Biomarkers and Genetic testing in Cancer: New opportunities and issues on the horizon

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Disclosure Information
Emil Lou, MD, PhD, FACP
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All disclosures are listed; those potentially relevant to this talk are underlined

I have the following financial relationships to disclose:

- Consultant for/Honoraria from:
  - Novocure: honoraria and travel expenses for Global Inovitro Users Meetings 2018, 2019, 2020, 2021; research talk and chairing Spring 2020 meeting.
  - GlaxoSmith Kline: Honorarium and travel expenses for research talk (2016).
  - Boston Scientific: Medical Consultant (2019).
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- Clinical Trial PI (associated % effort):
  - Celgene: Big Ten Cancer Research Consortium Phase II trial gastroesophageal cancers (Site PI)
  - Novocure: Phase III trial locally advanced pancreatic cancers (Site PI)
  - Intima Biosciences, Phase I/II cellular therapy trial GI cancers (2018-present)
  - National Cancer Institute – NCI-MATCH (2015-present)
  - Roche: TAPISTRY molecular oncology basket trial (2021-22)

I will discuss potential off label uses in my presentation; I may discuss investigational use of novel drugs and medical devices during my presentation.

Consultations, associations, collaborations – **no financial compensation**:

- Caris Precision Oncology Alliance
  - UMN site lead (2019-present)
  - Chair, GI Oncology Research group (June 2021-June 2022)

Learning Objectives

- 1. Understand the current landscape of tumor genomic profiling in oncology.
- 2. Learn about societal factors affecting oncologist-driven genetic testing.
- 3. Understand fundamental biological perspectives about targeted therapies, challenges, and forthcoming advances.

Precision Medicine in Cancer: One term, with many definitions

- One perspective, for oncology, from ASCO:

"Precision medicine is an approach to disease prevention and treatment that accounts for variability in the genes, environment, and lifestyle of each person.

Precision medicine approaches to identifying variability in genetics include the use of multiple testing techniques, including immunohistochemistry, fluorescence in situ hybridization, chromogenic in situ hybridization, flow cytometry, and next-generation sequencing.

These techniques are used either in combination or individually to identify molecular abnormalities in a patient's DNA with the hopes of identifying therapeutic targets."

Ref: JL Ersek et al. **Implementing Precision Medicine Programs and Clinical Trials in the Community-Based Oncology Practice: Barriers and Best Practices. ASCO Education Book 38, 2018**

ASCO special articles

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

Debyani Chakravarty, PhD[1]; Amber Johnson, PhD[2]; Jeffrey Sklar, MD, PhD[3]; Neal I. Lindeman, MD[4]; Kathleen Moore, MD[5]; Shridar Ganesan, MD, PhD[6]; Christine M. Lovly, MD, PhD[7]; Jane Perlmutter, PhD[8]; Stacy W. Gray, MA, MD[9]; Jimmy Hwang, MD[10]; Christopher Lieu, MD[11]; Fabrice André, MD, PhD[12]; Nilofer Azad, MD[13]; Mitesh Borad, MD[14]; Laura Tafe, MD[15]; Hans Messersmith, MPH[16]; Mark Robson, MD[1]; and Funda Meric-Bernstam, MD[2]

abstract

PURPOSE An ASCO provisional clinical opinion offers timely clinical direction to ASCO's membership following publication or presentation of potentially practice-changing data from major studies. This provisional clinical opinion addresses the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.

CLINICAL CONTEXT An increasing number of therapies are approved to treat cancers harboring specific genomic biomarkers. However, there is a lack of clarity as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection.

PROVISIONAL CLINICAL OPINION Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease. Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.

Additional information is available at www.asco.org/assays-and-predictive-markers-guidelines.

J Clin Oncol 40:1231-1258.

ASCO Provisional Clinical Opinion statement (2022)

What is Precision Oncology: "…the use of molecular biomarkers to aid in the diagnosis, prognosis, or treatment of cancer…"

TABLE 1. Definitions of Commonly Used Terms in Precision Oncology

Term	Definition
Basket trial	A trial investigating the efficacy of a therapy within various tumor types (baskets) that all harbor the same type of genomic alteration(s).
Biomarker	A biologic marker that can be detected and measured by a validated test to diagnose or treat disease. Cancer biomarkers include, but are not limited to, genes, genomic alterations, RNA transcripts, proteins, post-translationally modified forms of proteins, and signatures of combinations of the aforementioned biomarkers.
ctDNA	Tumor DNA shed into the plasma. **ctDNA-based genomic testing:** NGS sequencing performed on isolated ctDNA for the detection of somatic variants.
CLIA-certified	The laboratory performing the test has met specific standards of proper laboratory management and testing procedures, as defined by CLIA.
Clonal	Tumor cells derived from the division of a common ancestral tumor cell. **Clonal mutations:** identical mutations found within clonal cells derived from a common ancestral tumor cell. **Subclonal mutations:** mutations arising in distinct subpopulations of tumor cells that generally give further fitness advantages, such as those acquired after treatment. **Clonal sweep:** as a new driver mutation occurs that induces clonal expansion, these clones replace the existing population of cells
CDx (nucleic acid–based test)	A specific test approved by the FDA to detect the presence of biomarkers that are prescriptive for a therapy.
Genomic alteration	Alteration of a gene from its original wild-type (normal) status through mutation, CNV, or rearrangement.
CNV	Deviation from the expected two copies of a gene within a cell. **Amplification:** An increase in the number of gene copies within a cell beyond the expected two copies. Amplifications may be focal and limited to a specific gene or part of a broader, typically lower level, chromosomal gain. **Deletion:** A decrease in the number of copies of a gene because of the loss of a single copy (heterozygous deletion) or both copies (homozygous deletion).
Fusion	A novel gene product that is created from two previously separate and independent genes. Gene fusions may arise from genomic rearrangements such as: **Chromosomal translocations:** the joining of DNA that previously resided within different chromosomal locations. **Interstitial deletions:** deletions that occur because of two breakpoints and the rejoining of the terminal end to the main chromosome. **Inversions:** a region of chromosomal DNA that is reversed.

ITH	Within the same tumor, different populations of cells within distinct spatial regions have unique genomic alterations.
Knowledge base	A repository of expertly curated information. **Precision oncology knowledge base:** a repository containing expertly curated information regarding some or all of the following types of information: cancer genes, oncogenic mutations, genomic biomarker–linked therapies, genomically matched clinical trials, and levels of evidence for using a therapy within the context of a specific genomic alteration and tumor type.
MRD	The presence of tumor cells that have spread from the primary tumor but are not detectable by imaging.
Multigene panel	An NGS test that sequences a defined list of genes with at least 50 genes in total.
Neoantigens	Tumor-specific antigens that result from nonsynonymous somatic mutations and may trigger an immune response to cancer.
NGS	A technology that performs massively parallel DNA sequencing to detect genomic alterations.
Pathognomonic	Characteristic of a particular disease type.
Precision oncology	The use of molecular biomarkers to aid in the diagnosis, prognosis, or treatment of cancer.
Targeted therapy	A therapy that is designed to selectively inhibit cells that harbor a specific genomic alteration or protein.
Therapeutically actionable alteration	A genomic alteration predicted to confer sensitivity or resistance to an available therapy (FDA-approved or investigational). These alterations are typically functionally significant, in that they confer a change in the property of the encoded protein that promotes tumorigenesis, but may also affect drug binding and inhibition without affecting the activity of the protein.
Therapeutically actionable gene	Alterations of the gene that confer sensitivity or resistance to an available therapy (FDA-approved or investigational)
TMB	A measurement of the number of somatic mutations per megabase of DNA sequenced.
VAF	The fraction of alleles sequenced within a single tumor sample that contain the genomic alteration of interest.
Whole-exome sequencing	Sequencing of all of the protein-encoding regions (exons) of genes in the genome.
Whole-genome sequencing	Sequencing of the entire genome, including protein-coding and non–protein-coding regions.

Abbreviations: CDx, companion diagnostic; CLIA, Clinical Laboratory Improvement Amendments; CNV, copy-number variation; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization; GIS, genomic instability score; HRD, homologous recombination deficiency; IHC, immunohistochemistry; ITH, intratumoral heterogeneity; LOH, loss of heterozygosity; LST, large-scale state transitions; MRD, minimal residual disease; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; P/LP, pathogenic or likely pathogenic; SNV, single-nucleotide variation; SV, structural variant; TAI, telomeric allelic imbalance; TMB, tumor mutation burden; VAF, variant allele fraction.

We are fully immersed in the era of targeted therapy…

- …but [and] most of us trained before it took hold (even not so long ago).
- We are all learning as the field evolves…
- …and the field is evolving rapidly.
- My experience as a member of the ASCO Scientific Committee for GI Cancers (Non-colorectal track): 2012-15 – the scientific content became a completely different playing field within 5-10 years.
  - February 2, 2021 Press Release: *"ASCO Names Advance of the Year: Molecular Profiling Drives Progress in Gastrointestinal Cancers*".

- ASCO Developmental Therapeutics 2022-25: A whole new ballgame.
  - New strategies, new tactics (e.g. ADCs, antibody drug conjugates).
- State of the field: our ability to identify molecular alterations in tumors has matured a lot; we are trying to catch up in identifying strategies and tactics that affect those critical molecular targets in a way that leads to improved overall survival and quality of life in patients with cancer.

Frequency of known and standard care drivers in major cancer types in the American Association for Cancer Research (AACR) GENIE dataset

	No.	ALK Fusions (%)	BRAF V600 (%)	BRCA1 Drivers (%)	BRCA2 Drivers (%)	EGFR Drivers (%)	ERBB2 Amplification (%)	EZH2 Drivers (%)	FGFR2 Fusions (%)	FGFR3 Drivers (%)	FGFR3 Fusions (%)	IDH1 Drivers (%)	IDH2 Drivers (%)	KIT Drivers (%)	KRAS G12C (%)	NTRK1/2/3 Fusions (%)	PDGFRA Drivers (%)	PIK3CA Drivers (%)	RET Fusions (%)	RET Drivers (%)	ROS1 Fusions (%)
m	2,718	0.1	0.1	1.3	2.2	2.5	4.3	0.6	0.1	21.9	2.0	0.2	0.1	0.1	0.4	0.1		19.4	0.1	0.1	
Breast Cancer	12,724		0.1	1.3	1.9	1.3	10.4	0.3	0.2	0.1	0.1	0.1		0.3	0.1	0.2	0.2	38.1	0.1	0.1	0.1
Cervical Cancer	659			1.1	0.9	0.2	2.1	0.3		0.9	0.6				0.5			27.6			0.2
Cholangiocarcinoma	1,361		1.5	0.7	2.0	1.1	2.2	0.4	7.3		0.4	14.5	3.5	0.1	1.0	0.2	0.3	4.5	0.1	0.1	0.2
Colorectal Cancer	11,019	0.1	7.6	0.9	2.2	1.4	1.4	0.2	0.1	0.1		0.5	0.1	0.2	2.9	0.2	0.1	17.8	0.1	0.2	
Cutaneous Melanoma	1,666	0.1	31.7	0.9	1.4	0.9		1.1		0.1		2.6	0.3	3.9		0.2	0.8	2.2		0.1	0.1
Endometrial Cancer	3,400		0.1	1.4	4.1	1.2	3.5	1.1	0.1	0.1	0.3	0.3		0.1	1.2	0.1	0.3	48.5		0.3	
Esophagogastric Cancer	3,075		0.1	0.8	1.7	4.8	10.8	0.5	0.6	0.1	0.1		0.1	0.1	0.3	0.2	0.1	7.8	0.3	0.2	
Gallbladder Cancer	223			1.8	3.6	3.1	5.4				0.4	0.4			0.9	1.8		10.8	0.9		
Gastrointestinal Stromal Tumor	1,118	0.1	0.4		0.1	0.2		0.1				0.1	0.1	78.9		0.1	10.3	1.3		0.1	
Head and Neck Cancer	1,680	0.1	0.1	1.1	1.0	4.5	0.7	0.2	0.1	1.7	0.1	0.1	0.5	0.5	0.2	0.1	0.4	18.4	0.1	0.1	
Non-Small Cell Lung Cancer	16,669	2.0	1.3	0.6	0.9	26.9	0.8	0.3	0.1	0.1	0.1	0.3	0.1	0.4	11.3	0.1	0.3	5.2	1.0	0.1	0.8
Ovarian Cancer	4,208	0.1	0.9	5.7	2.9	0.4	1.7	0.3	0.1		0.1		0.1	0.1	0.4		0.1	9.9		0.1	0.1
Pancreatic Cancer	4,411	0.2	0.6	0.6	2.4	0.2	0.7	0.2	0.2			0.2			1.1	0.2		2.1		0.1	0.2
Prostate Cancer	4,010			0.5	5.0	0.4	0.1	0.3			0.1	0.4		0.1		0.2	0.1	3.8		0.1	0.1
Renal Cell Carcinoma	1,837	0.2		0.4	0.6	0.3		0.3		0.1				0.2	0.1		0.2	2.9	0.1		
Salivary Gland Cancer	791	0.8	0.4	0.6	0.5	0.5	4.6		0.1			0.5	0.1	1.4	0.1	3.4	1.3	8.7	0.1		0.3
Thyroid Cancer	1,614	0.4	38.0	0.3	0.9	0.2		0.1	0.1	0.1		0.1		0.2	0.2	1.9	0.1	3.7	5.1	8.1	

Alteration Frequencies

< 1% | < 5% | < 10% | < 50% | > 50%

CRC, colorectal cancer; NSCLC, non–small-cell lung cancer.

Published in: Debyani Chakravarty; Amber Johnson; Jeffrey Sklar; Neal I. Lindeman; Kathleen Moore; Shridar Ganesan; Christine M. Lovly; Jane Perlmutter; Stacy W. Gray; Jimmy Hwang; Christopher Lieu; Fabrice André; Nilofer Azad; Mitesh Borad; Laura Tafe; Hans Messersmith; Mark Robson; Funda Meric-Bernstam; *Journal of Clinical Oncology* 2022 401231-1258. DOI: 10.1200/JCO.21.02767

Disease-specific approvals of drugs targeting driver alterations (the 'first wave')

TABLE 2. Selected Genetic Alterations Linked to FDA Approvals as of June 2021[a]

Genetic Alterations	Tumor Type	Targeted Therapeutics
FDA-approved treatments for specific genetic alterations in specific tumor types		
ALK fusions	NSCLC	Crizotinib, ceritinib, alectinib Brigatinib, lorlatinib
BRAF V600E	Melanoma	Dabrafenib, vemurafenib
		Dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib, trametinib
	Anaplastic thyroid cancer	Dabrafenib + trametinib
	NSCLC	Dabrafenib + trametinib
	CRC	Encorafenib + cetuximab
BRAF V600K	Melanoma	Dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib, trametinib
Deleterious or suspected[a] deleterious germline or somatic mutations in *BRCA1* and/or *BRCA2*	Ovarian cancer, fallopian tube cancer, peritoneal cancer	Olaparib,[a] rucaparib, niraparib[a]
	Prostate cancer	Olaparib,[a] rucaparib[a]
Deleterious or suspected deleterious germline mutations in *BRCA1* and/or *BRCA2*	Ovarian cancer, pancreatic adenocarcinoma	Olaparib
	HER2-negative breast cancer	Olaparib, talazoparib
Deleterious or suspected deleterious germline or somatic mutations in *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*	Prostate cancer	Olaparib

Published in: Debyani Chakravarty; Amber Johnson; Jeffrey Sklar; Neal I. Lindeman; Kathleen Moore; Shridar Ganesan; Christine M. Lovly; Jane Perlmutter; Stacy W. Gray; Jimmy Hwang; Christopher Lieu; Fabrice André; Nilofer Azad; Mitesh Borad; Laura Tafe; Hans Messersmith; Mark Robson; Funda Meric-Bernstam; *Journal of Clinical Oncology* 2022 401231-1258.
DOI: 10.1200/JCO.21.02767

EGFR exon 19 deletions, L858R	NSCLC	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib
EGFR exon 20 insertions		Amivantamab
EGFR nonresistant mutations other than exon 19 deletions and L858R		Afatinib
EGFR T790M		Osimertinib
ERBB2 amplification	Breast cancer	Ado-trastuzumab emtansine, capecitabine + trastuzumab + tucatinib, neratinib, pertuzumab + trastuzumab, trastuzumab, trastuzumab deruxtecan
	Esophagogastric cancer	Trastuzumab
	Gastric cancer, gastroesophageal junction cancer	Trastuzumab deruxtecan
FGFR2 fusions	Bladder cancer	Erdafitinib
	Cholangiocarcinoma	Pemigatinib, infigratinib
FGFR3 fusions	Bladder cancer	Erdafitinib
Oncogenic mutations in *FGFR3*		
GIS-positive or HRD-positive	Ovarian cancer	Niraparib
KRAS G12C	NSCLC	Sotorasib
MET exon 14 skipping	NSCLC	Capmatinib, tepotinib
dMMR and/or MSI-H	CRC	Ipilimumab + nivolumab, nivolumab
	Endometrial cancer	Dostarlimab
PDGFRA exon 18 mutations	Gastrointestinal stromal tumor	Avapritinib
Oncogenic mutations in *PIK3CA*	HR+ HER2– breast cancer	Fulvestrant + alpelisib
RET fusions	NSCLC, thyroid cancer	Pralsetinib, selpercatinib
Oncogenic mutations in *RET*	Medullary thyroid cancer	Pralsetinib, selpercatinib
ROS1 fusions	NSCLC	Crizotinib, entrectinib

Published in: Debyani Chakravarty; Amber Johnson; Jeffrey Sklar; Neal I. Lindeman; Kathleen Moore; Shridar Ganesan; Christine M. Lovly; Jane Perlmutter; Stacy W. Gray; Jimmy Hwang; Christopher Lieu; Fabrice André; Nilofer Azad; Mitesh Borad; Laura Tafe; Hans Messersmith; Mark Robson; Funda Meric-Bernstam; *Journal of Clinical Oncology* 2022 401231-1258.
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‘Second wave’: **Tumor-agnostic** approvals

FDA-approved treatments for specific biomarkers in tumor type–agnostic indications		
NTRK1 or *NTRK2* or *NTRK3* fusions	Solid tumors	Entrectinib, larotrectinib
MSI-H, TMB-H	Solid tumors	Pembrolizumab
FDA-approved treatments that are not biomarker-linked in solid tumors characterized by specified genetic alterations		
Oncogenic mutations in *NF1*	Neurofibroma	Selumetinib
COL1A1-PDGFB fusions	Dermatofibrosarcoma protuberans	Imatinib
SMARCB1 deletions	Epithelioid sarcoma	Tazemetostat
Oncogenic mutations in *TSC1* and *TSC2*	SEGA	Everolimus
KIT exon 11, 9, 13, 14, and 17 mutations	Gastrointestinal stromal tumor	Imatinib, sunitinib (postprogression on imatinib), regorafenib (postprogression on imatinib and sunitinib), ripretinib (postprogression on ≥ 3 kinase inhibitors including imatinib)

Published in: Debyani Chakravarty; Amber Johnson; Jeffrey Sklar; Neal I. Lindeman; Kathleen Moore; Shridar Ganesan; Christine M. Lovly; Jane Perlmutter; Stacy W. Gray; Jimmy Hwang; Christopher Lieu; Fabrice André; Nilofer Azad; Mitesh Borad; Laura Tafe; Hans Messersmith; Mark Robson; Funda Meric-Bernstam; *Journal of Clinical Oncology* 2022 401231-1258.
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FDA-listed genetic alterations contraindicated for specific treatments		
KRAS and/or *NRAS* exon 2, 3, and 4 mutations	CRC	Panitumumab, cetuximab
NTRK1 and *NTRK3* known acquired resistance mutations (eg, *NTRK1* G595R and G667C; *NTRK3* F617L, G623R, and G696A)	Solid tumors	Entrectinib, larotrectinib
FDA-approved combination treatments with nontargeted therapies for specific genetic alterations		
BRAF V600	Melanoma	Atezolizumab + cobimetinib + vemurafenib
Deleterious germline or somatic mutations in *BRCA1* and/or *BRCA2*	Fallopian tube, ovarian, primary peritoneal carcinoma	Bevacizumab + olaparib
EGFR exon 19 deletions, L858R	NSCLC	Erlotinib + ramucirumab
ERBB2 amplification	Breast cancer	Hyaluronidase-zzxf/pertuzumab/ trastuzumab + chemotherapy (docetaxel)
		Trastuzumab + pertuzumab + (docetaxel) chemotherapy
		Trastuzumab + (docetaxel + carboplatin) or (doxorubicin + cyclophosphamide + paclitaxel or docetaxel) or paclitaxel
		Lapatinib + capecitabine or letrozole
		Neratinib + capecitabine
		Margetuximab + chemotherapy
	Esophagogastric cancer	Trastuzumab + cisplatin + capecitabine or fluorouracil

Abbreviations: CRC, colorectal cancer; dMMR, mismatch repair deficiency; FDA, US Food and Drug Administration; GIS, genomic instability score; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; NSCLC, non–small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; SEGA, subependymal giant-cell astrocytomas; TMB-H, tumor mutation burden-high.

[a]The table summarizes FDA approvals at data cutoff of June 2, 2021. Precision oncology is a rapidly evolving field, and this table is a static snapshot of the approved targeted therapies at a specific point in time and therefore is expected to be outdated beyond the date it was published. The table is being included to provide examples of approved agents linked to genomic biomarkers or in disease with common genomic drivers.

Published in: Debyani Chakravarty; Amber Johnson; Jeffrey Sklar; Neal I. Lindeman; Kathleen Moore; Shridar Ganesan; Christine M. Lovly; Jane Perlmutter; Stacy W. Gray; Jimmy Hwang; Christopher Lieu; Fabrice André; Nilofer Azad; Mitesh Borad; Laura Tafe; Hans Messersmith; Mark Robson; Funda Meric-Bernstam; *Journal of Clinical Oncology* 2022 401231-1258.
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Table 1. Genetic indications for targeted therapy in cancer

Mutated gene	Common genetic alterations	Tumors implicated	Drugs
ALK	Mutation, fusion	Non–small cell lung cancer	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
ATM	Mutation	Breast	Olaparib
BCR-ABL	Fusion	Chronic lymphocytic leukemia, acute lymphocytic leukemia	Bosutinib, dasatanib, imatinib, nilotinib, ponatinib, asciminib
BRAF	Mutation	Melanoma, colorectal, hairy cell leukemia, thyroid	Dabrafenib, encorafenib, vemurafenib, binimetinib, cobimetinib, trametinib
BRCA1/2	Mutation	Breast, ovarian, prostate	Olaparib, niraparib, rucaparib, talazoparib
CHEK2	Mutation	Breast, ovarian	Olaparib
CSF1R	Mutation, fusion	Giant cell tumor	Pexidartinib, sunitinib[A]
EGFR	Mutation, fusion, amplification	Non–small cell lung cancer	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, brigatinib[A], amivantamab
ERBB2/3/4	Amplification, mutation	Breast	Afatinib[A], lapatinib, neratinib, tucatinib, trastuzumab[B], pertuzumab[B], margetuximab
EZH2	Mutation	Lymphoma	Tazemetostat
FGFR1/2/3	Mutation, fusion	Cholangiocarcinoma	Erdafitinib, lenvatinib[A], pemigatinib, infigratinib
FLT3	Mutation	Myeloid leukemia	Gilteritinib, midostaurin, sorafenib[A]
IDH1/2	Mutation	Myeloid leukemia, cholangiocarcinoma, glioblastoma	Ivosidenib, enasidenib
JAK2	Mutation	Myeloproliferative syndrome	Fedratinib, ruxolitinib
KIT	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, melanoma	Avapritinib, imatinib, pazopanib[A], pexidartinib[A], ripretinib, sorafenib, nilotinib[A], sunitinib
KRAS	Mutation	Non–small cell lung cancer	Sotorasib
MET	Mutation, fusion	Non–small cell lung cancer	Cabozantinib[A], capmatinib, crizotinib[A], tepotinib
NTRK	Fusion	Many solid tumors at low frequency	Larotrectinib, entrectinib
PDGFRA/B	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, hypereosinophilic syndrome	Avapritinib, imatinib[A], sorafenib[A], sunitinib[A], lenvatinib[A], pazopanib[A], ripretinib[A]
PIK3CA	Mutation	Breast	Umbralisib[A], duvelisib[A], idelalisib[A], copanlisib[A], alpelisib, temsirolimus[A], everolimus[A]
PML-RARA	Fusion	Myeloid leukemia	Arsenic trioxide, retinoic acid
RET	Mutation, fusion	Renal, thyroid, non–small cell lung cancer	Pralsetinib, selpercatinib, cabozantinib[A]
ROS1	Fusion	Non–small cell lung cancer	Entrectinib, crizotinib
SMO/PTCH1	Mutation	Medulloblastoma, basal cell carcinoma	Vismodegib

[A]Mutation-specific treatment supported by National Comprehensive Cancer Network guidelines that does not have full FDA approval. [B]Base antibody used alone or as antibody-drug conjugate.

Table 1: Targeting mutations in cancer
J Clin Invest DOI: 10.1172/JCI154943 2022

Emerging patterns: Increasing numbers of drugs in the same category, same or nearly the same molecular target

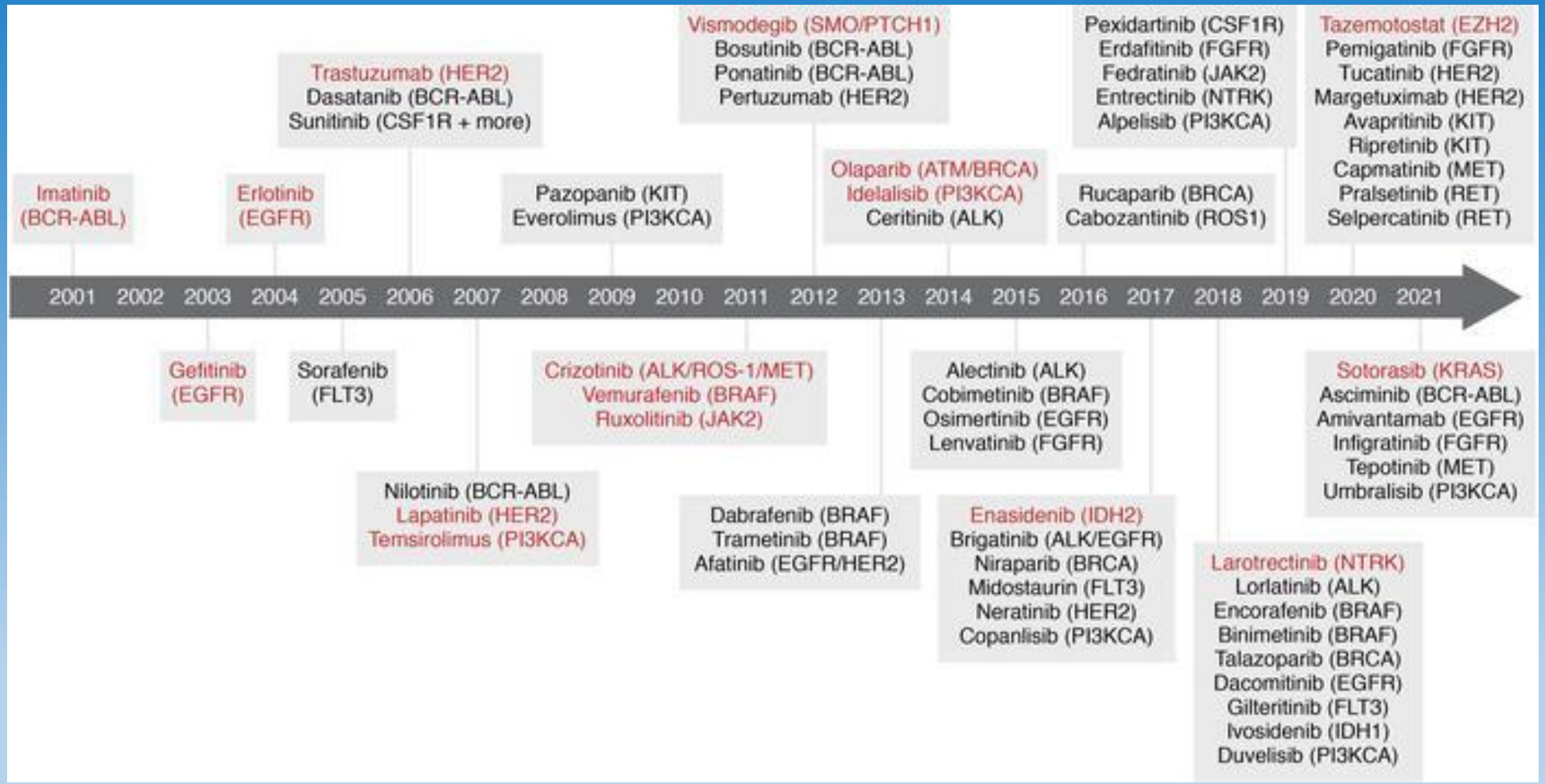


Figure 1: Targeting mutations in cancer

J Clin Invest DOI: 10.1172/JCI154943 2022

Chemotherapeutics: Reports of its death have been greatly exaggerated!
New ways to deliver it represent a current strategy: ADCs

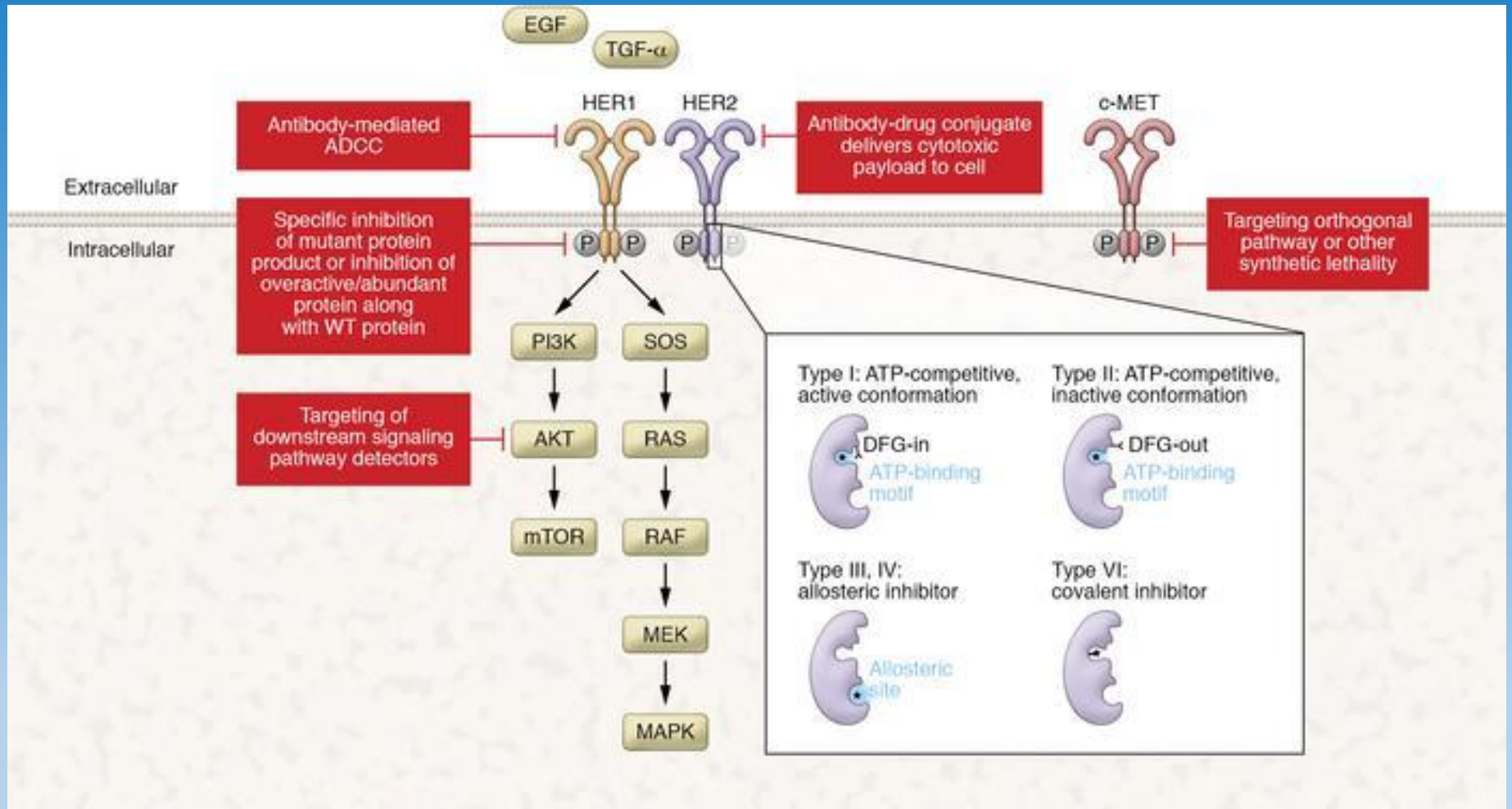
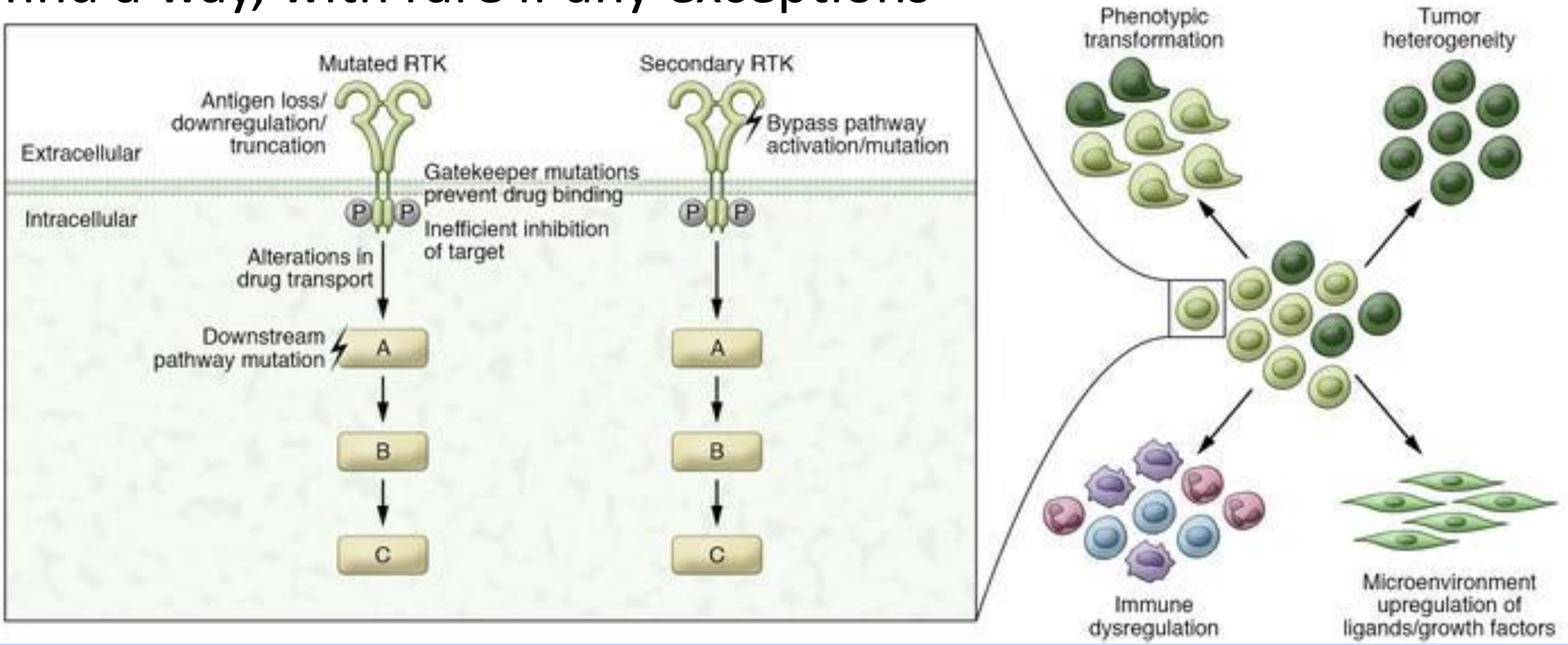


Figure 2: Targeting mutations in cancer

J Clin Invest DOI: 10.1172/JCI154943

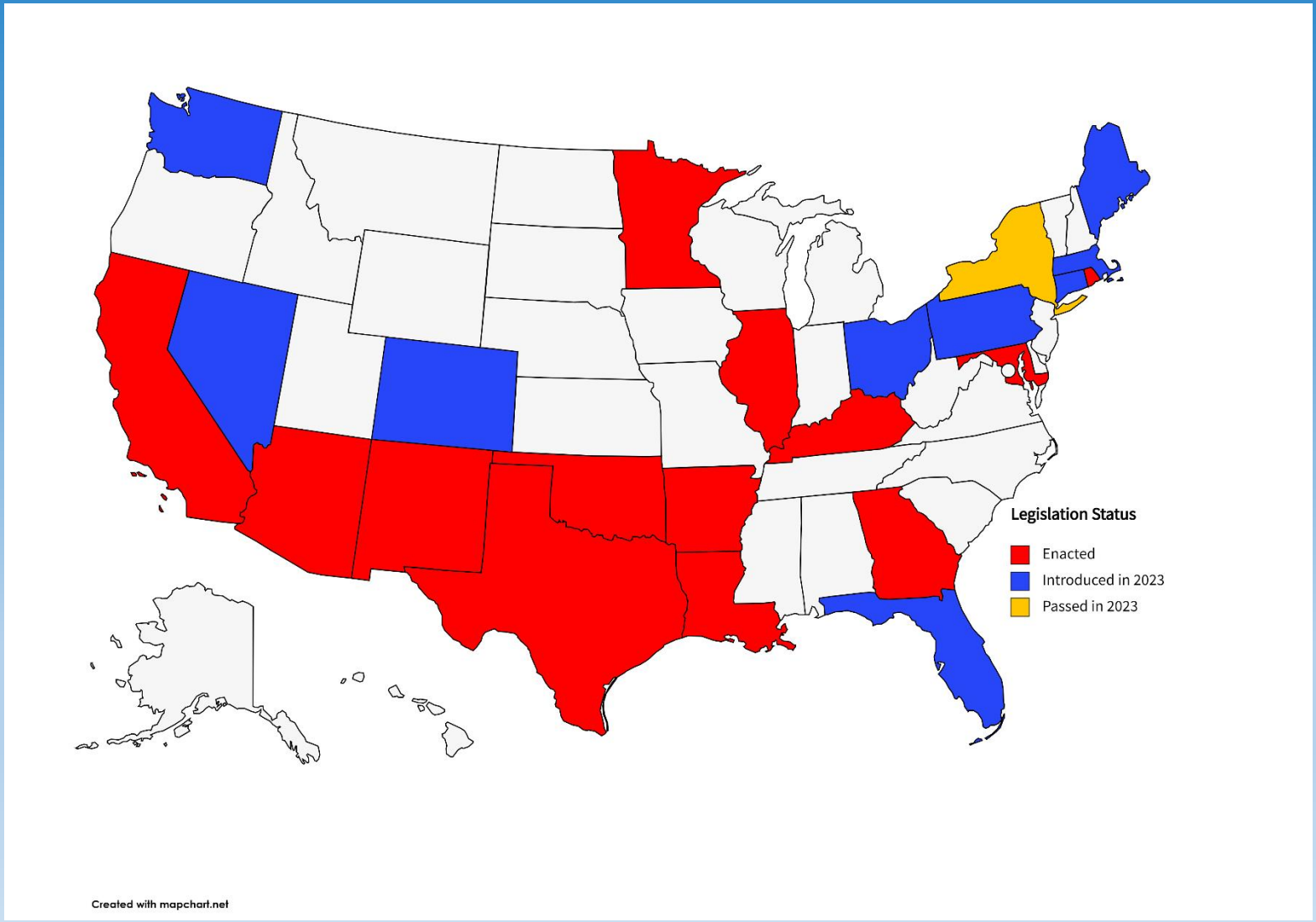
Rise of the Resistance – Cancer and its Molecular Pathway(s) find a way, with rare if any exceptions



Targeting mutations in cancer. Figure 3 in:

J Clin Invest DOI: 10.1172/JCI154943

The American Cancer Society Cancer Action Network (ACS CAN): example of nationwide advocacy efforts expand insurance coverage of comprehensive biomarker testing



https://www.fightcancer.org/what-we-do/access-biomarker-testing

Recommendations to Improve Access to Biomarker Testing in Cancer

Fightcancer.org

Barriers to biomarker testing can arise beginning at test development and persist through the interpretation of test results in the clinic. As precision medicine shifts the way health care providers and patients think about cancer treatments, it will be important to identify and address obstacles to appropriate biomarker testing. Addressing these barriers will require buy-in from diverse stakeholders across the health care system. ACS CAN proposes the following recommendations to increase the uptake of testing and advance the use of precision medicine in cancer care:

Patient Considerations

Insurer coverage is important for provider uptake and patient access to cancer biomarker testing. However, coverage of tests differs across the multiple public and private payers in the U.S. health care system.

1. Payers should provide coverage for National Comprehensive Cancer Network (NCCN) guideline-indicated biomarker tests and FDA-cleared or -approved companion and complementary diagnostics as necessary to evaluate patient eligibility for a given targeted cancer therapy.

    a. Coverage of biomarker testing should not be arbitrarily constrained to specific cancer stages (e.g. III, IV, metastatic), but rather coverage should follow guideline recommendations and FDA-cleared or -approved uses.

    b. Payers should ensure that any utilization review practices (e.g. prior authorization) are timely and efficient and do not delay the initiation of biomarker testing after a diagnosis.

    c. Coverage of biomarker testing should not be restricted to one single occurrence and should allow for retesting after a medically appropriate interval, indication of a change in the genetic makeup of the patient's cancer (e.g. such as acquired resistance), or if the test is designed to monitor disease progression and therefore must be serially administered.

    d. Payers should provide coverage for multi-gene panel testing as indicated by NCCN guidelines, when it is more efficient, when a single analyte test does not exist, or when tissue availability is too limited for use of multiple single analyte testing.

Provider and Institutional Considerations

Providers and institutions have a significant impact on which patients receive cancer biomarker testing and consequently whether they receive targeted cancer therapy. Despite evidence pointing to the clinical benefits, testing rates lag behind clinical guidelines and advancements in the field.

1. Biomarker tests should be reliable, valid, and relevant to a patient's cancer diagnosis. This should be realized with a harmonized system of regulatory oversight for all biomarker tests that features tiered requirements based on the risk posed by a given biomarker test.

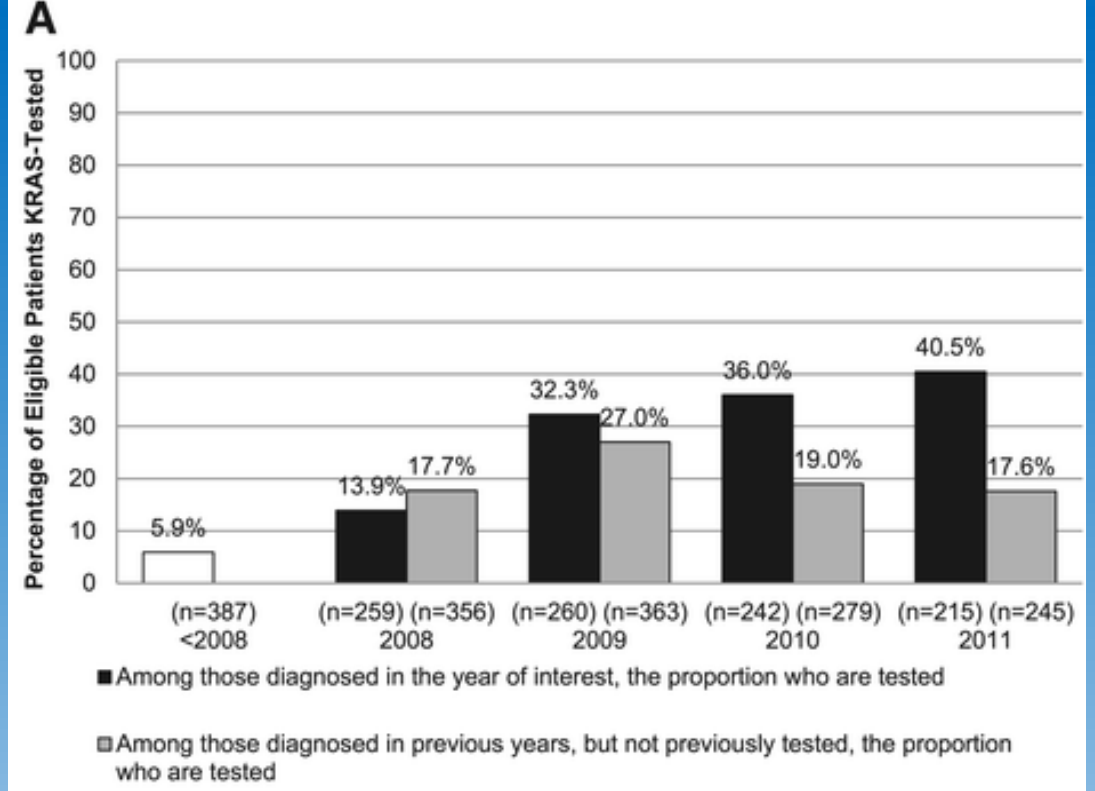
2. Providers and institutions should be equipped with tools (e.g. clinical decision support), resources (e.g. access to a tumor board), and training for the efficient and sufficient collection and handling of tissue for testing, and for proper test selection, administration, and interpretation.

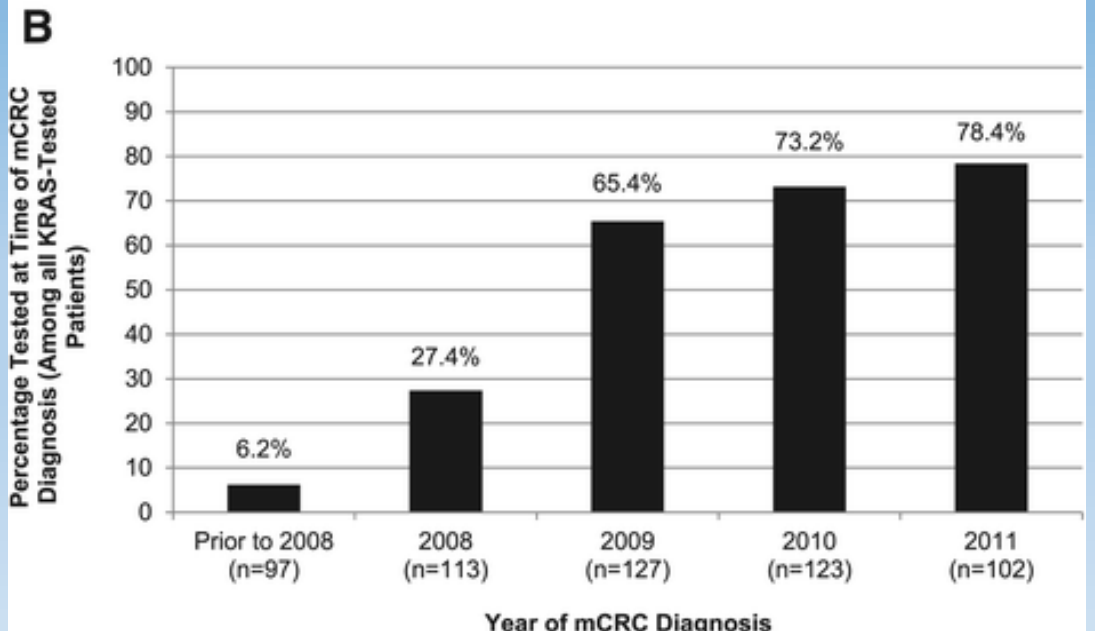
    a. Quality measures and accreditation standards should promote adoption and utilization of clinical decision support tools for biomarker testing that incorporate evidence-based clinical guidelines at the point of care to guide testing and treatment decisions.

    b. High-quality clinical biomarker testing guidelines should adhere to guideline development best practices including appropriate transparency, conflict of interest rules, systematic evidence review, and timely updating.

    c. Licensing and clinical specialty boards should encourage use of current biomarker testing guidelines through continuing education requirements.

The percent of patients getting standard-of-care tumor genetic testing: improving but not yet 100%

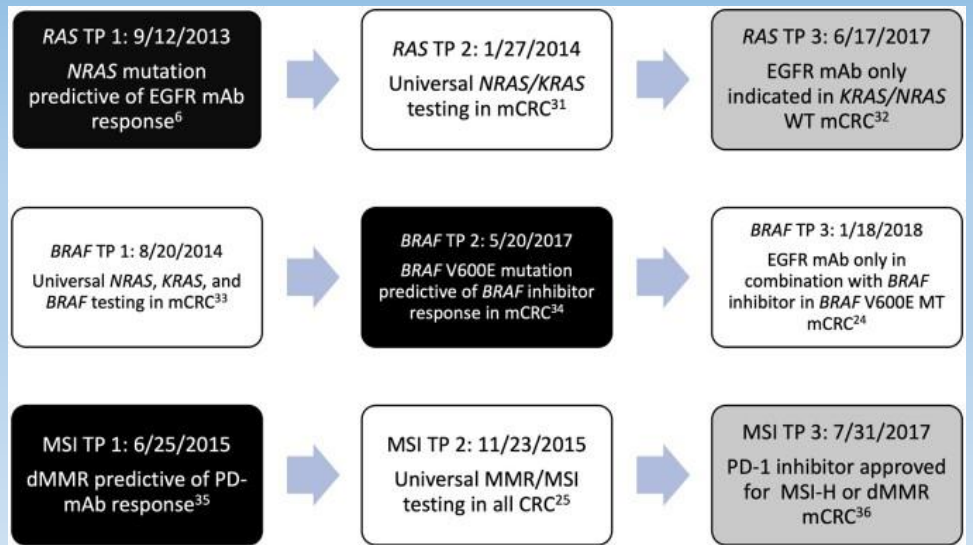


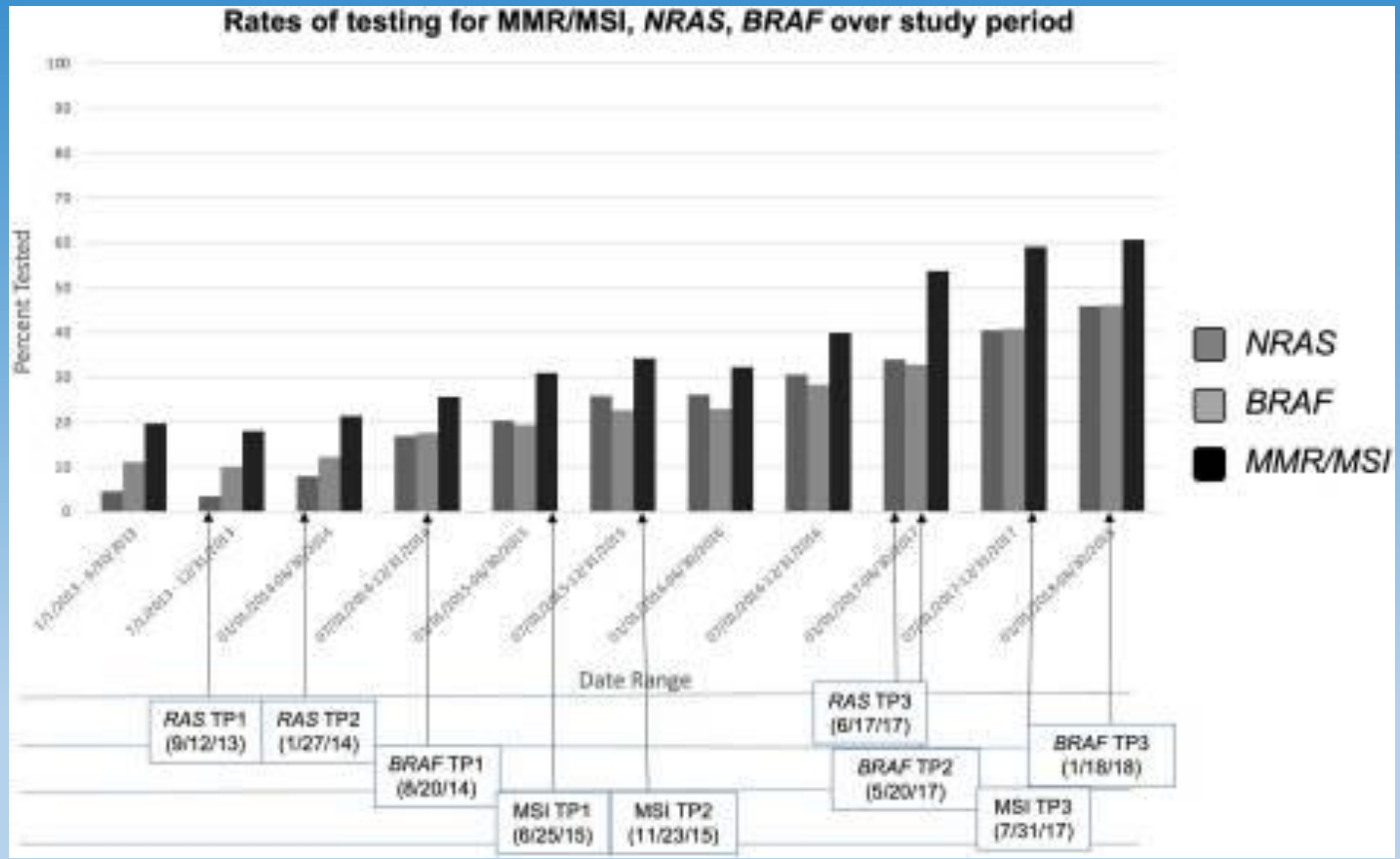


From: *KRAS* testing of patients with metastatic colorectal cancer in a community-based oncology setting: a retrospective database analysis. Carter et al., 2015.

The percent of patients getting standard-of-care tumor genetic testing: improving but not yet 100%

- 20,000+pts, retrospective, 2013-2018
- "as of June 30, 2018, the rate of test results was only 46% for *NRAS*, 56% for *KRAS*, and 46% for *BRAF*.
- "As of December 31, 2017, the rate of MMR/MSI testing was 59%."
- Higher documented testing rates were associated with younger age, lower Eastern Cooperative Oncology Group performance status, and commercial insurance.





JNCI Cancer Spectr. 2022 Dec. Iyer et al.

New models for how we help patients with solid tumor malignancies

- We need to do a lot better – for most advanced and metastatic solid tumor malignancies, treatment is given with ***palliative-intent***, as currently available forms of treatment do not have potential for inducing cure.
- Exceptional Responders – are exceptional.
  - NCI definition: "…someone who had a partial or complete **response** to a treatment that would be effective in less than 10% of similar patients. The duration of an **exceptional response** is one that lasts at least three times longer than the median **response** time."
- <u>But there is hope…</u>
  - The next frontier of clinical trial strategies in solid tumors
  - Informed by advances in molecular diagnostics, understanding of molecular drivers of cancer, and also non-molecular aspects of solid tumor biology that can be targeted effectively.

Ref from NCI: https://www.nih.gov/news-events/news-releases/study-exceptional-responders-yields-clues-cancer-potential-treatments#:~:text=The%20study%20defined%20an%20exceptional,than%20the%20median%20response%20time.

Precision Medicine: highlighting the opportunities

- Efficacy: How well do they work
- Evolving questions, pending answers
- To date, widely variable, even with the same target & *same drugs* in different cancer types

An evolving question

- NCI-MATCH as a paradigm for current and future strategies

Cancer Therapy Advisor

Home » Cancer Topics » General Oncology » NCI-MATCH Trial Identifies Actionable Alterations in More Than One-Third of Patients With Cancer

December 3, 2020

NCI-MATCH Trial Identifies Actionable Alterations in More Than One-Third of Patients With Cancer

Agata Boxe

https://www.cancertherapyadvisor.com/home/cancer-topics/general-oncology/molecular-alteration-cancer-treatment-risk-nci-match/2/
Accessed 5/10/22

Of the 6391 enrolled patients, 5954 had tumor samples available, and 5540 of those samples were sequenced successfully. Of all these sequenced samples, 2079 came from patients with NSCLC or breast, colorectal, or prostate cancers, whereas the majority — 3461 — came from patients with less common cancer types.

Study participants had undergone a median of 3 prior treatments, whereas less than 25% of all patients had received 1 treatment or no prior therapy.

The investigators detected actionable alterations in 37.6% of patients. Moreover, 17.8% were assigned to receive specific treatments based on their molecular results. The authors noted that 26.4% could have been assigned to treatments if all the protocols had been reached.

In the population of patients that were assigned to treatments, the assignment rate was 17.4% for patients with NSCLC, 13.7% for those with colorectal cancer, 17.8% for those with breast cancer, and 23% for those with prostate cancer. The researchers reported assignment rates greater than 25% in patients with CNS cancer, urothelial cancer, cholangiocarcinoma, pancreaticobiliary cancer, cervical cancer, gastroesophageal cancer, melanoma, uterine cancer, and anal cancer. The lowest assignment rates, below 6%, were identified in patients with pancreatic cancer, small cell lung cancer, and lymphoma.

Of all actionable alterations, *PIK3CA* and *PTEN* were observed most often, at 11.8% and 6.3%, respectively. Other actionable alterations were seen in 3% of patients or less.

However, 37.6% of patients with the most frequently identified actionable alterations were excluded from treatment because they had other mutations that have been shown to confer resistance. One example was those patients with *PIK3CA* alterations who also had *RAS* or *PTEN* resistance-conferring alterations.

An evolving question

- NCI-MATCH as a paradigm for current and future strategies

Razelle Kurzrock, MD, distinguished professor of medicine at the University of California San Diego School of Medicine, California, who was not involved in the new study, applauded the authors' ability to put together what she called an "enormous trial" conducted at a large number of sites. However, she said that the paper lacked information on patient outcomes. "I think that in the year 2020, we should know about patient outcomes in a publication," she said.

"What I would have liked to know is what happens to these patients," Dr Kurzrock said. "Did they respond? What was their progression-free survival? What was their overall survival?"

In response to Dr Kurzrock's comments, Dr Flaherty said that patient outcome data from some of the individual arms in the trial had been published by the time the researchers submitted their manuscript to the journal, and more such data were published while the manuscript was undergoing review and revision. Additional outcome data will be published in the future, he said.

"We will continue to publish the individual arms in a rolling fashion," Dr Flaherty wrote in an email. "As some of the arms target very rare subpopulations and are taking longer to accrue, we did not want to withhold this genomic landscape analysis while waiting for those remaining arms. We will certainly analyze and publish the outcomes for the whole study population in a separate paper, but are simply trying to get important components out as the data are ready."

In response, Dr Kurzrock said that the information provided by Dr Flaherty addressed her concerns about the lack of patient outcome data in the new paper.

https://www.cancertherapyadvisor.com/home/cancer-topics/general-oncology/molecular-alteration-cancer-treatment-risk-nci-match/2/ Accessed 5/10/22

The Value, in the economic sense: What am I getting

- ‘Comprehensive’ vs ‘Limited’ Tumor Genomic Profiling
  - What should I order?
  - When should I order it?
- ‘Bundling vs ‘a la carte’ testing – which approach is more cost-effective?
- What information do you ‘need’ to make a practical clinical decision in 2023, 2024, and beyond – now and for future lines of treatment, on or off trial?

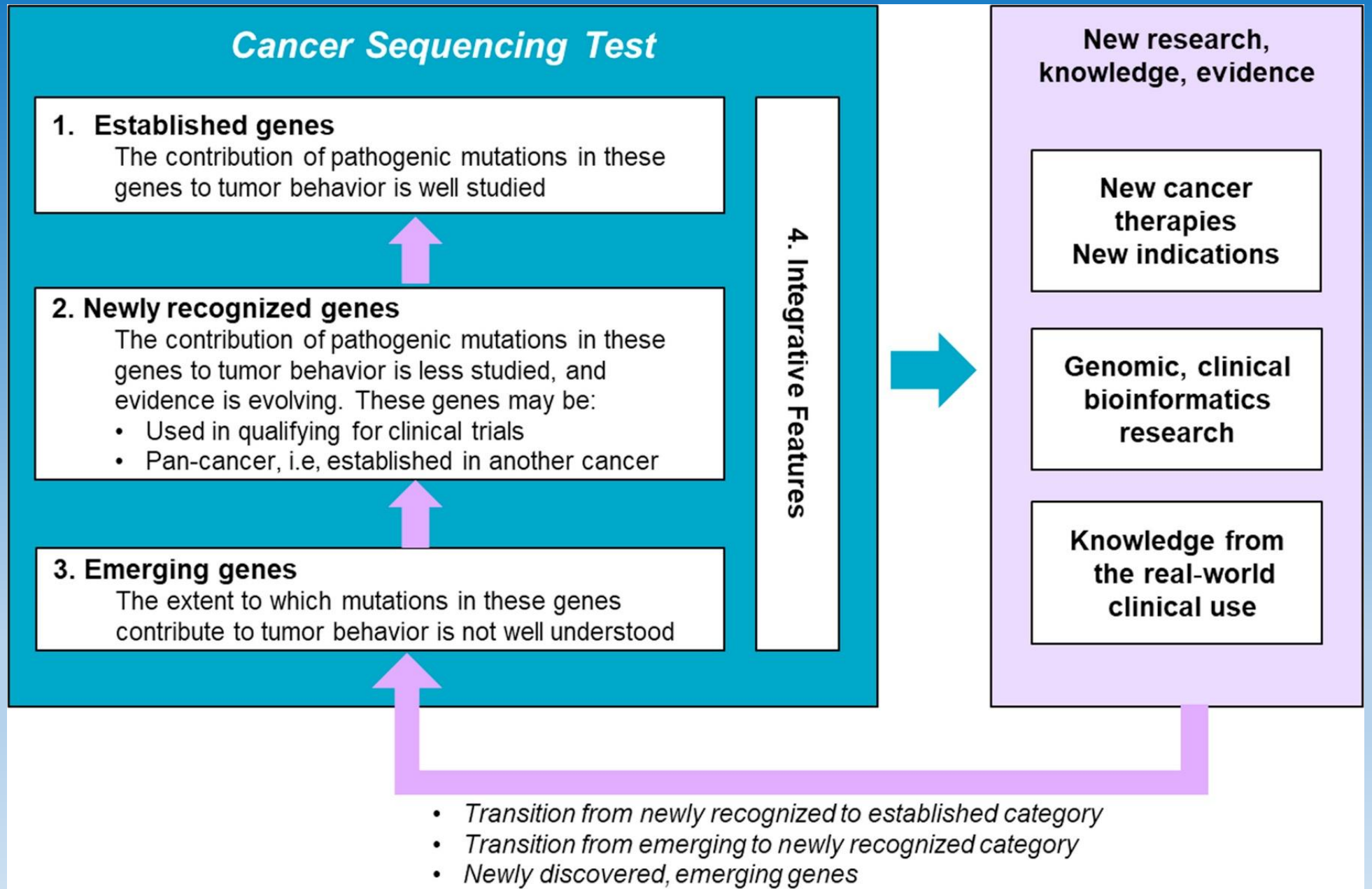
To test more or not to test more: What are the options, and how do we decide what to use?

- Itemization of testing
- Limited gene panels
- Comprehensive genomic profiling

Some questions:

- Is the testable biomarker linked to a therapeutic drug that has been approved for treatment of this patient's disease?
- Is the testable biomarker linked to a therapeutic drug available at your or a reasonably distanced center on clinical trial?

Value vs. Action: Mutually exclusive?



Ref: JR Trosman et al. From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing. Value in Health, 21(9): 1062-1068, 2018

Table 1. **Features of NGTS conflicting with the current insurance coverage framework**

NGTS, next-generation tumor sequencing.

NGTS feature	Conflict with the current insurance coverage framework
1.Dual utility: clinical and research	Applies to both "medically necessary" and "experimental/investigational" categories [15], [16]
2.Informing enrollment in clinical trials	Clinical trial is a guideline-recommended setting for cancer treatment, and is therefore both "medically necessary" and "experimental/investigational" [13], [32]
3.Comparative cost of NGTS, relative to single-gene testing	Cost is not a formal factor of coverage framework [19], [39]
4."Sequencing pathway" utility—serial use over time	Typically focused on one technology and one point in disease trajectory [6], [19]
5.Inherent evolutionary nature of evidence for tumor sequencing tests	Conflicts with the linear trajectory of evidence development and binary coverage decision [16], [19]
6.Informing pan-cancer use of drugs	Conflicts with medical necessity definition for a specific indication [6], [16], [19], [39]
7."Many-genes-to-many-drugs" utility	Conflicts with the one-marker-one-drug evaluation of medical necessity [6], [19], [39]
8.Integrative utility based on compound analysis of mutations	Sequencing is considered a "bundle" of individual gene tests [15], [16]

Ref: JR Trosman et al. From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing. Value in Health, 21(9): 1062-1068, 2018

Precision Oncology: what is the financial cost for testing?

Centers for Medicare & Medicaid Services

Cms.gov

Accessed 5/10/22

NCD - Next Generation Sequencing (NGS) (90.2)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Tracking Information

Publication Number

100-3

Manual Section Number

90.2

Manual Section Title

Next Generation Sequencing (NGS)

Version Number

2

Effective Date of this Version

01/27/2020

Implementation Date

11/13/2020

Description Information

Benefit Category

Diagnostic Laboratory Tests
Diagnostic Services in Outpatient Hospital
Diagnostic Tests (other)

Please Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

What are the national guidelines for financial coverage?

Item/Service Description

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for RNA sequencing and protein analysis.

Accessed 5/10/22

What are the national guidelines for financial coverage?

Indications and Limitations of Coverage

B. Nationally Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:

i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Accessed 5/10/22

What are the national guidelines for financial coverage?

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

a. Patient has:

i. ovarian or breast cancer; and,
ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
iii. a risk factor for germline (inherited) breast or ovarian cancer; and
iv. not been previously tested with the same germline test using NGS for the same germline genetic content.

b. The diagnostic laboratory test using NGS must have all of the following:

i. FDA-approval or clearance; and,
ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Accessed 5/10/22

What are the national guidelines for financial coverage?

C. Nationally Non-Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with acquired (somatic) cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1., above.

D. Other

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with advanced cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
b. not been previously tested with the same test using NGS for the same cancer genetic content, and
c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:

a. any cancer diagnosis; and,
b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
c. a risk factor for germline (inherited) cancer; and,
d. not been previously tested with the same germline test using NGS for the same germline genetic content.

(This NCD last reviewed January 2020)

Accessed 5/10/22

What are the national guidelines for financial coverage?

- Cms.gov:
- **Indications and Limitations of Coverage**
  B. Nationally Covered Indications
- 1. Somatic (Acquired) Cancer
- Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:
- a. Patient has:
  either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
- not been previously tested with the same test using NGS for the same cancer genetic content, and
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
- b. The diagnostic laboratory test using NGS must have:Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- an FDA-approved or -cleared indication for use in that patient's cancer; and,
- results provided to the treating physician for management of the patient using a report template to specify treatment options.

What are the national guidelines for financial coverage?

- Cms.gov:
- 2. Germline (Inherited) Cancer
- Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:
- a. Patient has:
  ovarian or breast cancer; and,
- a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
- a risk factor for germline (inherited) breast or ovarian cancer; and
- not been previously tested with the same germline test using NGS for the same germline genetic content.
- b. The diagnostic laboratory test using NGS must have all of the following:
  FDA-approval or clearance; and,
- results provided to the treating physician for management of the patient using a report template to specify treatment options.

Potential financial toxicities and implications for patients. A case example – 47 yr old woman with stage IV CRC; her oncologist orders NGS via an in-house limited panel.

Dr. Lou,

I do see a charge for molecular testing for 9/14/2020. There are three tests. Colorectal NGS panel, RNA fusion testing and MSI testing.

Colorectal panel is $1,815, Fusion $1,228 and MSI $1,509.

The total bill was $4,552.

XXXX Healthcare covered the MSI testing, but not the NGS or fusion testing.

I called XXXX Healthcare today and the reason for denial is that multi gene genetic panels are and deemed investigational under this patient's plan. The test is also not considered medically necessary for this patient by UHC.

REMARK CODES

6B: PAYMENT FOR THIS SERVICE IS DENIED. BASED ON THE INFORMATION PROVIDED AND THE CLINICAL REVIEW, THIS SERVICE IS NOT CONSIDERED MEDICALLY NECESSARY.

CLAIM ADJUSTMENT REASON CODES

50: THESE ARE NON-COVERED SERVICES BECAUSE THIS IS NOT DEEMED A "MEDICAL NECESSITY" BY THE PAYER.

The denial can still be appealed. Who would be the best person to help with the appeal information? I can create a template that will need to be filed in with additional information. I can email the template out to be reviewed and completed.

Controversies in Precision Oncology

- Inequities in access between high-income and low-income countries
- What is the cost-to-benefit ratio?
- Rapidly evolving technology – making a choice becomes less simple.

Summary: Principal issues and ongoing questions that are being addressed in the field

- Tumor genomic testing in patients with metastatic or advanced solid tumors has become extremely more sophisticated over the past decade.
- Transition from tumor type-specific panels to evaluating targets across tumor types ('tumor agnostic' approach).
- Challenges and questions:
  - When should we order it?
  - What assay(s) should we order?
  - How do we interpret the results?
    - The end goal is to be able to tailor therapy based on these results to result in overall improvement for patients suffering from cancer, ideally focused on improvements in overall survival.

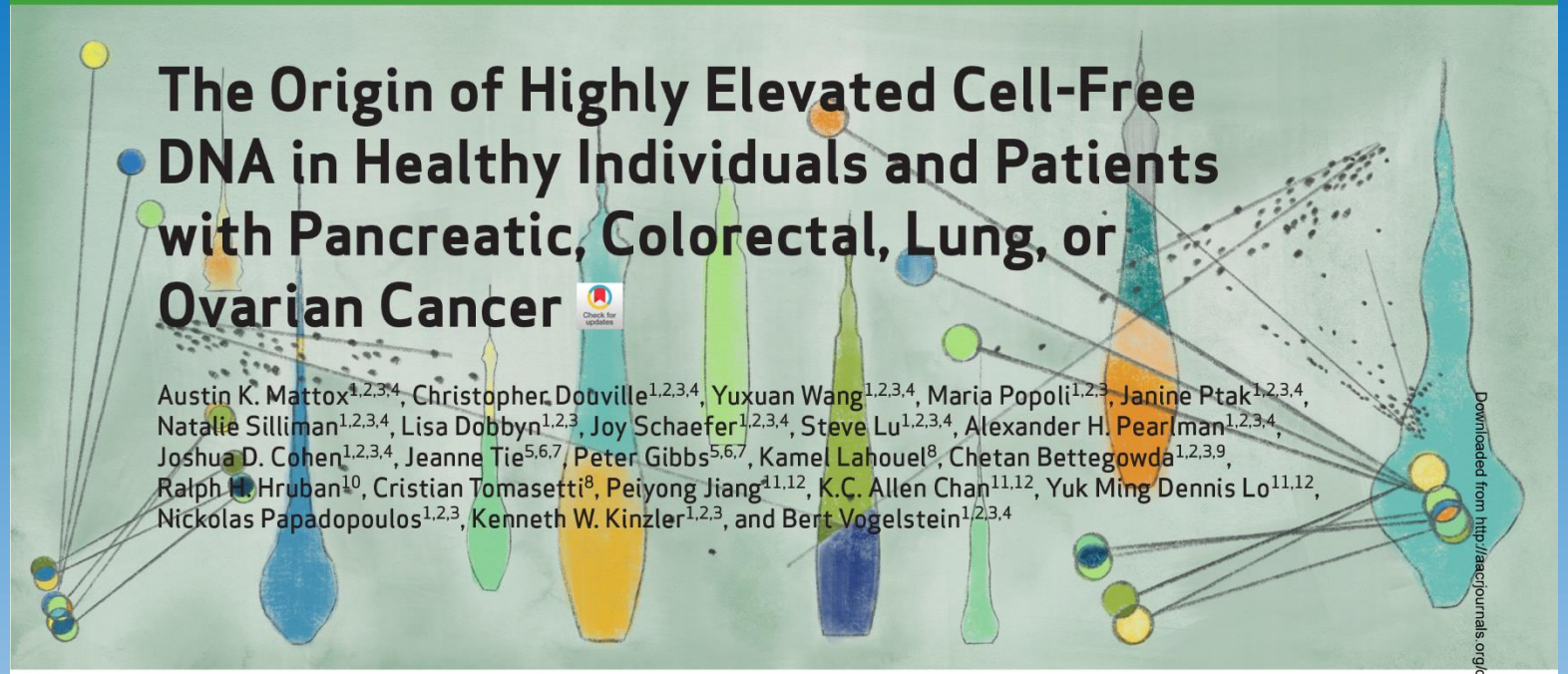
The “Liquid Biopsy”: State-of-the-Art or ’Not ready for Prime Time Player?”

- cfDNA (cell-free) vs. ct (circulating tumor) DNA
- What is it good for?
  - Diagnosis-- MCDE
  - Prognosis – MRD in solid tumor oncology?
- Borrowing the concept of Minimal Residual Disease (MRD) from hematologic malignancies
  - Does this translate well to solid tumors, and will the test be proven to be meaningful for clinical decision-making?

The “Liquid Biopsy”: State-of-the-Art or ’Not ready for Prime Time Player?”

- Sensitivities and specificities compared to tissue-based tumor profiling.
  - Increased concordance, near or exceeds 90%.
- Helpful tool when there is insufficient amount of tissue for testing.
- It can be detected; how should it be interpreted?
- Ongoing trials designed to address this
  - E.g. COBRA, adjuvant assessment following resection of early-to-mid stage colon cancer

RESEARCH BRIEF



The Origin of Highly Elevated Cell-Free DNA in Healthy Individuals and Patients with Pancreatic, Colorectal, Lung, or Ovarian Cancer

Austin K. Mattox[1,2,3,4], Christopher Douville[1,2,3,4], Yuxuan Wang[1,2,3,4], Maria Popoli[1,2,3], Janine Ptak[1,2,3,4], Natalie Silliman[1,2,3,4], Lisa Dobbyn[1,2,3], Joy Schaefer[1,2,3,4], Steve Lu[1,2,3,4], Alexander H. Pearlman[1,2,3,4], Joshua D. Cohen[1,2,3,4], Jeanne Tie[5,6,7], Peter Gibbs[5,6,7], Kamel Lahouel[8], Chetan Bettegowda[1,2,3,9], Ralph H. Hruban[10], Cristian Tomasetti[8], Peiyong Jiang[11,12], K.C. Allen Chan[11,12], Yuk Ming Dennis Lo[11,12], Nickolas Papadopoulos[1,2,3], Kenneth W. Kinzler[1,2,3], and Bert Vogelstein[1,2,3,4]

ABSTRACT Cell-free DNA (cfDNA) concentrations from patients with cancer are often elevated compared with those of healthy controls, but the sources of this extra cfDNA have never been determined. To address this issue, we assessed cfDNA methylation patterns in 178 patients with cancers of the colon, pancreas, lung, or ovary and 64 patients without cancer. Eighty-three of these individuals had cfDNA concentrations much greater than those generally observed in healthy subjects. The major contributor of cfDNA in all samples was leukocytes, accounting for ~76% of cfDNA, with neutrophils predominating. This was true regardless of whether the samples were derived from patients with cancer or the total plasma cfDNA concentration. High levels of cfDNA observed in patients with cancer did not come from either neoplastic cells or surrounding normal epithelial cells from the tumor's tissue of origin. These data suggest that cancers may have a systemic effect on cell turnover or DNA clearance.

SIGNIFICANCE: The origin of excess cfDNA in patients with cancer is unknown. Using cfDNA methylation patterns, we determined that neither the tumor nor the surrounding normal tissue contributes this excess cfDNA—rather it comes from leukocytes. This finding suggests that cancers have a systemic impact on cell turnover or DNA clearance.

See related commentary by Thierry and Pisareva, p. 2122.

Cancer Discovery
Volume 13, Issue 10
1 October 2023

Quality of assays: Are the results true?

- Another way of stating: Are the results accurate enough that you have confidence using this information to institute clinical decision-making for your patients?
- CLIA certification: Tumor genomic sequencing should take place in a clinical pathology lab setting that has been certified.
- Emerging questions and controversies:
  - Tissue or Liquid-based assessments – or both?
  - When do you order the test, and using which specimen?
    - Order when the patient needs it, or order it in advance.
    - Use the pre-treatment biopsy or surgical sample, or wait-and-see if further biopsies/surgical specimens will be available?
    - Some or all of the above?

Tumor-agnostic approvals in the U.S.: A Growing Category of Actionable Targets

- Definition of tumor agnostic: Approval of a drug for any tumor containing a biomarker target, independent of anatomic site of origin of that metastatic cancer.
- The current examples:
  - TMB-High
  - Mismatch repair (dMMR)
  - Neutrotrophic tyrosine receptor kinase (NTRK) fusions

Hot off the press!

- On October 20, 2023, the Food and Drug Administration granted accelerated approval to entrectinib (Rozlytrek, Genentech Inc.) for ***pediatric patients*** older than 1 month with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion
  - without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity,
  - and have progressed following treatment or have no satisfactory standard therapy.
- In August 2019, FDA granted accelerated approval to entrectinib for pediatric patients 12 years of age and older for this indication

Source: AACR FDA Approval Alert, October 24, 2023

Tumor-agnostic approvals in the U.S.: A Growing Category of Actionable Targets

- Do we have proof that utilizing the drug for actionable targets improves PFS and OS in every tumor type covered by the FDA approval?

- Spoiler alert: No, we do not.

When does potential off-label use justify wider-scale comprehensive genomic profiling for an individual patient's tumor?

- Evolving field of understanding molecular blueprints of Rare Tumors
- Genomic profiling is identifying molecular subsets of more common tumors, and further sub-stratifying tumors that were already considered less common or even Rare.
- How does tumor genomic profiling affect these cases?
  - ASCO Provision Clinical Opinion 2022: "Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease."

One conclusion on what to do…

- …and the story is still being written as we await results of current and forthcoming molecular biomarker-driven trials.
- ASCO Provision Clinical Opinion 2022: “For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker-linked options relative to other approved or investigational treatments.”

Common questions from patients

- A well-informed patient – regardless of the source – will likely be aware of our ability to order tumor genomic profiling, and will ask if you don't bring it up.
- If you bring it up first, they may or may not already be aware, but they will depend on us for judging the approach (which assay(s), which tests, and how to interpret the information).
- A central message I state to patients is that doing tumor genomic profiling does not guarantee a valid drug for treating their cancer will be identified.
  - In fact, far from it…but that answer may change, and quickly, in the coming years with rapid advances in testing and clinical trial results.

An approach to genomic testing and decision-making factors

- If I test, what will I do with this information, and why am I ordering the test.
- Can a target or set of targets be identified
- Is the target ‘actionable’
  - The target is identifiable with great accuracy using a readily available and orderable test, with high sensitivity and specificity, and the material to be tested is available.

An approach to genomic testing and decision-making factors

- Is the tumor type ‘target-rich’; and what does that even mean?
- Does a drug, or set of drugs, exist that will ‘hit’ that target
  - Have those drugs been proven to work when in the human setting
  - Have the drugs already been tested in humans in well-designed rational clinical trials
  - Have the results shown benefit in PFS, OS, and/or QOL for patients eligible for clinical trials, and possibly ‘real world’ clinical populations as well?
  - Financial coverage of these targeted drugs: What is the cost to the patient (symptoms and adverse physical events attributable to the treatment, as well as the potential for financial toxicity.

ASCO Guidelines

SOMATIC GENOMIC TESTING IN PATIENTS WITH METASTATIC OR ADVANCED CANCER
PROVISIONAL CLINICAL OPINION

WHICH METASTATIC OR ADVANCED SOLID TUMORS SHOULD UNDERGO GENOMIC SEQUENCING?

- All cancers with regulatory approved biomarkers that guide therapy choice.

WHAT SHOULD CLINICIANS CONSIDER FOR TREATMENT PLANNING WHEN RECEIVING THE RESULTS OF GENOMIC SEQUENCING?

- The functional impact of the targeted alteration.
- The expected efficacy of genomic biomarker-linked-options relative to other treatments.
- Clinical trials are encourage in the absense of standard-of-care options

WHERE SHOULD PATIENTS WITH METASTATIC OR ADVANCED CANCER UNDERGO GENOMIC SEQUENCING?

- In a certified laboratory.

WHEN SHOULD MULTIGENE PANEL TESTING BE CONDUCTED?

- Whenever more than one genomic biomarker is linked to regulatory agency-approved therapy in the patient's disease.

WHEN ELSE IS MULTIGENE PANEL TESTING BENEFICIAL?

- When considering immunotherapies with genomic biomarker-linked site-agnostic approvals.
- To identify additional targets when there are few or no genotype-based therapy approvals for the patient's disease.

Chakravarty et al *J Clin Oncol* 2022 asco.org/assays-and-predictive-markers-guidelines

The future of Precision Oncology

Making the undruggable…druggable

- RAS is the prototype.
- Recent reports 2020-21 of small molecule inhibitors having activity in patients with tumors harboring G12C variant of the oncogene KRAS.

The story of targeting RAS is still evolving, and more real(istic) than ever before

- The first direct KRAS inhibitor, Sotorasib, was approved for use in NSCLC expressing G12C-mutant KRAS was approved by the US FDA on Friday May 28, 2021.
- But like BRAF in melanoma vs. CRC, one size does not fit all:
  - ORR in NSCLC for KRAS G12C cases: 30-40%
  - ORR in CRC for KRAS G12C cases: <10%.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C

M.G. Fakih, L. Salvatore, T. Esaki, D.P. Modest, D.P. Lopez-Bravo, J. Taieb, M.V. Karamouzis, E. Ruiz-Garcia, T.-W. Kim, Y. Kuboki, F. Meriggi, D. Cunningham, K.-H. Yeh, E. Chan, J. Chao, Y. Saportas, Q. Tran, C. Cremolini, and F. Pietrantonio

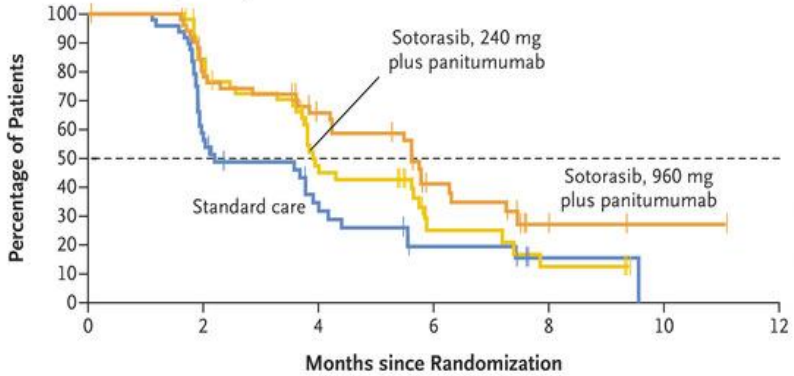
The NEW ENGLAND JOURNAL of MEDICINE

Progression-free Survival as Assessed by Blinded Independent Central Review (Intention-to-Treat Population).

Presented at #ESMO23

MG Fakih et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2

A Progression-free Survival (Intention-to-Treat Population)



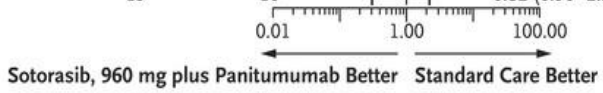
	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

No. at Risk

Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

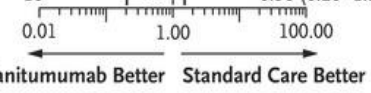
B Subgroup Analysis for Progression-free Survival — Sotorasib, 960 mg plus Panitumumab

Subgroup	Sotorasib, 960 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.49 (0.30–0.80)
Age			
<65 yr	32	27	0.52 (0.26–1.04)
≥65 yr	21	27	0.43 (0.20–0.92)
Sex			
Male	29	24	0.59 (0.30–1.15)
Female	24	30	0.35 (0.17–0.73)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.42 (0.20–0.84)
<18 mo	24	23	0.51 (0.24–1.07)
Location of tumor			
Right side	24	16	0.41 (0.19–0.90)
Left side	28	37	0.62 (0.32–1.20)
Body site at initial diagnosis			
Colon	37	37	0.45 (0.25–0.80)
Rectum	16	17	0.57 (0.24–1.31)
No. of lines of previous therapy for metastatic disease			
1 or 2	37	28	0.39 (0.21–0.72)
≥3	16	26	0.58 (0.22–1.47)
Liver metastasis			
Yes	38	38	0.35 (0.20–0.61)
No	15	16	0.82 (0.30–2.21)



C Subgroup Analysis for Progression-free Survival — Sotorasib, 240 mg plus Panitumumab

Subgroup	Sotorasib, 240 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.58 (0.36–0.92)
Age			
<65 yr	39	27	0.63 (0.32–1.23)
≥65 yr	14	27	0.36 (0.14–0.91)
Sex			
Male	26	24	0.71 (0.37–1.37)
Female	27	30	0.63 (0.31–1.27)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.49 (0.25–0.97)
<18 mo	22	23	0.78 (0.40–1.52)
Location of tumor			
Right side	17	16	0.59 (0.27–1.32)
Left side	36	37	0.58 (0.33–1.03)
Body site at initial diagnosis			
Colon	32	37	0.53 (0.30–0.95)
Rectum	21	17	0.47 (0.21–1.02)
No. of lines of previous therapy for metastatic disease			
1 or 2	29	28	0.56 (0.31–1.02)
≥3	24	26	0.58 (0.27–1.26)
Liver metastasis			
Yes	36	38	0.47 (0.28–0.80)
No	17	16	0.56 (0.20–1.51)



Precision Oncology is still relatively in its infancy: Are we doing a good job of Creating the Next Generation of Molecular Oncologists?

- We can no longer practice oncology in isolation and without at least a basic understanding of the underlying molecular biology that drives cancer genesis and also evolution of drug resistance.
- Many of the terms previously used in cancer research labs are now well integrated with clinical jargon.
- We now have a generation of Clinical Cancer Biologists whose job description entails grasping, if not mastering, biologic principles as they apply to direct patient care.

The future of Precision Oncology

- Are our trainees in the oncologic sciences, both clinically and in the lab, learning the nuances of interpretation of NGS correctly, or is their expectation that NGS is the end goal, rather than a means to uncovering targets for individually tailored treatment options?
- And are we conveying the fact that identification of a putative target does not absolutely equate to a corresponding drug working effectively?
- This is one of the great challenges that our field faces now and in the years to come:
  - understanding what Precision Oncology is, and what it is not,
  - how accurate analysis is performed, and most importantly when to use the results to help our patients in daily practice.

In Sum…

- ***The opportunities***
- ***Precision oncology and impact on improved survival***
  - An evolving question, not one size fits all
- ***The Controversies like cost***
- ***Today's learning objectives may have different answers and approaches over the next few years.***
- 1. Understand the current landscape of tumor genomic profiling in oncology.
- 2. Learn about societal factors affecting oncologist-driven genetic testing.
- 3. Understand fundamental biological perspectives about targeted therapies, challenges, and forthcoming advances.

Thank you for your attention!

- I welcome any questions or comments.

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