

The Ins and Outs of Test Requisition Forms



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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
<p>A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs</p>	<p>A gene that contains driver gene mutations or is expressed aberrantly in a fashion that confers a selective growth advantage</p>
<p>Not every mutation in an oncogene or tumor suppressor gene is a driver mutation.</p>	<p><i>Passenger mutations</i> have no direct or indirect effect on the selective growth advantage of the cell in which it occurred.</p>

Drivers Arise From Specific Genomic Alterations^{1,2}

Mutations

Single-Nucleotide Variation	<p>The substitution of one DNA nucleotide for another nucleotide (may be somatic/germline and synonymous/nonsynonymous)</p> <p>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</p>
Indel/Deletion-Insertion	<p>The replacement of more than one nucleotide by other nucleotides</p> <p>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</p>
Splice Site	<p>A mutation involving the conserved nucleotides at the exon-intron boundary that may disrupt RNA splicing</p> <p>May result in exon skipping, intron retention, frameshift, and premature protein truncation</p>
Extension	<p>The normal stop codon is lost, allowing translation to continue</p>
Truncating/Nonsense	<p>A premature stop codon is introduced</p>

Structural Variants

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

DETECTING GENOMIC ALTERATIONS

Biomarker Testing in Oncology Is Complex^{1,3}

As of June 2022, there are:

≥70

FDA-approved
biomarker-linked
indications

43

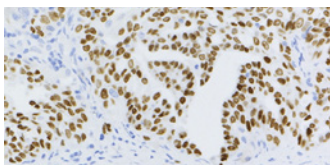
actionable
genomic
alterations

28

cancer types
treatable by
Precision Oncology

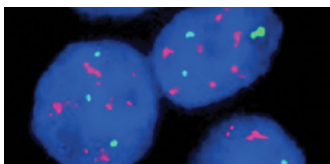


Single-Gene Testing



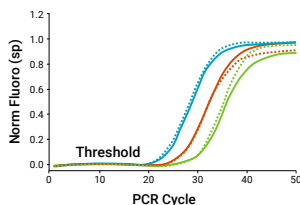
IHC: A test that uses an antibody to detect the expression, or loss of expression, of a specific protein or mutated protein form

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

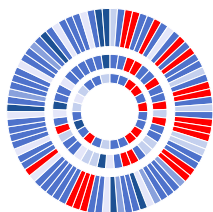
Can assess: *Rearrangements, CNVs*



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

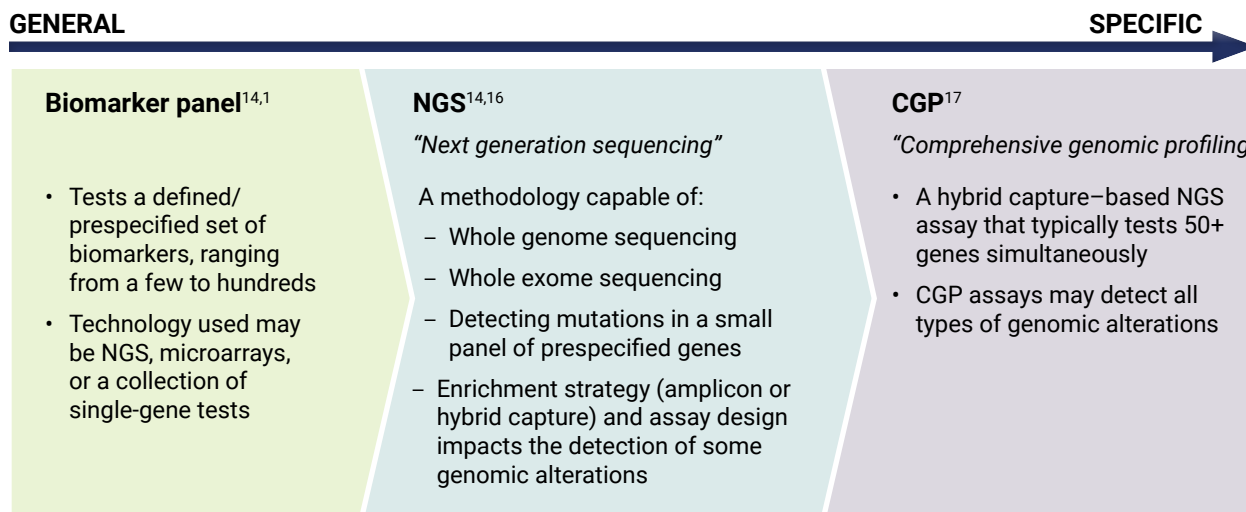
Can assess: *SNVs, indels, rearrangements, CNVs*

^aGenomic alterations and biomarkers tested will vary by assay.

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.



Additional Terms Explained

<p>Multigene Panel¹</p> <p>An NGS test that sequences a defined list of genes with at least 50 genes in total</p>	<p>VS</p>	<p>Hotspot Panel¹</p> <p>Sequencing select hotspot codons, which contain recurrently altered amino acids, for all genes on a panel</p>	<p>VS</p>	<p>Genetic Profile¹⁸</p> <p>General term referring to the information collected about specific genes, including variations and gene expression</p>
<p>SV¹</p> <p><i>“Structural variant”</i></p> <p>Large genomic alterations (> 50 bp) that typically contain CNVs, translocations, inversions, deletions, and/or insertions</p>	<p>VS</p>	<p>SNV¹</p> <p><i>“Single nucleotide variant”</i></p> <p>The substitution of one DNA nucleotide for another nucleotide</p>		
<p>CDx¹⁹</p> <p><i>“Companion diagnostic”</i></p> <p>A test approved by the FDA that provides information that is essential for the safe and effective use of a corresponding therapeutic product</p>	<p>VS</p>	<p>LDT²⁰</p> <p><i>“Laboratory developed test”</i></p> <p>A test that is designed, manufactured, and used within a single laboratory, but does not receive FDA oversight</p>		

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 documentation³¹



One community hospital system saw improvements in biomarker testing after creating a standard ordering process with minimal testing platforms to streamline laboratory processes³²

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 SOPs²⁴



Consider reviewing and incorporating recommendations from different guidelines at a cadence that keeps pace with updates²⁴

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.

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 status³⁴⁻³⁶

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 care³⁷



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 _____
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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 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}



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 TMB¹

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

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**

- | | | | | |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| <input type="checkbox"/> ATM | <input type="checkbox"/> BARD1 | <input type="checkbox"/> BRAF | <input type="checkbox"/> BRCA1 | <input type="checkbox"/> BRCA2 |
| <input type="checkbox"/> BRIP1 | <input type="checkbox"/> CDK12 | <input type="checkbox"/> CHEK1 | <input type="checkbox"/> CHEK2 | <input type="checkbox"/> EGFR |

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*[†]

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*For full gene list, see appendix.

Tumor-Specific Panels and Profiles*[†]

- | | | | | |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| <input type="checkbox"/> ATM | <input type="checkbox"/> BARD1 | <input type="checkbox"/> BRAF | <input type="checkbox"/> BRCA1 | <input type="checkbox"/> BRCA2 |
| <input type="checkbox"/> BRIP1 | <input type="checkbox"/> CDK12 | <input type="checkbox"/> CHEK1 | <input type="checkbox"/> CHEK2 | <input type="checkbox"/> EGFR |

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

PATHOLOGY REPORTS

The report is an essential part of the testing process. Incomplete, unclear, or missing reports can lead to incorrect patient management⁵¹

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 institutions⁵²



Joint consensus from ASCO, CAP, and AMP⁵¹:

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 Solutions⁵⁴:

- 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 Times⁵²:

- 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 Reports⁵⁴

- 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 Solutions⁵²:

- 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 Reports⁵³⁻⁵⁸

- 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 actionable¹

Difficult to interpret or “lost” reports may lead to patients not receiving biomarker-informed care²⁴

GENETIC REPORTS

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

Not every mutation in an oncogene or tumor suppressor gene is a driver mutation¹

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 meaningful⁵¹

Categorizing Genomic Alterations⁵¹: A joint consensus from ASCO, CAP, and AMP

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

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

Joint consensus from ASCO, CAP, and AMP⁵¹:
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)
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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 mutation⁵¹

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-making⁶³



Joint consensus from ASCO, CAP, and AMP⁵¹:

VAF should be included in the report when appropriate⁵¹

Summary

Joint Consensus from ASCO, CAP, and AMP on Reporting Genetic Variants⁵¹

- ✓ **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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