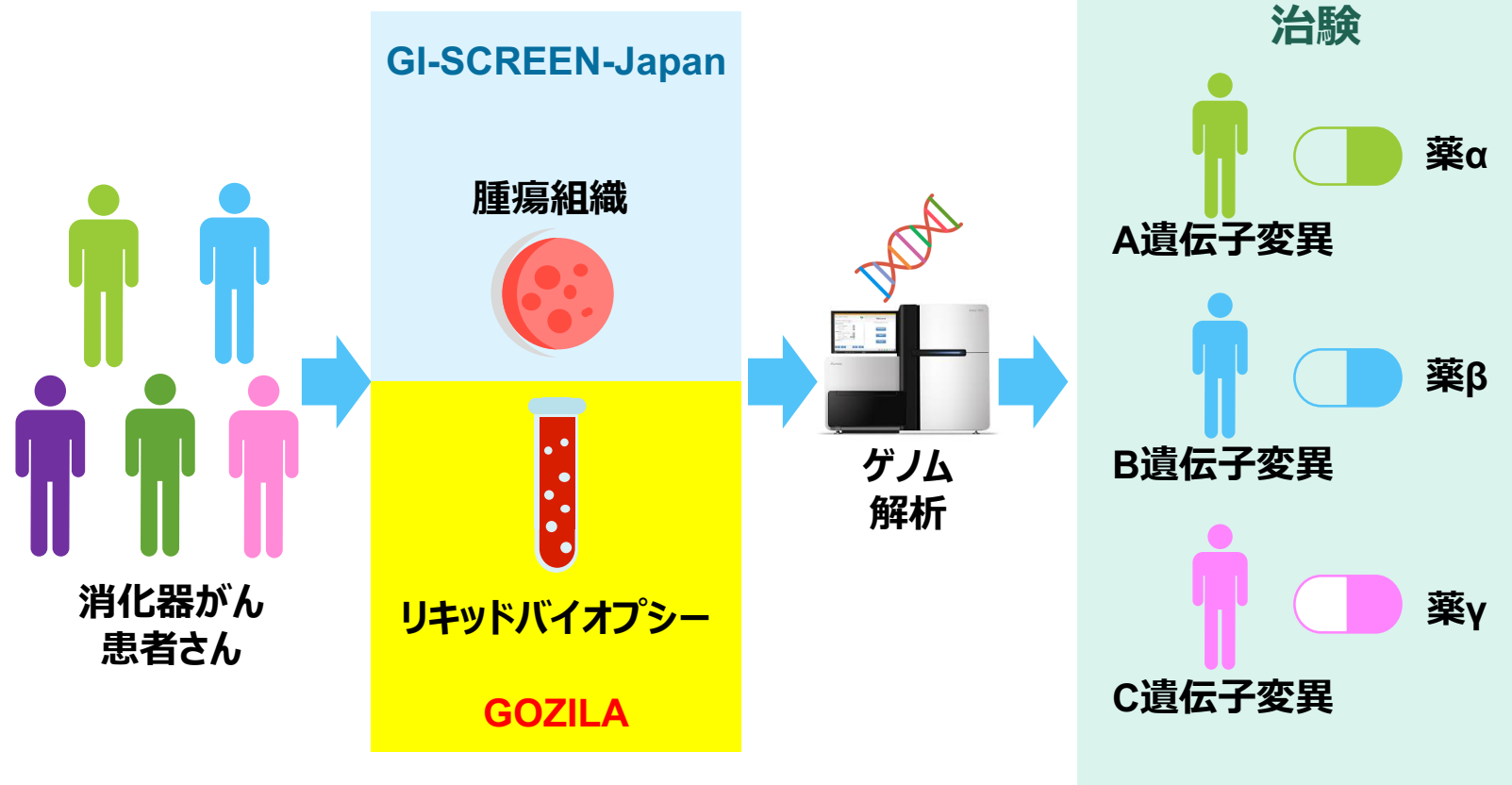
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ctDNA解析のゲノム医療に対する有用性

2015年2月に開始した腫瘍組織パネル検査のスクリーニングプロジェクト

5000名以上の患者さんが参加



GI-SCREEN-Japanと

GOZILAで以下の項目を比較

- 登録から結果到着までの期間
- 治験に登録された患者さんの割合
- 治験治療の効果

対象（～2019年8月）

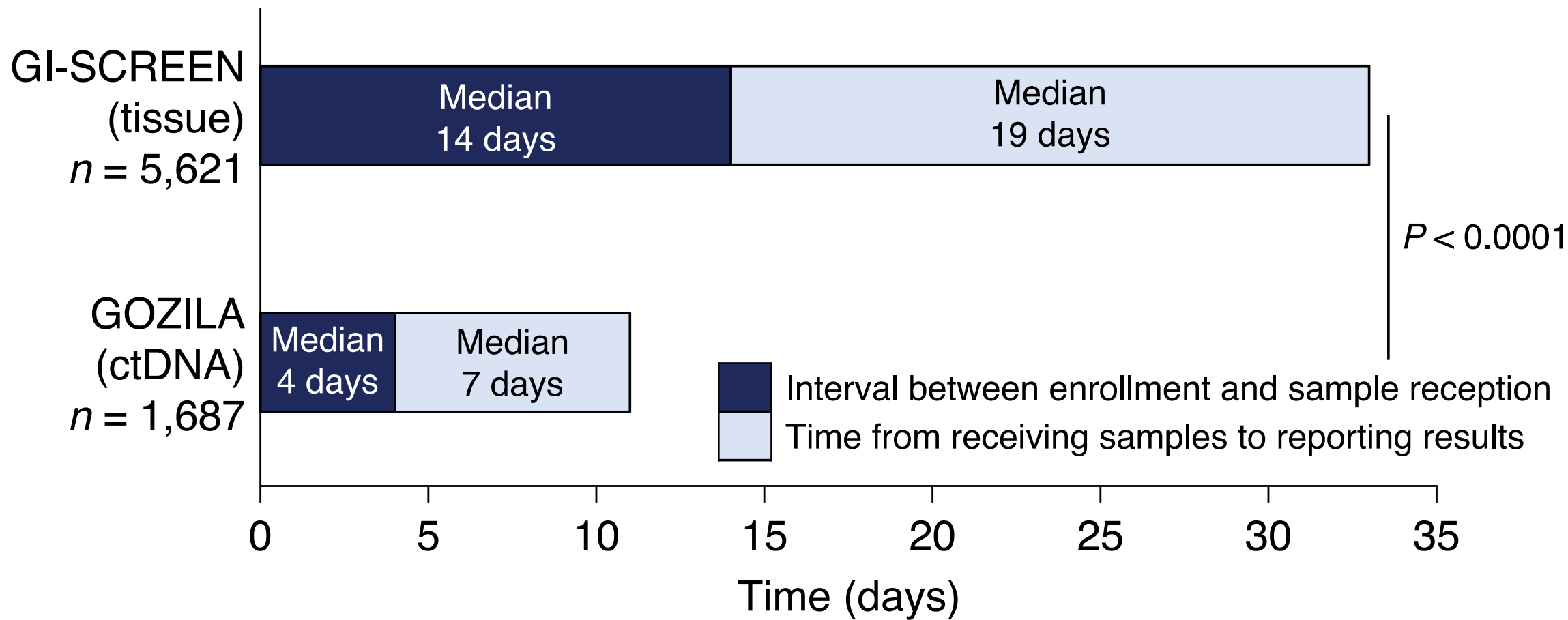
GI-SCREEN : 5743名

GOZILA : 1787名

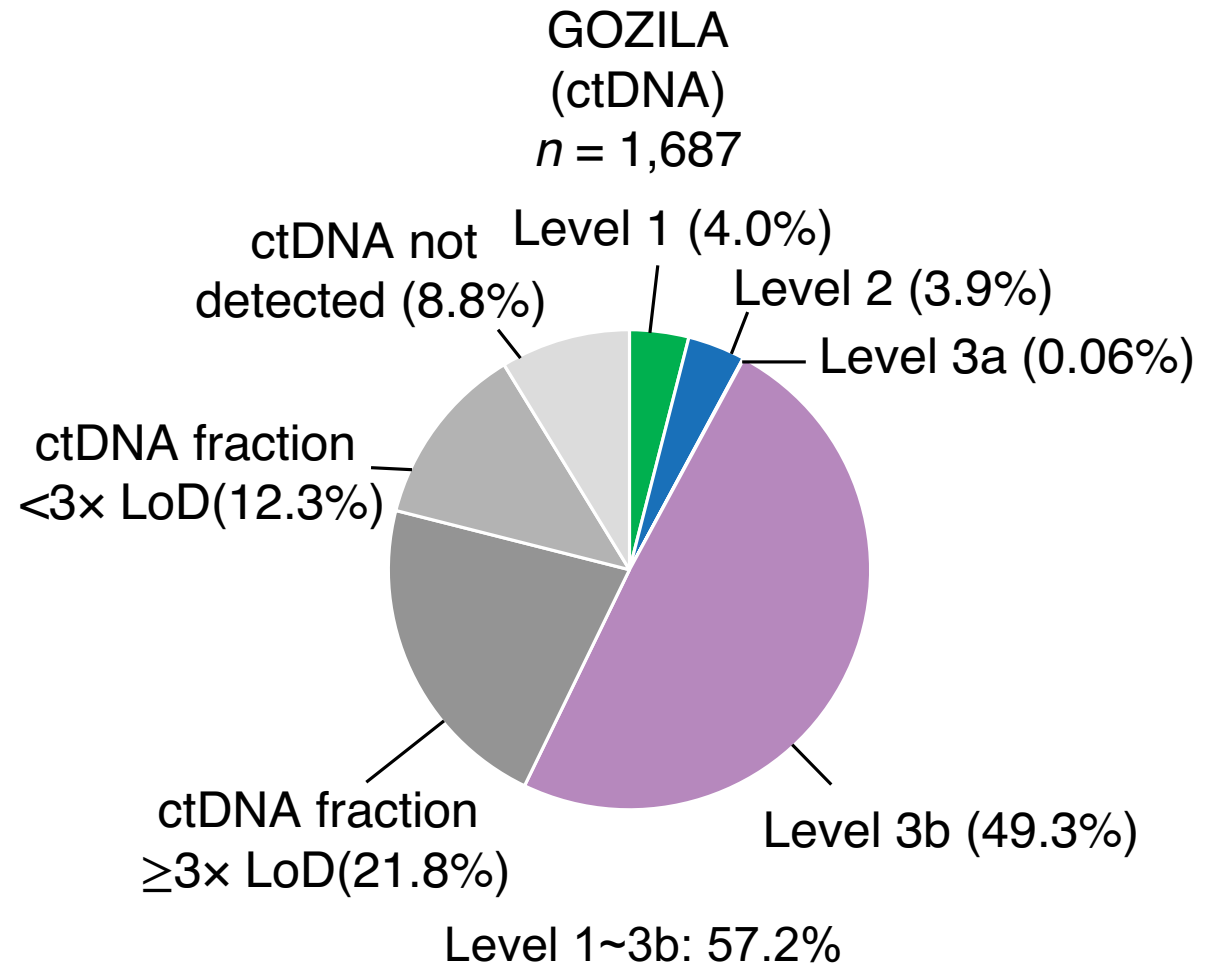
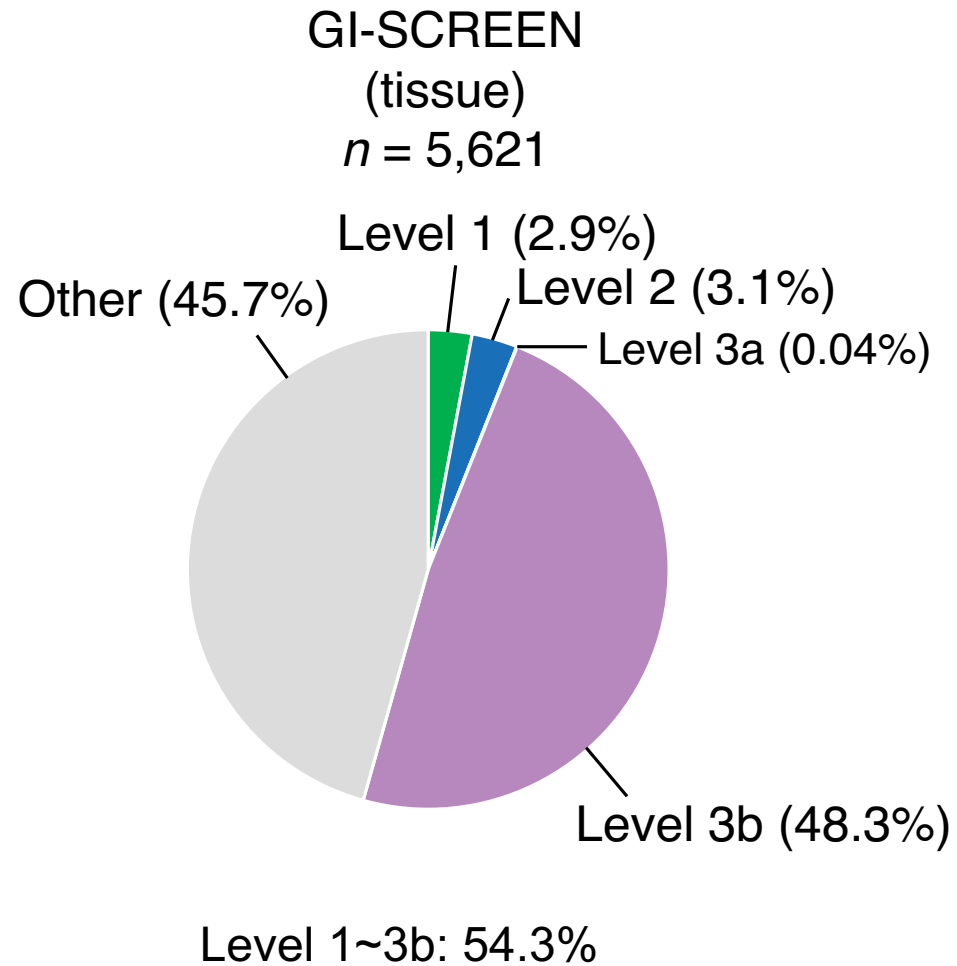
2018年1月に開始したctDNAパネル検査のスクリーニングプロジェクト

3000名以上の患者さんが参加

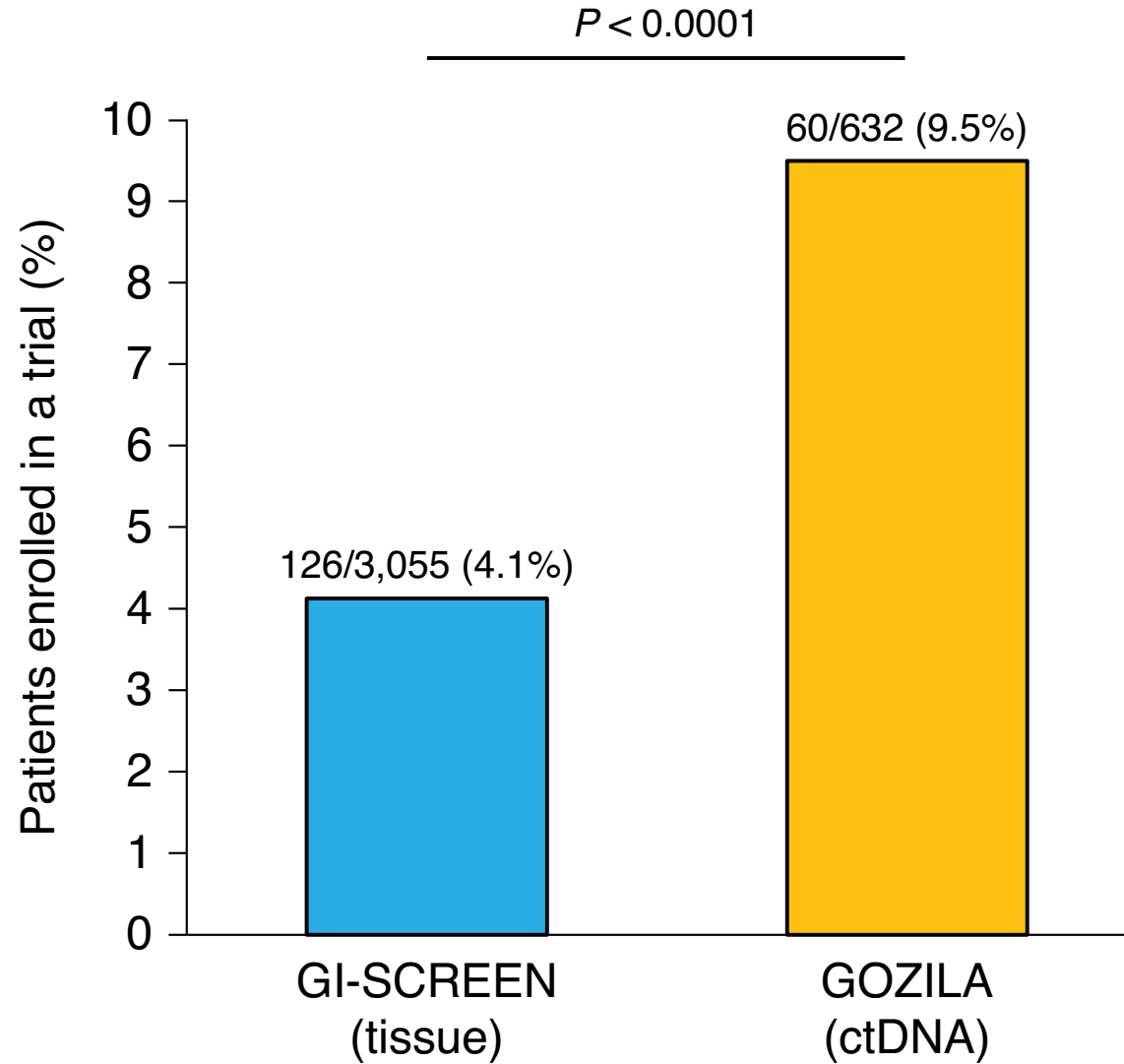
Turnaround Time



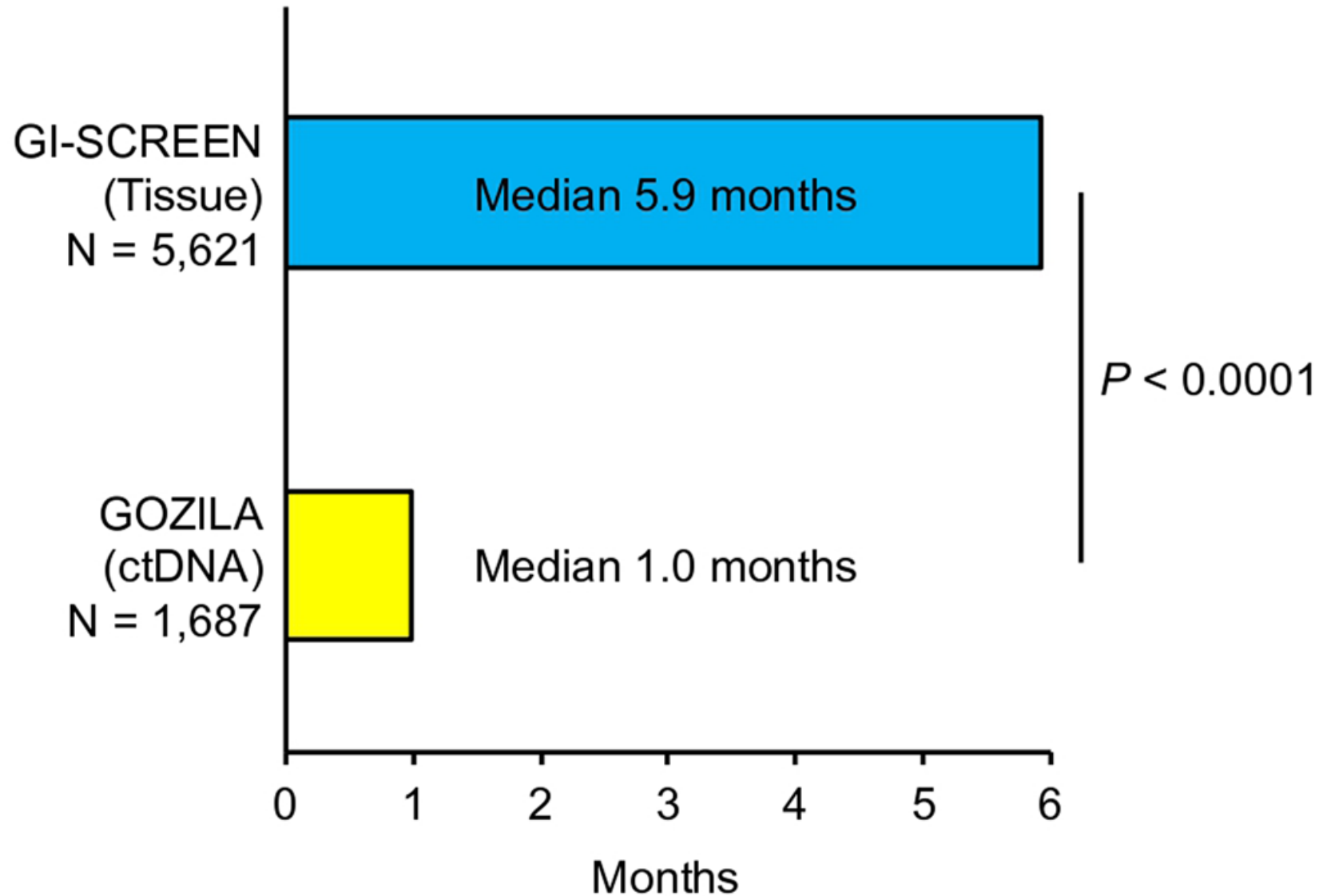
Proportion of Actionable Alteration



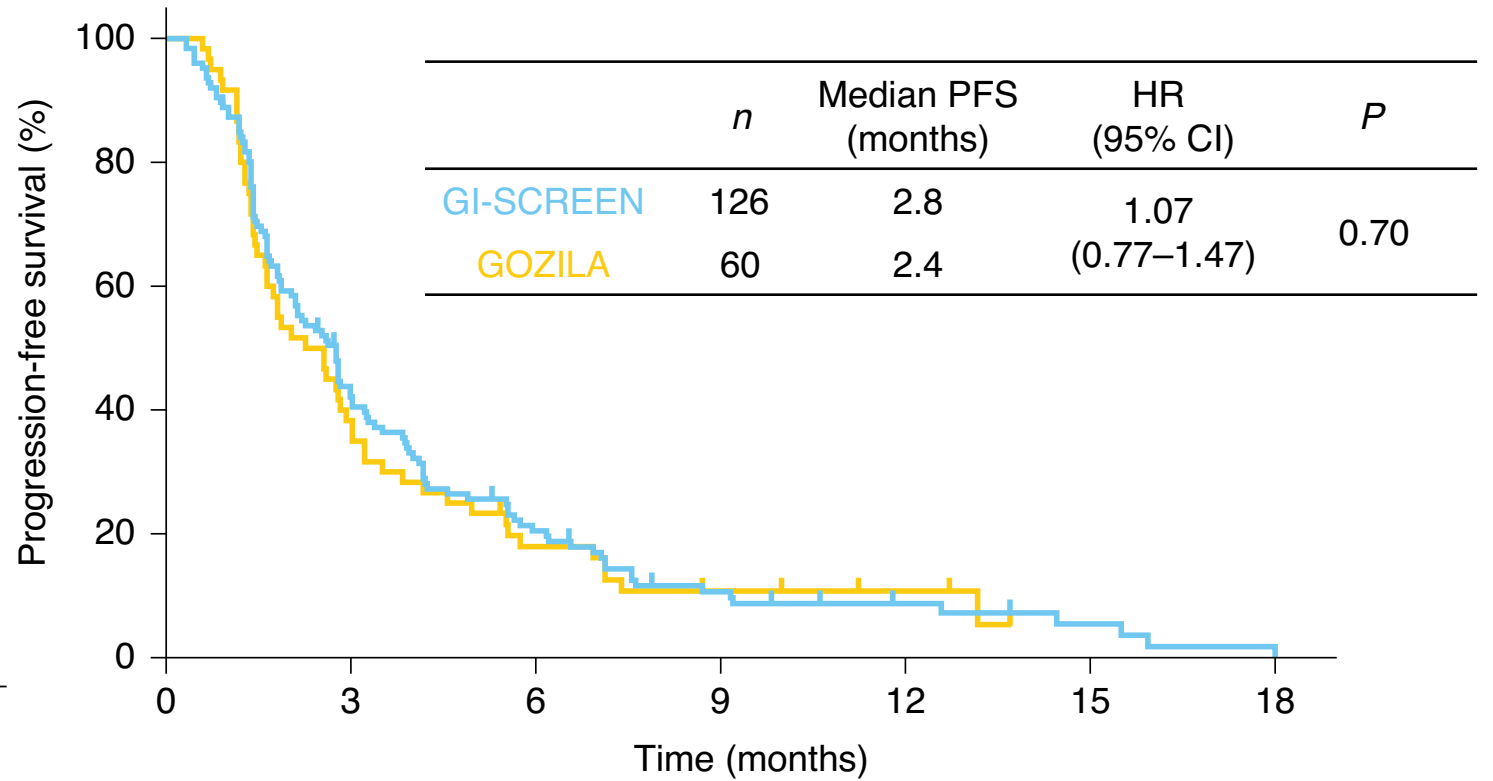
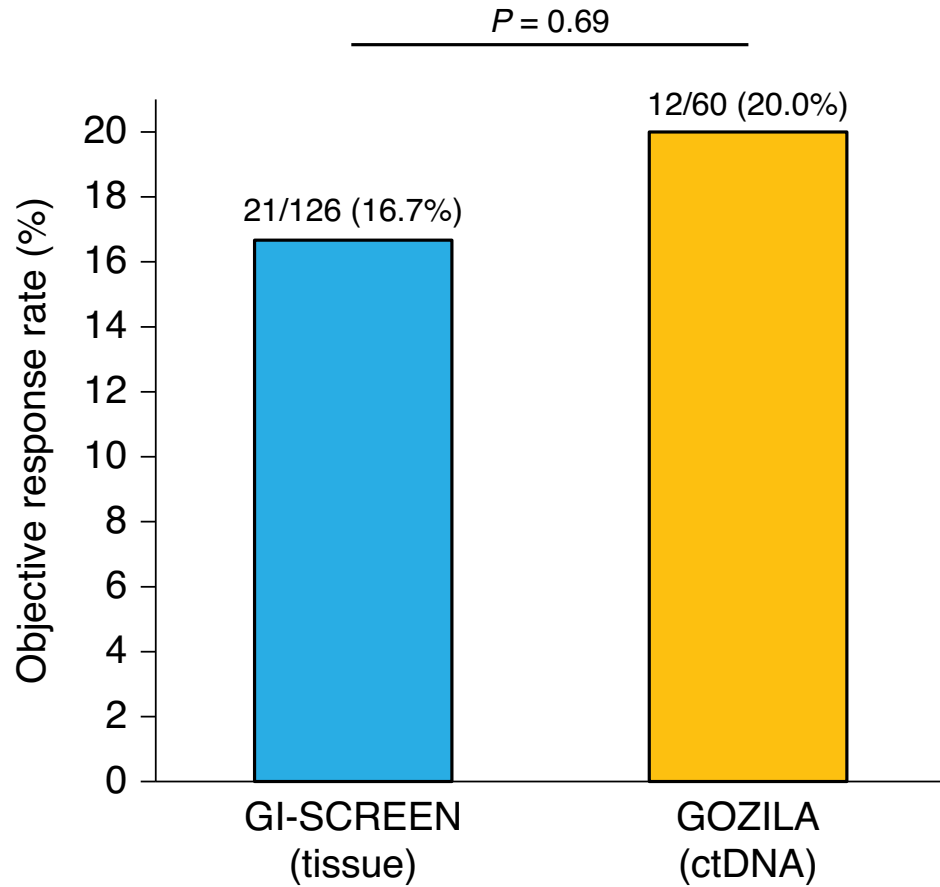
Clinical Trial Enrollment Rate



Interval between Screening and Trial Enrollment



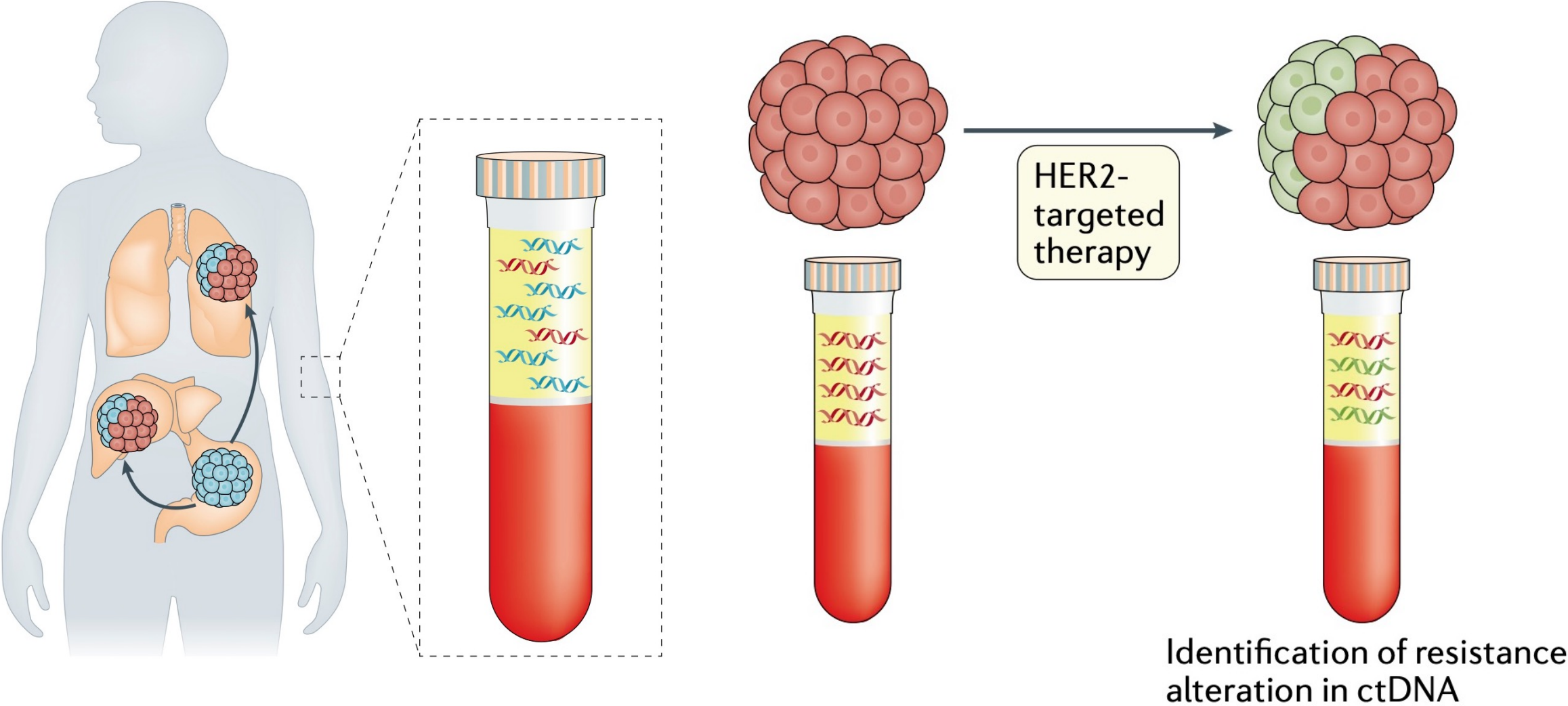
Efficacy of Clinical Trials



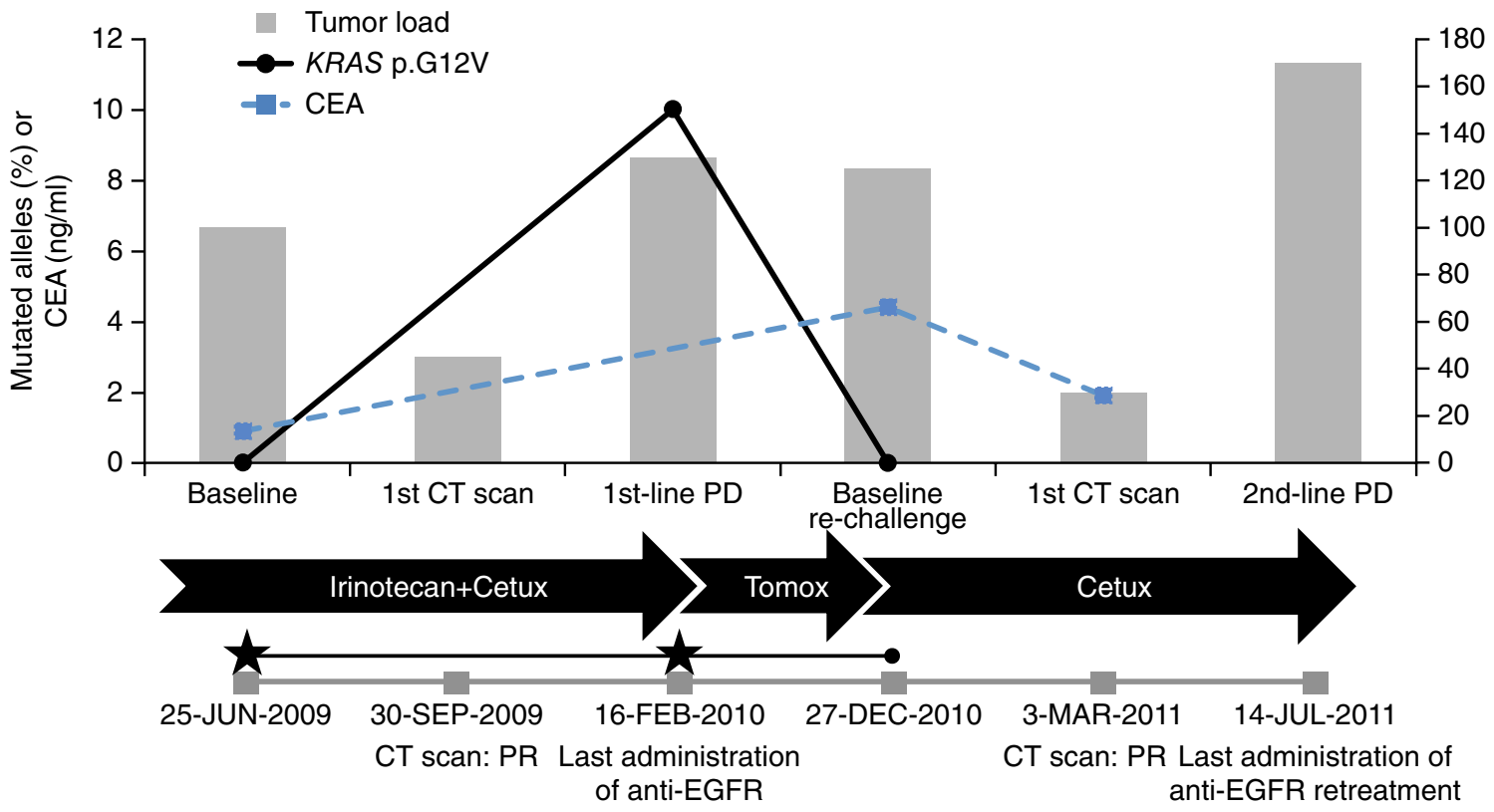
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Heterogeneity by ctDNA Analysis



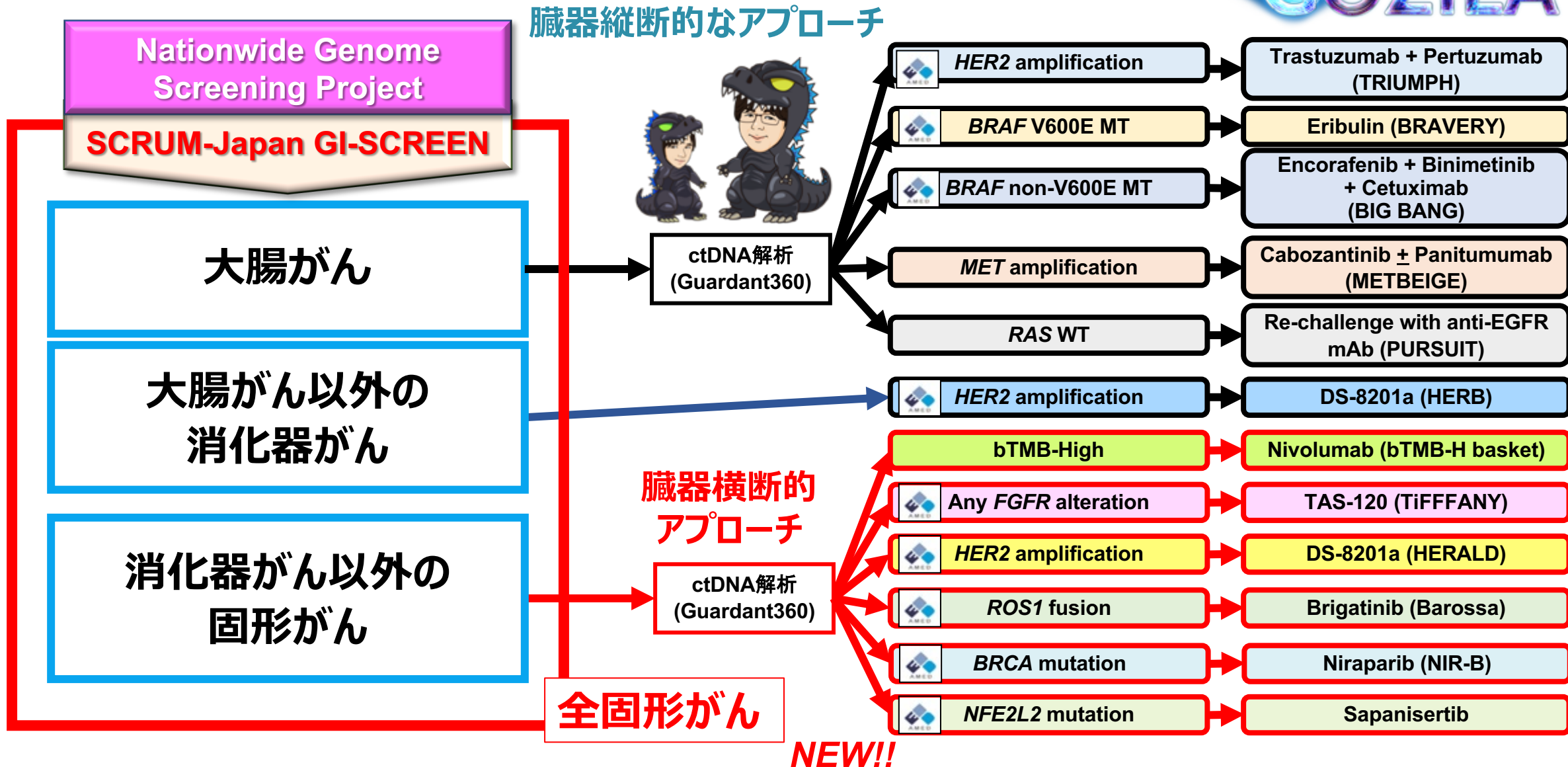
Clonal Evolution Captured by ctDNA Analysis



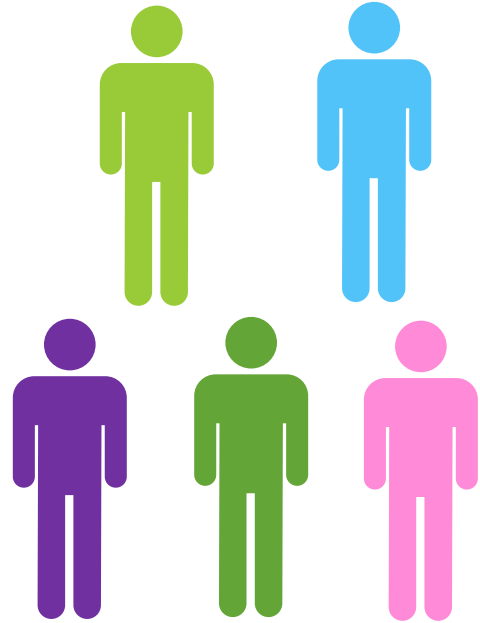
Tumor load (% of baseline)



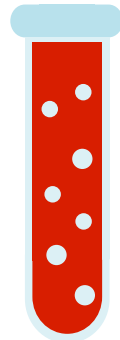
GOZILA IITs



MONSTAR-SCREEN



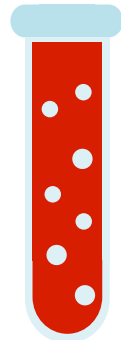
Solid tumors



F1L CDx



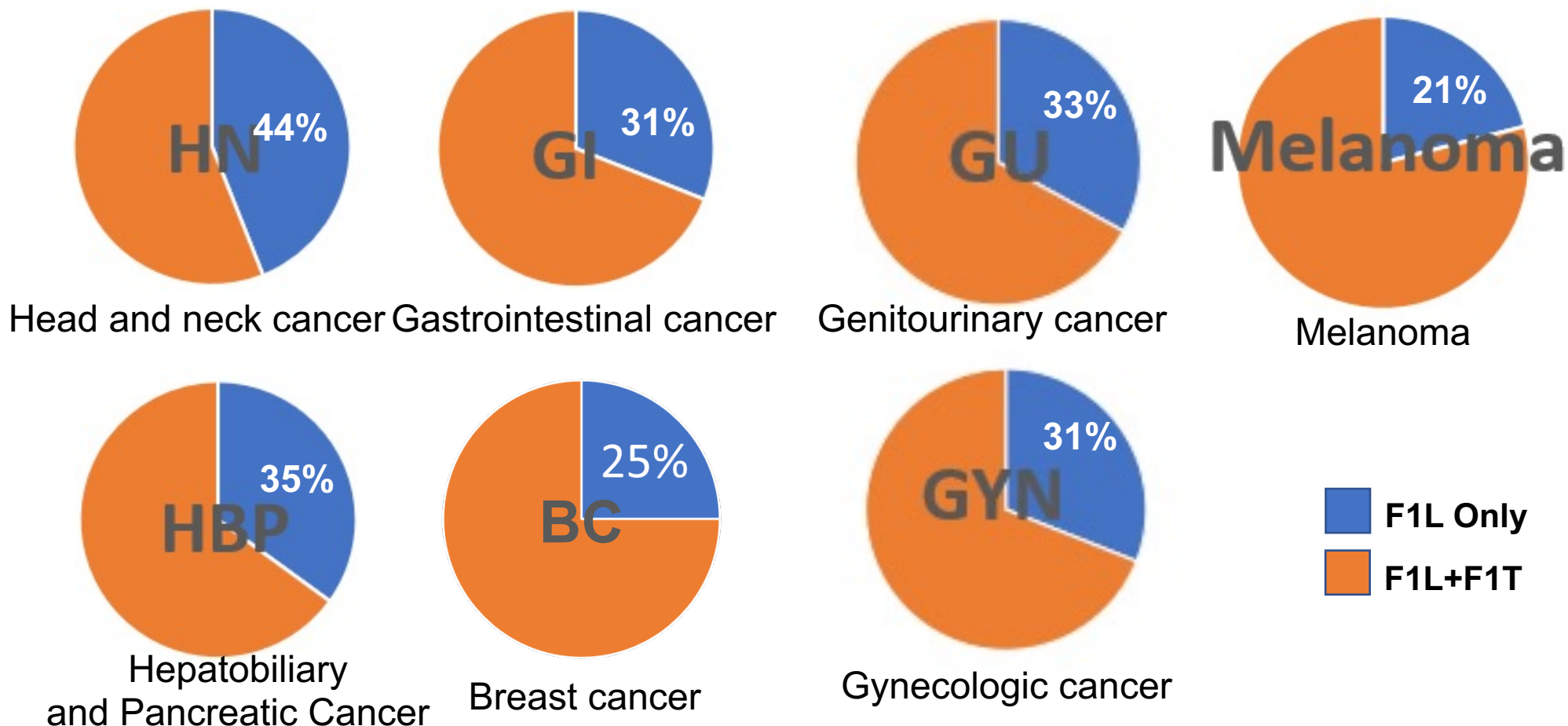
Microbiome



Assess temporal changes in cancer biomarkers thorough systemic therapy

Next stage MONSTAR-SCREEN will be launched soon with whole-exome transcriptome analysis of circulating tumor nucleic acids

Tissue/ctDNA Genotyping



F1Lで検出された変異全体の21%~44%がF1Lのみでしか検出されなかった。

ctDNA解析の欠点

- エビデンスが少ない
- ctDNAの滲出量が少ない症例では遺伝子異常の評価が困難
- Subclonal遺伝子異常の治療標的としての意義が不明
- クローン造血（Clonal hematopoiesis: CHIP）の区別が不可能

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ctDNA解析の前向きエビデンス

Phase	Drug	ctDNA Assay	Cancer	Alteration	Trial
3	Alpelisib	Therascreen PIK3CA RGQ	Breast cancer	<i>PIK3CA</i> mutation	SOLAR-1
3	Buparlisib	Inostics BEAMing	Breast cancer	<i>PIK3CA</i> mutation	BELLE-3
3	Osimertinib*	Cobas EGFR Guardant360	Non-small-cell lung cancer	<i>EGFR</i> mutation	FLAURA, AURA3
2	Pertuzumab + trastuzumab	Guardant360	Colorectal cancer	<i>HER2</i> amplification	TRIUMPH
2	Bemarituzumab	Not disclosed	Gastric cancer	<i>FGFR2</i> amplification	FIGHT
2	Tepotinib	Guardant360	Non-small-cell lung cancer	<i>MET</i> ex14 skipping	VISION
2	Rucaparib*	F1L CDx	Prostate cancer	<i>BRCA1/2</i> alteration	TRITON2

*検体採取は前向き、解析は後ろ向き

Prospective Evidence of ctDNA Analysis



Key eligibility criteria

- Metastatic CRC
- ECOG PS of 0 or 1
- Refractory or intolerant to standard therapy that included anti-EGFR monoclonal antibody
- *RAS* wild-type by tissue analysis
- HER2 positive by tissue analysis: IHC 3+ or FISH positive (*HER2/CEP17* ratio ≥ 2.0)
or
ERBB2-amplified and *RAS* wild-type identified by ctDNA analysis (NGS-based assay, Guardant360)

Meet
eligibility
criteria

Trastuzumab
8 mg/kg load then 6 mg/kg
+
Pertuzumab
840 mg load then 420 mg
Q3W until PD

Primary endpoint:

- Confirmed objective response rate (ORR) in *ERBB2* amp group confirmed by tissue analysis
- Confirmed ORR in *ERBB2* amp group confirmed by ctDNA analysis

Sample size and statistical plan: 25 with one-sided $\alpha = 2.5\%$, $\beta = 10\%$, $H_0 = 5\%$ ORR, and $H_1 = 30\%$ ORR for each tissue and ctDNA positive group, ≥ 5 responses needed to reject H_0 .

Prospective Evidence of ctDNA Analysis

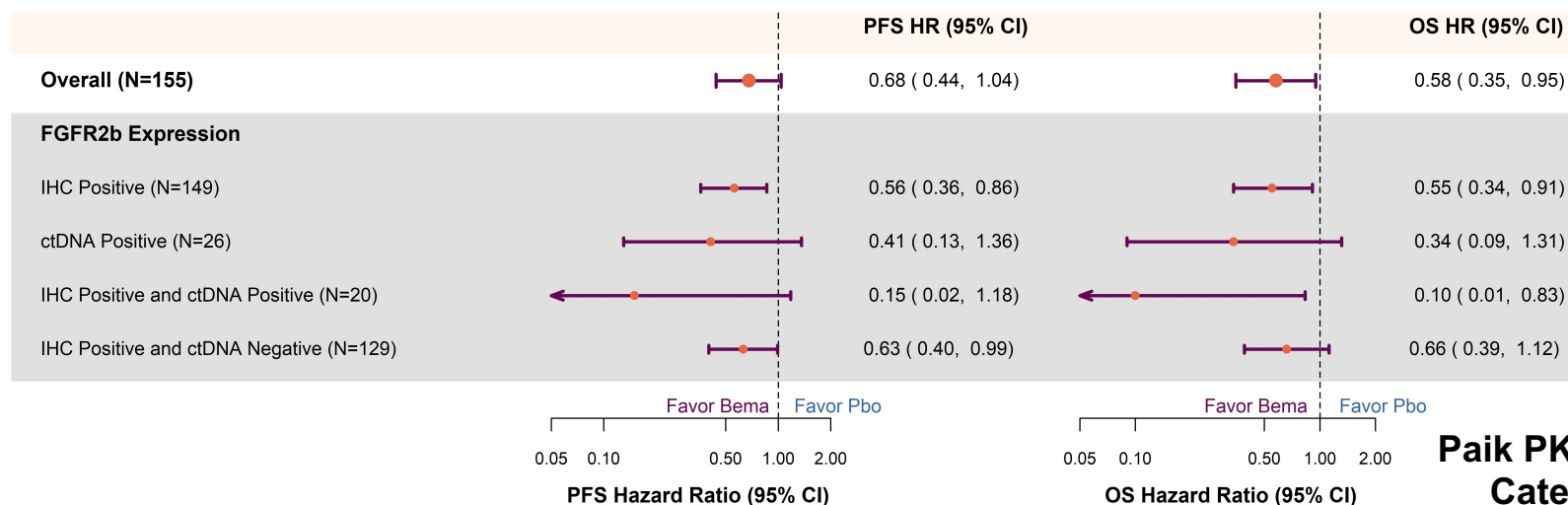
	ORR N (% [95% CI])	DCR N (% [95% CI])
Tissue positive group (N = 17)		
All	6 (35.3 [14.2-61.7])	11 (64.7 [38.3-85.8])
Tumor site		
Right-sided (N = 1)	1 (100.0 [2.5-100.0])	1 (100.0 [2.5-100])
Left-sided (N = 16)	5 (31.3 [11.0-58.7])	10 (62.5 [35.4-84.8])
ctDNA <i>RAS/BRAF/PIK3CA/ERBB2</i>*		
WT (N = 11)	6 (54.5 [23.4-83.3])	10 (90.9 [58.7-99.8])
MT (N = 5)	0 (0.0 [0.0-52.2])	0 (0.0 [0-52.2])
ctDNA positive group (N = 15)		
All	5 (33.3 [11.8-61.6])	9 (60.0 [32.3-83.7])
Tumor site		
Right-sided (N = 2)	1 (50.0 [13.0-98.7])	1 (50.0 [1.3-98.7])
Left-sided (N = 13)	4 (30.8 [9.1-68.4])	8 (61.5 [31.6-86.1])
ctDNA <i>RAS/BRAF/PIK3CA/ERBB2</i>		
WT (N = 11)	5 (45.5 [16.7-76.6])	9 (81.8 [48.2-97.7])
MT (N = 4)	0 (0.0 [0.0-60.2])	0 (0.0 [0.0-60.2])

Prospective Evidence of ctDNA Analysis

Tepotinib for MET+ NSCLC

Tepotinib 500 mg QD	Liquid biopsy (L+)		Tissue biopsy (T+)	
	IRC (n=48)	Investigator (n=47)	IRC (n=51)	Investigator (n=51)
BOR by RECIST 1.1, n (%)				
Complete response	0 (0)	3 (6.4)	0 (0)	3 (5.9)
Partial response	24 (50.0)	23 (48.9)	23 (45.1)	25 (49.0)
Stable disease	8 (16.7)	5 (10.6)	14 (27.5)	11 (21.6)
Progressive disease	7 (14.6)	10 (21.3)	8 (15.7)	6 (11.8)
Not evaluable	9 (18.8)	6 (12.8)	6 (11.8)	6 (11.8)
ORR,* n (%) [95% CI]	24 (50.0) [35.2, 64.8]	26 (55.3) [40.1, 69.8]	23 (45.1) [31.1, 59.7]	28 (54.9) [40.3, 68.9]
mDOR, months [95% CI]	12.4 [5.8, ne]	17.1 [7.1, ne]	15.7 [9.0, ne]	14.3 [5.7, ne]
DCR,† n (%) [95% CI]	32 (66.7) [51.6, 79.6]	31 (66.0) [50.7, 79.1]	37 (72.5) [58.3, 84.1]	39 (76.5) [62.5, 87.2]

Bemarituzumab for FGFR2+ gastric cancer



Paik PK, et al. N Engl J Med 2020.
Catenacci D, et al. ASCO 2021.

ctDNA解析の欠点

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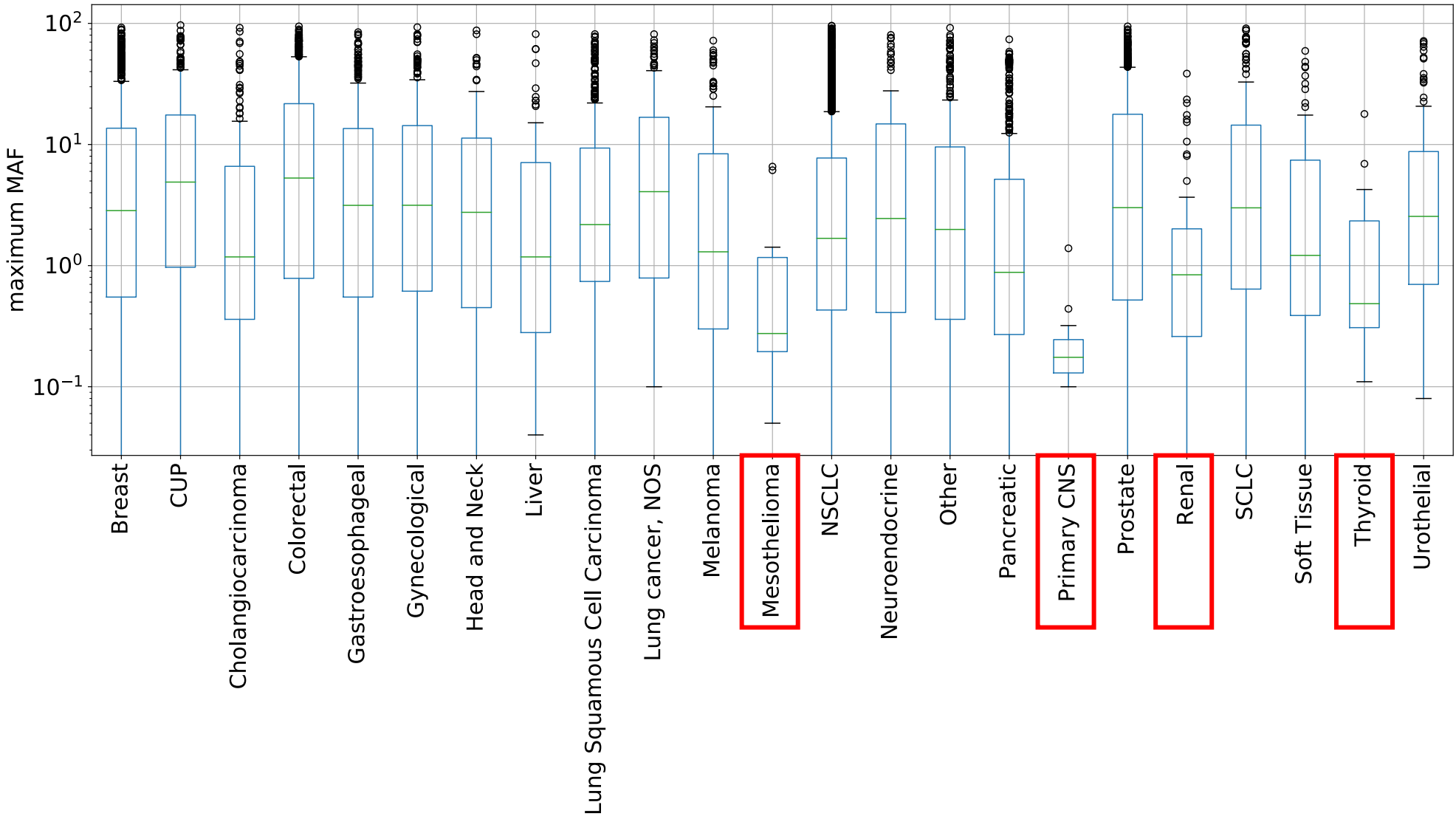
ctDNA滲出に影響を与える因子

□ 採血手順

□ 患者因子—日内変動、喫煙、妊娠、運動、合併症（炎症性疾患、貧血、心疾患、代謝性疾患、自己免疫性疾患など）、輸血、骨髄移植、臓器移植

□ 腫瘍因子—がん種、腫瘍量、転移臓器個数、転移臓器部位など

ctDNA Level across Cancer Types



ctDNA解析の欠点

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- **Subclonal遺伝子異常の治療標的としての意義が不明**
- **クローン造血（Clonal hematopoiesis: CHIP）の区別が不可能**

腫瘍組織解析とctDNA解析の使い分け（私見）

がん種	ctDNA滲出量が少ない (脳腫瘍、腎細胞がん、悪性黒色腫、etc.)	ctDNA滲出量が多い (消化器がん、乳がん、膀胱がん、etc.) 組織が入手しにくい、古い (胆道がん、膵がん、前立腺がんetc.)
腫瘍量	腫瘍量が少ない、肺転移単独	腫瘍量が多い、肝転移
治療ライン	治療中、病勢がstable	1st line前、治療変更時、標的治療後、 腫瘍組織に治療修飾が入っている
バイオマーカー	TMB-H、LOHを期待、Tissueベースの治験	

腫瘍組織解析Favor

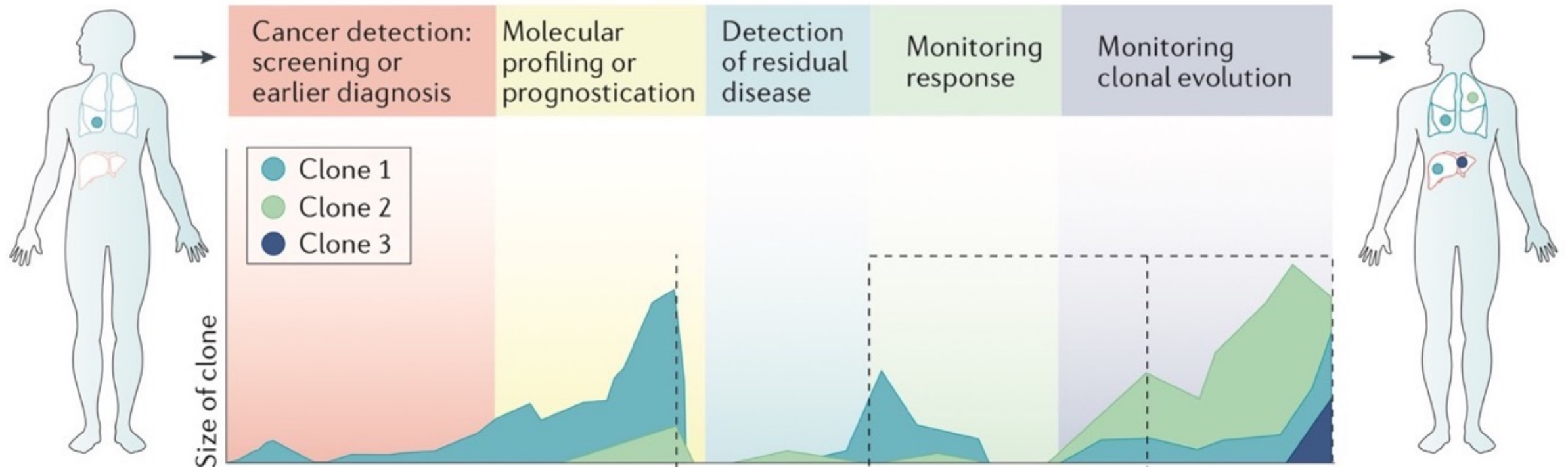
- ✓ 豊富なエビデンス
- ✓ 腫瘍量と関係なく評価可能
- ✓ Clonalな遺伝子異常のみ評価
- ✓ CHIPの懸念が少ない



ctDNA解析Favor

- ✓ TATが短い
- ✓ Heterogeneityを評価可能

Patient JourneyにおけるctDNA NGS



早期発見

✓ 症状出現前の
スクリーニング

予後予測

残存腫瘍の検出

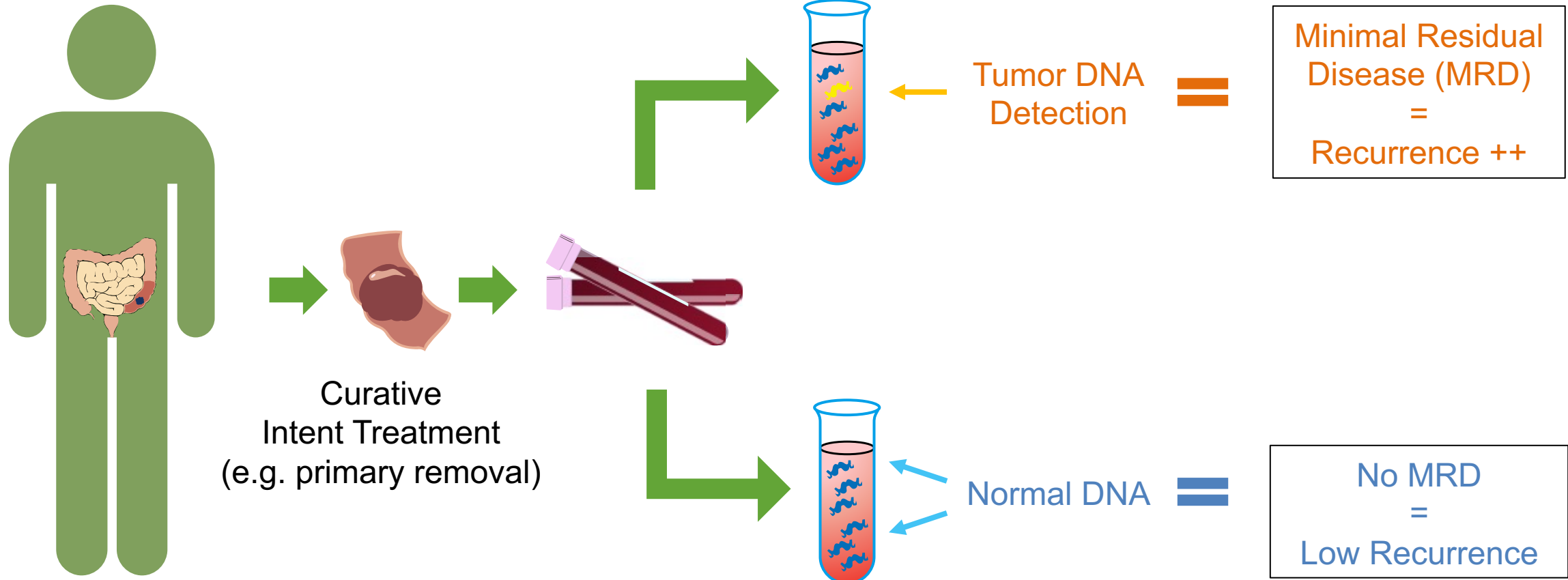
✓ MRD確認による
再発リスク評価

治療モニタリング

薬剤選択

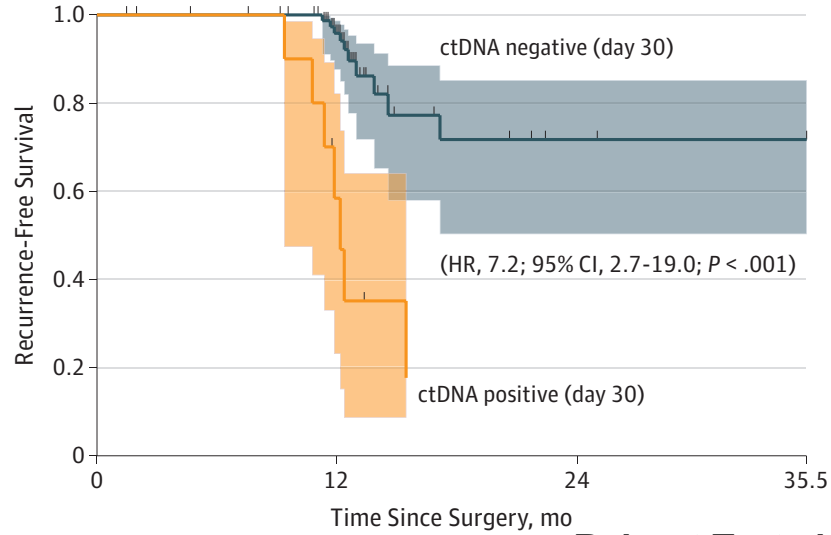
✓ 遺伝子異常に応じた標
的治療の選択

Assessment of MRD by ctDNA Analysis



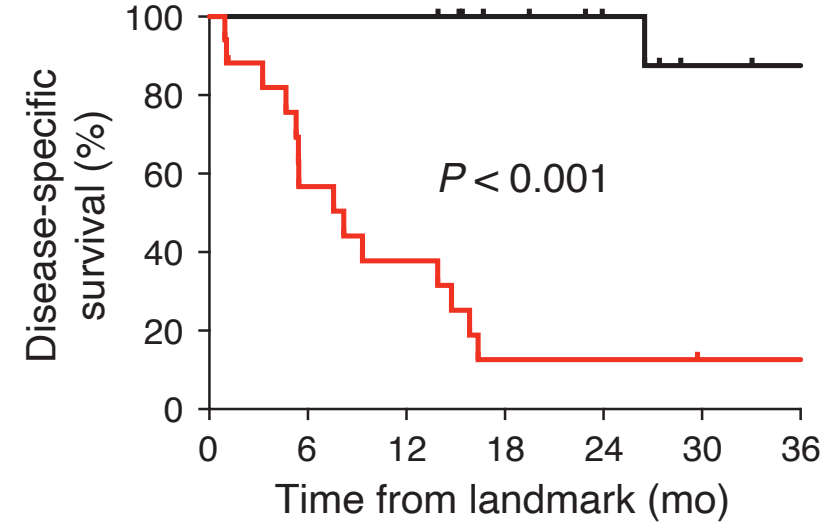
Post-operative ctDNA and Recurrence

Colorectal cancer (Signatera)



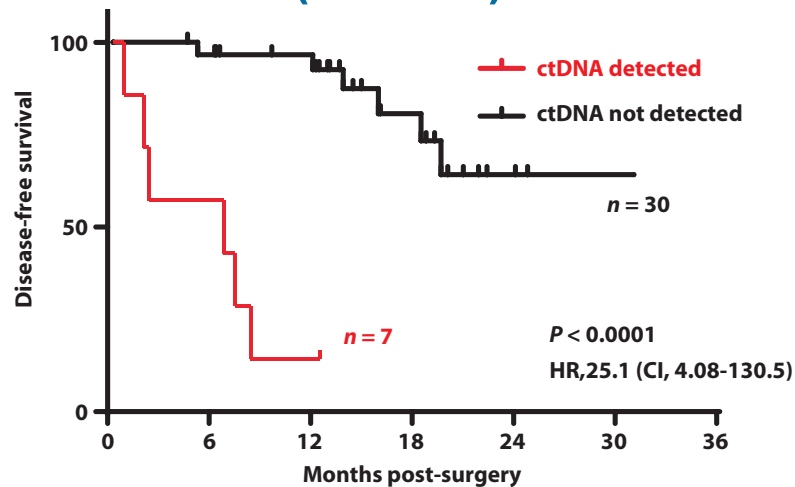
Reinert T, et al. JAMA Oncol 2019.

Lung cancer (CAPP-seq)



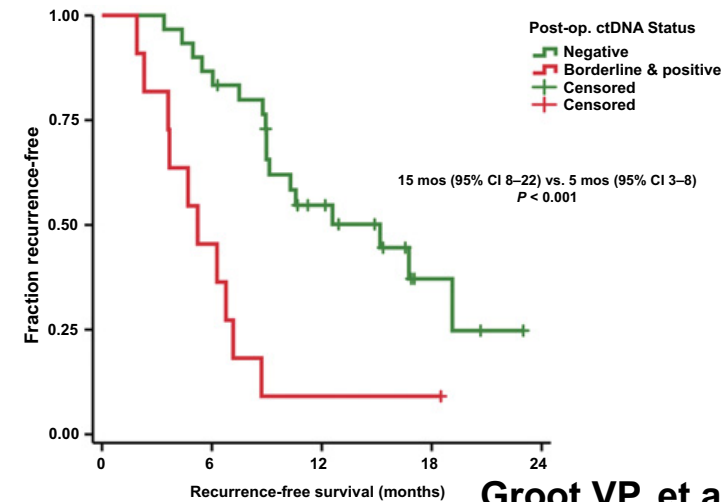
Chaudhuri AA, et al. Cancer Discov 2017.

Breast cancer (ddPCR)



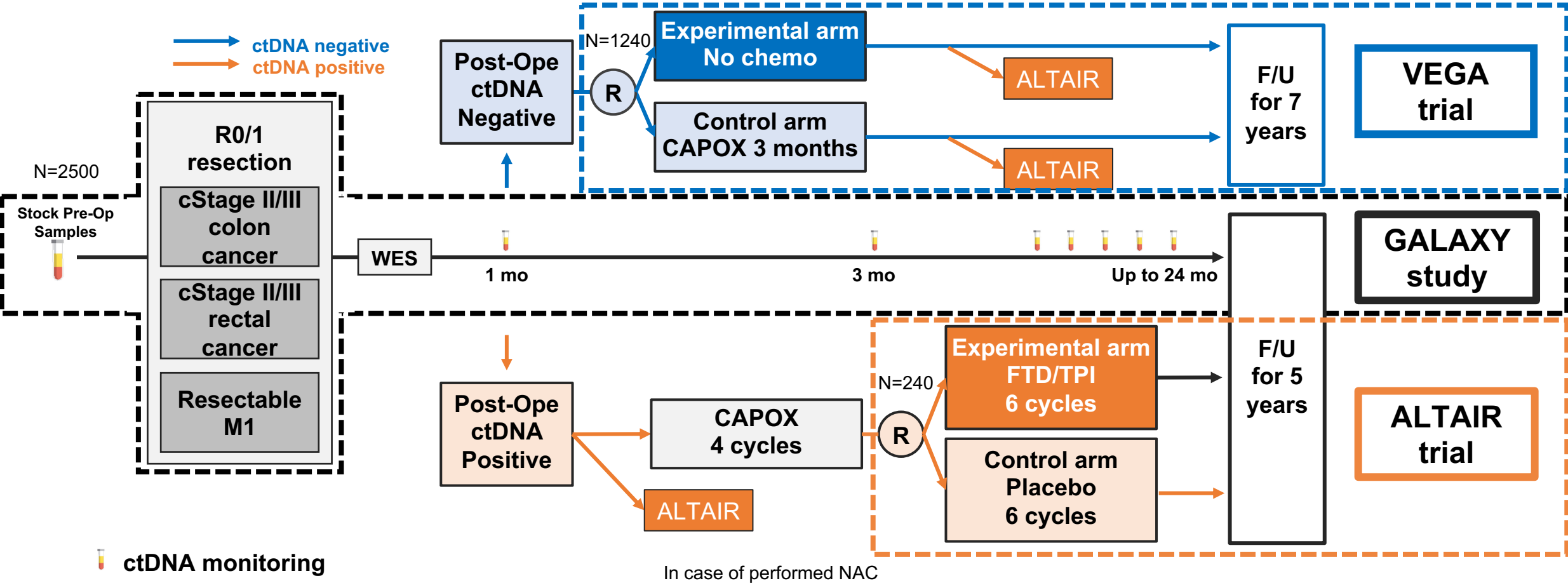
Garcia-Murillas I, et al. Sci Transl Med 2015.

Pancreatic cancer (ddPCR)



Groot VP, et al. Clin Cancer Res 2019.

CIRCULATE-Japan Project Since May 2020

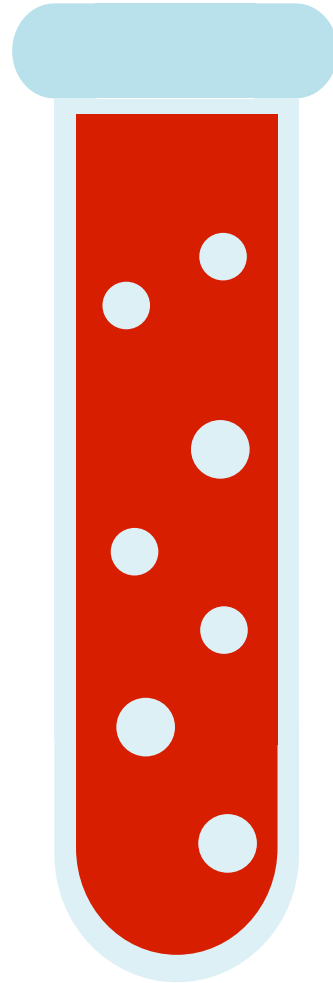
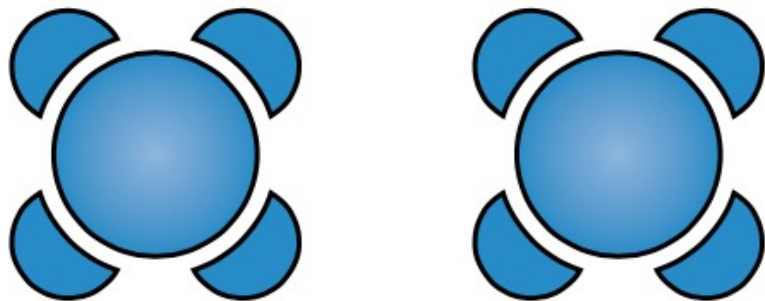


Liquid Biopsy Early Cancer Detection

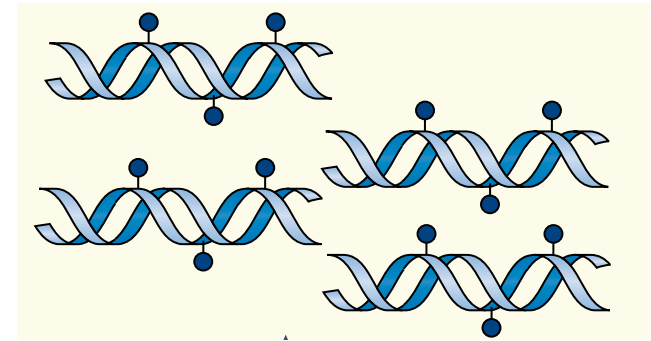
Genome



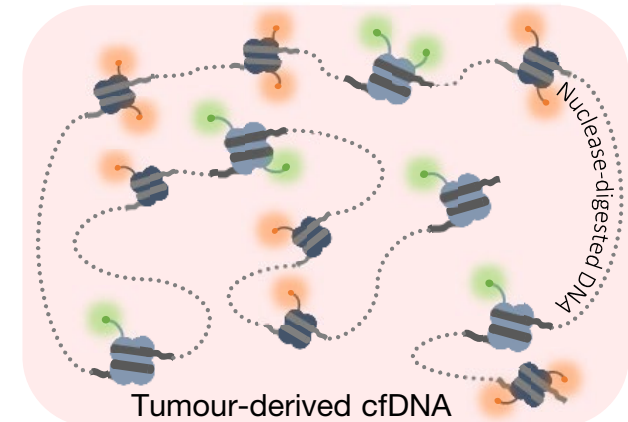
Proteome



Methylome



Fragmentome



COSMOS Project



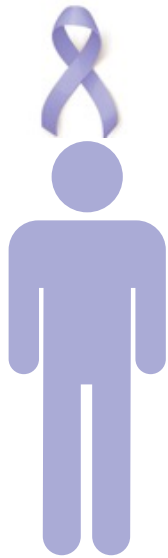
Liver



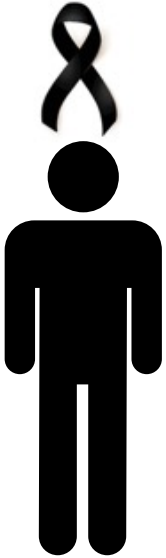
Pancreas



Colorectum

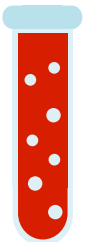


Stomach
GIST



Melanoma

LUNAR



Pre-op phase

Surgery

Post-op phase



Summary

- **ctDNA解析はがんゲノム医療において従来の組織ベースの遺伝子パネル検査を上回る有用性が示唆されており、進行大腸がんにおいてはがんゲノムプロファイリングやclonal evolutionの評価としての使用が増えてくることが予想される。**
- **さらに、ctDNA解析は腫瘍が無い状況のMRDや早期がんの同定に役立つ可能性があり、あらゆるがん種・あらゆるステージでの応用が期待されている。**

Acknowledgement

Patients and families

SCRUM-Japan MONSTAR SCREEN

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- Dpt. of Gastrointestinal Oncology

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Thank You For Kind Attention!!



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