Essential Elements of Biomarker Testing During the Diagnostic Journey

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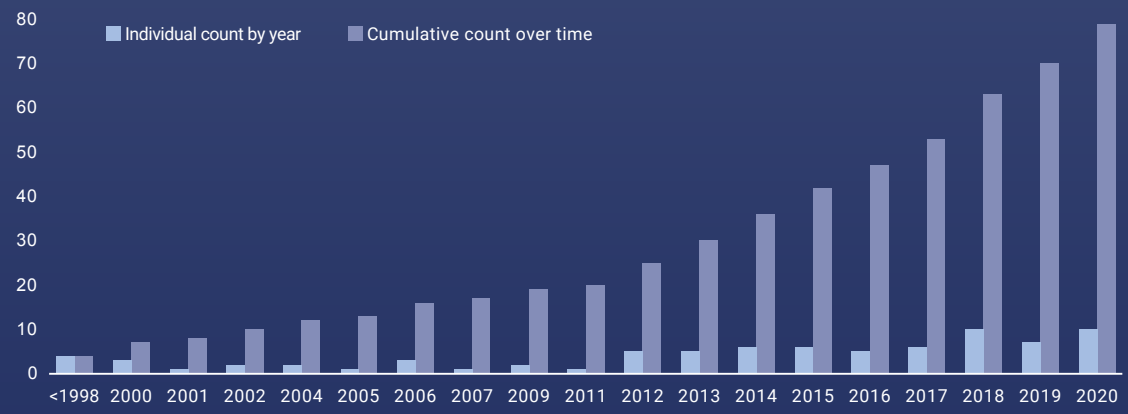
PRECISION ONCOLOGY OVERVIEW

Precision oncology, which aims to pair patients with therapeutic options suited to the biological basis for their cancer, has grown dramatically since the first targeted therapy for a solid tumor in 1998[1-5]

Number of US Oncology Approvals With Required or Recommended Predictive Biomarker Testing[2]



As of June 2022, there are:[1,6]

≥70
FDA-approved biomarker-linked indications

43
actionable genomic alterations

28
cancer types treatable by Precision Oncology

1in3
cancer patients may be candidates for an FDA-approved biomarker-linked therapy[7]

Precision Oncology Requires Molecular Diagnostics[1]

FDA, US Food and Drug Administration.

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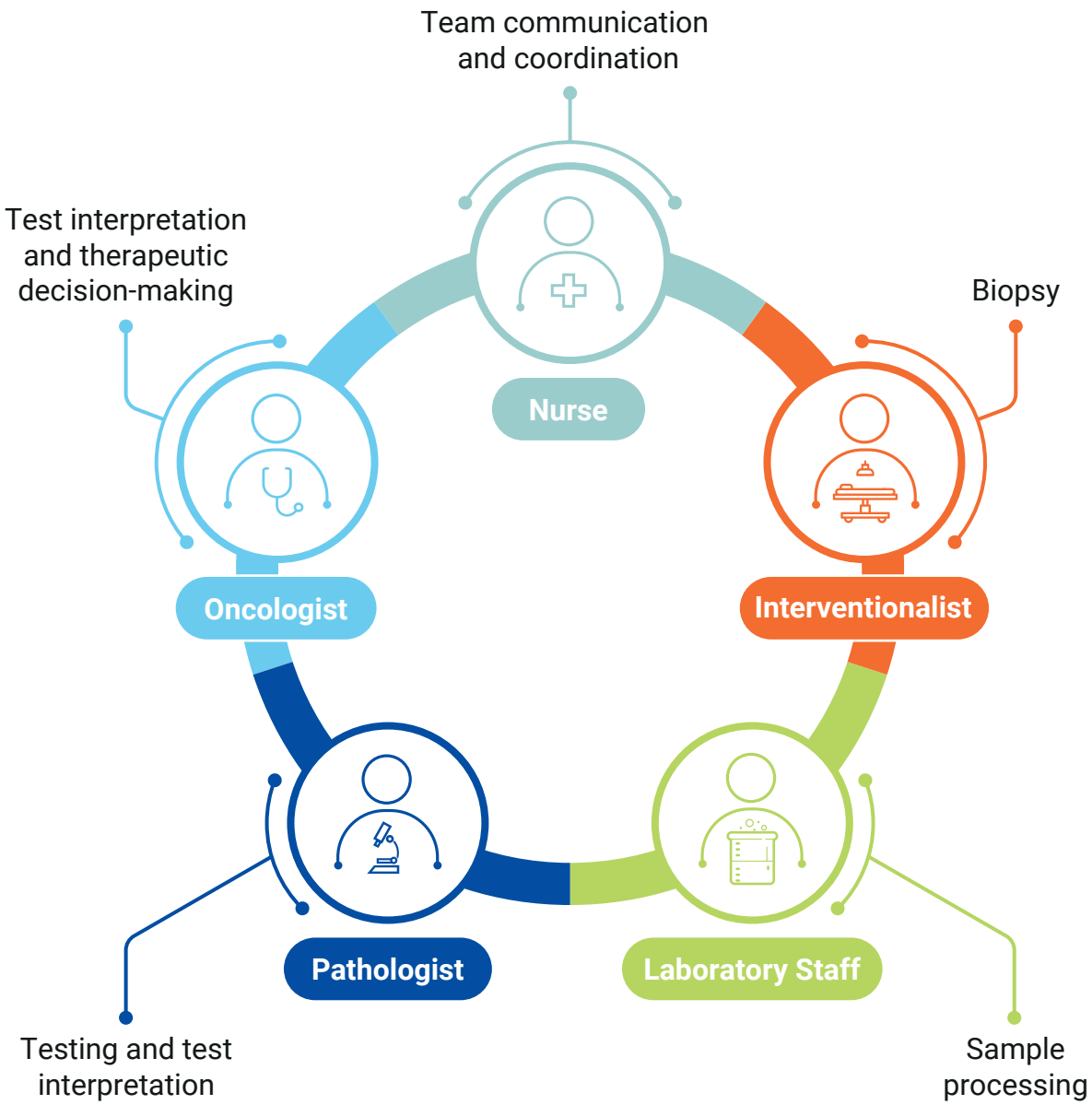
MOLECULAR DIAGNOSTICS OVERVIEW

Molecular diagnostics is a multistep process requiring collaboration among distinct disciplines[8,9]

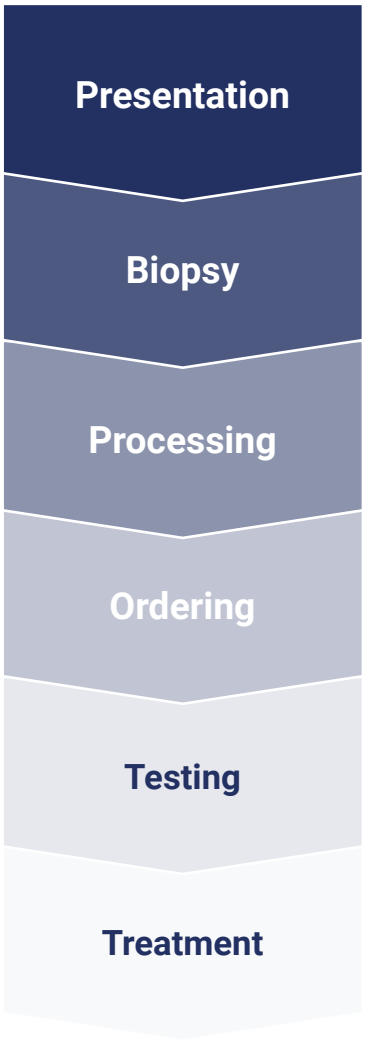
The Multidisciplinary Team (MDT)



MDT Roles in the Diagnostic Journey for Patients With Metastatic Cancer

Testing Navigation

Nurses can be the key point of contact between the patient and MDT or act as a tissue navigator to usher the tissue through the testing process[8,9]



Oncologist orders imaging and diagnostic tests after patient presents with suspected metastatic cancer[10]

Interventionalist collects tissue with potential input from **pathologist** to confirm sufficiency[8,10]

Laboratory staff prepare sample for evaluation and testing under **pathologist** supervision[8,10]

The **oncologist**, **surgeon/interventionalist,** and/or **pathologist** may order testing[8]

Pathologist interprets result(s) and prepares report after performing testing, with assistance from **laboratory staff**[8]

Oncologist may use biomarker test results to make treatment decisions. **Pathologist** may be consulted for test interpretation

Problems at Any Step in the Diagnostic Process May Negatively Impact Patient Care

Successful Biomarker Testing Depends on Key Factors

Testing tissue of sufficient quantity and quality[11]

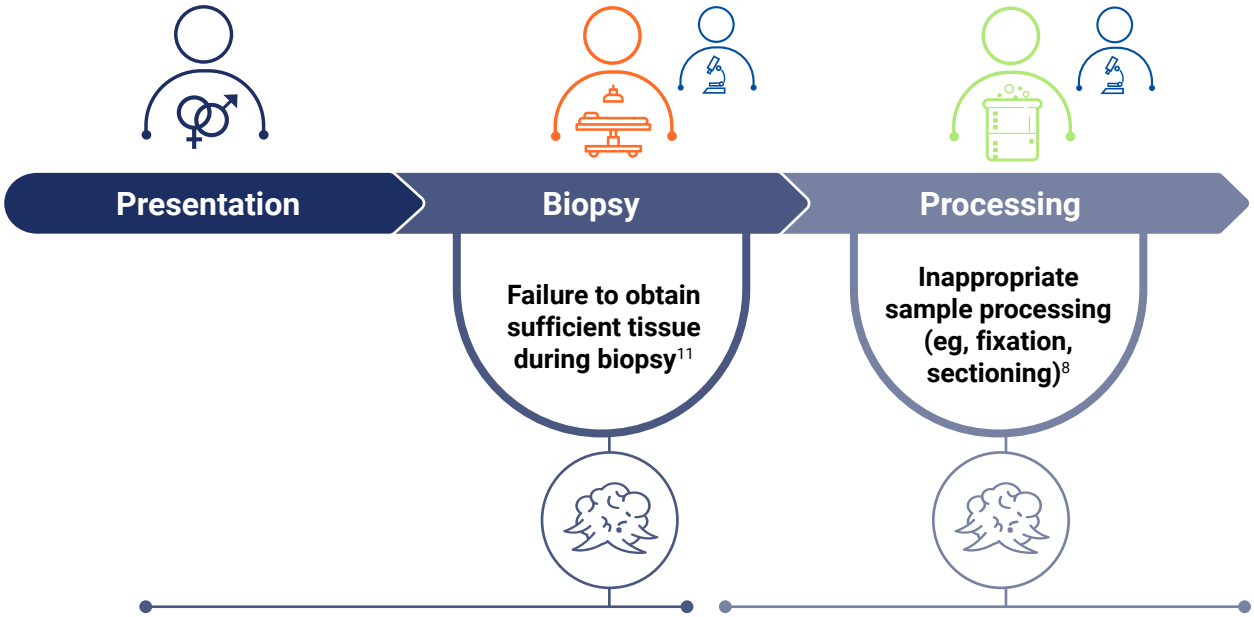
Ordering process for actionable biomarkers[1]

Use of appropriate tests[1]

Access to clear and searchable report data[12]

There May Be Solutions for Possible Challenges Associated With Each Key Factor

DIAGNOSTIC JOURNEY FOR PATIENTS WITH METASTATIC CANCER: **TISSUE SUFFICIENCY**



- In a survey, **57%** of oncologists cited **tissue sufficiency** as a barrier to multimarker tumor panel testing[11]
- **Core needle biopsies** may provide inadequate malignant tissue[13]
- Biomarker discordance between the primary tumor and a metastatic site may occur[14-16,a]
- **Bone biopsies** may have increased odds of containing insufficient tumor cells[13]

- **Prolonged ischemic** times may lead to sample degradation[8]
- **Fixation** may influence suitability for downstream testing[8]
- Preparing tissue using only one cassette may contribute to **tissue exhaustion**[8]
- **Necrotic regions** may be incompatible with PCR- and NGS-based sequencing[8]

- Working with the **MDT** to identify lesions to sample and potentially assess tissue adequacy during the procedure may help obtain sufficient tissue[8]
- Consider implementation of **ROSE** to overcome tissue inadequacy in small biopsies[17,18]

- Consider **limiting cold ischemia to <30 min** if performing RNA/proteomic analyses[8]
- Consider **downstream testing** when choosing fixation methods[8]
- Dividing tissues into **>1 cassette** may prevent tissue waste[8]
- **Microdissections** may increase viable tumor fraction[8,19]
  - NGS assays typically require 10-20% tumor nuclei[20]

[a]Based on a meta-analysis from 61 studies including more than 5,700 patients with metastatic colorectal cancer.
NGS, next generation sequencing; PCR, polymerase chain reaction; ROSE, rapid on-site evaluation.

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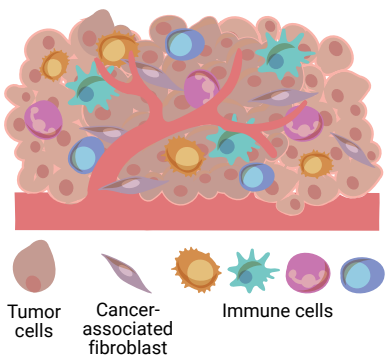
Ordering | Testing | Treatment

Tumor heterogeneity and overestimation of tumor content prior to testing[21]



The tumor microenvironment consists of heterogeneous cellular matrix and extracellular matrix components[13]

Lung Adenocarcinoma Example[21]
Tumor content 30% to 40%

- **Tumor heterogeneity** can affect tissue sufficiency and biomarker testing[22]
  - **False-negatives** may occur in samples with few tumor cells[23]
- Inaccurate estimation of tumor content is a potential challenge – **38%** of samples have overestimated tumor content[23]

Microdissections may increase tumor percentage and detectability of tumor DNA[24]

Successful Biomarker Testing Depends on Maintaining Tumor Tissue Quality[8,25]
Remember: What You Put in Is What You Get Out

Images adapted with permission from Baghban R et al. *Cell Commun Signal* and 2020;18(1):59. Mikubo M et al. *J Thorac Oncol*. 2020;15(1):130-137.

DIAGNOSTIC JOURNEY FOR PATIENTS WITH METASTATIC CANCER: **ORDERING**

Presentation | **Biopsy** | **Processing**

MDT communication[46]

- Common terms like "panel" may have **multiple interpretations**[26,27]
- Variability in **requisition forms** between different institutions may result in confusion among MDT members[28]
- Test requisition form **formatting** may impact test utilization, including under- or overtesting[29,30]

The American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion that includes **definitions** for biomarker testing terminology[1]

- **ASCO** defines a multigene panel as an "NGS test with a defined set of genes of at least 50 genes"

*Where are the **NGS** results? I thought we ordered a **panel**.*

*Our **panel** doesn't include **NGS**. Did you want a **CGP** as well?*

Establishing a common language with the MDT may help ensure that patients are not missed because of communication errors

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines® in Oncology (NCCN Guidelines®) Issues Evidence- And Consensus-Based Guidelines That Are Updated Continually, With At Least 1 Update Per Year[31]

CGP, comprehensive genomic profiling.

Ordering | Testing | Treatment

Multiple testing options[32]

Too many testing options (eg, multiple testing platforms or vendors, each with unique sample requirements), within a hospital system may lead to[32]:

- Confusion among providers
- Disorganized processes within the laboratory
- Potentially longer turnaround times

One community hospital system saw improvements in biomarker testing after **creating standard ordering processes** with **minimal testing platforms** to streamline laboratory processes[35]

Guideline differences[32]

Guidelines may differ based on the **timing** of their **most recent update**[32]

- NCCN Clinical Practice guidelines in Oncology (NCCN Guidelines®) update **at least once per year**[31]
- CAP Guidelines are reviewed and updated every **5 years**[33,34]

Consider reviewing and incorporating recommendations from different guidelines at a cadence that keeps pace with updates[32]

CAP Guidelines (Pathology Guidelines) Are Evidence-Based Guidelines[33,34]

CAP, College of American Pathologists.

DIAGNOSTIC JOURNEY FOR PATIENTS WITH METASTATIC CANCER: **USE OF APPROPRIATE TESTS**

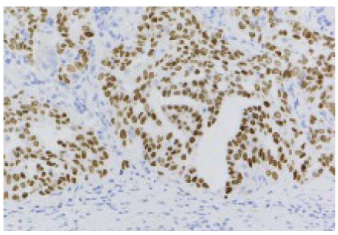
Presentation | **Biopsy** | **Processing**

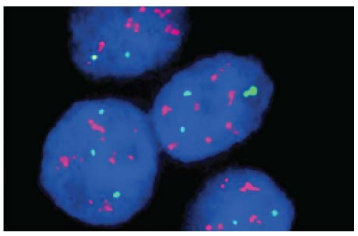
Use of tests that cannot detect the biomarker in question[1,19]

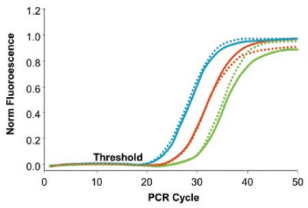
- Some biomarkers may be detected more reliably by **some specific testing techniques** than by others[1,19]
- **Gene rearrangements** can be reliably detected by **FISH** and **RNA**-based NGS; enrichment strategy for a **DNA**-based NGS assay impacts the detection of **fusions**[1,19]

- Understanding **assay limitations** is critical to identifying patients with actionable biomarkers[1]
- **ASCO** recommends being **familiar** with the genomic testing platforms available to ensure **fusion testing** is performed when indicated[1]

IHC[36]	FISH[37]	RT-PCR[38]







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

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; RT-PCR, real-time polymerase chain reaction.
Images adapted with permission from Yatabe Y et al. *J Thorac Oncol*. 2019;14(3):377-407, Yu J et al. *Sci Rep*. 2019;9(1):7518, and Kipf E et al. *J Mol Diagn*. 2022;24(1):57-68.

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Ordering | **Testing** | **Treatment**

Extensive turnaround time[39]

Multigene panels may have turnaround times of **>10 days**[39]

- Hybrid capture panels typically have longer turnaround times than amplicon panels but may detect more types of alterations

Reflex testing may speed turnaround times by streamlining the ordering process[39,40]

- Having results available for the **first visit** may speed the time to **treatment initiation**[41]

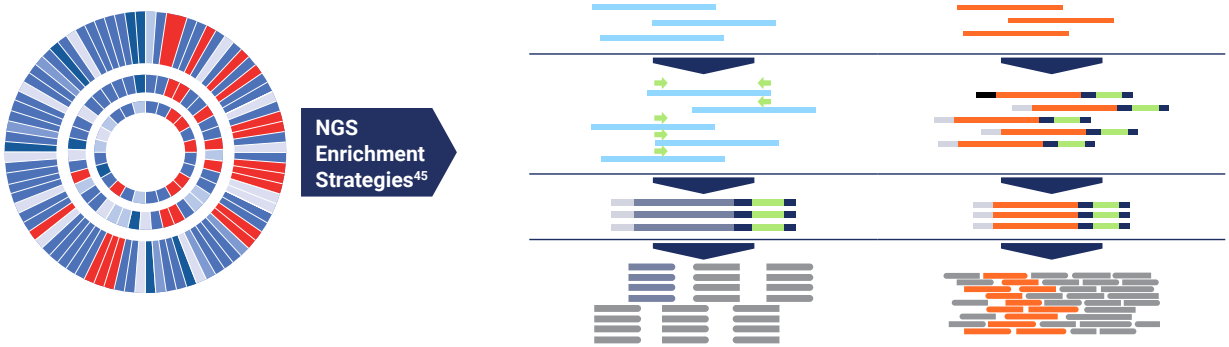
Sequential single-gene testing in some cancers[1,43]

In some cancers with multiple biomarkers, studies suggest **sequential single-gene testing** may contribute to tissue exhaustion, potentially leading to[42,43]:

- Patients **not receiving testing** for all biomarkers
- **Prolonged turnaround time** for all biomarkers (relative to a multigene panel)

For patients with advanced or metastatic cancers, **ASCO recommends multigene panel–based** genomic testing whenever **>1** genomic biomarker is linked to an FDA-approved therapy[1]

NGS[44] | **Amplicon** | **Hybrid capture**



Images adapted with permission from Cheng H et al. *Cell Rep.* 2018;25(5):1332-1345.e5 and Church A. Next-generation sequencing. In: Tafe L, Arcila M, eds. *Genomic Medicine*. Cham, Switzerland: Springer; 2020:25-40.

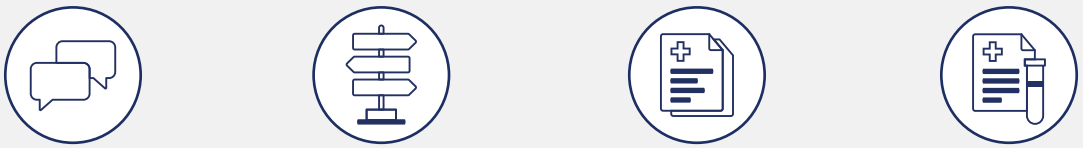
DIAGNOSTIC JOURNEY FOR PATIENTS WITH METASTATIC CANCER: **CLEAR AND SEARCHABLE REPORTS**

Presentation | **Biopsy** | **Processing**

Communication Issues May Arise During Biomarker Testing

In a survey, HCPs cited communication challenges across the MDT as 1 of the top 5 barriers to biomarker testing[46]

Sources of **communication** issues may include:



Use of jargon[12,32]

Guideline differences[32]

Requisition form variability and/or ambiguity[32]

Pathology reports and EHR incompatibility[12,32,47]

Multiple professional societies have developed resources to assist with testing barriers

Speaking the same language[1,48]
- ASCO provided definitions of common terms for clinicians
- Working group created common terms and their definitions for patients

Incorporating multiple guidelines[32]
- Frequently updated guidelines may be the source for updates to internal SOPs

Generating internal standards for testing documentation[49]
- Involving representatives of the MDT may address this issue

ASCO recommends using precision oncology knowledge databases to assess a list of genomic alterations considered clinically actionable[1]
- OncoKB monitors FDA-approved indications

EHR, electronic health record; HCPs, health care professionals; SOPs, standard operating procedures.

Ordering | Testing | Treatment

LIS/EHR incompatibility[12]

Confusing/narrative reports[12]

- Incompatibility between LIS and EHR systems may lead to missing or incomplete reports[12,32,47]
- When added as an addendum report, biomarker test results may be missed if not linked to pathology reports in the EHR[12]
  - Oncologists are not notified when addendum reports are added to the EHR

- Narrative reports may be challenging to interpret quickly[11,12,47,50-52]
- NGS reports may not state actionable genomic alterations, further complicating interpretability[11,12,47,50-52]

ACCC recommends[12]:

- Utilizing CAP electronic Cancer Checklists to facilitate structured data capture and reporting
- Exploring ways to improve report readability and searchability across electronic systems
- Minimizing the use of scanned reports
- Considering using pathology LIS modules built by the inpatient EHR vendor

ASCO recommends using precision oncology knowledge databases to assess a list of genomic alterations considered clinically actionable[1]

EHR, electronic health record; LIS, laboratory information system; NGS, next-generation sequencing.

SUCCESSFUL BIOMARKER TESTING DEPENDS ON KEY FACTORS:

Testing **tissue** of sufficient quantity and quality[11]

Failure to obtain sufficient tissue during biopsy	• Working with the MDT to identify lesions to sample and assess tissue adequacy during the procedure may help obtain sufficient tissue [8] • Consider implementation of ROSE to overcome tissue inadequacy in small biopsies[17,18]
Inappropriate sample processing (eg, fixation, sectioning)	• Consider limiting cold ischemia to <30 min if performing RNA/proteomic analyses[8] • Consider downstream testing when choosing fixation methods[8] • Dividing tissues into >1 cassette may prevent tissue waste[8] • Microdissections may increase viable tumor fraction[8,19]
Overestimation of tumor content prior to testing	

Ordering process for actionable biomarkers[1]

MDT communication	• Consider incorporating definitions for biomarker testing terminology included in an ASCO Provision Clinical Opinion
Multiple testing options	• Consider creating standard ordering processes with minimal testing platforms to streamline laboratory processes [35]
Guideline differences	• Consider reviewing and incorporating recommendations from different guidelines at a cadence that keeps pace with updates[32]

Use of **appropriate tests**[1]

Use of tests that cannot detect the biomarker in question	• Understand assay limitations to identify patients with actionable biomarkers[1] • ASCO recommends being familiar with genomic testing platforms available to ensure fusion testing is performed when indicated[1]
Sequential single-gene testing in some cancers	• For patients with advanced or metastatic cancers, ASCO recommends multigene panel–based genomic testing whenever >1 genomic biomarker is linked to an FDA-approved therapy[1]
Extensive turnaround time	• Consider reflex testing, which may speed turnaround times by streamlining the ordering process[39,40] • Having results available for the first visit may speed the time to treatment initiation[41]

Access to **clear and searchable** report data[12]

LIS/EHR incompatibility	• ACCC recommends utilizing CAP electronic Cancer Checklists to facilitate structured data capture and reporting[12] • ACCC recommends exploring ways to improve report readability and searchability across electronic systems[12] • ACCC recommends minimizing the use of scanned reports[12] • ACCC recommends considering using pathology LIS modules built by the inpatient EHR vendor[12]
Confusing/narrative reports	• ASCO recommends using precision oncology knowledge databases to assess a list of genomic alterations considered clinically actionable[1]

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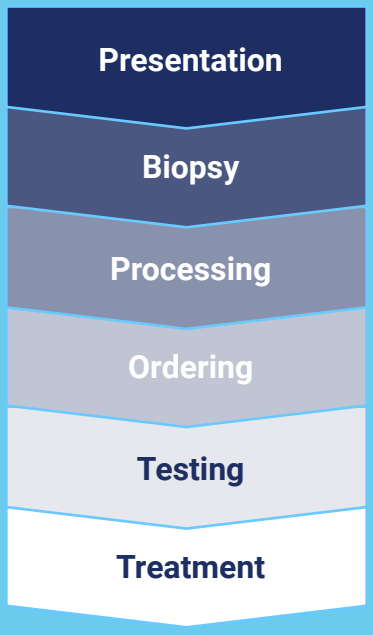
SUMMARY



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Multiple professional societies have developed resources to assist with testing barriers[1,32,48,49]

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