Making Sense of Molecular Testing in Solid Tumors

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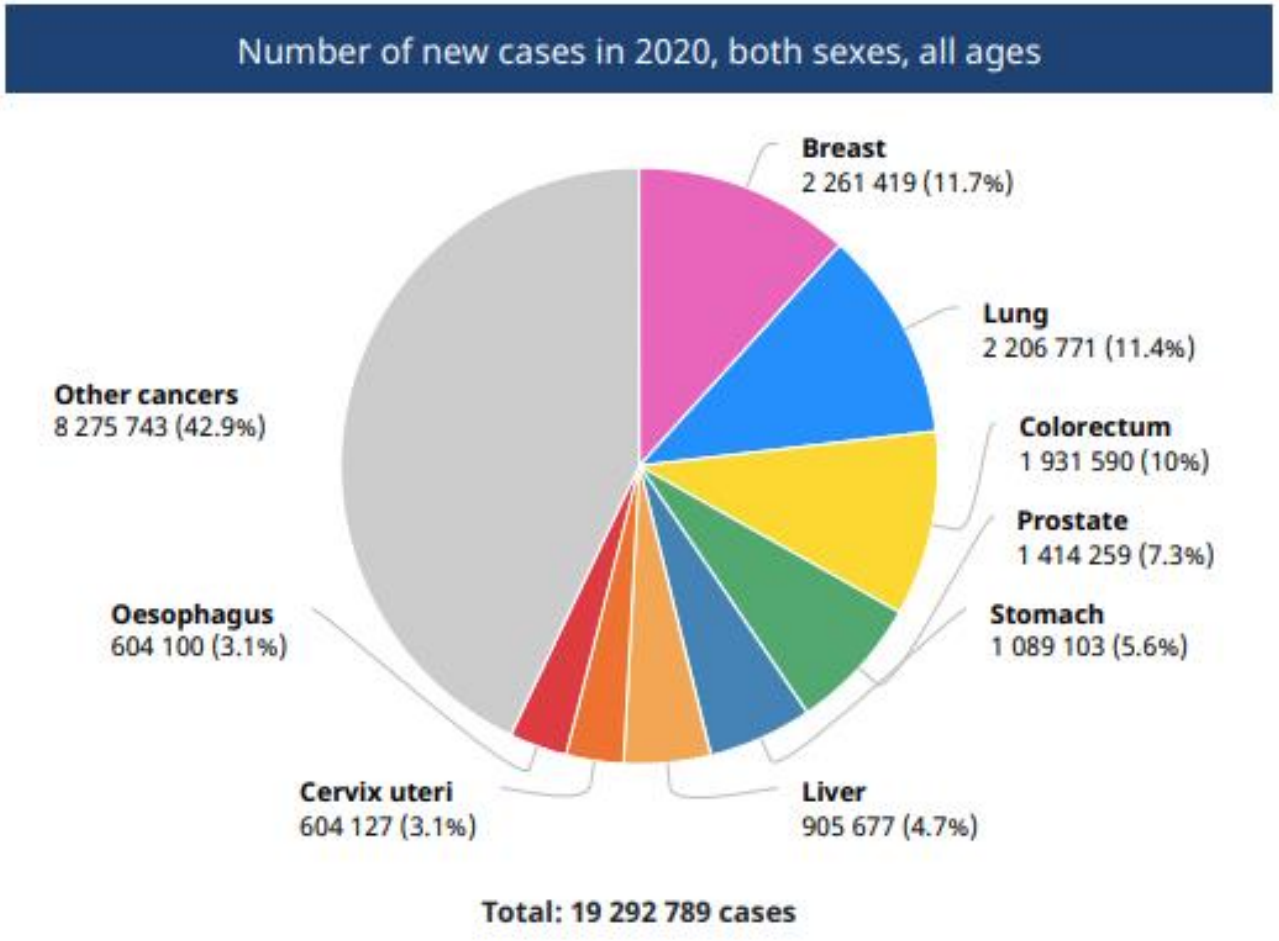
Disclosures

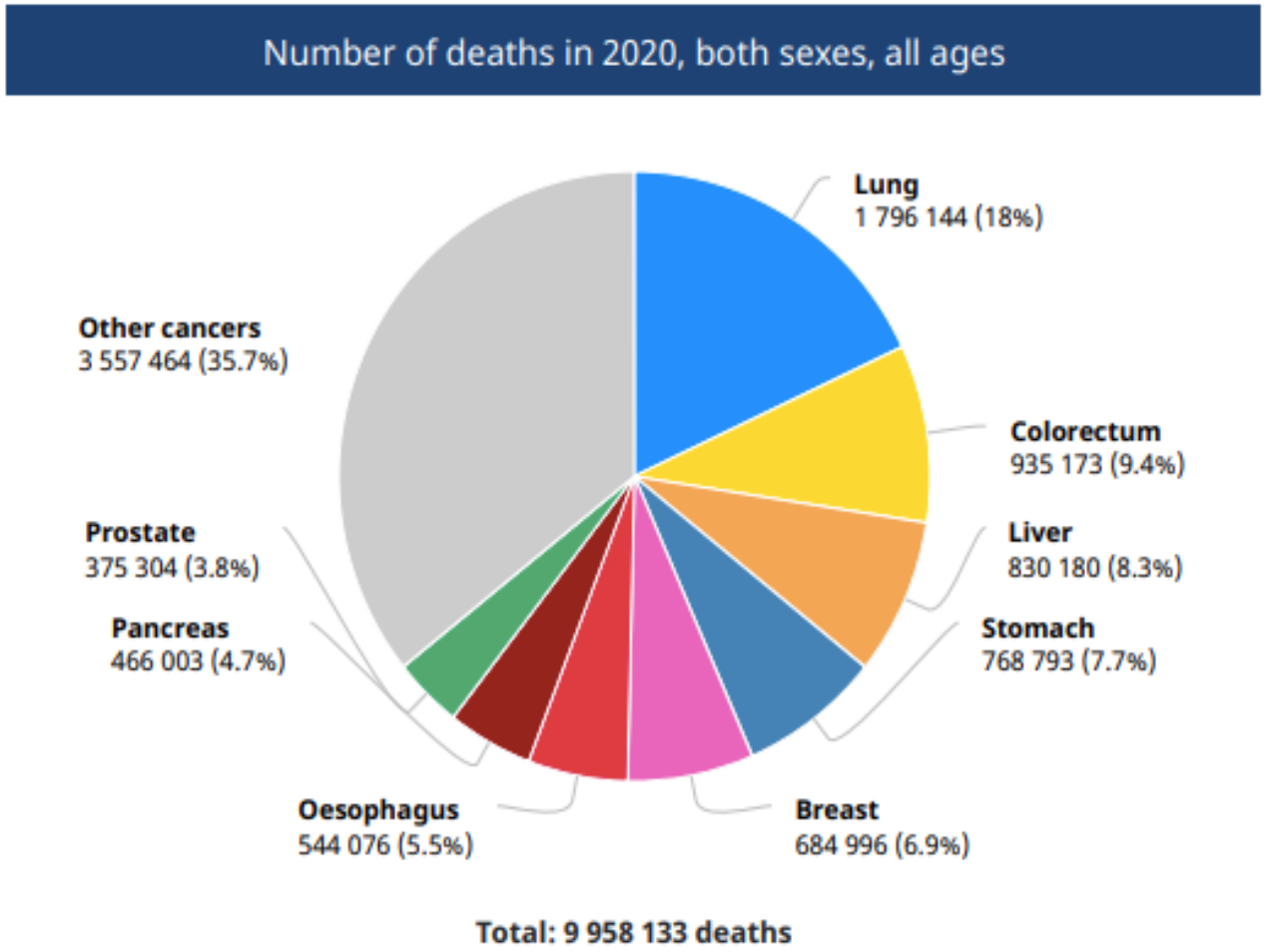
- Employee at Labcorp Oncology

Agenda

- Precision Medicine
- Testing Options for Solid Tumors
  - Single gene vs Targeted Panels
  - Tissue vs Liquid Biopsy
- Somatic vs Germline

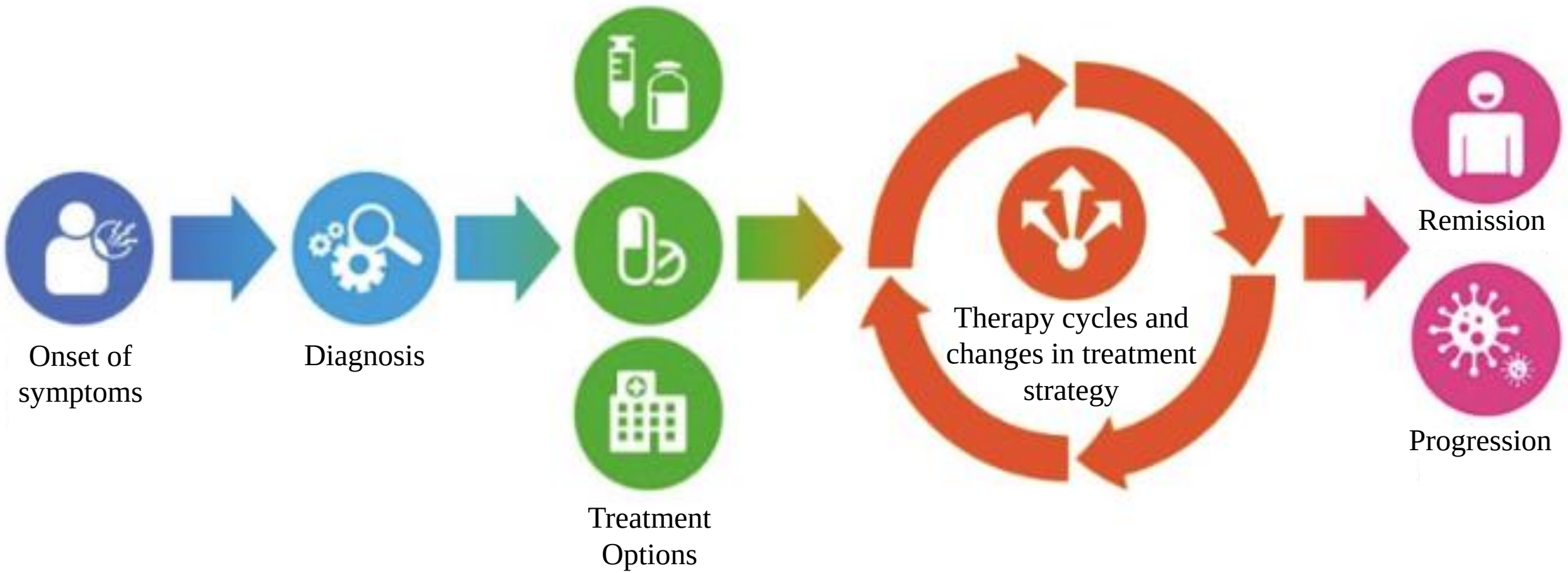
Cancer is a leading cause of death worldwide



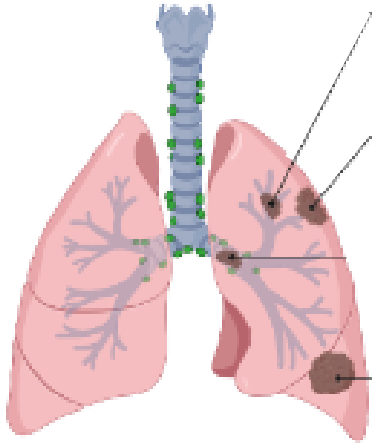


Sung H et al. *CA Cancer J Clin*. 2021 May;71(3):209-249.

Each cancer patient follows a unique journey



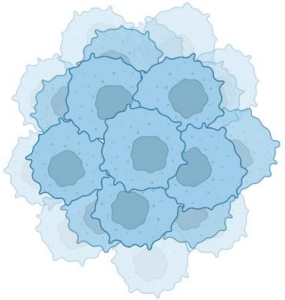
Standard treatment options for lung cancer patients



Diagnosis

Biopsy/ Resection

First Line therapy



Progression

Second Line therapy

Progression/ Remission

Conventional treatment options for cancer patients

Surgery

- Resection
- Biopsy
- Fine needle aspirations

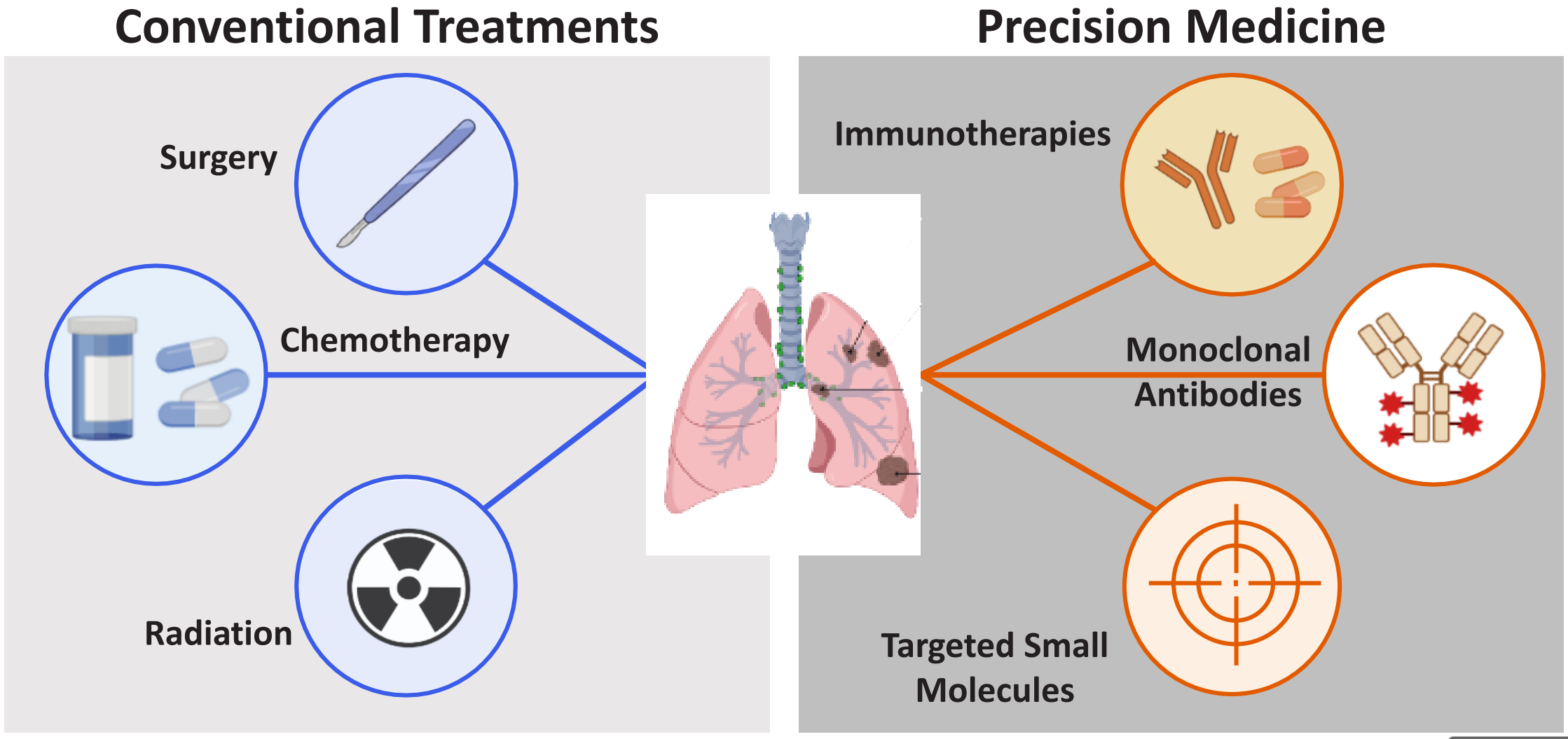
Chemotherapy

- Cytotoxic
- Neo-adjuvant or Adjuvant
- Maintenance regimens

Radiation

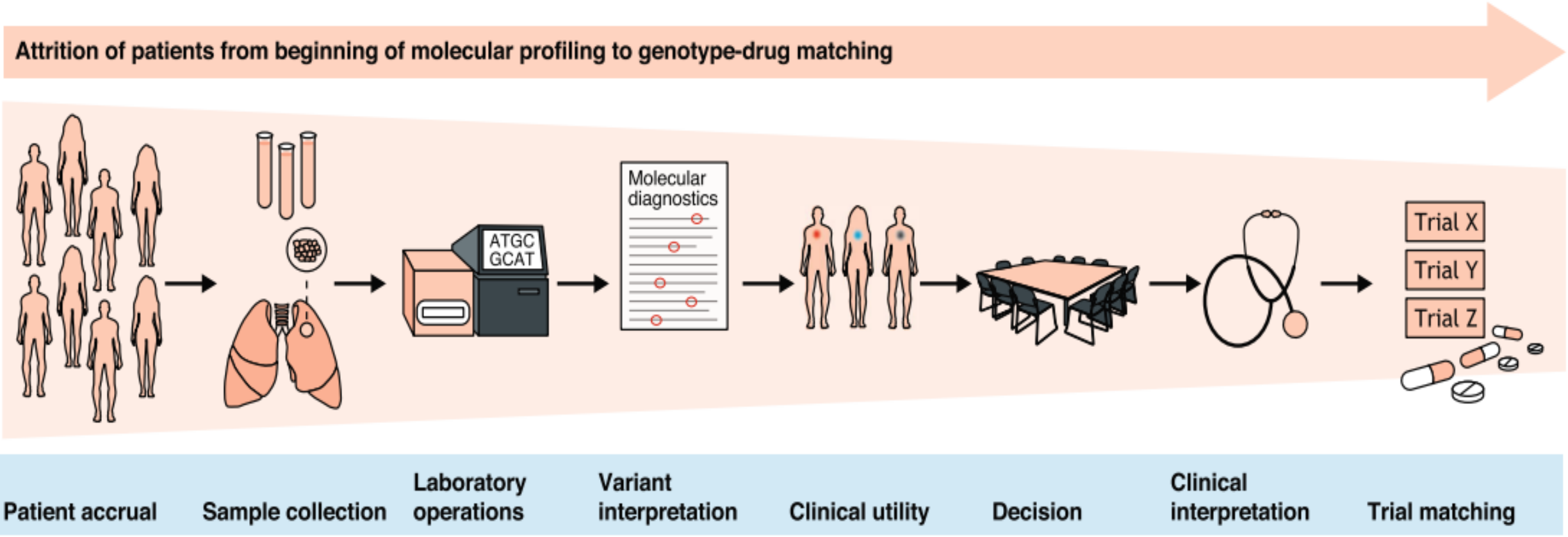
- External
- Internal

Advancement in treatment options



What is Precision Medicine?

The use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular or cellular biomarkers.

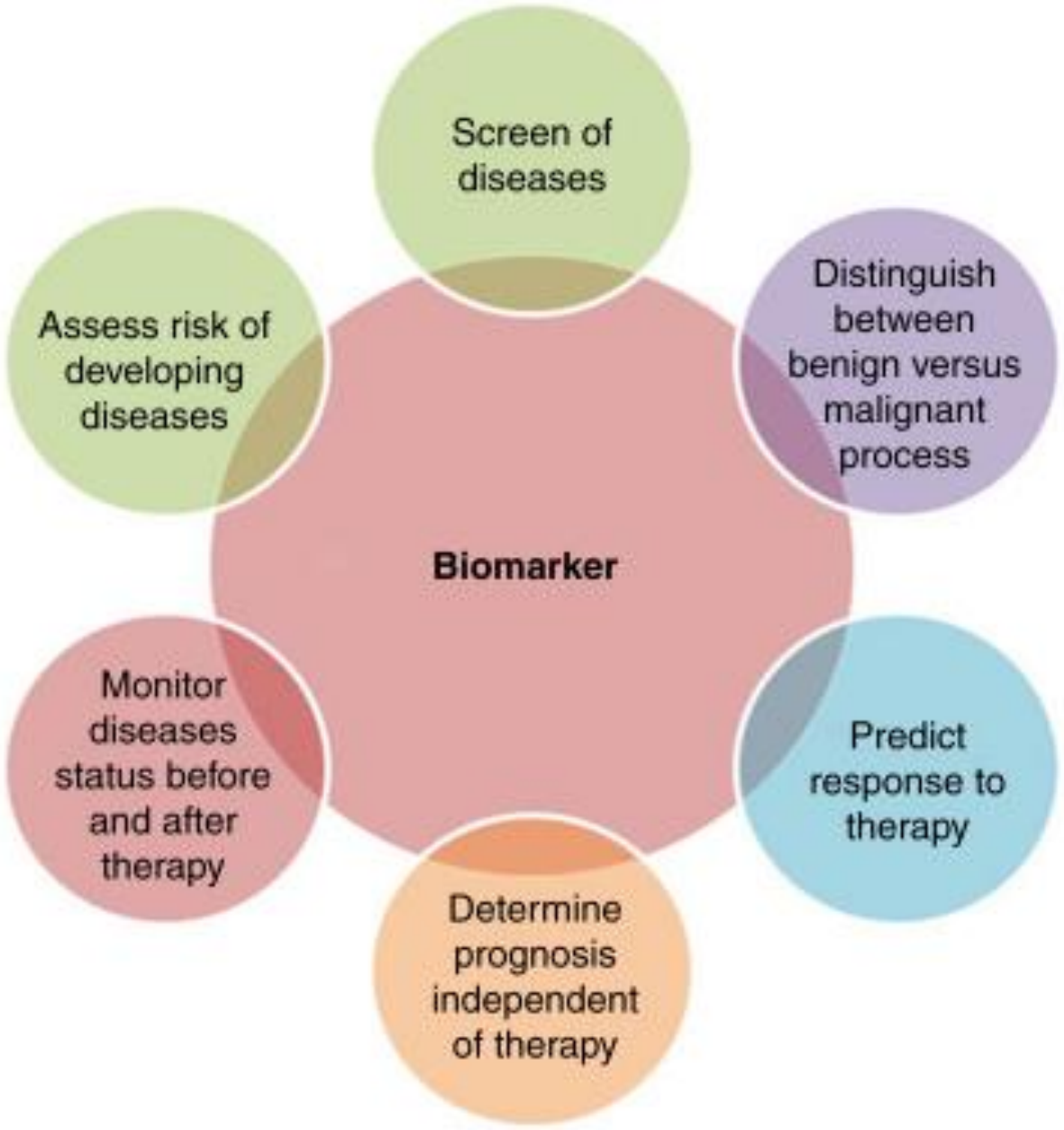


Malone et al. Genome Medicine (2020) 12:8

What are biomarkers?

Biomarker: “cellular, biochemical or molecular alterations that are measurable in human tissues, cells, or fluids”

Biomarker	Example
Physiological biomarker	Blood pressure
Inflammatory biomarker	C-reactive protein
Prostate cancer biomarker	PSA
Molecular biomarker	*EGFR*
Somatic mutational biomarker	*KRAS* G12D
Germline mutational biomarker	*BRCA1*
Tumor agnostic biomarker	TMB, MSI, NTRK
Immune biomarker	PDL1



Biomarkers guiding cancer care

Prior to Cancer	Diagnosis	After Cancer Diagnosis				Post Treatment
Am I at increased risk for cancer?	Do I have cancer? What type of cancer?	What is the expected course of my cancer?	Will my cancer respond to this drug?	Should I receive a normal or lower dose?	How's my cancer responding to this treatment?	Will my cancer come back?
Risk Assessment	Diagnosis	Prognosis	Predicting Treatment Response	Pharmaco-kinetics	Monitoring Treatment Response	Recurrence

Natl Compr Canc Netw. 2019

Currently more than 800 biomarker recommendations are included in NCCN Guidelines

- Determine risk of disease (BRCA-1/BRCA-2)
- Screening (PSA for prostate)
- Diagnostic (BCR/ABL in CML)
- Prognostic (CA 19-9 in pancreas)
- Predictive (ER/PR status in breast)
- Risk of toxicity (UGT1A1*28 allele for irinotecan)
- Response/disease monitoring (AFP; HCG in testicular)

Oncology drug development pipeline

How many studies are driven by oncology biomarkers?

<24 Months → Phase III Studies → FDA Special Status

121 oncology drugs approved - new and label expansion

779 studies across solid tumor and hematology

64 Solid Tumor unique drugs / drug combinations

FDA (Expedited Programs): faster approval timelines

42 Solid Tumor approvals

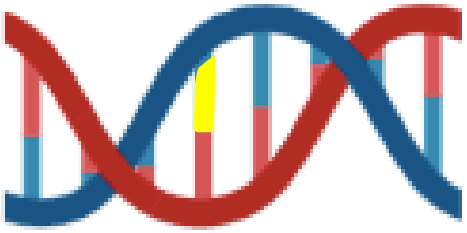
Top 15 Tumor Types*

Clinical Trials | Pharma and Government

2,374	1,948	1,839	1,820	1,531	1,155	1,083	1,051	989	935	953	848	831	772
Non-small cell lung	Breast	Non-Hodgkin's Lymphoma	Unspecified Solid tumor	Colorectal	Head/Neck	Liver	Esophageal	Leukemia, Acute Myeloma	Ovarian	Pancreas	Prostate	Melanoma	Multiple Myeloma
Pharma 1,480/ Govt 894	Pharma 1,183/ Govt 765	Pharma 1,013/ Govt 826	Pharma 1,458/ Govt 362	Pharma 814/ Govt 717	Pharma 666/ Govt 489	Pharma 538/ Govt 545	Pharma 584/ Govt 467	Pharma 440/ Govt 549	Pharma 625/ Govt 310	Pharma 566/ Govt 387	Pharma 527/ Govt 321	Pharma 590/ Govt 241	Pharma 492/ Govt 280

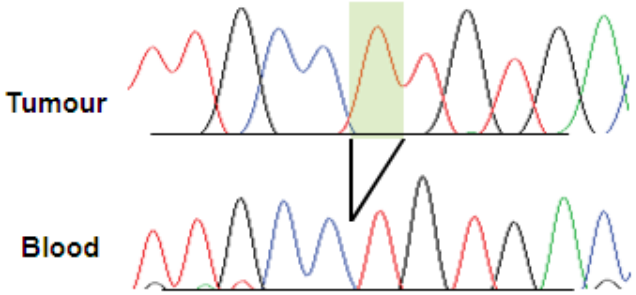
* Source: Trail trove: Jan 2022: Active, Oncology

Types of genomic alterations that define cancer biomarkers



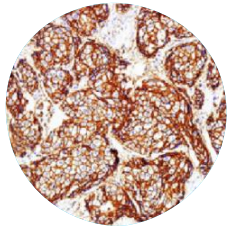
Base Pair Substitutions

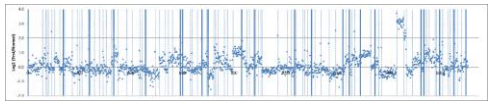
- Limited to a single base pair/region within a single gene
- **Examples**: *EGFR* L858R, T790M; *BRAF* V600E, *IDH1* R132H



Insertions/deletions

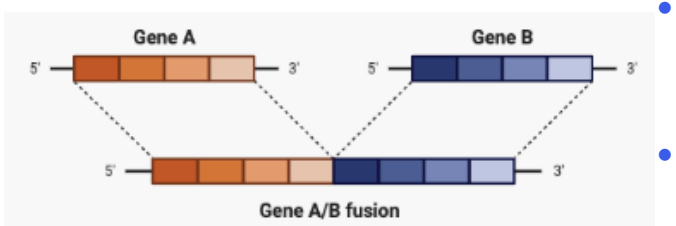
- Limited to single genes and small changes in DNA sequence
- **Examples:** *EGFR* exon 19 deletions, *MET* exon 14





Copy Number Alterations

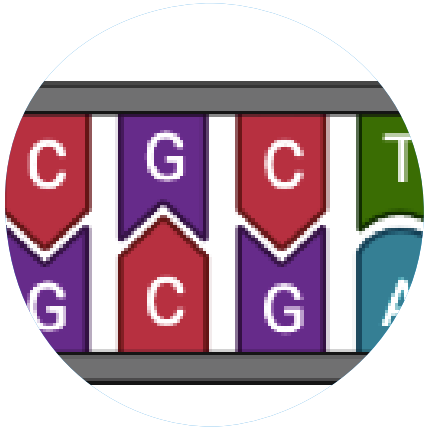
- Overexpression/amplification
- **Examples:** *HER2* amplification, *PDGFRA* amplification



Gene Rearrangements (Fusions)

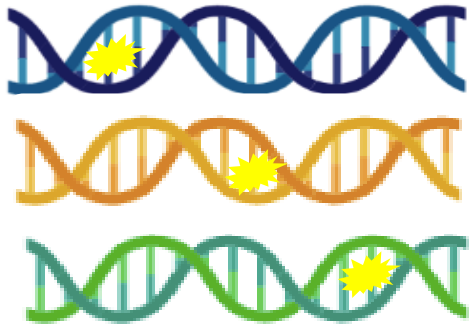
- Detected via DNA and RNA (ASCO recommends RNA)
- **Examples:** *ALK* fusions, *NTRK* fusions

Methodologies to detect cancer biomarkers



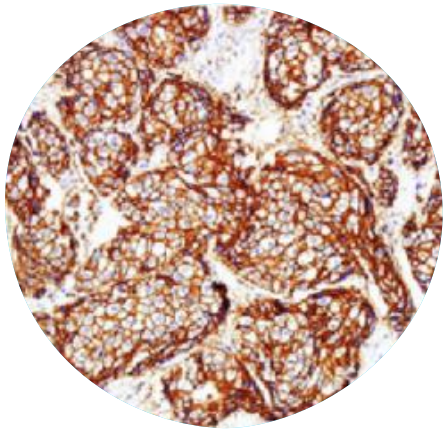
Single Gene Assays

Evaluate alterations in a single gene



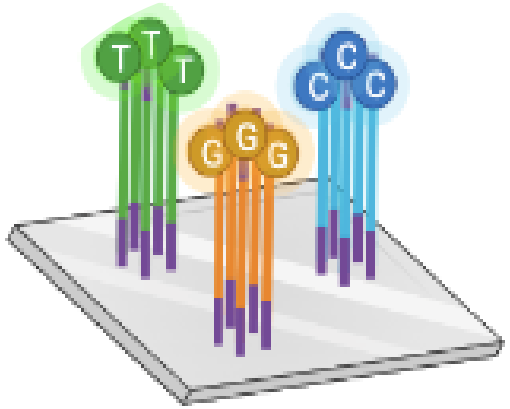
Hotspot Panels

Sequencing of select hotspot codons, and not the entire coding region, of the genes included on the panel.



Immunohistochemistry

Determines protein expression within tissue sample



Broad Panel (Comprehensive Genomic Profiling)

An NGS test that sequences a defined list of genes with at least 50 genes in total. May also include RNA testing

Which patients should have genomic testing performed for their cancer?

ASCO Guidelines

National Comprehensive Cancer Network®

ASCO Guidelines

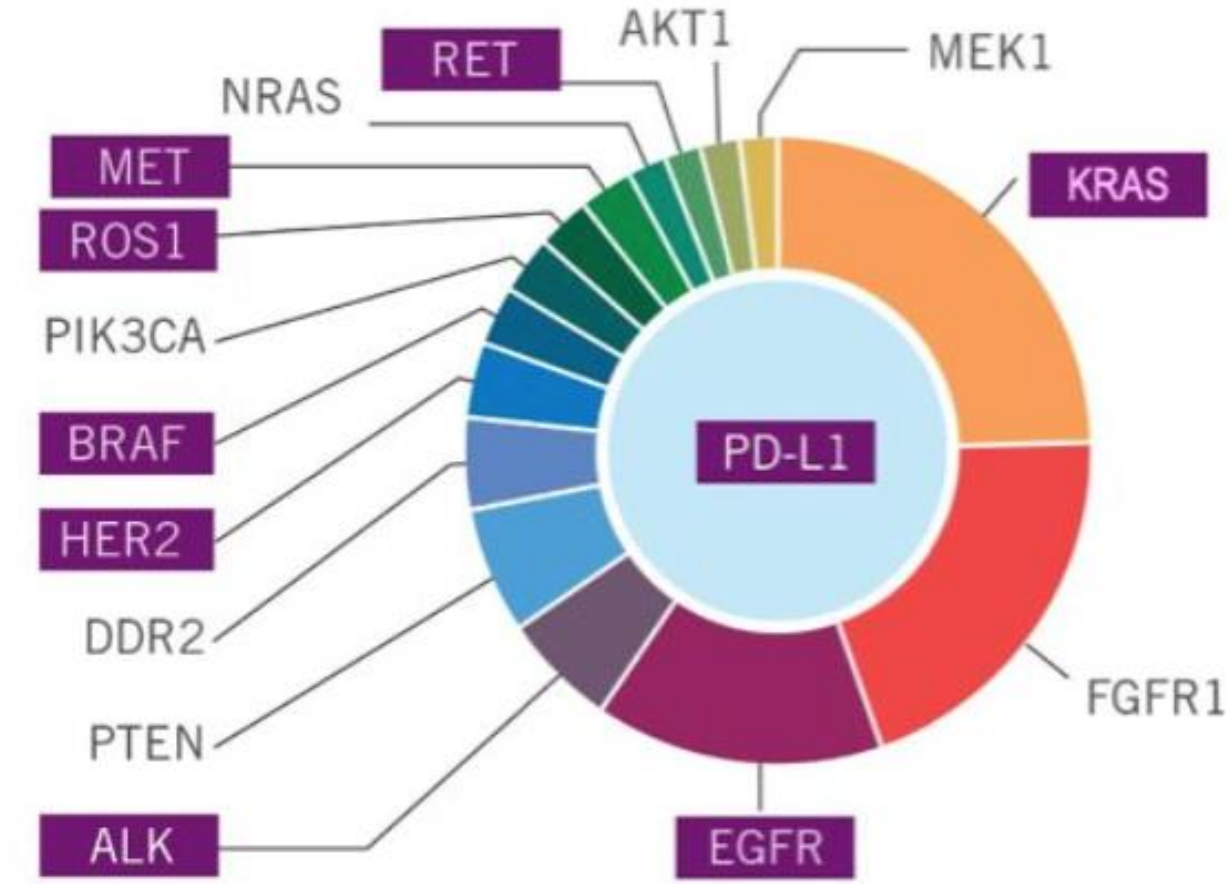
SOMATIC GENOMIC TESTING IN PATIENTS WITH METASTATIC OR ADVANCED CANCER
PROVISIONAL CLINICAL OPINION

WHICH METASTATIC OR ADVANCED SOLID TUMORS SHOULD UNDERGO GENOMIC SEQUENCING?

- Patients with metastatic or advanced solid tumors if there are genomic biomarker–linked therapies for that disease approved by the relevant regulatory agency (FDA)
- Patients with metastatic or advanced solid tumors if there are clearly defined resistance markers for a treatment being considered.

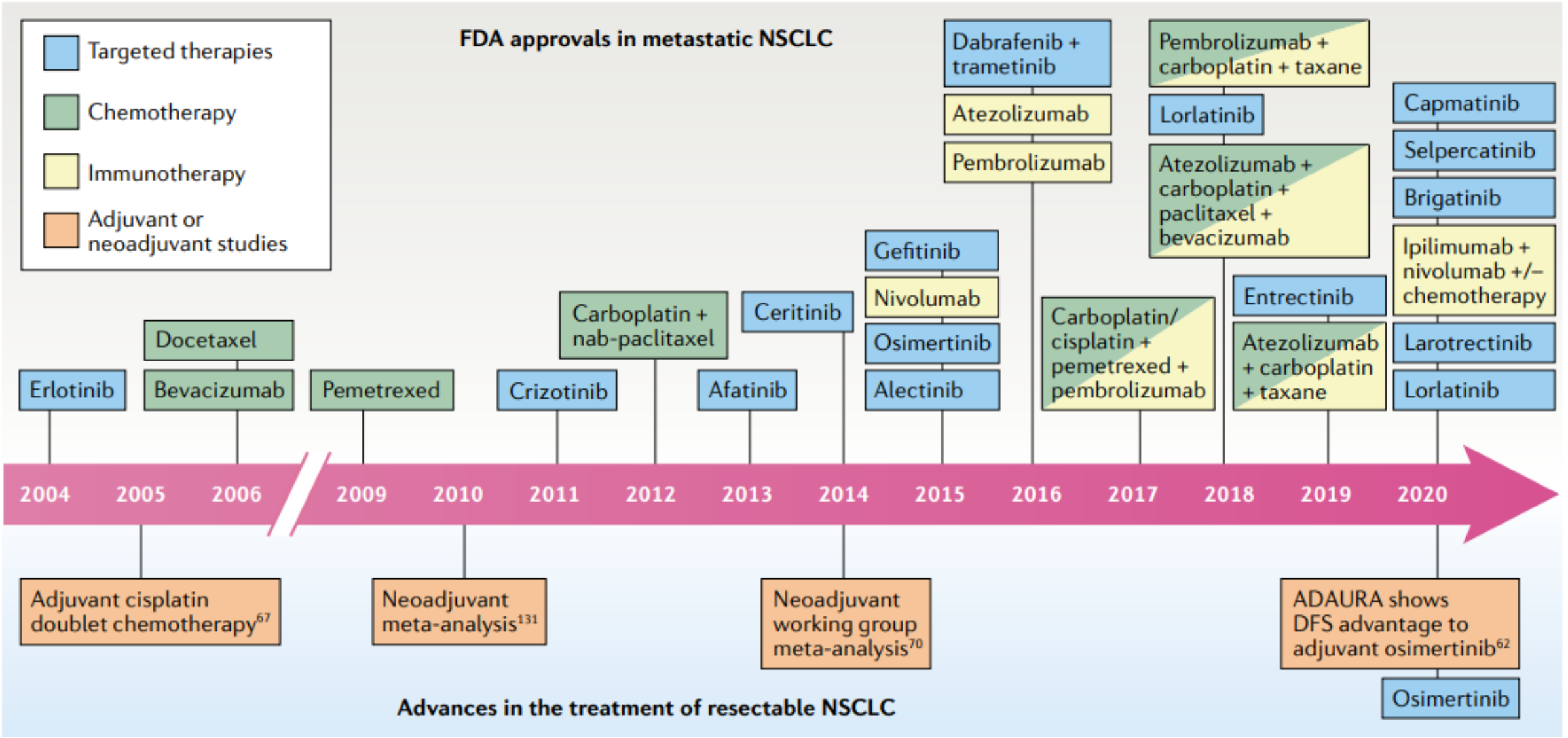
Chakravarty D et al. J Clin Oncol (2022) 40:1231-1258.

NCCN recommendations for biomarker testing in non-small cell lung cancer



Adapted from genetechnologycom and NCCN guidelines.

Biomarker approved therapies for NSCLC



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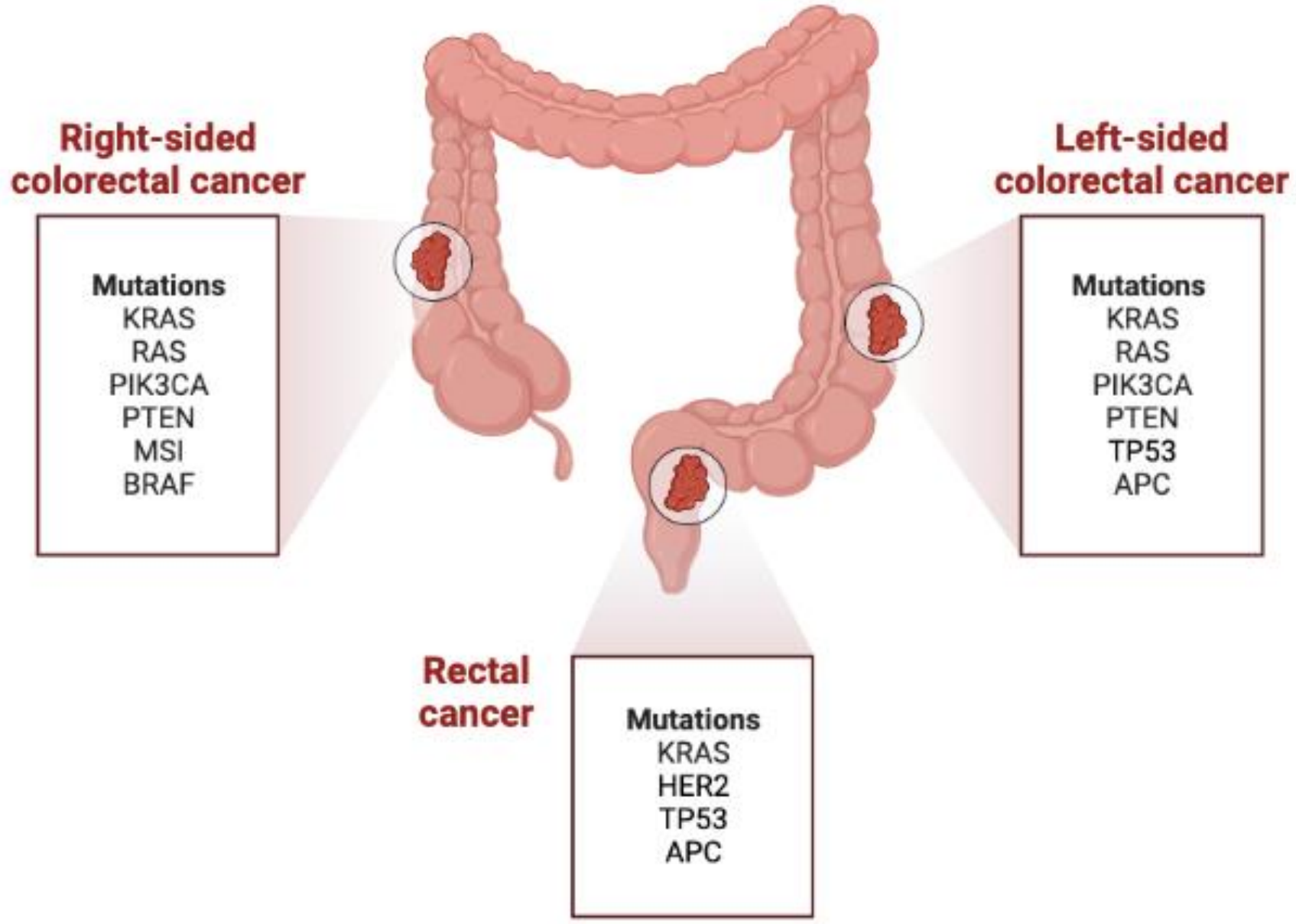
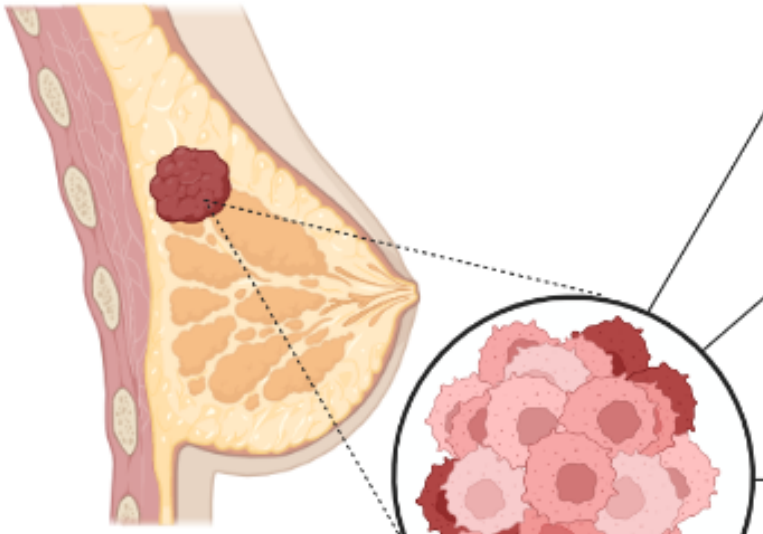
NCCN biomarkers in colorectal cancer



Intrinsic and molecular subtypes of breast cancer



Receptors
HR: Hormone
ER: Estrogen
PR: Progesterone
HER2

Luminal A (~40%)
HR+ (ER+ and/or PR+), HER2-

- Most prevalent subtype
- Low levels of Ki-67: control cancer cell growth
- Targeted therapy: Tamoxifen and CDK4/6 inhibitors

Normal-like (~2-8%)
HR+ (ER+ and/or PR+), HER2-

- Low levels of Ki-67: control cancer cell growth
- Slightly worse prognosis than Luminal A
- Targeted therapy: Tamoxifen and CDK4/6 inhibitors

Luminal B (~20%)
HR+ (ER+ and/or PR+), HER2+/-

- High levels of Ki-67: fast cancer cell growth
- Targeted therapy: Tamoxifen

HER2-enriched (~10-15%)
HR- (ER-, PR-), HER2+

- Amplification/overexpression of receptor HER2
- Faster growth than luminal subtypes
- Targeted therapy: Herceptin

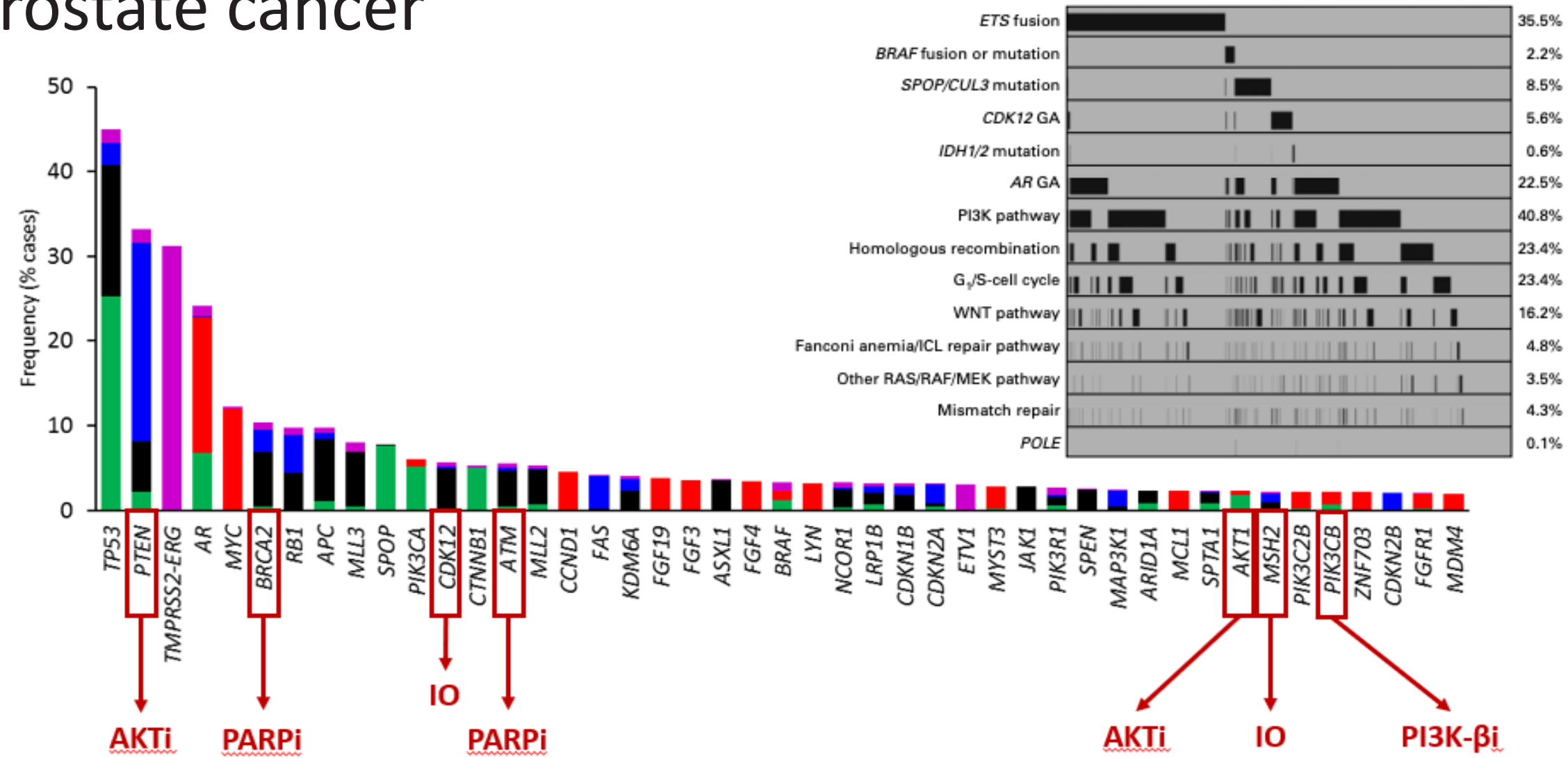
Triple Negative (~15-20%)
HR- (ER-, PR-), HER2-

- Most aggressive subtype
- Occurs more often in younger women
- Highest association to *BRCA1* mutations
- Targeted therapy: alpelisib (PIK3CA mutations)

Best prognosis

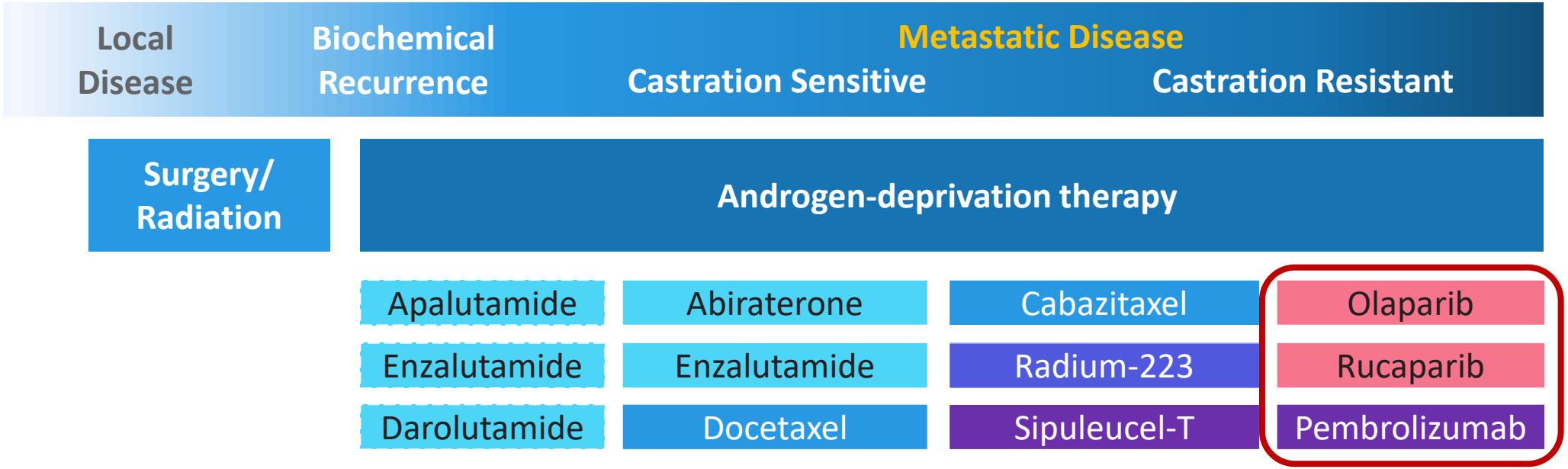
Worst prognosis

Genomic alterations and associated therapies in prostate cancer



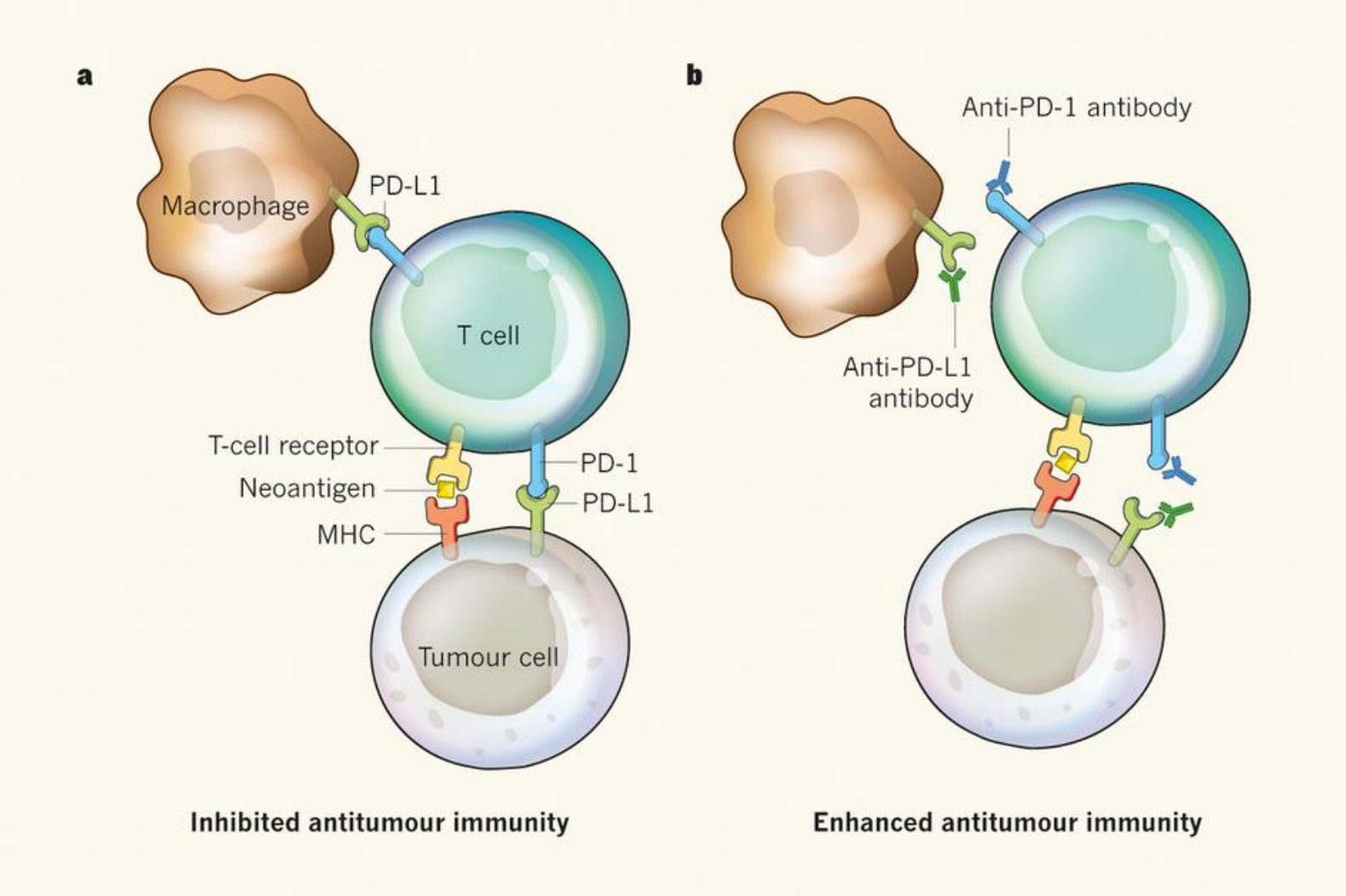
Chung JH et al. JCO Precis Oncol (2019) ;3:PO.18.00283.

Systemic treatment options for patients with prostate cancer throughout the continuum of care



Anti-PD-1/L1 therapies reactivate T cell activity

- Tumor mutational burden (TMB)
- MSI – High
- Positive PD-L1 IHC



Wolchok JD, and Chan TA. *Nature.* 2014;515:496-498.

Biomarker landscape in solid & hematologic cancers

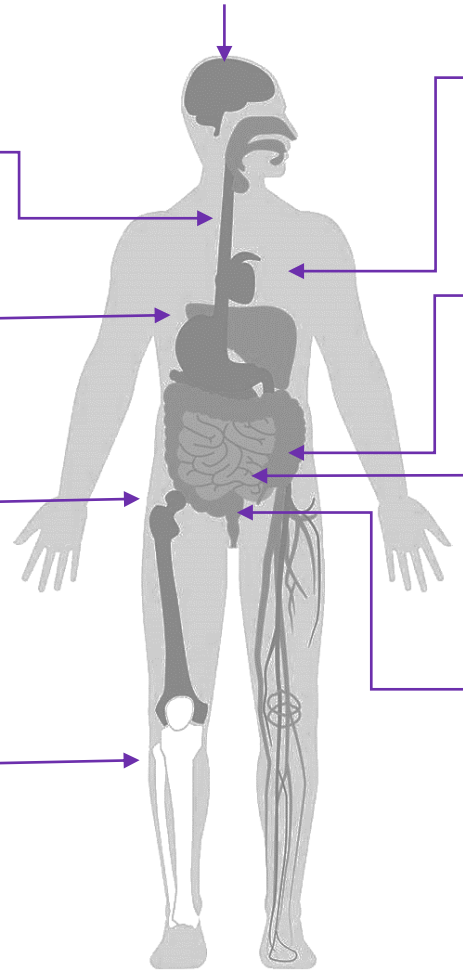
Brain: *MGMT, IDH1/2, pTERT,* 1p/19q co-deletion

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

Lung
EGFR, ALK, ROS1, RET, BRAS, KRAS, HER2

Melanoma
BRAF, KIT, NRAS, ROS1, ALK

Hematologic
ABL, FLT3, IDH1/2, KRAS, PDGFRA, WT1, KIT



Breast
PI3KCA, ERBB2, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, CDK4/6

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

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

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

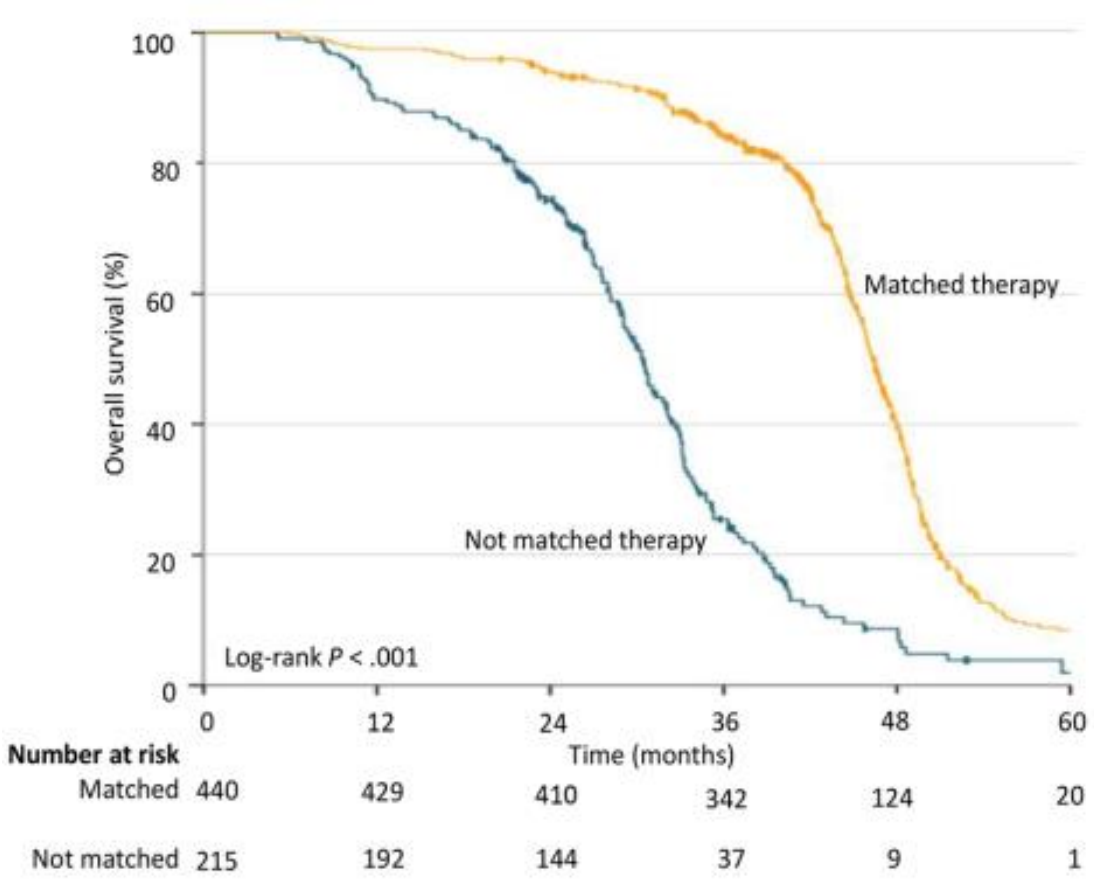
Tumor agnostic biomarkers in solid tumors: Fusions (NTRK), TMB, MSI

Selected Genetic Alterations Linked to FDA Approvals as of June 2021

Genetic Alterations	Tumor Type	Targeted Therapeutics
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
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

Chakravarty D et al. J Clin Oncol (2022) 40:1231-1258.

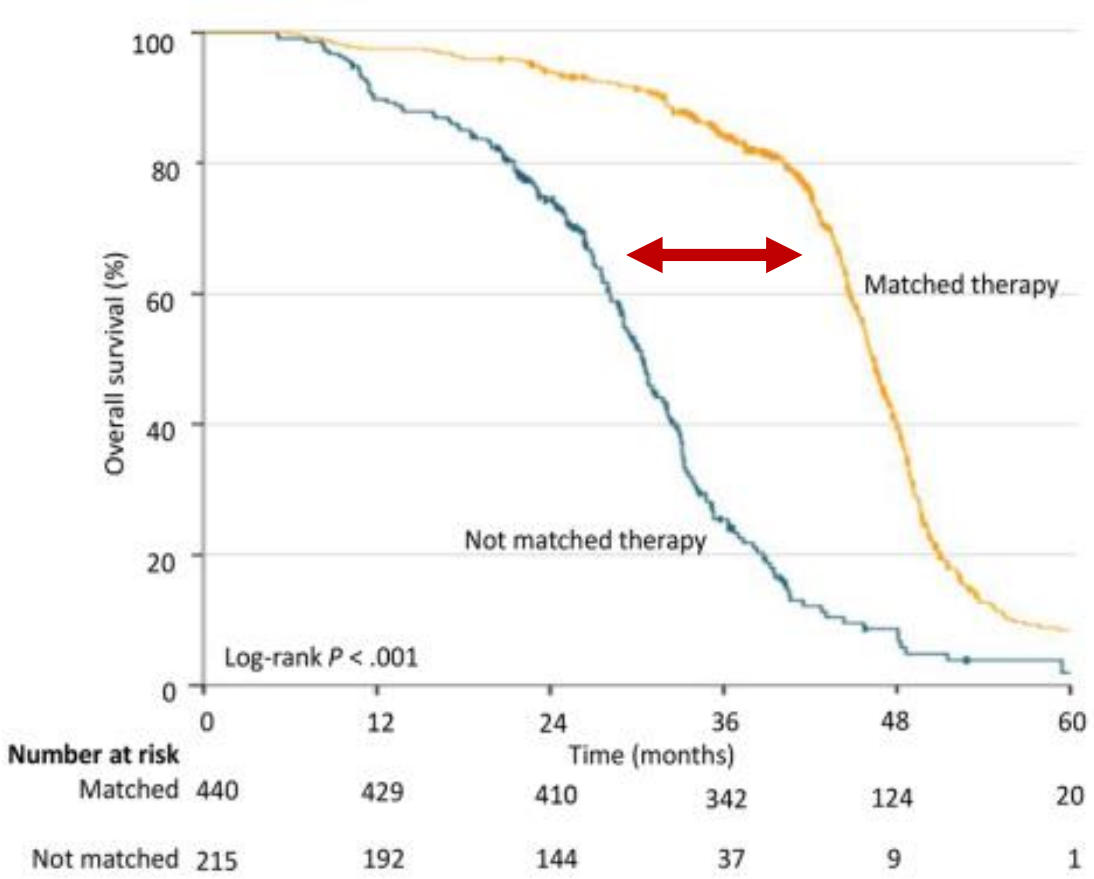
Why are Matched Therapies Important?



Patients Treated with Matched Therapy Live Longer

Zhao S *et al*. BMC Medicine (2021)19;223

Why are Matched Therapies Important?



Patients Treated with Matched Therapy Live Longer

Zhao S *et al*. BMC Medicine (2021)19;223

Why are Matched Therapies Important?

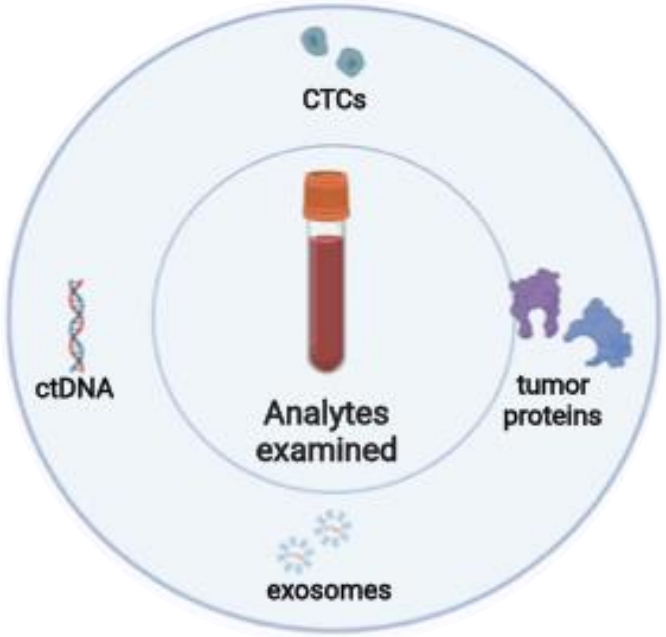
Gene	Patients tested % (n= 1,203)	Patients with TA in EGFR, ALK, ROS1, BRAF (n=163)	
		On targeted therapy	No targeted therapy
All 4 Genes (T4)	22%		
EGFR	54%	45%	55%
ALK	51%		
ROS1	43%		
BRAF	29%		

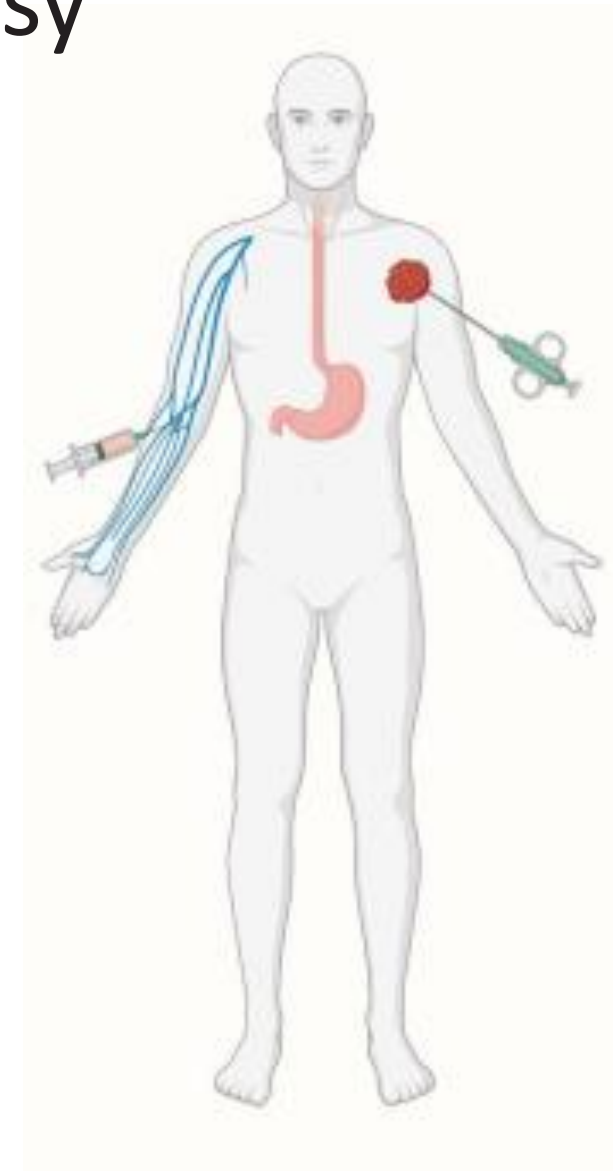
- Underutilization of genomic testing
- Underutilization of targeted therapies

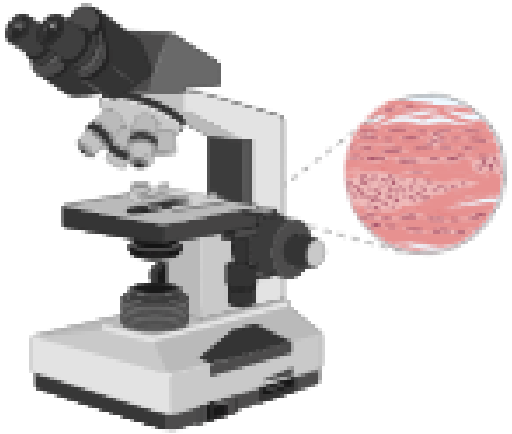
Gierman H et al. J. Clin. Oncol. 2019, 37, 1585

Now that we know which patients should be tested and why, how is this done?

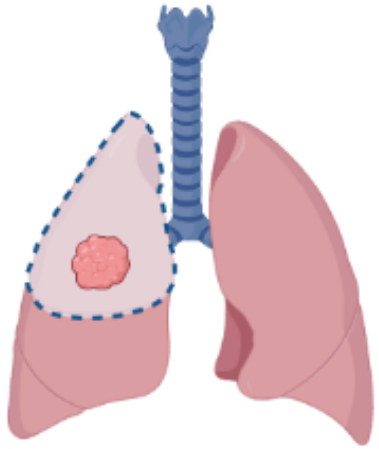
Cancer biomarker testing can be performed on a liquid or tissue biopsy





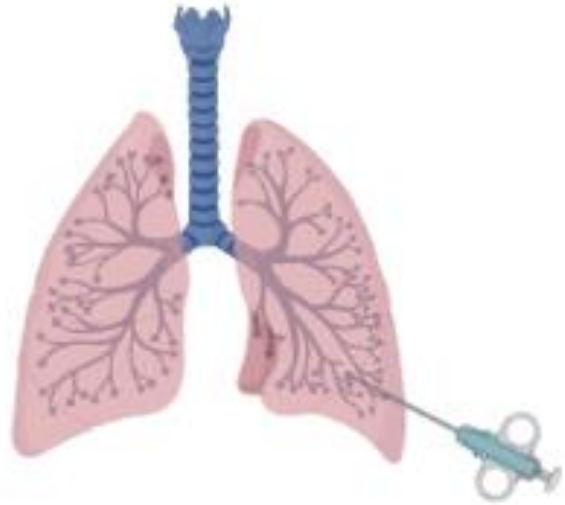


Tissue acquisition: What material does the clinician have to work with?



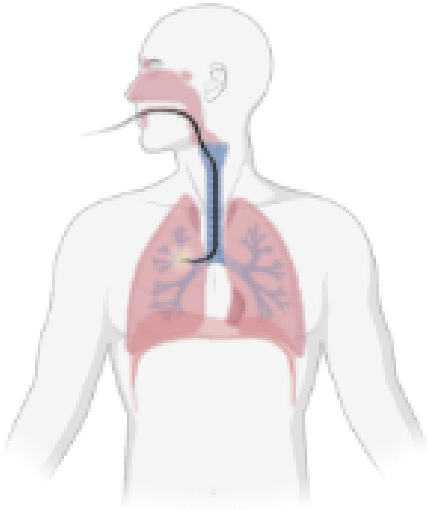
Tissue Resection

- Obtained for diagnosis and symptomatic relief
- Tumor cell percentage may be an issue
- CGP and multiple assays typically not a problem for tumor-rich samples



Biopsy

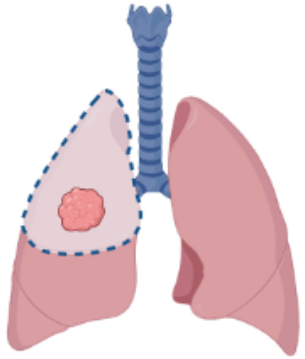
- Obtained for a diagnosis
- Testing options may be limited but depends on tumor content not necessarily tissue size



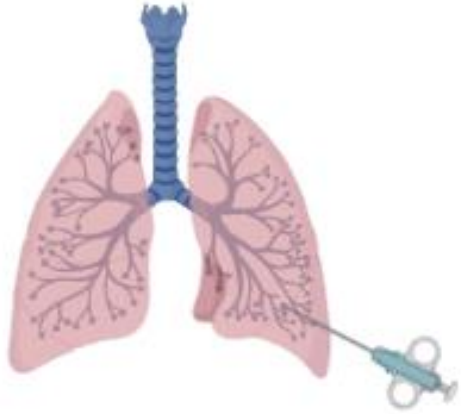
Endobronchial Ultrasound (EBUS)/ Fine Needle Aspiration

- Diagnosis can be made from very few cells
- Considered a cytology specimen
- May have significant limitations for testing

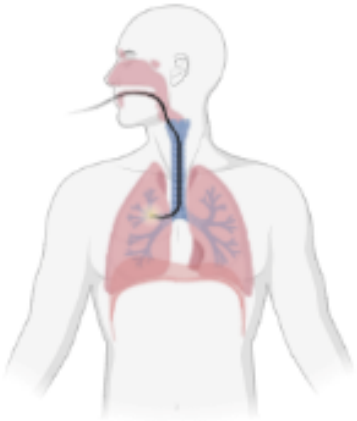
Tissue acquisition: What material does the clinician have to work with?



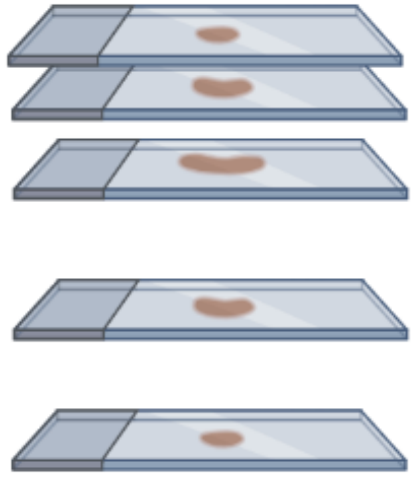
Tissue Resection



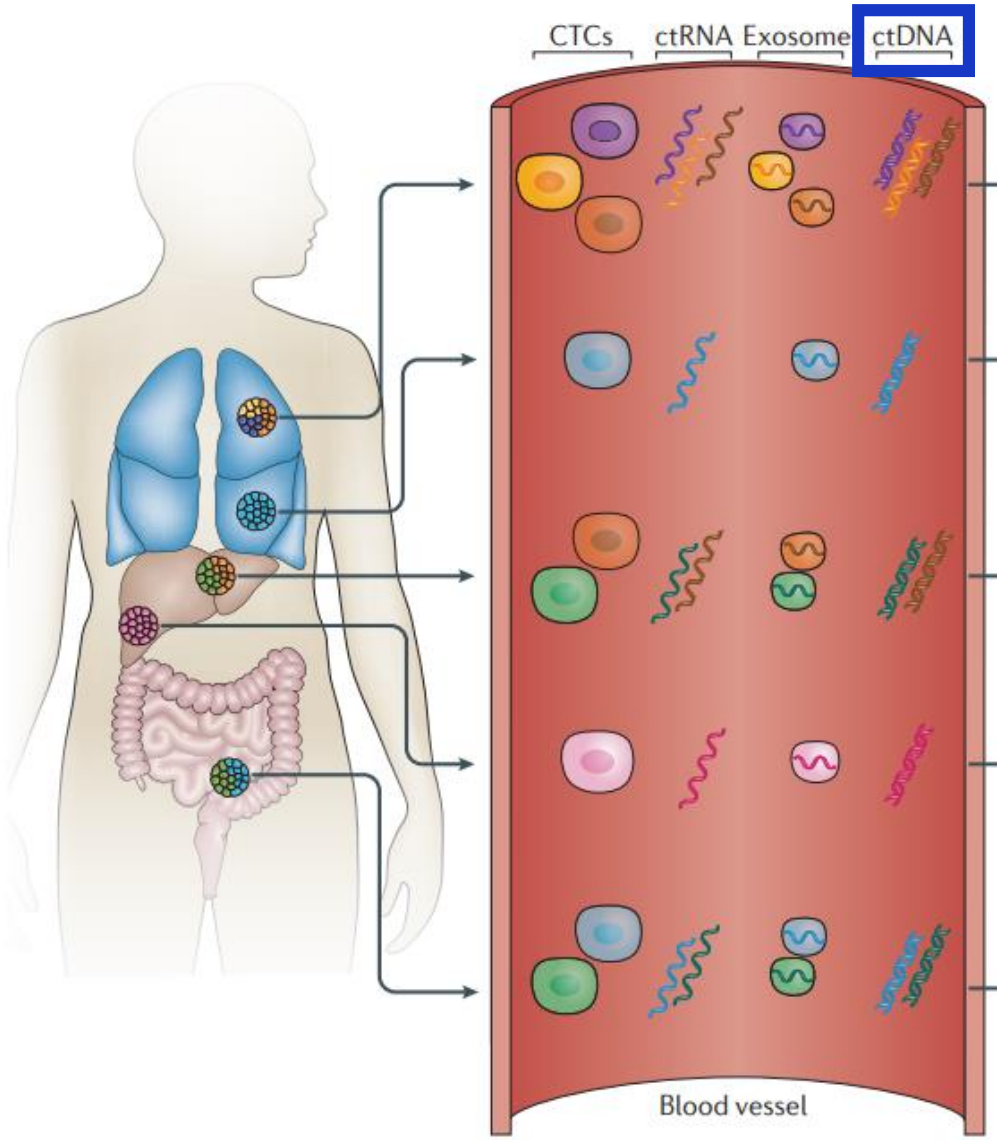
Biopsy



EBUS/FNA



Liquid biopsy: source of circulating tumor DNA (ctDNA)



- **ctDNA**: component of cell-free DNA which is tumor related
- **Cell-Free DNA Blood Collection Tubes**: specialized tubes required allow for isolation of plasma DNA up to 14 days after sample collection

Nat Rev Clin Oncol. 2017 Sep;14(9):531-548

Advantages and disadvantages of tumor versus liquid biopsy

Tumor Biopsy

Histological evaluation

Tumor microenvironment analysis

Clinical gold standard

- Surgery/needle biopsy
- Risk of complications
- Difficult to repeat
- Inpatient care & expensive
- Possible sampling bias
- Highly sensitive
- Longer TAT

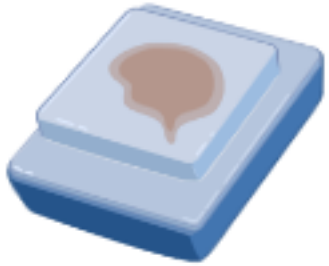
- Blood draw
- Minimal complications
- Easy & repeatable
- Quick & cost-efficient
- Less sampling bias
- Low/high sensitivity
- Rapid TAT

Liquid Biopsy

Non-invasive

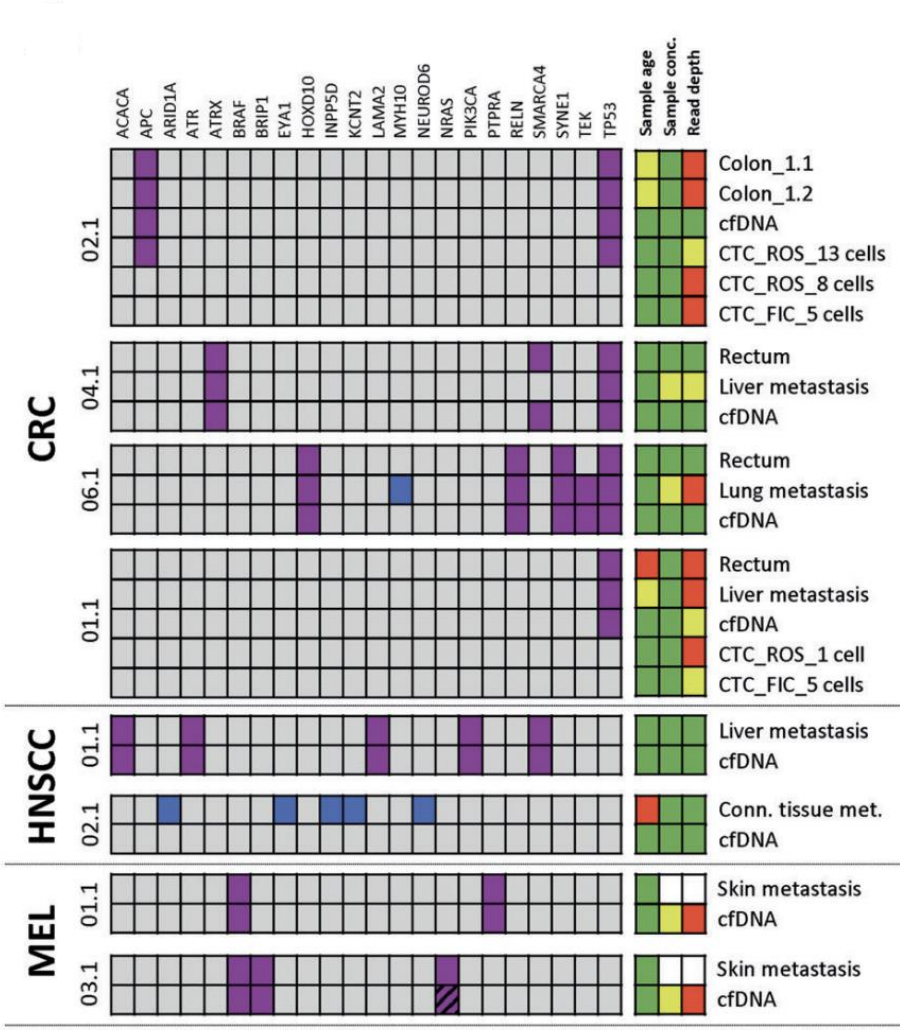
Compatible with longitudinal monitoring

Representative of tumor heterogeneity



Adapted from Corcoran et al Nature Medicine 2020

Liquid biopsy and tumor tissue concordance



- CRC: 11/12 (92%)
- HNSCC: 5/10 (50%)
- Melanoma: 5/5 (100%)

21/27 = 78%

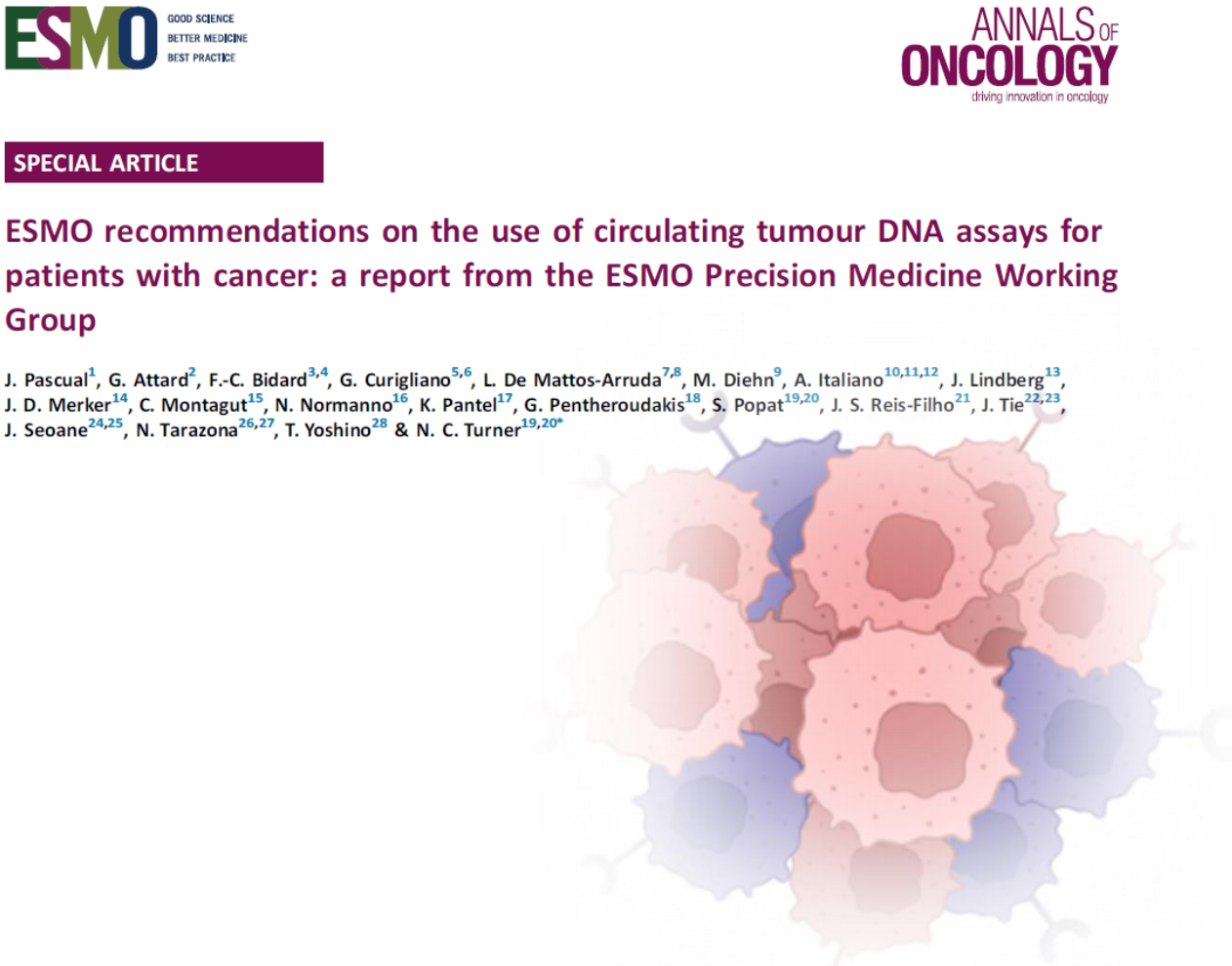
- Concordance depends on:
  - Heterogeneity
  - Quantity of cfDNA

Liebs et al., Oncogene 2021

ESMO Guidelines: Advanced cancer genotyping recommendations

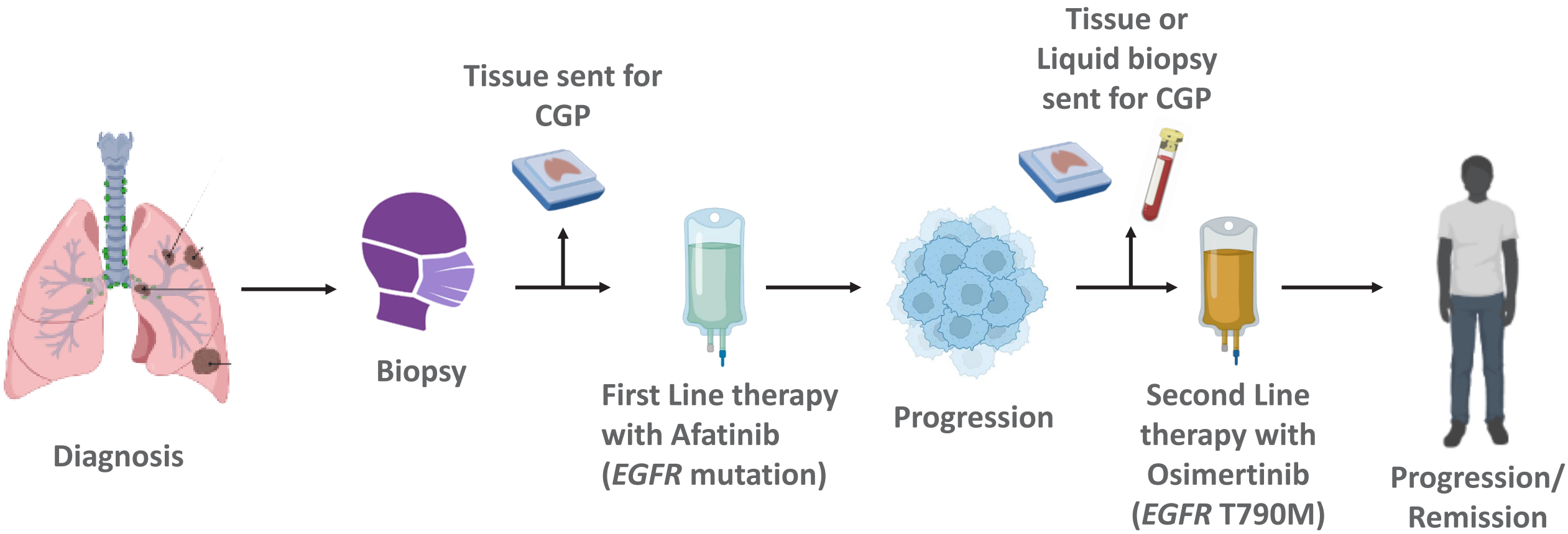
Liquid Biopsy Best Practice

- ✓ May be used in clinical practice when results impact treatment.
  - ✓ May be used in clinical scenarios first where time to result is clinically important.
  - ✓ Aggressive tumor type
  - ✓ No available tissue or biopsy not feasible
- ✓ Collect when tumor progressing (not regressing)
- ✓ Confirm testing if pathogenic variants of cancer susceptibility genes identified
- ✓ **Negative tests should prompt tissue testing**

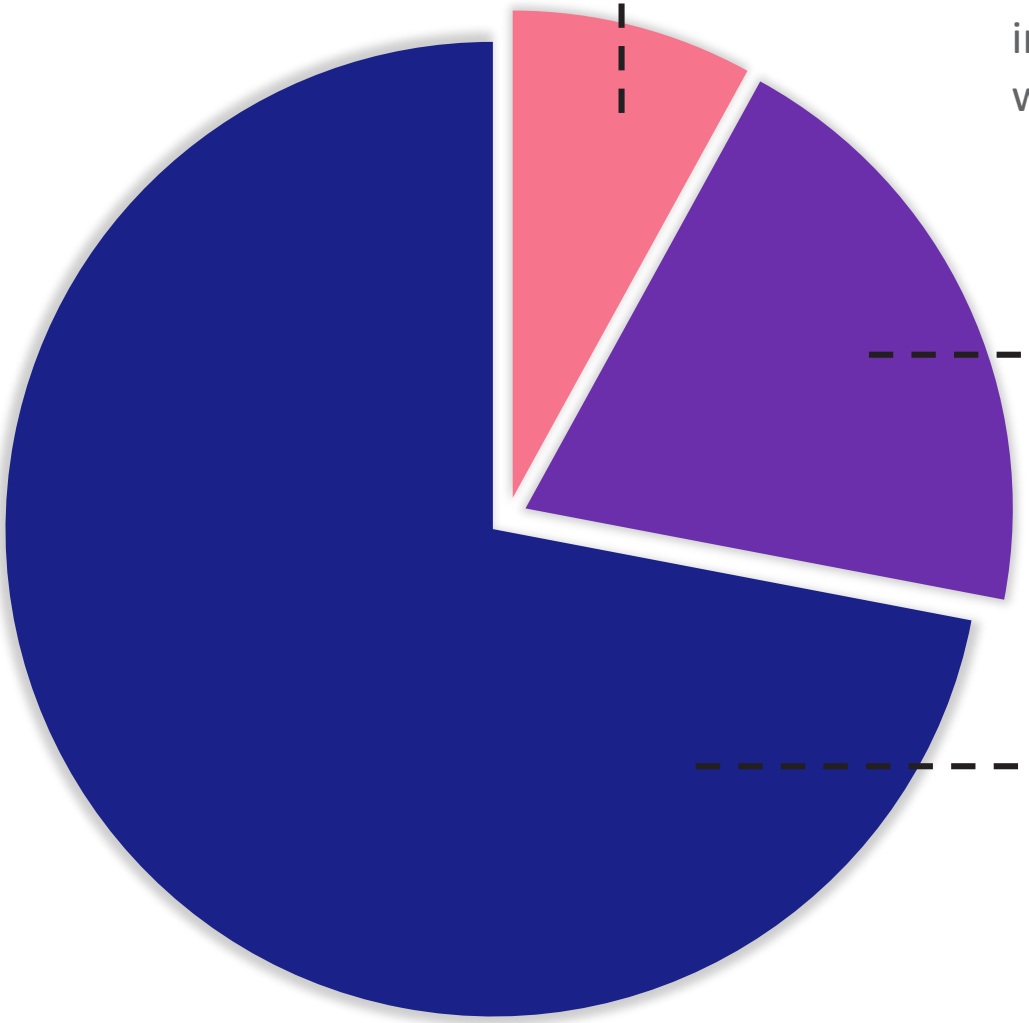


Adopted from Pascual *et al*. Annals of Oncology, 2022

Precision-medicine based treatment strategy for lung cancer patients



Majority of cancers are sporadic, but a subset are a result of inherited mutations



HEREDITARY CANCER
A clustering of cancer in a family due to inherited gene changes (mutations), which can be passed from parent to child

FAMILIAL CANCER
A clustering of cancer in a family that may be due to genes and/or other shared factors, such as environment and lifestyle

SPORADIC CANCER
Happens by chance in one or two related family members, typically at older ages

Understanding the differences between somatic and germline DNA changes

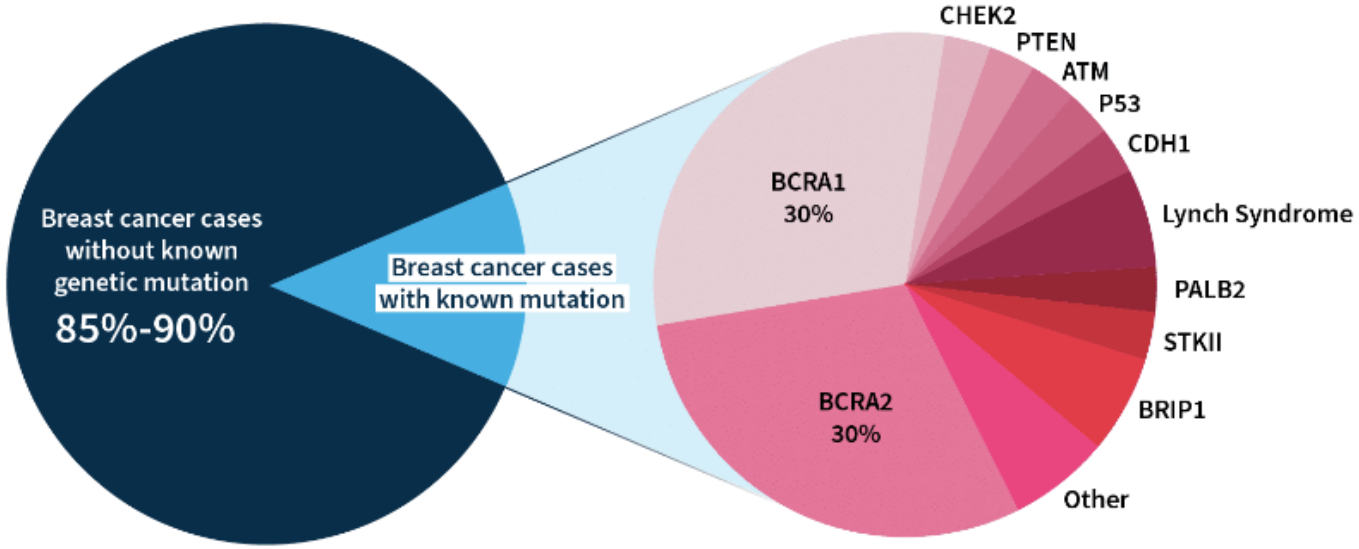
Somatic DNA Changes

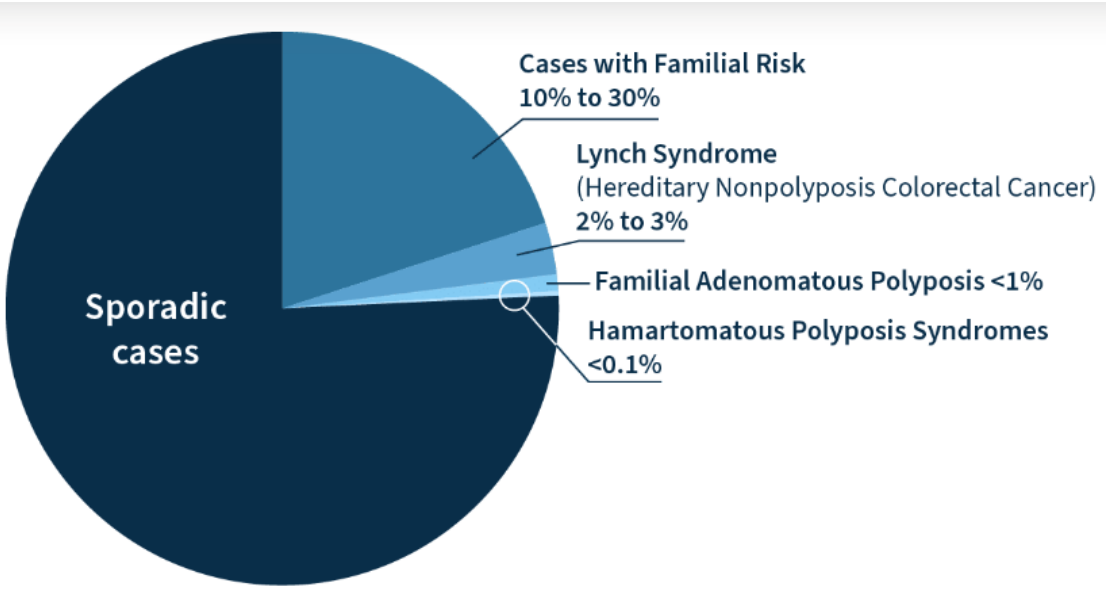
- Acquired over a person's lifetime in single cells
- Can lead to cancer
- CANNOT be inherited

Germline DNA Changes

- Present in every cell of the body including egg and sperm
- Can increase cancer susceptibility
- CAN be inherited

NCCN recommendations for hereditary colon, breast and ovarian cancers

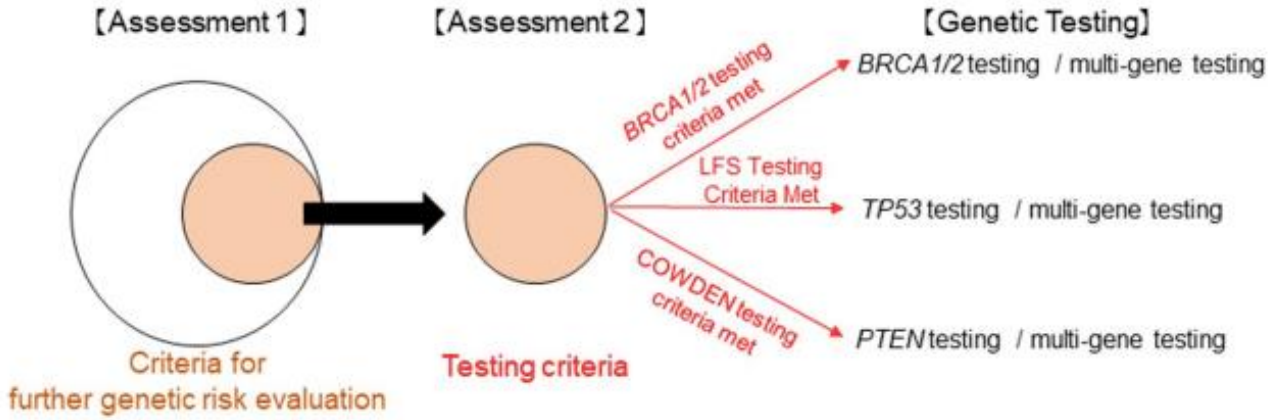




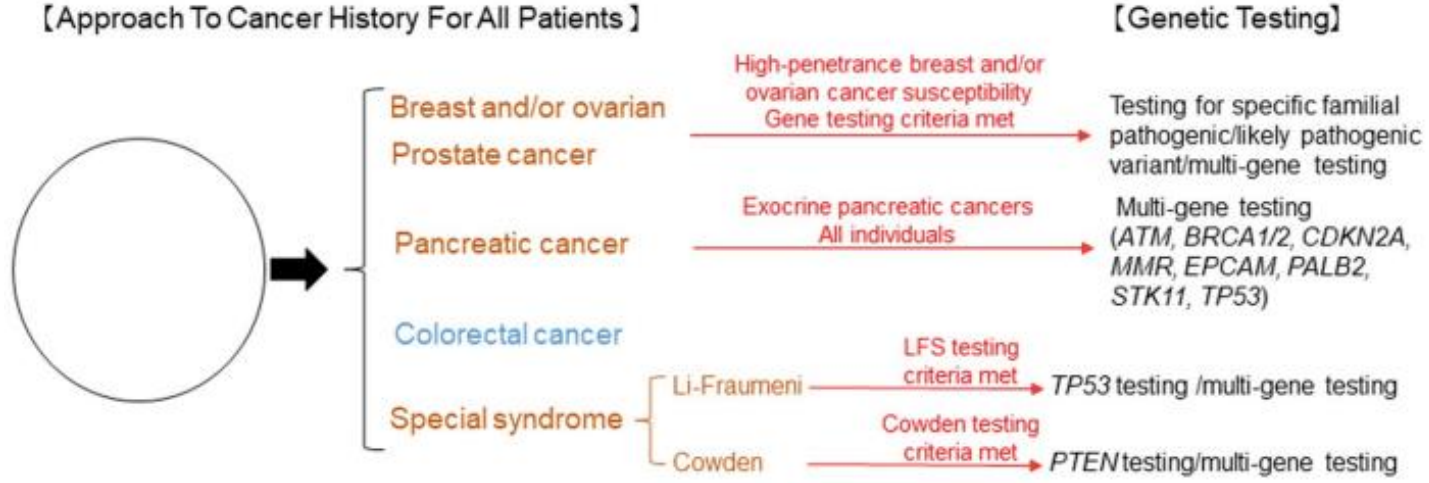
Yoshido R. Breast Cancer (2021) 28:1167–1180.

NCCN recommendations for hereditary colon, breast and ovarian cancers

2019 guidelines



2020 guidelines after PARPi



Yoshido R. Breast Cancer (2021) 28:1167–1180.

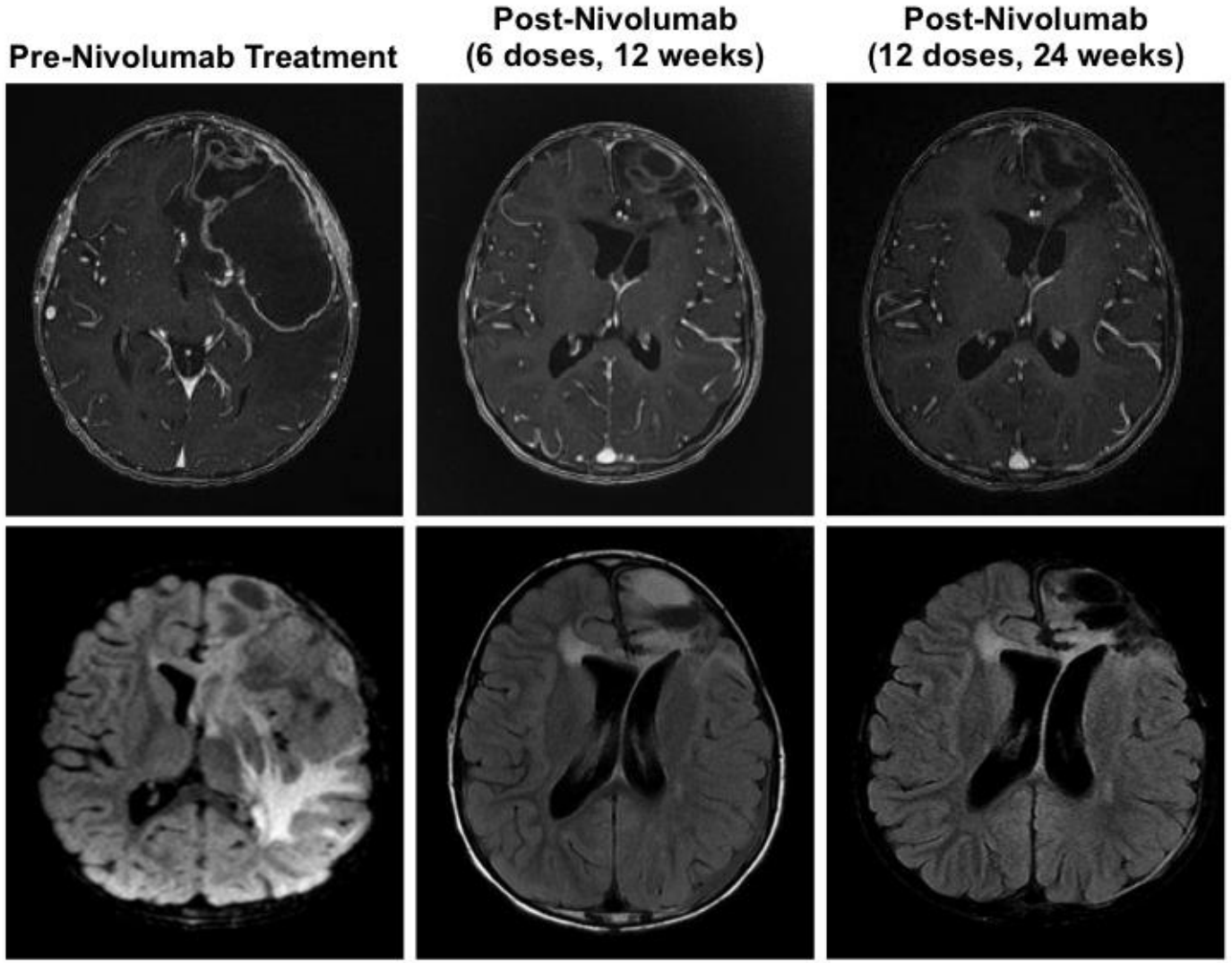
Targeted therapies for cancer patients with inherited mutations in genes associated with hereditary cancer syndromes

Table 2. Selected FDA Approvals for Germline Indications Across Cancer Types

Cancer Type	Drug	Germline Variant	Evidence
Breast cancer	Olaparib	*BRCA1/2*	OLYMPIAD (Robson et al[64])
	Talazoparib	*BRCA1/2*	EMBRACA (Litton et al[63])
Ovarian cancer	Olaparib	*BRCA1/2*	Study 42 (Domchek et al[67]) and SOLO1 (Moore et al[58])
	Rucaparib	*BRCA1/2*	Study 10/ARIEL2 (Swisher et al[59])
	Niraparib	*BRCA1/2*	QUADRA (Moore et al[61])
Metastatic prostate cancer	Olaparib	HR genes	PROfound (de Bono et al[66])
	Rucaparib	*BRCA1/2*	TRITON2 (Abida et al[65])
Pancreatic cancer	Olaparib	*BRCA1/2*	POLO (Golan et al[42])
Advanced/Metastatic solid tumors	Pembrolizumab	MMR-D (Lynch syndrome)	KEYNOTE 016 (Le et al[56])
Basal cell carcinoma	Vismodegib	*PTCH1* (Gorlin syndrome)	ClinicalTrials.gov identifier: NCT00833417 (Sekulic et al[50])
Thyroid cancer	Vandetanib	*RET* (MEN2)	ZETA (Wells et al[51])
	Selpercatinib	*RET* (MEN2)	LIBRETTO (Wirth et al[52])
Subependymal giant-cell astrocytoma	Everolimus	*TSC1/2* (tuberous sclerosis)	EXIST-1 (Krueger et al[55])
Renal angiomyolipoma	Everolimus	*TSC1/2* (tuberous sclerosis)	EXIST-2 (Bissler et al[53])
Plexiform neurofibromas	Selumetinib	*NF1* (neurofibromatosis type 1)	ClinicalTrials.gov identifier: NCT01362803 (Dombi et al[54])

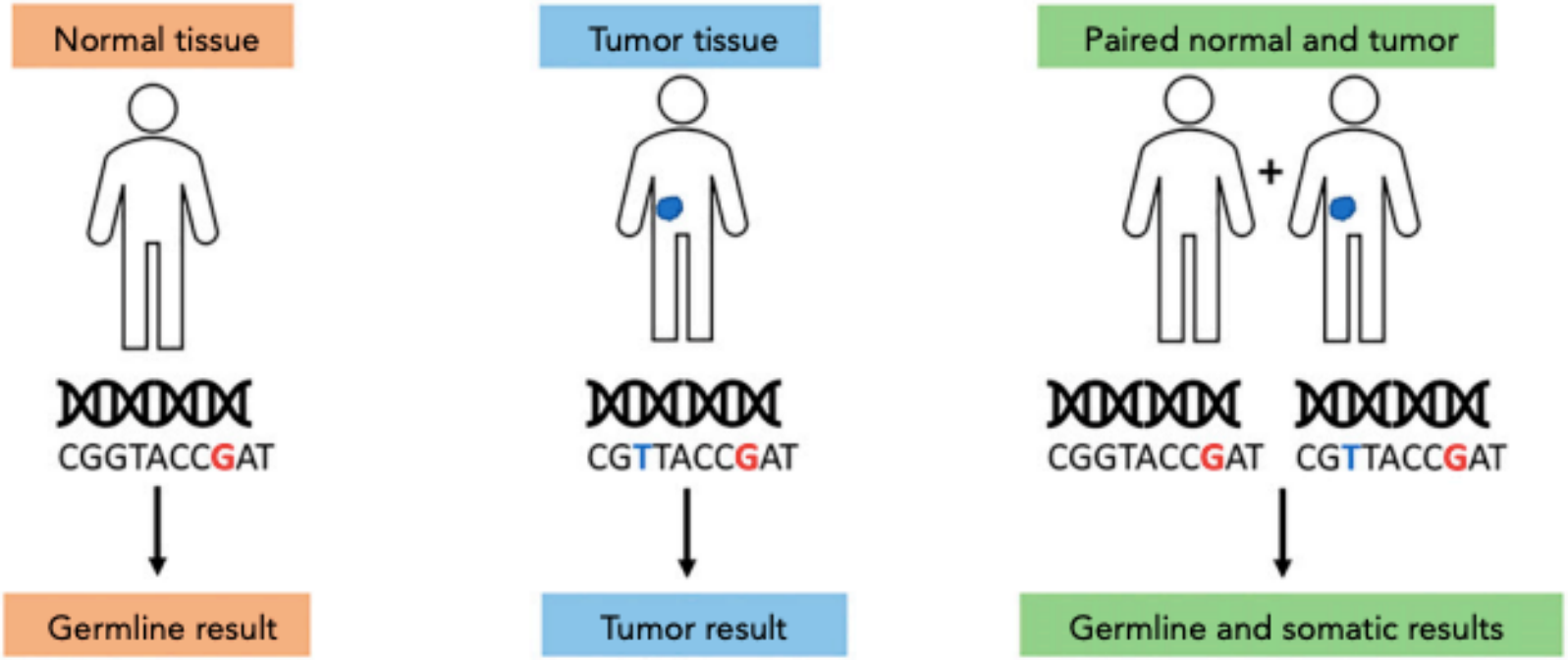
Liu Y *et al*. J Natl Compr Canc Netw 2021;19(7):871–878

Durable response to nivolumab in a pediatric patient with refractory glioblastoma and CMMRD



Abedalthagafi et al. Oncologist. 2018 Dec;23(12):1401-1406.

Precision medicine and the overlap with hereditary cancer syndromes



Pros	• Assess inherited risk • Cancer screening • Counseling for families • Reproductive planning	• Inform diagnosis and prognosis • Guide therapeutic decisions for targeted therapies • Assess MSI for immunotherapies	• Differentiation and integration of germline vs somatic variants • Guides therapy • Allows genetic counseling, screening, and reproductive planning
Cons	• Limited to patients who meet guidelines • Testing interpretation difficulties (eg. clonal hematopoiesis and mosaicism)	• Inability to distinguish somatic vs germline variants. • Inadequate surrogate for direct germline testing • Need for further genetic testing and potential delays in care	• Increased costs and resources, particularly related to genetic consents and counseling • Specialized curation and interpretation by molecular pathologist

Liu Y *et al*. J Natl Compr Canc Netw 2021;19(7):871–878

Summary

- Incorporating precision medicine into oncology treatment strategies improves patient outcomes across multiple cancer types
  - More matched therapies are on the way
- Testing for genomic or molecular biomarkers can be performed on tumor tissue or via a liquid biopsy
  - Use of single gene tests versus broad, multi-gene panel options
- Germline testing alone or in combination with somatic testing may be important

Questions?

Making Sense of Molecular Testing in Solid Tumors

08/26/2022

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