



CLINICAL GUIDELINES

Pediatric Oncology Imaging Guidelines

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eviCore healthcare Clinical Decision Support Tool Diagnostic Strategies: This tool addresses common symptoms and symptom complexes. Imaging requests for individuals with atypical symptoms or clinical presentations that are not specifically addressed will require physician review. Consultation with the referring physician, specialist and/or individual's Primary Care Physician (PCP) may provide additional insight.

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Abbreviations for Pediatric Oncology Imaging Guidelines

AFP	Alpha-fetoprotein (tumor marker)
ALCL	Anaplastic large cell lymphoma
ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
β-hCG	Human chorionic gonadotropin beta-subunit (tumor marker)
BKL	Burkitt's lymphoma
BWT	Bilateral Wilms tumor
CCSK	Clear cell sarcoma of the kidney
CNS	Central nervous system
COG	Children's Oncology group
CPT®	Current procedural terminology; trademark of the American Medical Association
CSF	Cerebrospinal fluid
CT	Computed tomography
CXR	Chest x-ray
DAWT	Diffuse anaplasia Wilms tumor
ESFT	Ewing sarcoma family of tumors
FAWT	Focal anaplasia Wilms tumor
FHWT	Favorable histology Wilms tumor
HL	Hodgkin lymphoma
HSCT	Hematopoietic stem cell transplant (bone marrow or peripheral blood)
HVA	Homovanillic acid
LL	Lymphoblastic lymphoma
MIBG	Metaiodobenzylguanidine (nuclear scan using ¹²³ I or ¹³¹ I)
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
NBL	Neuroblastoma
NED	No evidence of disease
NHL	Non-hodgkin lymphoma
NPC	Nasopharyngeal carcinoma
NRSTS	Nonrhabdomyosarcomatous soft tissue sarcomas
OS	Osteosarcoma
PET	Positron emission tomography
PMBCL	Primary mediastinal b-cell lymphoma
PNET	Primitive neuroectodermal tumor
RCC	Renal cell carcinoma
RMS	Rhabdomyosarcoma
US	Ultrasound
VMA	Vannilylmandelic acid
WBC	White blood cell count
XRT	Radiation therapy

PEDONC-1: General Guidelines

PEDONC-1.0: General Guidelines

PEDONC-1.1: Age Considerations

PEDONC-1.2: Appropriate Clinical Evaluations

PEDONC-1.3: Modality General Considerations

PEDONC-1.4: PET Imaging in Pediatric Oncology

PEDONC-1.5: Diagnostic Radiation Exposure in Pediatric Oncology

PEDONC-1.0: General Guidelines

- In general, a recent (within 60 days) detailed history and physical examination and appropriate laboratory studies should be performed prior to considering advanced imaging, unless the patient is undergoing guideline-supported scheduled off-therapy surveillance evaluation.
 - ◆ Because of the relatively small number of childhood cancer treatment centers, it is common to combine off-therapy visits with imaging and other subspecialist visits to accommodate families traveling long distances for their child's care.
- Unless otherwise stated in the diagnosis-specific guidelines, imaging for treatment response can be approved after every 2 cycles, which is usually ~6 weeks of therapy for solid tumors and usually ~8 to 12 weeks for CNS tumors
- Unless otherwise specified for a specific cancer type, once PET has been documented to be negative for a given patient's cancer or all PET-avid disease has been surgically resected, PET should not be used for continued disease monitoring or surveillance unless one of the following applies:
 - ◆ Conventional imaging (CT, MRI, US, plain film) reveals findings that are inconclusive or suspicious for recurrence
 - ◆ Residual mass that has not changed in size since the last conventional imaging does not justify PET imaging
 - ◆ PET avidity in a residual mass at the end of planned therapy is not an indication for PET imaging during surveillance

PEDONC-1.1: Age Considerations

The majority of malignancies occurring in the pediatric population are different diagnoses than those occurring in the adult population. For those diseases which occur in both pediatric and adult populations, minor differences may exist in management between pediatric and adult medical oncologists due to patient age, comorbidities, and differences in disease natural history between children and adults.

AGE APPROPRIATE GUIDELINES	
Age of Individual	Appropriate Imaging Guidelines
≥ 18 years old at initial diagnosis	➤ General Oncology Imaging Guidelines, except where directed otherwise by a specific guideline section
< 18 years old at initial diagnosis	➤ Pediatric Oncology Imaging Guidelines, except where directed otherwise by a specific guideline section
15 to 39 years old at initial diagnosis (defined as Adolescent and Young Adult (AYA) oncology individuals)	➤ When unique guidelines for a specific cancer type exist only in either Oncology or Pediatric Oncology, AYA individuals should be imaged according to the guideline section for their specific cancer type, regardless of the individual's age ➤ When unique guidelines for a specific cancer type exist in both Oncology and Pediatric Oncology, AYA individuals should be imaged according to the age rule in the previous bullet

PEDONC-1.2: Appropriate Clinical Evaluations

- The majority of pediatric oncology imaging indications are listed in the diagnosis-specific guideline sections, but for rare malignancies and other circumstances not specifically addressed elsewhere in the pediatric oncology guidelines, the following general principles apply:
 - ◆ Routine imaging of brain, spine, neck, chest, abdomen, pelvis, bones, or other body areas is not indicated in the absence of localizing symptoms or abnormalities on plain radiography or ultrasound.
- The overwhelming majority of pediatric oncology patients treated in the United States will be enrolled on or treated according to recent Children's Oncology Group (COG) protocols. These imaging guidelines are consistent with evaluations recommended by COG protocols commonly used for direct patient care (whether formally enrolled on study or not).
- For patients enrolled on a COG study, imaging recommended by COG protocols should generally be approved unless the imaging is being performed solely to address a study objective and would not be indicated in usual clinical care.

Phases of Pediatric Oncology Imaging:

- Pediatric malignancies, in general, behave more aggressively than adult cancers, and the time from initial suspicion of cancer to specific therapy initiation can be measured in hours to days for most pediatric cancers
- It is recommended that children with pediatric solid tumors undergo CT evaluation of the chest prior to general anesthesia for biopsy or resection due to the risk of post-operative atelectasis mimicking pulmonary metastasis resulting in inaccurate staging and/or delay in therapy initiation
- Unlike adult cancers, in most pediatric cancers surveillance does not begin until all planned multimodal therapy is completed. Pediatric cancers where surgical resection is considered curative are listed in the diagnosis-specific guideline sections
- Certain tumor types do not require surveillance with advanced imaging as patient outcomes following relapse are not improved by surveillance imaging. See diagnosis-specific guideline sections for details.
- Imaging may be indicated more frequently than recommended by guidelines with clinical documentation that the imaging results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance

Phases of Oncology Imaging	Definition
Screening	➤ Imaging requested for patients at increased risk for a particular cancer in the absence of known clinical signs or symptoms ➤ Screening using advanced imaging is only supported for conditions listed in <u>PEDONC-2: Screening Imaging in Cancer Predisposition Syndromes</u>

Phases of Oncology Imaging	Definition
Suspected/Initial Staging	➤ All imaging studies requested from the time cancer is first clinically suspected until the initiation of specific treatment ◆ CT Chest prior to anesthesia for biopsy or resection of solid tumors and CTs of other involved body areas are generally indicated and should be performed concurrently ◆ Metastatic CNS imaging and nuclear medicine imaging are generally deferred until after a histologic diagnosis is made, unless otherwise indicated by diagnosis-specific guideline
Treatment Response	➤ Imaging performed during any type of active treatment (chemotherapy or other medications, radiation therapy, or surgery), including evaluation at the end of planned active treatment ◆ Unless otherwise stated in the diagnosis-specific guidelines, imaging for treatment response can be approved after every 2 cycles, which is usually ~6 weeks of therapy for solid tumors and usually ~8 to 12 weeks for CNS tumors
Surveillance	➤ Imaging performed in patients who are asymptomatic or have chronic stable symptoms and not receiving any active treatment, even if residual imaging abnormalities are present ◆ PET imaging is not supported for surveillance imaging unless specifically stated in elsewhere in the diagnosis-specific guideline sections
Recurrence	➤ All imaging studies completed at the time a recurrence or progression of a known cancer is strongly suspected or documented based on clinical signs or symptoms, laboratory findings, or results of basic imaging studies such as plain radiography or ultrasound ➤ Following documented recurrence of childhood cancer, any studies recommended for initial staging of that cancer type in the diagnosis-specific imaging guideline section should be approved ◆ During active treatment for recurrent pediatric cancer, conventional imaging evaluation (CT or MRI, should use the same modality for ongoing monitoring as much as possible) of previously involved areas should be approved according to the treatment response imaging in the diagnosis-specific guideline section ■ Always refer to the diagnosis specific guideline for PET indications in recurrence.

Radiation Treatment Planning In Pediatric Oncology:

- Imaging performed in support of radiation therapy treatment planning should follow guidelines outlined in **ONC-1.5: Unlisted Procedure Codes in Oncology**.

Cardiac Function Assessment in Pediatric Oncology During Active Treatment:

Indication	Imaging Study
➤ Evaluation of cardiac function prior to cardiotoxic chemotherapy, at the discretion of the treating pediatric oncologist based on: ◆ Cumulative cardiotoxic therapy received to date ◆ Patient's age and gender ◆ Most recent echocardiogram results ◆ New or worsening cardiac symptoms	➤ Echocardiography (CPT® 93306, CPT® 93307, or CPT® 93308)
➤ For either of the following: ◆ Echocardiography yielded a borderline shortening fraction (< 30%) and additional left ventricular function data are necessary to make a chemotherapy decision OR ◆ Echocardiography windowing is suboptimal due to body habitus or tumor location	➤ Multi-gated acquisition (MUGA, CPT® 78472) blood pool nuclear medicine scanning

Immunosuppression during Pediatric Cancer therapy and imaging ramifications:

- Patients may be severely immunocompromised during active chemotherapy treatment and any conventional imaging request to evaluate for infectious complications during this time frame should be approved immediately
- Imaging requests for infectious disease concerns for all patients with absolute neutrophil count (ANC) < 500 or inconclusive findings on Chest x-ray or US at any ANC during active treatment should be approved as requested
- Additionally, patients may have therapy-induced hypogammaglobulinemia which requires supplemental intravenous immune globulin (IVIG) during maintenance therapy. Patients receiving supplemental IVIG should be treated similarly to patients with ANC < 500 with regards to imaging for infectious disease.
- Some patients are treated with very intensive chemotherapy regimens (including autologous stem cell transplantation - See **ONC-29: Hematopoietic Stem Cell Transplantation** and spend the majority of their chemotherapy treatment phase in the hospital. Due to the high risk of invasive infections, frequent CT may be indicated to evaluate known sites of invasive fungal infection, and in general these should be approved as requested.

- ◆ Surveillance imaging of asymptomatic patients to detect invasive fungal infection has not been shown to impact patient outcomes. Imaging requests in these circumstances should only be approved when acute clinical decisions will be made based on the imaging.

Hematopoietic Stem Cell Transplant (HSCT) in Pediatric Oncology:

- Transplantation of hematopoietic stem cells from bone marrow, peripheral blood, or cord blood is commonly used in the following clinical situations in pediatric hematology and oncology patients:
 - ◆ High risk or recurrent leukemia (allogeneic)
 - ◆ Recurrent lymphoma (allogeneic or autologous)
 - ◆ Hemophagocytic lymphohistiocytosis (allogeneic)
 - ◆ High risk sickle cell disease (allogeneic)
 - ◆ High risk neuroblastoma (autologous)
 - ◆ High risk CNS tumors (autologous)
 - ◆ Recurrent Ewing sarcoma family of tumors (autologous, rarely allogeneic)
- Imaging considerations for HSCT should follow guidelines in:
ONC-29: Hematopoietic Stem Cell Transplantation.

PEDONC-1.3: Modality General Considerations

- Plain radiography
 - ◆ Chest x-ray (CXR) can provide a prompt means to evaluate primary intrathoracic tumors and continues to be the initial imaging study recommended to detect complications, such as suspected infection, in symptomatic patients undergoing treatment.
 - ◆ CXR continues to be the initial imaging study recommended for pulmonary surveillance for some pediatric cancers. See diagnosis-specific guideline sections for details.
 - ◆ Plain radiography continues to be the initial imaging study recommended for evaluation of lesions involving the appendicular skeleton, both during and after completion of treatment. See diagnosis-specific guideline sections for details.
 - ◆ Plain abdominal radiographs have been replaced by ultrasound, CT, or MRI
- Ultrasound
 - ◆ Ultrasound is not widely used in pediatric oncology for staging, but is frequently used for surveillance in patients who have successfully treated (primarily abdominal or pelvic) tumors with little or no residual disease. See diagnosis-specific guideline sections for details.
- CT
 - ◆ CT with contrast is the imaging study of choice in pediatric patients with lymphomas or solid tumors of the neck, thorax, abdomen, and/or pelvis
 - If CT contrast use is contraindicated due to allergy or impaired renal function, either CT without contrast or MRI without and with contrast may be substituted at the discretion of the ordering physician
- MRI
 - ◆ MRI without and with contrast is the study of choice for CNS and musculoskeletal tumors
 - If MRI contrast use is contraindicated due to allergy or impaired renal function, MRI without contrast may be substituted at the discretion of the ordering physician
 - ◆ Due to the length of time for image acquisition and the need for stillness, anesthesia is required for almost all infants and young children (age < 7 years), as well as older children with delays in development or maturity. In this patient population, MRI imaging sessions should be planned with a goal of avoiding a short-interval repeat anesthesia exposure due to insufficient information using the following considerations:
 - MRI should always be performed without and with contrast unless there is a specific contraindication to gadolinium use, since the patient already has intravenous access for anesthesia.
 - Recent evidence based literature demonstrates the potential for gadolinium deposition in various organs including the brain, after the use of MRI contrast.

- The U.S. food and drug administration (FDA) has noted that there is currently no evidence to suggest that gadolinium retention in the brain is harmful and restricting gadolinium-based contrast agents (GBCAS) use is not warranted at this time. It has been recommended that GBCA use should be limited to circumstances in which additional information provided by the contrast agent is necessary and the necessity of repetitive MRIs with GBCAS should be assessed.
 - If requesting clinicians indicate that a non-contrast study is being requested due to concerns regarding the use of gadolinium, the exam can be approved.
 - If multiple body areas are supported by eviCore guidelines for the clinical condition being evaluated, MRI of all necessary body areas should be obtained concurrently in the same anesthesia session
- Nuclear medicine
- ◆ General PET imaging consideration can be found in **PEDONC-1.4: PET Imaging in Pediatric Oncology**.
 - ◆ Bone scan is frequently used for evaluation of bone metastases during initial treatment, treatment response, and surveillance in pediatric oncology.
 - CPT® 78315 has no specific indications for evaluation of malignant disease
 - ◆ ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy is the preferred metabolic imaging for neuroblastoma and is positive in 90 to 95% of neuroblastomas, and is also used for evaluation of pheochromocytomas, paragangliomas, ganglioneuromas, and ganglioneuroblastomas.

Study Type	Coding
Bone scan	➤ Any of the following codes can be approved: ◆ CPT® 78300 ◆ CPT® 78305 ◆ CPT® 78306 ◆ CPT® 78803, 78830, or 78832 ▪ May be approved alone or in combination with: ▪ CPT® 78305 ▪ CPT® 78306
¹²³ I-metaiodobenzylguanidine (MIBG) scintigraphy	➤ Any of the following codes can be approved: ◆ CPT® 78801 ◆ CPT® 78802 (preferred) ◆ CPT® 78804 (preferred) ◆ CPT® 78803, 78830, 78831, or 78832 ▪ May be approved alone or in combination with: ▪ CPT® 78801 ▪ CPT® 78802 ▪ CPT® 78804
Octreotide scan	Same coding as MIBG

Study Type	Coding
Bone scan	➤ Any of the following codes can be approved: ◆ CPT® 78300 ◆ CPT® 78305 ◆ CPT® 78306 ◆ CPT® 78803, 78830, or 78832 ■ May be approved alone or in combination with: ■ CPT® 78305 ■ CPT® 78306
Gallium scan	Same coding as MIBG

PEDONC-1.4: PET Imaging in Pediatric Oncology

Note: *Some payors have specific restrictions on PET imaging, and those coverage policies may supersede the recommendations for PET imaging in these guidelines.*

Throughout these guidelines, the term “PET” refers specifically to ¹⁸F-FDG-PET imaging and also applies to PET/CT fusion studies.

- PET imaging in pediatric Oncology should use PET/CT fusion imaging (CPT® 78815 or CPT® 78816)
- The decision whether to use skull base to mid-femur (“eyes to thighs”) procedure code for PET (CPT® 78812 or CPT® 78815) or whole body PET (CPT® 78813 or CPT® 78816) is addressed in the diagnosis-specific guideline sections.
- PET imaging is not reliable for the detection of anatomic lesions smaller than 8 mm in size.
- Delay PET/CT for at least 12 weeks after completion of radiation treatment, unless required sooner for imminent surgical resection. PET/CT requests < 12 weeks from completion of radiation treatment should be forwarded for Medical Director review.
- PET imaging using isotopes other than ¹⁸F-FDG and ⁶⁸Ga-DOTATATE is considered investigational at this time.
- PET has not been shown to be diagnostically useful in all forms of childhood cancer. PET is supported for pediatric malignancies with significant published evidence regarding its diagnostic accuracy and importance in accurately directing patient care decisions. See diagnosis-specific guideline sections for details.
- PET imaging is not specific to cancer, and has a high rate of false positivity. Inflammation, infection (especially granulomatous), trauma, and post-operative healing may show high levels of FDG uptake and be false-positive for malignant lesions.
- PET for rare malignancies not specifically addressed by eviCore guidelines is generally not indicated, due to lack of available evidence regarding diagnostic accuracy of PET in the majority of rare cancers. Conventional imaging studies should be used for initial staging and treatment response for these diagnoses. PET can be approved if **all** of the following apply:
 - ◆ Conventional imaging (CT, MRI, US, plain film) reveals findings that are equivocal or suspicious
 - ◆ No other specific metabolic imaging (MIBG, octreotide, technetium, etc.) is appropriate for the cancer type
 - ◆ The submitted clinical information describes a specific decision regarding the patient’s care that will be made based on the PET results
 - ◆ These requests will be forwarded for Medical Director review
- PET imaging is not supported for surveillance imaging unless specifically stated elsewhere in the diagnosis-specific guideline sections
- Unless otherwise specified for a specific cancer type, once PET has been documented to be negative for a given patient’s cancer or all PET-avid disease has been surgically resected, PET should not be used for continued disease monitoring or surveillance unless one of the following applies:
 - ◆ Conventional imaging (CT, MRI, US, plain film) reveals findings that are inconclusive or suspicious for recurrence

- Residual mass that has not changed in size since the last conventional imaging does **not** justify PET imaging
- PET avidity in a residual mass at the end of planned therapy is **not** an indication for PET imaging during surveillance.
- ◆ Very rare circumstances where tumor markers or obvious clinical symptoms show strong evidence suggesting recurrence and PET would replace conventional imaging modalities
- ◆ The patient is undergoing salvage treatment for a recurrent solid tumor with residual measurable disease on conventional imaging and confirmed repeat negative PET imaging will allow the patient to transition from active treatment to surveillance.
- ◆ These requests will be forwarded for Medical Director review.

PEDONC-1.5: Diagnostic Radiation Exposure in Pediatric Oncology

Young children are presumed to be at increased risk for malignancy from diagnostic radiation exposure, most commonly from CT and nuclear medicine imaging. They are more sensitive to radiation than adults and generally live longer after receiving radiation doses from medical procedures, resulting in a larger number of years during which to manifest a cancer.

- Because of this presumed increased risk in young children, requests to substitute MRI without and with contrast for CT with contrast to avoid radiation exposure can be approved if all of the following criteria apply:
 - ◆ The patient is presently a young child and the ordering physician has documented the reason for MRI, rather than CT, is to avoid radiation exposure.
 - ◆ The disease-specific guidelines do not list CT as superior to MRI for the current disease and time point, meaning the MRI will provide equivalent or superior information relative to CT.
 - ◆ The request is for a body area other than Chest as MRI is substantially inferior to CT for detection of small pulmonary metastases.

The guidelines listed in this section for certain specific indications are not intended to be all-inclusive; clinical judgment remains paramount and variance from these guidelines may be appropriate and warranted for specific clinical situations.

References- PEDONC-1

1. Krishnamurthy R, Daldrup-Link HE, Jones JY, et al. Imaging studies in the diagnosis and management of pediatric malignancies. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:185-238.
2. Allen-Rhoades W, Steuber CP. Clinical assessment and differential diagnosis of the child with suspected cancer. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:101-112.
3. Gottschalk S, Naik S, Hegde M, et al. Hematopoietic stem cell transplantation in pediatric oncology. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:419-440.
4. Freedman JL, Rheingold SR, and Fisher MJ. Oncologic emergencies. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:967-991.
5. Andrews J, Galel SA, Wong W, et al. Hematologic supportive care for children with cancer. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:992-1009.
6. Ardura MI, Koh AY. Infectious complications in pediatric cancer patients. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:1010-1057.
7. Shaikh R, Prabhu SP, Voss SD. Imaging in the evaluation and management of childhood cancer. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:2146-2254.
8. Sung L, Fisher BT, Koh AY. Infectious Disease in the pediatric cancer patient. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:2257-2266.
9. Mullen EA, Gratias E. Oncologic emergencies. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:2267-2291.
10. Weiser DA, Kaste SC, Siegel MJ, et al. Imaging in childhood cancer: A society for Pediatric Radiology and Children's Oncology Group joint task force report. *Pediatr Blood Cancer*. 2013;60(8):1253-1260. doi:10.1002/pbc.24533.
11. American College of Radiology. ACR-ASER-SCBT-MR-SPR Practice Parameter for the Performance of Pediatric Computed Tomography (CT). 2014. <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/CT-Ped.pdf>.
12. ACR-SPR Practice Parameter for the Performance and Interpretation of Pediatric Magnetic Resonance Imaging (MRI), Revised 2015 (Resolution 11). <https://www.acr.org/-/media/CB384A65345F402083639E6756CE513F.pdf>
13. Smith EA, Dillman JR. Current role of body MRI in pediatric oncology. *Pediatr Radiol*. 2016;46(6):873-880. doi:10.1007/s00247-016-3560-8.
14. The Center for Drug Evaluation and Research. Meeting of the Medical Imaging Drugs Advisory Committee, presented September 8, 2017. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM574746.pdf>.
15. Uslu L, Doing J, Link M, et al. Value of ¹⁸F-FDG PET and PET/CT for evaluation of pediatric malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
16. McCarville MB. PET-CT imaging in pediatric oncology. *Cancer Imaging*. 2009(1);9:35-43. doi:10.1102/1470-7330.2009.0008.
17. Matthews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ*. 2013;346:f2360. doi:10.1136/bmj.f2360.
18. Erdi YE. Limits of tumor detectability in nuclear medicine and PET. *Mol Imaging Radio Nucl Ther*. 2012;21(1):23-28. doi:10.4274/Mirt.138.
19. Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics*. 2012;130(3):e476-e485. doi:10.1542/peds.2011-3822.

20. Monteleone M, Khandji A, Cappell J, et al. Anesthesia in children: perspectives from nonsurgical pediatric specialists. *J Neurosurg Anesthesiol.* 2014;26(4):396-398. doi:10.1097/ANA.0000000000000124.
21. DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. *Anesth Analg.* 2011;113(5):1143-1151. doi:10.1213/ANE.0b013e3182147f42.
22. Brody AS, Guillerman RP. Don't let radiation scare trump patient care: 10 ways you can harm your patients by fear of radiation-induced cancer from diagnostic imaging. *Thorax.* 2014;69(8):782-784. doi:10.1136/thoraxjnl-2014-205499.
23. Meulepas JM, Ronckers CM, Smets AMJB, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands, *JNCI J Natl Cancer Inst.* 2019;111:256-2634. doi: 10.1093/jnci/djy104.
24. Bhatia S, Pappo AS, Acquazzino M, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020—July 11, 2019, Adolescent and Young Adult (AYA) Oncology, available at: https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf, referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Adolescent and Young Adult (AYA) Oncology V1.2020 7/11/19. ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.

PEDONC-2: Screening Imaging in Cancer Predisposition Syndromes

PEDONC-2.1: Screening Imaging in Cancer Predisposition Syndromes – General Considerations

PEDONC-2.2: Li-Fraumeni Syndrome (LFS)

PEDONC-2.3: Neurofibromatosis 1 and 2 (NF1 and NF2)

PEDONC-2.4: Beckwith-Wiedemann Syndrome (BWS)

PEDONC-2.5: Denys-Drash Syndrome (DDS)

PEDONC-2.6: Wilms Tumor-Aniridia-Growth Retardation (WAGR)

PEDONC-2.7: Familial Adenomatous Polyposis (FAP) and Related Conditions

PEDONC-2.8: Multiple Endocrine Neoplasias (MEN)

PEDONC-2.9: Tuberous Sclerosis Complex (TSC)

PEDONC-2.10: Von Hippel-Lindau Syndrome (VHL)

PEDONC-2.11: Rhabdoid Tumor Predisposition Syndrome

PEDONC-2.12: Familial Retinoblastoma Syndrome

PEDONC-2.13: Hereditary Paraganglioma-Pheochromocytoma (HPP) Syndromes

PEDONC-2.14: Costello Syndrome

PEDONC-2.15: Constitutional Mismatch Repair Deficiency (CMMRD or Turcot Syndrome)

PEDONC-2.16: Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

PEDONC-2.17: Other Renal Cell Cancer Predisposition Syndromes

PEDONC-2.1: Screening Imaging in Cancer Predisposition Syndromes – General Considerations

This section is intended to give guidance for screening imaging prior to diagnosis with a specific malignancy. Once a patient with a cancer predisposition syndrome has been diagnosed with a malignant disease, future imaging decisions should be guided by the appropriate disease-specific guidelines except as explicitly stated elsewhere in this section.

This section's guidelines are limited to cancer predisposition syndromes with screening imaging considerations. Syndromes requiring only clinical or laboratory screening are not discussed here.

- In general, a recent (within 60 days) detailed history and physical examination and appropriate laboratory studies should be performed prior to considering advanced imaging, unless the patient is undergoing guideline-supported scheduled screening evaluation identified in this section
- Where MRI is indicated in these guidelines, CT may be approved only if MRI is contraindicated, given the risk of radiation exposure in these syndromes.
- Many of these cancer predisposition syndromes also affect adults as survival continues to improve for these individuals. **Adults with syndromes covered in this section may follow these imaging guidelines except where contradicted by specific statements in the general imaging guidelines or payor-specific coverage policies.**
- Documentation of genetic or molecular confirmation of the appropriate syndrome with increased cancer risk is preferred for any patient to qualify for screening imaging. There are a number of complex ethical, social, and financial issues involved in the decision to complete genetic testing in a pediatric patient.
 - ◆ Note: Some payors consider certain genetic tests to be experimental, and those coverage policies supersede the recommendations for genetic testing in this section.
 - ◆ From the 2013 AAP Policy Statement, "Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality." ***Imaging surveillance is one such intervention and should not be performed without justifiable cause.***
 - ◆ Genetic testing should be performed in conjunction with genetic counseling for appropriate communication of risks identified by testing.
 - ◆ When genetic testing is not possible or not supported by health plan coverage policies, formal diagnosis after evaluation by a physician with significant training and/or experience in cancer predisposition syndromes (most commonly a geneticist or oncologist) is generally sufficient to confirm eligibility for screening imaging.

- Due to the length of time for image acquisition and the need for stillness, anesthesia is required for almost all infants and young children (age < 7 years), as well as older children with delays in development or maturity. In this patient population, MRI imaging sessions should be planned with a goal of avoiding a short-interval repeat anesthesia exposure due to insufficient information using the following considerations:
 - ◆ MRI should always be performed without and with contrast unless there is a specific contraindication to gadolinium use, since the patient already has intravenous access for anesthesia.
 - Recent evidence based literature demonstrates the potential for gadolinium deposition in various organs including the brain, after the use of MRI contrast.
 - The U.S. food and drug administration (FDA) has noted that there is currently no evidence to suggest that gadolinium retention in the brain is harmful and restricting gadolinium-based contrast agents (GBCAS) use is not warranted at this time. It has been recommended that GBCA use should be limited to circumstances in which additional information provided by the contrast agent is necessary and the necessity of repetitive MRIs with GBCAS should be assessed.
 - If requesting clinicians indicate that a non-contrast study is being requested due to concerns regarding the use of gadolinium, the exam can be approved.
 - ◆ If multiple body areas are supported by eviCore guidelines for the clinical condition being evaluated, MRI of all necessary body areas should be obtained concurrently in the same anesthesia session

PEDONC-2.2: Li-Fraumeni Syndrome (LFS)

- Syndrome inherited in an autosomal dominant manner (50% risk to offspring) associated with germline mutations in *TP53* resulted in an increased susceptibility to a variety of cancers.
- Eighty percent of individuals will have germline *TP53* mutation:
 - ◆ Tumor-specific *TP53* mutations are much more common than germline *TP53* mutations and are not associated with an increased risk for subsequent cancers
 - ◆ If *TP53*-negative, formal diagnosis of LFS should be assigned by a physician with significant training and/or experience in LFS (most commonly a geneticist or oncologist) based on specified clinical criteria prior to beginning a screening imaging program
 - ◆ *TP53* mutations may be present in 50 to 80% of pediatric adrenocortical carcinoma, 10% of pediatric rhabdomyosarcoma, and 10% of pediatric osteosarcoma
- Patients with LFS have an increased sensitivity to ionizing radiation, so screening strategies resulting in significant radiation exposure are not appropriate (CT and nuclear medicine).
- When a specific malignancy is suspected, the patient should be imaged according to the eviCore imaging guideline specific to the suspected cancer type

The following imaging studies should be considered appropriate in individuals with LFS:

- Annual complete detailed physical examinations, complete blood counts, and urinalyses form the backbone of LFS cancer screening.

Indication	Imaging Study
All individuals	➤ Both of the following, annually: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ Whole-body MRI (WBMRI, CPT® 76498) ■ 76498 is the only approvable code for whole-body MRI at this time. ➤ Every 3 months from birth to age 18: ◆ Abdominal (CPT® 76700) and pelvic (CPT® 76856) ultrasound ➤ Beginning at age 20: ◆ Annual Breast MRI (CPT® 77049), alternating every 6 months with breast ultrasound
Documented signs or symptoms suggestive of possible malignancy	➤ Targeted MRI without and with contrast of the involved body area(s)

PEDONC-2.3: Neurofibromatosis 1 and 2 (NF1 and NF2)

NF1:

- Common syndrome inherited in an autosomal dominant manner (50% risk to offspring) affecting 1 in 2500 people. The diagnosis is commonly made based on established clinical criteria including café-au-lait spots, lisch nodules of the iris, axillary freckling, family history, and the presence of NF-associated tumors.
- Genetic testing is encouraged for children with possible NF1 and no family history prior to assigning a diagnosis, but will not identify a mutation for all individuals with NF1. The majority of tumors are benign in nature, but malignant degeneration can occur. The most frequent neoplasms associated with NF1 in children are malignant peripheral nerve sheath tumor (MPNST), glioma, pheochromocytoma, and leukemia.
- NF1-affected persons have increased sensitivity to ionizing radiation, so CT and nuclear medicine imaging are not appropriate screening or surveillance studies for these individuals. CT and/or nuclear medicine studies may be indicated for acute clinical situations and should be judged on a case-by-case basis.
 - ◆ These requests will be forwarded for Medical Director review.
- Annual ophthalmology evaluation is strongly recommended beginning at the time of diagnosis of NF1 to evaluate for optic pathway abnormalities.
 - ◆ Screening MRIs of the brain and orbits for asymptomatic individuals are not generally recommended due to the ~60% rate of unidentified bright objects (UBOs, T2-weighted signal abnormalities) which mostly disappear by age 30
 - Routine follow up imaging of UBOs is not warranted in the absence of acute symptoms suggesting new or worsening intracranial disease
- Individuals with NF1 are at increased risk for plexiform neurofibromas (PN) and malignant peripheral nerve sheath tumors (MPNST— a high grade sarcoma).
 - ◆ Screening imaging of asymptomatic individuals for these tumors is not supported by evidence. PET imaging is not supported for PN surveillance in asymptomatic individuals at this time as the positive predictive value is only 60 to 65% even in symptomatic individuals.
- Although PET imaging has a positive predictive value of only 61 to 63% in NF1 with suspected transformation to MPNST, the negative predictive value is high (96 to 99%)
 - ◆ Inconclusive PET findings should lead to biopsy of the concerning lesion
 - ◆ Repeat PET studies are not indicated due to the poor positive predictive value in this setting

The following imaging studies should be considered appropriate in individuals with NF1:

Indication	Imaging Study
➤ Clarification of the diagnosis of NF1 if evaluation by a physician with significant training and/or experience in neurofibromatosis is inconclusive ◆ Most commonly a neurologist, geneticist, ophthalmologist, or oncologist	➤ One-time MRI Brain (CPT® 70553) and Orbits (CPT® 70543) without and with contrast
➤ New or worsening neurological or visual symptoms	➤ MRI Brain (CPT® 70553) and Orbits (CPT® 70543) without and with contrast
➤ Clinical symptoms suggestive of change in a known plexiform neurofibroma ◆ Examples include: pain, rapid growth, and neurologic dysfunction	➤ MRI without and with contrast
➤ Clinical symptoms concerning for malignant transformation of a known plexiform neurofibroma, and all of the following are met: ◆ Recent MRI is inconclusive regarding transformation or progression ◆ Negative PET will result in a decision to avoid biopsy in a difficult or morbid location	➤ PET (CPT® 78815 or 78816)
➤ New soft tissue mass(es)	➤ See: <u>MS 10.1</u> or <u>PEDMS 3.1</u> depending on the patient's age at the time the mass is discovered. Plain x-ray or ultrasound is not required prior to advanced imaging in these individuals.
➤ New bone mass(es)	➤ See: <u>PEDONC-9.1: Bone Tumors</u>
➤ Documented optic pathway gliomas	➤ See: <u>PEDONC-4.2: Intracranial Low Grade Gliomas</u>
➤ Known plexiform neurofibromas	➤ See: <u>PEDPN-2.1: Neurofibromatosis 1</u>

NF2:

- NF2 is substantially less common than NF1. It is inherited in an autosomal dominant manner (50% risk to offspring) affecting ~1 in 25000 people. NF2 is associated with increased risk for meningiomas (50% of affected individuals), vestibular schwannomas, and spinal tumors (75% of affected individuals).

The following imaging studies should be considered appropriate in individuals with NF2:

Indication	Imaging Study
➤ All individuals, beginning at age 10 years	➤ Annual MRI Brain without and with contrast (CPT® 70553)
➤ All individuals without a history of spinal tumors, beginning at age 10 years	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 3 years
➤ All individuals with a history of spinal tumors	➤ Annual MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
➤ Clinical symptoms of intracranial mass or vestibular disease	➤ MRI Brain without and with contrast (CPT® 70553)
➤ Any of the following: ◆ Clinical symptoms suggestive of new or progressive spinal or paraspinal tumors, including uncomplicated back pain or radiculopathy ◆ Recent diagnosis with a meningioma or vestibular schwannoma	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
➤ Surveillance for progression of unresected tumors in individuals with known vestibular schwannoma	➤ Annual MRI Brain without and with contrast (CPT® 70553)
➤ Known vestibular schwannomas and any of the following: ◆ New or worsening clinical symptoms including hearing loss ◆ Preoperative planning	➤ MRI Brain without and with contrast (CPT® 70553)
➤ Known meningioma	➤ See: <u>ONC-2.8: Meningiomas</u>
➤ Known ependymoma	➤ See: <u>PEDONC-4.8: Ependymoma</u>

PEDONC-2.4: Beckwith-Wiedemann Syndrome (BWS)

- Inherited syndrome characterized by macroglossia, hemihypertrophy, macrosomia, organomegaly, and neonatal hypoglycemia. Individuals with isolated hemihypertrophy are also imaged according to this guideline.
- Caused by mutation at chromosome 11p15, affected children are predisposed to Wilms tumor, hepatoblastoma, rhabdomyosarcoma, and adrenal tumors.

The following imaging studies should be considered appropriate in individuals with BWS:

Indication	Imaging Study
➤ All individuals, from birth to the 8 th birthday	➤ Abdominal ultrasound (CPT® 76700) every 3 months
➤ Purely cystic adrenal mass found on screening ultrasound	➤ Continue screening ultrasound (CPT® 76700 or 76705) every 3 months without additional imaging
➤ Solid or mixed adrenal mass found on screening ultrasound and: ◆ Patient age 0 to 5 months, and ◆ Mass 0 to 3 cm in diameter	➤ MIBG imaging (See: <u>PEDONC-1.3</u> for coding) and either CT or MRI Abdomen (contrast as requested)
➤ Solid or mixed adrenal mass found on screening ultrasound and: ◆ Patient age 0 to 5 months, and ◆ Mass > 3 cm in diameter	➤ MIBG imaging (See: <u>PEDONC-1.3</u> for coding) and MRI Abdomen (contrast as requested)
➤ Solid or mixed adrenal masses on screening ultrasound and: ◆ Patient age 6 months or greater	➤ MIBG imaging (See: <u>PEDONC-1.3</u> for coding) prior to biopsy or resection ◆ If no evidence of malignancy on biopsy or resection, resume screening abdominal ultrasound every 3 months
➤ Solid or mixed adrenal masses on screening ultrasound and: ◆ No evidence of malignancy based on MIBG, CT or MRI, Urine HVA/VMA, and serum ACTH	➤ Repeat abdominal ultrasound (CPT® 76700 or 76705) every 6 weeks for 2 years
➤ Known renal tumors	➤ See: <u>PEDONC-7: Pediatric Renal Tumors</u>
➤ Known hepatoblastoma	➤ See: <u>PEDONC-11.2: Hepatoblastoma</u>
➤ Known neuroblastoma	➤ See: <u>PEDONC-6: Neuroblastoma</u>
➤ Known adrenocortical carcinoma	➤ See: <u>PEDONC-14: Pediatric Adrenocortical Carcinoma</u>
➤ Known pheochromocytoma	➤ See: <u>ONC-15: Neuroendocrine Cancers and Adrenal Tumors</u>

PEDONC-2.5: Denys-Drash Syndrome (DDS)

- Characterized by pseudohermaphroditism, early renal failure, and > 90% risk of Wilms tumor development in each kidney. Associated with mutations at 11p13, risk of renal failure after detection of symptomatic Wilms tumor is 62%, so early detection may allow for renal-sparing surgical approaches.

The following imaging studies should be considered appropriate in individuals with DDS:

Indication	Imaging Study
➤ All individuals, from birth to the 8 th birthday	➤ Abdominal ultrasound (CPT® 76700) every 3 months
➤ Known renal tumors	➤ See: <u>PEDONC-7: Pediatric Renal Tumors</u>

PEDONC-2.6: Wilms Tumor-Aniridia-Growth Retardation (WAGR)

- Named for the components of the disorder, it is associated with mutations at 11p13. As the name suggests, individuals are predisposed to Wilms tumor, with 57% of individuals in one cohort developing Wilms tumor. Risk of renal failure after detection of symptomatic Wilms tumor is 38%, so early detection may allow for renal-sparing surgical approaches

The following imaging studies should be considered appropriate in individuals with WAGR:

Indication	Imaging Study
➤ All individuals, from birth to the 8 th birthday	➤ Abdominal ultrasound (CPT® 76700) every 3 months
➤ Known renal tumors	➤ See: <u>PEDONC-7: Pediatric Renal Tumors</u>

PEDONC-2.7: Familial Adenomatous Polyposis (FAP) and Related Conditions

- Inherited in an autosomal dominant manner (50% risk to offspring), it is also known as Adenomatous Polyposis Coli (APC). It is associated with the development of thousands of colonic polyps by age 20 and > 90% risk of colorectal carcinoma. Prophylactic total colectomy is recommended by age 20 for most individuals. FAP is also associated with hepatoblastoma, tumors of the pancreas and small bowel, medulloblastoma, and thyroid cancer.
- Individuals with Lynch, Gardner, and Turcot syndromes should also be imaged according to these guidelines.

The following imaging studies should be considered appropriate in individuals with FAP and related conditions:

- Individuals with FAP receive annual esophagogastroduodenoscopy beginning at age 10, serum AFP every 3 months to the 6th birthday, and annual colonoscopy beginning at age 10.

Indication	Imaging Study
➤ All individuals, from birth to the 6 th birthday	➤ Abdominal ultrasound (CPT® 76700) every 3 months
➤ All individuals, beginning at age 12 years	➤ Annual thyroid ultrasound (CPT® 76536)
➤ All individuals, beginning at age 30 years	➤ Annual pelvic ultrasound (CPT® 76856)
➤ Family history of desmoid tumors	➤ Abdominal ultrasound (CPT® 76700) annually for life after age 6
➤ Known colorectal tumors	➤ See: <u>ONC-16: Colorectal Cancer</u>
➤ Known desmoid tumors	➤ See: <u>PEDONC-8.3: Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)</u>

PEDONC-2.8: Multiple Endocrine Neoplasias (MEN)

- Inherited in an autosomal dominant manner (50% risk to offspring)
- MEN1 is characterized by parathyroid, pancreatic islet cell, and pituitary gland tumors (3 P's), as well as carcinoid tumors in the chest and abdomen, and 28% of individuals will develop at least one tumor by age 15.
- MEN2a is characterized by medullary thyroid carcinoma, parathyroid adenomas, and pheochromocytomas.
- MEN2b is characterized by ganglioneuromas of the GI tract and skeletal abnormalities presenting in infancy.

The following imaging studies should be considered appropriate in individuals with MEN1:

Indication	Imaging Study
➤ All individuals, beginning at age 5 years	➤ Annual MRI Brain without and with contrast (CPT® 70553) ➤ Annual MRI Abdomen without and with contrast (CPT® 74183), CT Abdomen with contrast (CPT® 74160), or ultrasound (CPT® 76700) ➤ Annual Octreotide study (see: PEDONC-1.3 for coding)
➤ All individuals, beginning at age 15 years	➤ Annual MRI Chest without and with contrast (CPT® 71552) or CT Chest with contrast (CPT® 71260)
➤ Known thyroid cancer	➤ See: <u>ONC-6: Thyroid Cancer</u>
➤ Known pheochromocytoma	➤ See: <u>ONC-15: Neuroendocrine Cancers and Adrenal Tumors</u>

The following imaging studies should be considered appropriate in individuals with MEN2a and MEN2b:

- Individuals with MEN2a and MEN2b receive annual measurement of catecholamines for pheochromocytoma screening

Indication	Imaging Study
➤ All individuals, beginning at age 5 years	➤ MRI Abdomen without and with contrast (CPT® 74183) can be approved every 3 years
➤ One of the following: ◆ Elevated catecholamines ◆ Inconclusive adrenal mass on MRI	➤ One of the following: ◆ Octreotide study (see: <u>PEDONC-1.3</u> for coding) ◆ Adrenal Nuclear Imaging (CPT® 78075)
➤ Known pheochromocytoma	➤ See: <u>ONC-15: Neuroendocrine Cancers and Adrenal Tumors</u>

PEDONC-2.9: Tuberous Sclerosis Complex (TSC)

Inherited in an autosomal dominant manner (50% risk to offspring), affecting ~1 in 6000 individuals, it is associated with benign tumors, hypopigmented skin macules (ash leaf spots), developmental delay, and epilepsy.

Malignancies associated with this syndrome include:

- Subependymal giant cell astrocytomas (SEGA tumors)
 - ◆ Historically, early surgery was important to reduce morbidity related to these tumors
 - ◆ More recently, everolimus has been successfully used to treat these tumors without surgery, and early detection remains an important feature for success
- Renal cell carcinoma
- Cardiac rhabdomyosarcoma
- Pulmonary lymphangioleiomyomatosis

The following imaging studies should be considered appropriate in individuals with TSC:

- Individuals with TSC receive annual ophthalmologic and dermatologic evaluation
- Abdominal MRI (CPT 74183) may be approved for women of childbearing age planning pregnancy.

Indication	Imaging Study
➤ All individuals, at the time of suspected diagnosis until age 25 years	➤ Annual Brain MRI without and with contrast (CPT® 70553)
➤ All individuals at diagnosis	➤ Single baseline MRI Abdomen without and with contrast (CPT® 74183)
➤ If no renal lesions seen on baseline MRI Abdomen	➤ From diagnosis through age 11: ◆ Annual Renal US (CPT® 76770) ➤ Age 12 (or 10 years earlier than the youngest family member with renal cell carcinoma, whichever comes earlier): ◆ MRI Abdomen without and with contrast (CPT® 74183) every 3 years in lieu of ultrasound
➤ For documented renal lesions on baseline MRI Abdomen or any ultrasound	➤ MRI Abdomen without and with contrast (CPT® 74183) annually
➤ All individuals, beginning at age 18 years	➤ CT Chest without contrast (CPT® 71250) every 5 years
➤ All individuals, for cardiac screening or follow up of known cardiac disease	➤ See: <u>PEDCD-8.2: Initial Transthoracic Echocardiography (TTE) Indications</u> and <u>PEDCD-8.3: Repeat Transthoracic Echocardiography Indications</u>
➤ Individuals with documented abnormalities on baseline CT Chest	➤ Additional CT Chest without contrast or with contrast (CPT® 71250 or 71260) may be approved every 1 year
➤ Any of the following: ◆ New pulmonary symptoms ◆ Worsening pulmonary function testing	➤ CT Chest without contrast (CPT® 71250)
➤ Known SEGA tumors	➤ See: <u>PEDONC-4.2: Intracranial Low Grade Gliomas (LGG)</u>
➤ Known renal cell carcinoma	➤ See: <u>PEDONC-7.4: Pediatric Renal Cell Carcinoma (RCC)</u>

PEDONC-2.10: Von Hippel-Lindau Syndrome (VHL)

- Inherited in an autosomal dominant manner (50% risk to offspring), it is associated with CNS hemangioblastomas, retinal angiomas, endolymphatic sac tumors (ELST), gastrointestinal stromal tumor (GIST), renal cell carcinoma (RCC), and pheochromocytomas and other neuroendocrine tumors (NETs). Pediatric individuals are at risk of developing hemangioblastomas and pheochromocytomas that can remain clinically occult until symptoms become severe. Historically, substantial mortality was attributable to RCC, pancreatic NET, and CNS hemangioblastoma.

The following imaging studies should be considered appropriate in individuals with VHL:

- Individuals with VHL receive annual ophthalmologic evaluation beginning at birth, annual measurement of catecholamines beginning at age 2, and audiology assessment every 2 years beginning at age 5

Indication	Imaging Study
➤ All individuals, beginning at age 8 years	➤ MRI Brain without and with contrast (CPT® 70553) and MRI Spine without and with contrast (Cervical-CPT® 72156), Thoracic-CPT® 72157, and Lumbar-CPT® 72158) every 2 years
➤ Individuals with frequent ear infections, prior to age 8	➤ One-time MRI Brain without and with contrast (CPT® 70553)
➤ All individuals, beginning at age 5 years	➤ Annual Abdominal US (CPT® 76700)
➤ All individuals, beginning at age 12 years	➤ MRI Abdomen without and with contrast (CPT® 74183) every 2 years
➤ One of the following: ◆ Elevated catecholamines ◆ Inconclusive adrenal mass on MRI	➤ Octreotide study (CPT® 78800, CPT® 78801, CPT® 78802, CPT® 78803, or CPT® 78804) or Adrenal Nuclear imaging (CPT® 78075)
➤ Individuals with known hemangioblastoma anywhere in the body (based on imaging) that has not been resected	➤ Both of the following, every 1 year: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156), Thoracic-CPT® 72157, and Lumbar-CPT® 72158)
➤ Known hemangioblastoma that has not been resected and new or worsening symptoms	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156), Thoracic-CPT® 72157, and Lumbar-CPT® 72158)
➤ Known (based on imaging) CNS hemangioblastoma	➤ See: <u>PEDONC-4.2: Intracranial Low Grade Gliomas (LGG)</u>
➤ Known renal cell carcinoma	➤ See: <u>PEDONC-7.4: Pediatric Renal Cell Carcinoma (RCC)</u>
➤ Known pheochromocytoma or other neuroendocrine tumor	➤ See: <u>ONC-15: Neuroendocrine Cancers And Adrenal Tumors</u>

PEDONC-2.11: Rhabdoid Tumor Predisposition Syndrome

- Inherited in an autosomal dominant manner (50% risk to offspring), it is associated with malignant rhabdoid tumors of the kidney and extrarenal locations, and atypical teratoid/rhabdoid tumors (ATRT) of the CNS. It is caused by a germline mutation in *INI1* or *SMARCB1*, and is associated with a more variable prognosis than de novo rhabdoid tumors.
- Note: Whole-body MRI resolution may not be sufficient to detect small rhabdoid tumors, so is not recommended in lieu of conventional MRI studies

The following imaging studies should be considered appropriate in individuals with Rhabdoid Tumor Predisposition Syndrome:

Indication	Imaging Study
➤ All individuals, from birth to 12 months of age	➤ All of the following, monthly: ◆ US Head (CPT® 76506) ◆ US Abdomen (CPT® 76700) ◆ US Pelvis (CPT® 76856)
➤ All individuals, from age 1 to 5 years	➤ All of the following, every 3 months: ◆ MRI Brain (CPT® 70553) ◆ MRI Spine (CPT® 72156, 72157, & 72158) without and with contrast ◆ MRI Abdomen and Pelvis (CPT® 74183 & 72197) OR Ultrasound Abdomen and Pelvis (CPT® 76700 & 76856)
➤ Clinical symptoms present suggesting malignancy	➤ Targeted advanced imaging of the suspected disease site (CT with or without contrast or MRI with and without contrast)
➤ Inconclusive findings on ultrasound	➤ MRI with and without contrast of the inconclusive US site ◆ MRI should be used in place of ultrasound for remainder of planned screening

PEDONC-2.12: Familial Retinoblastoma Syndrome

- This syndrome is inherited in an autosomal dominant manner (50% risk to offspring). As the name suggests, it is associated with retinoblastoma, as well as osteosarcoma, pediatric melanoma, and a significantly increased risk for radiation-related malignancies.
- Regular physical and ophthalmologic evaluations under anesthesia (EUA) are the hallmark of surveillance strategies for these individuals, and asymptomatic screening imaging does not have a defined role at this time.

The following imaging studies should be considered appropriate in individuals with Familial Retinoblastoma Syndrome:

Indication	Imaging Study
➤ Individuals with retinomas (pre-malignant retinal lesions)	➤ Annual MRI Orbits (CPT® 70543)
➤ Either of the following: ◆ Inconclusive EUA findings ◆ New symptoms	➤ US Orbits (CPT® 76512, 76510, or 76511) or MRI Orbits (CPT® 70543) ◆ These studies should be used if at all possible in lieu of CT or nuclear imaging to avoid radiation exposure

PEDONC-2.13: Hereditary Paraganglioma-Pheochromocytoma (HPP) Syndromes

- Caused by mutations in *SDHx* genes, this syndrome is inherited in an autosomal dominant manner (50% risk to offspring), and is associated with pheochromocytomas and paragangliomas.
- Individuals with multiple endocrine neoplasias should not use this guideline and should be imaged according to **PEDONC-2.8: Multiple Endocrine Neoplasias (MEN)**.
- MRI is preferred to CT to minimize radiation exposure given these individuals' lifelong need for screening

The following imaging studies should be considered appropriate in individuals with HPP Syndromes:

- All individuals with HPP receive annual measurement of catecholamines

Indication	Imaging Study
➤ All individuals with <i>SDHx</i> mutations, beginning at age 6	➤ Every 2 years, ONE of the following sets of imaging: ◆ Whole-body MRI (CPT® 76498) ■ 76498 is the only approvable code for whole-body MRI at this time - OR ◆ MRI Neck (CPT® 70543), Chest (CPT® 71552), Abdomen (CPT® 74183), Pelvis (CPT® 72197) without and with contrast OR ■ If MRI cannot be performed: CT Neck (CPT® 70491), Chest (CPT® 71260), and Abdomen/Pelvis (CPT® 74177) with contrast
➤ Known pheochromocytoma or other neuroendocrine tumors	➤ See: <u>ONC-15: Neuroendocrine Cancers and Adrenal Tumors</u>

PEDONC-2.14: Costello Syndrome

- Caused by mutations in *HRAS* genes, this syndrome is inherited in an autosomal dominant manner (50% risk to offspring), and is associated with rhabdomyosarcoma and neuroblastoma in early childhood, and transitional cell cancer of the bladder in older children and adults.

The following imaging studies should be considered appropriate in individuals with Costello Syndrome:

Indication	Imaging Study
➤ Following confirmation of gene mutation	➤ Any or all of the following: ◆ Echocardiogram ■ CPT® 93306 or ■ CPT® 93308 with 93321 and 93325 ◆ MRI Brain (CPT® 70553) without and with contrast ◆ MRI Cervical (CPT® 72156) and Thoracic Spine (CPT® 72157) without and with contrast
➤ All individuals, from birth to 10 th birthday	➤ Every 3 months: ◆ US Abdomen (CPT® 76700) and Pelvis (CPT® 76856)
➤ Known cardiac disease	➤ See: <u>PEDCD-8.2: Initial Transthoracic Echocardiography (TTE) Indications</u> and <u>PEDCD-8.3: Repeat Transthoracic Echocardiography Indications</u>
➤ Known rhabdomyosarcoma	➤ See: <u>PEDONC-8.2: Rhabdomyosarcoma (RMS)</u>
➤ Known neuroblastoma	➤ See: <u>PEDONC-6: Neuroblastoma</u>

PEDONC-2.15: Constitutional Mismatch Repair Deficiency (CMMRD or Turcot Syndrome)

- A highly penetrant and aggressive cancer predisposing syndrome resulting from autosomal recessive inheritance of biallelic mutations in mismatch repair genes, CMMRD syndrome leads to substantial risk for several commonly fatal childhood malignancies - high-grade CNS tumors (glioma, PNET, medulloblastoma) and hematologic malignancies (non-Hodgkin lymphoma, acute lymphoblastic leukemia). Individuals with CMMRD are also at increased risk for gastrointestinal tumors.

The following imaging studies should be considered appropriate in individuals with CMMRD/Turcot Syndrome:

Indication	Imaging Study
➤ All individuals, after CMMRD diagnosis is confirmed by genetic mutation	➤ MRI Brain without and with contrast (CPT® 70553) every 6 months
➤ All individuals, beginning at age 4 years	➤ Annual esophagogastroduodenoscopy and colonoscopy
➤ All individuals, beginning at age 6 years	➤ Annual whole-body MRI (CPT® 76498) ◆ 76498 is the only approvable code for whole-body MRI at this time

PEDONC-2.16: Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

- Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a disorder in which affected individuals tend to develop benign tumors containing smooth muscle tissue (leiomyomas) in the skin and, in females, the uterus. Approximately 20 percent of people with HLRCC develop renal cell cancer. People with HLRCC are commonly diagnosed with kidney cancer in their forties but cases have been reported in individuals as young as 11.
- In 2019, Forde et al published the first large, prospective study of screening for HLRCC and showed that most symptomatic individuals present with stage 3 or 4 RCC with a high risk of death, and one life is saved for every 5 individuals on an MRI screening protocol.

The following imaging studies should be considered appropriate in individuals with HLRCC:

Indication	Imaging Study
➤ Beginning at age 8 years, individuals with at least one of the following: ◆ Documented fumarate hydratase (FH) gene mutation/variant consistent with HLRCC ◆ Histologically confirmed multiple cutaneous piloleiomyomas ◆ At least two of the following manifestations: ■ Surgical treatment for symptomatic uterine leiomyomas before age 40 ■ Type 2 papillary renal cell carcinoma or collecting duct renal carcinoma before age 40 ■ A first-degree family member with either of the two above criteria	➤ MRI Abdomen with and without contrast (CPT® 74183), annually

PEDONC-2.17: Other Renal Cell Cancer Predisposition Syndromes

Birt-Hogg-Dube Syndrome (BHDS)

- Birt-Hogg-Dube Syndrome (BHDS) is an autosomal dominant disorder with a heterozygous pathogenic variant in FLCN gene.
- These individuals have, or may have:
 - ◆ Cutaneous manifestations (fibrofolliculomas, acrochordons, angiofibromas, oral papules, cutaneous collagenomas, and epidermal cysts)
 - ◆ Pulmonary cysts/history of pneumothorax
 - ◆ A seven-fold increase in renal tumors
 - The most common renal tumors are oncocytoma, chromophobe, and a hybrid of these two.
 - Renal tumors may be multifocal and bilateral.
 - Median age of renal tumor diagnosis is 48 years.

The following imaging studies should be considered appropriate in individuals with BHDS:

- In addition to the following imaging studies, these individuals should have a screening colonoscopy starting at age 40.
 - ◆ Earlier colonoscopy may be considered for those with a family history of colorectal cancer earlier than age 40.

Indication	Imaging Study
➤ All individuals, beginning at age 20 years	➤ Abdominal MRI with and without contrast (CPT® 74183) every 3 years

BAP1 Tumor Predisposition Syndrome

- BAP1 tumor predisposition syndrome (TPDS) is an autosomal dominant condition with a predisposition to melanoma (ocular and cutaneous), mesothelioma, clear cell renal cancer, and chromophobe renal cancer.

The following imaging studies should be considered appropriate in individuals with BAP1:

Indication	Imaging Study
➤ All individuals, beginning at age 30 years	➤ Abdominal MRI with and without contrast (CPT® 74183) every 2 years

Hereditary Papillary Renal Carcinoma (HPRC)

- Hereditary papillary renal carcinoma (HPRC) is an autosomal dominant condition involving the MET gene and predisposes individuals to multifocal, bilateral renal tumors.

Indication	Imaging Study
➤ All individuals, beginning at age 30 years	➤ Abdominal MRI with and without contrast (CPT® 74183) every 2 years

References – PEDONC-2

1. Plon SE, Malkin D. Childhood Cancer and Heredity. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:13-31.
2. Aplan PD, Shern JF, Khan J. Molecular and genetic basis of childhood cancer. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:32-62.
3. Zellel K, Lindell RB, Schiffman JD, et al. Genetic predisposition to cancer. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1270-1293.
4. Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol*. 2005;23(2):276-292. doi:10.1200/JCO.2005.10.042.
5. Holman JD, Dyer JA. Genodermatoses with malignant potential. *Current Opin Pediatr*. 2007;19(4):446-454. doi:10.1097/MOP.0b013e3282495939.
6. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med*. 2008;359:2143-2153. doi:10.1056/NEJMra0802968.
7. Schiffman JD, Geller JL, Mundt E, et al. Update on pediatric cancer predisposition syndromes. *Pediatr Blood Cancer*. 2013;60(8):1247-1252. doi:10.1002/pbc.24555.
8. American Academy of Pediatrics. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 2013;131(3):620-622. doi:10.1542/peds.2012-3680.
9. Monsalve J, Kapur J, Malkin D, Babyn PS. Imaging of cancer predisposition syndromes in children. *Radiographics*. 2011;31(1):263-280. doi:10.1148/rg.311105099.
10. D'Orazio JA. Inherited cancer syndromes in children and young adults. *J Pediatr Hematol Oncol*. 2010;32(3):195-228. doi:10.1097/MPH.0b013e3181ced34c.
11. Lu KH, Wodd ME, Daniels M, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. *J Clin Oncol*. 2014;32(8):833-841. doi:10.1200/JCO.2013.50.9257.
12. Farid M, Ngeow J. Sarcomas associated with genetic cancer predisposition syndromes: a review. *Oncologist*. 2016;21(8):1002-1013. doi:10.1634/theoncologist.2016-0079.
13. Tiwari R, Singh AK, Somwaru AS, et al. Radiologist's primer on imaging of common hereditary cancer syndromes. *RadioGraphics*. 2019;39:759-778. doi:10.1148/rg.2019180171.
14. Schneider K, Zellel K, Nichols KE, Garber J. Li-Fraumeni Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., ed. *GeneReviews*® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. <https://www.ncbi.nlm.nih.gov/books/NBK1311/>.
15. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol*. 2011;12(6):559-567. doi:10.1016/S1470-2045(11)70119-X.
16. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol*. 2016;17(9):1295-1305. doi:10.1016/S1470-2045(16)30249-2.
17. Ballinger ML, Best A, Mai PL, et al. Baseline surveillance in Li-Fraumeni Syndrome using whole-body magnetic resonance imaging a meta analysis. *JAMA Oncol*. 2017;3(12):1634-1639. doi:10.1001/jamaoncol.2017.1968.
18. Ruijs MWG, Loo CE, van Buchem CAJM, et al. Surveillance of Dutch patients with Li-Fraumeni Syndrome: the life-guard study. *JAMA Oncol*. 2017;3(12):1733-1734. doi:10.1001/jamaoncol.2017.1346.
19. Mai PL, Khincha PP, Loud JT, et al. Prevalence of Cancer at Baseline screening in the National Cancer Institute Li-Fraumeni Syndrome Cohort. *JAMA Oncol*. 2017;3(12):1640-1645. doi:10.1001/jamaoncol.2017.1350.
20. Kratz CP, Achatz MI, Brugières L, et al. Cancer screening recommendations for individuals with Li-Fraumeni Syndrome. *Clin Cancer Res*. 2017;23(11):e38-e45. doi:10.1158/1078-0432.CCR-17-0408.
21. Greer MC, Voss SD, States LJ. Pediatric cancer predisposition imaging: focus on whole-body MRI. *Clin Cancer Res*. 2017;23(11):e6-e13. doi:10.1158/1078-0432.CCR-17-0515.
22. Asdahl PH, Ojha RP, Hasle H. Cancer screening in Li-Fraumeni Syndrome. *JAMA Oncol*. 2017;3(12):1645-1646. doi:10.1001/jamaoncol.2017.2459.
23. Eutsler EP, Khanna G. Whole-body magnetic resonance imaging in children: technique and clinical applications. *Pediatr Radiol*. 2016;46(6):858-872. doi: 10.1007/s00247-016-3586-y.

24. Gottumukkalla RV, Gee MS, Hampilos PJ, Greer MC. Current and emerging roles of whole-body MRI in evaluation of pediatric cancer patients. *RadioGraphics*. 2019;39:516-534. doi:10.1148/rg.2019180130.
25. Daly MB, Pilarski R, Berry MP, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020—December 4, 2019. Genetic/Familial High-Risk Assessment: Breast and Ovarian, available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2020 12/4/2019 ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
26. Miller DT, Freedenberg D, Schorry E, et al. Health supervision for children with neurofibromatosis type 1. *Pediatrics*. 2019;143:e20190660. doi:10.1541/peds.2019-0660.
27. Sahin M. Neurocutaneous syndromes. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE, eds. *Nelson Textbook of Pediatrics*. Philadelphia, PA: Elsevier Saunders; 2011:2046-2048.
28. Ullrich NJ. Neurocutaneous syndromes and brain tumors. *J Child Neurol*. 2016;31(12):1399-1411. doi:10.1177/0883073815604220.
29. Korf BR and Bebin EM. Neurocutaneous disorders in Children. *Pediatr Rev*. 2017; 38(3):119-127. doi:10.1542/pir.2015-0118.
30. Campian J, Gutmann DH. CNS tumors in neurofibromatosis. *J Clin Oncol*. 2017; 35(21):2378-2385. doi:10.1200/JCO.2016.71.7199.
31. Friedman JM. Neurofibromatosis 1. In: Pagon RA, Adam MP, Ardinger HH et al., eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle;1998-2017. Version June 6, 2019. <https://www.ncbi.nlm.nih.gov/books/NBK1109/>.
32. Karajannis MA, Ferner RE. Neurofibromatosis-related tumors: emerging biology and therapies. *Curr Opin Pediatr*. 2015;27(1):26-33. doi:10.1097/MOP.0000000000000169.
33. Meany H, Dombi E, Reynolds J, et al. 18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) evaluation of nodular lesions in patients with neurofibromatosis Type 1 and Plexiform Neurofibromas (PN) or Malignant Peripheral Nerve Sheath Tumors (MPNST). *Pediatr Blood Cancer*. 2013;60(1):59-64. doi:10.1002/pbc.24212.
34. Tsai LL, Druback L, Fahey F, et al. [18F]-Fluorodeoxyglucose positron emission tomography in children with neurofibromatosis type 1 and plexiform neurofibromas: correlation with malignant transformation. *J Neuro Oncol*. 2012;108(3):469-475. doi:10.1007/s11060-012-0840-5.
35. Corbemale P, Valeyrie-Allanore L, Giammarile F, et al. Utility of 18F-FDG PET with a semi-quantitative index in the detection of sarcomatous transformation in patients with neurofibromatosis Type 1. *PLoS ONE*. 2014;9(2):e85954. doi:10.1371/journal.pone.0085954.
36. Chirindel A, Chaudhry M, Blakeley JO, Wahl R. 18F-FDG PET/CT Qualitative and quantitative evaluation in neurofibromatosis Type 1 Patients for detection of malignant transformation: comparison of early to delayed imaging with and without liver activity normalization. *J Nucl Med*. 2015;56(3):379-385. doi:10.2967/jnumed.114.142372.
37. Prada CE, Hufnagel RB, Hummel TR, et al. The use of magnetic resonance imaging screening for optic pathway gliomas in children with neurofibromatosis Type 1. *J Pediatr*. 2015;167(4):851-856. doi:10.1016/j.jpeds.2015.07.001.
38. Blakeley JO, Evans DG, Adler J, et al. Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis Type 2. *Am J Med Genet A*. 2012;158A(1):24-41. doi:10.1002/ajmg.a.34359.
39. Evans DG. Neurofibromatosis 2. In: Pagon RA, Adam MP, Bird TD et al., eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 2011. Version March 15, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1201/>.
40. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. *Orphanet J Rare Dis* 2009;4:16. doi:10.1186/1750-1172-4-16.
41. Ardern-Holmes S, Fisher G, North K. Neurofibromatosis Type 2: presentation, major complications, and management, with a focus on the pediatric age group. *J Child Neurol*. 2016;32(1):9-22. doi:10.1177/0883073816666736.

42. Shuman C, Beckwith JB, Weksberg R. Beckwith-Wiedemann syndrome. In: Pagon RA, Adam MP, Bird TD et al., eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 2016. Version August 11, 2016. <https://www.ncbi.nlm.nih.gov/pubmed/20301568>.
43. Choyke PL, Siegel MJ, Craft AW, Green DM, DeBaun MR. Screening for Wilms Tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. *Med Pediatr Oncol*. 1999;32(3):196-200. doi:10.1002/(SICI)1096-911X(199903)32:3<196::AID-MPO6>3.0.CO;2-9.
44. Mussa A, Molinatto C, Baldassare G, et al. Cancer risk in Beckwith-Wiedemann syndrome: A systematic review and meta-analysis outlining a novel (epi)genotype specific histotype targeted screening protocol. *J Pediatr*. 2016 September;176:142-149. doi:10.1016/j.jpeds.2016.05.038.
45. MacFarland SP, Mostoufi-Moab S, Zelle K, et al. Management of adrenal masses in patients with Beckwith-Wiedemann syndrome. *Pediatr Blood Cancer*. 2017;64(8):e26432. doi:10.1002/pbc.26432.
46. Dome JS and Huff V. Wilms tumor predisposition. In: Pagon RA, Adam MP, Bird TD et al., eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 2016. <https://www.ncbi.nlm.nih.gov/pubmed/20301471> Accessed January 3, 2018
47. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR Syndrome: A Clinical Review of 54 Cases. *Pediatrics*. 2005;116(4):984-988. doi:10.1542/peds.2004-0467.
48. Provenzale D, Gupta S, Ahnen DJ, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2017—October 10, 2017, Genetic/Familial High-Risk Assessment: Colorectal, available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Genetic/Familial High-Risk Assessment: Colorectal V2.2019 8/8/19. ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
49. Kennedy RD, Potter DD, Moir CR, Mounif E. The natural history of familial adenomatous polyposis syndrome: A 24 year review of a single center experience in screening, diagnosis, and outcomes, *J Pediatr Surg* 2014;49(1):82-86. doi:10.1016/j.jpedsurg.2013.09.033.
50. Jasperson KW, Patel SG, Ahnen DJ. APC-Associated Polyposis Conditions. In: Pagon RA, Adam MP, Bird TD, et al., ed. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 2017. Version February 2, 2017. <https://www.ncbi.nlm.nih.gov/books/NBK1345/>.
51. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. *J Clin Oncol*. 2015;33(2):209-217. doi:10.1200/JCO.2014.58.1322.
52. Giusti F, Marini F, Brandi ML. Multiple endocrine neoplasia Type 1. In: Pagon RA, Adam MP, Ardinger HH et al, ed. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. Version December 14, 2017. <https://www.ncbi.nlm.nih.gov/books/NBK1538/>.
53. Thakker RV, Newey PJ, Walls GV, et al. Clinical Practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97(9):2990-3011. doi:10.1210/jc.2012-1230
54. Giri D, McKay V, Weber A, Blair JC. Multiple endocrine neoplasia syndromes 1 and 2: manifestations and management in childhood and adolescence. *Arch Dis Child*. 2015;100(10):994-999. doi:10.1136/archdischild-2014-307028.
55. Eng C. Multiple endocrine neoplasia Type 2. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1999-2019. Version August 15, 2019. <https://www.ncbi.nlm.nih.gov/books/NBK1257/>.
56. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous Sclerosis Complex. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; Version September 3, 2015. <https://www.ncbi.nlm.nih.gov/pubmed/20301399>.
57. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous sclerosis complex. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle;1993-2019. Version July 12, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1220/>.
58. Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. *Neurology*. 2013;80(6):574-580. doi:10.1212/WNL.0b013e3182815428.

59. Wheless JW, Klimo P. Subependymal giant cell astrocytomas in patients with tuberous sclerosis complex: considerations for surgical or pharmacotherapeutic intervention. *J Child Neurol*. 2014;29(11):1562-1571. doi:10.1177/0883073813501870.
60. van Leeuwen RS, Ahmad S, Links TP, Giles RH. Von Hippel-Lindau Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. Version September 6, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1463/>.
61. Nielsen SM, Rhodes L, Blanco I, et al. Von Hippel-Lindau Disease: genetics and role of genetic counseling in a Multiple Neoplasia Syndrome. *J Clin Oncol*. 2016;34(18):2172-2181.
62. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res*. 2017;23:e68-e75. doi: 10.1158/1078-0432.CCR-17-0547.
63. Kordes U, Bartelheim K, Modena P, et al. Favorable outcome of patients affected by rhabdoid tumors due to Rhabdoid Tumor Predisposition Syndrome (RTPS). *Pediatr Blood Cancer*. 2014;61(5):919-921. doi:10.1002/pbc.24793.
64. Sredni ST, Tomita T. Rhabdoid Tumor Predisposition Syndrome. *Pediatr Dev Pathol*. 2015;18(1):49-58. doi:10.2350/14-07-1531-MISC.1.
65. Nemes K, Bens S, Bourdeaut F, et al. Rhabdoid tumor predisposition syndrome. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. Version December 7, 2017. <https://www.ncbi.nlm.nih.gov/books/NBK469816/>.
66. Lohmann DR, Gallie BL. Retinoblastoma. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. Version November 21, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1452/>.
67. Kirmani S, Young WF. Hereditary Paraganglioma-Pheochromocytoma Syndromes. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 2008-2014. Version November 6, 2014. <https://www.ncbi.nlm.nih.gov/pubmed/20301715>.
68. Gripp KW, Lin AE. Costello Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1999-2019. Version January 12, 2012. <https://www.ncbi.nlm.nih.gov/books/NBK1507/>.
69. Tabori U, Hansford JR, Achatz MI, et al. Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood. *Clin Cancer Res*. 2017;23:e32-e37. doi: 10.1158/1078-0432.CCR-17-0574.
70. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management:
 - a. recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.
 - b. *Pediatr Neurol*. 2013;49(4):255–265. doi:10.1016/j.pediatrneurol.2013.08.002.
71. Campen CJ, Gutmann DH. Optic pathway gliomas in neurofibromatosis type 1. *J Child Neurol*. 2018;33(1):73–81. doi:10.1177/0883073817739509.
72. Rosser T. Neurocutaneous disorders. *CONTINUUM (MINNEAPOLIS)*. 2018;24(1, Child Neurology):96-129. doi:10.1212/CON.0000000000000562.
73. Motzer RJ, Jonasch E, Agarwal N, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2021 – July 15, 2020. Kidney Cancer, available at: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Kidney Cancer V1.2021 – 7/15/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
74. Tuberous Sclerosis Alliance. *Diagnosis, surveillance, and management of individuals with tuberous sclerosis complex*. Silver Spring, MD. Tuberous Sclerosis Alliance; 2014. <https://www.tsalliance.org/healthcare-professionals/diagnosis/>
75. Lam H, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: pathogenesis and therapy. *Nat Rev Nephrol*. 2018;14(11):704-706. doi:10.1038/s41581-018-0059-6.
76. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetic and surveillance recommendations in childhood. *Clin Cancer Res*. 2017;23:e68-e75. doi: 10.1158/1078-0432.CCR-17-0547.

77. Sattler EC, Ortud KS. Birt-Hogg-Dube Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews*™ [Internet]. Seattle, WA: University of Washington, Seattle;1993-2020. Version January 30, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK1522/>.
78. Pilarski R, Rai K, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews*™ [Internet]. Seattle, WA: University of Washington, Seattle;1993-2020. Version January 30, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK390611/>.
79. Gläsker S, Vergauwen E, Koch CA, Kutikov A, Vortmeyer AO. Von Hippel-Lindau disease: current challenges and future prospects. *Onco Targets Ther*. 2020;13;5669-5690. doi:10.2147/OTT.S190753.
80. VHL Alliance. VHLA suggested active surveillance guidelines. Boston, MA. VHL Alliance; 2020. <https://www.vhl.org/wp-content/uploads/2020/07/Active-Surveillance-Guidelines-2020-2.pdf>

PEDONC-3: Pediatric Leukemias**PEDONC-3.1: Pediatric Leukemia General Considerations****PEDONC-3.2: Acute Lymphoblastic Leukemia (ALL)****PEDONC-3.3: Acute Myeloid Leukemia (AML)**

PEDONC-3.1: Pediatric Leukemia General Considerations

The overwhelming majority of leukemias occurring in children are acute. Chronic myelogenous leukemia (CML) is rare in children, and the occurrence of chronic lymphocytic leukemia (CLL) appears to have only been reported once in pediatric patients to date.

- MRI Brain without and with contrast (CPT® 70553) can be performed in patients exhibiting CNS symptoms.
 - ◆ Imaging due to CSF tumor burden has not been shown to improve the detection of CNS involvement compared with CSF alone.
- Routine advanced imaging is not indicated in the evaluation and management of chronic myeloid leukemia in the absence of specific localizing clinical symptoms or clearance for hematopoietic stem cell transplantation. See: **ONC-29: Hematopoietic Stem Cell Transplantation** for imaging guidelines related to transplant.

PEDONC-3.2: Acute Lymphoblastic Leukemia (ALL)

- The majority of ALL patients have B-precursor ALL and routine advanced imaging is not necessary.
- Patients with B-precursor or T-cell lymphoblastic lymphoma without bone marrow involvement are treated similarly to leukemia patients of the same cell type and should be imaged according to this guideline section.
- This section does not apply to patients with mature B-cell histology (primarily Burkitt's in children). Please refer to **PEDONC-5.3: Pediatric Aggressive Mature B-Cell Non-Hodgkin Lymphomas (NHL)** for guidelines for these patients.
- CXR should be performed to evaluate for mediastinal mass in suspected cases or upon initial diagnosis.
 - ◆ If mediastinal widening is seen on CXR, CT Chest with contrast (CPT® 71260) is indicated immediately to evaluate for airway compression and anesthesia safety prior to attempting histologic diagnosis.
 - ◆ Patients with known or strongly suspected T-cell histology or other suspected lymphoblastic lymphoma involvement can have either of the following approved for initial staging purposes:
 - CT Neck (CPT® 70491), CT Chest (CPT® 71260) and CT Abdomen/Pelvis (CPT® 74177) with contrast OR
 - PET/CT (CPT® 78815 or 78816)
- MRI Brain without and with contrast (CPT® 70553) can be performed in patients exhibiting CNS symptoms.
 - ◆ Imaging due to CSF tumor burden has not been shown to improve the detection of CNS involvement compared with CSF alone.
- Additional imaging in lymphoblastic lymphoma:
- Follow up CT to assess response to therapy is indicated only for patients with known bulky nodal disease (usually with T-cell histology) at the end of induction (~4 to 6 weeks). Patients with residual masses can be evaluated with every new therapy phase (Consolidation, Interim maintenance, etc., generally every 8 to 12 weeks) until disease resolution is seen.
 - ◆ PET/CT (CPT® 78815) can be approved when residual mass ≥ 8 mm in diameter is present on recent CT imaging and there is documentation of how PET findings will affect immediate treatment decision making. These requests should be forwarded for Medical Director review.
- Once CT imaging shows no evidence of disease, further surveillance should use CXR or Abdominal Ultrasound (CPT® 76700) only, as indicated by site(s) of bulky disease present at diagnosis.
 - ◆ Patients with persistent residual masses can have CT of all involved bulky nodal areas performed as part of an end of therapy evaluation

Immunosuppression during ALL therapy and imaging ramifications:

- ALL patients are severely immunocompromised during the first 4 to 6 weeks of treatment (induction) and any conventional imaging request to evaluate for infectious complications during this time frame should be approved immediately.
- CT or MRI imaging requests for infectious disease concerns for ALL patients with absolute neutrophil count (ANC) < 500 or inconclusive findings on chest x-ray or US at any ANC during active treatment should be approved as requested.
- Additionally, patients may have therapy-induced hypogammaglobulinemia which requires supplemental intravenous immune globulin (IVIG) during maintenance therapy. Patients receiving supplemental IVIG should be treated similarly to patients with ANC < 500 with regards to imaging for infectious disease.
- Intracranial hemorrhage in patients treated with asparaginase
 - ◆ MRA/MRV of the head (CPT® 70544, 70545, or 70546) to rule out bleeding associated with sinus venous thrombosis

Imaging during therapy for relapsed ALL:

- Relapsed ALL patients are treated with very intensive chemotherapy regimens and most patients spend the majority of their chemotherapy treatment phase in the hospital. Due to the high risk of invasive infections, frequent CT or MRI imaging may be indicated to evaluate known or suspected new sites of invasive fungal or other aggressive infections, and in general these should be approved as requested.
 - ◆ Surveillance imaging of asymptomatic patients to detect invasive fungal infection has not been shown to impact patient outcomes. Imaging requests in these circumstances should only be approved when acute clinical decisions will be made based on the imaging.

Imaging of known or suspected osteonecrosis in ALL:

- Osteonecrosis (ON) in ALL patients is a relatively common complication of ALL and its treatment, primary corticosteroids. Approximately 3% of younger children and 12 to 15% of adolescents are affected by ON at some point during therapy. The peak incidence occurs approximately one year from the time of diagnosis.
 - ◆ For patients with symptoms suggesting osteonecrosis, MRI without contrast or without and with contrast of the affected joint(s) can be approved.
 - CT without contrast can be approved when MRI is contraindicated or unavailable, or for diagnosis of suspected subchondral fracture
 - ◆ Screening MRI of asymptomatic patients age ≤ 10 years to detect osteonecrosis has not been shown to impact patient outcomes, and it is not standard to alter treatment based on imaging findings alone without symptoms
 - A single screening MRI Bilateral Hips (CPT® 73721 or CPT® 73723 with modifier -50) can be approved 6 to 9 months after diagnosis for patients age ≥ 11 years
 - ◆ If osteonecrosis is detected on initial MRI, corticosteroids are often withheld during maintenance chemotherapy (but continued in earlier phases of therapy).
 - ◆ In patients whose symptoms have resolved and are still receiving active treatment, repeat MRI without contrast of the affected joint(s) can be approved every 2 cycles of maintenance (~every 6 months) if reintroduction of corticosteroids is being considered.
 - ◆ MRI without contrast of the affected joint(s) can be approved if requested for preoperative planning in patients undergoing core decompression
 - ◆ See: **PEDONC-19.4: Osteonecrosis In Long Term Cancer Survivors** for information on osteonecrosis in ALL patients who have completed therapy

PEDONC-3.3: Acute Myeloid Leukemia (AML)

The majority of AML patients do not have any bulky disease and routine advanced imaging is not necessary.

Advanced imaging may be indicated for rare patients with bulky tumor masses (commonly referred to as chloromas, leukemic sarcomas, or myeloid sarcomas) noted on physical examination or other imaging such as plain film or ultrasound.

- AML patients are treated with very intensive chemotherapy regimens and spend the majority of their chemotherapy treatment phase in the hospital. Due to the high risk of invasive infections, frequent CT or MRI imaging may be indicated to evaluate known sites of invasive fungal infection, and in general these should be approved as requested.
 - ◆ Surveillance imaging of asymptomatic patients to detect invasive fungal infection has not been shown to impact patient outcomes. Imaging requests in these circumstances should only be approved when acute clinical decisions will be made based on the imaging.

References – PEDONC-3

1. Rabin KR, Gramatges MM, Margolin JF, et al. Acute Lymphoblastic Leukemia. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:463-497.
2. Arceci RJ, Meshinchi S. Acute Myeloid Leukemia and Myelodysplastic disorders. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:498-544.
3. Rau R, Loh ML. Myeloproliferative neoplasms of childhood. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:545-567.
4. Gutierrez A, Silverman LB. Acute Lymphoblastic Leukemia. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1527-1554.
5. Berman JN, Look AT. Pediatric Myeloid Leukemia, Myelodysplasia, and Myeloproliferative Disease. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1555-1613.
6. Kobos R, Shukla N, and Armstrong SA. Infant Leukemias. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1614-1625.
7. Kaplan JA. Leukemia in children. *Pediatr Rev*. 2019;40:319-331. doi: 10.1542/pir.2018-0192.
8. Brown P, Inaba H, Annesley C, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020—November 25, 2019, *Pediatric Acute Lymphoblastic Leukemia*, available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Pediatric Acute Lymphoblastic Leukemia V2.2020 11/25/19. ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
9. Ranta S, Palomäki M, Levinsen M, et al. Role of neuroimaging in children with Acute Lymphoblastic Leukemia and central nervous system involvement at diagnosis. *Pediatr Blood Cancer*. 2016;64:64-70. doi:10.1002/pbc.26182/epdf.
10. Agrawal AK, Saini N, Gildengorin G et al. Is routine computed tomographic scanning justified in the first week of persistent febrile neutropenia in children with malignancies? *Pediatr Blood Cancer*. 2011;57(4):620-624. doi:10.1002/pbc.22974/epdf.
11. Pui C-H, Yang JJ, Hunger SP, et al. Childhood Acute Lymphoblastic Leukemia: progress through collaboration. *J Clin Oncol*. 2015;33(27):2938-2948. doi: 10.1200/JCO.2014.59.1636.
12. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. *Blood Journal*. 2011;117(8):2340-2347. doi:10.1182/blood-2010-10-311969.
13. Marcucci G, Beltrami G, Tamburini A, et al. Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors. *Ann Oncol* 2019;30:908-920. doi:10.1093/annonc/mdz120.
14. Vora A. Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia. *Br J Haematol*. 2011;155(5):549-560. doi:10.1111/j.1365-2141.2011.08871.x.
15. Kaste SC, Pei D, Cheng C, et al. Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids. *J Clin Oncol*. 2015;33(6):610-615. doi:10.1200/JCO.2014.57.5480.
16. Niinimäki T, Harila-Saari A, Niinimäki R. The diagnosis and classification of osteonecrosis in patients with childhood Leukemia. *Pediatr Blood Cancer*. 2015;62(2):198-203. doi:10.1002/pbc.25295.
17. Murphey MD, Roberts CC, Bencardino JT, et al. Osteonecrosis of the hip. *ACR Appropriateness Criteria®* 2015;1-12. <https://acsearch.acr.org/docs/69420/Narrative/>.
18. Karol SE, Mattano LA, Yang W, et al. Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia. *Blood Journal*. 2016;127(5):558-564. doi:10.1182/blood-2015-10-673848.
19. Chavhan GB, Babyn PS, Nathan PC, et al. Imaging of acute and subacute toxicities of cancer therapy in children. *Pediatr Radiol*. 2016;46(1):9-20. doi:10.1007/s00247-015-3454-1.

20. Lauer M, Kernen E, Schwabe D, Lehrnbecher T, Porto L. The role of magnetic resonance imaging in the diagnosis of central nervous system involvement in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2020;e28294. doi:10.1002/pbc.28294.

PEDONC-4: Pediatric CNS Tumors

PEDONC-4.1: Pediatric CNS Tumors General Considerations
PEDONC-4.2: Intracranial Low Grade Gliomas (LGG)
PEDONC-4.3: High Grade Gliomas (HGG)
PEDONC-4.4: Medulloblastoma (MDB), Supratentorial Primitive Neuroectodermal Tumors (sPNET), and Pineoblastoma
PEDONC-4.5: Atypical Teratoid/Rhabdoid Tumors (ATRT)
PEDONC-4.6: Pineocytomas
PEDONC-4.7: CNS Germinomas and Non-Germinomatous Germ Cell Tumors (NGGCT)
PEDONC-4.8: Ependymoma
PEDONC-4.9: Malignant Tumors of the Spinal Cord
PEDONC-4.10: Craniopharyngioma and Other Hypothalamic/Pituitary Region Tumors
PEDONC-4.11: Primary CNS Lymphoma
PEDONC-4.12: Meningiomas
PEDONC-4.13: Choroid Plexus Tumors

PEDONC-4.1: Pediatric CNS Tumors General Considerations

- Central nervous system tumors are the second most common form of childhood cancer, accounting for ~20% of all pediatric malignancies

Red flag symptoms raising suspicion for CNS tumors include:
Any headache complaint from a child age ≤ 5 years
Headaches awakening from sleep
Focal findings on neurologic exam
Clumsiness (common description of gait or coordination problems in young children)
Headaches associated with morning nausea/vomiting
New onset of seizure activity with focal features
Papilledema on physical exam

MRI Considerations

- MRI is the preferred imaging modality for all pediatric CNS tumors. The primary imaging study for pediatric brain tumors is MRI Brain without and with contrast (CPT® 70553)
 - ◆ For children able to undergo MRI without sedation, MRI Brain without contrast (CPT® 70551) can be approved if requested for initial evaluation of suspected CNS tumor
 - ◆ Younger patients requiring sedation for MRI should have their initial MRI performed without and with contrast in order to avoid a second anesthesia exposure
- MRI Spine with contrast only (Cervical-CPT® 72142, Thoracic-CPT® 72147, Lumbar-CPT® 72149) can be substituted where MRI Spine without and with contrast is indicated, if being performed immediately following a contrast-enhanced MRI Brain

CT Considerations:

- CT can be approved for evaluation of ventriculomegaly or other operative considerations, or for children who cannot undergo MRI safely
 - ◆ Because of the significant percentage of pediatric CNS tumors occurring in the posterior fossa, CT is not a recommended study for evaluation of pediatric headache when brain tumor is clinically suspected because of its limited diagnostic accuracy in this area. MRI should be used as first line imaging in these cases.
 - ◆ CT should not be used in place of MRI to avoid sedation in young children when red flag symptoms for CNS tumors are present
 - ◆ CT can also be approved for evaluation of headaches related to head trauma or evaluation of skull or facial bone abnormalities

MRA/CTA and Perfusion Studies:

- MRA or CTA are not routinely indicated in pediatric CNS tumors but can be approved for preoperative planning or to clarify inconclusive findings on MRI or CT.
- CT and MRI Perfusion
 - ◆ See: **HD-24.5: CT or MRI Perfusion** in the Head Imaging guidelines

MR Spectroscopy (MRS, CPT® 76390):

Note: *Some payors have specific restrictions on MR Spectroscopy, and those coverage policies may supersede the recommendations for MRS in these guidelines.*

- MRS is only supported for use in brain tumors of specified histologies where diagnostic accuracy has been established in peer-reviewed literature
- See diagnosis-specific guidelines for MRS indications
- MRS is considered investigational/experimental for all other histologies and indications not listed in a diagnosis-specific guideline section
- MR spectroscopy is not indicated for routine surveillance
- Requests for MRS should be forwarded for Medical Director review

PET Brain Imaging (CPT® 78608 and CPT® 78609):

Note: *Some payors have specific restrictions on PET Brain Metabolic imaging, and those coverage policies may supersede the recommendations for this study in these guidelines.*

- PET Brain Metabolic imaging (CPT® 78608) is only supported for use in brain tumors of specified histologies where diagnostic accuracy has been established in peer-reviewed literature
 - ◆ See diagnosis-specific guidelines for PET indications
- PET Brain Metabolic imaging is considered investigational/experimental for all other histologies and indications not listed in a diagnosis-specific guideline section
- PET Brain Perfusion imaging (CPT® 78609) is not indicated in the evaluation or management of primary CNS tumors
- Fusion PET/CT studies (CPT® 78814, CPT® 78815, or CPT® 78816) are not indicated in the evaluation or management of primary CNS tumors
- PET Brain Metabolic is not indicated for routine surveillance
- Requests for PET Brain Metabolic should be forwarded for Medical Director review

Timing and Frequency of Imaging:

- Definitive imaging should be completed prior to considering biopsy given the high degree of morbidity associated with operating on the CNS
 - ◆ Occasionally biopsy is not necessary because the imaging findings provide a definitive diagnosis.
 - Examples include diffuse intrinsic pontine glioma and optic pathway gliomas in a patient with known neurofibromatosis.
- Perioperative imaging frequency
 - ◆ Children may undergo very frequent imaging in the immediate perioperative period around resection or debulking of a CNS tumor due to the small anatomic spaces involved.
 - Requests for imaging during this time period to specifically evaluate postoperative course or ventriculoperitoneal shunt functioning should, in general, be approved as requested.
 - ◆ A one-time MRI Brain without and with contrast (CPT® 70553) can be approved in the immediate preoperative period (even if another study has already been completed) to gain additional information which can be important in optimizing patient outcomes, such as:
 - Completion of additional specialized MRI sequences such as diffusion-tensor imaging
 - Perfusion imaging
 - Tractography
 - Other sequences not reported under a separate CPT® code but not part of a routine MRI Brain series
 - ◆ Repeat MRI Brain that is being requested solely for loading into operative navigation software should not be requested as a diagnostic code, but can be approved under a treatment planning code (CPT® 76498). These requests should be forwarded for Medical Director review.

PEDONC-4.2: Intracranial Low Grade Gliomas (LGG)

Includes the following tumors:

- ◆ Pilocytic Astrocytoma
- ◆ Fibrillary (or Diffuse) Astrocytoma
- ◆ Optic Pathway Gliomas
- ◆ Pilomyxoid Astrocytoma
- ◆ Oligodendroglioma
- ◆ Oligoastrocytoma
- ◆ Oligodendrocytoma
- ◆ Subependymal Giant Cell Astrocytoma (SEGA)
- ◆ Ganglioglioma
- ◆ Gangliocytoma
- ◆ Dysembryoplastic Infantile Astrocytoma (DIA)
- ◆ Dysembryoplastic Infantile Ganglioglioma (DIG)
- ◆ Dysembryoplastic Neuroepithelial Tumor (DNT)
- ◆ Tectal Plate Gliomas
- ◆ Cervicomedullary Gliomas
- ◆ Pleomorphic Xanthoastrocytoma (PXA)
- ◆ Any other glial tumor with a WHO grade of I or II

General Considerations:

- Account for 40 to 60% of pediatric CNS tumors.
- These tumors are defined as having a WHO histologic grade of I or II (out of IV), can occur anywhere in the CNS

Treatment Considerations:

- Patients with neurofibromatosis and small optic pathway tumors may not undergo biopsy or resection and will proceed directly to treatment or surveillance
- Patients on observation without specific treatment should be imaged according to surveillance guidelines for LGG
- Patients who undergo complete resection should be imaged according to surveillance guidelines after post-resection imaging
- Patients age > 10 years with incompletely resected tumors usually receive adjuvant radiation therapy
- Patients age ≤ 10 years with incompletely resected tumors are commonly treated with chemotherapy
- MR Spectroscopy and PET Brain Metabolic are not indicated for routine surveillance

Indication	Imaging Study
Initial staging of all LGG	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
➤ Either of the following: ◆ Determining the need for biopsy when transformation to high grade glioma is suspected based on clinical symptoms or recent MRI findings ◆ Evaluation of a brain lesion of indeterminate nature when the PET findings will be used to determine whether biopsy/resection can be safely postponed	➤ PET Brain Metabolic imaging (CPT® 78608) ◆ Requests for PET Brain Metabolic imaging should be forwarded for Medical Director review
➤ Any of the following: ◆ Distinguish low grade from high grade gliomas ◆ Evaluate a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed ◆ Distinguish radiation-induced tumor necrosis from progressive disease within 18 months of completing radiotherapy	➤ MR Spectroscopy (MRS, CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Baseline imaging after resection	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response at the completion of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response on chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) approved every 2 cycles during active treatment and at the end of planned chemotherapy
Additional treatment response imaging during induction chemotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 2 cycles
Surveillance for all patients	➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 2 years, then every 6 months for 3 years, then annually thereafter

Indication	Imaging Study
Surveillance imaging for patients with optic pathway glioma and either a history of intra-orbital involvement or a history of NF1	➤ Every 3 months for 2 years, then every 6 months for 3 years, then annually thereafter: ◆ MRI Brain without and with contrast (CPT® 70553) and ◆ MRI Orbits without and with contrast (CPT® 70543)
Additional surveillance imaging for patients with cord involvement at diagnosis	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 3 months for 2 years, then every 6 months for 3 years, then annually thereafter
Suspected spinal cord recurrence	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.3: High Grade Gliomas (HGG)**Includes the following tumors:**

- ◆ Anaplastic astrocytoma
- ◆ Glioblastoma multiforme
- ◆ Diffuse intrinsic pontine glioma (DIPG, or “Brainstem glioma”)
- ◆ Gliomatosis cerebri
- ◆ Gliosarcoma
- ◆ Anaplastic oligodendroglioma
- ◆ Anaplastic ganglioglioma
- ◆ Anaplastic mixed glioma
- ◆ Anaplastic mixed ganglioneuronal tumors
- ◆ Any other glial tumor with a WHO grade of III or IV

General Considerations:

- Rare in children compared with the adult population, but represent 10 to 20% of pediatric CNS tumors
- Prognosis is very poor, and survival significantly beyond 3 years from diagnosis is rare, even with complete surgical resection at initial diagnosis
- These tumors are defined as having a WHO histologic grade of III or IV (out of IV) can occur anywhere in the CNS (though the majority occur in the brain)

Treatment Considerations:

- Patients who undergo complete resection should be imaged according to surveillance guidelines after post-resection imaging
- Patients with incompletely resected tumors are commonly treated with chemotherapy

Indication	Imaging Study
Initial staging of all HGG	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
➤ Any of the following: ◆ Distinguishing radiation-induced tumor necrosis from progressive disease within 18 months of completing radiotherapy ◆ Evaluating inconclusive MRI findings when the PET findings will be used to determine need for biopsy or change in therapy, including a change from active therapy to surveillance ◆ Evaluation of a brain lesion of indeterminate nature when the PET findings will be used to determine whether biopsy/resection can be safely postponed	➤ PET Brain Metabolic Imaging (CPT® 78608) ◆ Requests for PET Brain Metabolic imaging should be forwarded for Medical Director review
➤ Any of the following: ◆ To distinguish low grade from high grade gliomas ◆ To evaluate a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed ◆ To distinguish radiation-induced tumor necrosis from progressive disease within 18 months of completing radiotherapy	➤ MR Spectroscopy (MRS, CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Baseline imaging following resection	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response at the completion of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response on chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) every 2 cycles during active treatment and at the end of planned chemotherapy
Additional treatment response imaging during induction chemotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 2 cycles
Surveillance for all patients	➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 3 years, then every 6 months thereafter
Additional surveillance imaging for patients with cord involvement at diagnosis	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 3 months for 3 years, then every 6 months thereafter
Suspected spinal cord recurrence	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.4: Medulloblastoma (MDB), Supratentorial Primitive Neuroectodermal Tumors (sPNET), and Pineoblastoma

Includes the following tumors:	
➤ Medulloblastoma and Pineoblastoma	
➤ sPNET	
◆ Medulloepithelioma	
◆ Cerebral or cerebellar neuroblastoma	
◆ Cerebral or cerebellar ganglioneuroblastoma	
◆ Ependymoblastoma	
Risk assessment is important in determining optimal treatment	
High risk features include the following:	
➤ Spinal metastasis (including cytology positive only)	
➤ Multifocal intracranial tumors	
➤ Anaplastic histology	
➤ All sPNET and pineoblastomas	
➤ > 1.5 cm ² residual tumor area on postoperative MRI and age < 3 years	
Patients without any high risk features are considered “average risk”	

General Considerations:

- Account for 15 to 25% of pediatric CNS tumors
- Prognosis is generally favorable
- Leptomeningeal spread is common and can occur after initial diagnosis
- MR Spectroscopy and PET Brain Metabolic are not indicated for routine surveillance

Treatment Considerations:

- Patients generally proceed to chemoradiotherapy within 31 days of surgical resection
 - ◆ All patients receive adjuvant chemotherapy lasting 6 to 12 months that begins ~6 weeks after completion of chemoradiotherapy

Indication	Imaging Study
Initial staging for all patients, preoperatively	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
➤ Any of the following: ◆ To distinguish radiation-induced tumor necrosis from progressive disease within 18 months of completing radiotherapy ◆ To evaluate inconclusive MRI findings when the PET findings will be used to determine need for biopsy or change in therapy, including a change from active therapy to surveillance ◆ To evaluate a brain lesion of indeterminate nature when the PET findings will be used to determine whether biopsy/resection can be safely postponed	➤ PET Brain Metabolic Imaging (CPT® 78608) ◆ Requests for PET Brain Metabolic imaging should be forwarded for Medical Director review
➤ Any of the following: ◆ To evaluate a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Postoperative (preferably within 48 hours of surgery) to quantify residual tumor volume	➤ MRI Brain without and with contrast (CPT® 70553)
Within 28 days post-op, if spinal imaging was not performed preoperatively	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Treatment response	➤ At the start of adjuvant chemotherapy and every 2 cycles until therapy is completed: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic CPT® 72157, Lumbar-CPT® 72158)
Children age < 3 years treated with multiple cycles of high dose chemotherapy with autologous stem cell rescue in lieu of radiotherapy	➤ Disease evaluations (imaging per treatment response guidelines) may occur prior to each cycle (every 4 to 6 weeks) if needed for response determination.

Indication	Imaging Study
End of treatment evaluation	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine with contrast (Cervical-CPT® 72142, Thoracic-CPT® 72147, Lumbar-CPT® 72149) or MRI spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Surveillance	➤ Every 3 months for 3 years, then every 6 months for 2 years, then annually for 10 years: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.5: Atypical Teratoid/Rhabdoid Tumors (ATRT)

General Considerations:

- Highly aggressive tumor occurring primarily in very young children that has a clinical presentation very similar to medulloblastoma with a much higher rate of leptomeningeal spread.
- Metastases can occur outside the CNS, and associated tumors can also arise in the kidneys (Malignant Rhabdoid Tumor of the Kidney, MRT).
 - ◆ Rhabdoid malignancies occurring outside the CNS should be imaged according to **PEDONC-7.6: Malignant Rhabdoid Tumor of the Kidney (MRT) and Other Extracranial Sites**.
- Overall prognosis is poor, with < 20% of patients surviving beyond 2 years from diagnosis.
- PET Brain Metabolic does not have a defined role in the evaluation of ATRT at this time
- Patients generally proceed to induction chemotherapy shortly following surgical resection or biopsy.
- Following completion of chemotherapy some patients will proceed to radiotherapy.
 - ◆ MRI performed at the end of consolidation therapy should serve as the diagnostic MRI prior to radiotherapy.
- MR Spectroscopy is not indicated for routine surveillance

Indication	Imaging Study
Initial staging for all patients, preoperatively	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) ➤ Renal US (CPT® 76770) ◆ If renal US is abnormal, refer to: <u>PEDONC-7.6: Malignant Rhabdoid Tumor of the Kidney (MRT) and Other Extracranial Sites</u>
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Postoperative (preferably within 48 hours of surgery) to quantify residual tumor volume	➤ MRI Brain without and with contrast (CPT® 70553)
Within 28 days post-op, if spinal imaging was not performed preoperatively	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Treatment response to induction chemotherapy	➤ After every 2 cycles: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Patients treated with consolidation chemotherapy and autologous stem cell rescue	➤ Disease evaluation is indicated following the end of the planned stem cell rescues but may occur prior to each cycle (every 4 to 6 weeks) if needed for response determination
End of treatment evaluation	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Surveillance	➤ Every 3 months for 2 years, then every 6 months for 3 years, then annually for 10 years: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.6: Pineocytomas

General Considerations:

- Low grade malignancy that is similar in presentation to low grade glioma (LGG)
- PET Brain Metabolic imaging and MR Spectroscopy do not have a defined role in the evaluation of pineocytoma
- Surgical resection is curative for most patients
 - ◆ Patients with a complete resection should then be imaged according to surveillance guidelines
- Patients with incompletely resected tumors may receive adjuvant radiation therapy
 - ◆ After end of radiotherapy imaging, these patients should be imaged according to surveillance guidelines

Indication	Imaging Study
Initial staging for all patients	➤ MRI Brain without and with contrast (CPT® 70553)
Additional initial staging imaging for patients with: ◆ Multicentric tumors ◆ Atypical histology including pineoblastoma-like elements ◆ Clinical signs or symptoms suggesting spinal cord involvement	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Baseline imaging following resection	➤ MRI Brain without and with contrast (CPT® 70553)
End of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553)
Additional imaging at end of radiotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Surveillance	➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually thereafter
Additional surveillance imaging for patients with cord involvement at diagnosis	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) after completion of therapy every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually thereafter
Suspected spinal cord recurrence	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.7: CNS Germinomas and Non-Germinomatous Germ Cell Tumors (NGGCT)

Includes the following tumors:

- CNS Germinoma
- Non-Germinomatous Germ Cell Tumors (NGGCT)
 - ◆ Embryonal carcinoma
 - ◆ Yolk sac tumor
 - ◆ Choriocarcinoma
 - ◆ Teratoma
 - ◆ Mixed germ cell tumor

General Considerations:

- More common in older school age children and younger adolescents, but can occur throughout the pediatric age range
- Although leptomeningeal spread is common, prognosis is excellent due to high sensitivity to chemotherapy and radiotherapy
- PET Metabolic Brain imaging does not have a defined role in the evaluation of CNS GCT
- Patients generally proceed to chemotherapy shortly following surgical resection or biopsy and will usually receive 2 to 4 cycles
- Following completion of chemotherapy, patients with residual disease will proceed to second-look surgery and/or radiotherapy

Indication	Imaging Study
Initial staging for all patients	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Treatment response to induction chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) every 2 cycles
Additional treatment response to induction chemotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 2 cycles
End of induction chemotherapy for patients with localized intracranial tumors	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Prior to second-look surgery	➤ MRI of all known sites of measurable disease
Prior to radiotherapy	➤ MRI of all known sites of measurable disease
At the end of all planned therapy	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine (with or without and with contrast)
Surveillance	➤ Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually until 5 years after completion of therapy: ◆ MRI Brain without and with contrast (CPT® 70553) ◆ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Patients in long term follow up after CNS tumor treatment that included radiation therapy	➤ See: <u>PEDONC-19.3: Second Malignant Neoplasms (SMN)</u>
Suspected recurrence - new or worsening neurologic symptoms (including worsening of diabetes insipidus)	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.8: Ependymoma

General Considerations:

- Occur primarily intracranially, roughly 2/3 in the posterior fossa
- Overall prognosis is very good, with supratentorial tumors faring better
- Primary spinal tumors can also occur, and are more common in adult patients than pediatric patients.
- Surgery is the primary treatment modality
 - ◆ Patients with a complete resection should then be imaged according to surveillance guidelines
- Radiotherapy +/- chemotherapy is used for:
 - ◆ Incompletely resected tumors
 - ◆ Anaplastic histology
 - ◆ Infratentorial location
 - Patients with incomplete resection or high risk histology that receive adjuvant radiation therapy should then be imaged according to surveillance guidelines after end of radiotherapy imaging.
- PET Brain Metabolic imaging does not have a defined role in the evaluation of ependymoma
- Patients with gain of chromosome 1q have worse progression-free survival and overall survival outcomes
- RELA-fusion supratentorial ependymoma did not portend worse overall survival outcomes in recent Clinical Oncology Group studies, and is generally not considered an indication for more frequent surveillance imaging
- MR Spectroscopy is not indicated for routine surveillance

Indication	Imaging Study
Initial staging for all patients	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Baseline imaging following resection	➤ MRI Brain without and with contrast (CPT® 70553) or MRI without and with contrast of involved spinal level(s)
Completion of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553) or MRI without and with contrast of involved spinal level(s)
Prior to radiotherapy	➤ MRI of all known sites of measurable disease
Treatment response to induction chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) or MRI without and with contrast of involved spinal level(s) every 2 cycles
End of induction chemotherapy and again at end of all therapy	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Prior to second-look surgery	➤ MRI of all known sites of measurable disease
Surveillance, primary intracranial ependymoma and NO history of spinal cord involvement	➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years ◆ Patients with gain of chromosome 1q: ■ MRI Brain without and with contrast (CPT® 70553) every 3 months for 3 years, then annually for 10 years ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) can be approved annually for 2 years
Surveillance, primary intracranial ependymoma AND metastatic cord involvement at diagnosis	➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years ◆ Patients with gain of chromosome 1q: ■ MRI Brain without and with contrast (CPT® 70553) every 3 months for 3 years, then annually for 10 years ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years

Indication	Imaging Study
Surveillance, primary <u>intras</u> spinal ependymoma and NO history of intracranial involvement	➤ MRI without and with contrast of the involved spinal level(s) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years ➤ MRI Brain without and with contrast (CPT® 70553) annually for 2 years
Surveillance, primary <u>intra</u> spinal ependymoma AND metastatic intracranial involvement at diagnosis	➤ MRI without and with contrast of the involved spinal level(s) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years ➤ MRI Brain without and with contrast (CPT® 70553) every 3 months for 1 year, then every 6 months for 1 year, then annually for 10 years

PEDONC-4.9: Malignant Tumors of the Spinal Cord

- Treatment principles are the same as tumors of the brain, and should follow imaging guidelines according to the specific histologic type
- Multiple spinal cord tumors should raise suspicion for neurofibromatosis
- Common histologies of primary spinal cord tumor in children include:
 - ◆ Low Grade Glioma, see: **PEDONC-4.2: Intracranial Low Grade Glioma (LGG)** for guidelines
 - ◆ Ependymoma, see: **PEDONC-4.8: Ependymoma** for guidelines
 - ◆ Any type can occur, but other histologies are rare
- Primary site imaging should always include MRI Spine without and with contrast of all involved levels (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
 - ◆ Entire spine imaging may be indicated based on the histologic type
 - ◆ For rare histologies not specified in these guidelines, MRI of the total spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) should be approved for initial staging and every 2 cycles for treatment response.
 - Requests for surveillance imaging should be sent to MD review.
- MRI Brain without and with contrast (CPT® 70553) is indicated at initial diagnosis, but may be not be necessary during treatment response and surveillance
 - ◆ Given the rarity of primary spinal cord tumors in children, MRI Brain requests should, in general, be approved for surveillance after recent evaluation by a physician with significant training and/or experience in pediatric spinal cord tumors (most commonly a pediatric neurosurgeon or pediatric oncologist) as the need for intracranial surveillance is highly individualized
- Asymptomatic surveillance imaging should generally end at the time point appropriate for the specific tumor type

PEDONC-4.10: Craniopharyngioma and Other Hypothalamic/Pituitary Region Tumors

General Considerations:

- Imaging guidelines and treatment approaches for pediatric pituitary tumors other than craniopharyngioma are consistent with those used for adults with pituitary tumors
 - ◆ For these tumors follow guidelines in **HD-19: Pituitary**
- Craniopharyngiomas are less common, accounting for 6 to 8% of pediatric CNS tumors.
- Most commonly affects children in the preadolescent ages
- Several key imaging findings can be used to differentiate the tumors in this region including the presence of calcifications, cysts, and T1/T2 enhancement patterns in craniopharyngiomas
 - ◆ These are best evaluated using a COMBINATION of both MRI and CT modalities. Preoperative prediction is much more successful when BOTH modalities are obtained prior to biopsy.
- Other less common tumors in the optic chiasm, sella, and suprasella region may include Germ Cell Tumors (GCT, see: **PEDONC-4.7**) and Langerhans Cell Histiocytosis (LCH, see: **PEDONC-18**)
- PET Brain Metabolic Imaging and MR Spectroscopy do not have a defined role in the evaluation of craniopharyngioma

Treatment Considerations:

- Surgical resection is curative for many patients
 - ◆ Those with a complete resection should then be imaged according to surveillance guidelines after post-resection imaging is completed
- Patients with incomplete resection and receiving adjuvant radiation therapy can have a single approved at completion of radiotherapy and should then be imaged according to surveillance guidelines

Indication	Imaging Study
Initial staging for all patients	➤ MRI Brain without and with contrast (CPT® 70553) ◆ Concurrent CT Head without contrast (CPT® 70450) can be approved in addition to MRI if craniopharyngioma is suspected
➤ Additional initial staging for patients with: ◆ Multicentric tumors ◆ Clinical signs or symptoms suggesting spinal cord involvement	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Operative planning or image guidance	➤ MRA Head (CPT® 70544, 70545, or 70546) OR ➤ CTA Head (CPT® 70496)
Baseline imaging following resection	➤ MRI Brain without and with contrast (CPT® 70553)
Completion of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response to chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) approved every 2 cycles during active treatment and at the end of planned chemotherapy
Additional treatment response imaging during induction chemotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 2 cycle
Surveillance	➤ MRI Brain without and with contrast (CPT® 70553) can be approved every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually until 10 years after completion of therapy as late progressions can occur ◆ For additional imaging guidelines for patients in long term follow up after CNS tumor treatment that included radiation therapy, see: <u>PEDONC-19.3: Second Malignant Neoplasms (SMN)</u>
Suspected spinal cord recurrence	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)

PEDONC-4.11: Primary CNS Lymphoma

- Primary CNS lymphoma is a solitary or multifocal mass occurring in the brain without evidence of systemic (bone marrow or lymph node) involvement
- Usually associated with immunodeficiency, this is a very rare entity in pediatrics accounting for < 0.1% of pediatric malignancies, so age-specific guidelines have not been established
- Primary CNS lymphoma imaging indications in pediatric patients are identical to those in the general imaging guidelines. See: **ONC-2.7: CNS Lymphoma** for imaging guidelines
- CNS lymphomas also involving bone marrow and/or lymph nodes should be imaged according to: **PEDONC-5.3: Pediatric Aggressive Mature B-Cell Non-Hodgkin Lymphomas (NHL)**

PEDONC-4.12: Meningiomas

- Account for 1 to 3% of pediatric CNS tumors
- Usually associated with neurofibromatosis type 2 (NF-2) or prior therapeutic radiation exposure to the brain
 - ◆ Lifetime risk may be as high as 20% for young children receiving whole brain radiotherapy, most commonly occurring 15 to 20 years after radiation exposure
- Meningioma imaging indications in pediatric patients are identical to those in the general imaging guidelines
 - ◆ See: **ONC-2.8: CNS Meningioma** for imaging guidelines

PEDONC-4.13: Choroid Plexus Tumors

General Considerations:

- As a group these account for 1 to 4% of pediatric CNS tumors, and 70% of choroid plexus tumors present within the first 2 years of life
- Includes the following tumors:
 - ◆ Choroid plexus papilloma
 - ◆ Choroid plexus adenoma, or atypical choroid plexus papilloma
 - ◆ Choroid plexus carcinoma
- PET Metabolic Brain imaging does not have a defined role in the evaluation of choroid plexus tumors

Choroid Plexus Papilloma:

- Choroid plexus papillomas outnumber other choroid plexus tumors by 4 to 5 times.
- These ventricular tumors commonly present with hydrocephalus caused by increased CSF production, resulting in signs of increased intracranial pressure.
- Appearance on MRI is typical, and they are usually treated by excision.
- Regrowth is rare

Indication	Imaging Study
Suspected/Diagnosis	➤ MRI Brain without and with contrast (CPT® 70553)
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Suspected return of hydrocephalus, or return of hydrocephalus seen on CT imaging	➤ MRI Brain without and with contrast (CPT® 70553)

Choroid Plexus Adenoma or Atypical Choroid Plexus Papilloma:

- These are extremely rare tumors with features midway in the malignant spectrum between papillomas and carcinomas
- They are more prone to local invasion, but rarely to metastasis
- Presenting symptoms are similar to papillomas
- Appearance on MRI is typical, and they are usually treated by excision
- Spinal imaging may be approved if requested at initial diagnosis
- Regrowth is rare

Indication	Imaging Study
Suspected/Diagnosis	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Suspected return of hydrocephalus, or return of hydrocephalus seen on CT imaging	➤ MRI Brain without and with contrast (CPT® 70553)

Choroid Plexus Carcinoma

- This is a very aggressive malignancy, with high rates of metastasis to other parts of the CNS
 - ◆ Overall incidence of metastases in choroid plexus carcinoma is 12–50%, which is associated with a worse outcome
- Prognosis is significantly less favorable than for papillomas with overall survival rates of 35 to 40%
- *TP53* mutations and alternative lengthening telomeres (ALT) are common in patients with choroid plexus carcinoma
- Surgical gross total resection is curative for many patients
- Patients with confirmed gross total resection should then be imaged according to surveillance guidelines
- Patients with incomplete resection who receive adjuvant radiation therapy should be imaged according to surveillance guidelines after end of radiotherapy imaging
- MR Spectroscopy is not indicated for routine surveillance

Indication	Imaging Study
Initial staging of all patients	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Evaluation of a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed	➤ MR Spectroscopy (CPT® 76390) ◆ Requests for MRS should be forwarded for Medical Director review
Baseline imaging following resection	➤ MRI Brain without and with contrast (CPT® 70553)
Prior to radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553) and MRI with and without contrast of all known sites with measurable disease prior to radiotherapy.
Completion of radiotherapy	➤ MRI Brain without and with contrast (CPT® 70553)
Treatment response to chemotherapy	➤ MRI Brain without and with contrast (CPT® 70553) every 2 cycles during active treatment
Additional treatment response to chemotherapy for patients with measurable spinal cord disease on MRI	➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 2 cycles during active treatment
Prior to second-look surgery	➤ MRI of all known sites of measurable disease
End of all planned therapy	➤ MRI Brain without and with contrast (CPT® 70553) ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158)
Surveillance, no history of spinal cord involvement	➤ MRI Brain without and with contrast (CPT® 70553) every 4 months for 3 years, then every 6 months for 2 years after completion of therapy ◆ For additional imaging guidelines for patients in long term follow up after CNS tumor treatment that included radiation therapy, see: <u>PEDONC-19.3: Second Malignant Neoplasms (SMN)</u> ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) at 12 and 24 months after completion of therapy
Surveillance, patients with cord involvement at diagnosis	➤ MRI Brain without and with contrast (CPT® 70553) every 4 months for 3 years, then every 6 months for 2 years after completion of therapy ◆ For additional imaging guidelines for patients in long term follow up after CNS tumor treatment that included radiation therapy, see: <u>PEDONC-19.3: Second Malignant Neoplasms (SMN)</u> ➤ MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) every 4 months for 3 years, then every 6 months for 2 years after completion of therapy

References –PEDONC-4

1. Parsons DW, Pollack IF, Hass-Kogan DA, et al. Gliomas, ependymomas, and other nonembryonal tumors of the central nervous system. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:628-670.
2. Chintagumpala MM, Paulino A, Panigraphy A, et al. Embryonal and pineal region tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:671-699.
3. Kieran MW, Chi SN, Manley PE, et al. Tumors of the Brain and Spinal Cord. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1779-1885.
4. Nabors LB, Portnow J, Ahluwalia M, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020—April 30, 2020. Central Nervous System Cancers, available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf, referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Central Nervous System Cancers V2.2020 4/30/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
5. Menashe SJ, Iyer RS. Pediatric Spinal neoplasia: a practical imaging overview of intramedullary, intradural, and osseous tumors. *Curr Probl Diagn Radiol*. 2013;42(6):249-265. doi:10.1067/j.cpradiol.2013.05.003.
6. Warmuth-Metz M. Imaging guidelines for pediatric brain tumor patients. In: Warmuth-Metz M, ed. *Imaging and Diagnosis in Pediatric Brain Tumor Studies*. Switzerland; Springer, Cham:2017:55-67.
7. Warren KW, Poussaint TY, Vezina G, et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr Blood Cancer*. 2013;60(9):1397-1401. doi:10.1002/pbc.24562.
8. Zukotynski K, Fahey F, Kocak M, et al. ¹⁸F-FDG PET and MR Imaging associations across a spectrum of pediatric brain tumors: a report from the Pediatric Brain Tumor Consortium. *J Nucl Med*. 2014;55(9):1473-1480. doi:10.2967/jnumed.114.139626.
9. Gajjar A, Bowers DC, Karajannis MA, Leary S, Witt H, Gottardo NG. Pediatric brain tumors: innovative genomic information is transforming the diagnostic and clinical landscape. *J Clin Oncol*. 2015;33(27):2986-2998. doi:10.1200/JCO.2014.59.9217.
10. Brandão LA, Poussaint TY. Pediatric brain tumors. *Neuroimag Clin N Am*. 2013 August;23(3):499-525. Accessed January 3, 2018. [http://www.neuroimaging.theclinics.com/article/S1052-5149\(13\)00017-8/abstract](http://www.neuroimaging.theclinics.com/article/S1052-5149(13)00017-8/abstract).
11. Brandão LA and Castillo M. Adult brain tumors: clinical applications of magnetic resonance spectroscopy. *Neuroimag Clin N Am*. 2013;23(3):527-555. doi:10.1016/j.nic.2013.03.003
12. Zarifi M, Tzika AA. Proton MRS imaging in pediatric brain tumors. *Pediatr Radiol*. 2016;46(7):952-962. doi:10.1007/s00247-016-3547-5.
13. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrop-Link HE. Value of ¹⁸F-FDG-PET and PET/CT for evaluation of pediatric malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
14. Soffietti R, Baumert BG, Bello L, et al. Guidelines on management of low-grade gliomas: report of an EFSN-EANO* Task Force. *Eur J Neurol*. 2010;17(9):1124-1133. doi:10.1111/j.1468-1331.2010.03151.x.
15. Kruer MC, Kaplan AM, Etzl MM Jr, et al. The value of positron emission tomography and proliferation index in predicting progression in low-grade astrocytomas of childhood. *J Neurooncol*. 2009;95(2):239-245. doi:10.1007/s11060-009-9922-4.
16. Chamdine O, Broniscer A, Wu S, Gajjar A, Qaddoumi I. Metastatic low-grade gliomas in children: 20 years' experience at St. Jude Children's Research Hospital. *Pediatr Blood Cancer*. 2016;63(1):62-70. doi:10.1002/pbc.25731.
17. Chalil A, Ramaswamy V. Low grade gliomas in children. *J Child Neurol*. 2016;31(4):517-522. doi:10.1177/0883073815599259.
18. Krishnatry R, Zhukova N, Stucklin ASG, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer*. 2016;122(8):1261-1269. doi:10.1002/cncr.29907.

19. Ullrich NJ. Neurocutaneous Syndromes and brain tumors. *J Child Neurol.* 2016;31(12):1399-1411. doi:10.1177/0883073815604220.
20. Campian J, Gutmann DH. CNS tumors in neurofibromatosis. *J Clin Oncol.* 2017; 35(21):2378-2385. doi:10.1200/JCO.2016.71.7199.
21. Morris EB, Gajjar A, Okuma JO, et al. Survival and late mortality in long-term survivors of pediatric CNS tumors. *J Clin Oncol.* 2007;25(12):1532-1538. doi:10.1200/JCO.2006.09.8194.
22. Karthigeyan M, Gupta K, Salunke P. Pediatric central neurocytoma: a short series with literature review. *J Child Neurol.* 2016;32(1):53-59. Accessed January 3, 2018 doi:10.1177/0883073816668994.
23. Tisnado J, Young R, Peck KK, et al. Conventional and advanced imaging of diffuse intrinsic pontine glioma. *J Child Neurol.* 2016;31(12):1386-1393. doi:10.1177/0883073816634855.
24. Greenfield JP, Heredia AC, George E, Keiran MW, Morales La Madrid A. Gliomatosis cerebri: a consensus summary report from the First International Gliomatosis cerebri Group Meeting, March 26-27, 2015, Paris, France. *Pediatr Blood Cancer.* 2016;63(12):2072-2077. doi:10.1002/pbc.26169.
25. Zaky W, Dhall G, Ji L, et al. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the head start III experience. *Pediatr Blood Cancer.* 2014;61(1):95-101. doi:10.1002/pbc.24648.
26. Gururangan S, Hwang E, Herndon JE II, et al. [18F]Fluorodeoxyglucose-Positron Emission Tomography in patients with medulloblastoma. *Neurosurgery.* 2004;55(6):1280-1289. doi:10.1227/01.NEU.0000143027.41632.2B.
27. Millard NE and DeBraganca KC. Medulloblastoma. *J Child Neurol.* 2016;31(12):1341-1353. doi:10.1177/0883073815600866.
28. Koschmann C, Bloom K, Upadhyaya S, Geyer JR. Survival after relapse of medulloblastoma. *J Pediatr Hematol. Oncol.* 2016;38(4):269-273. doi:10.1097/MPH.0000000000000547.
29. Martinex S, Khakoo Y, Giheeney S, et al. Marker (+) CNS germ cell tumors in remission: are surveillance MRI scans necessary? *Pediatr Blood Cancer.* 2014;61(5):853-854. Accessed January 3, 2018. doi:10.1002/pbc.24888.
30. Goldman S, Bouffet E, Fisher PG, et al. Phase II trial assessing the ability of neoadjuvant chemotherapy with or without second-look surgery to eliminate measurable disease for nongerminomatous germ cell tumors: a children's oncology group study. *J Clin Oncol.* 2015;33(22):2464-2471. doi:10.1200/JCO.2014.59.5132.
31. Abu Arja MH, Bouffet E, Finlay JL, AbdelBaki MS. Critical review of the management of primary central nervous system germ cell tumors. *Pediatr Blood Cancer.* 2019;66:e27658. doi:10.1002/pbc.27658.
32. Vitanza NA, Partap S. Pediatric Ependymoma. *J Child Neurol.* 2016;31(12):1354-1366. doi:10.1177/0883073815610428
33. Norris GA, Garcia J, Hankinson TC, et al. Diagnostic accuracy of neuroimaging in pediatric optic chiasm/suprasellar tumors. *Pediatr Blood Cancer.* 2019;66:e27860. doi:10.1002/pbc.27680.
34. McCrea HJ, George E, Settler A, et al. Pediatric suprasellar tumors. *J Child Neurol.* 2016;31(12):1367-1376. doi:10.1177/0883073815620671.
35. Grommes C, DeAngelis LM. Primary CNS lymphoma. *J Clin Oncol.* 2017;35(21):2410-2418. doi:10.1200/JCO.2017.72.7602.
36. Larrew T, Eskandari R. Pediatric intraparenchymal meningioma, case report and comparative review. *Pediatr Neurosurg.* 2016;51(2):83-86. doi:10.1159/000441008.
37. Li Z, Li H, Wang S, et al. Pediatric skull base meningiomas: clinical features and surgical outcomes. *J Child Neurol.* 2016;31(14):1523-1527. doi:10.1177/0883073816664669.
38. Horská A, Barker PB. Imaging of brain tumors: MR Spectroscopy and metabolic imaging. *Neuroimaging Clin N Am.* 2010;20(3):293-310. doi:10.1016/j.nic.2010.04.003.
39. Sundgren PC. MR Spectroscopy in radiation injury. *AJNR Am J Neuroradiol.* 2009;30(8):1469-1476. doi:10.3174/ajnr.A1580.
40. Zaky W, Dhall G, Khatua S, et al. Choroid plexus carcinoma in children: the head start experience. *Pediatr Blood Cancer.* 2015;62(5):784-789. doi:10.1002/pbc.25436.
41. Zaky W, Finlay JL. Pediatric choroid plexus carcinoma: Biologically and clinically in need of new perspectives. *Pediatr Blood Cancer* 2018;65:e27031. doi:10.1002/pbc.27031.

42. Kramer K. Rare primary central nervous system tumors encountered in pediatrics. *J Child Neurol.* 2016;31(12):1394-1398. doi:10.1177/0883073815627878.
43. Merchant TE, Bendel AE, Sabin ND, et.al. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. *J Clin Oncol.* 2019;37(12):974-983. doi:10.1200/JCO.18.01765.
44. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Medulloblastoma and Other Central Nervous System Embryonal Tumors Treatment. Bethesda, MD: National Cancer Institute. Updated 03/23/2020. Available at: <https://www.cancer.gov/types/brain/hp/child-cns-embryonal-treatment-pdq>. Accessed 04/14/2020. [PMID: 26389418]
45. Burns J, Policeni B, Bykowski J, et al. ACR Appropriateness Criteria® Acute Trauma to the Foot. Available at <https://acsearch.acr.org/docs/69485/Narrative/>. American College of Radiology. Accessed 7/21/2020.

PEDONC-5: Pediatric Lymphomas

PEDONC-5.1: Pediatric Lymphoma – General Considerations

PEDONC-5.2: Pediatric Hodgkin Lymphoma (HL)

PEDONC-5.3: Pediatric Aggressive Mature B-Cell Non-Hodgkin Lymphomas (NHL)

PEDONC-5.4: Anaplastic Large Cell Lymphoma (ALCL)

PEDONC-5.1: Pediatric Lymphoma – General Considerations

- Lymphoma mostly commonly involves the lymph nodes (LNs). However, lymphoma can also arise from primary lymphoid tissues (bone marrow or thymus) or various secondary lymphoid tissues (spleen, mucosa-associated lymphoid tissue) or non-lymphoid organs (skin, bone, brain, lungs, liver, salivary glands, etc).
- Pediatric lymphomas are generally Hodgkin Lymphomas, Aggressive B-Cell Non-Hodgkin Lymphomas, Lymphoblastic Lymphomas, or Anaplastic Large Cell Lymphomas
- Patients with Lymphoblastic Lymphoma (even those with bulky nodal disease) are treated using the leukemia treatment plan appropriate to the cell type (B or T cell). These patients should be imaged using guidelines in **PEDONC-3.2: Acute Lymphoblastic Leukemia (ALL)**.
- Other histologies are rare in pediatric patients, and should be imaged according to the following guidelines:
 - ◆ Follicular lymphoma: **ONC-27.3: Follicular Lymphoma**
 - ◆ Marginal zone or MALT lymphomas: **ONC-27.4: Marginal Zone Lymphomas**
 - ◆ Mantle cell lymphomas: **ONC-27.5: Mantle Cell Lymphoma**
 - ◆ Cutaneous lymphomas: **ONC-27.8: Cutaneous Lymphomas and T Cell Lymphomas**
 - **Exception:** Cutaneous B-Lymphoblastic Lymphoma should be imaged using guidelines in **PEDONC-3.2: Acute Lymphoblastic Leukemia (ALL)**
 - ◆ Castleman's Disease: **ONC-31.11: Castleman's Disease (Unicentric and Multicentric)**
- All CT imaging recommended in this section refers to CT with contrast only.
 - ◆ Noncontrast CT imaging has not been shown to be beneficial in the management of pediatric lymphomas
 - ◆ Given the limited utility of noncontrast CT imaging in pediatric lymphomas, MRI without or without and with contrast is recommended in place of CT for patients who cannot tolerate CT contrast due to allergy or impaired renal function
- MRI without and with contrast of symptomatic or previously involved bony areas can be approved in known lymphoma patients without prior plain x-ray or bone scan evaluation
 - ◆ Bone scan is inferior to MRI for evaluation of known or suspected bone metastases in lymphoma
- MRI Brain without and with contrast (CPT® 70553) is the preferred study for evaluation of suspected Brain metastases in pediatric lymphoma
 - ◆ CT Head with (CPT® 70460) or without and with contrast (CPT® 70470) can be approved when MRI is contraindicated

PEDONC-5.2: Pediatric Hodgkin Lymphoma (HL)

- Pediatric patients have a high rate of neck and Waldeyer's ring involvement with Hodgkin Lymphoma
- Early treatment response evaluations involve both PET and CT as decisions about chemotherapy drug selection and radiation treatment are frequently made based on both anatomic (CT-based) and metabolic (PET/CT-based) responses.
- Most patients experiencing recurrence are detected based on physical findings, and frequent CT surveillance imaging of Hodgkin Lymphoma after completion of therapy does not improve post-recurrence overall survival.

Indication	Imaging Study
Initial staging	➤ CT Neck (CPT® 70491) ➤ Chest (CPT® 71260) ➤ CT Abdomen/Pelvis (CPT® 74177) ➤ CT with contrast or MRI without and with contrast of any other symptomatic body area ➤ PET/CT (CPT® 78815) ◆ Can be performed prior to biopsy if necessary for patient scheduling ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of skull or distal lower extremity involvement ➤ CT or MRI of other body areas may be indicated for rare patients based on physical findings or PET/CT results
Restaging during early treatment response evaluations	➤ All of the following, as often as every 2 cycles of chemotherapy: ◆ CT of Neck (CPT® 70491) ◆ CT Chest with contrast (CPT® 71260) ◆ CT Abdomen/Pelvis (CPT® 74177) ◆ CT of other previously involved visceral areas ■ PET/CT (CPT® 78815) preferred for bony involvement ◆ MRI Brain with and without contrast (CPT® 70553) for known CNS involvement - AND ➤ After cycles 2 and 4 of chemotherapy (or cycles 1 and 3 for patients with low risk (stage IA or IIA) mixed cellularity Hodgkin lymphoma) ◆ PET/CT (CPT® 78815)
Restaging after negative PET/CT (either Deauville or Lugano 1, 2 or 3 as reported in formal radiology interpretation)	➤ All of the following, as often as every 2 cycles of chemotherapy, and at the end of therapy: ◆ CT of Neck (CPT® 70491) ◆ Chest (CPT® 71260) ◆ CT Abdomen/Pelvis (CPT® 74177) ◆ CT of other previously involved visceral areas ■ PET/CT (CPT® 78815) preferred for bony involvement ➤ MRI Brain with and without contrast (CPT® 70553) for known CNS involvement

Indication	Imaging Study
Surveillance, patients with stage I or II HL	➤ CT of the Neck/Chest (CPT® 70491 and CPT® 71260) and other previously involved areas at 6 months and 12 months after completing therapy ➤ Surveillance at other time points from the end of therapy should use physical exam and CXR only
Surveillance, patients with stage III or IV HL	➤ CT of the Neck (CPT® 70491), Chest (CPT® 71260), and Abdomen/Pelvis (CPT® 74177) and other previously involved areas at 6 months and 12 months after completing therapy ➤ Surveillance at other time points from the end of therapy should use physical exam and CXR only
Surveillance, patients with recurrent HL and no evidence of disease following successful treatment	➤ CT of the Neck/Chest/Abdomen/Pelvis every 3 months for 1 year after completing therapy for recurrence
Clarify inconclusive findings on conventional imaging to evaluate the need for biopsy to establish recurrence	➤ PET/CT ➤ These requests should be forwarded for Medical Director review.
Clinical symptoms suggesting recurrence	➤ CT of the Neck (CPT® 70491) and Chest (CPT® 71260) and CT Abdomen/Pelvis (CPT® 74177) and CT of other previously involved visceral areas or currently symptomatic areas ➤ MRI Brain with and without contrast (CPT® 70553) for known CNS involvement or new signs or symptoms suggesting intracranial disease - OR ➤ PET/CT (CPT® 78815 or 78816) ➤ PET/CT preferred for bony involvement

PEDONC-5.3: Pediatric Aggressive Mature B-Cell Non-Hodgkin Lymphomas (NHL)

- Aggressive mature B-Cell NHL includes all of the following diagnoses, all of which should be imaged according to this section:
 - ◆ Burkitt's lymphoma/leukemia (BL)
 - ◆ Diffuse Large B-Cell Lymphoma (DLBCL)
 - ◆ Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
 - ◆ Post-transplant Lymphoproliferative Disorder (PTLD)
 - Most commonly occurs following solid organ or stem cell transplantation
 - ◆ Viral-associated lymphoproliferative disorders
 - Most commonly occurs following hematopoietic stem cell transplantation or in patients with primary immunodeficiency
- Initial treatment is usually 7 days of low intensity therapy, with early response evaluation determining next steps in therapy using CT with contrast or MRI without and with contrast of previously involved areas performed around day 6
 - ◆ Patients are customarily still inpatient for this evaluation so outpatient requests should be rare for this time point
- Routine asymptomatic surveillance with advanced imaging has not been found to impact patient outcomes as the majority of these patients present clinically at relapse due to the highly aggressive nature of these lymphomas

Indication	Imaging Study
Initial staging	➤ CT of the Neck (CPT® 70491), ➤ CT Chest (CPT® 71260) ➤ CT Abdomen/Pelvis (CPT® 74177) ◆ May substitute MRI Abdomen without and with contrast (CPT® 74183) and MRI Pelvis without and with contrast (CPT® 72197) in place of CT Abdomen/Pelvis, if requested. ◆ Abdominal ultrasound (CPT® 76700 or 76705) may be approved at initial presentation if CT/MRI not available. ➤ CT with contrast or MRI without and with contrast any other symptomatic body area ➤ PET/CT (CPT® 78815) ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of skull or distal lower extremity involvement.
Additional initial staging if symptoms or extent of disease suggest intracranial extension or metastasis	➤ MRI Brain without and with contrast (CPT® 70553)

Indication	Imaging Study
Restaging for treatment response (following initial response evaluation)	➤ As often as every cycle of chemotherapy (~every 3 weeks): ◆ CT with contrast or MRI without and with contrast (should be same modality as initial diagnosis if possible) of previously involved areas ◆ PET/CT (CPT® 78815) ■ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of, or known, skull or distal lower extremity involvement.
Restaging for all subsequent treatment response, including end of therapy evaluation, after negative PET/CT (either Deauville or Lugano 1, 2 or 3 as reported in formal radiology interpretation)	➤ CT with contrast or MRI without and with contrast (should be same modality as initial diagnosis if possible) of previously involved areas, as often as every 2 cycles of chemotherapy, and at the end of therapy
Assessment of disease activity in inconclusive residual masses seen on conventional imaging	➤ PET/CT (CPT® 78815) ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of, or known, skull or distal lower extremity involvement.
Patients being treated with Rituximab who present with abdominal pain, due to risk of bowel perforation and obstruction	➤ CT Abdomen/Pelvis with contrast (CPT® 74177) ◆ US, x-ray, or other red flags are not required prior to CT
Surveillance of asymptomatic patients with residual masses in the chest or abdomen/pelvis	➤ CXR and Abdominal (CPT® 76700) and Pelvic (CPT® 76856) ultrasound
Clinical symptoms or laboratory findings suggesting recurrence	➤ CT of the Neck (CPT® 70491) and ➤ Chest (CPT® 71260) and ➤ CT Abdomen/Pelvis (CPT® 74177) and ➤ CT of other previously involved visceral areas or currently symptomatic areas ◆ PET/CT (CPT® 78815) is preferred for bony involvement ➤ MRI Brain with and without contrast (CPT® 70553) for history of CNS involvement or new signs or symptoms suggesting intracranial disease OR ➤ PET/CT (CPT® 78815) ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of, or known, skull or distal lower extremity involvement.
Suspected PTLD recurrence with documentation of new palpable nodes, rising LDH, or rising quantitative EBV PCR	➤ PET/CT (CPT® 78815) ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of, or known, skull or distal lower extremity involvement.
Clarify inconclusive findings on conventional imaging to evaluate the need for biopsy to establish recurrence	➤ PET/CT ◆ These requests should be forwarded for Medical Director review.

PEDONC-5.4: Anaplastic Large Cell Lymphoma (ALCL)

- Similar in presentation to Hodgkin Lymphoma, and may be indistinguishable until immunocytology and molecular studies are complete.

Indication	Imaging Study
Initial staging	➤ CT of the Neck/Chest/Abdomen/Pelvis (CPT® 70491, CPT® 71260, and CPT® 74177) ➤ MRI without and with contrast of affected area ◆ may be substituted for CT in cases of paraspinal or soft tissue extremity primary tumors ➤ CT with contrast or MRI without and with contrast any other symptomatic body area ➤ PET/CT (CPT® 78815) ◆ Can be performed prior to biopsy if necessary for patient scheduling. ◆ Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of skull or distal lower extremity involvement.
Additional initial staging for patients with bony primary tumors or metastatic disease	➤ Bone scan (See: <u>PEDONC-1.3: Modality General Considerations</u>)
Restaging at the end of induction chemotherapy (commonly 4 to 6 weeks)	➤ CT with contrast or MRI without and with contrast of previously involved areas (should be same modality as initial diagnosis if possible)
Treatment response in patients treated with cytotoxic chemotherapy	➤ Every 2 cycles: ◆ CT of previously involved areas ■ If CT is performed for primary treatment response, PET/CT can be approved to clarify inconclusive findings detected on conventional imaging - OR ◆ PET/CT ■ If PET/CT is performed for primary treatment response, CT or MRI can be approved to clarify inconclusive findings detected on PET imaging
Restaging after negative PET/CT (either Deauville or Lugano 1, 2 or 3 as reported in formal radiology interpretation)	➤ CT with contrast of previously involved areas
Surveillance	➤ CT with contrast or MRI without and with contrast of all previously involved areas is indicated at 3, 6, 12, and 18 months after therapy is completed.
Additional surveillance for patients with bony primary tumors or metastatic disease	➤ Bone scan (See: <u>PEDONC-1.3: Modality General Considerations</u>) is indicated at 3, 6, 12, and 18 months after therapy is completed
Clinical symptoms suggesting recurrence	➤ CT of the Neck (CPT® 70491), Chest (CPT® 71260), Abdomen/Pelvis (CPT® 74177) and other previously involved or currently symptomatic areas
Clarify inconclusive findings on conventional imaging to evaluate the need for biopsy to establish recurrence	➤ PET/CT ◆ These requests should be forwarded for Medical Director review

References – PEDONC-5

1. Davies K, Barth M, Armenian S, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020—April 10, 2020, *Pediatric Aggressive Mature B-Cell Lymphomas*, available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_b-cell.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Pediatric Aggressive Mature B-Cell Lymphomas V2.2020 4/10/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
2. Metzger ML, Krasin MJ, Choi JK, et al. Hodgkin lymphoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:568-586.
3. Allen CE, Kamdar KY, Bollard CM, et al. Malignant Non-Hodgkin lymphomas in Children. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:587-603.
4. Hayashi RJ, Wistinghausen B, Shiramizu B. Lymphoproliferative Disorders and Malignancies Related To Immunodeficiencies. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:604-616.
5. Alexander S, Ferrando AA. Pediatric lymphoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1626-1671.
6. Lee Chong A, Grant RM, Ahmed BA, Thomas KE, Connolly BL, Greenberg M. Imaging in pediatric patients: time to think again about surveillance. *Pediatr Blood Cancer*. 2010;55(3):407-413. doi:10.1002/pbc.22575.
7. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrup-Link H. Value of 18F-FDG-PET and PET/CT for evaluation of pediatric malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
8. Ceppi F, Pope E, Ngan B, Abila O. Primary cutaneous lymphomas in children and adolescents. *Pediatr Blood Cancer*. 2016;63(11):1886-1894. doi:10.1002/pbc.26076.
9. Flerlage JE, Kelly KM, Beishuizen A, et al. Staging evaluation and response criteria harmonization (SEARCH) for childhood, adolescent, and young adult Hodgkin Lymphoma (CAYAHL): Methodology statement. *Pediatr Blood Cancer*. 2017;64(7):e26421. doi:10.1002/pbc.26421.
10. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658. doi:10.1200/JCO.2013.52.5410.
11. Schwartz CL, Chen L, McCarten K, et al. Childhood Hodgkin International Prognostic Score (CHIPS) predicts event-free survival in Hodgkin lymphoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2017;64(4):e26278. doi:10.1002/pbc.26278.
12. Friedmann AM, Wolfson JA, Hudson MM, et al. Relapse after treatment of Hodgkin lymphoma: outcome and role of surveillance after therapy. *Pediatr Blood Cancer*. 2013;60(9):1458-1463. doi:10.1002/pbc.24568.
13. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol*. 2015;33(27):2975-2985. doi:10.1200/JCO.2014.59.4853.
14. Voss SD, Chen L, Constine LS, et al. Surveillance computed tomography imaging and detection of relapse in intermediate- and advanced-stage pediatric Hodgkin's lymphoma: A report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(21):2635-2640. doi:10.1200/JCO.2011.40.7841.
15. Voss SD. Surveillance Imaging in Pediatric Hodgkin Lymphoma. *Curr Hematol Malig Rep*. 2013;8(3):218-225. doi:10.1007/s11899-013-0168-z.
16. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34(20):2372-2379. doi:10.1200/JCO.2015.65.3469.
17. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised international pediatric non-Hodgkin lymphoma staging system. *J Clin Oncol*. 2015;33:2112-2118. doi:10.1200/JCO.2014.59.7203.
18. Sandlund JT, Guillerman RP, Perkins SL, et al. International pediatric Non-Hodgkin lymphoma response criteria. *J Clin Oncol*. 2015;33(18):2106-2111. doi:10.1200/JCO.2014.59.0745.

19. Eissa HM, Allen CE, Kamdar K, et al. Pediatric Burkitt's lymphoma and Diffuse B-cell lymphoma: are surveillance scans required? *Pediatr Hematol Oncol*. 2014;31(3):253-257. doi:10.3109/08880018.2013.834400.
20. Minard-Colin V, Brugieres L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. *J Clin Oncol*. 2015;33(27):2963-2974. doi:10.1200/JCO.2014.59.5827.
21. Dierickx D, Tousseym T, and Gheysens O. How I treat posttransplant lymphoproliferative disorders. *Blood*. 2015;126(20):2274-2283. doi:10.1182/blood-2015-05-615872.
22. Vali R, Punnett A, Bajno L, Moineddin R, Shamma A. The value of ¹⁸F-FDG PET in pediatric patients with post-transplant lymphoproliferative disorder at initial diagnosis. *Pediatr Transplant*. 2015;19(8):932-939. doi:10.1111/ptr.12611.
23. Hapgood G and Savage KJ. The biology and management of systemic anaplastic large cell lymphoma. *Blood*. 2015;126(1):17-25. doi:10.1182/blood-2014-10-567461.
24. Kempf W, Kazakov DV, Belousova IE, Mitteldorf C, Kerl K. Pediatric cutaneous lymphomas: a review and comparison with adult counterparts. *J Eur Acad Dermatol Venereol*. 2015;29(9):1696-1709. doi:10.1111/jdv.13044.
25. Hochberg J, Flower A, Brugieres L, Cairo MS. NHL in adolescents and young adults: a unique population. *Pediatr Blood Cancer*. 2018;65:e27073. doi.org/10.1002/pbc.27073.
26. Buhtoiarov IN. Pediatric lymphoma. *Pediatr In Rev*. 2017;38(9):410-423. doi:10.1542/pir.2016-0152.

PEDONC-6: Neuroblastoma**PEDONC-6.1: Neuroblastoma – General Considerations****PEDONC-6.2: Staging and Risk Grouping – Neuroblastoma****PEDONC-6.3: Neuroblastoma – Initial Staging****PEDONC-6.4: Neuroblastoma – Treatment Response Imaging (Risk Group Dependent)****PEDONC-6.5: Neuroblastoma – Surveillance Imaging (Risk Group Dependent)**

PEDONC-6.1: Neuroblastoma – General Considerations

Note: Some payors consider PET to be experimental for the treatment of neuroblastoma, and those coverage policies may supersede the recommendations for PET in this section.

- Neuroblastoma is the most common extracranial solid tumor of childhood, and generally arises from the adrenal gland or along the sympathetic chain. Neuroblastoma is divided into very low, low, intermediate, and high risk disease based on International Neuroblastoma Risk Group (INRG) Staging System (see: **PEDONC-6.2: Staging and Risk Grouping**). The treatment approaches for each risk group vary widely and have distinct imaging strategies.
- 90 to 95% of neuroblastomas secrete homovanillic acid (HVA) and vanillylmandelic acid (VMA) in the urine, and urine HVA/VMA should be performed at every disease evaluation for patients with positive HVA or VMA at diagnosis.
- 99mTc-MDP bone scan does not identify foci of disease that affect staging or clinical management and provides no advantage over MIBG scintigraphy and is not used for evaluation of most patients with neuroblastoma.
- For metabolic imaging in patients who are MIBG positive at diagnosis and then become MIBG negative in response to treatment:
 - ◆ Continue to use MIBG (see: **PEDONC-1.3** for coding)

PET imaging is inferior to MIBG in neuroblastoma, and should not be used unless one of the exceptions below is present:

Indication	Imaging Study
➤ Any of the following: ◆ Patients with MIBG-negativity documented at initial diagnosis ◆ At major decision points (such as hematopoietic stem cell transplant or surgery), if MIBG and CT/MRI findings are inconclusive	➤ Whole body PET/CT (CPT® 78816)
➤ Patients currently receiving medications that may interfere with MIBG uptake that cannot be safely discontinued prior to imaging, including: ◆ Tricyclic antidepressants (amitriptyline, imipramine, etc.) ◆ Selective serotonin reuptake inhibitors (SSRI's, sertraline, paroxetine, escitalopram, etc.) ◆ Neuroleptics (risperidone, haloperidol, etc.) ◆ Antihypertensive drugs (alpha or beta blockers, calcium channel blockers) ◆ Decongestants (phenylephrine, ephedrine, pseudoephedrine) ◆ Stimulants (methylphenidate, dextroamphetamine, etc.)	➤ PET should only be approved for this indication when specific documentation of the medication interaction is included with the current PET imaging request. ◆ These requests will be forwarded for Medical Director review.

PEDONC-6.2: Staging and Risk Grouping – Neuroblastoma

- Most recent treatment protocols are using the recently validated International Neuroblastoma Risk Group (INRG) staging system, which is primarily defined by the complexity of local tumor extension and the presence or absence of distant metastases:
 - ◆ L1: Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
 - Image-defined risk factors include a list of specific imaging findings defining patients less likely to be candidates for complete surgical resection
 - These risk factors involve the encasement of major blood vessels, airway, skull base, costovertebral junction, brachial plexus, spinal canal, or major organs or structures
 - ◆ L2: Locoregional tumor with presence of one or more image-defined risk factors
 - ◆ M: Distant metastatic disease (except stage MS)
 MS: Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow with < 10% involvement (MIBG must be negative in bone and bone marrow)

INRG Neuroblastoma Risk Grouping	
Very low risk neuroblastoma (28% of patients, event-free survival > 85%) includes:	
➤ Stage L1 or L2 maturing ganglioneuroma or intermixed ganglioneuroblastoma	
➤ Stage MS patients meeting all of the following:	
◆ Age < 18 months	
◆ Without <i>MYCN</i> amplification	
◆ Without 11q aberration	
Low Risk Neuroblastoma (27% of patients, event-free survival > 75 to ≤ 85%) includes:	
➤ Stage L2 patients age < 18 months meeting all of the following:	
◆ Any histology except maturing ganglioneuroma or intermixed ganglioneuroblastoma	
◆ Without <i>MYCN</i> amplification	
◆ Without 11q aberration	
➤ Stage L2 patients age ≥ 18 months meeting all of the following:	
◆ Differentiating neuroblastoma or nodular ganglioneuroblastoma	
◆ Without <i>MYCN</i> amplification	
◆ Without 11q aberration	
➤ Stage M patients meeting all of the following:	
◆ Age < 18 months	
◆ Without <i>MYCN</i> amplification	
◆ With hyperdiploidy (tumor DNA index > 1)	

Intermediate Risk Neuroblastoma (9% of patients, event-free survival ≥ 50 to $\leq 75\%$) includes:

- Stage L2 patients age < 18 months meeting all of the following:
 - ◆ any histology except maturing ganglioneuroma or intermixed ganglioneuroblastoma
 - ◆ With 11q aberration
- Stage L2 patients age ≥ 18 months meeting all of the following:
 - ◆ Neuroblastoma or nodular ganglioneuroblastoma
 - ◆ Without *MYCN* amplification
 - ◆ With 11q aberration
- Stage M patients meeting all of the following:
 - ◆ Age < 18 months
 - ◆ Without *MYCN* amplification
 - ◆ With diploidy (tumor DNA index = 1)

High Risk Neuroblastoma (36% of patients, event-free survival $< 50\%$, includes the following)

- All patients age ≥ 18 months with stage M disease regardless of other factors
- All patients with neuroblastoma and *MYCN* amplification regardless of other factors
- All stage MS patients with 11q aberration regardless of other factors

PEDONC-6.3: Neuroblastoma – Initial Staging

- MIBG provides superior sensitivity and sensitivity for detecting viable osseous disease compared with bone scintigraphy so technetium bone scan is not necessary when MIBG is utilized. MIBG is positive in 90 to 95% of neuroblastomas.
 - ◆ Most MIBG imaging studies are SPECT/CT studies using CT for localization only. Separate diagnostic CT codes should not be approved for this purpose.
 - ◆ Occasionally MIBG cannot be performed prior to initiation of therapy. In this circumstance, MIBG should be completed within 3 weeks of therapy initiation as the reduction in MIBG avidity in response to chemotherapy is not immediate. Inability to complete MIBG before starting therapy is not an indication to approve PET imaging.
- PET imaging is inferior to MIBG in neuroblastoma, and should not be used unless one of the exceptions stated in section **PEDONC-6.1** is present
- MRI Brain of asymptomatic patients with no history of brain metastases is not indicated for neuroblastoma.

The following imaging studies should be considered appropriate in the initial staging of patients with Neuroblastoma:

Indication	Imaging Study
Initial staging for all patients	➤ 123I-metaiodobenzylguanidine (MIBG - CPT® 78800, 78801, 78802, 78803, or 78804) scintigraphy - AND ➤ One of the following sets of imaging: ◆ CT with contrast of the Neck/Chest/Abdomen/Pelvis (CPT® 70491, 71260, and 74177) OR ◆ MRI without and with contrast of the Neck/Chest/Abdomen/Pelvis (CPT® 70543, 71552, 74183, and 72197)
Evaluation of paraspinal tumors where cord compression is a possibility	➤ MRI without and with contrast of the appropriate spinal level
Evaluation of suspected adrenal neuroblastoma, ganglioneuroblastoma, or ganglioneuroma when CT or MRI is inconclusive	➤ Adrenal nuclear imaging (CPT® 78075)
Clinical signs/symptoms suggest brain involvement	➤ MRI Brain without and with contrast (CPT® 70553)

PEDONC-6.4: Neuroblastoma – Treatment Response Imaging (Risk Group Dependent)

Risk grouping will not be known at the time of initial staging, but is critical for all imaging decisions after initial staging is complete. **The treating oncologist should always know the patient's risk grouping.** It is not possible to establish the appropriate imaging plan for a neuroblastoma patient without knowing his/her risk group.

All Very Low Risk and Low Risk Neuroblastoma Not Receiving Chemotherapy:

- Many patients will be treated with surgical resection only without adjuvant therapy, and these patients enter immediately into surveillance.

Indication	Imaging Study
All patients, 6 to 8 weeks after diagnosis to determine if additional treatment is necessary	➤ CT with contrast or MRI without and with contrast of the primary tumor site ◆ Ultrasound may be used in place of CT or MRI to avoid radiation and/or anesthesia exposure in low risk patients

All Intermediate Risk Neuroblastoma and Very Low Risk or Low Risk Neuroblastoma Receiving Chemotherapy:

- Patients generally receive 2 to 12 cycles of moderate-intensity chemotherapy depending on response to treatment.
- Surgical resection may occur prior to or following chemotherapy depending on disease stage. Restaging prior to surgery is appropriate.

Indication	Imaging Study
Prior to surgical resection	➤ Restaging imaging (MIBG and CT or MRI, as performed at initial diagnosis)
Treatment response, as often as every 2 cycles of chemotherapy (~every 6 weeks and at the end of planned treatment)	➤ CT with contrast of the Chest/Abdomen/Pelvis (CPT® 71260, and CPT® 74177) - OR: ➤ MRI without and with contrast, (CPT® 71552, CPT® 74183, and CPT® 72197) - AND: ➤ CT or MRI of other sites with prior measurable disease
In addition to treatment response listed above, every 4 cycles, and at the end of planned chemotherapy treatment	➤ MIBG scan (CPT® 78800, 78801, 78802, 78803, or 78804)

High Risk Neuroblastoma:

- This group of patients receives highly aggressive therapy using sequential chemotherapy, surgery, high dose chemotherapy with stem cell rescue, radiotherapy, monoclonal antibody (mAb) immunotherapy, and biologic therapy.

Indication	Imaging Study
➤ Any of the following: ◆ Treatment response ■ As often as every 2 cycles of chemotherapy, mAb, or biologic therapy (~every 6 weeks) ◆ Change in modality ■ Prior to surgery, HSCT, XRT, or mAb therapy ◆ End of therapy	➤ CT with contrast, of the Chest/Abdomen/Pelvis (CPT® 71260, and CPT® 74177) OR: ➤ MRI without and with contrast, (CPT® 71552, CPT® 74183, and CPT® 72197) AND: ➤ CT or MRI of other sites with prior measurable disease ➤ MIBG scan (CPT® 78800, 78801, 78802, 78803, or 78804)
At completion of 131I-MIBG therapy	➤ 123I-MIBG scan ◆ FDG-PET cannot be used after 131I-MIBG therapy
Preoperative planning	➤ More frequent imaging with any of the above modalities can be approved around the time of surgery if needed

PEDONC-6.5: Neuroblastoma – Surveillance Imaging (Risk Group Dependent)

- CT Chest is not indicated in asymptomatic surveillance imaging of any stages of neuroblastoma patients with no prior history of thoracic disease
- Urine HVA/VMA (if positive at diagnosis) at 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after surgery

Very Low Risk and Low Risk Neuroblastoma:

Indication	Imaging Study
All patients	➤ CT with contrast or MRI without and with contrast of the primary tumor site 3, 6, 9, 12, 18, 24, and 36 months after surgery. ◆ If negative at 36 months, no further advanced imaging is necessary.
Clarification of findings on CT or MRI suspicious for disease recurrence	➤ MIBG (CPT® 78800, 78801, 78802, 78803, or 78804)

Intermediate Risk Neuroblastoma:

- Urine HVA/VMA (if positive at diagnosis) every month until 12 months after completion of therapy, then at 14, 16, 18, 21, 24, 30, and 36 months after completion of therapy, then annually until 10 years after completion of therapy

Indication	Imaging Study
All patients	➤ CT with contrast or MRI without and with contrast of the primary tumor site and known metastatic sites at 3, 6, 9, 12, 18, 24, and 36 months after completion of therapy. ◆ If negative at 36 months, no further advanced imaging is necessary. ◆ Ultrasound may be sufficient to evaluate the primary tumor site for certain patients and may be approved if requested to replace CT or MR
➤ Both of the following: ◆ Patients with stage 4, or M disease, or 4S, or MS disease AND ◆ Positive MIBG at completion of therapy	➤ MIBG scan (CPT® 78800, 78801, 78802, 78803, or 78804) at 3, 6, 9, 12, 24, and 36 months after completion of therapy. ◆ If negative at 36 months, no further MIBG imaging is necessary. ➤ MIBG (or PET, if MIBG-negative at initial diagnosis) not indicated for all other intermediate risk patients

High Risk Neuroblastoma:

- Urine HVA/VMA (if positive at diagnosis) at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after completion of therapy, then annually until 10 years after completion of therapy, and for suspected recurrence.
- Early detection of recurrence with ¹²³I-MIBG has been shown to improve post-relapse outcomes in high risk neuroblastoma

Indication	Imaging Study
All patients	➤ CT with contrast or MRI without and with contrast of the primary tumor site at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months, then annually until 10 years after completion of therapy. ◆ If negative at 10 years, no further advanced imaging is necessary. ➤ MIBG scan (CPT® 78800, 78801, 78802, 78803, or 78804) at 3, 6, 9, 12, 18, 24, 30, and 36 months after completion of therapy. ◆ If negative at 36 months, no further MIBG or PET imaging is necessary.
Suspected recurrence	➤ CT with contrast, of the Chest/Abdomen/Pelvis (CPT® 71260, and CPT® 74177) or MRI without and with contrast, (CPT® 71552, CPT® 74183, and CPT® 72197) and other sites of prior measurable disease or current symptoms ➤ MIBG scan (CPT® 78800, 78801, 78802, 78803, or 78804)

References – PEDONC-6

1. Brodeur GM, Hogarty MD, Bagatell R, et al. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:772-797.
2. Shusterman S and George RE. Neuroblastoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1675-1713.
3. Sharp SE, Gelfand MJ, Shulkin BL. Pediatrics: diagnosis of neuroblastoma. *Semin Nucl Med*. 2011;41(5):345-353. doi:10.1053/j.semnuclmed.2011.05.001.
4. Kushner BH, Kramer K, Modak S, et al. Sensitivity of surveillance studies for detecting asymptomatic and unsuspected relapse of high-risk neuroblastoma. *J Clin Oncol*. 2009;27(7):1041-1046. doi:10.1200/JCO.2008.17.6107.
5. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrop-Link HE. Value of ¹⁸F-FDG PET and PET/CT for evaluation of pediatric malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
6. Nuchtern JG, London WB, Barnewolt CE, et al. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: A Children's Oncology Group Study. *Ann Surg*. 2012 October;256(4):573-580. doi:10.1097/SLA.0b013e31826cbbbd.
7. Brisse HJ, McCarville MB, Granata C, et al. Guidelines for imaging and staging of neuroblastic tumors: Consensus report from the International Neuroblastoma Risk Group Project. *Radiology*. 2011;261(1):243-257. doi:10.1148/radiol.11101352.
8. Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG task force report. *J Clin Oncol*. 2009;27(2):298-303. doi:10.1200/JCO.2008.16.6876.
9. Cohn SL, Pearson ADJ, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force Report. *J Clin Oncol*. 2009;27(2):289-297. doi:10.1200/JCO.2008.16.6785.
10. GE Healthcare. AdreView™ Iobenguane I 123 Injection prescribing information. Revised September 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/222901bl.pdf
11. Bombardieri E, Giammarile F, Aktolun C, et al. 131I/123I-Metaiodobenzylguanidine (MIBG) scintigraphy: procedure guidelines for tumor imaging. *Eur J Nucl Med Mol Imaging*. 2010;37(12):2436-2446. http://snmmi.files.cms-plus.com/docs/hpra/2010_published_OC_131I_123I_Metaiodobenzylguanidine_Scintigraphy.pdf.
12. Mueller WP, Coppenrath E, Pfluger T. Nuclear medicine and multimodality imaging of pediatric neuroblastoma. *Pediatr Radiol*. 2013;43(4):418-427. doi:10.1007/s00247-012-2512-1.
13. Sharp SE, Gelfand MJ, Shulkin BL. Pediatrics: Diagnosis of neuroblastoma. *Semin Nucl Med*. 2011;41(5):345-353. doi:10.1053/j.semnuclmed.2011.05.001.
14. McCarville MB. What MRI can tell us about neurogenic tumors and rhabdomyosarcoma. *Pediatr Radiol*. 2016;46(6):881-890. doi:10.1007/s00247-016-3572-4.
15. Pinto NR, Applebaum MA, Volchenboum SL, et al. Advances in risk classification and treatment strategies for neuroblastoma. *J Clin Oncol*. 2015;33(27):3008-3017. doi:10.1200/JCO.2014.59.4648.
16. Park JR, Bagatell R, Cohn SL, et al. Revisions to the International Neuroblastoma Response Criteria: A consensus statement from the National Cancer Institute clinical trials planning meeting. *J Clin Oncol*. 2017;35(22):2580-2587. doi:10.1200/JCO.2016.72.0177.
17. Federico SM, Brady SL, Pappo A, et al. The role of chest computed tomography (CT) as a surveillance tool in children with high risk neuroblastoma. *Pediatr Blood Cancer*. 2015;62(6):976-981. doi:10.1002/pbc.25400.
18. Gauguier J-M, Pace-Emerson T, Grant FD, et al. Evaluation of the utility of 99mTC-MDP bone scintigraphy versus MIBG scintigraphy and cross-sectional imaging for staging patients with neuroblastoma. *Pediatr Blood Cancer*. 2017;64:e26601. doi:10.1002/pbc.26601.
19. Venkatramani R, Pan H, Furman WL, et al. Multimodality treatment of pediatric esthesioneuroblastoma. *Pediatr Blood Cancer*. 2016;63(3):465-470. doi:10.1002/pbc.25817.
20. Owens C, Li BK, Thomas KE, et al. Surveillance imaging and radiation exposure, in the detection of relapsed neuroblastoma. *Pediatr Blood Cancer*. 2016;63(10):1786-1793. doi:10.1002/pbc.26099.
21. Allen-Rhoades W, Whittle SB, Rainusso N. Pediatric solid tumors of infancy: an overview. *Pediatr In Rev*. 2018;39(2):57-67. doi:10.1542/pir.2017-0057.

22. Park JR, Kreissman SG, London WB. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma. *JAMA*. doi:10.1001/jama.2019.11642

PEDONC-7: Pediatric Renal Tumors**PEDONC-7.1: Pediatric Renal Tumors – General Considerations****PEDONC-7.2: Unilateral Wilms Tumor (UWT)****PEDONC-7.3: Bilateral Wilms Tumor (BWT)****PEDONC-7.4: Pediatric Renal Cell Carcinoma (RCC)****PEDONC-7.5: Clear Cell Sarcoma of the Kidney (CCSK)****PEDONC-7.6: Malignant Rhabdoid Tumor of the Kidney (MRT) and Other Extracranial Sites****PEDONC-7.7: Congenital Mesoblastic Nephroma (CMN)**

PEDONC-7.1: Pediatric Renal Tumors – General Considerations

Note: Some payors consider PET imaging to be experimental for the treatment of Wilms tumor and other kidney tumors, and those coverage policies may supersede the recommendations for PET imaging in this section.

- A variety of tumors can occur in the pediatric kidney, and include the following:
 - ◆ Wilms Tumor
 - Favorable Histology (FHWT)
 - Focal Anaplasia (FAWT)
 - Diffuse Anaplasia (DAWT)
 - Bilateral Wilms Tumor (BWT)
 - ◆ Renal Cell Carcinoma (RCC)
 - ◆ Clear Cell Sarcoma of the Kidney (CCSK)
 - ◆ Malignant Rhabdoid Tumor of the Kidney (MRT)
 - ◆ Congenital Mesoblastic Nephroma (CMN)
 - ◆ Other cancers occurring in the kidney:
 - Neuroblastoma
 - Primitive Neuroectodermal Tumor
 - Rhabdomyosarcoma
 - Non-Rhabdomyosarcoma Soft Tissue Sarcomas
 - These and other rare tumors have been reported occurring primarily in the kidney and should be imaged according to the guidelines for the specific histologic diagnosis.
- For suspected renal tumor, cell type unknown, image according to **PEDONC-7.4: Pediatric Renal Cell Carcinoma (RCC)**

PEDONC-7.2: Unilateral Wilms Tumor (UWT)

Unilateral Wilms Tumor Initial Staging:

Many patients will present with an asymptomatic abdominal mass, and will undergo ultrasound as a primary evaluation. Doppler ultrasound to evaluate for tumor thrombus is no longer necessary unless CT findings are inconclusive, and should not be performed if CT is already completed.

- CT Abdomen/Pelvis with contrast (CPT® 74177) is indicated for all unilateral Wilms tumor patients
 - ◆ If bilateral renal lesions are noted on ultrasound or CT, MRI Abdomen (CPT® 74183) and Pelvis (CPT® 72197) without and with contrast should be strongly considered for better characterization
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) should be completed prior to anesthesia exposure if possible
- MRI Brain without and with contrast (CPT® 70553) is indicated for initial staging for any patient with neurologic signs or symptoms raising suspicion of CNS metastases as only ~0.5% of Wilms tumor patients will ever develop brain metastases
- Bone scan (see: **PEDONC-1.3**) is indicated for any patient with signs or symptoms raising suspicion of bony metastases
- PET is not indicated in the initial staging of any pediatric renal tumor

Unilateral Wilms Tumor Treatment Response:

A very low risk subset of stage I FHWT will be observed after nephrectomy, and enter directly into surveillance.

The majority of patients will receive chemotherapy with or without XRT, beginning within 14 days of initial surgery.

- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy
- CT Abdomen/Pelvis with contrast (CPT® 74177) or MRI Abdomen (CPT® 74183) and Pelvis (CPT® 72197) without and with contrast can be performed every 2 cycles during treatment and at the end of planned therapy
- PET is not routinely utilized to assess treatment response in Wilms tumor.
 - ◆ However, since most Wilms tumors are FDG-avid, rare circumstances may occur where PET imaging should be approved to establish the presence of active disease only when a major therapeutic decision depends on PET avidity.
 - ◆ These requests will be forwarded for Medical Director review.

Unilateral Wilms Tumor Surveillance Imaging:

There are no data to support the use of PET imaging for routine surveillance in any patient with Wilms tumor.

- Very low risk FHWT treated with nephrectomy only:
 - ◆ CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) OR CXR at 3, 6, 12, and 18 months after nephrectomy
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) OR Ultrasound (CPT® 76700 and 76506) of Abdomen and Pelvis at 3, 6, 12, and 18 months after nephrectomy
 - ◆ Surveillance pelvic imaging is indicated in this patient group due to higher risk of recurrence in surgery only treatment
 - ◆ Other surveillance imaging should be by Abdominal US (CPT® 76700) and CXR
- FHWT treated with chemotherapy with or without XRT:
 - ◆ CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) every 6 months for 3 years after completion of all therapy
 - ◆ CT Abdomen with contrast (CPT® 74160), MRI Abdomen without and with contrast (CPT® 74183), or Ultrasound (CPT® 76700) of the Abdomen every 6 months for 3 years after completion of all therapy
 - ◆ Pelvic imaging is not indicated for surveillance unless prior pelvic involvement has been documented or there was tumor rupture at diagnosis
 - ◆ Other surveillance imaging should be by Abdominal US and CXR
- FAWT or DAWT treated with chemotherapy with or without XRT:
 - ◆ CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) every 3 months for 2 years after completion of all therapy
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) every 3 months for 2 years after completion of all therapy
 - ◆ Other surveillance imaging should be by Abdominal US and CXR
- Surveillance imaging with CT of the Chest/Abdomen/Pelvis (CPT® 71260 and CPT® 74177) following successful treatment for recurrent unilateral Wilms tumor can be approved at every 3 months for 1 year after completing therapy for recurrence.
 - ◆ Surveillance imaging later than 12 months after completing therapy for recurrence should follow the standard timing listed in this surveillance section.

PEDONC-7.3: Bilateral Wilms Tumor (BWT)

Bilateral Wilms Tumor Initial Staging:

Many patients will present with an asymptomatic abdominal mass, and will undergo ultrasound as a primary evaluation. Doppler ultrasound to evaluate for tumor thrombus is no longer necessary unless CT findings are inconclusive, and should not be performed if CT is already completed.

Patients with bilateral Wilms Tumor may begin therapy without a histologic diagnosis to preserve a localized disease stage and attempt to shrink the tumors to allow for renal-sparing surgical approaches.

- MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) is the preferred imaging modality for patients with bilateral Wilms tumor
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) is often performed prior to discovery of bilateral lesions and should not prevent MRI from being approved
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) may be used for patients with a contraindication to MRI
 - Avoidance of anesthesia exposure is not a contraindication to MRI for these patients
- CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) is indicated in the initial workup of all pediatric renal tumors and should be completed prior to anesthesia exposure if possible
- MRI Brain without and with contrast (CPT® 70553) is indicated for initial staging for any patient with neurologic signs or symptoms raising suspicion of CNS metastases as only ~0.5% of Wilms tumor patients will ever develop brain metastases
- Bone scan (see: **PEDONC-1.3** for coding) is indicated for any patient with signs or symptoms raising suspicion of bony metastases
- PET is not indicated in the initial staging of any pediatric renal tumor

Bilateral Wilms Tumor Treatment Response:

- MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) can be performed every 2 cycles during treatment and at the end of planned therapy
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) may be used for patients with a contraindication to MRI
 - ◆ If treating with chemotherapy without a biopsy, disease evaluation is indicated at week 6. If either tumor has not shrunk 50%, then open biopsy is indicated to confirm favorable histology.
 - ◆ If partial nephrectomy still not feasible at week 6, the next disease evaluation is at week 12. Surgical resection should occur no later than week 12.
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy
- PET is not routinely utilized to assess treatment response in Wilms tumor.
 - ◆ However, since most Wilms tumors are FDG-avid, rare circumstances may occur where PET should be approved to establish the presence of active disease only when a major therapeutic decision depends on PET avidity.
 - ◆ These requests will be forwarded for Medical Director review.

Bilateral Wilms Tumor Surveillance Imaging:

- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 6 months for 3 years after completion of all therapy
- CT Abdomen with contrast (CPT® 74160) or MRI Abdomen without and with contrast (CPT® 74183) every 6 months for 3 years after completion of therapy
 - ◆ “Extra” one-time imaging is supported at 3 months after completion of all therapy because close surgical margins occur frequently in patients undergoing nephron-sparing surgical approaches, and the risk for early local recurrence is higher
- Pelvic imaging is not indicated for surveillance unless prior pelvic involvement has been documented or there was tumor rupture at diagnosis
- Other surveillance imaging should be by Abdominal US (CPT® 76700) and CXR
 - ◆ When CT or MRI Abdomen no longer indicated, patients with bilateral Wilms tumor should have screening Abdominal ultrasound every 3 months until age 8
- Surveillance imaging with CT of the Chest/Abdomen/Pelvis (CPT® 71260 and CPT® 74177) following successful treatment for recurrent bilateral Wilms tumor can be approved every 3 months for 1 year after completing therapy for recurrence.
 - ◆ Surveillance imaging later than 12 months after completing therapy for recurrence should follow the standard timing listed in this surveillance section.

PEDONC-7.4: Pediatric Renal Cell Carcinoma (RCC)

A majority of pediatric cases have a novel subtype involving TFE3 or TFEB translocations, which have a different natural history than “adult type” RCC. Patients of any age with TFE3 or TFEB translocated RCC should be imaged according to this guideline section.

40 to 45% of pediatric RCC cases have similar histologies to adult RCC (clear cell, papillary, chromophobe, etc.) and imaging decisions will be similar to general oncology guidelines. Patients with all other subtypes of RCC should be imaged according to **ONC-17: Renal Cell Cancer (RCC)**.

Pediatric Renal Cell Carcinoma Initial Staging:

Many patients will present with an asymptomatic abdominal mass, and will undergo ultrasound as a primary evaluation. Doppler ultrasound to evaluate for tumor thrombus is no longer necessary unless CT findings are inconclusive, and should not be performed if CT is already completed.

- CT Abdomen and Pelvis with contrast (CPT® 74177) is indicated in all patients
 - ◆ If bilateral renal lesions are noted on ultrasound or CT, MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) should be strongly considered
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) should be completed prior to anesthesia exposure if possible
- Other staging imaging should be deferred until a histologic diagnosis is made, by complete nephrectomy for most unilateral renal tumors and biopsy for bilateral renal tumors or inoperable unilateral tumors
- MRI Brain without and with contrast (CPT® 70553) is indicated for any patient with neurologic signs or symptoms raising suspicion of CNS metastases
- Bone scan (See: **PEDONC-1.3** for coding) is indicated for any patient with signs or symptoms raising suspicion of bony metastases
- PET scan is not indicated in the initial staging of any pediatric renal tumor

Pediatric Renal Cell Carcinoma Treatment Response:

Most patients will have surgical resection of all disease at the time of diagnosis and will enter directly into surveillance.

- Patients with residual measurable disease after initial surgery and receiving adjuvant medical therapy can have CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) and CT Abdomen with contrast (CPT® 74160) every 2 cycles during active treatment
- Pelvic imaging is not indicated unless prior pelvic involvement has been documented
- PET is not routinely utilized to assess treatment response in pediatric RCC.
 - ◆ However, since some RCC tumors are FDG-avid, rare circumstances may occur where PET should be approved to establish the presence of active disease only when a major therapeutic decision depends on PET avidity.
 - ◆ These requests will be forwarded for Medical Director review.

Pediatric Renal Cell Carcinoma Surveillance Imaging:

- All pediatric RCC patients:
 - ◆ MRI Brain without and with contrast (CPT® 70553) every 6 months for 2 years after completion of all therapy only for patients with documented CNS metastases or new signs/symptoms suggestive of CNS recurrence.
- TFE3 or TFEB subtype:
 - ◆ CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) every 3 months for 2 years, then every 6 months for 2 years after completion of all therapy
 - ◆ CT Abdomen with contrast (CPT® 74160) or MRI Abdomen without and with contrast (CPT® 74183) every 3 months for 2 years, then every 6 months for 2 years after completion of all therapy
 - ◆ Pelvic imaging is not indicated for surveillance unless prior pelvic involvement has been documented
- All other histologies:
 - ◆ Surveillance imaging is appropriate as listed in the general Oncology Imaging Guidelines: **ONC-17.4: Renal Cell Cancer (RCC) – Surveillance**

PEDONC-7.5: Clear Cell Sarcoma of the Kidney (CCSK)

Be careful not to confuse the diagnosis with clear cell RCC. See ONC-17: Renal Cell Cancer (RCC) for imaging guidelines.

Clear Cell Sarcoma Of The Kidney Initial Staging:

Many patients will present with an asymptomatic abdominal mass, and will undergo ultrasound as a primary evaluation. Doppler ultrasound to evaluate for tumor thrombus is no longer necessary unless CT findings are inconclusive, and should not be performed if CT is already completed.

- CT Abdomen and Pelvis with contrast (CPT® 74177) is indicated in all patients
 - ◆ If bilateral renal lesions are noted on ultrasound or CT, MRI Abdomen and Pelvis without and with contrast should be strongly considered
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) should be completed prior to anesthesia exposure if possible
- Other staging imaging should be deferred until a histologic diagnosis is made, by complete nephrectomy for most unilateral renal tumors and biopsy for bilateral renal tumors or inoperable unilateral tumors
- MRI Brain without and with contrast (CPT® 70553) is indicated for initial staging in all patients with clear cell sarcoma of the kidney
- Bone scan (see: **PEDONC-1.3** for coding) is indicated in all patients with clear cell sarcoma of the kidney
- PET is not indicated in the initial staging of any pediatric renal tumor

Clear Cell Sarcoma Of The Kidney Treatment Response:

- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy
- CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) can be performed every 6 weeks during treatment and at the end of planned therapy
- MRI Brain without and with contrast (CPT® 70553) can be performed:
 - ◆ Every 2 cycles during treatment for patients with CNS metastases at initial staging
 - ◆ At the end of planned therapy for all patients with CCSK
- Bone scan (see: **PEDONC-1.3** for coding) at the end of planned therapy
- PET is not routinely utilized to assess treatment response in CCSK
 - ◆ However, since clear cell sarcomas have been shown to be FDG-avid in other anatomic locations, rare circumstances may occur where PET should be approved to establish the presence of active disease only when a major therapeutic decision depends on PET avidity.
 - ◆ These requests will be forwarded for Medical Director review.

Clear Cell Sarcoma Of The Kidney Surveillance Imaging:

- CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) every 3 months for 2 years after completion of all therapy
- CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) every 3 months for 2 years after completion of all therapy
- MRI Brain without and with contrast (CPT® 70553) every 6 months for 3 years after completion of all therapy
- Bone scan (see: **PEDONC-1.3** for coding) every 3 months for 1 year, then every 6 months for 2 years after completion of all therapy
 - ◆ If negative at 36 months, no further advanced imaging is necessary.
- Other surveillance imaging should be by Abdominal US (CPT® 76700) and CXR

PEDONC-7.6: Malignant Rhabdoid Tumor of the Kidney (MRT) and Other Extracranial Sites

Be careful not to confuse the diagnosis with rhabdomyosarcoma. See PEDONC-8.2: Rhabdomyosarcoma (RMS) for Imaging Guidelines.

A highly aggressive histologic variant that can also occur in other locations and all non-CNS sites should follow these guidelines.

Primary CNS rhabdoid malignancies should be imaged according to **PEDONC-4.5: Atypical Teratoid/Rhabdoid Tumors (ATRT)**.

Malignant Rhabdoid Tumor Initial Staging:

Many patients will present with an asymptomatic abdominal mass, and will undergo ultrasound as a primary evaluation. Doppler ultrasound to evaluate for tumor thrombus is no longer necessary unless CT findings are inconclusive, and should not be performed if CT is already completed.

- CT Abdomen and Pelvis with contrast (CPT® 74177) is indicated in all patients
 - ◆ If bilateral renal lesions are noted on ultrasound or CT, MRI Abdomen and Pelvis without and with contrast should be strongly considered
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) should be completed prior to anesthesia exposure if possible
- Other staging imaging should be deferred until a histologic diagnosis is made, by complete nephrectomy for most unilateral renal tumors and biopsy for bilateral renal tumors or inoperable unilateral tumors
- MRI Brain without and with contrast (CPT® 70553) is indicated for all patients with MRT of the kidney or other non-CNS site
- Bone scan (see: **PEDONC-1.3** for coding) is indicated in all patients with MRT of the kidney or other non-CNS site
- PET is not indicated in the initial staging of any pediatric renal tumor

Malignant Rhabdoid Tumor Treatment Response:

- CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy
- CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) can be performed every 2 cycles during treatment and at the end of planned therapy
 - ◆ If primary site other than kidney, perform CT with contrast or MRI without and with contrast of primary site in place of abdominal and pelvic imaging
- MRI Brain without and with contrast (CPT® 70553) can be performed:
 - ◆ Every 2 cycles during treatment for patients with CNS metastases at initial staging
 - ◆ At the end of planned therapy for all patients with MRT
- Bone scan (see: **PEDONC-1.3** for coding) at the end of planned therapy only if positive at initial diagnosis
- PET is not routinely utilized to assess treatment response in MRT.
 - ◆ However, since malignant rhabdoid tumors have been shown to be FDG-avid, rare circumstances may occur where PET should be approved to establish the presence of active disease only when a major therapeutic decision depends on PET avidity.
 - ◆ These requests will be forwarded for Medical Director review.

Malignant Rhabdoid Tumor Surveillance Imaging:

- CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) every 3 months for 2 years after completion of all therapy
- CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) every 3 months for 3 years after completion of all therapy
 - ◆ If primary site other than kidney, perform CT with contrast or MRI without and with contrast of primary site in place of abdominal imaging
- MRI Brain without and with contrast (CPT® 70553) every 3 months for 1 year, then every 6 months for 1 year after completion of all therapy
- Bone scan (see: **PEDONC-1.3** for coding) every 3 months for 1 year, then every 6 months for 2 years after completion of all therapy only if positive at initial diagnosis
 - ◆ If negative at 36 months, no further advanced imaging is necessary
- Other surveillance imaging should be by Abdominal US (CPT® 76700) and CXR

PEDONC-7.7: Congenital Mesoblastic Nephroma (CMN)

This is the most common primary renal tumor occurring in young infants, and the overall prognosis is very good.

Complete surgical removal is curative in most cases, and histologically confirmed metastatic disease or bilateral disease has never been reported.

Congenital Mesoblastic Nephroma Initial Staging

Many patients will present with an asymptomatic abdominal mass at the time of birth or abnormal prenatal ultrasound, and will undergo ultrasound as a primary evaluation.

- CT Abdomen and Pelvis with contrast (CPT® 74177) is indicated in all patients
- CT Chest with (CPT® 71260) can be approved to evaluate inconclusive findings on Chest x-ray
- PET is not indicated in the initial staging of any pediatric renal tumor

Congenital Mesoblastic Nephroma Treatment Response:

- Surgical resection is curative in most patients. Children who have resection of the tumor can have a single CT Abdomen and Pelvis with contrast (CPT® 74177) approved following resection to establish baseline imaging and those with a complete resection should then be imaged according to surveillance guidelines
- Some patients will receive preoperative chemotherapy to facilitate safer resection and can have CT Abdomen and Pelvis with contrast (CPT® 74177) approved every 2 cycles of therapy until surgery, and should then be imaged according to surveillance guidelines after their postoperative baseline imaging study

Congenital Mesoblastic Nephroma Surveillance Imaging

- Recurrences are rare, but most occur within 12 months of diagnosis
- Given the young age of the patients with CMN, ultrasound is the preferred surveillance imaging modality to avoid radiation and anesthesia exposures
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) can be approved every 3 months for 1 year after completion of all therapy for patients with residual abnormalities present on post-operative imaging or inconclusive findings on ultrasound

References – PEDONC-7

1. Fernandez C, Geller JI, Ehrlich PF, et al. Renal tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:753-771.
2. Dome JS, Mullen EA, and Argani P. Pediatric renal tumors. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:1714-1746.
3. Kaste SC, Brady SL, Yee B, et al. Is routine pelvic surveillance imaging necessary in patients with Wilms tumor? *Cancer*. 2013;119(1):182-188. doi:10.1002/cncr.27687.
4. Malkan AD, Loh A, Bahrami A, et al. An approach to renal masses in pediatrics. *Pediatrics*. 2015;135(1):142-158. doi:10.1542/peds.2014-1011.
5. Khanna G, Rosen N, Anderson JR, et al. Evaluation of diagnostic performance of CT for detection of tumor thrombus in children with Wilms tumor: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;58(4):551-555. doi:10.1002/pbc.23222.
6. Kieran K and Ehrlich PF. Current surgical standards of care in Wilms tumor. *Urol Oncol*. 2016;34(1):13-23. doi:10.1016/j.urolonc.2015.05.029.
7. Moinul Hossain AK, Shulkin BL, Gelfand MJ, et al. FDG positron emission tomography/computed tomography studies of Wilms' tumor. *Eur J Nucl Med Mol Imaging*. 2010;37(7):1300-1308. doi:10.1007/s00259-010-1396-2.
8. Misch D, Steffen IG, Schönberger S, et al. Use of positron emission tomography for staging, preoperative response assessment and post therapeutic evaluation in children with Wilms tumor. *Eur J Nucl Med Mol Imaging*. 2008;35(9):1642-1650. doi:10.1007/s00259-008-0819-9.
9. Servaes S, Khanna G, Naranjo A, et al. Comparison of diagnostic performance of CT and MRI for abdominal staging of pediatric renal tumors: a report from the Children's Oncology Group. *Pediatr Radiol*. 2015;45(2):166-172. doi:10.1007/s00247-014-3138-2.
10. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrup-Link HE. Value of ¹⁸F-FDG PET and PET/CT for Evaluation of Pediatric Malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
11. Dome JS, Graf N, Geller JI, et al. Advances in Wilms tumor treatment and biology: progress through international collaboration. *J Clin Oncol*. 2015;33(27):2999-3007. doi:10.1200/JCO.2015.62.1888.
12. Venkatramani R, Chi Y-Y, Coppes MJ, et al. Outcome of patients with intracranial relapse enrolled on National Wilms Tumor Study Group clinical trials. *Pediatr Blood Cancer*. 2017;64(7):e26406. doi:10.1002/pbc.26406.
13. Mullen EA, Chi Y-Y, Hibbitts E, et al. Impact of surveillance imaging modality on survival after recurrence in patients with favorable-histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol*. 2018;36:3396-3403. doi:10.1200/JCO.18.00076.
14. Ehrlich P, Chi Y-Y, Chintagumpala MM, et al. results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. *Ann Surg*. 2017;266(3):470-478. doi:10.1097/SLA.0000000000002356.
15. Geller JI, Ehrlich PF, Cost NG, et al. Characterization of adolescent and pediatric renal cell carcinoma: a report from the Children's Oncology Group study AREN03B2. *Cancer*. 2015 July; 121(14):2457-2464. doi:10.1002/cncr.29368.
16. Rialon KL, Gulack BC, Englum BR, Routh JC, Rice HE. Factors impacting survival in children with renal cell carcinoma. *J Pediatr Surg*. 2015;50(6):1014-1018. doi:10.1016/j.jpedsurg.2015.03.027.
17. Young EE, Brown CTG, Merguerian PA, Akhavan A. Pediatric and adolescent renal cell carcinoma. *Urol Oncol*. 2016;34(1):42-49. doi:10.1016/j.urolonc.2015.06.009.
18. Gooskens SL, Houwing ME, Vujanic GM, et al. Congenital mesoblastic nephroma 50 years after its recognition: a narrative review. *Pediatr Blood Cancer*. 2017; 64(7):e26437. doi:10.1002/pbc.26437.
19. Seibel NL, Chi YY, et al. Impact of cyclophosphamide and etoposide on outcome of clear cell sarcoma of the kidney treated on the National Wilms Tumor Study-5 (NWTS-5). *Pediatr Blood and Cancer*. 2019;66(1):e27450. doi:10.1002/pbc.27450.

PEDONC-8: Pediatric Soft Tissue Sarcomas**PEDONC-8.1: Pediatric Soft Tissue Sarcomas – General Considerations****PEDONC-8.2: Rhabdomyosarcoma (RMS)****PEDONC-8.3: Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)**

PEDONC-8.1: Pediatric Soft Tissue Sarcomas – General Considerations

Note: Some payors consider PET to be experimental for the treatment of rhabdomyosarcoma and other soft tissue sarcomas, and those coverage policies may supersede the recommendations for PET in this section.

Soft tissue sarcomas occur in both adult and pediatric patients, but some histologic types are more common in one age group than the other. Unless specified below, patients who are <18 years old should be imaged according to this guideline section. Exceptions include:

- Rhabdomyosarcoma patients of all ages should be imaged according to guidelines in **PEDONC-8.2: Rhabdomyosarcoma (RMS)**
- Kaposi's sarcoma patients of all ages should be imaged according to guidelines in **ONC-31.10: Kaposi's Sarcoma**

Pediatric soft tissue sarcomas are divided into **two** groups:

1. Rhabdomyosarcoma (RMS) accounts for ~60% of soft tissue sarcomas in young patients, but only ~25% of soft tissue sarcomas in adolescents
 2. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) which encompasses all other histologic subtypes
- Evaluation of soft tissue masses of uncertain nature prior to biopsy should follow general imaging guidelines in **PEDMS-3: Soft Tissue and Bone Masses** for patients who are age 0 (newborn) through 17 years old, and **MS-10: Soft Tissue Mass or Lesion of Bone** for patients who are ≥18 years old.

PEDONC-8.2: Rhabdomyosarcoma (RMS)

Rhabdomyosarcoma Initial Staging:

- Because RMS can arise from any muscle tissue, the presenting symptoms and primary tumor sites vary widely and strongly influence the appropriate imaging decisions
 - ◆ Either CT with contrast or MRI without and with contrast is acceptable for primary site imaging of RMS arising in the abdomen or pelvis at the discretion of the treating oncologist.
 - ◆ CT with contrast is the preferred primary site imaging modality for RMS arising in the thoracic cavity (not the chest wall).
 - ◆ MRI without and with contrast is the preferred primary site imaging modality for RMS occurring in all other anatomic locations, including the chest wall.
- Evaluation for lung metastases using CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) is indicated in the initial workup of all pediatric soft tissue sarcomas and should be completed prior to anesthesia exposure if possible
- Other staging imaging should be deferred until a histologic diagnosis is made
 - ◆ PET/CT is superior to conventional imaging for detection of nodal and bony metastases in pediatric RMS and is indicated in the initial staging of all patients after histologic diagnosis is established
 - Whole body PET/CT (CPT® 78816) is the preferred study for initial staging of RMS
 - Bone scan (see: **PEDONC-1.3** for coding) may be substituted for PET imaging if PET not available
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) is not routinely indicated in the initial metastatic staging of all patients with pediatric RMS, but can be approved in the following situations:
 - Evaluation of inconclusive PET findings
 - Primary site of abdomen or pelvis
 - Lower extremity primary sites
 - ◆ MRI Brain (CPT® 70553) and Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) is indicated for initial staging in the following pediatric RMS:
 - Primary site involving the paraspinal or paravertebral region
 - PET or bone scan-avid lesions in skull, neck, vertebrae
 - Any patient with neurologic signs or symptoms raising suspicion of CNS metastases

Rhabdomyosarcoma Treatment Response:

- CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy for all patients
- Primary site imaging:
 - ◆ CT with contrast or MRI without and with contrast can be performed every 2 cycles during treatment and at the end of planned therapy
 - ◆ Restaging imaging is appropriate after local control surgery (complete or partial resection) is completed
- Metastatic site imaging:
 - ◆ Repeat imaging of all known metastatic sites using the same modality as during initial staging is appropriate whenever primary site imaging is necessary
- PET is not routinely utilized to assess treatment response in RMS, but is indicated in the following circumstances:
 - ◆ Response assessment prior to local control surgery or radiation therapy
 - ◆ Evaluation of residual mass visible on conventional imaging as part of end of therapy evaluation
 - ◆ Response assessment of disease visible on PET but not conventional imaging
 - ◆ Once PET has been documented to be negative for a given patient's cancer or all PET-avid disease has been surgically resected, PET should not be used for continued disease monitoring or surveillance unless one of the exceptions in section **PEDONC-1: General Guidelines** applies. These requests will be forwarded for Medical Director review.
 - ◆ PET is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. These requests will be forwarded for Medical Director review.

Rhabdomyosarcoma Surveillance Imaging:

- All patients with localized RMS:
 - ◆ Primary tumor site should be imaged with either CT with contrast or MRI without and with contrast every 3 months for 1 year, then every 4 months for 2 years, then every 6 months for 1 year after completion of all therapy
 - ◆ CXR every 3 months for 1 year, then every 4 months for 2 years, then every 6 months for 1 year after completion of all therapy
 - CT Chest with (CPT® 71260) or without contrast (CPT® 71250) is indicated for new or worsening clinical symptoms of chest disease or new findings on CXR
- All patients with metastatic RMS:
 - ◆ Primary tumor site should be imaged with either CT with contrast or MRI without and with contrast every 3 months for 1 year, then every 4 months for 2 years, then every 6 months for 1 year after completion of all therapy
 - ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) and all known metastatic sites every 3 months for 1 year, then every 4 months for 2 years, then every 6 months for 1 year after completion of all therapy
 - ◆ Nuclear bone scan (see: **PEDONC-1.3** for coding) should be used for surveillance of known bony metastases every 3 months for 1 year, then every 4 months for 2 years, then every 6 months for 1 year after completion of all therapy
- PET should not be used for surveillance imaging of RMS unless one of the following applies:
 - ◆ Conventional imaging (CT, MRI, US, plain film) reveals findings that are inconclusive or suspicious for recurrence and PET avidity will determine whether biopsy or continued observation is appropriate
 - Residual mass that has not changed in size since the last conventional imaging does **not** justify PET imaging
 - PET avidity in a residual mass at the end of planned therapy is **not** an indication for PET imaging during surveillance.
 - ◆ Rare circumstances where obvious clinical symptoms show strong evidence suggesting recurrence and PET would replace conventional imaging modalities. These requests will be forwarded for Medical Director review.

PEDONC-8.3: Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)

All soft tissue sarcomas other than RMS fall into this category.

NRSTS Initial Staging:

- Because soft tissue sarcomas can arise from any soft tissue, the presenting symptoms and primary tumor sites vary widely and strongly influence the appropriate imaging decisions.
 - ◆ Either CT with contrast or MRI without and with contrast is acceptable for primary site imaging of NRSTS arising in the abdomen or pelvis at the discretion of the treating oncologist.
 - ◆ CT with contrast is the preferred primary site imaging modality for NRSTS arising in the thoracic cavity (not the chest wall).
 - ◆ MRI without and with contrast is the preferred primary site imaging modality for NRSTS occurring in all other anatomic locations, including the chest wall.
- In addition, evaluation for lung metastases using CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250) is indicated in the initial workup of all pediatric soft tissue sarcomas and should be completed prior to anesthesia exposure if possible
- Other staging imaging should be deferred until a histologic diagnosis is made:
 - ◆ PET/CT (CPT® 78815) may be considered in the following:
 - Desmoplastic small round cell tumor
 - Prior to neoadjuvant chemotherapy
 - Evaluating inconclusive findings found on conventional imaging
 - Whole body PET/CT (CPT® 78816) may be approved if there is clinical suspicion of skull or distal lower extremity involvement
 - ◆ Nuclear bone scan (see: **PEDONC-1.3** for coding) is used to evaluate for bony metastases but should be omitted if PET is performed
 - ◆ CT Abdomen and Pelvis with contrast (CPT® 74177) is not routinely indicated in the initial metastatic staging of pediatric NRSTS, but can be approved in the following situations:
 - Evaluation of inconclusive PET findings
 - Primary site of abdomen or pelvis
 - Lower extremity primary sites
 - Desmoplastic small round cell tumor
 - ◆ MRI Brain (CPT® 70553) and Spine (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) without and with contrast is indicated for initial staging in the following pediatric NRSTS:
 - Primary site of paraspinal or paravertebral region
 - PET or nuclear bone scan-avid lesions in skull, neck, vertebrae
 - Any patient with neurologic signs or symptoms raising suspicion of CNS metastases

NRSTS Treatment Response:

Many patients with NRSTS will be treated with surgical resection alone, and these patients enter immediately into surveillance

- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned therapy
- Primary site imaging:
 - ◆ CT with contrast or MRI without and with contrast can be performed every 2 cycles during treatment and at the end of planned therapy
 - ◆ Restaging imaging is appropriate after local control surgery (complete or partial resection) is completed
- Metastatic site imaging:
 - ◆ Repeat imaging of all known metastatic sites using the same modality as during initial staging is appropriate whenever primary site imaging is necessary
- PET imaging is not routinely utilized to assess treatment response in NRSTS, but is indicated in the following circumstances if positive at initial diagnosis.
 - ◆ Response assessment prior to local control surgery or radiation therapy
 - ◆ Evaluation of residual mass visible on conventional imaging as part of end of therapy evaluation
 - ◆ Response assessment of disease visible on PET but not conventional imaging
 - ◆ Once PET has been documented to be negative for a given patient's cancer or all PET-avid disease has been surgically resected, PET should not be used for continued disease monitoring or surveillance unless one of the exceptions in section **PEDONC-1: General Guidelines** applies. These requests will be forwarded for Medical Director review.
 - ◆ PET imaging is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET imaging may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. These requests will be forwarded for Medical Director review.

Surveillance Imaging:

- All patients with localized NRSTS:
 - ◆ Patients treated with chemotherapy:
 - Primary site should be imaged with either CT with contrast or MRI without and with contrast every 6 months for 5 years after completion of all therapy.
 - ◆ Patients who did NOT receive chemotherapy (patients who underwent resection with or without radiation):
 - Primary site should be imaged with CT with contrast or MRI without and with contrast every 3 months for the first 12 months, then every 6 months in years 2-5 to complete 5 years surveillance after completion of therapy.
 - ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 6 months for 5 years after completion of all therapy
- All patients with metastatic NRSTS:
 - ◆ Primary site should be imaged with either CT with contrast or MRI without and with contrast every 6 months for 5 years after completion of all therapy
 - ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) and all known metastatic sites every 6 months for 3 years after completion of all therapy
 - ◆ CT with contrast of all known metastatic sites every 6 months for 5 years after completion of all therapy
 - ◆ Nuclear bone scan (see: **PEDONC-1.3** for coding) should be used for surveillance of known bony metastases every 6 months for 5 years after completion of all therapy
- Surveillance after recurrence:
 - ◆ Surveillance imaging using CT Chest (CPT® 71260) and CT with contrast or MRI without and with contrast of the primary site following successful treatment for recurrent NRSTS can be approved every 3 months for 1 year after completing therapy for recurrence.
 - Surveillance imaging later than 12 months after completing therapy for recurrence should follow the standard timing listed in this surveillance section.
- PET should not be used for surveillance imaging of NRSTS unless one of the following applies:
 - ◆ Conventional imaging (CT, MRI, US, plain film) reveals findings that are inconclusive or suspicious for recurrence and PET avidity will determine whether biopsy or continued observation is appropriate
 - Residual mass that has not changed in size since the last conventional imaging does **not** justify PET
 - PET avidity in a residual mass at the end of planned therapy is **not** an indication for PET imaging during surveillance.
 - ◆ Rare circumstances where obvious clinical symptoms show strong evidence suggesting recurrence and PET would replace conventional imaging modalities
 - ◆ These requests will be forwarded for Medical Director review.

References – PEDONC-8

1. Wexler LH, Skapek SX, Helman LJ. Rhabdomyosarcoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:798-826.
2. Spunt SL, Million L, and Coffin C. The Nonrhabdomyosarcoma soft tissue sarcomas. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:827-854.
3. Womer RB, Barr FG, Linardic CM. Rhabdomyosarcoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:1906-1945.
4. Davis IJ, Perez-Atayde AR, Fisher DE. Nonrhabdomyosarcoma soft tissue sarcomas and other soft tissue tumors. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:1946-1982.
5. McCarville MB. What MRI can tell us about neurogenic tumors and rhabdomyosarcoma. *Pediatr Radiol*. 2016;46(6):881-890. doi:10.1007/s00247-016-3572-4.
6. Federico SM, Spunt SL, Krasin MJ, et al. Comparison of PET-CT and Conventional Imaging in staging pediatric rhabdomyosarcoma. *Pediatr Blood Cancer*. 2013;60(7):1128-1134. doi:10.1002/pbc.24430.
7. Dharmarajan KV, Wexler LH, Gavane S, et al. Positron Emission Tomography (PET) evaluation after initial chemotherapy and radiation therapy predicts local control in rhabdomyosarcoma. *Int J Radiat Biol Oncol Phys*. 2012;84(4):996-1002. doi:10.1016/j.ijrobp.2012.01.077.
8. Arnold MA, Anderson JA, Gastier-Foster JM, et al. Histology, fusion status, and outcome in alveolar rhabdomyosarcoma with low-risk clinical features: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(4):634-639. doi:10.1002/pbc.25862.
9. Völker T, Denecke T, Steffen I, et al. Positron Emission Tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. *J Clin Oncol*. 2007; 25(34):5435-5441. doi:10.1200/JCO.2007.12.2473.
10. Ostermeier A, McCarville MB, Navid F, et al. FDG PET/CT imaging of desmoplastic small round cell tumor: findings at staging, during treatment and at follow-up. *Pediatr Radiol*. 2015;45(9):1308-1315. doi:10.1007/s00247-015-3315-y.
11. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrop-Link HE. Value of ¹⁸F-FDG PET and PET/CT for evaluation of pediatric malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
12. Roberts CC, Kransdorf MJ, Beaman FD, et al. Follow-Up of malignant or aggressive musculoskeletal tumors. *ACR Appropriateness Criteria®* 2015:1-15. <https://acsearch.acr.org/docs/69428/Narrative/>.
13. Ferrari A, Chi Y-Y, De Salvo GL, et al. Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: a joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group. *Eur J Cancer*. 2017;78:1-6. doi:10.1016/j.ejca.2017.03.003.
14. Spunt SL, Million L, Chi YY, et. al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol*. 2020;21(1):145-161. doi:10.1016/S1470-2045(19)30672-2.

PEDONC-9: Bone Tumors**PEDONC-9.1: Bone Tumors – General Considerations****PEDONC-9.2: Benign Bone Tumors****PEDONC-9.3: Osteogenic Sarcoma (OS)****PEDONC-9.4: Ewing Sarcoma Family of Tumors (ESFT), Including
Primitive Neuroectodermal Tumors (PNET)**

PEDONC-9.1: Bone Tumors – General Considerations

These guidelines include both benign and malignant lesions.

- Bone tumors occur in both adult and pediatric patients, but some are more common in one age group than the other. Unless specified below, patients who are < 18 years old should be imaged according to this guideline section. Exceptions include:
 - ◆ Osteogenic sarcoma patients of all ages should be imaged according to guidelines in **PEDONC-9.3: Osteogenic Sarcoma (OS)**
 - ◆ Ewing sarcoma and primitive neuroectodermal tumor patients of all ages should be imaged according to guidelines in **PEDONC-9.4: Ewing Sarcoma and Primitive Neuroectodermal Tumors (ESFT)**
 - ◆ Chondrosarcoma patients of all ages should be imaged according to guidelines in **ONC-12.6: Bone Sarcomas – Initial Work-up/Staging**
 - ◆ Chordoma patients of all ages should be imaged according to guidelines in **ONC-12.6: Bone Sarcomas – Initial Work-up/Staging**
 - ◆ Giant cell tumor of bone and enchondroma patients of all ages should be imaged according to guidelines in **ONC-12.9: Benign Bone Tumors – General Considerations**
 - ◆ Other benign bone tumor patients of all ages should be imaged according to guidelines in **PEDONC-9.2: Benign Bone Tumors**
- Prosthetic devices for children after surgery for bony tumors are nearly all customized.
 - ◆ CT, contrast as requested in alignment with prosthetic manufacturer specifications, is appropriate when requested by the operating surgeon for planning for customized-to-patient joint replacement or prosthetic surgery
- All bone tumors should be evaluated by plain x-ray prior to any advanced imaging.
- PET does not reliably distinguish between benign and malignant bone tumors and should not be performed prior to biopsy.
- CT Chest is superior to PET/CT for the detection of pulmonary metastases, and is indicated in the initial workup of all suspected malignant bone tumors.
 - ◆ CT Chest should be completed prior to anesthesia exposure, if possible.

PEDONC-9.2: Benign Bone Tumors

- Osteochondroma
 - ◆ Plain x-ray appearance is diagnostic for the majority of patients and advanced imaging is generally unnecessary

Indication	Imaging Study
Preoperative planning	➤ MRI without and with contrast can be approved after evaluation by the operating surgeon ➤ See: <u>PEDONC-9.1: General Considerations</u> for requests related to prosthetic planning
➤ Any of the following: ◆ Concern for malignant transformation ◆ New or worsening pain/symptoms ◆ Change on a recent plain x-ray	➤ MRI without contrast or without and with contrast

- Osteoid osteoma

Indication	Imaging Study
Suspected, based on clinical history and plain film findings	➤ CT without contrast
➤ Any of the following: ◆ CTs are not characteristic for diagnosis ◆ Patient has bone pain not localized to the area of findings on CT or x-ray	➤ ONE of the following: ◆ Triple phase bone scan (CPT® 78315) ◆ SPECT (CPT® 78803) ◆ Hybrid SPECT/CT (CPT® 78830)
Patients with new pain who have been previously treated with radiofrequency ablation of curettage	➤ Bone scan (CPT® code 78830, 78315, or 78803 – as requested)

- Other benign tumors
 - ◆ A variety of diagnoses, including: osteoid osteoma, osteoblastoma, aneurysmal bone cysts, fibrous dysplasia, chondroblastoma, and others.
 - ◆ Plain x-ray appearance is diagnostic for many benign bone tumors, and advanced imaging is generally unnecessary except for preoperative planning.

Indication	Imaging Study
Plain x-ray is non-diagnostic	➤ MRI without and with contrast
Preoperative planning	➤ MRI without and with contrast OR ➤ CT (contrast as requested) after evaluation by the operating surgeon
Surveillance	➤ Plain x-ray
Any of the following: ◆ New findings on plain x-ray ◆ New/worsening clinical symptoms not explained by recent plain x-ray	➤ MRI without and with contrast

PEDONC-9.3: Osteogenic Sarcoma (OS)

Indication	Imaging Study
Suspected/Diagnosis	➤ MRI without and with contrast of the primary site OR ➤ CT, contrast as request, of the primary site if there is a contraindication to MRI - AND ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ◆ CT Chest is indicated in initial workup of all suspected malignant bone tumors in children and should be completed prior to anesthesia exposure if possible
Initial Staging	➤ Whole body PET/CT (CPT® 78816) ◆ Nuclear bone scan (see: PEDONC-1.3 for coding) may be substituted if PET not available ➤ CT Abdomen and Pelvis with contrast (CPT® 74177) is not routinely indicated in the initial metastatic staging of pediatric OS, but can be approved in the following situations: ◆ Evaluation of inconclusive PET findings ◆ Primary site of abdomen or pelvis
Suspected bony metastatic sites noted on PET or bone scan	➤ MRI without and with contrast of the suspected metastatic site OR ➤ CT with contrast of the suspected metastatic site
Restaging after 10 to 12 weeks of neoadjuvant chemotherapy prior to local control surgery	➤ MRI without and with contrast of primary site ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ➤ Whole body PET/CT (CPT® 78816) or bone scan (see: PEDONC-1.3 for coding)
Patients with metastatic disease undergoing current chemotherapy	➤ CT Chest with (CPT®) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned chemotherapy ➤ MRI without and with contrast of primary site can be performed every 2 cycles during treatment and at the end of planned chemotherapy ➤ If previously positive for bony metastases, whole body PET/CT (CPT® 78816) or bone scan (see: PEDONC-1.3 for coding) every 2 cycles during treatment and at the end of planned chemotherapy ➤ Imaging may be indicated more frequently around the time of surgical resection of primary or metastatic lesions to assess for resectability

Indication	Imaging Study
Preoperative planning for local control surgery	➤ CT, contrast as requested ➤ MRA and/or CTA may rarely be indicated for complicated surgical resections, and can be approved after evaluation by the operating surgeon to clarify inconclusive MRI findings for preoperative planning ◆ Requests for MRA and/or CTA will be forwarded for Medical Director review ➤ See: <u>PEDONC-9.1: General Considerations</u> for advancing imaging requests related to prosthetic planning
Following local control surgery, until the end of planned adjuvant chemotherapy	➤ MRI without and with contrast of primary site ~6 weeks after surgical procedure, and at the end of planned chemotherapy ➤ Plain x-rays of the primary site and chest every 2 months ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250): ◆ Measurable pulmonary metastases: every 6 weeks, and at the end of planned chemotherapy ◆ No measurable pulmonary metastases: every 4 months, and at the end of planned chemotherapy ➤ Bone scan (see: <u>PEDONC-1.3 for coding</u>) every 4 months, and at the end of planned chemotherapy ◆ Whole body PET/CT (CPT® 78816) can be used in place of bone scan, if positive for distant bone metastases at initial diagnosis
Recurrent metastatic or recurrent unresectable disease on treatment	➤ The following may be approved every 2 cycles of treatment, and at the end of planned chemotherapy: ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ◆ MRI without and with contrast of primary site can be performed every 2 cycles during treatment and at the end of planned chemotherapy ◆ PET is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET imaging may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. ■ These requests will be forwarded for Medical Director review.

Indication	Imaging Study
Surveillance – Appendicular bone primary tumor site	➤ CT or MRI as performed during suspected or initial disease workup (provided the patient does not have an endoprosthesis that will cause MRI or CT artifact): ◆ Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 3 months for 1 year, then every 4 months for 1 year after completion of all therapy ◆ After 24 months, chest x-ray (CXR) should be used for pulmonary recurrence surveillance, and CT Chest can be approved to clarify inconclusive CXR findings ◆ Bone scan (see: PEDONC-1.3 for coding) every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy
Surveillance – Axial bone primary tumor site	➤ MRI without and with contrast of the primary tumor site: ◆ Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 3 months for 1 year, then every 4 months for 1 year after completion of all therapy ◆ After 24 months, chest x-ray (CXR) should be used for pulmonary recurrence surveillance, and CT Chest can be approved to clarify inconclusive CXR findings ◆ Bone scan (see: PEDONC-1.3 for coding) every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy
Additional surveillance for patients with recurrent or metastatic disease	➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy ➤ Bone scan (see: PEDONC-1.3 for coding) should be used for evaluation of distant bony metastases every 3 months for 1 year, then every 6 months for 2 years, then annually for 2 years after completion of all therapy

Indication	Imaging Study
➤ For suspected recurrence, any of the following: ◆ Conventional imaging reveals findings that are inconclusive or suspicious for recurrence and PET avidity will determine whether biopsy or continued observation is appropriate ◆ Rare circumstances where obvious clinical symptoms show strong evidence suggesting recurrence and PET would replace conventional imaging modalities	➤ PET/CT ◆ These requests will be forwarded for Medical Director review
➤ Biopsy proven recurrence	➤ Refer to initial imaging section studies for suspected recurrence ➤ PET/CT may be approved for biopsy proven recurrence ➤ If disease is considered potentially resectable, follow osteosarcoma treatment response as previous

PEDONC-9.4: Ewing Sarcoma Family of Tumors (ESFT), Including Primitive Neuroectodermal Tumors (PNET)

- Bone and bone marrow metastases can occur in ESFT, and cause a significant change in treatment approach.
- PET/CT can replace bone scan and bone marrow biopsy in ESFT patients and is indicated in the initial staging of all ESFT patients after histologic diagnosis is established

Indication	Imaging Study
Suspected/Diagnosis – ill-defined or non-discrete soft tissue mass without bony involvement	➤ US (CPT® 76881 or 76882)
Suspected/Diagnosis – Primary site	➤ MRI without and with contrast ◆ CT, contrast as requested, if there is a contraindication to MRI ➤ MRA and/or CTA may rarely be indicated for complicated surgical resections, and can be approved after evaluation by the operating surgeon to clarify inconclusive MRI findings for preoperative planning ◆ Requests for MRA and/or CTA should be forwarded for Medical Director review ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ◆ CT Chest is indicated in initial workup of all suspected malignant bone tumors in children and should be completed prior to anesthesia exposure if possible
Suspected/Diagnosis – Chest wall primary	➤ MRI Chest without and with contrast AND ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ◆ CT Chest is indicated in initial workup of all suspected malignant bone tumors in children and should be completed prior to anesthesia exposure if possible
Initial Staging	➤ Whole body PET/CT (CPT® 78816) ◆ Bone scan (see: PEDONC-1.3 for coding) may be substituted for PET imaging if PET not available
➤ For any of the following: ◆ Evaluation of inconclusive PET findings ◆ Primary site involving the abdomen or pelvis	➤ CT Abdomen and Pelvis with contrast (CPT® 74177)

Indication	Imaging Study
Restaging after 10 to 12 weeks of neoadjuvant chemotherapy prior to local control surgery	➤ MRI without and with contrast of the primary site ➤ CT (contrast as requested) may be approved if requested per valuation by the operating surgeon for pre-operative planning ◆ See: <u>PEDONC-9.1: General Considerations</u> for imaging requests related to prosthetic planning ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ➤ Whole body PET/CT (CPT® 78816) or bone scan (see: <u>PEDONC-1.3</u> for coding)
Treatment response following local control surgery	➤ MRI without and with contrast of primary site 3 months after surgical procedure and at the end of planned chemotherapy ➤ Plain x-rays of the primary site and chest immediately after local control then every 3 months ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250): ◆ Measurable pulmonary metastases: every 6 weeks and at the end of planned chemotherapy ◆ No measurable pulmonary metastases: every 3 months and at the end of planned chemotherapy ➤ Whole body PET/CT (CPT® 78816) or bone scan (see: <u>PEDONC-1.3</u> for coding) at the end of planned chemotherapy
Patients with metastatic disease undergoing current chemotherapy	➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be performed every 2 cycles during treatment and at the end of planned chemotherapy ➤ MRI without and with contrast of primary site can be performed every 2 cycles during treatment and at the end of planned chemotherapy ➤ If previously positive for bony metastases, whole body PET/CT (CPT® 78816) or bone scan (see: <u>PEDONC-1.3</u> for coding) every 2 cycles during treatment and at the end of planned chemotherapy ➤ Imaging may be indicated more frequently around the time of surgical resection of primary or metastatic lesions to assess for resectability

Indication	Imaging Study
Recurrent metastatic or recurrent unresectable disease on treatment on treatment	➤ The following may be approved every 2 cycles of treatment, and at the end of planned chemotherapy: ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) ◆ MRI without and with contrast of primary site can be performed every 2 cycles during treatment and at the end of planned chemotherapy ◆ PET is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET imaging may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. ■ These requests will be forwarded for Medical Director review.
Surveillance – any primary site	➤ Plain film x-rays AND ➤ MRI without and with contrast OR CT with contrast of the primary tumor site: ◆ Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 1 year, then annually for 2 years after completion of all therapy ➤ Bone scan (see: PEDONC-1.3 for coding) every 3 months for one year, then every 4 months for one year, then every 6 months for one year, and then annually for 2 years after completion of all therapy ➤ CT Chest with (CPT® 71260) or without contrast (CPT® 71250) every 3 months for 1 year then every 4 months for 1 year after completion of all therapy ➤ Patients with metastatic or recurrent ESFT may have CT Chest annually for an additional two years (for a total of four years of surveillance) ➤ For patients with localized ESFT, Chest x-ray (CXR) should be used for pulmonary recurrence surveillance after the initial 24 months of surveillance, and CT Chest can be approved to clarify inconclusive CXR findings

Indication	Imaging Study
➤ For suspected recurrence, any of the following: ◆ Conventional imaging reveals findings that are inconclusive or suspicious for recurrence and PET avidity will determine whether biopsy or continued observation is appropriate ◆ Rare circumstances where obvious clinical symptoms show strong evidence suggesting recurrence and PET would replace conventional imaging modalities	➤ PET/CT ◆ These requests will be forwarded for Medical Director review
Biopsy proven recurrence	➤ Refer to ESFT initial imaging for studies for suspected recurrence. ➤ PET/CT whole body (CPT® 78816) ➤ If disease is considered potentially resectable, follow ESFT treatment response as previously noted

References – PEDONC - 9

1. Hawkins DS, Brennan BMD, Bölling T, et al. Ewing Sarcoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:855-876.
2. Gorlick R, Janeway K, and Marina N. Osteosarcoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:877-898.
3. DuBois SG, Grier HE, and Lessnick SL. Ewing Sarcoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:1983-2017.
4. Janeway KA. Osteosarcoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2018-2055.
5. Azouz EM. Magnetic resonance imaging of benign bone lesions: cysts and tumors. *Top Magn Reson Imaging*. 2002 August;13(4):219-230.
6. Wolf M. Knee pain in children, part III: stress injuries, benign bone tumors, growing pains. *Pediatr Rev*. 2016;37(3):114-119. doi:10.1542/pir.2015-0042.
7. Uslu L, Doing J, Link M, Rosenberg J, Quon A, Daldrop-Link HE. Value of ¹⁸F-FDG PET and PET/CT for Evaluation of Pediatric Malignancies. *J Nucl Med*. 2015;56(2):274-286. doi:10.2967/jnumed.114.146290.
8. Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer*. 2017 March;123(12):2206-2218.
9. Hurley C, McCarville MB, Shulkin BL, et al. Comparison of 18F-FDG-PET-CT and Bone Scintigraphy for evaluation of osseous metastases in newly diagnosed and recurrent osteosarcoma. *Pediatr Blood Cancer*. 2016;63(8):1381-1386. Accessed January 4, 2018. doi:10.1002/pbc.26014.
10. Byun BH, Kong CB, Lim I, et al. Comparison of (18)F-FDG PET/CT and (99m)TC-MDP bone scintigraphy for detection of bone metastasis in osteosarcoma. *Skeletal Radiol*. 2013;42(12):1673-1681.
11. Quartuccio N, Treglia G, Saisano M, et al. The role of Fluorine-18-Fluorodeoxyglucose positron emission tomography in staging and restaging of patients with osteosarcoma. *Radiol Oncol*. 2013;47(2):97-102. doi:10.2478/raon-2013-0017.
12. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: current treatment and a collaborative pathway to success. *J Clin Oncol*. 2015;33(27):3029-3035. doi:10.1200/JCO.2014.59.4895.
13. Newman EN, Jones RL, Hawkins DS. An evaluation of [F-18]-Fluorodeoxy-D-Glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. *Pediatr Blood Cancer*. 2013;60(7):1113-1117. doi:10.1002/pbc.24406.
14. Roberts CC, Kransdorf MJ, Beaman FD, et al. Follow-up of malignant or aggressive musculoskeletal tumors. *ACR Appropriateness Criteria®* 2015:1-15. <https://acsearch.acr.org/docs/69428/Narrative/>.
15. Meyer JS, Nadel HR, Marina N, et al. Imaging guidelines for children with Ewing sarcoma and osteosarcoma: a report from the Children's Oncology Group Bone Tumor Committee. *Pediatr Blood Cancer*. 2008;51(2):163-170. doi:10.1002/pbc.21596.
16. Gaspar N, Hawkins DS, Dirksen U, et al. Ewing sarcoma: current management and future approaches through collaboration. *J Clin Oncol*. 2015;33(27):3036-3046. doi:10.1200/JCO.2014.59.5256.
17. Mascarenhas L, Felgenhauer JL, Bond MC, et al. Pilot study of adding vincristine, topotecan, and cyclophosphamide to interval-compressed chemotherapy in newly diagnosed patients with localized Ewing sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(3):493-498. doi:10.1002/pbc.25837.
18. Weiser DA, Kaste SC, Siegel MJ, et al. Imaging in childhood cancer: a society for pediatric radiology and children's oncology group joint task force report. *Pediatr Blood Cancer*. 2013;60(8):1253-1260. doi:10.1002/pbc.24533.
19. Dimitrakopoulou-Strauss A, Strauss LG, Heichel T, et al. The role of quantitative 18F-FDG PET studies for the differentiation of malignant and benign bone lesions. *J Nucl Med*. 2002;43(4):510-518.
20. Bestic JM, Wessell DE, Beaman FD, et al. Primary bone tumors. *ACR Appropriateness Criteria®*, 2019;1-13. Date of origin: 1995 Last review date: 2019 <https://acsearch.acr.org/docs/69421/Narrative/>.

21. Biermann JS, Chow W, Adkins DR, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020 – August 12, 2019. Bone cancer, available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Bone Cancer V1.2020–August 12, 2019. ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
22. Jeys L, Abudu A, Grimer R. *Expandable prostheses*. In: Wiesel SW, ed. *Operative Techniques in Orthopaedic Surgical Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2015:1-9.
23. PDQ® Pediatric Treatment Editorial Board. PDQ Osteosarcoma and Malignant Fibrous Histiocytoma of Bone Treatment. Bethesda, MD: National Cancer Institute. Updated 03/25/2020. Available at: <https://www.cancer.gov/types/bone/hp/osteosarcoma-treatment-pdq>. Accessed 08/03/2020. [PMID: 26389179]

PEDONC-10: Pediatric Germ Cell Tumors

General Considerations:

- Malignant pediatric germ cell tumors commonly include one of four histologic subtypes:
 - ◆ Yolk sac tumor
 - ◆ Choriocarcinoma
 - ◆ Embryonal carcinoma
 - ◆ Mixed histology
- Tumors can occur in testicular, ovarian or extragonadal primary locations
- Ovarian masses that are <10 cm in size, have minimal or no visible solid component on ultrasound, and have normal tumor markers are almost universally benign teratomas or functional cysts
 - ◆ Advanced imaging is not necessary
- Sex cord stromal tumors (granulosa cell, theca, sertoli, and leydig tumors) are rare in pediatrics and should be imaged according to general guidelines in: **ONC-20: Testicular, Ovarian and Extragonadal Germ Cell Tumors** in the Oncology Imaging Guidelines.
- This section applies to primary germ cell tumors occurring outside the central nervous system in children who are ≤15 years old at the time of initial diagnosis.
 - ◆ For patients who are >15 years old at diagnosis, the overall prognosis is inferior and these patients should be imaged according to general guidelines in: **ONC-20: Testicular, Ovarian and Extragonadal Germ Cell Tumors** in the Oncology Imaging Guidelines.
- For CNS germ cell tumors, use the imaging guidelines in: **PEDONC-4.7: CNS Germinomas and Non-Germinomatous Germ Cell Tumors (NGGCT)**.

Treatment Considerations:

- Overall treatment strategies are similar for all malignant germ cell tumors.
- Patients with localized GCT are often cured with surgery alone and do not receive adjuvant therapy.
 - ◆ These patients should be imaged using surveillance guidelines after surgery is completed.
- Patients receiving adjuvant chemotherapy are usually treated with 4 to 6 cycles of combination chemotherapy.

Imaging Modality Considerations:

- Initial evaluation of: Ovarian, testicular, and abdominal extragonadal suspected GCT should be completed by ultrasound and tumor markers (AFP, β -hCG)
 - ◆ Once a primary mass suspected to be GCT is discovered, initial staging is indicated prior to histologic confirmation
 - ◆ The degree of abdominal exploration and node sampling necessary for adequate staging is determined in part by imaging findings and is required for preoperative planning
- The primary method of response assessment is by tumor marker decrease
- The primary method of surveillance in pediatric GCT is frequent assessment of serum tumor markers, unless tumor markers were not elevated at diagnosis
- Surveillance imaging of the chest in disease stages I-IV should generally be performed using chest x-ray
 - ◆ See surveillance indications below for specific imaging recommendations
- There has been no published evidence to date supporting the routine use of PET/CT in the evaluation of pediatric GCT
 - ◆ Additionally, PET has been found to have similar efficacy to CT imaging in initial staging of adults with non-seminomatous GCT (the majority of pediatric GCT are non-seminomatous)
- PET as a marker of treatment response has been shown not to be predictive of patient outcomes in GCT and should not be approved
 - ◆ Suspicious lesions seen on conventional imaging should be biopsied to confirm active disease

Indication	Imaging Study
Initial staging	➤ CT Abdomen/Pelvis with contrast (CPT® 74177) ◆ Testicular primary tumors can defer abdominal imaging until after histologic confirmation at the discretion of the operating surgeon ➤ CT Chest with contrast (CPT® 71260) ◆ Should be completed prior to anesthesia exposure if possible
Clarify inconclusive initial staging CT findings or for a known contraindication to CT contrast	➤ MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197)
Additional initial evaluation for patients with symptoms suggesting CNS metastases	➤ MRI Brain without and with contrast (CPT® 70553)
Additional initial evaluation for patients with systemic symptoms or bone pain	➤ Nuclear bone scan (See: <u>PEDONC-1.3: Modality General Considerations</u>)
Restaging in patients with disease not completely resected at initial diagnosis	➤ Every 2 cycles (~every 6 weeks) and at the end of planned therapy: ◆ CT Chest/Abdomen/Pelvis (CPT® 71260 and CPT® 74177) with contrast ■ CT imaging may be indicated more frequently to assess for surgical resectability in patients who have received more than 4 cycles of chemotherapy ◆ Imaging of any metastatic sites with the same modality used during initial staging
➤ Suspicious lesion seen on CT and both of the following: ◆ Relapse risk is determined to be low by the treating physician ◆ Biopsy would cause unnecessary morbidity for the patient	➤ Short-interval CT study of the involved area can be approved ◆ These requests should be sent for MD review
Surveillance, patients with normal (not elevated) tumor markers at the time of diagnosis	➤ CT Abdomen/Pelvis with contrast (CPT® 74177) every 6 months for 2 years, then every 12 months for 3 years to complete a total of 5 years of surveillance
Stage I patients age 0-10 years treated with surgery only	➤ Chest x-ray (CXR) should be completed every 3 months for 1 year after completion of all therapy ◆ For those with primary mediastinal tumors at diagnosis, CT Chest with contrast (CPT® 71260) should be approved in lieu of CXR according to the above schedule. ➤ CT Abdomen/Pelvis with contrast (CPT® 74177) every 3 months for 1 year

Indication	Imaging Study
Stage I patients ages 11+ years treated with surgery only	➤ Chest x-ray (CXR) should be completed every 4 months for 2 years, then every 6 months for 1 year, then every 12 months for 1 year to complete 4 years surveillance imaging after completion of all therapy. ◆ For patients with primary mediastinal tumors at diagnosis, CT Chest with contrast (CPT® 71260) should be approved in lieu of CXR on the above schedule. ➤ CT Abdomen/Pelvis with contrast (CPT® 74177) every 4 months for 2 years, then every 6 months for 1 year, then in 12 months to complete 4 years surveillance
Stage II-IV patients	➤ Chest x-ray (CXR) should be completed every 6 months for 2 years then every 12 months for 1 year after completion of all therapy. ◆ For patients with primary mediastinal tumors at diagnosis, CT Chest with contrast (CPT® 71260) should be approved in lieu of CXR on the above schedule. ➤ CT Abdomen/Pelvis with contrast (CPT® 74177) every 6 months for 2 years, then in 12 months to complete 3 years surveillance ➤ Patients with brain or bone metastases should have surveillance imaging on the same schedule as the primary site imaging with the same modality used during initial staging.
➤ Either of the following: ◆ Any clinically significant rise in tumor markers ◆ Symptoms suggesting recurrent disease ◆ Abnormal CXR	➤ CT Chest/Abdomen/Pelvis with contrast (CPT® 71260 and CPT® 74177)

References – PEDONC-10

1. Frazier AL, Olson TA, Schneider DT, et al. Germ cell tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:899-918.
2. Frazier AL, Billmire D, Amatruda J. Pediatric germ cell tumors. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2056-2099.
3. Gilligan T, Lin DW, Aggarwal R, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2020—May 12, 2020, Testicular Cancer, available at: https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Testicular Cancer V3.2020 5/12/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
4. Armstrong DK, Plaxe SC, Alvarez RD, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020—March 11, 2020 Ovarian Cancer, available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Ovarian Cancer V1.2020 3/11/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
5. de Wit M, Brenner W, Hartmann M, et al. [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumors: results of the German multicentre trial. *Ann Oncol*. 2008;19(9):1619-1623. doi:10.1093/annonc/mdn170.
6. Huddart RA, O'Doherty MJ, Padhani A, et al. ¹⁸Fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC trial TE22--the NCRI testis tumor clinical study group. *J Clin Oncol*. 2007;25(21):3090-3095. doi:10.1200/JCO.2006.09.3831.
7. Papic JC, Finnell MA, Slaven JE, et al. Predictors of ovarian malignancy in children: overcoming clinical barriers of ovarian preservation. *J Pediatr Surg*. 2014;49(1):144-148. doi:10.1016/j.jpedsurg.2013.09.068.
8. Olson TA, Murray MJ, Rodriguez-Galindo C, et al. Pediatric and adolescent extracranial germ cell tumors: the road to collaboration. *J Clin Oncol*. 2015;33(27):3018-3028. doi:10.1200/JCO.2014.60.5337.
9. Fresneau B, Orbach D, Faure-Conter C, et al. Sex-cord stromal tumors in children and teenagers: results of the TGM-95 study. *Pediatr Blood Cancer*. 2015;62(12):2114-2119. doi:10.1002/pbc.25614.
10. Fonseca A, Xia C, Lorenzo AJ et al, Detection of Relapse by Tumor Markers Versus Imaging in Children and Adolescents With Nongerminomatous Malignant Germ Cell Tumors: A Report From the Children's Oncology Group, *J Clin Oncol* 2019;37:396-402. doi:10.1200/JCO.18.00790.

PEDONC-11: Pediatric Liver Tumors**PEDONC-11.1: Pediatric Liver Tumors – General Considerations****PEDONC-11.2: Hepatoblastoma****PEDONC-11.3: Pediatric Hepatocellular Carcinoma (HCC)**

PEDONC-11.1: Pediatric Liver Tumors – General Considerations

Note: Some payors consider PET imaging to be experimental for the treatment of hepatobiliary tumors, and those coverage policies may supersede the recommendations for PET imaging in this section.

Pediatric liver tumors primarily include hepatoblastoma and hepatocellular carcinoma, but hepatic germ cell tumors and primary hepatic sarcomas occur with some frequency. Tumormarkers are useful for initial evaluation as well as treatment response, particularly in hepatoblastoma. Early consideration of liver transplant may be undertaken in children and adolescents with unrespectable localized disease, provided that the disease remains confined to the liver.

- Primary hepatic germ cell tumors should follow imaging guidelines in: **PEDONC-10: Pediatric Germ Cell Tumors**.
- Primary hepatic sarcomas should follow imaging guidelines in: **PEDONC-8.3: Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)**.
- Imaging requests relating to liver transplant surgery and surveillance should follow guidelines in section **AB-42: Transplant** in the Abdomen Imaging Guidelines.

PEDONC-11.2: Hepatoblastoma

Hepatoblastoma Initial Staging:

Hepatoblastoma occurs most commonly in very young children (median diagnosis age of 19 months). Most cases of hepatoblastoma are sporadic, but some are associated with genetic abnormalities, including Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and trisomy 18. Most suspected liver tumors will have ultrasound and tumormarkers (AFP, β -HCG, CEA) as part of the initial evaluation.

- Ultrasound may be approved even after MRI or CT imaging in order to allow evaluation for tumor thrombus
- Once a primary liver mass is discovered, definitive imaging is indicated prior to histologic diagnosis, and may involve any of the following:
 - ◆ MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) is preferred for evaluating tumor margins and vascular anatomy
 - ◆ CT Abdomen/Pelvis with contrast (CPT® 74177)
 - Noncontrast imaging is not indicated due to the increased radiation exposure and limited additive benefit
 - ◆ Some tumors may require both MRI and CT during initial evaluation
 - ◆ MRA (CPT® 74185) or CTA (CPT® 74175) Abdomen are often indicated to evaluate vascular invasion
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) is indicated in the initial work-up of all pediatric liver tumors and should be completed prior to anesthesia exposure if possible
- MRI Brain without and with contrast (CPT® 70553) can be approved only for patients with symptoms suggesting CNS metastases
- Bone scan (See: **PEDONC-1.3: Modality General Considerations**) should be used for initial evaluation of bony metastases only in patients with systemic symptoms or bone pain
- There has been no published evidence to date supporting the routine use of PET/CT imaging in the evaluation of pediatric hepatoblastoma
 - ◆ PET/CT should only be considered in very rare circumstances for preoperative planning when MRI and CT scans are insufficient for surgical decision making.
 - ◆ PET/CT should not be approved in lieu of biopsy of suspicious lesions
 - ◆ These requests will be forwarded for Medical Director review.

Hepatoblastoma Treatment Response:

Patients with localized hepatoblastoma of pure fetal histology are often cured with surgery alone and do not receive adjuvant therapy. These patients should be imaged using surveillance guidelines after surgery is completed.

Patients receiving adjuvant chemotherapy are usually treated with 2 to 8 cycles of combination chemotherapy. Tumor marker decrease is important in response assessment but does not eliminate the need for advanced imaging in patients with unresected hepatoblastoma.

- For patients with disease not completely resected at initial diagnosis, the following can be approved every 2 cycles (~6 weeks) and at the end of planned therapy for all patients:
 - ◆ CT Chest with (CPT® 71260) or without contrast (CPT® 71250)
 - ◆ CT Abdomen/Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197)
 - While the majority of patients will require abdomen and pelvis imaging at all time points, the pelvis imaging may be omitted at the discretion of the ordering physician based on the patient's specific clinical situation
 - MRA (CPT® 74185) or CTA (CPT® 74175) Abdomen are often indicated to evaluate vascular invasion
 - ◆ Imaging of any metastatic sites with the same modality used during initial staging
- Imaging may be indicated more frequently to assess for surgical resectability in patients who have received more than 4 cycles of chemotherapy.
- Abdominal ultrasound is indicated if tumor thrombus was detected at initial diagnosis
 - ◆ If no tumor thrombus was present, continued ultrasound evaluations are not indicated without a specific reason documented in the clinical records
- PET/CT should only be considered in very rare circumstances for preoperative planning when MRI and CT scans are insufficient for surgical decision making.
 - ◆ PET/CT should not be approved in lieu of biopsy of suspicious lesions.
 - ◆ These requests will be forwarded for Medical Director review.

Hepatoblastoma Surveillance Imaging:

The primary method of surveillance in hepatoblastoma is frequent assessment of serum tumor markers (primarily AFP).

- No specific imaging is indicated for surveillance in patients with an AFP of >100 ng/ml at diagnosis or recurrence.
 - ◆ CT Chest and Abdomen with contrast (CPT® 71260 and CPT® 74160) can be approved for any clinically significant rise in tumor markers or symptoms suggesting recurrent disease
- For patients with AFP ≤100 ng/ml at diagnosis or recurrence, the following imaging is appropriate:
 - ◆ CT Abdomen with contrast (CPT® 74160) should be completed every 3 months for 2 years then every 4 months for 2 years after completion of all therapy
 - ◆ Chest x-ray or CT Chest with contrast (CPT® 71260) should be completed every 3 months for 2 years then every 4 months for 2 years after completion of all therapy
 - ◆ Patients with brain or bone metastases should have surveillance imaging on the same schedule as the primary site imaging with the same modality used during initial staging.
- PET/CT has no documented role in the surveillance evaluation of pediatric hepatoblastoma

PEDONC-11.3: Pediatric Hepatocellular Carcinoma (HCC)

Pediatric HCC Initial Staging:

HCC, including its rare histologically distinct variant fibrolamellar hepatocellular carcinoma (FL-HCC), occurs mostly in older children and adolescents. Despite recent advances in treatment, overall survival of pediatric HCC diagnosed in advanced stages remains exceedingly poor, with five-year survival of only 17% to 22% for all stages of pediatric HCC (and FL-HCC). Most suspected liver tumors will have ultrasound and tumor markers (AFP, β -HCG, CEA) as initial evaluation.

- Ultrasound may be approved even after MRI or CT imaging in order to allow evaluation for tumor thrombus.
- Once a primary liver mass is discovered, definitive imaging is indicated prior to histologic diagnosis, and may involve any of the following:
 - ◆ CT Abdomen/Pelvis with contrast (CPT® 74177)
 - ◆ MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197)
 - ◆ Some tumors may require both MRI and CT during initial evaluation
 - ◆ MRA (CPT® 74185) or CTA (CPT® 74175) Abdomen are often indicated to evaluate vascular invasion
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) is indicated in the initial work-up of all pediatric liver tumors and should be completed prior to anesthesia exposure if possible
- MRI Brain without and with contrast (CPT® 70553) can be approved only for patients with symptoms suggesting CNS metastases
- Nuclear bone scan (See **PEDONC-1.3: Modality General Considerations**) should be used for initial evaluation of bony metastases only in patients with systemic symptoms or bone pain
- PET/CT should only be considered in very rare circumstances for preoperative planning when MRI and CT are insufficient for surgical decision making.
 - ◆ PET/CT should not be approved in lieu of biopsy of suspicious lesions
 - ◆ These requests require Medical Director review.

Pediatric HCC Treatment Response:

The majority of hepatocellular carcinoma patients are treated with surgery alone and do not receive adjuvant therapy. Patients with successful upfront gross total resection should be imaged using surveillance guidelines after surgery is completed.

- For patients with disease not completely resected at initial diagnosis, the following can be approved every 2 cycles (~6 weeks) and at the end of planned therapy for all patients:
 - ◆ CT Chest with (CPT® 71260) *or* without contrast (CPT® 71250)
 - ◆ CT Abdomen/Pelvis with contrast (CPT® 74177) or MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197)
 - While the majority of patients will require abdomen and pelvis imaging at all time points, the pelvis imaging may be omitted at the discretion of the ordering physician based on the patient's specific clinical situation
 - MRA (CPT® 74185) or CTA (CPT® 74175) Abdomen are often indicated to evaluate vascular invasion
 - ◆ Imaging of any metastatic sites with the same modality used during initial staging
- Abdominal ultrasound is indicated if tumor thrombus was detected at initial diagnosis
 - ◆ If no tumor thrombus was present, continued ultrasound evaluations are not indicated without a specific reason documented in the clinical records
- PET/CT should only be considered in very rare circumstances for preoperative planning when MRI and CT scans are insufficient for surgical decision making.
 - ◆ PET/CT should not be approved in lieu of biopsy of suspicious lesions
 - ◆ These requests will be forwarded for Medical Director review.

Pediatric HCC Surveillance Imaging:

- CT Abdomen/Pelvis with contrast (CPT® 74177) can be completed every 3 months for 1 year then every 6 months for 1 year, then annually for 3 years after completion of all therapy
- Chest x-ray or CT Chest with contrast (CPT® 71260) should be every 3 months for 1 year then every 6 months for 1 year, then annually for 3 years after completion of all therapy
- Patients with brain or bone metastases should have surveillance imaging on the same schedule as the primary site imaging with the same modality used during initial staging.
- PET/CT has no documented role in the surveillance evaluation of pediatric hepatocellular carcinoma

References – PEDONC-11

1. Meyers RL, Trobaugh-Lotario AD, Malogolowkin MH, et al. Pediatric liver tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:726-752.
2. Tomlinson GE. Hepatoblastoma and other liver tumors in children. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:1886-1905.
3. Pugmire BS, Towbin AJ. Magnetic resonance imaging of primary pediatric liver tumors. *Pediatr Radiol*. 2016;46:764-777. doi:10.1007/s00247-016-3612-0.
4. Chavhan GB, Shelmerdine S, Jhaveri K, Babyn PS. Liver MR Imaging in children: current concepts and technique. *RadioGraphics*. 2016;36(5):1517-1532. doi:10.1148/rg.2016160017.
5. Rai P, Feusner H. Cerebral metastasis of hepatoblastoma: a review. *J Pediatr Hematol Oncol*. 2016;38(4):279-282. doi:10.1097/MPH.0000000000000554.
6. Allen-Rhoades W, Whittle SB, and Rainusso N, Pediatric Solid Tumors of Infancy: An Overview, *Pediatr Rev* 2018;39:57-67. doi:10.1542/pir.2017-0057.
7. Allan BJ, Wang B, Davis JS, et al. A review of 218 pediatric cases of hepatocellular carcinoma. *J Pediatr Surg*. 2014;49(1):166-171. doi:10.1016/j.jpedsurg.2013.09.050.
8. Pappo AS, Furman WL, Schulz KA, Ferrari A, Helman L, Krailo MD. Rare tumors in children: progress through collaboration. *J Clin Oncol*. 2015;33(27):3047-3054. doi:10.1200/JCO.2014.59.3632.
9. Benson AB, D'Angelica MI, Abbott DE, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2020—June 19, 2020, *Hepatobiliary Cancers*, available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Hepatobiliary Cancers V4.2020 6/19/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
10. D'Souza AM, Shah R, Gupta A, et al, Surgical management of children and adolescents with upfront completely resected hepatocellular carcinoma, *Pediatr Blood Cancer* 2019;65:e27293. doi:10.1002/pbc.27293.
11. Weeda VB, Aronson DC, Verheij J, and Lamers WH, Is hepatocellular carcinoma the same disease in children and adults? Comparison of histology, molecular background, and treatment in pediatric and adult patients, *Pediatr Blood Cancer* 2019;66:e27475. doi:10.1002/pbc.27475.

PEDONC-12: Retinoblastoma**PEDONC-12.1: Retinoblastoma – General Considerations****PEDONC-12.2: Retinoblastoma – Imaging**

PEDONC-12.1: Retinoblastoma – General Considerations

- Retinoblastoma (RB) is primarily a disease of the infant and young child, and presents with leukocoria (loss of red reflex).
- About 75% of patients are diagnosed before the age of two years (bilateral RB presents at 12 months of age).
- Retinoblastoma can occur as heritable (25% of cases) or nonheritable (75%) disease.
 - ◆ Heritable RB is associated with a germline mutation in the RB1 gene often resulting typically in bilateral disease.
 - ◆ Individuals who carry the RB1 mutation also have increased risk of developing other cancers, such as osteosarcoma, soft tissue sarcomas, or melanoma. For more information on heritable retinoblastoma, see: **PEDONC-2.12: Familial Retinoblastoma Syndrome**.
 - ◆ Whole body MRI has shown poor sensitivity and specificity in patients with predisposition to systemic malignancy due to germline RB1 mutations, and is not supported.
- Detailed evaluation by a physician with significant training and/or experience in retinoblastoma (most commonly a pediatric ophthalmologist or pediatric oncologist) is indicated prior to considering advanced imaging.
- Retinoblastoma can be unilateral, bilateral, or trilateral (involving the pineal gland). Extraocular spread of retinoblastoma is rare and generally confined to the brain.

PEDONC-12.2: Retinoblastoma – Imaging

Retinoblastoma Initial Staging

- Tumor biopsy is NOT required prior to imaging
- MRI Orbits (CPT® 70543) and Brain (CPT® 70553) without and with contrast can be approved in the initial work-up of all patients with retinoblastoma
 - ◆ Brain imaging may be omitted or deferred at the discretion of the treating ophthalmologist or oncologist
- MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) may be approved if there is evidence of CNS metastasis on:
 - ◆ Ophthalmologic exam
 - ◆ MRI Brain
 - ◆ Lumbar CSF cytology
- CT should generally be avoided in retinoblastoma patients under one year of age or with family history of retinoblastoma (heritable) due to substantially increased risks for secondary malignancy
 - ◆ CT Chest (CPT® 71260) and MRI Abdomen and Pelvis without and with contrast (CPT® 74183 and CPT® 72197) can be approved for patients with clinical symptoms to suggest metastatic disease
- CT Orbital (contrast as requested) and orbital ultrasound can be approved if ordered by the treating ophthalmologist for a specified indication
- Nuclear bone scan (See: **PEDONC-1.3: Modality General Considerations**) is the preferred imaging modality for patients with systemic bone pain suggestive of bony metastases
- PET has no documented role in the evaluation of retinoblastoma

Retinoblastoma Treatment Response:

- MRI Orbits (CPT® 70543) and/or Brain (CPT® 70553) can be approved every 2 cycles (~ every 6 weeks) and at the end of planned therapy
- For patients with metastatic disease, imaging of known positive areas using the same modality at initial staging can be approved every 2 cycles (~6 to 8 weeks) and at the end of planned therapy

Retinoblastoma Surveillance:

- The primary method of surveillance in retinoblastoma is examination under anesthesia (EUA), although some older children can be sufficiently evaluated by exam without anesthesia (EWA).
 - ◆ Surveillance using advanced imaging is generally not indicated for unilateral retinoblastoma after enucleation or exenteration, but can be approved for evaluation of specific clinical concerns.
 - ◆ Patients undergoing ocular salvage treatment approaches can have MRI Orbits (CPT® 70543) and Brain (CPT® 70553) approved every 6 months for 2 years following completion of therapy.
- Patients with bilateral retinoblastoma or germline mutation in RB1 are at increased risk for subsequent pineoblastoma, so MRI Brain without and with contrast (CPT® 70553) can be approved every 6 months for 5 years from the time of diagnosis with retinoblastoma
 - ◆ Routine MRI follow up for pineal disease is not currently supported by evidence in unilateral retinoblastoma patients without germline RB1 mutations

References – PEDONC-12

1. Hurwitz RL, Shields CL, Shields JA, et al. Retinoblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:700-725.
2. Rodriguez-Galindo C, Wilson MW, and Dyer M. Retinoblastoma. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:1747-1778.
3. de Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, Moll AC. Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol*. 2014;15(10):1157-1167. doi:10.1016/S1470-2045(14)70336-5.
4. De Graaf P, Göricke S, Rodjan F, et al. Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. *Pediatr Radiol*. 2012;42(1):2-14. doi:10.1007/s00247-011-2201-5.
5. Allen-Rhoades W, Whittle SB, and Rainusso N, Pediatric Solid Tumors of Infancy: An Overview, *Pediatr Rev* 2018;39:57-67. doi:10.1542/pir.2017-0057.
6. Lohmann DR, Gallie BL. Retinoblastoma. In: Pagon RA, Adam MP, Ardinger HH et al, eds. *GeneReviews™* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2019. version November 21, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1452/>.
7. Freidman DN, Lis E, Sklar CA, et al. Whole-body magnetic resonance imaging (WB-MRI) as surveillance for subsequent malignancies in survivors of hereditary retinoblastoma: a pilot study. *Pediatr Blood Cancer*. 2014;61(8):1440-4. doi:10.1002/pbc.24835.

PEDONC-13: Pediatric Nasopharyngeal Carcinoma

PEDONC-13.1: Pediatric Nasopharyngeal Carcinoma – General Considerations

PEDONC-13.2: Pediatric NPC – Imaging

PEDONC-13.1: Pediatric Nasopharyngeal Carcinoma – General Considerations

Pediatric nasopharyngeal carcinoma (NPC) is rare in comparison to adult NPC but is responsible for up to 50% of nasopharyngeal cancers in children and has higher rates of aggressive type III EBV-associated histology than adult NPC.

Metastasis frequently occurs in cervical lymph nodes and retropharyngeal space. Distal metastasis usually appears in bones, lungs, mediastinum, and rarely, in the liver. In many patients, the initial presentation is a cervical adenopathy, and diagnosis is made with a lymph node biopsy.

Standard upfront treatment in pediatric NPC consists of 3 to 4 cycles of neoadjuvant chemotherapy followed by definitive chemoradiotherapy. Rare patients with lower stage disease may be treated with radiotherapy alone.

PEDONC-13.2: Pediatric NPC – Imaging

Pediatric NPC Initial Staging:

Quantitative EBV DNA PCR should be measured at initial diagnosis, as it can serve as an effective tumor marker if elevated at initial diagnosis.

- MRI Brain without and with contrast (CPT® 70553) and MRI Neck without and with contrast (CPT® 70543) is indicated in the initial staging of all pediatric NPC patients
 - ◆ CT Head without and with contrast (CPT® 70470), CT Maxillofacial without and with contrast (CPT® 70488) and/or CT Neck with contrast (CPT® 70491) can be approved for patients with documented contraindication to MRI imaging (**avoidance of sedation should not be the sole reason**)
 - ◆ Skull base invasion is common in pediatric NPC and has a dramatic impact on prognosis, and is more easily recognized on MRI imaging
- CT Chest with contrast (CPT® 71260) is indicated in initial staging of all patients
- Whole body PET/CT (CPT® 78816) is approvable after histologic confirmation of NPC to evaluate for distant metastases
 - ◆ Bone scan (See: **PEDONC-1.3: Modality General Considerations**) can be used for patients when PET/CT is unavailable
 - ◆ If PET/CT unavailable, CT Abdomen with contrast (CPT® 74160) is supported for any of the following:
 - Initial EBV DNA load ≥ 4000 copies/mL
 - Signs and symptoms of liver disease (including abdominal pain and elevated LFTs)

Pediatric NPC Treatment Response:

- MRI Brain without and with contrast (CPT® 70553) and MRI Neck without and with contrast (CPT® 70543) are indicated for response assessment at the following time points:
 - ◆ Following completion of neoadjuvant chemotherapy
 - ◆ Following completion of chemoradiotherapy
- CT Chest with contrast (CPT® 71260) and whole body PET/CT (CPT® 78816) or bone scan (See: **PEDONC-1.3: Modality General Considerations**) are indicated at the following time points:
 - ◆ Following completion of neoadjuvant chemotherapy only if positive at initial diagnosis
 - ◆ Following completion of chemoradiotherapy
- PET is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. These requests will be forwarded for Medical Director review.

Pediatric NPC Surveillance:

- MRI Brain without and with contrast (CPT® 70553) and MRI Neck without and with contrast (CPT® 70543) are indicated every 3 months for 1 year, then every 6 months for 2 years after completion of all planned therapy
- CT Chest with contrast (CPT® 71260) is indicated every 3 months for 1 year, then every 6 months for 2 years after completion of all planned therapy
- Whole body PET/CT (CPT® 78816) or bone scan (See: **PEDONC-1.3: Modality General Considerations**) are not indicated for routine surveillance in asymptomatic patients but can be approved in the following situations:
 - ◆ Clarification of specified inconclusive findings seen on conventional imaging (should not replace biopsy)
 - ◆ Restaging to identify sites of disease when EBV PCR levels are abnormally high and conventional imaging is negative
 - ◆ Restaging after histologically confirmed recurrence of NPC
 - ◆ These requests will be forwarded for Medical Director review.

References – PEDONC-13

1. Pappo AS, Rodriguez-Galindo C, and Furman WL. Management of infrequent cancers of childhood. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:1098-1123.
2. Goldberg JM, Pappo AS, and Bishop M. Rare tumors of childhood. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2123-2145.
3. Cheuk DKL, Sabin ND, Hossain M, et al. Positron emission tomography-computed tomography for staging and follow-up of pediatric nasopharyngeal carcinoma. *Eur J Nucl Med Mol Imaging*. 2012;39(7):1097-1106. doi:10.1007/s00259-012-2091-2.
4. Stambuk HE, Patel SG, Mosier KM, Wolder SL, Holodny AI. Nasopharyngeal carcinoma: recognizing the radiographic features in children. *Am J Neuroradiol*. 2005;26(6):1575-1579.
5. Sahai P, Mohanti BK, Sharma A, et al. Clinical outcome and morbidity in pediatric patients with nasopharyngeal cancer treated with chemotherapy. *Pediatr Blood Cancer*. 2017;64(2):259-266. doi:10.1002/pbc.26240.
6. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Nasopharyngeal Cancer Treatment – Health Professional Version. Bethesda, MD: National Cancer Institute. Updated 01/31/2020. Available at: https://www.cancer.gov/types/head-and-neck/hp/child/nasopharyngeal-treatment-pdq#_913. Accessed 06/04/2020.
7. Zhang, Lu et al. Plasma Epstein-Barr viral DNA complements TNM classification of nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy. *ONcotarget*. 2015;7(5):6221-6231.

PEDONC-14: Pediatric Adrenocortical Carcinoma

PEDONC-14.1: Pediatric Adrenocortical Carcinoma – General Considerations

PEDONC-14.2: Pediatric ACC – Imaging

PEDONC-14.1: Pediatric Adrenocortical Carcinoma – General Considerations

- Pediatric Adrenocortical Carcinoma (ACC) is a rare but aggressive tumor, with fewer than 25 cases diagnosed each year.
 - ◆ Most patients are diagnosed because of virilizing symptoms, Cushing syndrome, and rarely with feminization and hyperaldosteronism or detection on screening imaging recommended for specified cancer predisposition syndromes.
- The mainstay of treatment is surgery.
 - ◆ Chemotherapy, adrenal suppression, and radiotherapy typically follow resection.
 - ◆ Many ACC patients are treated with surgery alone and do not receive adjuvant therapy. These patients should be imaged using surveillance guidelines after surgery is completed.
- PET has no documented role in the evaluation and treatment of pediatric ACC.
- See: **PEDONC-2.2: Li-Fraumeni Syndrome (LFS)** and **PEDONC-2.4: Beckwith-Wiedemann Syndrome (BWS)** for screening recommendations for patients known to have these syndromes.

PEDONC-14.2: Pediatric ACC – Imaging

Indication	Imaging Study
Initial staging	➤ CT Chest without contrast (CPT® 71250) or with contrast (CPT® 71260) ➤ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183) ➤ Nuclear bone scan (see: PEDONC-1.3 for coding)
After complete resection, with no plans for chemotherapy or radiotherapy	➤ See surveillance below
Restaging, for all unresected primary or metastatic disease on chemotherapy	➤ Every 2 cycles (~6 weeks) during chemotherapy, and following completion of all planned chemotherapy: ◆ CT Chest without contrast (CPT® 71250) or with contrast (CPT® 71260) ◆ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183) ➤ If positive for distant metastases at initial diagnosis: ◆ Nuclear bone scan (see: PEDONC-1.3 for coding) every 2 cycles (~6 weeks) during chemotherapy and following completion of all planned chemotherapy
Response assessment at the completion of radiotherapy	➤ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183)
Surveillance, patients with only localized disease at diagnosis	➤ Every 3 months for 2 years, then every 6 months for 3 years: ◆ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183)
Surveillance, patients with metastatic ACC	➤ Every 3 months for 2 years, then every 6 months for 3 years: ◆ CT Chest without contrast (CPT® 71250) or with contrast (CPT® 71260) ◆ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183)
Recurrence	➤ CT Chest without contrast (CPT® 71250) or with contrast (CPT® 71260) ➤ CT Abdomen without and with contrast (CPT® 74170) or MRI Abdomen without and with contrast (CPT® 74183)
Suspected bone recurrence	➤ Nuclear bone scan (see: PEDONC-1.3 for coding)

References – PEDONC-14

1. Waguespack SG, Huh WW, and Bauer AJ. Endocrine tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:919-945.
2. Michalkiewicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from The International Pediatric Adrenocortical Tumor Registry. *J Clin Oncol*. 2004;22(5):838-845. doi:10.1200/JCO.2004.08.085.
3. Flynt KA, Dillman JR, Davenport MS, et al. Pediatric adrenocortical neoplasms: can imaging reliably discriminate adenomas from carcinomas? *Pediatr Radiol*. 2015;45(8):1160-1168. doi:10.1007/s00247-015-3308-x.
4. Gupta N, Rivera M, Novotny P, et al. Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017, *Horm Res Paediatr* 2018;90:8-18. doi:10.1159/000488855.
5. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Adrenocortical Carcinoma Treatment. Bethesda, MD: National Cancer Institute. Updated 06/08/2020. Available at: <https://www.cancer.gov/types/adrenocortical/hp/child-adrenocortical-treatment-pdq>. Accessed 06/19/2020.
6. Wasserman JD, Novokmet A, Eichler-Jonsson C, et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. *J Clin Oncol*. 2015;33(6):602-9. doi:10.1200/JCO.2013.52.6863.
7. Shah MH, Goldner WS, Benson III AB, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020 – July 24, 2020. Neuroendocrine tumors, available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Neuroendocrine and Adrenal tumors V2.2020 – 7/24/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to [NCCN.org](https://www.nccn.org)

PEDONC-15: Pediatric Melanoma and Other Skin Cancers

Pediatric melanoma is historically rare, but has a steadily rising incidence, especially in adolescents and young adults (AYAs). Staging is assigned using the American Joint Committee on Cancer (AJCC) staging for adult melanoma. Most cases of melanoma arising in children and AYAs (~75%) are localized at diagnosis, and approximately 90% of patients with pediatric melanoma are amenable to radical excision. The clinical management of adolescents and young adults with melanoma is still challenging and evolving because it is difficult to diagnose, and there is no standard treatment.

Non-melanoma skin cancers (mostly basal cell carcinoma and squamous cell carcinoma) are extremely rare in pediatric patients. In many cases, predisposing factors such as prolonged immunosuppression, radiation therapy, chemotherapy, voriconazole use, or a combination of the factors are present, and established age-specific guidelines for management of these skin tumors do not exist.

Imaging guidelines and treatment approaches are consistent with those used for adults with melanoma and other skin cancers, and these patients should follow the imaging guidelines in section **ONC-5: Melanomas and Other Skin Cancers**.

References – PEDONC-15

1. Rodriguez-Galindo C, Furman WL, Pappo AS. Rare pediatric tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:946-966.
2. Goldberg JM, Pappo AS, Bishop M. Rare tumors of childhood. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2123-2145.
3. Swetter SM, Thompson JA, Coit DG, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2020—May 18, 2020, Cutaneous Melanoma, available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Melanoma V3.2020 5/1/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
4. Senerchia AA, Ribiero KB, Rodriguez-Galindo C. Trends in incidence of primary cutaneous malignancies in children, adolescents, and young adults: a population-based study. *Pediatr Blood Cancer*. 2014;61(2):211-216. doi:10.1002/pbc.24639.
5. Kollandjian NA, Wei C, Burke A, Bedikian AY. Malignant melanoma in teenagers and young adults. *J Pediatr Hematol Oncol*. 2014;36(7):552-558. doi:10.1097/MPH.0000000000000231.
6. Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: A European study. *Pediatr Blood Cancer* 2018;65:e26974. doi:10.1002/pbc.26974.
7. Indini A, Brecht I, Del Vecchio M, et al. Cutaneous melanoma in adolescents and young adults. *Pediatr Blood Cancer* 2018;65:e27292. doi:10.1002/pbc.27292.
8. Kohsravi H, Schmidt B, and Huang JT. Characteristics and outcomes of nonmelanoma skin cancer (NMSC) in children and young adults. *J Am Acad Dermatol* 2015;73:785-790. doi:10.1016/j.aad.2015.08.007.

PEDONC-16: Pediatric Salivary Gland Tumors

The majority of pediatric salivary gland tumors arise in the parotid gland. Approximately 10 to 15% of tumors arise in the submandibular, sublingual, or minor salivary glands.

Roughly 75% of pediatric salivary gland tumors are benign, most commonly pleomorphic adenoma.

The most common malignant tumors occurring in the salivary glands are mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, undifferentiated carcinoma, and rarely adenocarcinoma.

American Joint Committee on Cancer (AJCC) staging is used for pediatric as well as adult salivary gland tumors.

Imaging and treatment guidelines for malignant pediatric salivary gland tumors are consistent with those used for adults with salivary gland tumors, and these patients should follow the imaging guidelines in section **ONC-4: Salivary Gland Cancers**.

References – PEDONC-16

1. Rodriguez-Galindo C, Furman WL, and Pappo AS. Rare pediatric tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:946-966.
2. Goldberg JM, Pappo AS, and Bishop M. Rare tumors of childhood. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2123-2145.
3. Pfister DG, Spencer S, Adelstein D, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020—June 9, 2020, Head and Neck Cancers, available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf, referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Head and Neck Cancers V2.2020 6/9/2020. ©2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org
4. Chiaravalli S, Guzzo M, Bisogno G, et al. Salivary gland carcinomas in children and adolescents: The Italian TREP project experience. *Pediatr Blood Cancer*. 2014;61(11):1961-1968.
5. Rebours C, Couloigner V, Galmiche L, et al. Pediatric salivary gland carcinomas: diagnostic and therapeutic management. *Laryngoscope*. 2017;127:140-147.
6. Zamani M, Gronhoj C, Jensen JS, et al. Survival and characteristics of pediatric salivary gland cancer: A systematic review and meta-analysis. *Pediatr Blood Cancer*. 2019;66:e27543. doi:10.1002/pbc.27543.

PEDONC-17: Pediatric Breast Masses

Less than 1% of pediatric breast lesions are malignant, and advanced imaging is generally not recommended without histological confirmation of malignancy.

- Ultrasound (CPT® 76641 and CPT® 76642) is the primary and preferred modality used for evaluation of pediatric breast masses
- Mammography has limited utility in pediatric breast mass evaluation due to the high mammographic breast density in this age group, and the risk of the radiation exposure outweighs the benefit of this modality. As a result, mammography is NOT recommended for evaluation of pediatric or adolescent breast masses.
 - ◆ BI-RADS classification may overstate the risk of malignancy or need for biopsy in pediatric patients.
- MRI has very limited utility in evaluation of pediatric breast masses prior to biopsy, but may be indicated in rare cases for surgical planning when ultrasound is non-diagnostic.
 - ◆ All advanced imaging requests for pediatric breast masses should be forwarded for Medical Director review.
- Pediatric patients with confirmed breast cancer should be imaged according to section **ONC-11: Breast Cancer**.

References – PEDONC-17

1. Rodriguez-Galindo C, Furman WL, Pappo AS. Rare pediatric tumors. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th edition. Philadelphia, PA: Wolters Kluwer; 2016:946-966.
2. Goldberg JM, Pappo AS, Bishop M. Rare Tumors of Childhood. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015:2123-2145.
3. Kaneda HJ, Mack J, Kasales CJ, Schetter S. Pediatric and adolescent breast masses: a review of pathophysiology, imaging, diagnosis, and treatment. *AJR Am J Roentgenol*. 2013;200(2):W204-W212. doi:10.2214/AJR.12.9560.
4. Koning JL, Davenport KP, Poole PS, Kruk PG, Grabowski JE. Breast Imaging-Reporting and Data System (BI-RADS) classification in 51 excised palpable pediatric breast masses. *J Pediatr Surg*. 2015;50(10):1746-1750. doi:10.1016/j.jpedsurg.2015.02.062.
5. Siegel MJ, Chung EM. Breast. In: Siegel MJ, ed. *Pediatric Sonography*. 5th ed. Philadelphia, PA: Wolters Kluwer; 2019:196-210.
6. Siegel MJ, Chung EM. Breast masses in children and adolescents. *Applied Radiology*. 2017;46(9):12-17.
7. Johnson RH, Anders CK, Litton JK, Ruddy KJ, Bleyer A. Breast cancer in adolescents and young adults. *Pediatr Blood Cancer*. 2018;65:e27397. doi:10.1002/pmb.27397.
8. Sanders LM, Sharma P, El Madany M, et al. Clinical breast concerns in low-risk pediatric patients: practice review with proposed recommendations. *Pediatr Radiol*. 2018;48:186-195. doi:10.1007/s00247-017-4007-6.

PEDONC-18: Histiocytic Disorders**PEDONC-18.1: Histiocytic Disorders – General Considerations****PEDONC-18.2: Langerhans Cell Histiocytosis (LCH)****PEDONC-18.3: Hemophagocytic Lymphohistiocytosis (HLH)****PEDONC-18.4: Non-Langerhans Cell Histiocytoses**

PEDONC-18.1: Histiocytic Disorders – General Considerations

The majority of histiocytic disorders occurring in the pediatric population are either Langerhans Cell Histiocytosis (LCH) or Hemophagocytic Lymphohistiocytosis (HLH).

The Non-Langerhans cell histiocytoses encompass a variety of diseases, and have limited imaging considerations except as specified later in this section.

PEDONC-18.2: Langerhans Cell Histiocytosis (LCH)

Includes a heterogeneous group of disorders formerly known by other names, including histiocytosis X, eosinophilic granuloma, Letterer-Siwe Disease, Hand-Schuller-Christian Disease, and diffuse reticuloendotheliosis. LCH has a widely variable clinical presentation, ranging from single indolent lesions to disseminated multisystem disease.

Most common sites of involvement are skin, bones, liver, lung, and pituitary, though other sites are possible.

This guideline may be used for all ages of patients.

LCH Initial Imaging Studies:

- For all patients:
 - ◆ Chest X-ray (CXR)
 - ◆ Abdominal ultrasound (CPT® 76700)
 - ◆ Skeletal survey
 - PET should not be used to replace skeletal survey in LCH
- MRI Brain without and with contrast (CPT® 70553) for any of the following:
 - ◆ Headaches or visual or neurologic disturbances
 - ◆ Polyuria/polydipsia or other endocrine abnormalities
 - ◆ Skull or craniofacial (including jaw) bone involvement
 - ◆ Otorrhea or hearing loss (CT Temporal Bone may be substituted if requested)
 - ◆ Other signs or symptoms suggesting intracranial involvement, including neurodegeneration syndrome
 - ◆ CTA/MRA Head (CPT® 70496/70544) may be approved as part of operative planning or image guidance
- CT Chest with (CPT® 71260) or without contrast (CPT® 71250) for any of the following:
 - ◆ Abnormal CXR
 - ◆ Symptoms of pulmonary involvement and normal CXR
- MRI Abdomen without and with contrast (CPT® 74183) for any of the following:
 - ◆ Elevated liver function tests (usually > 5x upper limit of normal)
 - ◆ Abnormalities seen on abdominal ultrasound
 - ◆ CT Abdomen with contrast (CPT® 74160) can be substituted if requested by ordering physician to avoid general anesthesia
- MRI Spine without and with contrast (Cervical-CPT® 72156, Thoracic-CPT® 72157, Lumbar-CPT® 72158) for any of the following:
 - ◆ Vertebral lesions seen on skeletal survey
 - ◆ Clinical symptoms (including back pain) suggesting spinal involvement and negative skeletal survey
- Whole body PET/CT (CPT® 78816) for any of the following:
 - ◆ Multifocal bone involvement seen on skeletal survey
 - ◆ Bone pain and negative skeletal survey
 - ◆ Other clinical symptoms suggesting multisite disease

- Whole body Tc-99m bone scan (CPT®78306) can be approved in lieu of PET for the same indications if PET is unavailable

LCH Treatment Response:

Patients with localized or single site disease are often treated only with local therapies or observed, and should be imaged according to surveillance guidelines

- Patients receiving systemic therapy will usually undergo treatment for ~12 months. Treatment response is assessed using any modalities showing disease at initial diagnosis after ~6 weeks of treatment.
 - ◆ Those with persistent measurable disease will usually be evaluated again after week 12 of therapy
 - Once PET/CT shows no remaining FDG-avid lesions, additional PET imaging is not indicated
 - As a general rule, both PET/CT and CT with contrast or MRI without and with contrast should not be approved for simultaneous treatment response evaluation without specific documentation showing that both are necessary
- Following the initial phase, patients can have treatment response evaluation every ~3 months while receiving active treatment.
 - ◆ Shorter interval imaging can be approved for documented signs or symptoms concerning for disease progression
- All patients should have the following studies at the end of planned therapy:
 - ◆ Chest X-ray (CXR)
 - ◆ Abdominal ultrasound (CPT® 76700)
 - ◆ Skeletal survey
 - ◆ Repeat of all additional imaging studies positive at initial workup (except PET)
- PET is generally not indicated during active treatment for recurrent pediatric cancer. In rare circumstances, PET may be appropriate when results are likely to result in a treatment change for the patient, including a change from active treatment to surveillance. These requests will be forwarded for Medical Director review.

LCH Surveillance Imaging:

Surveillance imaging is determined by areas of disease involvement.

- Bone involvement
 - ◆ Plain x-ray of involved bony areas at 6 weeks, then at 3 and 6 months after completion of therapy
 - ◆ Additional films are not necessary unless symptoms suggest new or recurrent disease
 - ◆ PET is not indicated for surveillance, but can be considered to evaluate patients with recurrent disease
 - ◆ Skull or craniofacial (including jaw) bone involvement at diagnosis are at higher risk for CNS recurrence, and should be imaged according to CNS involvement section below
- Pulmonary involvement
 - ◆ CXR every 6 months after completion of therapy
 - CT Chest with (CPT® 71260) or without contrast (CPT® 71250) can be approved for new abnormalities on CXR or new pulmonary symptoms with a negative CXR
- CNS involvement
 - ◆ CNS LCH has a particularly high rate of refractory and recurrent disease, and requires longer imaging surveillance
 - ◆ MRI Brain without and with contrast (CPT® 70553) is indicated for patients with previously documented measurable intracranial lesions at 6 weeks, 3 months, and 6 months after completion of all therapy.
 - If negative at that time, continued surveillance is indicated at 1, 2, 4, 7, and 10 years after completion of all planned therapy
 - If residual measurable intracranial lesions are present at 6 months, imaging can be repeated every 3 months until negative or unchanged on two consecutive studies, at which time the schedule in the previous bullet should begin
 - ◆ MRI Brain without and with contrast (CPT® 70553) is indicated for patients with documented hypothalamic-pituitary dysfunction at 1, 2, 4, 7, and 10 years after completion of all planned therapy.
 - MRI can be approved at any time for worsening neurologic symptoms
 - ◆ Intraspinal lesions are rare, but should be imaged according to the same guidelines as brain imaging using MRI without and with contrast of all involved spine levels
- Liver involvement
 - ◆ Persistent liver involvement is rare, and imaging after completion of LCH therapy will be highly individualized depending on degree of liver dysfunction and plans for supportive therapy or liver transplant
 - ◆ Most patients with liver involvement will receive surveillance Abdominal ultrasound (CPT® 76700) every 6 months

PEDONC-18.3: Hemophagocytic Lymphohistiocytosis (HLH)

There are no standard imaging studies required for the diagnosis and initial evaluation of HLH. Most cases are diagnosed with a combination of physical findings, laboratory testing, and bone marrow evaluation. Advanced imaging studies may be necessary to assess organ dysfunction as HLH commonly affects the liver, spleen, and bone marrow, and less commonly the kidneys, lungs, and brain

- Any or all of the following may be approved for the initial evaluation of HLH include:
 - ◆ Abdominal ultrasound (CPT® 76700)
 - ◆ CT Abdomen and/or Pelvis (contrast as requested)
 - ◆ MRI Abdomen (CPT® 74183) and/or Pelvis (CPT® 72197) without and with contrast
 - ◆ CXR
 - ◆ CT Chest with contrast (CPT® 71260)
 - ◆ MRI Brain without and with contrast (CPT® 70553)
 - ◆ CTA/MRA Head (CPT® 70496/70544) may be approved as part of operative planning or image guidance

It is NOT required to perform ultrasound or plain film in a stepwise fashion if CT or MRI is planned as patients with HLH can deteriorate rapidly.

- There is no established standard role for PET in the diagnosis or treatment response evaluation of HLH
 - ◆ Secondary HLH is very difficult to treat if the primary cause is not concurrently treated
 - ◆ In these cases, if conventional imaging has been completed and is unrevealing, whole body PET/CT (CPT® 78816) can be considered for the purpose of identifying a site for tissue diagnosis of a primary source of infection or malignancy
 - ◆ If a malignancy is identified as the inciting factor for HLH, additional imaging decisions for that malignancy should be based on the appropriate diagnosis-specific guidelines

PEDONC-18.4: Non-Langerhans Cell Histiocytoses

Includes diagnoses such as juvenile xanthogranuloma (JXG), sinus histiocytosis with lymphadenopathy (Rosai-Dorfman Disease, RDD), and Erdheim-Chester Disease (ECD).

In general, these are localized cutaneous or nodal disease without need for regular advanced imaging, but important exceptions are listed in this section.

Juvenile Xanthogranuloma (JXG):

- Generally involves only skin or cervical nodes, and involutes spontaneously, imaging of involved nodal areas may be appropriate using CT with contrast of appropriate area
- Systemic JXG is associated with multi-organ involvement and imaging studies may include:
 - ◆ MRI Brain (CPT® 70553) and/or Orbits (CPT® 70543) without and with contrast
 - ◆ CT Neck (CPT® 70491), Chest (CPT® 71260), and/or Abdomen (CPT® 74160) with contrast
 - ◆ CTA/MRA Head (CPT® 70496/70544) may be approved as part of operative planning or image guidance
- There is no established role for PET in the diagnosis or treatment of JXG

Rosai-Dorfman Disease (RDD):

Characterized by bulky adenopathy (usually cervical) with frequent systemic involvement

Appropriate imaging studies may include:

- MRI Brain (CPT® 70553) and/or Orbits (CPT® 70543) without and with contrast
- CTA/MRA Head (CPT® 70496/70544) may be approved as part of operative planning or image guidance
- Nuclear bone scan (See: **PEDONC-1.3: Modality General Considerations**)
- CT Neck (CPT® 70491), Chest (CPT® 71260) and/or Abdomen/Pelvis (CPT® 74177) with contrast
- There is no established role for PET in the diagnosis or treatment of RDD, but whole body PET/CT (CPT® 78816) may be approved if PET/CT will provide critical information for major treatment decision making that cannot be obtained using conventional imaging or biopsy.
 - ◆ Because of the paucity of evidence for PET in RDD, PET/CT should not be used to replace tissue confirmation for any clinical scenario in RDD.
 - ◆ These requests will be forwarded for Medical Director review.
- There is no established role for routine surveillance imaging of asymptomatic patients after treatment for RDD, but CT with contrast can be approved for evaluation of new or worsening clinical symptoms suggesting recurrent disease

Erdheim-Chester Disease (ECD):

An aggressive histiocytic disorder with overall poor prognosis that is characterized by long bone involvement with frequent spread to multiple organs

ECD Initial Imaging Studies:

Appropriate imaging studies at initial diagnosis may include:

- MRI Brain (CPT® 70553) and/or Orbits (CPT® 70543) without and with contrast
- CTA/MRA Head (CPT® 70496/70544) may be approved as part of operative planning or image guidance
- Nuclear bone scan (See: **PEDONC-1.3: Modality General Considerations**)
- Whole body PET/CT (CPT® 78816)
- CT Neck (CPT® 70491), Chest (CPT® 71260) and/or Abdomen/Pelvis (CPT® 74177) with contrast
- CTA or MRA of Chest (CPT® 71275 or CPT® 71555) or Abdomen (CPT® 74175 or CPT® 74185) to evaluate vascular tree involvement
- Cardiac MRI without and with contrast (CPT® 75561)

ECD Treatment Response:

- Most patients will receive systemic therapy. Treatment response imaging can be approved every 3 months during active treatment using any modalities showing disease at initial diagnosis, including PET/CT.
 - ◆ Once PET/CT shows no remaining FDG-avid lesions, additional PET imaging is not indicated unless conventional imaging studies are inconclusive and acute treatment decisions will be made based on PET results. These requests will be forwarded for Medical Director review.

ECD Surveillance Imaging:

- Surveillance imaging can be approved every 3 months for the first year after completion of treatment, then every 6 months using any modalities showing disease at initial diagnosis.
- PET/CT is not supported for routine surveillance of ECD, but can be approved if conventional imaging is inconclusive for suspected recurrence. These requests will be forwarded for Medical Director review.

References – PEDONC-18

1. McClain KL, Allen CE, Hicks MJ. Histiocytic diseases. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:617-627.
2. Degar BA, Fleming MD, Rollins BJ, et al. Histiocytoses. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:2100-2122.
3. Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer*. 2013;60(2):175-184. doi:10.1002/pbc.24367.
4. Chandrakasan S, Filipovich AH. Hemophagocytic Lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. *J Pediatr*. 2013;163(5):1253-1259. doi:10.1016/j.jpeds.2013.06.053.
5. Phillips M, Allen C, Gerson P, et al. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. *Pediatr Blood Cancer*. 2009;52(1):97-101. doi:10.1002/pbc.21782.
6. Chellapandian D, Shaiki F, van den Bos C, et al. Management and outcome of patients with langerhans cell histiocytosis and single-bone CNS-risk lesions: a multi-institutional retrospective study. *Pediatr Blood Cancer*. 2015;62(12):2162-2166. doi:10.1002/pbc.25645.
7. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. *Blood*. 2015;126(1):26-35. doi:10.1182/blood-2014-12-569301.
8. Schram AM, Berliner N. How I treat Hemophagocytic lymphohistiocytosis in the adult patient. *Blood*. 2015;125(19):2908-2914. doi:10.1182/blood-2015-01-551622.
9. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer*. 2005;45(3):256-264. doi:10.1002/pbc.20246.
10. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. *Blood*. 2014;124(4):483-492. doi:10.1182/blood-2014-03-561381.

PEDONC-19: Long Term Pediatric Cancer Survivors

PEDONC-19.1: Long Term Pediatric Cancer Survivors – General Considerations

PEDONC-19.2: Cardiotoxicity and Echocardiography

PEDONC-19.3: Second Malignant Neoplasms (SMN)

PEDONC-19.4: Osteonecrosis in Long Term Cancer Survivors

PEDONC-19.1: Long Term Pediatric Cancer Survivors – General Considerations

This section applies to patients who have passed the end of the surveillance imaging period for their specific cancer, or 5 years after completion of therapy, whichever occurs first.

As these are long term survivors, many patients falling under this guideline section will have reached adult age. However, these guidelines relate specifically to late effects of childhood cancer treatment and should be applied to all long term childhood cancer survivors regardless of current age.

The Children's Oncology Group has published comprehensive guidelines for the management of long-term childhood cancer survivors, and these are available at: <http://www.survivorshipguidelines.org>.

A summary of cancer treatment should be available for all patients in this category and should generally include, at minimum:

- Type of cancer and stage
 - Dates of diagnosis, recurrence, cancer-related surgeries, beginning and end dates of chemotherapy, radiotherapy, and/or stem cell transplant
 - Protocol number used for treatment and cumulative chemotherapy drug dose exposures
 - Cumulative radiation dose, fraction number, modality, and field exposure
- Annual detailed history and complete physical examination is a critical component of cancer survivorship care and along with laboratory testing serves as the primary method of screening for the majority of late effects.
- Advanced imaging for asymptomatic screening is not routinely indicated except as specified in this section.
 - Imaging requests related to new clinical signs or symptoms in a long term cancer survivor not explicitly covered in this section should be reviewed according to the guideline for the patient's cancer type or the relevant non-malignant clinical problem.

PEDONC-19.2: Cardiotoxicity and Echocardiography

Exposure to cardiotoxic anthracycline chemotherapy agents is common in pediatric Oncology due to the high success rate of this drug class in the treatment of pediatric cancers. Screening echocardiography (CPT® 93306, CPT® 93307, or CPT® 93308) for life is indicated after exposure to anthracycline chemotherapy, cardiotoxic immunotherapy, or cardiac exposure to radiotherapy.

Cardiac risk is assessed based on the age of the patient at the time of treatment initiation, the cumulative drug exposure expressed as doxorubicin equivalent mg/m², and the presence or absence of radiotherapy exposure to cardiac muscle.

SCREENING ECHOCARDIOGRAM INDICATIONS			
Age at time of Exposure	Cumulative Doxorubicin Equivalent Dose	Cumulative radiation dose to cardiac muscle	Echocardiogram frequency
All ages	None	None	None
0-0.99 years	≥250 mg/m ²	None	Annual
	0-249 mg/m ²	Any dose	Annual
	0-249 mg/m ²	None	Every 2 years
1-4.99 years	≥250 mg/m ²	Any dose	Annual
	0-249 mg/m ²	15+ Gy	Annual
		0-14.99 Gy	Every 2 years
	None	35+ Gy	Annual
		15-34.99 Gy	Every 2 years
0-14.99 Gy		Every 5 years	
5+ years	≥250 mg/m ²	Any dose	Every 2 years
	0-249 mg/m ²	15+ Gy	Every 2 years
		0-14.99 Gy	Every 5 years
		None	35+ Gy
	15-34.99 Gy		Every 5 years
0-14.99 Gy	None		
All ages with known ventricular dysfunction			Annual

- Stress echocardiography is not indicated as a screening study for anthracyclines cardiotoxicity in the absence of coronary artery disease symptoms. See: **CD-1.4: Stress Testing with Imaging – Indications** for imaging guidelines.
- Female cancer survivors who are pregnant or planning to become pregnant:
 - ◆ If any of the following are present, echocardiogram is recommended as a baseline exam and in the 3rd trimester, and as clinically indicated for symptoms (see: **CD-11.4: Pregnancy - Maternal Imaging**).
 - Anthracycline or cardiotoxic chemotherapy/immunotherapy exposure
 - Chest radiotherapy

PEDONC-19.3: Second Malignant Neoplasms (SMN)

SMN—Breast Cancer

Clinical breast exam every 6 months supplemented with:

- Annual Breast MRI (CPT® 77049) and annual mammogram is recommended beginning at age 25 or 8 years after completion of radiotherapy (whichever occurs **later**- screening breast MRI is not supported prior to age 25) for patients receiving therapeutic radiation exposure in the following fields for any pediatric cancer
 - ◆ Chest (thorax)
 - ◆ Whole lung
 - ◆ Mediastinal
 - ◆ Axilla
 - ◆ Mini-mantle, mantle, or extended mantle
 - ◆ Total (TLI) or subtotal (SLTI) lymphoid irradiation
 - ◆ Total body irradiation (TBI)

SMN – CNS Tumors

These are associated with radiation exposure to the brain and with neurofibromatosis.

- Routine surveillance of asymptomatic patients with normal neurologic exams is not supported by evidence, with the exception of NF1 and NF2 below:
 - ◆ MRI Brain without and with contrast (CPT® 70553) can be approved every 2 years after completion of radiotherapy for patients with NF1 or NF2
- MRI Brain without and with contrast (CPT® 70553) should be approved if requested for any patient with history of brain radiotherapy and new neurologic symptoms including simple headache
- MRI Cervical (CPT® 72156), Thoracic (CPT® 72157), and Lumbar spine (CPT® 72158) without and with contrast should be approved if requested for any patient with history of spine radiotherapy and new neurologic symptoms including change in quality of pain
 - ◆ MRI Spine can be performed with contrast only (Cervical-CPT® 72142, Thoracic-CPT® 72147, Lumbar-CPT® 72149) if being performed immediately following a contrast-enhanced MRI Brain
- For patients with history of brain radiotherapy and persistent neurologic symptoms, annual MRI Brain without and with contrast (CPT® 70553) can be approved
- For patients with history of spine radiotherapy and persistent neurologic symptoms, annual MRI Cervical (CPT® 72156), Thoracic (CPT® 72157), and Lumbar spine (CPT® 72158) without and with contrast can be approved
 - ◆ MRI Spine can be performed with contrast only (Cervical-CPT® 72142, Thoracic-CPT® 72147, Lumbar-CPT® 72149) if being performed immediately following a contrast-enhanced MRI Brain

SMN—Colorectal Cancer

Colonoscopy is recommended every 5 years beginning at age 30 or 5 years after radiation exposure (whichever is later) for patients with ≥ 30 Gy radiation exposure to the following fields:

- ◆ Thoracic, Lumbar, Sacral, or Whole Spine
- ◆ Abdomen
- ◆ Pelvis
- ◆ Total Body Irradiation (TBI)

Colonoscopy is also recommended every 5 years beginning at age 30 or 5 years after radiation exposure (whichever is later) for patients with:

- ◆ Personal history of ulcerative colitis, GI malignancy, adenomatous polyps, or hepatoblastoma
- ◆ Familial polyposis
- ◆ Family history of colorectal cancer or polyps in a first degree (parent or sibling) relative

While the American Cancer Society recently added computed tomographic colonography (CTC) (AKA “Virtual Colonoscopy”) as an acceptable option for colorectal cancer screening of average-risk adults, the National Comprehensive Cancer Network and United States Preventive Services Task Force concluded that data was too premature to warrant its use in screening. ***Colonoscopy remains the preferred screening modality for survivors at highest risk of colorectal cancer.***

PEDONC-19.4: Osteonecrosis in Long Term Cancer Survivors

Osteonecrosis is associated with corticosteroid, chemotherapy, and radiation exposure during treatment for ALL, NHL, and allogeneic HSCT in pediatrics. Osteonecrosis occurs primarily in hips, knees, and ankles and is frequently multifocal.

Osteoradionecrosis of the jaw can occur in patients receiving radiotherapy to the mandible or maxilla; those receiving ≥ 40 Gy are at highest risk. Although unusual, it can also occur in any bone without symptoms. It is rare in other disease types.

- Plain films of symptomatic areas are indicated prior to advanced imaging.
- Routine bone density screening using DEXA or Quantitative CT screening has not been well normalized in the pediatric population, but imaging can be approved for those with symptoms to suggest bone density issues
 - ◆ DEXA or Quantitative CT screening is generally not recommended until age 18 unless a specific intervention will be planned based on the imaging results.
- Serial advanced imaging is not indicated in osteonecrosis without specific documentation regarding how the advanced imaging will change current patient management
 - ◆ When advanced imaging is necessary for acute management decisions, MRI without contrast of the affected joint(s) can be approved.
 - ◆ Surveillance imaging of asymptomatic patients to detect osteonecrosis has not been shown to impact patient outcomes, and it is not standard to alter treatment based on imaging findings alone without symptoms.
 - Follow up MRI of incidentally discovered osteonecrosis findings in asymptomatic patients has not been shown to impact patient outcomes and is not necessary
- See: **PEDONC-3.2: Acute Lymphoblastic Leukemia (ALL)** for information on imaging osteonecrosis in ALL patients during active treatment.

References – PEDONC-19

1. Landier W, Armenian SH, Meadows AT, et al. Late effects of childhood cancer and its treatment. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2016:1173-1196.
2. Vrooman L, Diller L, and Kenney LB. Childhood cancer survivorship. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:2397-2434.
3. Children's Oncology Group. *Long-term follow up guidelines for survivors of childhood, adolescent and young adult cancers, version 5.0*. Monrovia, CA: Children's Oncology Group; October 2018; Available on-line: www.survivorshipguidelines.org
4. Ryerson AB, Border WL, Wasilewski-Masker K, et al. Assessing anthracycline-treated childhood cancer survivors with advanced stress echocardiography. *Pediatr Blood Cancer*. 2015;62(3):502-508. doi:10.1002/pbc.25328.
5. Tieu MT, Cigsar C, Ahmed S, et al. Breast cancer detection among young survivors of pediatric Hodgkin lymphoma with screening magnetic resonance imaging. *Cancer*. 2014;120(16):2507-2513. doi:10.1002/cncr.28747.
6. Lange JM, Takashima JR, Peterson SM, Kalapurakal JA, Green DM, Breslow NE. Breast cancer in female survivors of Wilms tumor: a report from the national Wilms tumor late effects study. *Cancer*. 2014;120(23):3722-3730. doi:10.1002/cncr.28908.
7. Bevers TB, Helvie M, Bonaccio E, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2019—May 17, 2019, Breast Cancer Screening and Diagnosis, available at: https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf, Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Breast Cancer Screening and Diagnosis V1.2019 5/17/19. ©2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org.
8. Recht M, Mostoufi-Moab S, McFadden J, et al. Bone health in pediatric hematology-oncology. In: *American Society of Pediatric Hematology/Oncology Annual Meeting*. Chicago; 2014.
9. Bhatia S, Armenian SH, Armstrong GT, et al. Collaborative research in childhood cancer survivorship: the current landscape. *J Clin Oncol*. 2015;33(27):3055-3064. doi:10.1200/JCO.2014.59.8052.
10. Chavhan GB, Babyn PS, Nathan PC, Kaste SC. Imaging of acute and subacute toxicities of cancer therapy in children. *Pediatr Radiol*. 2016;46(1):9-20. doi:10.1007/s00247-015-3454-1.
11. Karol SE, Mattano LA, Yang W, et al. Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia. *Blood Journal*. 2016;127(5):558-564. doi:10.1182/blood-2015-10-673848.
12. Marcucci G, Beltrami G, Tamburini A, et al. Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors. *Ann Oncol*. 2019;30:908-920. doi:10.1093/annonc/mdz120.
13. Sanders LM, Sharma S, El Madany M, King AB, Goodman KS, Sanders AE. Clinical breast concerns in low-risk pediatric patients: practice review with proposed recommendations. *Pediatr Radiol*. 2018(48):186–195. doi:10.1007/s00247-017-4007-6.