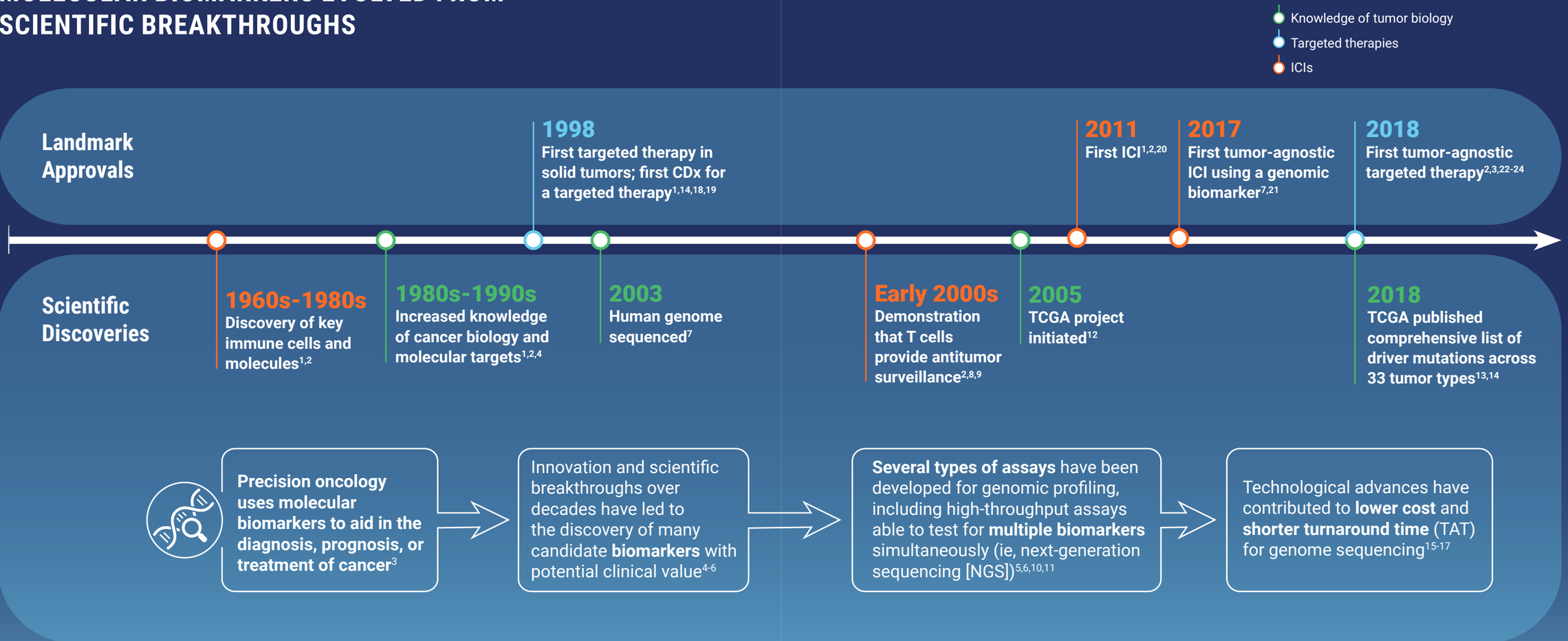
# Molecular Diagnostics in Personalized Cancer Care

## Best Practices and Overcoming Challenges

Precision Medicine

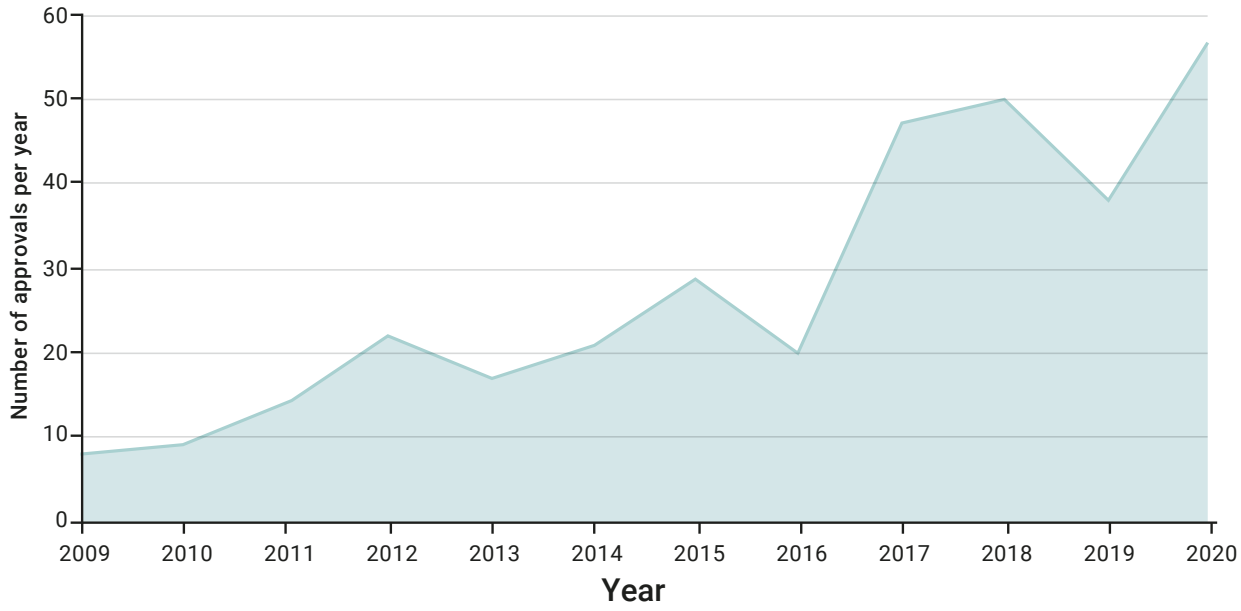
# PRECISION ONCOLOGY AND THE USE OF MOLECULAR BIOMARKERS EVOLVED FROM SCIENTIFIC BREAKTHROUGHS




CDx, companion diagnostic; ICI, immune checkpoint inhibitor; TCGA, The Cancer Genome Atlas.

# INCREASE OF THERAPEUTIC OPTIONS IN ONCOLOGY

## Total Number of Anticancer Therapies Approved by the FDA Between 2009 and 2020[25]




Between 2009 and 2020, there were 332 new anticancer therapy approvals, some of which require biomarker testing[25]

## As of June 2022, there are[3,26]:

**≥70**
**FDA-approved biomarker-linked indications**

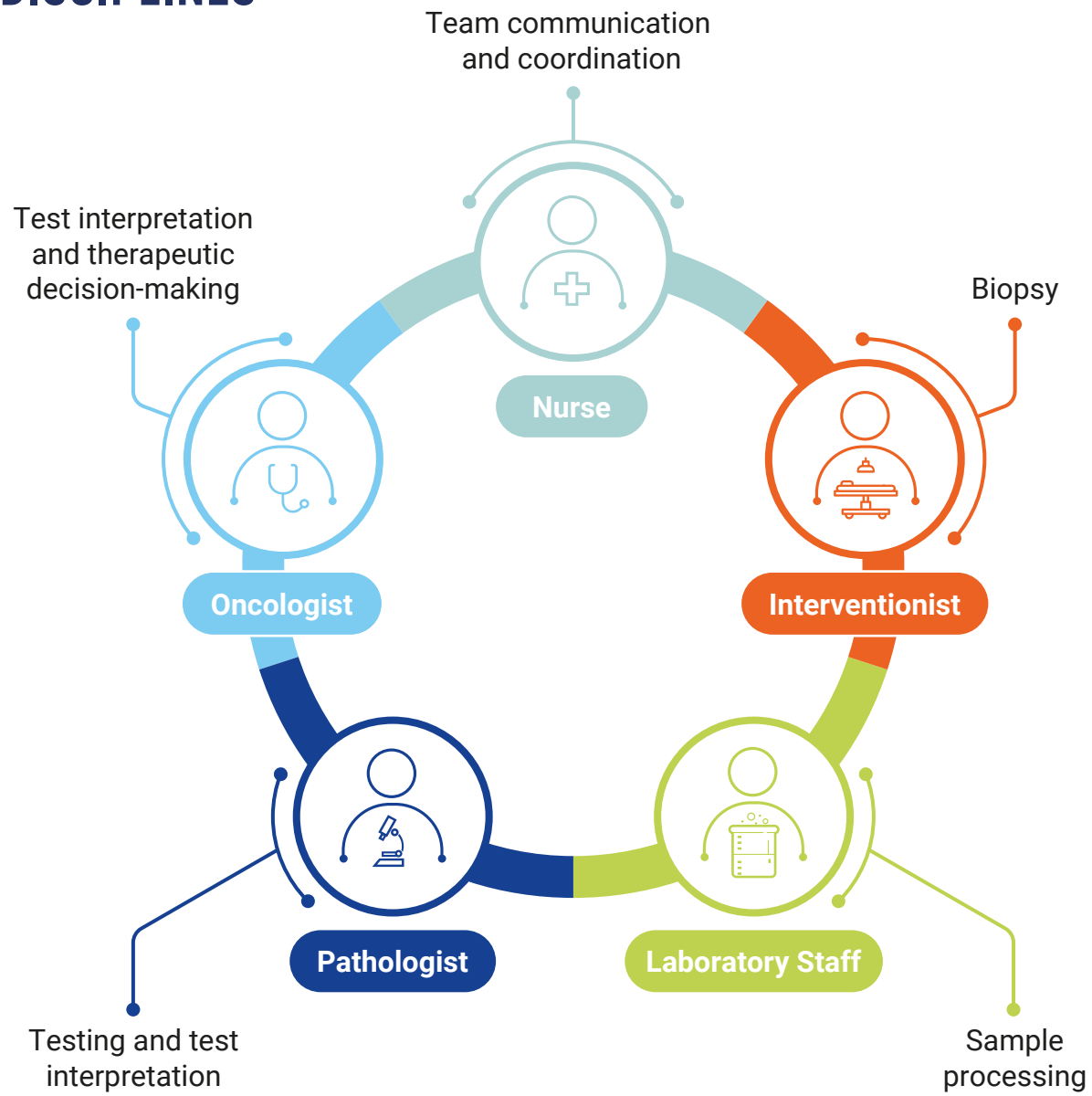
**43**
**actionable genomic alterations**

**28**
**cancer types treatable by Precision Oncology**

**Biomarker testing is a fundamental component of precision oncology[3]**

FDA, US Food and Drug Administration.

# MOLECULAR DIAGNOSTICS IS A MULTISTEP PROCESS REQUIRING COLLABORATION AMONG DISTINCT DISCIPLINES[27,28]

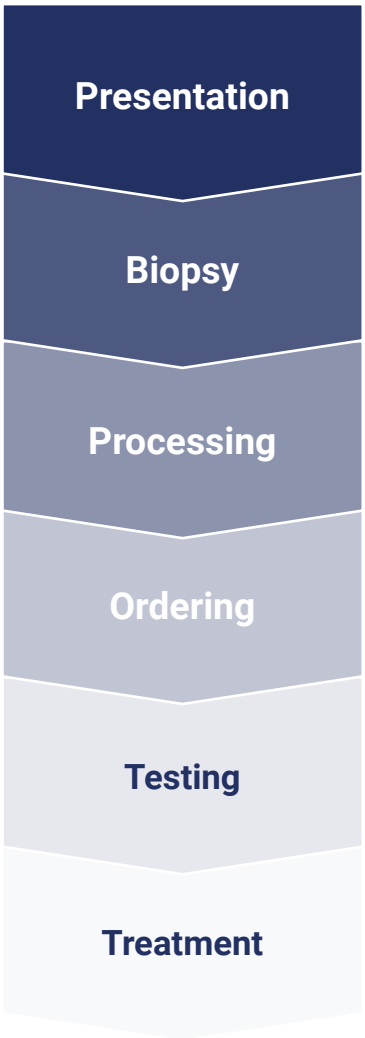



**Communication and coordination between members of the core and expanded multidisciplinary team (MDT) are important to the implementation of precision oncology[27,29,30]**

# DIAGNOSTIC JOURNEY IN PATIENTS WITH METASTATIC CANCER

## Testing Navigation

The **Oncology nurse navigator** is a key point of contact between the patient and the MDT and aims to facilitate team communication and coordination during testing[27]




The **oncologist** orders imaging and diagnostic tests after patient presents with suspected metastatic cancer[31]

The **interventionalist** collects tissue with potential input from the **pathologist** to confirm sufficiency[27,31]

The **laboratory staff** prepares a sample for evaluation and testing under **pathologist** supervision[27,31]

The **oncologist**, **surgeon/interventionalist,** and/or **pathologist** may order testing[27]

The **pathologist** interprets result(s) and prepares a report after performing testing, with assistance from **laboratory staff**[27]

The **oncologist** may use biomarker test results to make treatment decisions. The **pathologist** may be consulted for test interpretation[27,31]

# SUCCESSFUL BIOMARKER TESTING DEPENDS ON KEY FACTORS

Testing **tissue** of sufficient quantity and quality[32]

Use of appropriate **tests**[3]

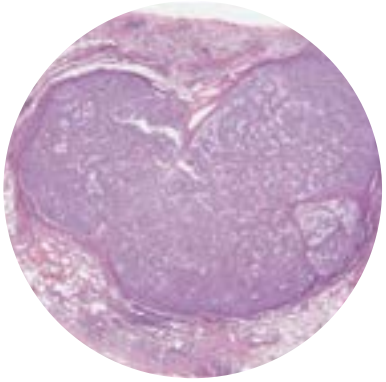
**Ordering** process for actionable biomarkers[3]

Access to clear and searchable **report** data[33]

# TESTING FOR BIOMARKERS GENERALLY REQUIRES 20% OF TUMOR NUCLEI IN SAMPLES[34,35]

## Lung Adenocarcinoma Example

- Accurate detection of biomarkers may be difficult in samples with low numbers of tumor cells[36]
- Interobserver variability and misestimation of tumor content are potential challenges[34,36]
  - A study demonstrated that 38% of samples have overestimated tumor content[36]
- Training may help lower discrepancies in estimating tumor content[34]



Lung Adenocarcinoma Example[34]

**Tumor content**

**30%–40%**

Figure used with permission from Mikubo M et al. *J Thorac Oncol*. 2020;15(1):130-137.

## Biopsy Choice May Impact Testing Outcomes

### Biopsy Site

- Biomarker discordance between the primary tumor and a metastatic site may occur[37,38]
- Additional/different drivers/ mutations may occur through clonal evolution over the course of the disease[39-41]

### Bone Biopsy

- Bone biopsy requires decalcification, which may impair sample yield and integrity, potentially negatively impacting biomarker testing outcomes[42]

### Rebiopsy

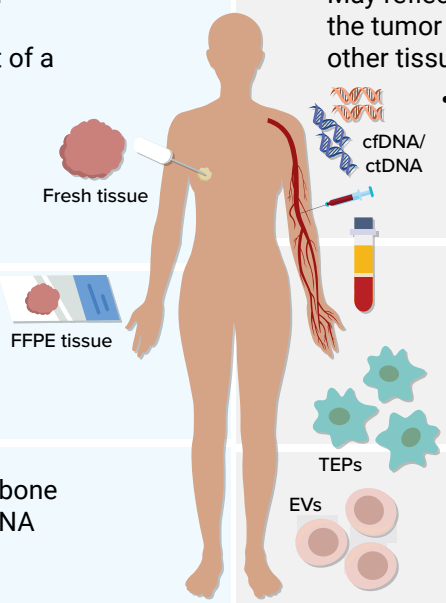
- Rebiopsy after disease progression may provide important and/or new information[43]
- In certain cancers, receptor status may change over the course of the disease[44-46]

# LIQUID BIOPSY OVERVIEW

## Key Characteristics of Liquid Biopsy[47,48]

| ADVANTAGES | DISADVANTAGES |
|---|---|
| ✓ Is minimally invasive | ✗ Cannot directly correlate ctDNA results with histology or cellular phenotype |
| ✓ Can capture tumor genetic heterogeneity and follow subclonal evolution through serial biopsy | ✗ Genetic analyses may have biased representation from differential tumor cell turnover |
| ✓ Potentially represents genetic make-up from entire tumor and metastatic sites | ✗ May be associated with false negatives |
| ✓ May have a shorter overall TAT than tissue-based NGS relative to the date the test is ordered | ✗ Special processing and handling required |

| Tissue Biopsy Testing | Liquid Biopsy Testing |
|---|---|
| May provide a snapshot of the cellular and molecular characteristics of one part of a single tumor[49]<br>• *Does not provide information from all cancer cells* | May reflect overall genomic landscape of the tumor and all metastatic sites (bone or other tissues)[51,52]<br>• *Does not provide information on TME[53]* |
| May miss an alteration if it is not present in the tested sample[50] | May miss an alteration if ctDNA concentration is below the LOD, leading to a false negative<br>• *ctDNA levels may vary significantly[52,54,55]* |
| Processing of biopsies of bone metastases may lead to DNA degradation[50] | CTCs and ctDNA levels may be impacted by the number and sites of metastases, including bone[52,54-56] |




cfDNA, cell-free DNA; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; EVs, extracellular vesicles; FFPE, formalin-fixed, paraffin-embedded; LOD, limit of detection; TEPs, tumor-educated platelets; TME, tumor microenvironment.

Image adapted from Alba-Bernal A et al. *EbioMedicine*. 2020;62:103100.

# CHARACTERISTICS OF A GOOD BIOMARKER TEST

## Clinical Guidelines and Expert Opinions[57-63]

- Is **actionable, prognostic, and/or predictive**[57,58]
- Provides **reproducible results** (>95%)[59,60]
- Is supported by the highest level of evidence[57]
- Has **tightly controlled specimen** collection, handling, and processing[57]
- Has **predetermined cutoff** points/categories[57]
- Delivers **timely** results that impact treatment decisions[61-63]
- Possesses sufficient **sensitivity, specificity, accuracy, and precision (<1% to 5% LOD) to detect actionable biomarkers**[57-60]

# ESSENTIAL QUESTIONS ABOUT A BIOMARKER TEST

| | Analytical Validity | Clinical Validity | Clinical Utility |
|---|---|---|---|
| **Definition**[64] | The test is able to accurately and reliably measure the presence or absence of a biomarker in the appropriate specimen | The test can accurately and reliably identify a biologically defined disorder or separate into two or more groups with distinct clinical or biological outcomes or differences | The test has high levels of evidence that use of the biomarker can result in guiding clinical decisions that result in improved clinical outcomes compared with those if the biomarker test results were not applied |
| **Essential question**[48] | *Is the test for the biomarker sensitive, accurate, and reliable?* | *Does the test accurately identify a disorder with distinct clinical or biological outcomes?* | *Is the test predictive of clinical outcomes?* |

**Analytical and clinical validity is the foundation of *all* biomarker testing.**
In addition, to gain FDA approval, a CDx must be evaluated in a clinical study[48,64-66]

**Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.**



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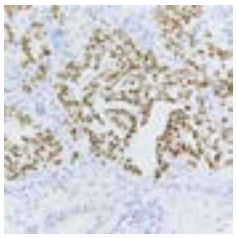
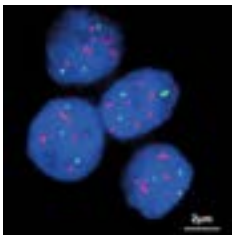
# BIOMARKER TESTING METHODS[3]

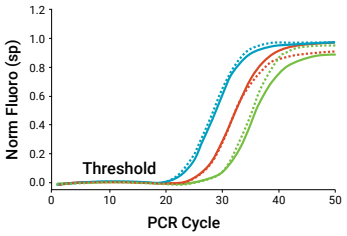
## IHC



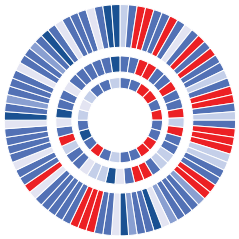
## FISH



## RT-PCR




## NGS



Images adapted with permission from Yu J et al. *Sci Rep*. 2019;9(1):7518, Yatabe Y et al. *J Thorac Oncol*. 2019;14(3):377-407, Kipf E et al. *J Mol Diagn*. 2022;24(1):57-68, and Goldbio. https://www.goldbio.com/articles/article/how-to-fragment-DNA-for-NGS. Accessed April 28, 2022.

# USE OF APPROPRIATE TESTS

- Some biomarkers may be detected more reliably by **some specific testing technologies** than by others[3,60]
- **Gene rearrangements** can be reliably detected by **FISH** and **RNA**-based NGS; enrichment strategy for a **DNA**-based NGS assay impacts the detection of **fusions**[3,60]

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- Understanding **assay limitations** is critical to identifying patients with actionable biomarkers[3]
- **The American Society of Clinical Oncology (ASCO)** recommends being **familiar** with the genomic testing platforms available to ensure **fusion testing** is performed when indicated[3]

**Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.**

# NGS MAY BE USED TO IDENTIFY THERAPEUTICALLY ACTIONABLE ALTERATIONS[3]

## ASCO recommends multigene panel-based genomic testing or NGS for:

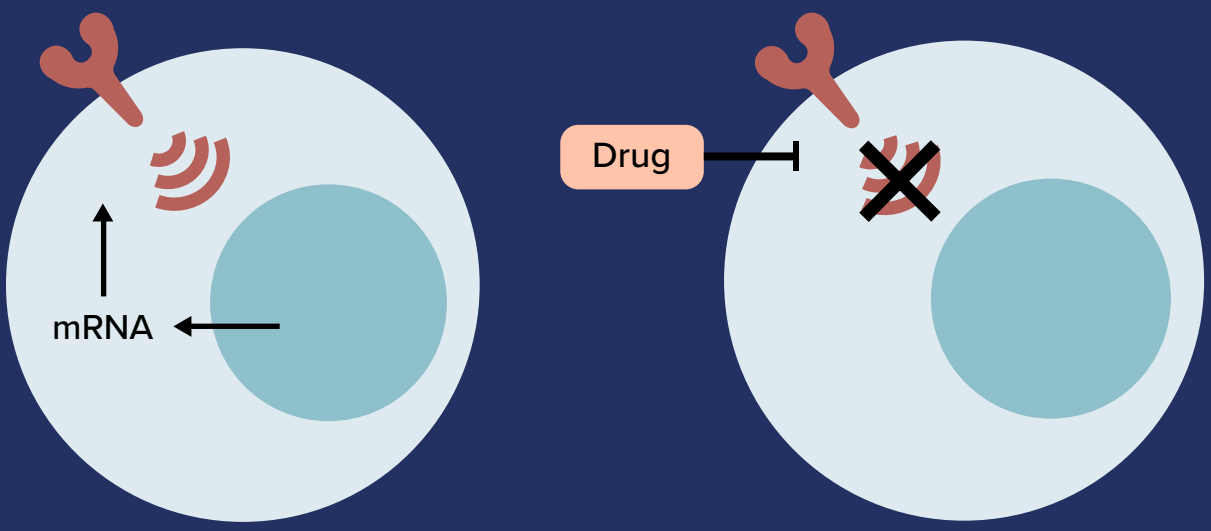
| Patients eligible for an approved genomic biomarker–linked therapy | Patients potentially eligible for more than 1 approved genomic biomarker–linked therapy |
|---|---|
| To detect tumor-agnostic actionable biomarkers like dMMR and/or MSI-H, TMB-H, and *NTRK* fusions, which may not be detected by single-gene tests | To provide the most efficient use of limited tumor biopsy tissue |

**ASCO recommends using NGS for the most efficient utilization of limited biopsy tissue; it may allow simultaneous testing for multiple approved targeted therapies**

dMMR, deficient mismatch repair; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, real-time polymerase chain reaction; TMB-H, tumor mutation burden-high.

# BIOMARKERS FOR TARGETED THERAPIES ARE DIFFERENT THAN BIOMARKERS FOR ICIS

## Targeted Therapy Biomarkers

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Targeted therapies inhibit cells harboring a specific genomic alteration or protein[3]

Responses to targeted therapies may be primarily influenced by the presence of a driver alteration assumed to be present in most tumor cells[67-70]

## Biomarkers for targeted therapies[67]:

- May be categorial or continuous depending on the alteration (eg, mutation or amplification)[68,71,a]
- Are assumed to be present in most tumor cells[68]

[a]Except for gene amplifications, which are continuous.
mRNA, messenger RNA.



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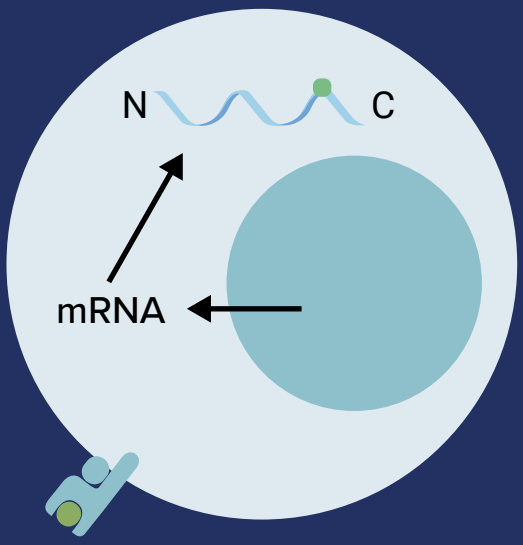
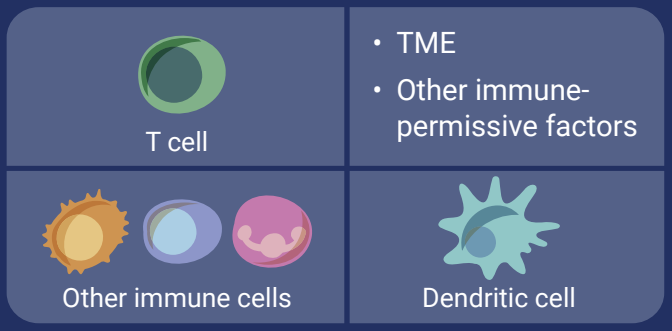
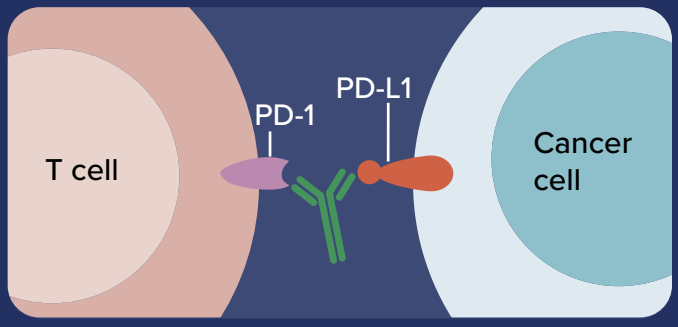
# BIOMARKERS FOR TARGETED THERAPIES ARE DIFFERENT THAN BIOMARKERS FOR ICIS

## ICI Biomarkers




ICIs reduce T-cell exhaustion by disrupting the immune checkpoint[72-75]

Responses to ICIs may be influenced by complex interactions between multiple different cell types[67,76]

## Biomarkers for ICIs are[67]:

- Continuous with arbitrary cutoffs[77-79]
- Spatially and temporally variable[79,80]

PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

# OVERVIEW OF SELECT BIOMARKER TESTING CHALLENGES

## Failure to obtain **sufficient tissue** during biopsy

- Core needle biopsies (CNBs) may provide inadequate malignant tissue[81]
- Biomarker discordance between the primary tumor and a metastatic site may occur[82-84,a]
- Bone biopsies may have increased odds of containing insufficient tumor cells[81]

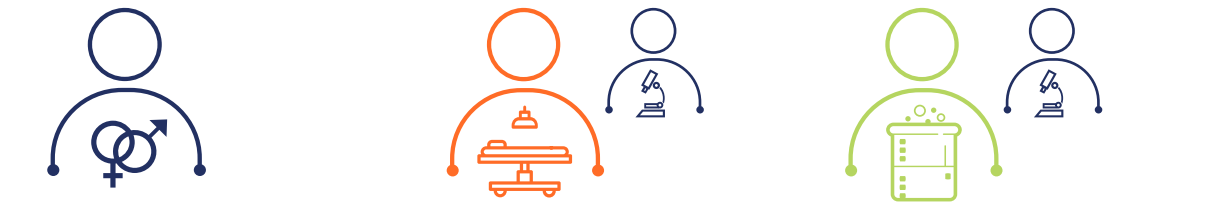
**In a survey:**


of oncologists cited **tissue sufficiency** as a barrier to multimarker tumor panel testing[32,b]

[a]Based on a meta-analysis of 61 studies including more than 5,700 patients with metastatic colorectal cancer.[32]
[b]Based on the 2017 National Survey of Precision Medicine in Cancer Treatment by the National Cancer Institute. A total of 1,281 medical oncologists participated in this survey.[32]

## **Overall complexities** associated with biomarker testing

- Failure to obtain sufficient tissue during biopsy[32]
- MDT communication[85]
- Multiple testing options[86]
- Guideline differences[86]



# OVERVIEW OF SELECT BIOMARKER TESTING CHALLENGES

## Extensive TAT

In some cancers with multiple biomarkers, studies suggest sequential single-gene testing may contribute to tissue exhaustion, potentially leading to:

- Patients *not* receiving testing for all biomarkers
- Prolonged TAT for all biomarkers (relative to a multigene panel)[87,88]

**Multigene panels may have TATs of**

**>10 days**[88]

**Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA approved CDx.**

## **Overall complexities** associated with biomarker testing

- Confusing/ narrative reports[88]
- NGS report interpretation[32,33,89-92]

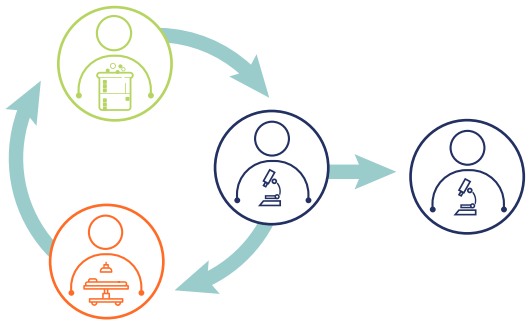
Ordering[27] → Testing[27] → Treatment[27,31]

# POTENTIAL SOLUTIONS TO OVERCOME CHALLENGES

## Failure to obtain **sufficient tissue** during biopsy

### ROSE May Improve Biopsy Yield

Implementation of ROSE has been associated with an **increase in diagnostic yield**

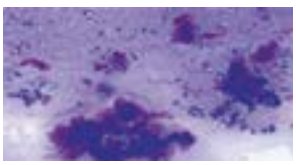
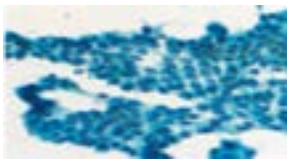
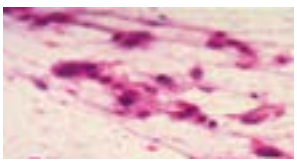


Up to **10%** in cytology procedures[93,a]

**≈6%** in endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) procedures[94,b]

- With ROSE at a single center, presence of tumor material was confirmed in 86% of biopsies, 96% of which were sufficient for molecular testing[95,c]
- In one study with ROSE, ≈98% of samples obtained were deemed adequate[96,d]
  - Some studies report that the diagnostic yield and accuracy were comparable in procedures done with and without ROSE[97,98]

## ROSE Stains Show Different Cytologic Details

| Diff-Quik | Rapid Papanicolaou | H&E | Toluidine Blue |
|---|---|---|---|
|  |  |  |  |
| • Stain of choice for ROSE | • Most commonly used stain in cytopathology<br>• Very reliable and may be applied to various cytologic preparations | • Standard stain for histopathologic evaluation; rapid H&E stain for cytologic specimens<br>• Widely used for intraoperative frozen service | • A basic thiazine metachromatic dye with high affinity for acidic tissue components |

Images adapted with permission from Cai G. Facility, equipment, specimen preparation, and stains. In: Cai G, Adeniran AJ, eds. *Rapid On-site Evaluation (ROSE)*. Cham, Switzerland: Springer Cham; 2019:13-27 and Kim K et al. *J Med Dent Sci*. 2005;52:163-170

[a]Based on a retrospective study of 144 fine needle aspiration (FNA) and CNB specimens.

[b]Based on a prospective study of 348 patients.

[c]Based on a prospective study of 79 cases from 56 patients who underwent FNA or CNB at the University of Pittsburgh Medical Center Hillman Cancer Center.

[d]Based on a retrospective study of 12 patients who underwent EBUS-TBNA thyroid biopsy from February 2010 to February 2013 at the Michael E. DeBakey Veterans Affairs Medical Center and the New York Methodist Hospital.

H&E, hematoxylin and eosin; ROSE, rapid on-site evaluation.

## Extensive **TAT**

### Reflex Testing Can Help Streamline Biomarker Testing

**Reflex testing is the automatic addition of tests in the SOPs by pathologists[99] in specific situations, such as:**

An equivocal HER2 IHC result in breast cancer[43]

Reflex testing may be integrated into the electronic health record[100]

Reflex testing is dependent on the cancer type, staging, and institution protocol[101,102]

### Reflex Testing May Reduce TAT[102,103]

**A retrospective review of 166 patients** diagnosed with **lung adenocarcinoma between 2016 and 2018** at a community center assessed biomarker testing rates and TATs for molecular testing[103]

**Reflex ordered testing** was implemented in February 2017[103]

**TATs were compared before and after reflex testing implementation**[103]

TAT was defined as the date of the anatomic pathology report confirming lung adenocarcinoma diagnosis to the date of the final molecular diagnostics report[103]

**TAT before reflex testing**[103]

**52.6 days**

**TAT with reflex testing**[103]

**15.6 days**

**Reduced TAT after reflex testing has been observed in other tumor types as well**[102]

HER2, human epidermal growth factor receptor 2; SOPs, standard operating procedures.

# POTENTIAL SOLUTIONS TO OVERCOME CHALLENGES (CONTINUED)

**Overall complexities** associated with biomarker testing

## MTBs May Help Navigate the Complexities of Precision Oncology

**Cancer treatment recommendations from MTBs may be based on many factors, including[104]:**

- Tumor type
- Molecular alterations
- Performance status
- Comorbidities

**Many specialties may be part of an MTB to help foster discussion[104]**

- Clinical oncologists
- Pathologists
- Geneticists — *to facilitate discussions on germline mutations*
- Bioinformaticians and molecular biologists — *to aid in interpretation of big data sets*
- Pharmacists

**Real-world evidence from a retrospective review of 782 patients with solid tumors tested with NGS in a tertiary care center suggests MTBs may help in appropriate and actionable clinical decision-making[105]**

MTB, molecular tumor board.

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# SUMMARY

**Precision oncology has contributed to improved care** for patients[3]

Each member of the MDT is important to biomarker testing **collaboration and communication**[27]

**Improving MDT communication and collaboration** may increase the number of patients receiving biomarker-informed care[27]

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