**Protocol for the Examination of Specimens from Patients with Paraganglioma and Pheochromocytoma**

**Version:** 1.0.0.0

**Protocol Posting Date:** March 2025

**CAP Laboratory Accreditation Program Protocol Required Use Date:** December 2025

The use of this protocol is required for accreditation purposes for both sympathetic and parasympathetic paragangliomas, pheochromocytomas, composite paragangliomas and composite pheochromocytomas.

**For accreditation purposes, this protocol should be used for the following procedures AND tumor types:**

|  |  |
| --- | --- |
| **Procedure** | **Description** |
| Resection | Adrenalectomy and Extra-adrenal tumor (paraganglioma) excision |
| **Tumor Type** | **Description** |
| Tumors of the adrenal medulla and extra-adrenal paraganglia | Pheochromocytoma (adrenal paraganglioma), extra-adrenal paragangliomas from all anatomic sites, composite paraganglioma, composite pheochromocytoma |

**The following tumor types should NOT be reported using this protocol:**

|  |
| --- |
| **Tumor Type** |
| Neuroblastic tumors |
| Peripheral nerve sheet tumors |
| Cauda equina neuroendocrine tumor (formerly known as cauda equine paraganglioma) |
| Composite gangliocytoma/neuroma and neuroendocrine tumor-COGNET (formerly known as gangliocytic paraganglioma) |

**Version Contributors**

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**Glossary:**

**Author:** Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.

**Expert Contributors:** Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

**Accreditation Requirements**

Synoptic reporting with core and conditional data elements for designated specimen types is required for accreditation.

* Data elements designated as core must be reported.
* Data elements designated as conditional only need to be reported if applicable.
* Data elements designated as optional are identified with “+”. Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under [Accreditation Checklists](https://www.cap.org/laboratory-improvement/accreditation/accreditation-checklists).

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols [website](https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates).

**Synoptic Reporting**

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

* Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
* The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
* Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  + Anatomic site or specimen, laterality, and procedure
  + Pathologic Stage Classification (pTNM) elements
  + Negative margins, as long as all negative margins are specifically enumerated where applicable
* The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
* Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

**Summary of Changes**

**v 1.0.0.0**

* New protocol

**Reporting Template**

**Protocol Posting Date:** March 2025

**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (Paraganglioma and Pheochromocytoma)**

**Standard(s)**: AJCC 8

**CLINICAL (Note** [**A**](#N14477)**)**

**+Clinical History (select all that apply)**

\_\_\_ Family history of paraganglioma / pheochromocytoma or genetic syndrome (specify):

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Personal history of paraganglioma / pheochromocytoma or genetic syndrome (specify):

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Functional Status**

\_\_\_ Biochemically functioning

*Select all that apply*

\_\_\_ Metanephrine and / or adrenaline

\_\_\_ Normetanephrine and / or noradrenaline

\_\_\_ 3-Methoxytyramine and / or dopamine

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Nonfunctional (biochemically non-functioning)

\_\_\_ Biochemical analysis not performed

\_\_\_ Not known (no information provided)

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Tumor Scintigraphy or PET Avidity (select all that apply)**

\_\_\_ DOTATATE or DOTATOC PET

\_\_\_ 123I-metaiodobenzylguanidine (MIBG) scintigraphy

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Anatomic Location from Imaging (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**+Tumor Size from Imaging Studies**

\_\_\_ Greatest dimension of tumor size from imaging studies in Centimeters (cm): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

**+Additional Dimension of Tumor Size from Imaging Studies in Centimeters (cm): \_\_\_\_ x \_\_\_\_**

**cm**

**Greatest Dimension of Second Dominant Tumor from Imaging Studies in Centimeters (cm)**

**(required only if multifocal): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm**

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**SPECIMEN (Note** [**B**](#N14478)**)**

**Procedure**

\_\_\_ Right adrenalectomy

\_\_\_ Left adrenalectomy

\_\_\_ Bilateral adrenalectomy

\_\_\_ Adrenalectomy, NOS

\_\_\_ Extra-adrenal excision (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**+Specimen Integrity**

\_\_\_ Intact

\_\_\_ Fragmented

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**TUMOR (Notes** [**C**](#N14479)**,** [**D**](#N14480)**)**

**Tumor Number (Note** [**C**](#N14479)**)**

\_\_\_ Unifocal

\_\_\_ Multifocal

**+Specify Number of Tumors: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Location (Note** [**C**](#N14479)**)**

\_\_\_ Intra-adrenal

\_\_\_ Extra-adrenal (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Tumor Size (Note** [**C**](#N14479)**)**

\_\_\_ Greatest dimension in Centimeters (cm): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

**+Additional Dimension in Centimeters (cm): \_\_\_\_ x \_\_\_\_ cm**

**Greatest Dimension of Second Dominant Tumor in Centimeters (cm) (required only if**

**multifocal): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm**

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Histologic Type(s) (Note** [**C**](#N14479)**)**

\_\_\_ Paraganglioma

\_\_\_ Pheochromocytoma (adrenal paraganglioma)

\_\_\_ Micro-pheochromocytoma (subcentimeter adrenal paraganglioma)

\_\_\_ Composite paraganglioma

\_\_\_ Paraganglioma and ganglioneuroma, mature

\_\_\_ Paraganglioma and ganglioneuroma, maturing

\_\_\_ Paraganglioma and ganglioneuroblastoma, intermixed type

\_\_\_ Paraganglioma and ganglioneuroblastoma, nodular type

\_\_\_ Paraganglioma and neuroblastoma, undifferentiated type

\_\_\_ Paraganglioma and neuroblastoma, poorly differentiated type

\_\_\_ Paraganglioma and neuroblastoma, differentiating type

\_\_\_ Paraganglioma and neuroblastic tumor, NOS

\_\_\_ Paraganglioma and malignant peripheral nerve sheath tumor

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Composite pheochromocytoma

\_\_\_ Pheochromocytoma and ganglioneuroma, mature

\_\_\_ Pheochromocytoma and ganglioneuroma, maturing

\_\_\_ Pheochromocytoma and ganglioneuroblastoma, intermixed type

\_\_\_ Pheochromocytoma and ganglioneuroblastoma, nodular type

\_\_\_ Pheochromocytoma and neuroblastoma, undifferentiated type

\_\_\_ Pheochromocytoma and neuroblastoma, poorly differentiated type

\_\_\_ Pheochromocytoma and neuroblastoma, differentiating type

\_\_\_ Pheochromocytoma and neuroblastic tumor, NOS

\_\_\_ Pheochromocytoma and malignant peripheral nerve sheath tumor

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other histologic type not listed (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Histologic Type(s) of Additional Tumors (required only if multiple tumors present) (select all**

**that apply)**

\_\_\_ Not applicable (multiple tumors not present)

\_\_\_ Paraganglioma

\_\_\_ Pheochromocytoma (adrenal paraganglioma)

\_\_\_ Micro-pheochromocytoma (subcentimeter adrenal paraganglioma)

\_\_\_ Composite paraganglioma

\_\_\_ Paraganglioma and ganglioneuroma, mature

\_\_\_ Paraganglioma and ganglioneuroma, maturing

\_\_\_ Paraganglioma and ganglioneuroblastoma, intermixed type

\_\_\_ Paraganglioma and ganglioneuroblastoma, nodular type

\_\_\_ Paraganglioma and neuroblastoma, undifferentiated type

\_\_\_ Paraganglioma and neuroblastoma, poorly differentiated type

\_\_\_ Paraganglioma and neuroblastoma, differentiating type

\_\_\_ Paraganglioma and neuroblastic tumor, NOS

\_\_\_ Paraganglioma and malignant peripheral nerve sheath tumor

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Composite pheochromocytoma

\_\_\_ Pheochromocytoma and ganglioneuroma, mature

\_\_\_ Pheochromocytoma and ganglioneuroma, maturing

\_\_\_ Pheochromocytoma and ganglioneuroblastoma, intermixed type

\_\_\_ Pheochromocytoma and ganglioneuroblastoma, nodular type

\_\_\_ Pheochromocytoma and neuroblastoma, undifferentiated type

\_\_\_ Pheochromocytoma and neuroblastoma, poorly differentiated type

\_\_\_ Pheochromocytoma and neuroblastoma, differentiating type

\_\_\_ Pheochromocytoma and neuroblastic tumor, NOS

\_\_\_ Pheochromocytoma and malignant peripheral nerve sheath tumor

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other histologic type not listed (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Histologic Type Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Tumor Necrosis (Note** [**C**](#N14479)**)**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Angioinvasion (vascular invasion) (Note** [**C**](#N14479)**)**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Lymphatic Invasion (Note** [**C**](#N14479)**)**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Extent (Note** [**C**](#N14479)**) (select all that apply)**

\_\_\_ Tumor confined to adrenal with no adrenal capsule invasion or no peritumoral soft tissue invasion

\_\_\_ Adrenal capsule invasion without extra-adrenal tumor spread

\_\_\_ Peri-adrenal or peri-tumoral soft tissue invasion

\_\_\_ Adjacent organ / tissue invasion (e.g., liver, pancreas, spleen, kidney) (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Proliferative Activity (Note** [**D**](#N14480)**)**

**Ki-67 Labeling Index#**

*# The Ki-67 proliferation assessment should follow the IARC / WHO guidelines. Visual estimation based on routine*

*microscopic examination (also known as eyeballing) is not allowed.*

\_\_\_ Specify Ki-67 percentage: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ %

**Ki-67 Methodology**

\_\_\_ Manual count

\_\_\_ Automated image analysis

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Pending (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Mitotic Count**

\_\_\_ Specify number of mitoses per 2 mm2: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ mitoses per 2 mm2

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**MARGINS**

**Margin Status**

\_\_\_ All margins negative for tumor

**+Distance from Tumor to Closest Margin**

*Specify in Millimeters (mm)*

\_\_\_ Exact distance: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ mm

\_\_\_ At least: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ mm

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Tumor present at margin

**Margin(s) Involved by Tumor**

\_\_\_ Specify involved margin(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Margin Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**REGIONAL LYMPH NODES**

**Regional Lymph Node Status**

\_\_\_ Not applicable (no regional lymph nodes submitted or found)

\_\_\_ Regional lymph nodes present

\_\_\_ All regional lymph nodes negative for tumor

\_\_\_ Tumor present in regional lymph node(s)

**Number of Lymph Nodes with Tumor**

\_\_\_ Exact number (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ At least (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Number of Lymph Nodes Examined**

\_\_\_ Exact number (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ At least (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Regional Lymph Node Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**DISTANT METASTASIS (Note** [**E**](#N14481)**)**

**Distant Site(s) Involved, if applicable (select all that apply)**

\_\_\_ Not applicable

\_\_\_ Bone: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Liver: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Lung: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**pTNM CLASSIFICATION (AJCC 8th Edition) (Note** [**F**](#N14482)**)**

*Applied to all sympathetic paragangliomas and pheochromocytomas. Currently there is no defined TNM Classification for parasympathetic paragangliomas and composite paragangliomas / pheochromocytomas but users can apply the TNM staging below (based on the tumor size cutoff of 5 cm and the status of invasion) to facilitate uniform data collection.*

*Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician’s responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.*

**Modified Classification (required only if applicable)  (select all that apply)**

\_\_\_ Not applicable

\_\_\_ y (post-neoadjuvant therapy)

\_\_\_ r (recurrence)

**pT Category**

\_\_\_ pT not assigned (cannot be determined based on available pathological information)

\_\_\_ pT1: Pheochromocytoma less than 5 cm in greatest dimension, no extra-adrenal invasion

\_\_\_ pT2: Pheochromocytoma greater than or equal to 5 cm or paraganglioma-sympathetic of any size, no

extra-adrenal invasion

\_\_\_ pT3: Tumor any size with invasion into surrounding organs / tissues (e.g., liver, pancreas, spleen,

kidneys)

**T Suffix (required only if applicable)**

\_\_\_ Not applicable

\_\_\_ (m) multiple primary synchronous tumors in a single organ

**pN Category**

\_\_\_ pN not assigned (no nodes submitted or found)

\_\_\_ pN not assigned (cannot be determined based on available pathological information)

\_\_\_ pN0: No lymph node metastasis

\_\_\_ pN1: Regional lymph node metastasis

**pM Category (required only if confirmed pathologically)**

\_\_\_ Not applicable - pM cannot be determined from the submitted specimen(s)

*pM1: Distant metastasis*

\_\_\_ pM1a: Distant metastasis to only bone

\_\_\_ pM1b: Distant metastasis to only distant lymph nodes / liver or lung

\_\_\_ pM1c: Distant metastasis to bone plus multiple other sites

\_\_\_ pM1 (subcategory cannot be determined)

**ADDITIONAL FINDINGS (Note** [**G**](#N14484)**)**

**Adrenal Medullary Hyperplasia (required for all adrenalectomy specimens)**

\_\_\_ Not applicable

\_\_\_ Present

\_\_\_ Absent

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Additional Findings (select all that apply)**

\_\_\_ None identified

\_\_\_ Other tumors (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**SPECIAL STUDIES (Note** [**H**](#N14483)**)**

**+Keratins (e.g., low molecular weight keratin, AE1 / AE3)**

\_\_\_ Positive (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Negative

**+Chromogranin-A**

\_\_\_ Positive

\_\_\_ Negative

**+Tyrosine Hydroxylase**

\_\_\_ Positive

\_\_\_ Negative

**+GATA3**

\_\_\_ Positive

\_\_\_ Negative

**+S100 and / or SOX10-positive Sustentacular Cell Network**

\_\_\_ Present

\_\_\_ Not identified

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+SDHB**

\_\_\_ Loss (deficient)

\_\_\_ Retained (normal staining)

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Alpha-inhibin**

\_\_\_ Positive

\_\_\_ Negative

**+CAIX**

\_\_\_ Positive

\_\_\_ Negative

**+FH**

\_\_\_ Loss (deficient)

\_\_\_ Retained (normal staining)

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+2-SC**

\_\_\_ Positive

\_\_\_ Negative

**+ATRX**

\_\_\_ Loss (deficient)

\_\_\_ Retained (normal staining)

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Other Markers (repeat this section for up to 10 markers)**

**+Other Marker (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Specify Results: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**COMMENTS**

**Comment(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Explanatory Notes**

**A. Clinical**

Paraganglia are neural crest-derived neuroendocrine organs that produce predominantly catecholamines (dopamine, norepinephrine and epinephrine).[1,](#R67446)[2,](#R67447)[3](#R67448) Paraganglia are typically divided into two groups based on parasympathetic or sympathetic nervous system origin. Sympathetic paraganglia are further divided into two subgroups: the adrenal medulla, so-called “sympathoadrenal paraganglia” and extra-adrenal sympathetic paraganglia.[1,](#R67446)[2,](#R67447)[3](#R67448) The anatomic site impacts the nomenclature of tumors arising from paraganglia; while tumors arising from the adrenal medulla are termed “pheochromocytomas or adrenal paragangliomas”, tumors arising from extra-adrenal locations are called “paragangliomas (PGLs)” regardless of their sympathetic or parasympathetic origins.[1,](#R67446)[2,](#R67447)[3,](#R67448)[4](#R67449) Pheochromocytomas and paragangliomas are collectively referred to PPGLs in the medical literature.

The etiology of most sporadic PGLs including pheochromocytomas is not known. However, it is now well-recognized that at least 40% of these tumors in adults are hereditary.[1,](#R67446)[2,](#R67447)[3,](#R67448)[4,](#R67449)[5,](#R67450)[6,](#R67451)[7](#R67452) caused by germline variants of at least 23 genes. Hereditary pheochromocytomas and extra-adrenal PGLs (PPGLs) arising in patients with different genotypes have characteristic distributions and biochemical profiles and different likelihoods of metastasis.[1,](#R67446)[2,](#R67447)[3,](#R67448)[4,](#R67449)[5,](#R67450)[6](#R67451) In addition, a widening spectrum of associated tumors — including but not limited to gastrointestinal stromal tumors, renal cell carcinomas, and pituitary neuroendocrine tumors — are associated with multiple hereditary tumor syndromes. Discoveries of new susceptibility genes and genotype-phenotype correlations have led to the realization that individual patient care requires a complete integration of clinical, genetic, biochemical, imaging, and pathology findings. [2](#R67447) While most patients lack family history, the identification of personal or family history of PPGL is often regarded a sign of hereditary disease in these neoplasms.

While pheochromocytomas and the majority of sympathetic PGLs are often associated with clinical symptoms, only a small percentage of parasympathetic PGLs are clinically symptomatic.[1,](#R67446)[8](#R67453) The functional status of a PPGL should be based on the biochemical status of the tumor. Specific genotype-biochemical correlations highlight the importance of laboratory testing to characterize patterns of catecholamine excess. Since catecholamines (dopamine, norepinephrine, and epinephrine) are not continuously secreted in normal physiology, biochemical testing for the O-methylated metabolites of dopamine, norepinephrine and epinephrine (3-methoxytyramine, normetanephrine and metanephrine, respectively) in plasma and/or urine is superior to measurement of the parent catecholamines.[3](#R67448)

Progress in molecular biology has established genotype-phenotype correlations in PPGLs with respect to anatomic tumor distribution (e.g., intra-adrenal vs extra-adrenal), catecholamine production and risk of metastasis.[2,](#R67447)[3,](#R67448)[4](#R67449) For instance, functional *VHL*-driven PPGLs tend to be associated with norepinephrine excess whereas functional *SDHx*-related PPGLs can be associated with either mixed dopamine and norepinephrine or dopamine excess.[1,](#R67446)[2,](#R67447)[3,](#R67448)[4,](#R67449)[9](#R67454). *RET*-, *NF1*-, *TMEM127*- and *MAX*-related PPLs are associated with epinephrine production.[1,](#R67446)[2,](#R67447)[3,](#R67448)[4](#R67449) Moreover, the risk of malignancy is increased in tumors with immature secretory phenotype characterized by the absence of epinephrine excess (e.g., *SDHB*-related PPGLs). *SDHB*-related tumors are more frequently observed in extra-adrenal locations and can reach larger tumor sizes with much lower tissue concentrations of catecholamines than other PGLs.[3](#R67448) These data are of clinical significance in that integration of the biochemical profile with other information, such as tumor location and dimensions, becomes an important part of comprehensive synoptic reporting. Similar to epithelial neuroendocrine neoplasms, PPGLs can produce and secrete other peptides that occasionally cause clinical hormone excess syndromes.[8,](#R67453)[10](#R67455)

Somatostatin receptor-based functional imaging techniques have revolutionized our ability to image neuroendocrine neoplasms including PPGLs. Functional imaging with radiotracers such as 123/131I-metaiodobenzylguanidine (123/131I-MIBG) have long been recognized as integral components in the diagnostic and therapeutic planning of patients with PPGLs.[11](#R67456) Subsequently, the reduced sensitivity in extra-adrenal PGL and metastatic forms of the disease prompted investigations of other tracers. Gallium 68 (68GA)-DOTATATE PET/CT, which received FDA approval in 2016, has emerged as the most commonly used functional imaging radiotracer for detection of SSTR positive disease.[12](#R67457) More recently in 2020, the FDA approved Copper DOTATATE PET (64Cu) imaging for these lesions. In a prospective head-to-head comparison between [64Cu]Cu-DOTATATE and [68Ga]Ga-DOTATOC PET/CT, Johnbeck et al. reported a slightly higher detection rate for the former (99.1% vs. 95.6%), with 701 concordant lesions on both scans.[13](#R67458)  The integration of functional imaging data is of clinical interest to ensure completeness of the synoptic report since it provides staging, prognostic, and potentially theranostic information in tumors that over-express SSTR2.

References

1. Juhlin CC, Mete O. Advances in Adrenal and Extra-adrenal Paraganglioma: Practical Synopsis for Pathologists. Adv Anat Pathol. 2023 Jan 1;30(1):47-57.
2. Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR, Tischler A. Overview of the 2022 WHO Classification of Paragangliomas and Pheochromocytomas. Endocr Pathol. 2022 Mar;33(1):90-114.
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**B. Specimen**

The procedure used to resect a tumor is based on anatomic locations/organs (e.g., adrenalectomy for pheochromocytomas/adrenal PGLs). In some cases, PPGLs are resected laparoscopically resulting in morcellation/extensive fragmentation that can compromise the ability to determine completeness of surgical resection and microscopic assessment of the invasive growth.

**C. Tumor**

The issue of tumor multifocality is very important and should be included in the synoptic report. Patients with multiple PPGLs should be investigated for the possibility of underlying genetic susceptibility and thus genetic testing is considered in the setting of multifocal PPGL.[1,](#R67459)[2,](#R67460)[3](#R67461) Multifocal PPGL include multiple pheochromocytomas including their subcentimeter counterparts (also known as micro-pheochromocytoma) or a combination of an extra-adrenal PGL with a pheochromocytoma or multifocal extra-adrenal PGLs.

The anatomic location(s) of the tumor must be provided to the pathologist and be clearly documented in the synoptic report with the appropriate classification based on location. Similar to other guidelines, tumor size is a required field in surgical pathology reports. This information is required for tumor staging (see note F). Although the tumor size is not a universally accepted independent prognostic parameter in PPGLs, it is a component of the dynamic risk stratification since larger PPGLs (>5-7 cm) may be associated with an increased risk of metastasis..[1,](#R67459)[2,](#R67460)[3,](#R67461)[4,](#R67462)[5](#R67463)

The concept of “benign” or “malignant” PPGL has been abandoned since the 2017 WHO classification of endocrine tumors. PPGLs are malignant non-epithelial neuroendocrine neoplasms originating from paraganglia.[1,](#R67459)[2,](#R67460)[3,](#R67461)[4,](#R67462)[5,](#R67463)[6](#R67464).Similar to other epithelial NENs, the term “metastatic PGL or pheochromocytoma” should be used in the setting of metastatic disease.[3](#R67461) PPGLs are associated with varying risk of metastatic spread without any clear-cut morphological harbingers. The 2022 WHO classification of PPGLs does not endorse the use of multifactorial scoring systems (e.g., PASS, GAPP, modified GAPP, COPPS)[1,](#R67459)[5,](#R67463)[7](#R67465) since all PPGLs are malignant neoplasms and PPGLs with higher scores may lead to overestimation of risk for metastasis, particularly in some subgroups.[7](#R67465)

The current histological classification of PPGLs (Table 1) follow the 2022 WHO classification endocrine and neuroendocrine neoplasms[7](#R67465). In the 2022 WHO classification, the tumor formerly known as cauda equina PGL is now classified as cauda equina neuroendocrine tumor and the neoplasm known as gangliocytic paraganglioma has been renamed composite gangliocytoma/neuroma and neuroendocrine tumor (CoGNET).[1,](#R67459)[7,](#R67465)[8,](#R67466)[9,](#R67467)[10](#R67468) These unusual epithelial NENs are not PPGLs and should not be reported with this worksheet.[1,](#R67459)[7,](#R67465)[8,](#R67466)[9](#R67467)

The rare composite PPGLs are diagnosed when a typical PPGL is combined with developmentally-related distinct tumor component including ganglioneuroma (mature or maturing), ganglioneuroblastoma (nodular or intermixed), neuroblastoma (undifferentiated, poorly differentiated or differentiating) or malignant peripheral nerve sheath tumors.[1,](#R67459)[3,](#R67461)[4,](#R67462)[7](#R67465) Scattered ganglion-like cells or neuropil-like degenerated stroma seen in PPGLs should not be misinterpreted as a component of a composite tumor. The composite elements are diagnosed and subtyped using universally defined histomorphology criteria (International Neuroblastoma Pathology Committee-INPC)[11](#R67469) and/or biomarker features.[7](#R67465) In the 2022 WHO classification, a minimum cut-off of 5% has been proposed for each tumor element to qualify as a composite PPGL; however, this would require adequate/thorough tumor sampling in an attempt to capture intra-tumoral heterogeneity.[1,](#R67459)[7](#R67465) Composite PPGLs are not well studied and most prognostic variables are less recognized. At this time, diagnosticians can also document the extent of composite elements and mitotic-karyorrhectic index (MKI) in neuroblastic elements of composite PPGLs. Composite PPGLs may occur in the setting of pathogenic RET, MAX and NF1 variants.[1,](#R67459)[12](#R67470)

Irrespective of the anatomic location, PPGLs show overlapping cytomorphologic features. They display a variety of growth patterns. Sympathetic PPGLs often consist of polygonal cells (chromaffin cells) with amphophilic to basophilic cytoplasm, whereas parasympathetic PGLs consist of polygonal cells (chief cells) with relatively clearer cytoplasm than their sympathetic counterparts. Genotype-phenotype correlations underscored that VHL-related PPGLs contain usually a thick vascular capsule, hyalinized vascular and myxoid stroma, round tumor cells intermingled with small vessels, oncocytic cells, cells with predominantly amphophilic and clear cell cytoplasm, absence of intracytoplasmic hyaline globules and lipid degeneration.[1,](#R67459)[2,](#R67460)[7,](#R67465)[13](#R67471) SDHx-related PPGLs are often composed of tumor cells with variable intra-cytoplasmic vacuoles and/or oncocytic change.[1,](#R67459)[2,](#R67460)[6,](#R67464)[14](#R67472)

Expanded large confluent nests with central comedo necrosis have been described in a subset of metastastic PPGLs.[3](#R67461) Degenerative changes should not be mistaken as tumor necrosis. Vascular and lymphatic invasion are critical elements in the dynamic risk stratification of PPGLs.[1,](#R67459)[3,](#R67461)[5](#R67463) Vascular invasion in endocrine neoplasia requires the documentation of tumor cells invading through a vessel wall and forming intravascular tumor-platelet/thrombus complex or intravascular tumor cells admixed with platelets-thrombus.[6](#R67464) In cases with subtle findings, CD61 immunohistochemistry can be used to highlight platelets admixed with intravascular tumor cells.

The 8th edition AJCC TNM criteria[15](#R67473) also requires diagnosticians to document the text of histologically confirmed invasion into adjacent tissues/structures and organs. Therefore, local invasion into surrounding organs should be clearly documented to facilitate the staging. In addition, the extent of invasiveness of these tumors may affect the ability to obtain a surgical cure.[16](#R67474) In morcellated or fragmented resection specimens, the status and extent of invasive growth and the completeness of the tumor excision cannot be assessed.

**Table 1. Classification of Pheochromocytomas and Extra-Adrenal Paragangliomas**

\_\_\_Paraganglioma

\_\_\_Pheochromocytoma (adrenal paraganglioma)

\_\_\_Micro-pheochromocytoma (subcentimeter adrenal paraganglioma)

\_\_\_Composite paraganglioma

     \_\_\_Paraganglioma and Ganglioneuroma, mature

     \_\_\_Paraganglioma and Ganglioneuroma, maturing

     \_\_\_Paraganglioma and Ganglioneuroblastoma, intermixed type

     \_\_\_ Paraganglioma and Ganglioneuroblastoma, nodular type

     \_\_\_Paraganglioma and Neuroblastoma, undifferentiated type

     \_\_\_Paraganglioma and Neuroblastoma, poorly differentiated type

     \_\_\_Paraganglioma and Neuroblastoma, differentiating type

     \_\_\_Paraganglioma and Neuroblastic tumor, NOS

     \_\_\_Paraganglioma and Malignant peripheral nerve sheath tumor

     \_\_\_Other (specify): \_\_\_\_\_\_\_\_\_

\_\_\_Composite pheochromocytoma

     \_\_\_Pheochromocytoma and Ganglioneuroma, mature

     \_\_\_Pheochromocytoma and Ganglioneuroma, maturing

     \_\_\_Pheochromocytoma and Ganglioneuroblastoma, intermixed type

     \_\_\_Pheochromocytoma and Ganglioneuroblastoma, nodular type

     \_\_\_Pheochromocytoma and Neuroblastoma, undifferentiated type

     \_\_\_Pheochromocytoma and Neuroblastoma, poorly differentiated type

     \_\_\_Pheochromocytoma and Neuroblastoma, differentiating type

     \_\_\_Pheochromocytoma and Neuroblastic tumor, NOS

     \_\_\_Pheochromocytoma and Malignant peripheral nerve sheath tumor

     \_\_\_Other (specify): \_\_\_\_\_\_\_\_\_

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**D. Tumor Proliferative Activity**

Like epithelial NENs, clinical behavior and prognosis are determined in part by growth rate that is reflected in Ki-67 labeling and mitotic count.[1](#R67475)  The value of Ki-67 in tumor-related progression and metastasis has also been confirmed in the TCGA data.[2](#R67476)  Although there is no formal WHO grading for PPGLs, increased proliferative activity is an important variable in the dynamic risk stratification of PPGLs.[1,](#R67475)[3,](#R67477)[4](#R67478)

As specified by the 2022 WHO classification and based on accuracy studies, the Ki-67 assessment from hot spots should be based on printout of a photo or an automated image analysis algorithm; eyeball estimates are not accurate or acceptable.[5,](#R67479)[6](#R67480) Similar to epithelial NENs, PPGLs can show intra-tumoral proliferative heterogeneity. In general, selecting multiple small hot spots (at least 500 tumor cells) from different hot spot regions of the tumor rather than a single larger area of the same tumor are often recommended.[7](#R68452) In the 2022 WHO classification proliferation in general is regarded as a dynamic variable rather than a static threshold, therefore, a precise numeric percentage or count should be provided for Ki67 labeling index or mitotic count of all neuroendocrine neoplasms.[6](#R67480)

The mitotic rate should be reported as number of mitoses per 2mm2, at least 10mm2 evaluated in the most mitotically active part(s) of the tumor. The hot spot mitotic counting may apply contiguous round fields or random counting that uses a randomization method to avoid bias.[8](#R68453) The documentation of the methodology used to count mitosis is also encouraged. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei should not be counted. The application of phosphoHistone-H3 immunohistochemistry can also be used to count mitotic figures.[5,](#R67479)[6](#R67480). Because of variations in field size, the number of high-power fields (HPF) (at 40X magnification) for 10mm2 (thereby 2mm2) must be determined for each microscope (Table 2).

**Table 2. Number of HPF Required for 10mm2 and 2mm2 Using Microscopes with Different Field Diameter**

|  |  |  |  |
| --- | --- | --- | --- |
| **Field Diameter (mm)** | **Area (mm)** | **Number of HPF for 10 mm** | **Number of HPF for 2 mm** |
| 0.40 | 0.125 | 80 | 16 |
| 0.41 | 0.132 | 75 | 15 |
| 0.42 | 0.139 | 70 | 14 |
| 0.43 | 0.145 | 69 | 14 |
| 0.44 | 0.152 | 65 | 13 |
| 0.45 | 0.159 | 63 | 13 |
| 0.46 | 0.166 | 60 | 12 |
| 0.47 | 0.173 | 58 | 12 |
| 0.48 | 0.181 | 55 | 11 |
| 0.49 | 0.189 | 53 | 11 |
| 0.50 | 0.196 | 50 | 10 |
| 0.51 | 0.204 | 49 | 10 |
| 0.52 | 0.212 | 47 | 9 |
| 0.53 | 0.221 | 45 | 9 |
| 0.54 | 0.229 | 44 | 9 |
| 0.55 | 0.238 | 42 | 8 |
| 0.56 | 0.246 | 41 | 8 |
| 0.57 | 0.255 | 39 | 8 |
| 0.58 | 0.264 | 38 | 8 |
| 0.59 | 0.273 | 37 | 7 |
| 0.60 | 0.283 | 35 | 7 |
| 0.61 | 0.292 | 34 | 7 |
| 0.62 | 0.302 | 33 | 7 |
| 0.63 | 0.312 | 32 | 6 |
| 0.64 | 0.322 | 31 | 6 |
| 0.65 | 0.332 | 30 | 6 |
| 0.66 | 0.342 | 29 | 6 |
| 0.67 | 0.353 | 28 | 6 |
| 0.68 | 0.363 | 28 | 6 |
| 0.69 | 0.374 | 28 | 5 |

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**E. Distant Metastases**

Metastases are typically defined as PGLs in locations where normally paraganglia do not exist.[1](#R67481) The 2022 WHO classification of PPGLs has addressed to concerns on the distinction of metastases.[1](#R67481) Knowledge of the distribution of the autonomous nervous system and recognition of germline disease related multifocal PPGLs have improved our distinction of metastatic disease from multifocal disease in anatomic locations that have been traditionally considered as a metastatic site (e.g., liver, lung).[1,](#R67481)[2](#R67482) Lymph node and bone are the only reliable sites for unequivocal evidence of metastasis.[1,](#R67481)[2](#R67482)

Primary PGLs can occur in several organs including but not limited to lung, liver, prostate, kidney, urinary bladder, heart, mesentery.[1,](#R67481)[2,](#R67482)[3](#R67483) However, without the knowledge on germline status of a patient, the distinction of multifocal primary PPGLs from metastatic disease can be difficult. The status of intratumoral sustentacular cell network has now been recognized as a useful tool to facilitate this distinction.[1](#R67481) S100 and SOX10-positive sustentacular cells are thought to represent the non-neoplastic cellular component of PPGLs,[4](#R67484) and metastases have been associated with the lack of sustentacular cell network.[5](#R67485)

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**F. pTNM Classification**

The 8th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) is now recommended for staging sympathetic PGLs and pheochromocytomas.[1](#R67598) Accordingly, TNM staging is based on size, location and invasiveness of the primary tumor, the presence or absence of locoregional metastases, and both the presence and site of distant metastases. Bone metastases alone are associated with longer survival than metastases to lung or liver. Currently there is no TNM classification for parasympathetic PGLs and composite PPGLs; however, the authors of this protocol encourage all users to apply the current template (based on the tumor size cutoff of 5 cm and the status of invasion) to facilitate uniform data collection.

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

**T Category Considerations**

The “m” designation applies only to grossly recognizable, synchronous primary tumors and not to a single, grossly detected tumor with multiple separate microscopic foci. If more than 1 tumor is present, the tumor with the highest T category should be classified according to the pT definitions, and either the multiplicity (“m”) or the actual number of simultaneous multiple tumors (e.g., “3”) should be indicated in parentheses after the T category of the primary tumor (e.g., pT3[m] or pT3[2]).

Four stage groups are compiled from the TNM data:

**TNM staging**

**Tumor (pT)**

* TX: Primary tumor cannot be assessed
* T1: Pheochromocytoma less than 5 cm in greatest dimension, no extra-adrenal invasion
* T2: Pheochromocytoma greater than or equal to 5 cm or sympathetic paraganglioma of any size, no extra-adrenal invasion
* T3: Tumor any size with invasion into surrounding organs/tissues (e.g., liver, pancreas, spleen, kidneys)

**Regional lymph nodes**

* N0: Regional lymph nodes cannot be assessed
* N0: No lymph node metastasis
* N1: Regional lymph node metastasis

**Distant metastasis**

* M0: No distant metastasis
* M1a: Distant metastasis to only bone
* M1b: Distant metastasis to only distant lymph nodes/liver or lung
* M1c: Distant metastasis to bone plus multiple other sites

**Stage groups**

* Stage 1: T1, N0, M0
* Stage 2: T2, N0, M0
* Stage 3: T1, N1, M0 or T2, N1, M0 or T3, any N, M0
* Stage 4: any T, any N, M1

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**G. Additional Findings**

Diffuse (non-nodular) expansion of adrenal medulla, which expands to comprise more than one-third of the adrenal gland thickness, qualifies for adrenal medullary hyperplasia that is a precursor lesion for inherited PPGLs in association with pathogenic *RET* (most common), *MAX*, *TMEM127*, and *NF1* variants.[1,](#R67486)[2,](#R67487)[3,](#R67488)[4,](#R67489)[5,](#R67490)[6,](#R67491)[7](#R67492) Diagnosticians should also remember that adrenal medulla is normally present only in the head and body of the adrenal gland, but not in the tail of the gland with only minimal extension into the alae. So an abnormal location of the medulla (e.g., extension of the adrenal medulla into the tail) also warrants a diagnosis of diffuse adrenal medullary hyperplasia.[2,](#R67487)[3,](#R67488)[8](#R67493) Therefore, the non-tumorous adrenal gland should be sampled in toto. Irrespective of the size, any distinct nodular proliferation of chromaffin cell origin in the medulla would warrant a diagnosis of micro-pheochromocytoma.[1,](#R67486)[3](#R67488) In the setting of diffuse compact cell adrenal cortical hyperplasia, the possibility of ectopic ACTH/CRH-production from a pheochromocytoma should be considered.[8](#R67493)

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**H. Special Studies**

The application of routine immunohistochemical biomarkers is essential in the field of NENs including PPGLs. In the 2022 WHO classification of NENs, testing of keratin expression status is recommended for all NENs.[1,](#R67494)[2,](#R67495)[3,](#R67496)[4](#R67497) While negativity alone does not exclude an epithelial NENs, PPGLs are typically negative for keratins. Chromogranin A is the classical biomarker to confirm neuroendocrine differentiation, and INSM1 is also useful in the appropriate morphological setting.[1,](#R67494)[2,](#R67495)[3,](#R67496)[4](#R67497) The demonstration of intratumoral sustentacular cell network is not specific for PPGLs and can be seen in epithelial NENs.[1,](#R67494)[2](#R67495) Positivity for GATA3 is commonly used to confirm the paraganglia origin in keratin-negative NENs; however, GATA3 is also expressed in other NENs which can sometimes be keratin-negative (e.g., gonadotroph tumor).  There are also other less frequently adopted markers including but not limited to PHOX2B[5](#R67498) and they have been shown to support the paraganglia origin, thus a PPGL diagnosis in the setting of a keratin-negative NEN.[6,](#R67499)[7](#R67500)PHOX2B is also used in the distinction of ganglioneuronal elements of composite tumors.S100 and SOX10 can be used to highlight schwannian stroma in composite tumors.[1](#R67494) Tyrosine hydroxylase (the rate limiting enzyme in the synthesis of catecholamines) is typically positive in most functional PPGLs.[1,](#R67494)[2,](#R67495)[3,](#R67496)[4](#R67497)  However, immunohistochemical biomarkers should be used in a panel as positivity of a single marker may be misleading. Parasympathetic PGLs can have absent to reduced expression for chromogranin-A and tyrosine hydroxylase. The demonstration of intratumoral sustentacular cell network can facilitate the distinction of multifocal primary PPGLs from metastatic disease as discussed on note E. More importantly, reduced intra-tumoral sustentacular cell network in a primary PPGL is of interest as an emerging variable in the dynamic risk stratification of PPGLs.[1,](#R67494)[2](#R67495)  Loss of ATRX and increased MIB1 (Ki-67) labeling index (often >3%) are also adverse parameters in the dynamic risk stratification.[1,](#R67494)[2,](#R67495)[4,](#R67497)[7](#R67500)

The highly heritable nature of PPGLs and lack of family history in most affected patients have resulted in reflex biomarker testing regarding their pathogenesis. The desirable molecular immunohistochemistry tools include SDHB, alpha-inhibin, CAIX, FH and 2SC.[1](#R67494) Global loss of cytoplasmic SDHB expression is referred to SDH deficiency and can be associated with any *SDHx* alterations.[1](#R67494) Positivity for alpha-inhibin can occur in PGLs and pheochromocytomas that are associated with pseudohypoxia pathway (e.g., *SDHx*- and *VHL*-related PPGLs) that manifest with dopaminergic or mixed dopaminergic and adrenergic tumors as well as in the setting of pure noradrenergic immature secretory phenotype.[1,](#R67494)[7](#R67500) Membranous CAIX is also regarded a feature of *VHL*-related PPGLs.[1,](#R67494)[7,](#R67500)[8,](#R67504)[9](#R67505)*FH*-related pathogenesis can be screened by loss of FH (fumarate hydratase) and positivity for 2-SC (2-succinocystein).[1,](#R67494)[10](#R67503) If available, menin can be used to screen for MEN1-related pathogenesis.[1,](#R67494)[2,](#R67495)[11](#R67501)The current experiences with MAX antibody (MEN5-related manifestation) are conflicting among experts. BAP1 immunohistochemistry is also unreliable.[12](#R67502) Although immunohistochemical biomarkers are very helpful in raising the possibility of heritable disease and/or underlying pathogenesis, the gold standard is germline genetic testing which should be offered in all patients with PPGLs.

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