The Ins and Outs
of Test Requisition Forms

Precision Medicine

PRECISION MEDICINE ESSENTIALS

Oncogenic Drivers[1,2]

Driver mutations are genomic alterations that directly or indirectly provide a selective advantage to cancer cells by promoting cancer growth, development, and/or survival

Driver Alteration	Driver Gene
A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs	**A gene that contains driver gene mutations or is expressed aberrantly in a fashion that confers a selective growth advantage**

Not every mutation in an oncogene or tumor suppressor gene is a driver mutation.

Passenger mutations have no direct or indirect effect on the selective growth advantage of the cell in which it occurred.

Drivers Arise From Specific Genomic Alterations[1,2]

Mutations

Single-Nucleotide Variation	The substitution of one DNA nucleotide for another nucleotide (may be somatic/germline and synonymous/nonsynonymous) Includes **missense mutations**, which result in the substitution of the wild-type amino acid for an alternate amino acid and **silent mutations**, which do not alter the encoded amino acid
Indel/Deletion-Insertion	The replacement of more than one nucleotide by other nucleotides May be "**in-frame**" if the deletion/insertion occurs in multiples of three nucleotides or "**frameshift**" if the deletion/insertion shifts the reading frame, resulting in novel amino acids
Splice Site	A mutation involving the conserved nucleotides at the exon-intron boundary that may disrupt RNA splicing May result in exon skipping, intron retention, frameshift, and premature protein truncation
Extension	The normal stop codon is lost, allowing translation to continue
Truncating/Nonsense	A premature stop codon is introduced

Structural Variants

Copy Number Variation	A deviation from the expected two copies of a gene via an increase (**amplification**) or decrease (**deletion**) in the number of copies
Translocation	A rearrangement in which regions from two nonhomologous chromosomes are joined
Fusion	A novel gene product created from two previously separate and independent genes May arise from chromosomal translocations, interstitial deletions, inversions, or tandem duplications

DETECTING GENOMIC ALTERATIONS

Biomarker Testing in Oncology Is Complex[1,3]

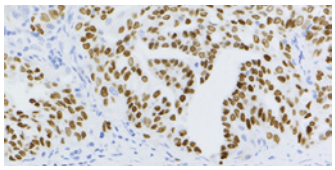
As of June 2022, there are:

≥70
FDA-approved biomarker-linked indications

43
actionable genomic alterations

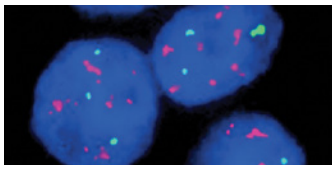
28
cancer types treatable by Precision Oncology

Single-Gene Testing



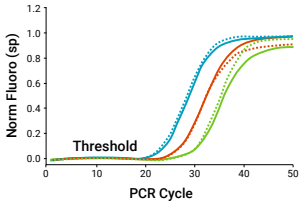
IHC: A test that uses an antibody to detect the expression, or loss of expression, of a specific protein or mutated protein form

Can assess: ***Protein expression***



FISH: An assay using a DNA probe that typically binds to target sequences in chromosome DNA; assessed under a fluorescence microscope

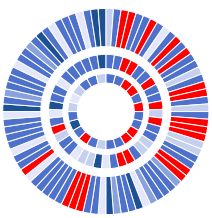
Can assess: ***Rearrangements, CNVs***



RT-PCR: An assay that amplifies and measures DNA from extracted RNA

Can assess: ***SNVs, indels, known rearrangements***

Multigene Testing



NGS[a]: A technology that performs massively parallel DNA sequencing to detect genomic alterations

Can assess: ***SNVs, indels, rearrangements, CNVs***

[a]Genomic alterations and biomarkers tested will vary by assay.

UNDERSTANDING NGS

NGS Assays Are Not Identical[5-9]

Enrichment Strategy[1,7,9,10]

		Amplicon	Hybrid capture
Variant detection	SNVs, small indels	✓	✓
	Fusions/ rearrangements	Nucleic acid dependent	✓
	Exon skipping	Nucleic acid dependent	✓
	CNV		✓
Bioinformatic analysis complexity		Less	More
Nucleic acid requirements		>10 ng	>100-200 ng

Nucleic Acid Selection

RNA-based NGS may be more sensitive than DNA-based NGS in detecting fusions and exon skipping[1,9,11-13]

Understanding assay limitations is critical to identifying patients with actionable biomarkers[1]

Recommendations for NGS[1]

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

Patients eligible for an 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

Patients eligible for >1 approved genomic biomarker–linked therapy

- 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

UNDERSTANDING TESTING TERMS

Establishing Common Testing Terminology

Specialty-specific definitions for jargon may impact MDT communication and coordination. Establishing a common language, as below, with the MDT may help ensure that patients are not missed because of communication errors.

GENERAL → **SPECIFIC**

Biomarker panel[14,1]

- Tests a defined/ prespecified set of biomarkers, ranging from a few to hundreds
- Technology used may be NGS, microarrays, or a collection of single-gene tests

NGS[14,16]

"Next generation sequencing"

A methodology capable of:

- Whole genome sequencing
- Whole exome sequencing
- Detecting mutations in a small panel of prespecified genes

– Enrichment strategy (amplicon or hybrid capture) and assay design impacts the detection of some genomic alterations

CGP[17]

"Comprehensive genomic profiling"

- A hybrid capture–based NGS assay that typically tests 50+ genes simultaneously
- CGP assays may detect all types of genomic alterations

Additional Terms Explained

Multigene Panel[1]

An NGS test that sequences a defined list of genes with at least 50 genes in total

VS

Hotspot Panel[1]

Sequencing select hotspot codons, which contain recurrently altered amino acids, for all genes on a panel

VS

Genetic Profile[18]

General term referring to the information collected about specific genes, including variations and gene expression

SV[1]

"Structural variant"

Large genomic alterations (> 50 bp) that typically contain CNVs, translocations, inversions, deletions, and/or insertions

VS

SNV[1]

"Single nucleotide variant"

The substitution of one DNA nucleotide for another nucleotide

CDx[19]

"Companion diagnostic"

A test approved by the FDA that provides information that is essential for the safe and effective use of a corresponding therapeutic product

VS

LDT[20]

"Laboratory developed test"

A test that is designed, manufactured, and used within a single laboratory, but does not receive FDA oversight

Precision Medicine

TEST REQUISITION FORMS (TRFs)

TRFs serve as a primary mode of communication between clinical and pathology team members during biomarker ordering[21,22]

of HCPs reported communication breakdowns during biomarker test ordering[23,*]

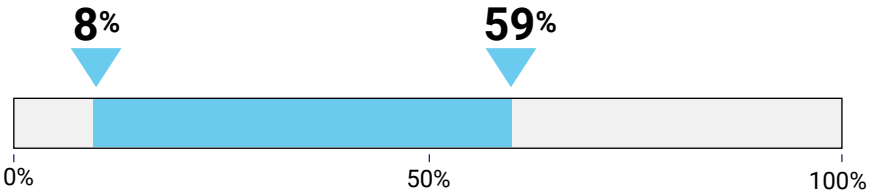
Common TRF Roadblocks

Confusion may result from:

- Too many testing options (eg, multiple testing platforms or vendors, each with unique sample requirements)[24]
- Requisition form variability between different institutions/ reference labs[22]

Incomplete or Incorrect Data Entry

The Rate of Incomplete TRFs Received by Laboratories Across Three Clinical Practices[21,25,26]



- **Data entry errors** are more common with handwritten compared to electronic forms[27]

Under- or Overtesting

Format of TRF may impact test utilization, resulting in potential under- or overtesting[28,29]

- Overtesting or inappropriate testing arises when testing exceeds guideline-recommended testing

*The Association of Community Cancer Centers, the Association of Molecular Pathology, the American Society for Clinical Pathology, and CAP conducted a survey in June 2018 with 659 responses from a multidisciplinary group and different cancer program settings.

THE IMPORTANCE OF TRF LAYOUT

TRF format and layout vary between institutions and can impact ordering, information processing, and results[22,30]

Considerations

Multiple professional societies have developed resources to assist with testing barriers:

Reduce Variability and Complexity

by generating internal standards for testing documentation[31]

One community hospital system saw improvements in biomarker testing after creating a standard ordering process with minimal testing platforms to streamline laboratory processes[32]

Ensure a Common Language

ASCO provided definitions of common terms for clinicians[1,33]

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

Keep Forms Up-to-Date

by incorporating multiple guidelines; frequently updated guidelines may be the source for updates to internal SOPs[24]

Consider reviewing and incorporating recommendations from different guidelines at a cadence that keeps pace with updates[24]

Introduction to Hypothetical TRFs

In the next section, 1 hypothetical TRFs is reviewed. This form provides a way to highlight important components of TRFs and details to consider including. In practice, TRFs should be carefully designed to maximize clear communication between members of the MDT.

The form in the following section is purely hypothetical, includes guideline recommendations, and is not intended to be used in practice

HYPOTHETICAL TRF BASIC INFORMATION

Test Requisition Form

Basic Information

Patient Information

Medical Record # _____ Name _____ Sex _____ DOB _____

Address _____ Phone Number _____

Clinical Information

Diagnosis / Diagnosis Code _____ Disease Stage _____

Number of Prior Therapies _____

Original Activating Mutation _____ Reason for Testing _____

Attachments: ☐ Pertinent Laboratory Results ☐ Test results from molecular assays

Physician Information

Requisition Completion Date _____ Completed By _____

Address (results will be sent to this address) _____

Ordering Physician Name _____ NPI # _____ Phone/Fax _____

Treating Physician Name _____ NPI # _____ Phone/Fax _____

Authorizing Physician Signature _____

Referring Pathologist Name _____ NPI # _____ Phone/Fax _____

Specimen Information

Specimen ID _____ Specimen Type _____ Block ID _____

Site of Biopsy _____ Primary or Metastasis _____

Collection Date and Time _____ Retrieved Date_____

Fixation Method _____ Fixation Duration _____

Billing Information

Bill to: ☐ Insurance ☐ Medicare ☐ Medicaid ☐ Patient Self Pay ☐ Direct Bill ☐ Other

Insurance Information _____

Billing contact information _____

Specimen Origin: ☐ Hospital In-Patient ☐ Hospital Out-Patient ☐ Non-Hospital Patient

This form is purely hypothetical and is not intended to be used in practice; content is based on guideline-recommended testing

DOB, date of birth; NPI, national provider identifier.

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HYPOTHETICAL TRF EXPLAINED BASIC INFORMATION

Patient Information lists basic identifying information for the patient

Clinical Information provides details on the disease, stage, and clinical history of the patient

Disease stage and number of prior therapies *are important details for the pathology team, as these may impact mutation status*[34-36]

The ability to include attachments of prior pathology results allows pathologists to see the most relevant and up-to-date information that may impact patient care[37]

Physician Information provides relevant contact information and a mailing address for results

Specimen Information communicates details about the specimen submitted for testing

Fixation method and duration *are important to note, as these factors may impact biomarker testing results*[38,39]

Test Requisition Form

Basic Information

Patient Information
Medical Record # _____ Name _____ Sex _____ DOB _____
Address _____ Phone Number _____

Clinical Information
Diagnosis / Diagnosis Code _____ Disease Stage _____
Number of Prior Therapies _____
Original Activating Mutation _____ Reason for Testing _____

Attachments: ☐ Pertinent Laboratory Results ☐ Test results from molecular assays

Physician Information
Requisition Completion Date _____ Completed By _____
Address (results will be sent to this address) _____

Ordering Physician Name _____ NPI # _____ Phone/Fax _____
Treating Physician Name _____ NPI # _____ Phone/Fax _____
Authorizing Physician Signature _____
Referring Pathologist Name _____ NPI # _____ Phone/Fax _____

Specimen Information
Specimen ID _____ Specimen Type _____ Block ID _____
Site of Biopsy _____ Primary or Metastasis _____
Collection Date and Time _____ Retrieved Date_____
Fixation Method _____ Fixation Duration _____

Billing Information
Bill to: ☐Insurance ☐Medicare ☐Medicaid ☐Patient Self Pay ☐Direct Bill ☐Other

Insurance Information _____
Billing contact information _____

Specimen Origin: ☐Hospital In-Patient ☐Hospital Out-Patient ☐Non-Hospital Patient

Billing Information provides important details for billing of the testing

Specimen origin and date of collection *may affect insurance coverage, particularly with Medicare*[40,41]

HYPOTHETICAL TRF TEST SELECTION

Test Requisition Form

Featured Oncology Testing

Cell-Free DNA (cfDNA)

☐ Single gene test 1

☐ Single gene test 2

☐ Panel test 1 (list number of genes included)

Replicate fields to reflect all cfDNA testing options available at your institution

Pan Tumor Marker 1

☐ Marker by PCR

☐ IHC for protein X

Pan Tumor Marker 2

☐ Marker 2 fusion hotspot panel

☐ Marker 2 pan-protein IHC

Programmed Death-Ligand 1 (PD-L1)

☐ PD-L1 antibody 1 IHC

☐ PD-L1 antibody 2 IHC

☐ Other PD-L1 antibody IHC

Can replicate fields to reflect current number of antibodies available

Solid Tumor NGS Panel*

☐ 359-gene hybrid capture NGS panel

DNA-based assay including all pan tumor markers including TMB as well as actionable markers in multiple disease states. Please see second page for full gene list.

Tumor-Specific Panels and Profiles*,†

†Profile options include all biomarkers linked to FDA-approved or contraindicated therapies, by tumor type (current as of June 2022).

☐ **Melanoma NGS panel**

50 gene hotspot NGS panel; includes all NCCN-recommended biomarkers

☐ **Lung NGS panel**

121 gene hybrid capture DNA NGS panel; includes all NCCN-recommended biomarkers (current as of January 2022)

☐ *Reflex to 15 gene hotspot assay if insufficient DNA for larger panel*

Replicate fields to reflect all reflex testing options at your institution.

☐ **Breast profile**

PCR and IHC; includes all NCCN-recommended biomarkers (current as of January 2022)

☐ *Reflex to FISH if HER equivocal*

Replicate fields to reflect all reflex testing options at your institution.

☐ **Colon profile**

PCR and IHC; includes all NCCN-recommended biomarkers except TMB (current as of January 2022)

☐ *Reflex to FISH if IHC is unclear*

Replicate fields to reflect all reflex testing options at your institution.

Replicate fields to reflect all reflex panels and profile testing options at your institution.

**For full gene list, see appendix.*

Tumor-Specific Panels and Profiles*,†

☐ ATM	☐ BARD1	☐ BRAF	☐ BRCA1	☐ BRCA2
☐ BRIP1	☐ CDK12	☐ CHEK1	☐ CHEK2	☐ EGFR

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HYPOTHETICAL TRF EXPLAINED TEST SELECTION

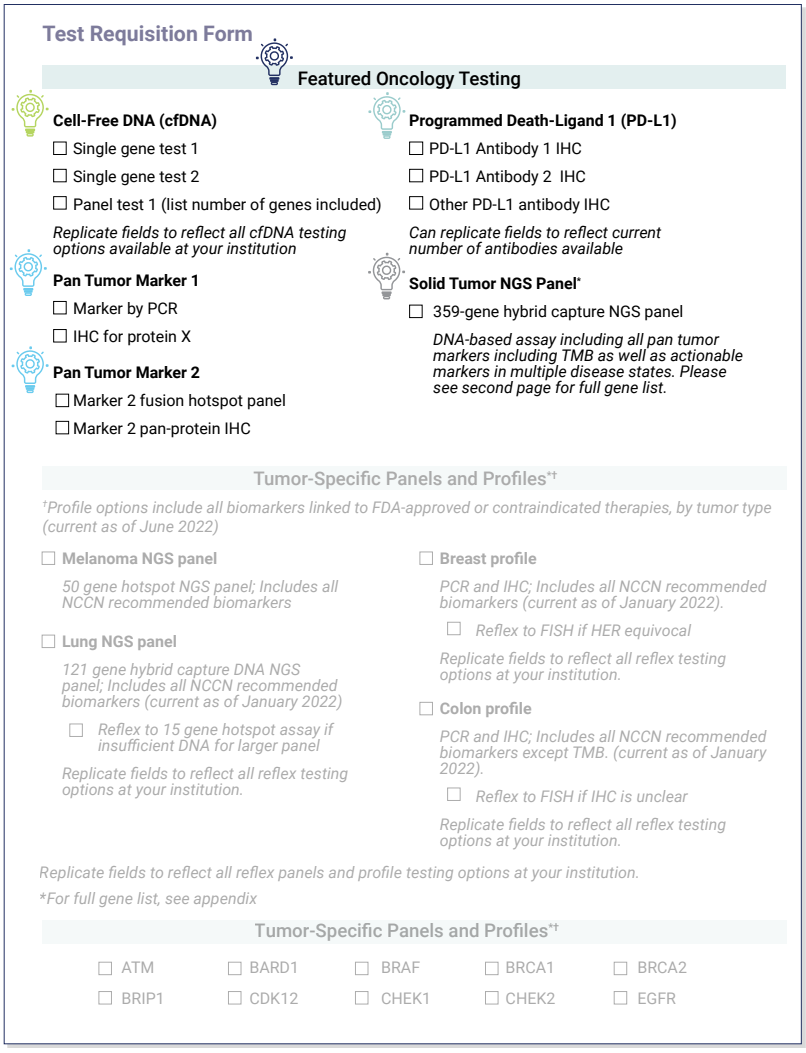
Featured Oncology Testing provides tests that inform the use of tumor agnostic therapeutics

cfDNA: *cfDNA can be used in single gene testing or in panel testing. All available options should be clearly listed. Reflex testing to tissue testing may be included in the order*[42,43]

PD-L1: *PD-L1 antibodies are associated with specific therapies and are not interchangeable.*[44,45] *Forms should list available options and, potentially, the associated therapy*

Pan-tumor markers: *Pan-tumor markers can be detected with multiple different methods. Each pan-tumor marker and the method(s) may be listed.*[1]

When different isoforms of the same gene function as the same biomarker, consider clarifying if the method can assess 1 isoform or all isoforms.[46,47]



Test Requisition Form

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- ☐ Marker by PCR
- ☐ IHC for protein X

Pan Tumor Marker 2

- ☐ Marker 2 fusion hotspot panel
- ☐ Marker 2 pan-protein IHC

Programmed Death-Ligand 1 (PD-L1)

- ☐ PD-L1 Antibody 1 IHC
- ☐ PD-L1 Antibody 2 IHC
- ☐ Other PD-L1 antibody IHC

Can replicate fields to reflect current number of antibodies available

Solid Tumor NGS Panel*

- ☐ 359-gene hybrid capture NGS panel

DNA-based assay including all pan tumor markers including TMB as well as actionable markers in multiple disease states. Please see second page for full gene list.

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☐ *Reflex to 15 gene hotspot assay if insufficient DNA for larger panel*

Replicate fields to reflect all reflex testing options at your institution.

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PCR and IHC; Includes all NCCN recommended biomarkers (current as of January 2022).

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**For full gene list, see appendix*

Tumor-Specific Panels and Profiles*†

☐ ATM ☐ BARD1 ☐ BRAF ☐ BRCA1 ☐ BRCA2
☐ BRIP1 ☐ CDK12 ☐ CHEK1 ☐ CHEK2 ☐ EGFR

Solid tumor NGS panel: *Because the ability to detect fusions in an NGS assay is impacted by the genes tested, nucleic acid input, and enrichment strategy, all pieces of information may be listed on the form.*[1,31] *Additionally, if the assay can detect TMB, it may also be explicitly stated. It is important to remember that TMB, which refers to the number of somatic mutations per megabase of DNA sequenced, can be influenced by the size of the panel, or assay coverage. The benchmark method to measure TMB is whole-exome sequencing. However, multigene panel-based sequencing with fewer genes (324-595 genes) can be used. Smaller panels cannot accurately estimate TMB*[1]

Finally, if using an outside vendor, consider including the name of the vendor along with aforementioned information.

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HYPOTHETICAL TRF EXPLAINED TEST SELECTION

Tumor-Specific Panels and Profiles: *Tumor specific panels and profiles allow physicians to assess a group of select biomarkers and genes that are relevant to different tumor types.*

To minimize confusion among providers, consider implementing ASCO definitions in forms (eg, a panel is an NGS assay of at least 50 genes)[1]

Reflex testing *can improve turnaround time by streamlining the ordering process. Incorporating it on the form provides ordering physicians the ability to select the most appropriate option for their patient.[7,48]*

Description of assays: *Biomarkers are constantly being added across disease states[49]; staying current is a well-established challenge.[24] Guideline recommendations can help practitioners stay current, but it is important to remember that guidelines may not reflect the most recent evidence, as advances may have occurred after a publication or update.[24,50] Therefore, incorporating details on guideline recommendations (and the associated guideline date) provides important context for the assay's clinical relevance. Complete gene lists may accompany TRFs on subsequent pages.[24]*

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Single Gene Testing Options *allow for the customized selection of individual genes of interest that may not be included in tumor-specific panels or profiles.*

PATHOLOGY REPORTS

The report is an essential part of the testing process. Incomplete, unclear, or missing reports can lead to incorrect patient management[51]

Electronic Record Compatibility

While pathologists may rely on a **laboratory information system (LIS)**, clinicians routinely use the **electronic health record (EHR)**.

- Interoperability of these systems varies across institutions[52]

Joint consensus from ASCO, CAP, and AMP[51]:
Pathology reports should be in a format that enables integration with the electronic health record

Common Reporting Pitfalls and Solutions

Reports are Lost / Missing in the EHR[24,53,54]:

- Reports may not be fully integrated into EHRs because of a lack of compatibility between LIS and EHR
- Pages may be lost when reports are scanned in the EHR

ACCC-Recommended Solutions[54]:

- 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

Multiple Reports are Generated at Different Times[52]:

- Confusion may result when several individual reports are created for each specimen or test ordered for a single patient

CAP-Recommended Solutions:

- Provide a single, comprehensive report

Addendum Reports[54]

- Biomarker test reports are often added as an addendum and may be missed if:
- Oncologists are not notified when addendum reports are added to the EHR
- Addendum reports are not linked to pathology reports in the EHR

CAP-Recommended Solutions[52]:

- Link the final pathology report to all subsequent addendum reports in the EHR
- When issuing the final report, pathologists should indicate that an addendum report is pending
- Utilize electronic notifications to alert clinicians that an addendum report has been entered into the chart
- Optimize the use of optical character recognition software to allow clinicians to search scanned reports using keywords

Challenging Reports[53-58]

- Narrative reports may be challenging to interpret quickly
- NGS reports may not state actionable genomic alterations, complicating interpretability
- Not every gene in an NGS report may be actionable
- Not every mutation in a driver gene is actionable

CAP-Recommended Solutions[51,52]:

- Use synoptic style reporting with layout continuity
- Use headlines to emphasize key findings
- Use clear and unambiguous nomenclature
- Provide patient management options, when possible, based on evidence

ASCO-Recommended Solutions:

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

Difficult to interpret or "lost" reports may lead to patients not receiving biomarker-informed care[24]

GENETIC REPORTS

Genomic Alterations: Drivers vs. variants of unknown significance (VUS)

Not every mutation in an oncogene or tumor suppressor gene is a driver mutation[1]

For example, the driver gene BRAF (shown below) may contain mutations that are considered driver alterations *(black)* or alterations not associated with oncogenesis *(gray)*[59]

If a patient is positive for an alteration, it is important to determine whether the alteration is clinically meaningful[51]

Categorizing Genomic Alterations[51]**:** A joint consensus from ASCO, CAP, and AMP

Alterations are categorized into four categories based on their clinical impact:

TIER I Variants of Strong Clinical Significance	TIER II Variants of Potential Clinical Significance	TIER III Variants of Unknown Clinical Significance	TIER IV Benign or Likely Benign Variants
Therapeutic, prognostic & diagnostic	*Therapeutic, prognostic & diagnostic*		
Level A Evidence FDA–approved therapy Included in professional guidelines **Level B Evidence** Well-powered studies with consensus from experts in the field	**Level C Evidence** FDA–approved therapies for different tumor types of investigational therapies Multiple small published studies with some consensus **Level D Evidence** Pre-clinical trials or a few case reports without consensus	Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variance databases No convincing published evidence of cancer association	Observed at significant allele frequency in the general or specific subpopulation databases No existing published evidence of cancer association

Joint consensus from ASCO, CAP, and AMP[51]**:**

Only tier I–III alterations should be included within a report; these should be listed in descending order of clinical importance

Databases Help Distinguish Actionable Driver Alterations

Several publicly available knowledge bases maintain up-to-date records that list driver alterations targeted by FDA-approved therapies. These include[1,60]:

The Memorial Sloan Kettering Cancer Center (MSK) OncoKB	MD Anderson Precision Oncology Decision Support (PODS)	The Catalogue of Somatic Mutations in Cancer (COSMIC)

The Impact of Variant Allele Frequency (VAF)

VAF corresponds to the proportion of genetic sequencing reads that harbor a specific allelic variant. VAF may be an indicator of the proportion of tumor cells that carry the variant.[1,61]

Somatic mutations generally have a VAF < 50% due to contaminating normal tissue. A VAF of ~50% or 100% may indicate a potential germline mutation[51]

Consider consulting a molecular tumor board (MTB) when needed.[62]
82 patients with solid tumors tested with NGS in a tertiary care center suggests that MTBs may help in appropriate and actionable clinical decision-making[63]

Joint consensus from ASCO, CAP, and AMP[51]:
VAF should be included in the report when appropriate[51]

Summary

Joint Consensus from ASCO, CAP, and AMP on Reporting Genetic Variants[51]

✓	**Classify alterations into tiers based on clinical impact** • Only include tier I-III alterations in the report
✓	**Provide a list of tested genes, including only those that were capable of being fully analyzed by assay used**
✓	**Prioritize clear communication** • Standard nomenclature should be used, in addition to colloquial nomenclature as needed, to convey meaning with clarity
✓	**Include relevant negative findings** • For tier I variants, pertinent negative results should be reported
✓	**Detail the clinical significance of detected variants** • For tier I and II variants, provide interpretive comments with clinicopathologic context to inform management decisions

GLOSSARY

ACCC, ASSOCIATION OF COMMUNITY CANCER CENTERS

AMP, ASSOCIATION FOR MOLECULAR PATHOLOGY

ASCO, AMERICAN SOCIETY OF CLINICAL ONCOLOGY

BRAF, V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1

CAP, COLLEGE OF AMERICAN PATHOLOGISTS

CNV, COPY NUMBER VARIATION

EHR, ELECTRONIC HEALTH RECORD

FDA, U.S. FOOD AND DRUG ADMINISTRATION

FISH, FLUORESCENCE IN-SITU HYBRIDIZATION

IHC, IMMUNOHISTOCHEMISTRY

LIS, LABORATORY INFORMATION SYSTEM

MDT, MULTIDISCIPLINARY TEAM

NGS, NEXT-GENERATION SEQUENCING

RT-PCR, REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION

SNV, SINGLE NUCLEOTIDE VARIANT

TRF, TEST REQUISITION FORM

VAF, VARIANT ALLELE FREQUENCY

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SUMMARY

Biomarker testing is fundamental to breast cancer care and is essential to guiding therapeutic decisions[85]

TRF format and layout vary and can impact biomarker ordering. Professional societies recommend:

- Reducing form variability and complexity[31,52]
- Ensure use of a common language[33,51]
- Keeping forms up-to-date[24]

Pathology reports are critical to ensure correct patient management. These reports should ideally be integrated into the EHR and should be as consolidated, clear, and synoptic as possible[52]

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