

Histology-Agnostic Therapies: Clinical Pearls for Practice



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One Drug Fits All: Emergence of Histology-Agnostic Treatments¹

- **Standard approach:** Treat cancers based on organ of origin (eg, gastric cancer and breast cancer are treated differently)
- **New approach:** Targeted drugs approved for certain biomarkers can be used to treat different cancer types with a shared molecular alteration (Figure 1)
- Biomarkers with histology-agnostic indications include microsatellite instability–high (MSI-H), mismatch repair deficient (dMMR), tumor mutational burden–high (TMB-H), *NTRK* fusions, *RET* fusions, and the *BRAF* V600E mutation (Table 1)

Figure 1. Pathway to histology-agnostic approval.

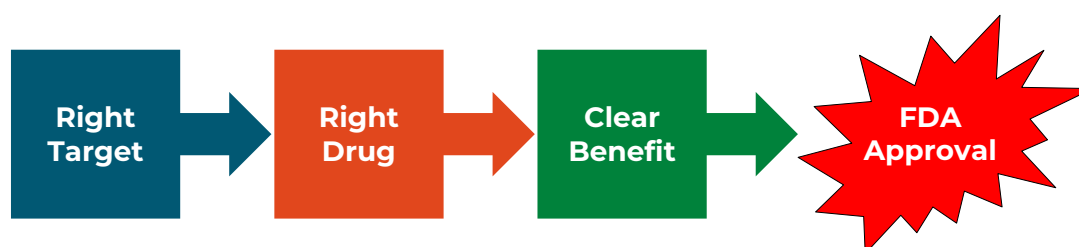


Table 1. Approved Histology-Agnostic Therapies²⁻⁷

Treatment	Histology-Agnostic Indication (Approval Date)	Key Supporting Trials	Response Rate, %
Pembrolizumab	• Unresectable/metastatic MSI-H or dMMR solid tumors that progressed after previous treatment with no satisfactory alternative treatment options (May 2017) • Unresectable/metastatic TMB-H (≥10 mut/Mb) solid tumors that progressed after previous treatment with no satisfactory alternative treatment options (June 2020)	• KEYNOTE-016, -164, -012, -028, -158 • KEYNOTE-158	40 (n = 59) 29 (n = 102)
Dostarlimab	• Recurrent/advanced dMMR solid tumors that progressed on or after previous treatment with no satisfactory alternative treatment options (August 2021)	• GARNET	42 (n = 209)
Entrectinib	• Unresectable/metastatic <i>NTRK</i> gene fusion–positive solid tumors without a known acquired resistance mutation that progressed after previous treatment or with no satisfactory alternative treatment options (August 2019)	• ALKA, STARTRK-1, STARTRK-2	57 (n = 54)
Larotrectinib	• Unresectable/metastatic <i>NTRK</i> gene fusion–positive solid tumors without a known acquired resistance mutation that progressed after previous treatment or with no satisfactory alternative treatment options (November 2018)	• LOXO-TRK-14001, SCOUT, NAVIGATE	75 (n = 55)
Dabrafenib + trametinib	• Unresectable/metastatic solid tumors with <i>BRAF</i> V600E mutation that progressed after previous treatment with no satisfactory alternative treatment options (June 2022)	• BRF117019, NCI-MATCH, BRF113928, CTMT212X2101, COMBI-d, COMBI-v	41 (n = 131)
Selpercatinib	• Locally advanced/metastatic solid tumors with a <i>RET</i> gene fusion that progressed on or after previous treatment or with no satisfactory alternative treatment options (September 2022)	• LIBRETTO-001	44 (n = 41)

The HER2-targeted antibody–drug conjugate trastuzumab deruxtecan is indicated across multiple HER2-altered tumor types⁸

- Unresectable/metastatic **HER2-positive breast cancer** after prior anti-HER2–based treatment either in the metastatic setting or in the neoadjuvant or adjuvant setting with disease recurrence ≤ 6 months of therapy
- Unresectable/metastatic **HER2-low breast cancer** after prior chemotherapy in the metastatic setting or disease recurrence ≤ 6 months of completing adjuvant chemotherapy
- Unresectable/metastatic **non-small-cell lung cancer (NSCLC) with activating HER2 mutations** after prior systemic therapy
- Locally advanced/metastatic **HER2-positive gastric or gastroesophageal junction adenocarcinoma** after prior trastuzumab-based therapy

Approaches to Tissue-Agnostic Biomarker Testing

- Comprehensive tissue-based testing platforms are available (Table 2), with substantial data supporting treatment selection across multiple tumor types (early and advanced stages of disease)⁹
- Multigene testing (eg, by next-generation sequencing [NGS]) facilitates the simultaneous detection of multiple biomarkers^{10,11}
 - Minimizes use of tumor tissue
 - Can be less costly overall
 - NGS testing platforms are often restricted to larger academic centers, with more complex analysis required
- Multigene testing should be performed in the following cases¹²
 - The tumor type has more than 1 biomarker-linked therapy
 - The tumor type has no approved biomarker-linked therapies
 - The patient is being evaluated for immunotherapy
- Single-gene testing may be routine in community practice, with good speed and sensitivity, as well as is required for biomarkers detected by IHC¹³
 - **CAUTION:** Tumor tissue samples are often inadequate for multiple tests, which may lead to repeat biopsy

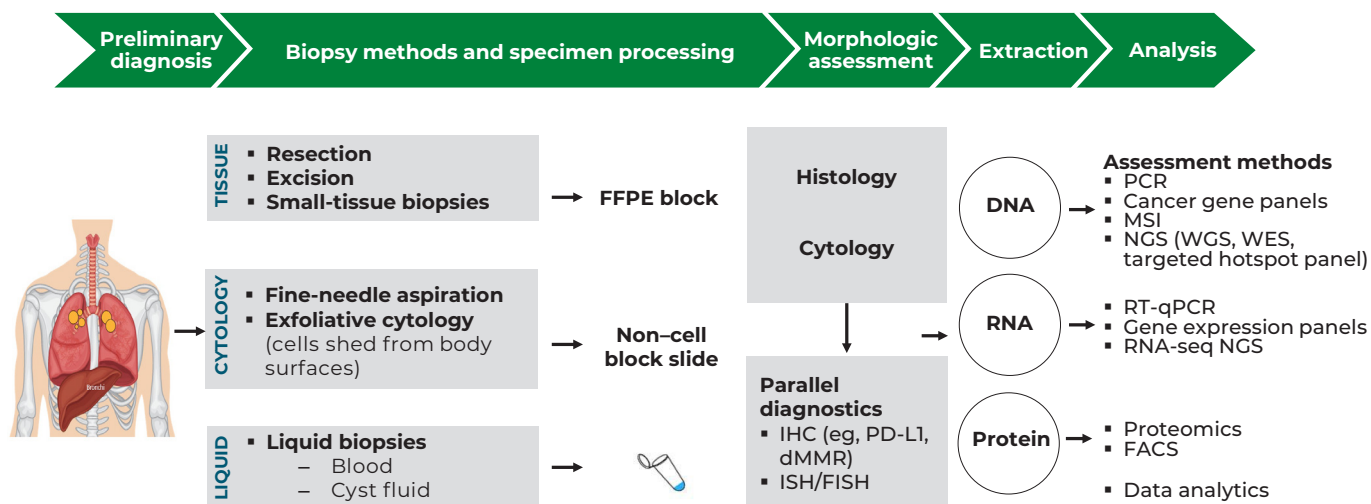
Table 2. Optimal Testing Approaches for Approved Histology-Agnostic Biomarkers^{12,14–17}

	IHC	FISH	RT-PCR	DNA NGS	RNA NGS
Advantages	✓ Rapid results ✓ Low cost as single test ✓ High sensitivity and specificity	✓ Rapid results ✓ Relatively inexpensive	✓ Fast, relatively inexpensive ✓ Qualitative or quantitative	✓ Potential for multiplexed testing ✓ Less depletion of tissue	✓ Potential for multiplexed testing ✓ Less depletion of tissue ✓ Identifies actively transcribed fusions
Disadvantages	– Tissue depletion – For gene fusions, partner and position unknown; potential for false negatives	– Tissue depletion – For gene fusions, partner and position unknown	– Low sensitivity – For gene fusions, no novel fusion partner detection; may or may not be multiplexed with other targets	– Longer wait time for results – May detect structural variants that do not result in fusion proteins	– Longer wait time for results
Approved Histology-Agnostic Biomarker	dMMR	N/A	N/A	MSI TMB BRAF V600E RET fusions	NTRK fusions RET fusions

Guidance on Specimens for Biomarker Testing

- Samples acceptable for testing: biopsy (primary tumor or metastasis), resection, ANY cytology (fine needle aspirate cell blocks OR smear preparations) (Figure 2)
- Optimal tissue collection and preservation are critical to maintain biochemical and nucleic acid integrity for accurate biomarker testing (Table 3)¹⁸
 - Fixation/processing¹⁹
 - FFPE: 10% buffered formalin
 - Alcohol-fixed cytology smears
 - Avoid acid-based decalcification. If decalcification is needed, alternative protocols (eg, EDTA) are recommended
 - Tumor purity is often more important than size of tissue, but amount of available tissue may limit ability to run multiple tests
- Liquid biopsy (ie, plasma cell-free DNA analysis) is an option for tumor types where there is sufficient shedding of tumor DNA (eg, lung cancer)^{20,21}
 - Sample acquisition is minimally invasive
 - Contains cell-free DNA shed from multiple sources, including DNA shed from tumor
 - Captures both primary tumor and metastatic sites, with the potential to overcome intratumoral heterogeneity
 - A negative result with liquid biopsy is uninformative and should be confirmed with a tissue biopsy
- **IMPORTANT: Assay needs to be validated for the type of sample used**

Figure 2. Tissue journey: biopsy to analysis.²²



FACS, fluorescence-activated cell sorting; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; ISH, in situ hybridization; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Table 3. Best Practices for Biopsy Sample Collection

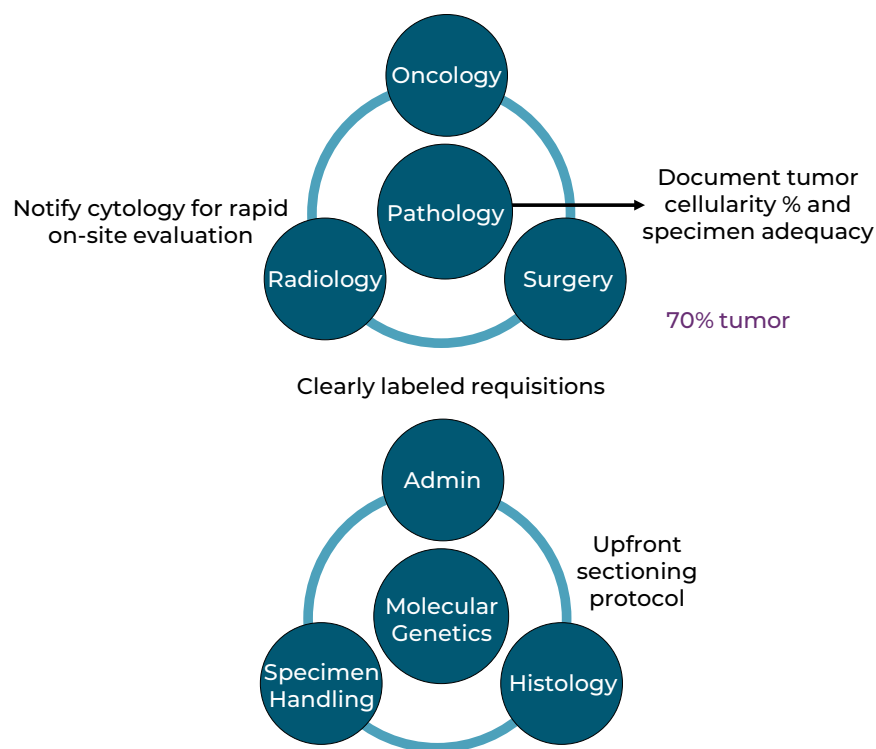
	Cell Blocks	Direct Smears	Liquid-Based Cytology	Surgical Biopsy
Performance in molecular diagnostics	✓	✓✓	✓✓*	✓
On-site assessment	—	✓	—	✓
Fixative	Formalin	Alcohol	Variable	Formalin
Nuclei preservation (FISH)	—	✓	✓	—
Slide-based record retained	✓	—	—	✓

*Archival liquid-based cytology specimens inferior to archival direct smears.

Strategies to Improve Biomarker Testing

- It is important to use testing centers that adhere to the highest standards of laboratory quality to ensure accuracy and reliability of testing processes, including key elements in reports to unambiguously convey molecular results²³
- Clear communication between departments involved in all aspects of biomarker testing is critical (Figure 3)¹⁸
 - Medical oncology and interventionalists (eg, radiology, pulmonary) to ensure sufficient tissue
 - Medical oncology, radiology, and pathologists to conserve tissue
 - Clearly labeled requisitions
 - Standardized indication terminology
 - Active lines of email or phone communication
- Educate technical staff on specimen handling and colleagues who may not regularly engage with molecular diagnostics
- Institutional considerations
 - Consider reflex testing to shorten the time from biopsy to result²⁴
 - The pathologist orders biomarker testing at the time of metastatic diagnosis
 - Consider rapid on-site cytology in biopsy area²⁵

Figure 3. Biomarker testing: best practices for communication.¹⁸



Future Directions in Histology-Agnostic Therapies

- Various histology-agnostic therapies are under investigation in patients with biomarker-positive cancers who are ineligible for or refractory to current standard-of-care therapies (Table 3)

Table 3. Select Ongoing Trials for Histology-Agnostic Therapies in Metastatic/Advanced Solid Tumors

Trial	Phase	Planned N	Histology-Agnostic Therapy	Biomarker+ Population	Primary Endpoint
TAPISTRY (NCT04589845)	II	770	- Entrectinib - Entrectinib - Alectinib - Atezolizumab - Ipatasertib - TDM-1 - Idasanutlin - Inavolisib - Belvarafenib - Belvarafenib - Pralsetinib	<i>ROS1</i> fusion+ tumors (no NSCLC) <i>NTRK1/2/3</i> fusion+ tumors <i>ALK</i> fusion+ tumors (no NSCLC) - TMB-H tumors <i>AKT1/2/3</i> mutant+ tumors <i>HER2</i> mutant+ tumors - MDM2 amplified, <i>TP53</i> wild-type tumors[†] <i>PIK3CA</i> multiple mutant+ tumors <i>BRAF</i> class II mutant+ or fusion+ tumors <i>BRAF</i> class III mutant+ tumors <i>RET</i> fusion+ tumors	ORR by IRC
IMPARP-HRD (NCT04985721)	II	60	Pamiparib + tiselizumab	HRD+ tumors (germline and/or somatic except no germline <i>BRCA1/2</i> mutations); no prior PARPi tx	CBR
EMERGE-201 (NCT05126433)	II	60*	Lurbinectedin (histology-agnostic arm)	HRD+ tumors (germline and/or somatic)	ORR by inv
PRECISION 1 (NCT05103358)	II	120	Nab-sirolimus	<i>TSC1</i> or <i>TSC2</i> mTOR pathway inactivating alterations; no prior mTORi tx	ORR
DETERMINE (NCT05722886)	II/III	825	- Alectinib - Atezolizumab - Entrectinib - Trastuzumab + pertuzumab - Vemurafenib + cobimetinib	<i>ALK</i>+ tumors - TMB-H, MSI-H, or diagnosed CMMRD tumors (no UC, NSCLC, ES-SCLC, HCC, or TNBC) <i>ROS1</i> fusion+ tumors (no <i>ROS1</i> mutant+ NSCLC) <i>HER2</i> amplified or <i>HER2</i> mutant+ tumors (no <i>HER2</i>+ BC) <i>BRAF</i> V600E+ tumors (no <i>BRAF</i> V600+ melanoma)	ORR, DCB
CRESTONE (NCT04383210) [§]	II	75	Seribantumab	<i>NRG1</i> fusion+ tumors	ORR
eNRGy (NCT02912949)	II	250	Zenocutuzumab	<i>NRG1</i> fusion+ tumors	ORR by inv, DoR by inv
NCT04410653	II	60	Afatinib	<i>NRG1</i> fusion+ tumors	DCR

CBR, clinical benefit rate; CMMRD, constitutional mismatch repair deficiency; DCB, durable clinical benefit; HRD, homologous recombination deficiency; HR+, hormone receptor positive; IRC, independent review committee; inv, investigator; ORR, overall response rate.

*Histology-agnostic arm is one of 3 planned arms (other arms: urothelial cancer and poorly differentiated neuroendocrine carcinoma).

[†]Closed for enrollment. [‡]Endometrial, urothelial, triple-negative breast cancer, HR+/HER2- breast cancer, biliary tract, pancreatic, gastric, or esophageal solid tumors. [§]Active, not recruiting.

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