Precision Medicine in Oncology – Today and the Future

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Evolution of cancer molecular targets, testing, and related therapeutics

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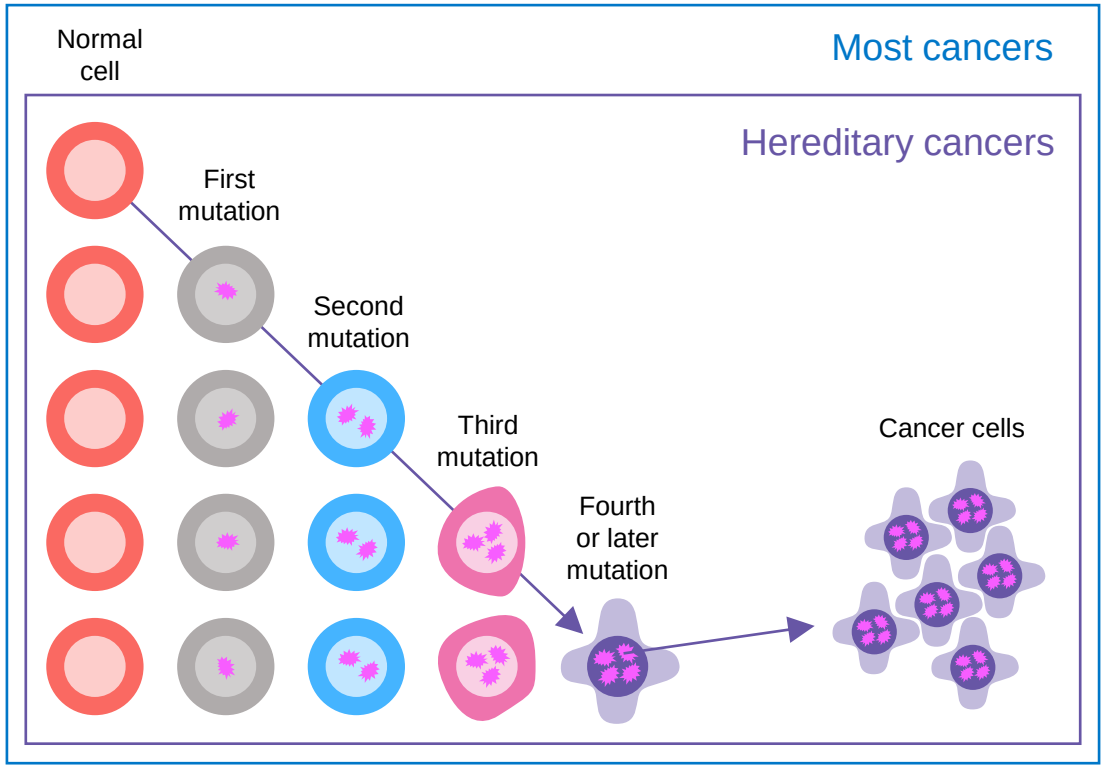
Cancer: A Disease of the Genome

- DNA mutations cause cancer by changing the genome of cells, leading to uncontrolled cell growth
- In 5–10% of cancers, people inherit mutations that predispose them to cancer
- Mutations in several growth-controlling genes are needed for cells to become cancerous



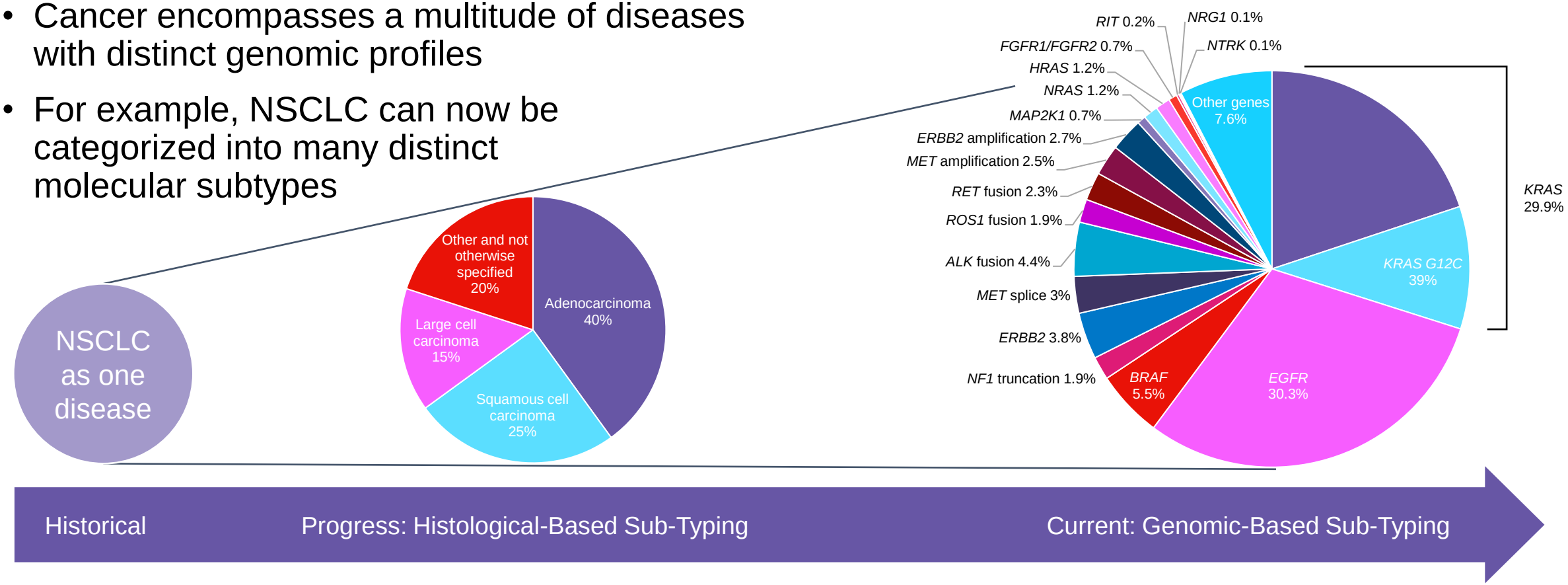
National Cancer Institute

Ref: https://www.cancer.gov/about-cancer/causes-prevention/genetics.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Cancer Is Increasingly Defined and Treated Based on Mutations that Drive its Growth

- Cancer encompasses a multitude of diseases with distinct genomic profiles
- For example, NSCLC can now be categorized into many distinct molecular subtypes



NSCLC=non-small cell lung cancer

1. Addeo A et al. *Cancer Treatment Rev* 2021;96:102179; 2. Skoulidis F, Heymach JV. *Nat Rev Cancer* 2019;19:495–509;
3. Schabath MB, Cote ML. *Cancer Epidemiol Biomarkers Prev* 2019;28:1563–79.

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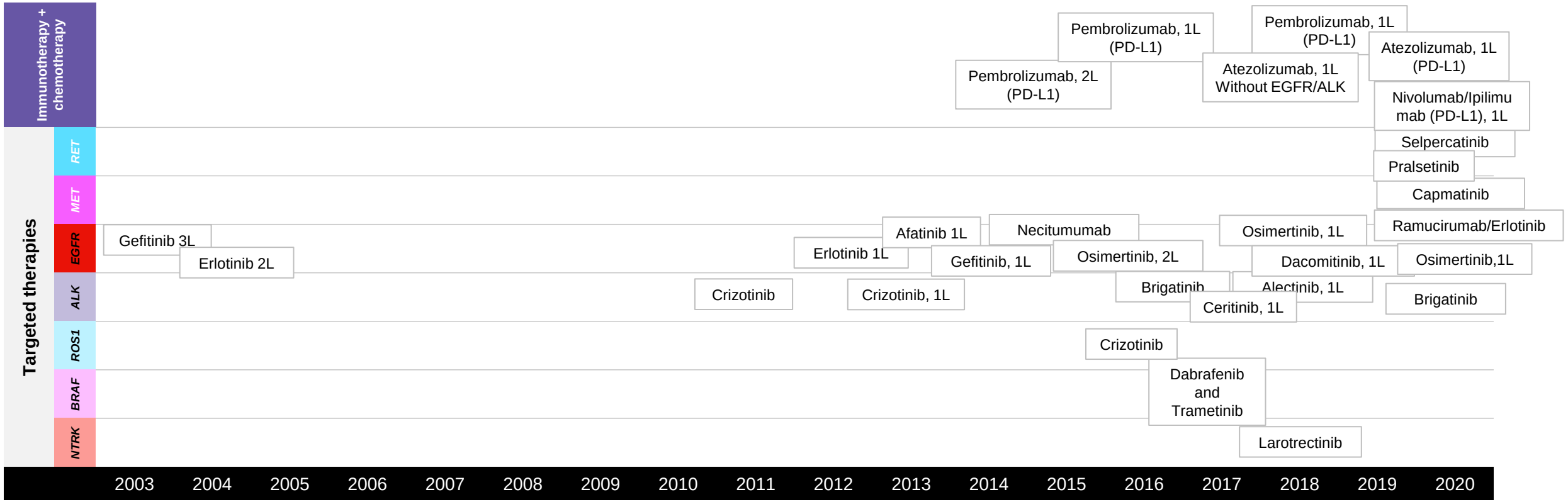
Fast Pace of Biomarker-Driven Indications

*29 NSCLC biomarker-driven indications since 2003 in the US**



US FDA-approved indications of NSCLC treatments since 2003. Abbreviations: 1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; del19, deletion in exon 19; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; NTRK, neurotropic tropomyosin receptor kinase; PD-L1, programmed-death ligand 1; ROS1, c-ros1 oncogene; SqCC, squamous cell carcinoma.

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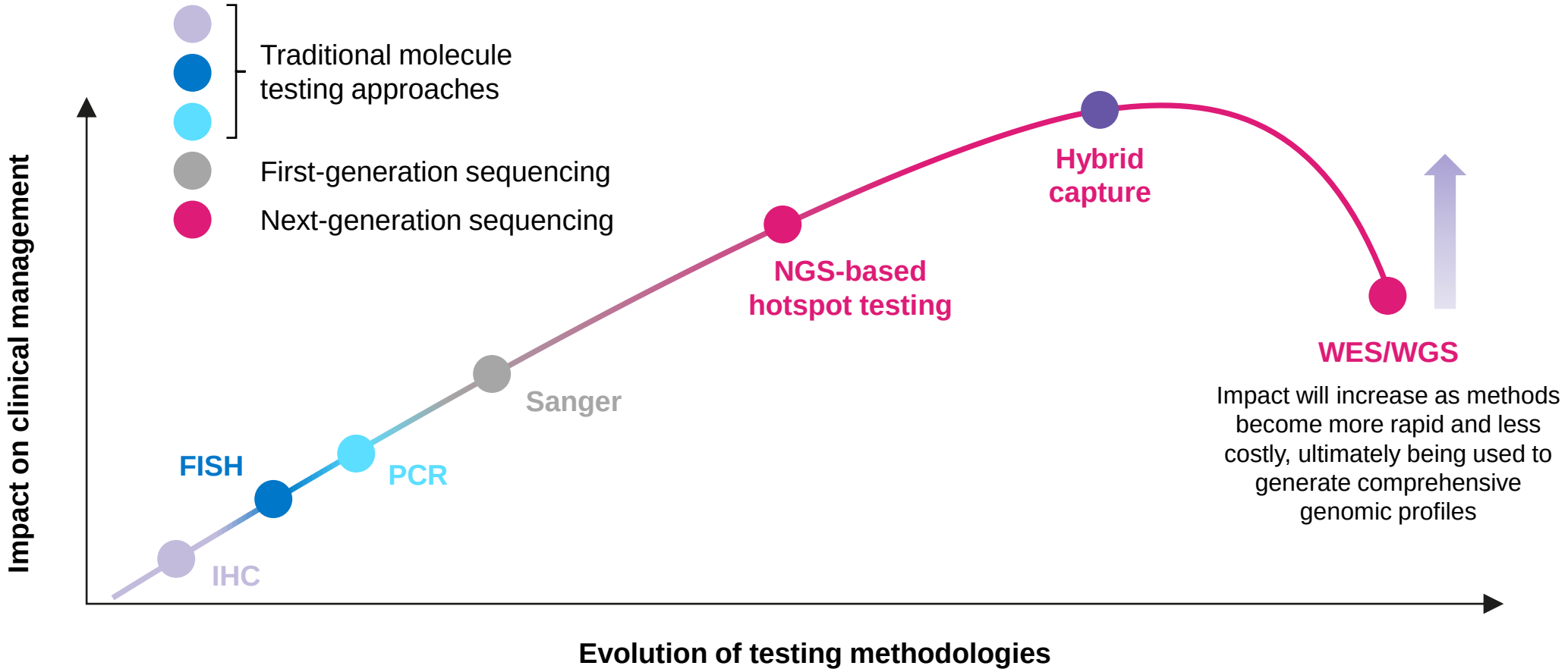
NSCLC=non-small cell lung cancer

*Buchhalter I, Rempel E, Endris V,et al. *Int J Cancer*. 2019;144(4):848-858.

The Evolution of Molecular Testing

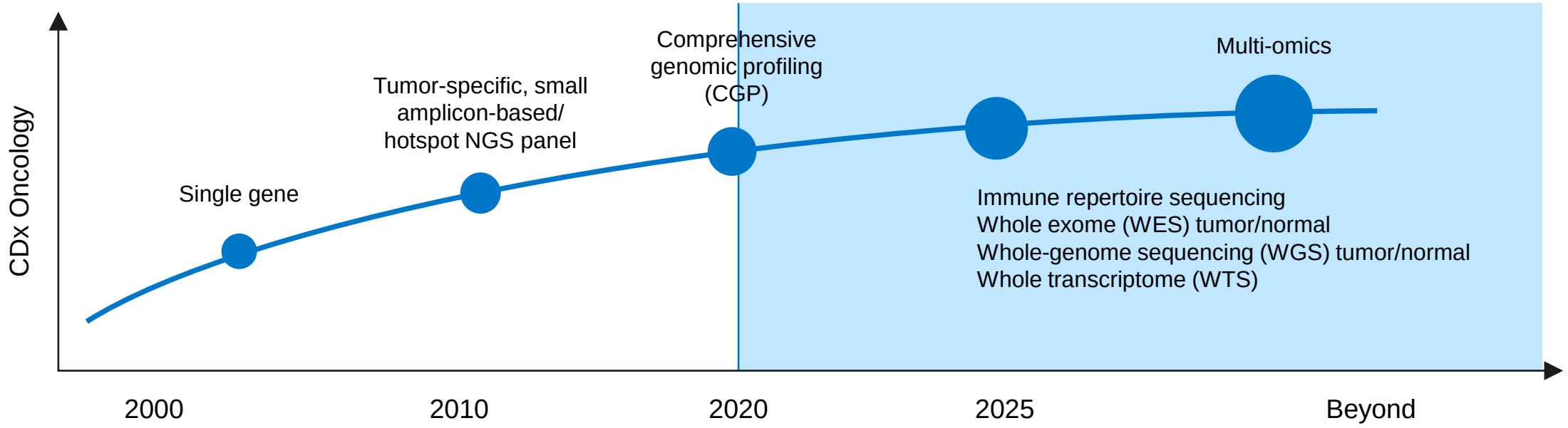


FISH=fluorescence in situ hybridisation; IHC=immunohistochemistry; NGS= next-generation sequencing; PCR=polymerase chain reaction; WES=whole exome sequencing; WGS=whole-genome sequencing.

Netto GJ, et al. *Proc Bayl Univ Med Cent* 2003;16:379-83; de Matos LL, et al. *Biomark Insights* 2010;5:9-20; Dong L, et al. *Curr Genomics* 2015;16:253-63.

Next-Generation Sequencing

- Next-generation sequencing (NGS) is the segment of oncology companion diagnostics projected to grow at the fastest rate



Companion Diagnostics Market by Product & Service (Assay, Kit, Software & Service), Technology (PCR, NGS, ISH, IHC), Indication (Breast, Lung & Gastric Cancer, Neurological Disease), End-User (Pharma Companies, CRO), Region - Global Forecast to 2025. Published by MarketsandMarkets™.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Precision Medicine: 20 Years of Advances

1971
Tamoxifen

1998
Trastuzumab

2001
Imatinib

2004
Gefitinib

2006
Cetuximab

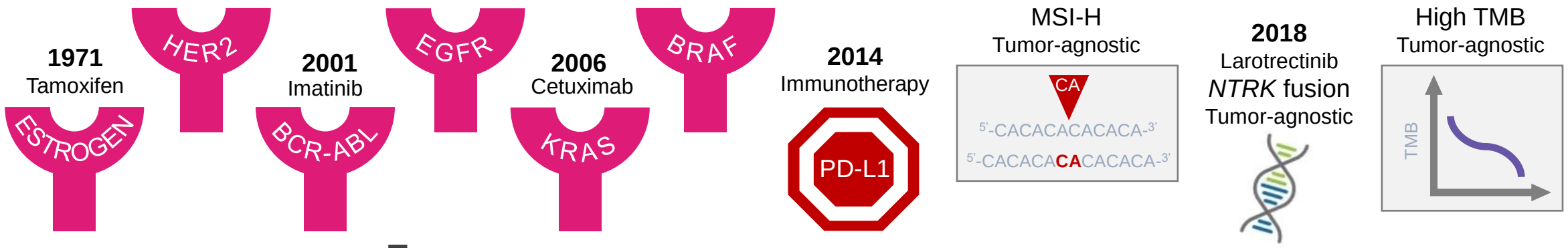
2011
Vemurafenib

2014
Immunotherapy

2015
Pembrolizumab
MSI-H
Tumor-agnostic

2018
Larotrectinib
NTRK fusion
Tumor-agnostic

2020
Pembrolizumab
High TMB
Tumor-agnostic



THERAPEUTIC LANDMARKS AND THEIR MOLECULAR TARGETS

1970 1990 2000 2010 2020

DIAGNOSTIC TECHNOLOGIES

1982
First oncogene isolated

2000
Gene expression profiling for chemotherapy selection

2005
NGS technology

2011
FoundationOne CLIA certification

2014
MSK-Impact™ launched

REGULATORY LANDMARKS

2017
FDA approves:
FoundationOne
MSK-Impact™
Thermo Fisher Oncomine™ Dx Target Test
Illumina Praxis RAS panel

2018
NGS Funding Guidelines
CMS coverage

2019
FDA breakthrough designation:
Illumina TruSight(TM) Oncology product

2020
FDA approves:
FoundationOne Liquid CDx

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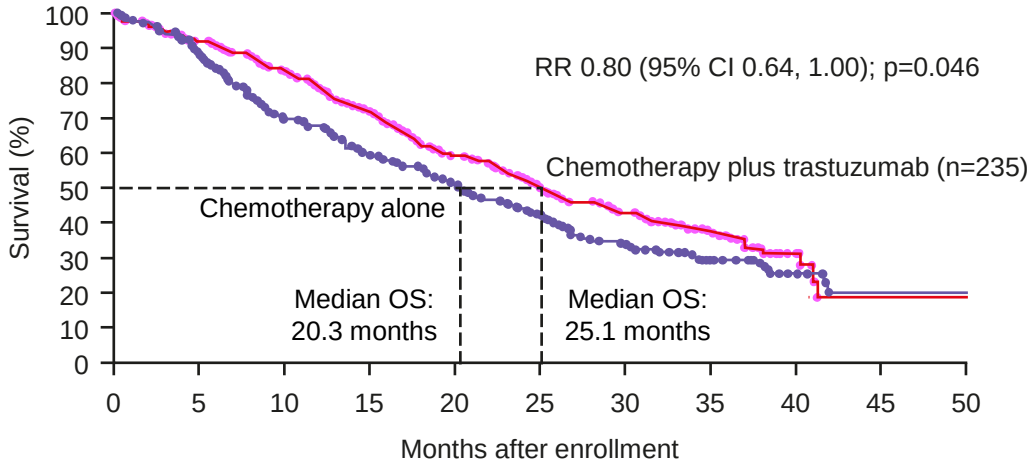
NGS=next-generation sequencing; MSI-H=microsatellite instability high
Adapted from: Colomer R et al. *E Clinical Medicine* 2020; 25:100487.

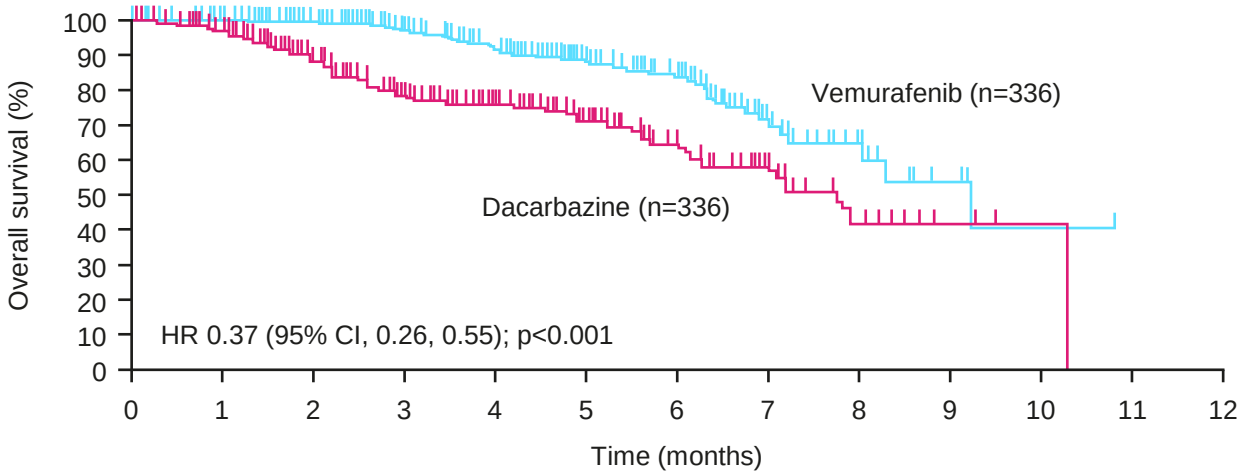
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Targeted Therapies Have Dramatically Improved Outcomes

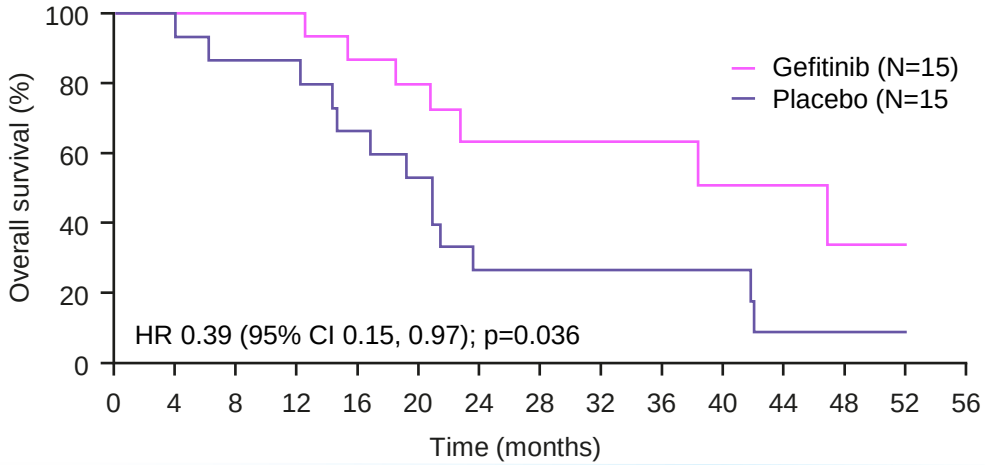
HER2+ metastatic breast cancer: trastuzumab[1]



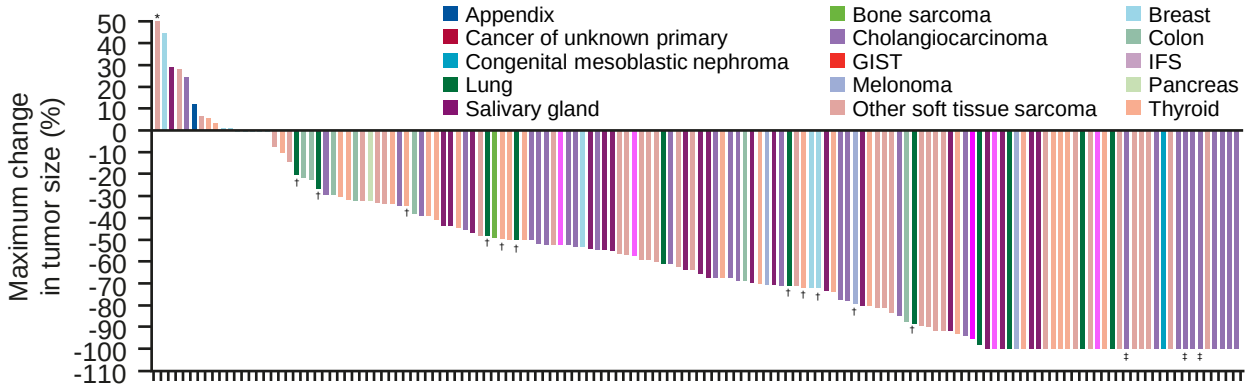
BRAF V600E+ metastatic melanoma: vemurafenib[3]



EGFR+ locally advanced/metastatic NSCLC: gefitinib[2]



TRK-fusion+ solid tumors: larotrectinib[4]

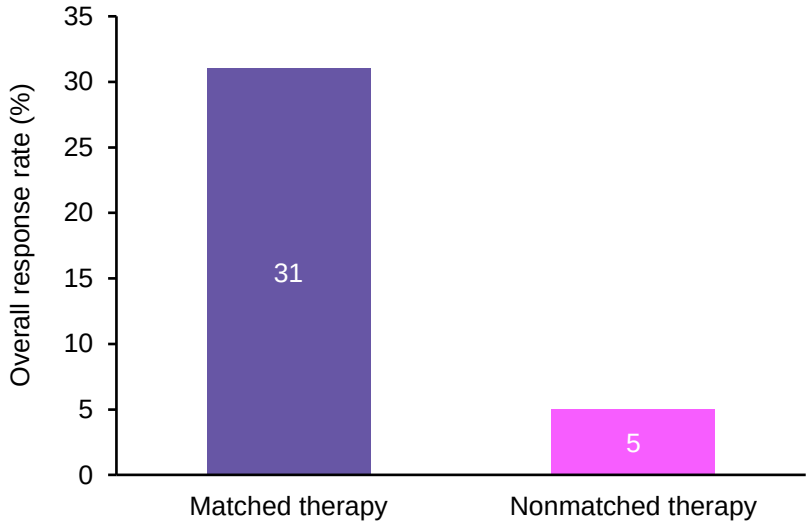


NSCLC=non-small cell lung cancer

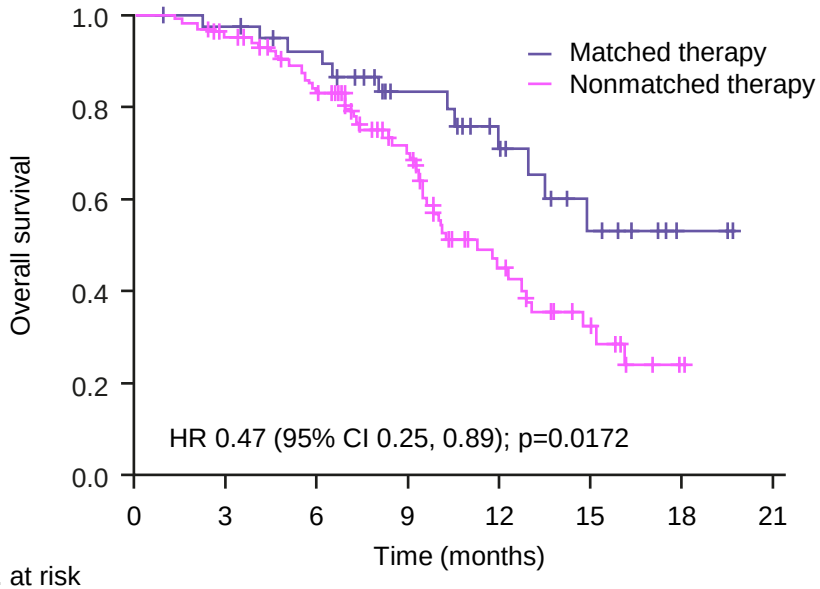
1. Slamon DJ et al. *NEJM* 2001;344:783-92; 2. Zhao H et al. *J Thorac Oncol* 2015;10:655-64; 3. Chapman PB et al. *NEJM* 2011;364:2507-16; 4. Hong DS et al. *Lancet Oncol* 2020;21:531-40.

Response Rates and Survival Are Improved with Genomically Matched vs Unmatched Therapy Across Tumor Types

Meta-analysis: Outcomes in phase 1 studies that used biomarker-based selection strategy vs those that did not[1]



Outcomes in prospective study of genomically matched therapy vs unmatched therapy[2]



No. at risk								
Matched therapy	40	38	34	22	15	8	2	0
Nonmatched therapy	108	96	70	45	21	10	1	0

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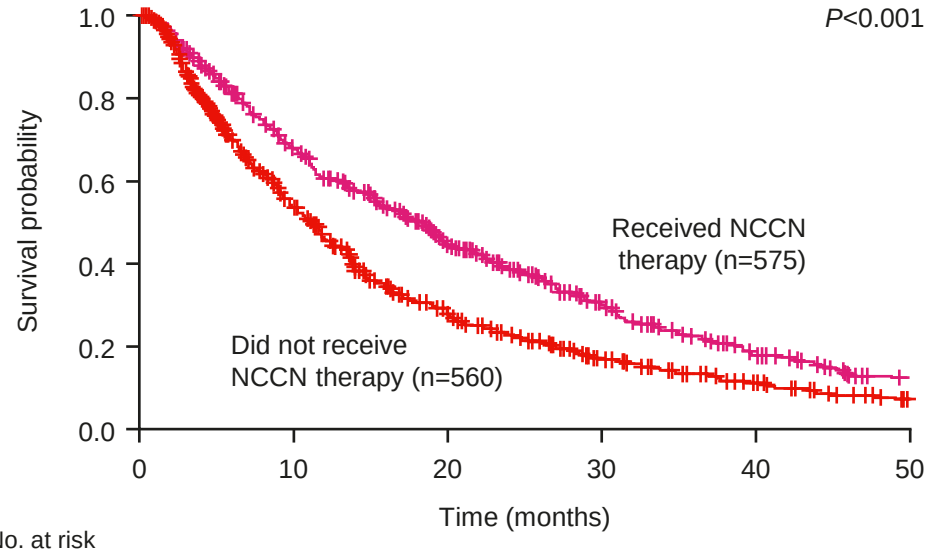
1. Schwaederle M et al. *JAMA Oncol* 2016; 2:1452-9. 2. Kopetz S et al. *JCO Precis Oncol* 2019; 3:PO.18.00213.

Improved Survival with Genomically-Matched Therapies in NSCLC

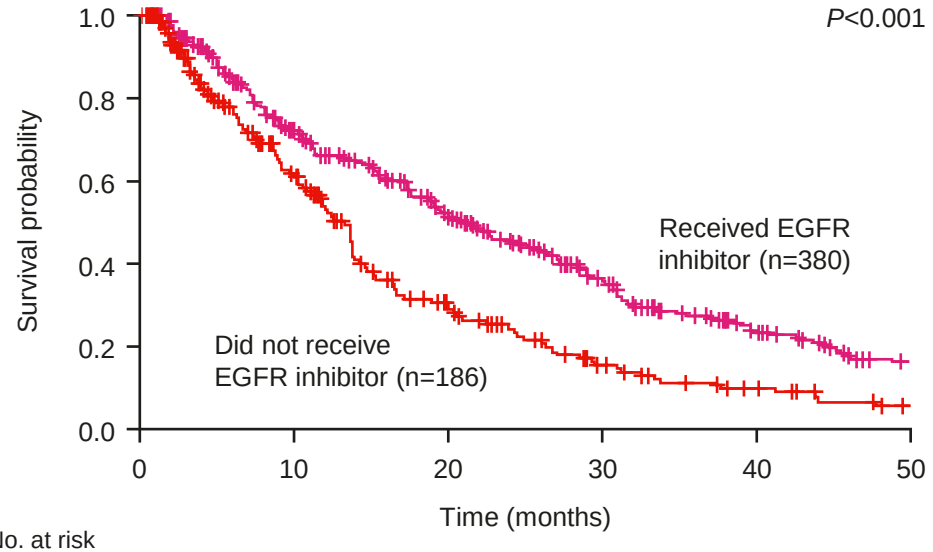
- Analysis using electronic health record clinical data linked with CGP results for 4,064 NSCLC patients revealed associations between driver mutations and response to targeted therapy

NCCN-directed therapy



No. at risk						
Received NCCN therapy	2	168	142	91	59	32
Did not receive NCCN therapy	55	196	93	54	28	12

EGFR inhibitor receipt status

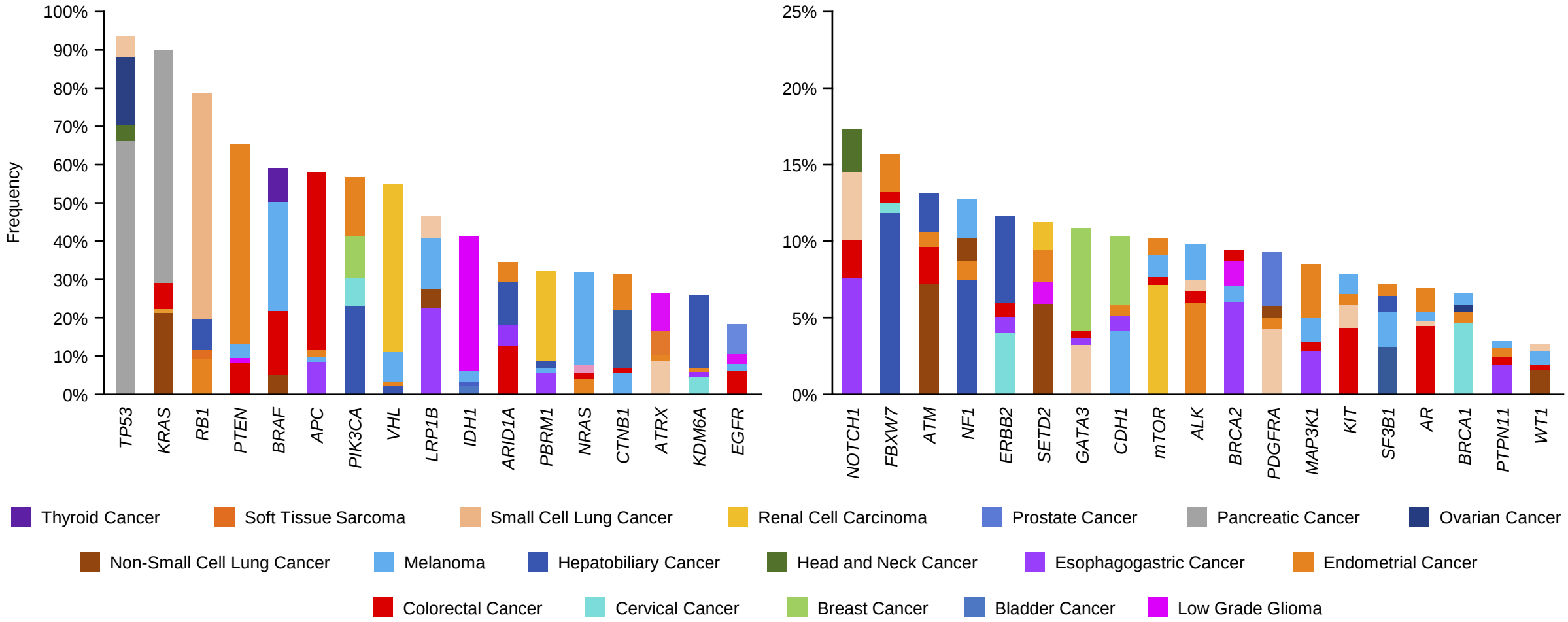


No. at risk						
Received EGFR inhibitor	1	119	103	67	41	22
Did not receive EGFR inhibitor	21	70	33	18	11	5

NSCLC=non-small cell lung cancer; CGP=comprehensive genomic profiling; NCCN=National Comprehensive Cancer Network

Singal G et al. *JAMA* 2019;321:1391-9.

Spectrum of Genomic Alterations Across Tumor Types



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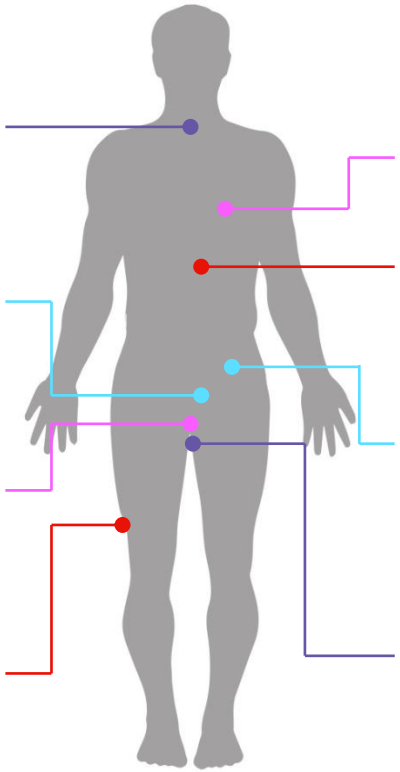
Rahal Z et al. *Am J Cancer Res*. 2018; 8:1356-86.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Beyond NSCLC: A Growing List of Biomarkers

Biomarkers in US guidelines and drug labels for highly prevalent tumors[1, 2]



Thyroid
ALK, HRAS, NRAS, BRAF, TERT, RET

Colorectal
BRAF, KRAS & NRAS, ERBB2, MLH1, MSH2, MSH6, PMS2

Bladder
FGFR2, FGFR3

Melanoma
BRAF, KIT, NRAS, ROS1, ALK

Breast
PIK3CA, ERBB2, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2

Gastrointestinal
KIT, PDGFRA, MSH2, MSH6, PMS2, ERBB2, MLH1

Ovarian
BRCA1, BRCA2, PMS2, MLH1, MSH2, MSH6

Prostate
BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, PTEN, AR

Solid tumors (pan-cancer)

NTRK	**TMB**	**MSI**

NSCLC=non-small cell lung cancer; TMB=tumor mutational burden; MSI=microsatellite instability

1. https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications (accessed on December 21st 2020)
2. www.nccn.org (accessed on April 1st, 2020).

Robust Pipeline of Personalized Therapies

New emerging biomarkers expected to be added to diagnostic algorithm over time

Beyond 2021: Robust pipeline* of biomarker-linked clinical trials will drive new indications and new biomarkers added to guidelines.

Ongoing clinical trials linked to a genetic biomarker	Globally	Europe
NSCLC	262	86
All cancer types	4,021	1,061

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NSCLC=non-small cell lung cancer

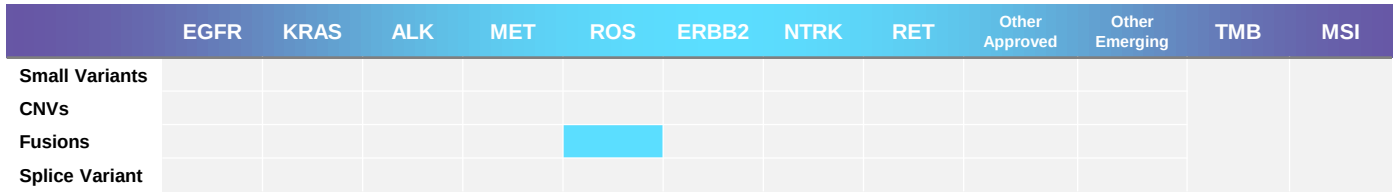
*www.clinicaltrials.gov (assessed on 01/25/2021; search terms combination: “genetic” or “genomic” or” DNA” or “RNA”).

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Comprehensive Genomic Profiling (CGP) tests

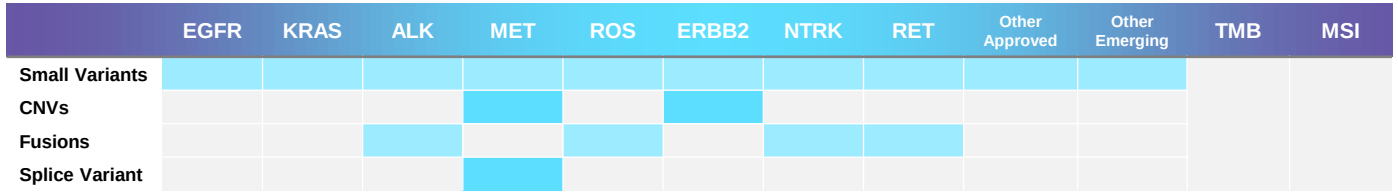
Can identify more potentially clinically relevant variants than conventional testing approaches, such as single-gene tests and hotspot NGS panels[1-5]

Single gene



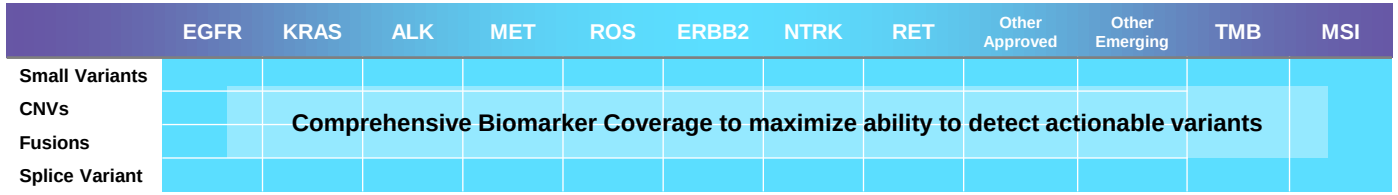
Single Gene and non-NGS Tests:
Require an algorithm where the tissue, effort and time required are becoming less feasible due to expanding oncogenic driver alterations[4]

Hotspot panel



Small Hotspot NGS Panels:
Can miss **81%** actionable mutations in patients with refractory cancers, based on study with 10,000 patients[2]

CGP



Comprehensive Genomic Profiling
Detects **more** actionable variants than small panels and single gene tests[1-5]

NGS=next-generation sequencing

1. Reitsma et al., *Journal of Managed Care & Specialty Pharmacy.* 2019 Jan 11:1-10. 2. Zehir A, Benayed R, Shah R et al. *Nat Med* . 2017 Jun;23(6):703-713.
3. Kopetz S, Shaw K, Lee J, et al. JCO Precision Oncology. 2019;3:1-14. 4. Drilon A, Wang L, Arcila ME, et al. Broad, Clin Cancer Res. 2015;21(16):3631-3639.
5. Ali SM, Hensing T, Schrock AB, et al. Oncologist. 2016 Jun;21(6):762-70.

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In a Study with 6,832 NSCLC Patients

CGP was able to identify a potentially clinically relevant genomic alteration for 71% of samples[1]

Among the patients studied, 4,876 (**71%**) harbored at least one potentially actionable alteration[1].

Multiple studies have demonstrated the ability of CGP to identify clinically relevant genomic alterations, across different tumor types:

Some studies:

Prospective study with **339** patients (multiple histologies)[2]	Prospective study with **100** patients (multiple histologies)[3]	Prospective study with **10,000** patients (multiple histologies)[4]	Retrospective study with **96** patients (multiple histologies)[5]
…detected actionable alterations in…			
93.5%	**94.5%**	**36.7%**	**90%**

The percent of actionable alterations identified in each study is variable, according to patient cohort, study type, NGS panel used, and criteria for qualifying a genomic alteration as actionable.

Conclusion: CGP enables a large number of patients to be genomically matched to approved or investigational therapies[2-6]

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NSCLC=non-small cell lung cancer; CGP=comprehensive genomic profiling

1. Suh JH, et al. 2016; 21(6):684-91; 2. Wheler JJ, et al.*Cancer Res.* 2016 Jul 1;76(13):3690-701; 3. Hirschfield KM. *Oncologist* . 2016 Nov;21(11):1315-1325; 4. Soumerai TE, et al. *Clin Cancer Res.* 2018 Dec 1;24(23):5939-5947; 5. Zehir A, et al. *Nat Med.* 2017; 23(6):703-713.

Genomically Matching Patients to Targeted Therapies or Immunotherapies

Linked to improved clinical outcomes[1-6]

Some relevant studies:

- Retrospective NSCLC study : 15 community oncology centers[3]
- Compared molecularly matched-therapy regimen with cytotoxic chemotherapy
- **Matched-Therapy led to higher overall survival (OS):**
  - ❖ **Matched-therapy: 31.8 months; 95% CI**
  - ❖ **Chemotherapy: 12.7 months; 95% CI**

- ~1,135 NSCLC patients study[4]
- Compared molecularly matched-therapy regimen with non-matched regimen
- **Matched-Therapy led to higher overall survival (OS):**
  - ❖ **Matched-therapy: 18.6 months; 95% CI**
  - ❖ **Non-matched therapy: 11.4 months; 95% CI**

- CGP performed in 101 lung adenocarcinoma patients[6]
- ~50% received matched-therapy regimens
- ❖ **Overall response rate (ORR): 65%.**

NSCLC=non-small cell lung cancer; CGP=comprehensive genomic profiling

1. Zehir A, Benayed R, Shah R et al *Nat Med* . 2017 Jun;23(6):703-713. 2. Soumerai TE, Donoghue MT, Bandlamudi C et al. *Clin Cancer Res*. 2018 Dec 1;24(23):5939-5947.
3. Gutierrez ME, Choi K, Lanman RB, et al. *Clinical lung cancer.* 2017;18(6):651-659. 4. Singal G, Miller PG, Agarwala V, et al. *JAMA*. 2019;321(14):1391-1399. 5.
5. Kato S, Kim KH, Lim HJ, et al. *Nat Commun*. 2020 Oct 2;11(1):4965. 6. Rozenblum AB, Ilouze M, Dudnik E, et al. *J Thorac Oncol*. 2017 Feb;12(2):258-268.

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Whole Genome Transcriptome Sequencing Potential Applications in Breast Cancer

1.1

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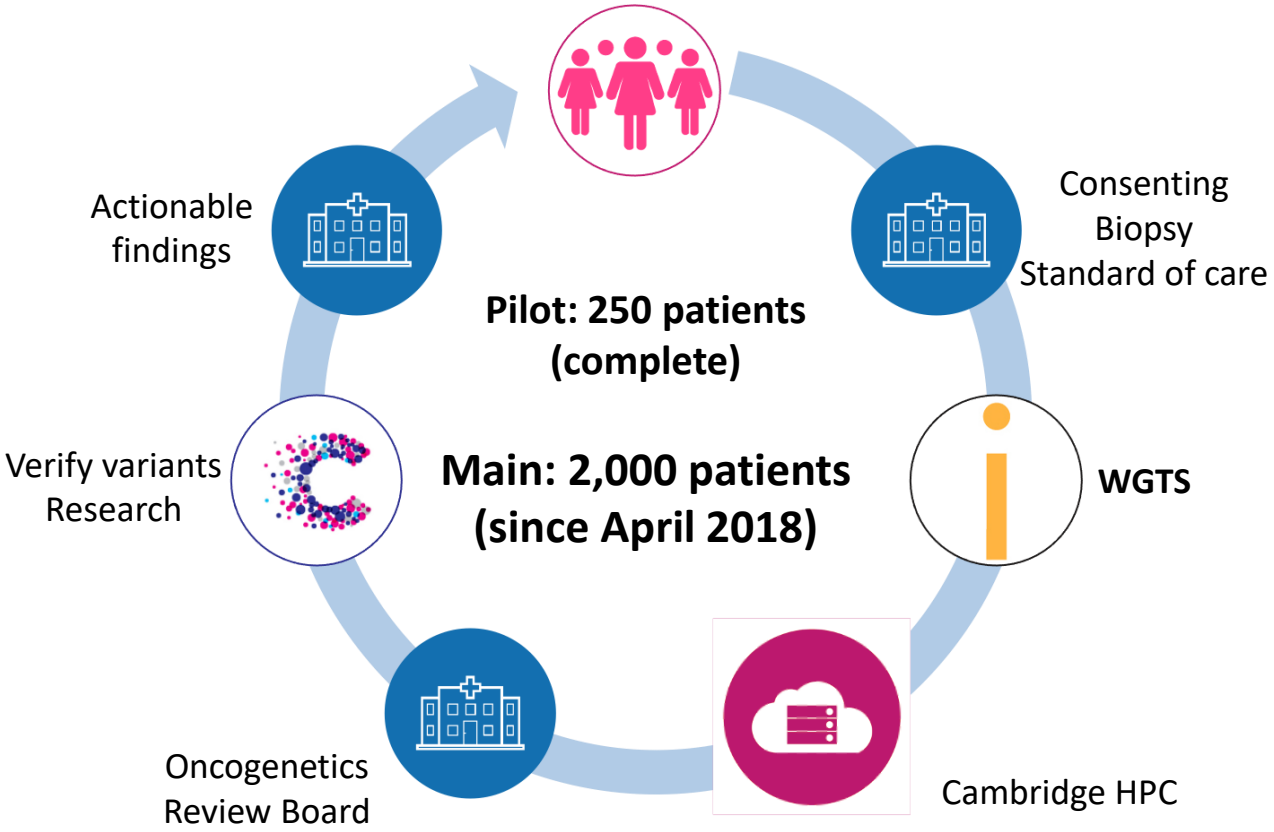
Personalised Breast Cancer Programme

WGTS to change real-time clinical management of breast cancer patients



- 81% of eligible patients were enrolled
- 832 patients have had WGS data delivered (Nov 2021)
- All actionable somatic variants were verified
  - No false negative calls at >5% VAF
- Actionable information in >60% cases
  - Minority have a change to current therapy
  - Majority are co-consented onto clinical trials
  - Increased referral to NHS Genetics
- WTS is currently used in research

With Carlos Caldas, Jean Abraham and colleagues

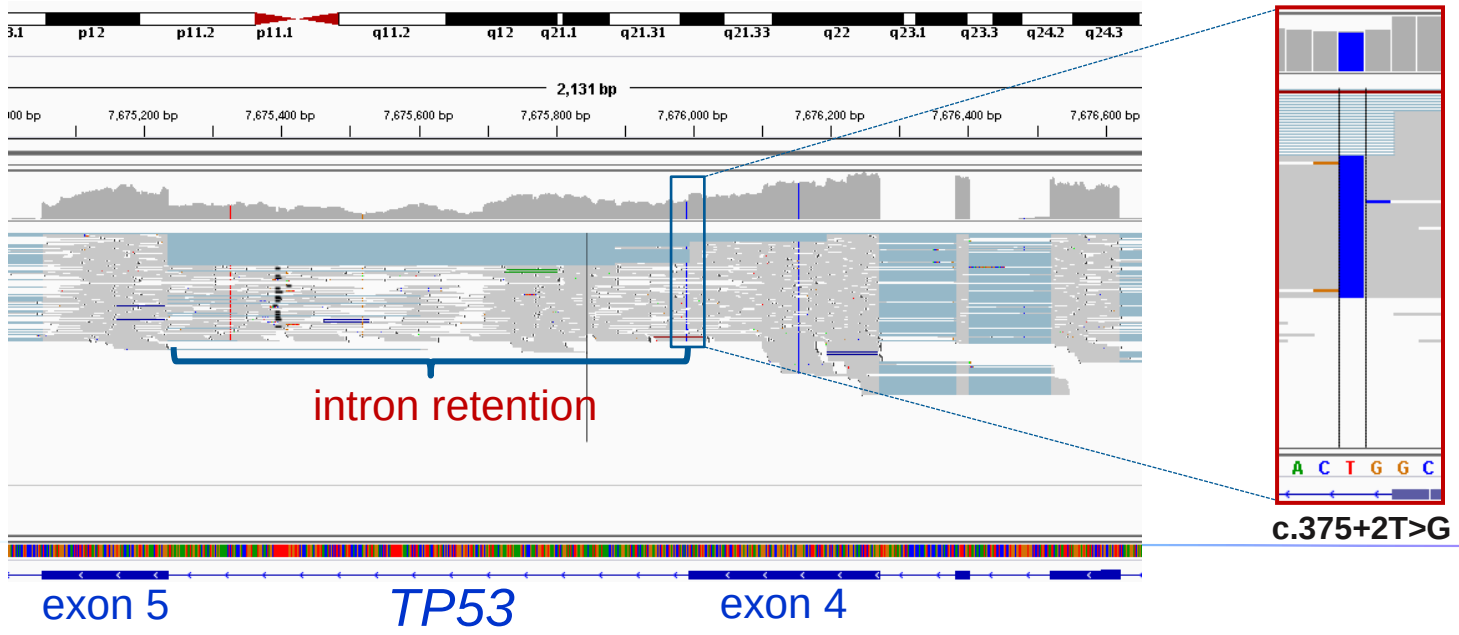
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Integrating DNA and RNA

- Total RNA sequencing from tumour
  - Impact of DNA variants on expression levels, evidence for predicted fusion genes, impact of variants on splicing, expression signatures, tumour microenvironment

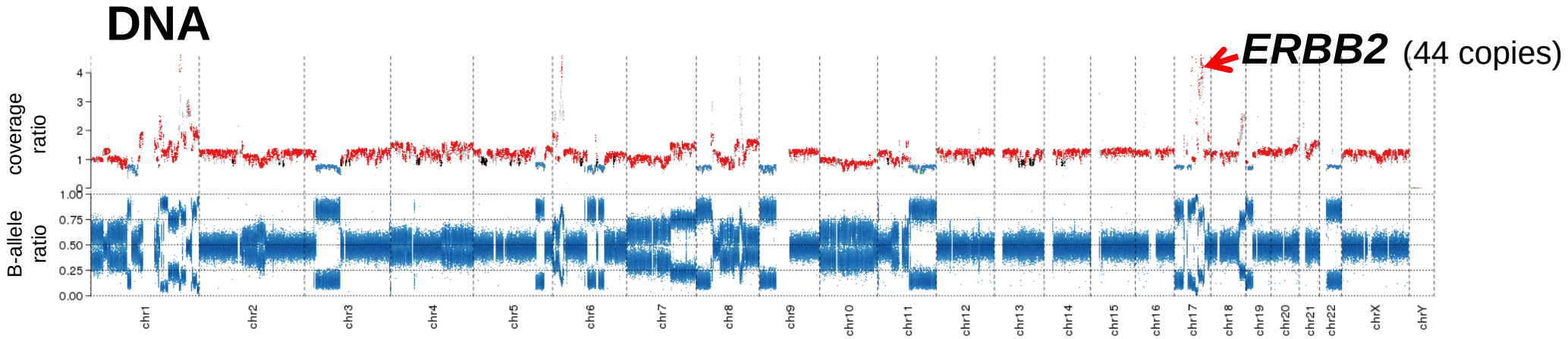
gene	chromosome	position	consequence	hgvs	sift	polyphen	VRF DNA	VRF RNA
TP53	chr17	7675992	splice donor variant	c.375+2T>G			0.55	0.98

RNA Tumour



Impact of a CNV on gene expression

- *ERBB2* focal amplification in DNA; also over-expressed in RNA
- Targeted cancer therapy available for *ERBB2* over-expression



RNA information

gene	chromosome	start	end	copy number	gene TPM	log2FoldChange
ERBB2	chr17	39639229	39748113	44	760	6

Evolution of clinical trials

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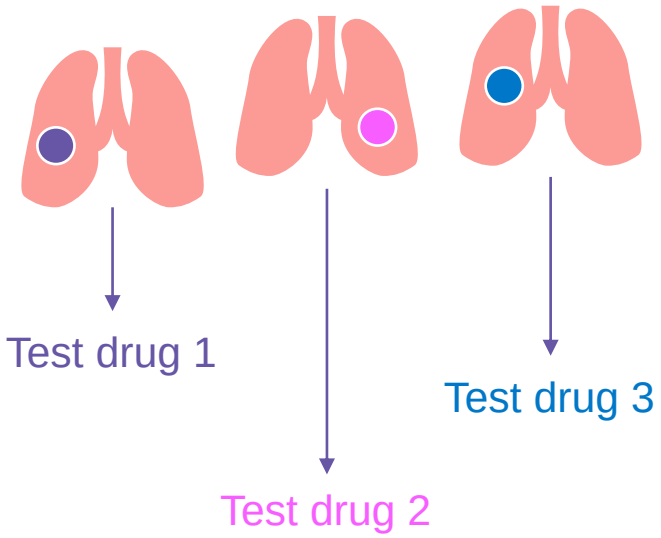
Evolution in Trial Design for Precision Medicine

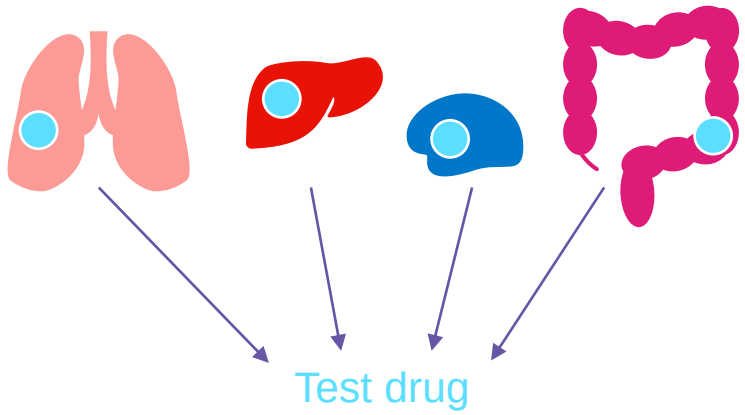
Umbrella trial

1 type of cancer
Different genetic mutation (●●●)



Basket trial

Multiple types of cancer
1 common genetic mutation (●)



- Identification of actionable targets in small subgroups of patients
- Trial participants can be from many locations without the need to travel to distant sites
- Rapid testing and approval of new therapies

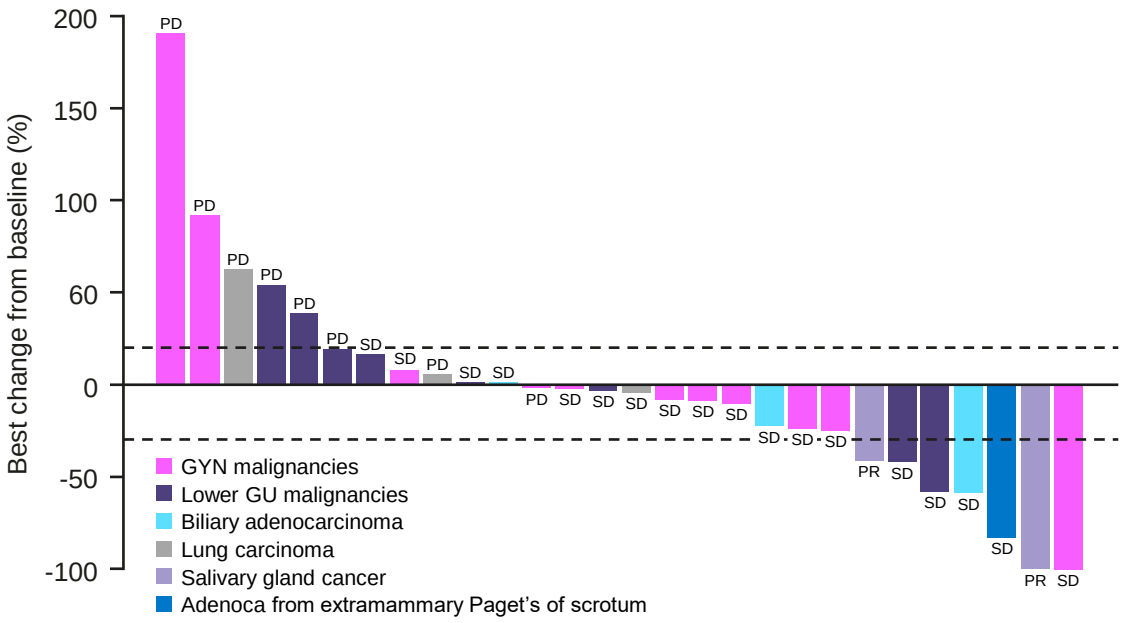
West HJ. *JAMA Oncol* 2017;3:423.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

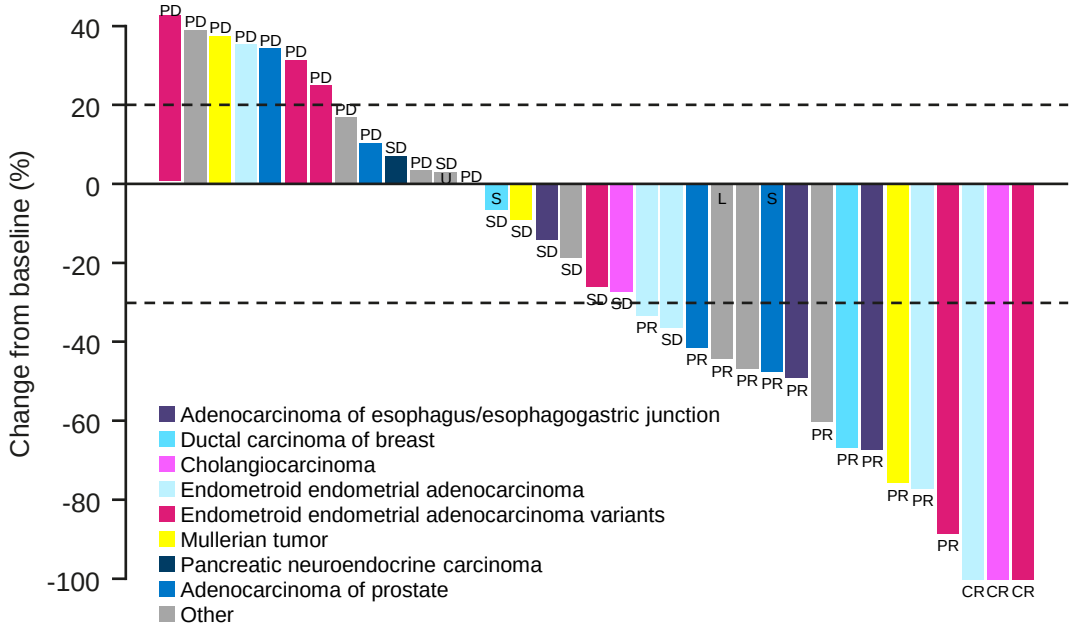
Basket Trials: NCI-MATCH

- Phase 2 trial in patients with refractory cancers identifying efficacy signals of treatments targeted to actionable molecular alterations found in any tumor type

Ado-trastuzumab emtansine: activity in *HER2*-amplified salivary gland tumors[1]



Nivolumab: activity in mismatch repair-deficient noncolorectal cancers[2]

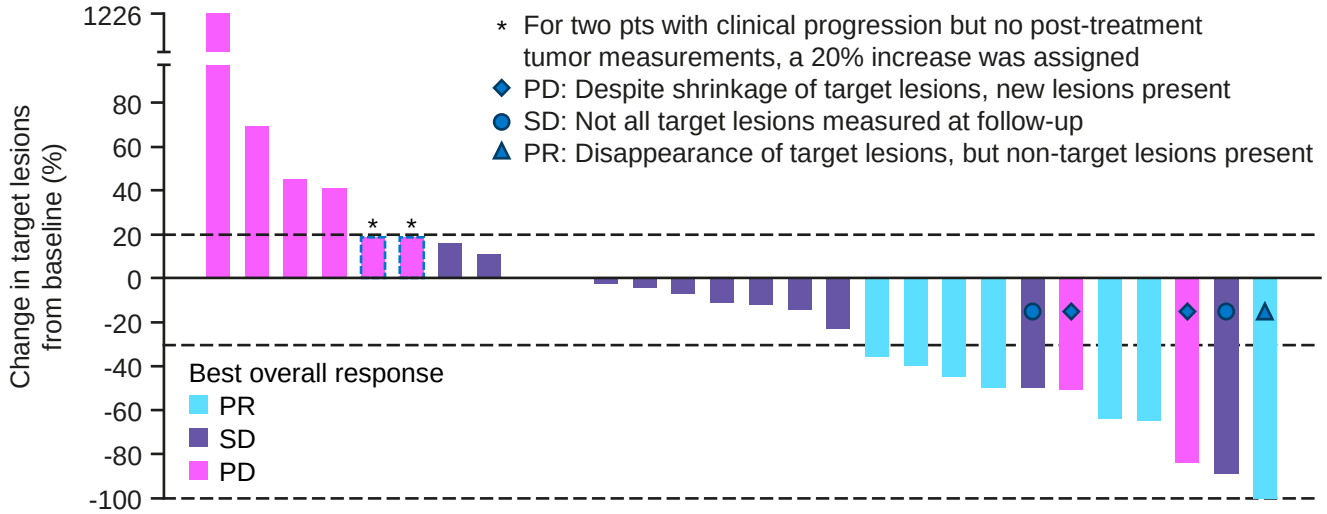


1. Jhaveri KL et al. *Ann Oncol* 2019; 30:1821–30; 2. Azad NS et al. *J Clin Oncol* 2019;38:214-222.

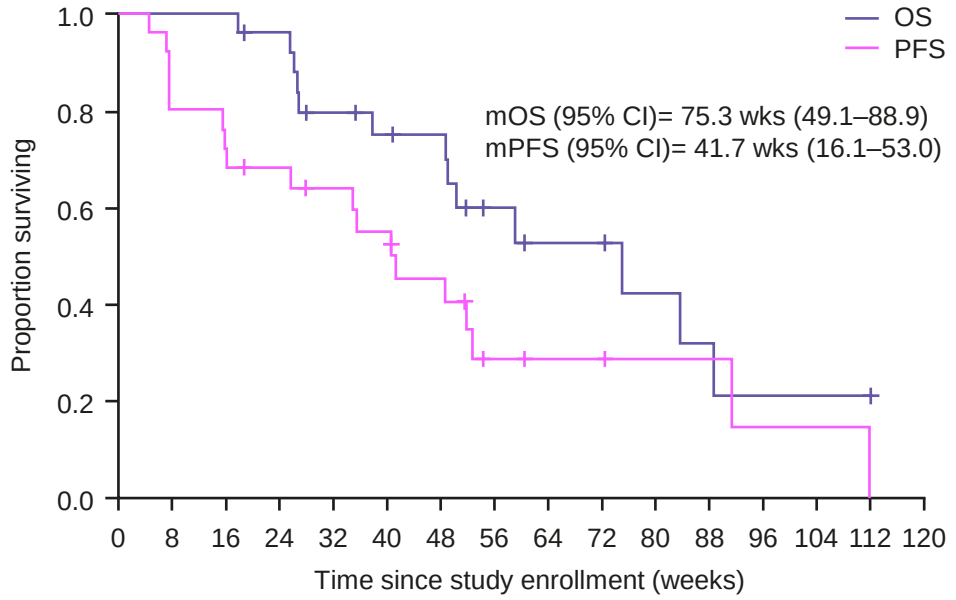
Basket Trials: TAPUR

- Phase 2 trial evaluating the anti-tumor activity of FDA-approved drugs matched to prespecified genomic targets in advanced cancers, outside of approved indications

Pertuzumab + trastuzumab: anti-tumor activity in CRC with *ERBB2* amplification or overexpression[2]



Olaparib: anti-tumor activity in prostate cancer with *BRCA1/2*-inactivating mutations[3]



CRC=colorectal cancer

1. Mangrat PK et al. *JCO Precis Oncol* 2018;2018:10.1200/PO.18.00122; 2. Gupta R et al. *J Clin Oncol* 2020;38(4 suppl):132; 3. Pisick E et al. *J Clin Oncol* 2020;38(15 suppl):5567.

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Basket Trials: MyPathway

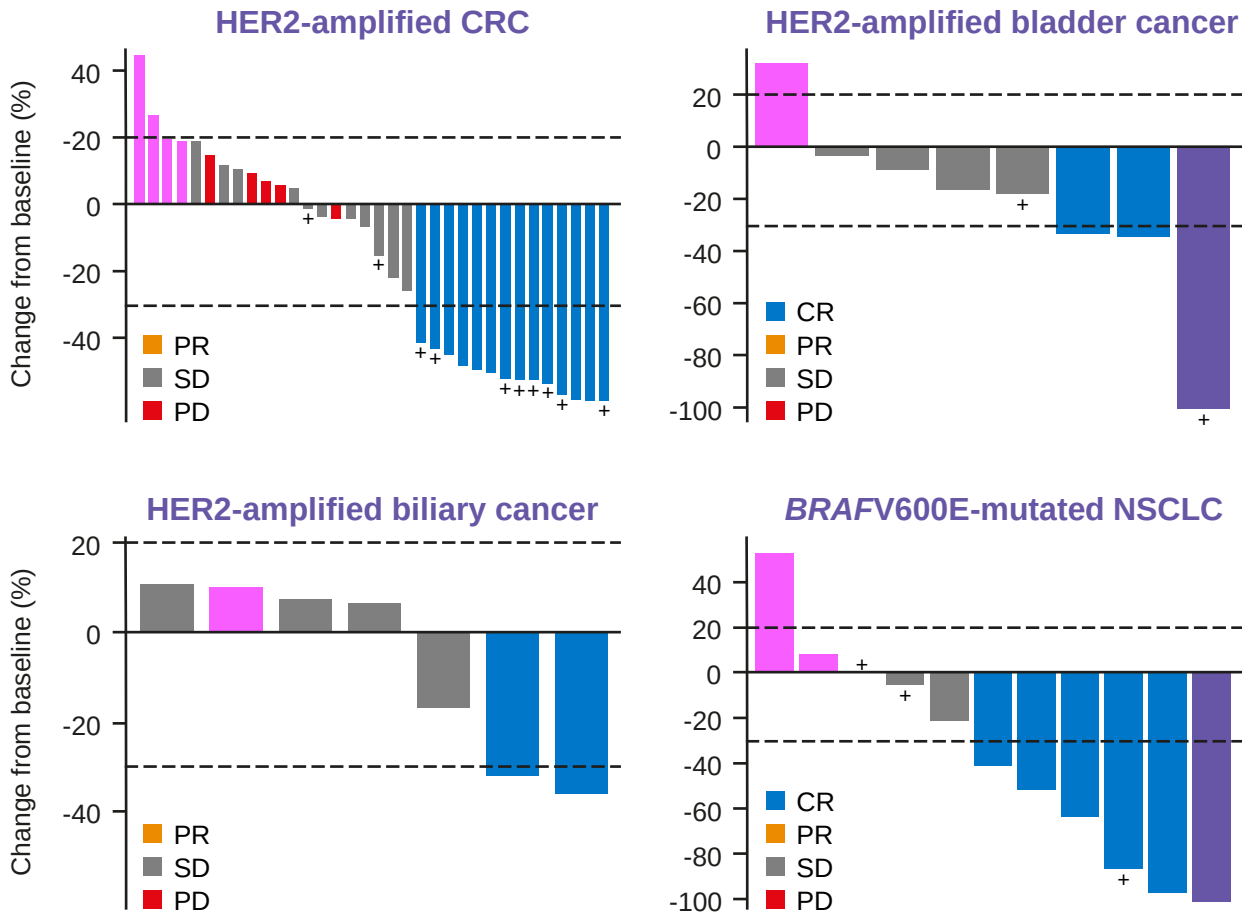
- Phase 2a trial evaluating the efficacy of drugs targeting molecular alterations in *HER2, EGFR, BRAF*, or the Hedgehog pathway in advanced refractory solid tumors, outside approved indications

Hedgehog pathway (n=21): 3 PR

- Squamous skin cancer
- Salivary gland cancer
- Unknown primary cancer

EGFR (n=9): 1 PR

- Urethral adenocarcinoma



CRC=colorectal cancer; NSCLC=non-small-cell lung cancer.
Hainsworth et al. *J Clin Oncol* 2018; 36:536–542.

Molecular genomic testing coverage and reimbursement

3

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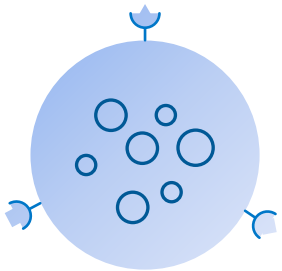
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Benefits of Comprehensive Genomic Profiling (CGP)

Comprehensive detection of medically necessary biomarkers with approved, on-label therapies

Tissue preservation and reduced need of re-biopsy

Improvement in patient outcomes in patients eligible for on-label therapies



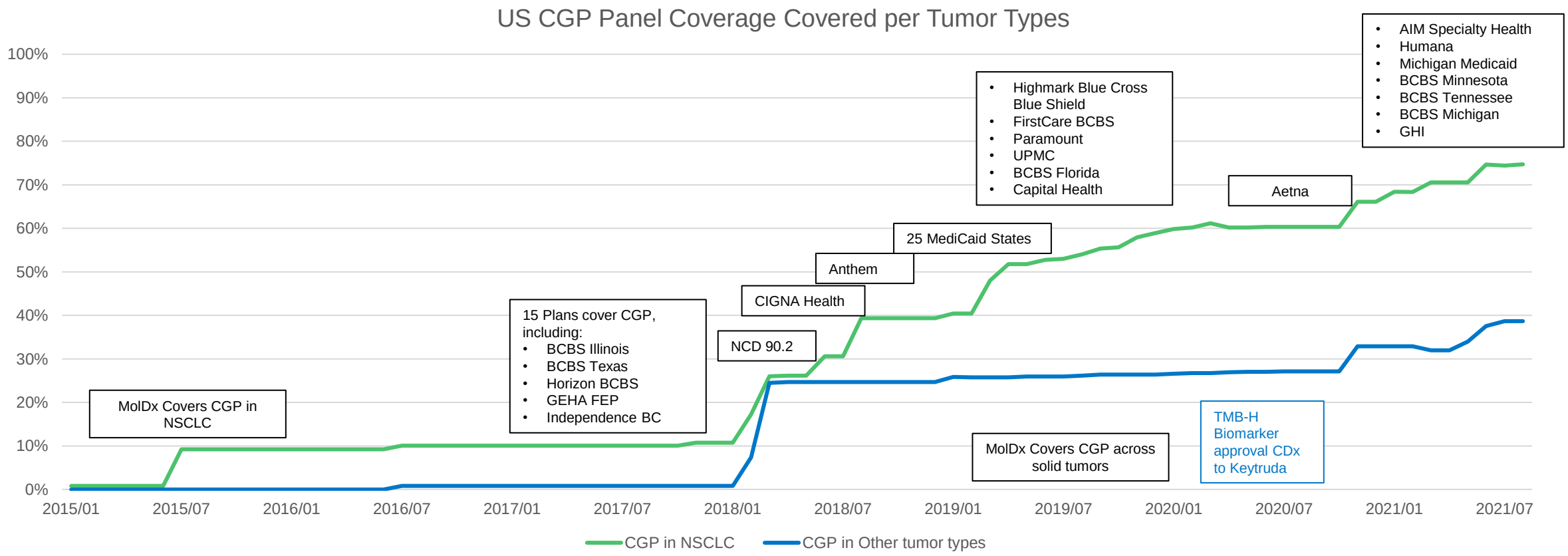
TMB status can **only** be determined using CGP. FDA-approved therapy requires TMB status for advanced solid cancer treatment

Improvement in clinical trial eligibility and enrollment, which is recommended by NCCN

Cost-effective approach with test consolidation

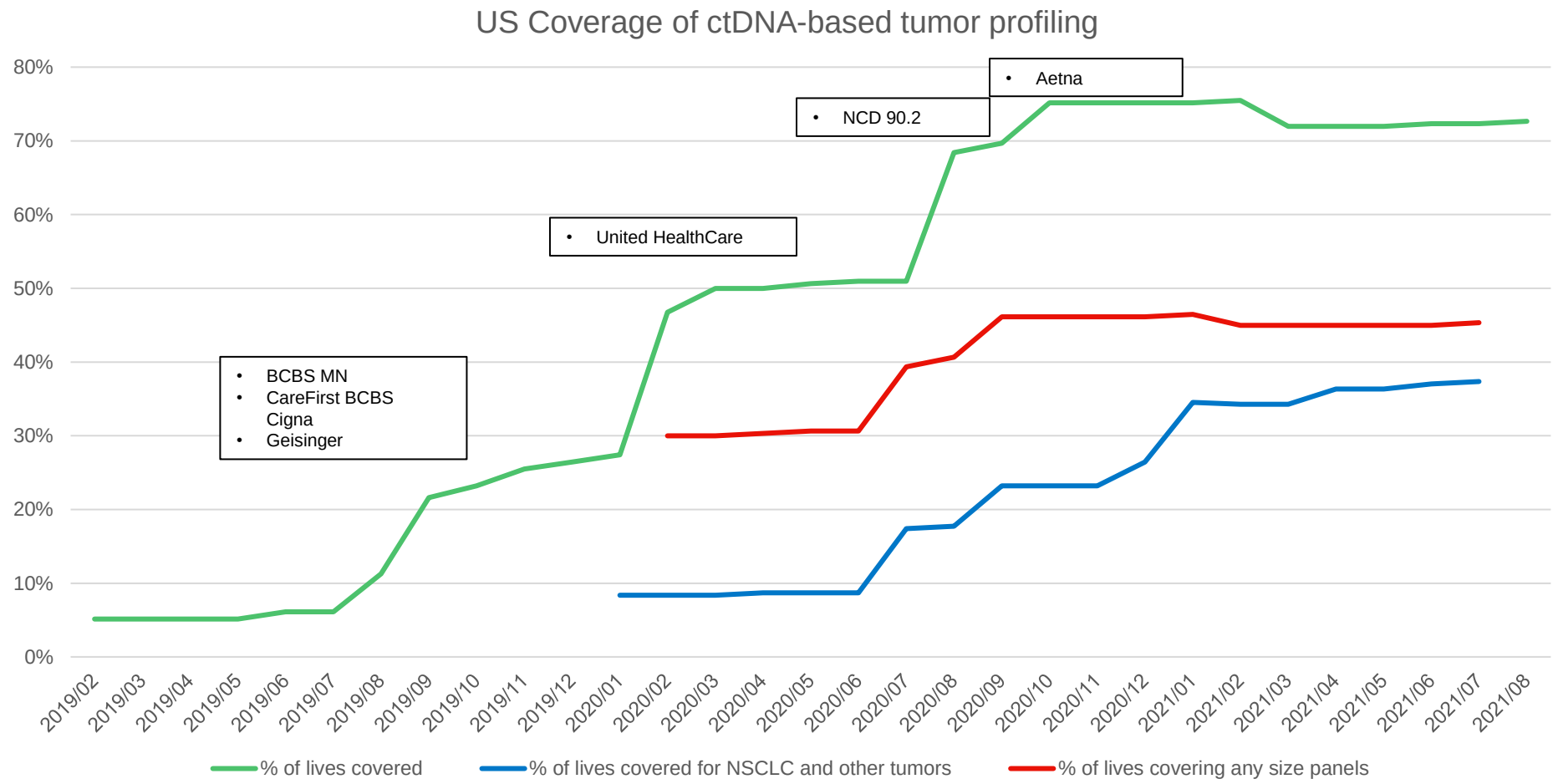
NCCN=National Comprehensive Cancer Network ; TMB=tumor mutational burden

CGP Coverage in NSCLC and other tumor types



NSCLC=non-small cell lung cancer; CGP=comprehensive genomic profiling
Data on file.

ctDNA NGS-based Tumor Profiling Coverage

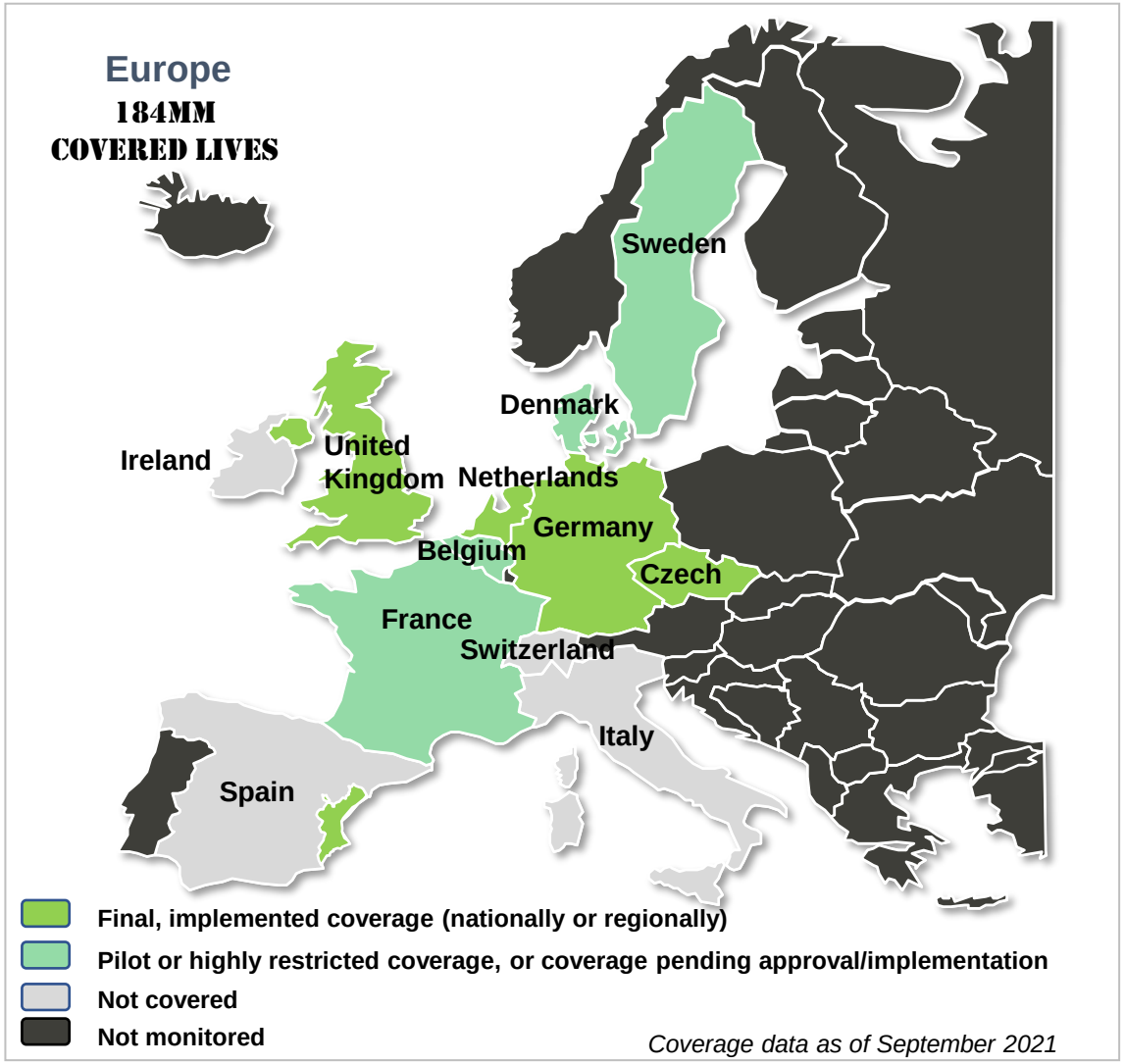


NSCLC=non-small cell lung cancer; NGS=next-generation sequencing
Data on file.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Oncology Panels and Comprehensive Genomic Profiling

Reimbursement in Western Europe



Country	Oncology Coverage
France	Temporary Coverage Limited to Panels ≤500Kb
Germany	All Panel Sizes Covered
Italy	Not Covered
Spain	Varies by Region – 1/17 Region Covered
United Kingdom	Varies by Cancer Type
Belgium	Pilot Program Only
Czech Republic	All Panel Sizes Covered
Denmark	Local funding
Ireland	Not Covered
Netherlands	All Panel Sizes Covered
Sweden	limited reimbursement
Switzerland	Not Covered

Data on file

Comprehensive Genomic Profiling Coverage

Coverage Snapshot August 2021

216M Lives
United States

233M Lives
Europe, Middle East, Africa

178M Lives
Asia

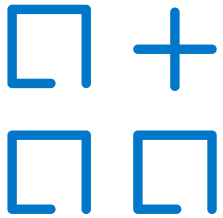
Note: CGP is defined as expanded panels with >50 genes.
Several other US payers and countries provide coverage for targeted panels and single gene tests which is not reflected here
EMEA and Asia: Covered lives represent total population according to World Bank and does not represent prevalence.

Data on file

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Trends in Coverage

Increase Coverage of CGP



Coverage beyond NSCLC

Coverage early at advanced cancer diagnosis

- More FDA-approved targeted therapies
  - Across tumor types (pancancer/ tissue agnostic)
  - In more tumor types
- Test consolidation
  - More Complex Genomic Signature that can only be done with CGP
  - To realize the full value of CGP and the promise of Precision Medicine, comprehensive tumor profiling needs to happen early, ahead of advanced cancer 1L treatment selection

NSCLC=non-small cell lung cancer; CGP=comprehensive genomic profiling
Data on file.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Clinical Utility is a Key Factor Driving Coverage Decisions

Complex biomarkers such as TMB, HRD, MSI increase the clinical utility of CGP because they cannot be performed with a small panel.

- TMB is currently approved as a Companion Diagnostic in the United States
- The TMB indication has not been submitted for approval in other markets yet

Tissue-agnostic indications* also add to the clinical utility of CGP, as they more rapidly expand the number of biomarkers that need to be tested in each tumor type

- United States (MSI, *NTRK* and TMB)
- Europe (*NTRK*)
- Japan (MSI, *NTRK*)
- Australia (MSI, *NTRK* pending)

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* Tissue-agnostic therapies use the same drug to treat all cancer types that have the genetic mutation or biomarker that is targeted by the drug.
CGP=comprehensive genomic profiling; MSI=microsatellite instability; NGS= next-generation sequencing; TMB= tumor mutational burden.

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Summary

- Cancer patient care has shifted from one size fits for all to more personalized treatment
- Increasing numbers of approved targeted drugs and immunotherapies have substantially improved cancer patient survival
- Comprehensive genomic profiling of cancers has been increasingly utilized for tumor biomarker identification and improved patient care
- The coverage of genomic testing is increasing worldwide, which enables patients receiving the right drug at the right time
- The combination of targeted therapies and comprehensive genomic profiling will further improve cancer patient management, and facilitate the realization of precision/personalized medicine

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