



DLL3 Pathology Assessment & Reporting Checklist



Before Ordering DLL3 Immunohistochemistry (IHC)

Diagnosis and Specimen Readiness

- ✓ Confirm a diagnosis of poorly differentiated neuroendocrine carcinoma (NEC) via morphology and established markers.¹⁻³
- ✓ Confirm the requested delta-like ligand 3 (DLL3) testing aligns with the clinical question (eg, advanced disease, biomarker evaluation, or clinical trial screening).^{4,5}
- ✓ Review prior pathology reports and ancillary studies.⁶
- ✓ Confirm adequate and viable tumor tissue is available and sufficient for DLL3 testing.⁷⁻⁹
- ✓ Assess tissue quality for:^{3,8,10,11}
 - Necrosis
 - Crush artifact
 - Adequate tumor preservation and appropriate fixation time
 - Low cellularity
 - Background staining

Consider tissue stewardship practices if additional biomarker or molecular testing may be required.^{5,7}



IHC Interpretation

Evaluate the Correct Tumor Population

- ✓ Confirm which tumor component is being evaluated:¹²
 - Pure NEC
 - Mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN)
 - Metastatic lesion
- ✓ Evaluate and score the neuroendocrine carcinoma component separately when appropriate.¹²
- ✓ Correlate staining with morphology and established neuroendocrine markers.^{1,2,8}
- ✓ Confirm appropriate positive and negative controls.¹¹
- ✓ Use a laboratory-validated assay performed according to institutional protocols.¹¹
- ✓ Ensure sufficient viable tumor cells are visible for reliable assessment before scoring.⁷
- ✓ Exclude:⁸
 - Necrotic debris
 - Crushed cells
 - Edge artifact
 - Inflammatory cells
 - Nonspecific background staining



DLL3 IHC Scoring

Document the Required Features

- ✓ Record percentage of evaluable tumor cells staining positive.^{3,8}
- ✓ Document staining intensity according to assay-specific scoring criteria.¹¹
- ✓ Assess staining localization according to assay methodology:⁸
 - Membranous
 - Cytoplasmic
 - Combined
- ✓ Note heterogeneous staining, if present.⁸
- ✓ Apply the appropriate assay- or study-specific scoring algorithm.^{3,8,13}

Scoring reminder: “DLL3-positive” and “DLL3-high” are not interchangeable.

Always apply the scoring system specified by the assay or clinical study. Because DLL3 IHC assays, scoring algorithms, and positivity thresholds continue to evolve, interpretation should follow the assay used and its intended clinical application.^{3,4,8,13}



Reporting

Communicate Results Clearly

To aid clinician interpretation, ensure standardized reporting of:

- Assay, antibody clone, and platform^{6,8}
- Specimen tested⁶
- Scoring methodology^{3,6,8}
- Expression threshold or cutoff used^{4,8,13}
- Final expression category:^{3,8}
 - DLL3-positive
 - DLL3-high
 - Other assay-specific designation
- Interpretation statement^{6,13}

Document any factors that may affect interpretation:^{8,11}

- Small biopsy or limited tumor volume
- Poor preservation
- Suboptimal or heterogeneous staining
- Artifact
- Necrosis

Practical Takeaways:

Establish the NEC diagnosis before interpreting DLL3.¹⁻³

Assess DLL3 protein expression by IHC; DLL3 expression is not measured by next-generation sequencing.^{7,8}

Report the assay and scoring methodology—not simply “positive” or “negative.”^{3,6,8}

Interpret DLL3 results within the appropriate clinical context.^{4,13}

Consider the emerging need for standardized DLL3 reporting as DLL3-directed therapies evolve.^{6,8,13}

References

1. Hadoux et al. *ESMO Open*. 2024;9(10):103664.
2. Pavel et al. *Ann Oncol*. 2020;31(7):844-860.
3. Schmitt et al. *Endocr Pathol*. 2025;36:9.
4. Pavel et al. *J Clin Oncol*. 2026;44(suppl 7):TPS2.
5. Robinson et al. *Ther Adv Med Oncol*. 2023;15:17588359231156870.
6. Hayes. *Mol Oncol*. 2015;9(5):960-966.
7. Hofman et al. *Cancers (Basel)*. 2018;10(3):70.
8. Serrano et al. *NPJ Precis Oncol*. 2024;8:268.
9. Dong et al. *J Thorac Dis*. 2017;9(8):2375-2382.
10. de Matos et al. *Biomark Insights*. 2010;5:9-20.
11. O'Hurley et al. *Mol Oncol*. 2014;8(4):783-798.
12. La Rosa. *Endocr Pathol*. 2021;32(2):245-257.
13. Peddio et al. *Crit Rev Oncol Hematol*. 2024;204:104524.

