1. You are seeing a 12-year-old female who presented to the emergency department with the sudden onset of severe abdominal pain. Imaging that was obtained to rule out appendicitis revealed a mass adjacent to the bladder. The mass was surgically resected, and pathology demonstrated a paraganglioma. Which of the studies below would be most useful to determine disease stage for this patient?
2. Bone Scan
3. Lumbar puncture for cerebrospinal fluid cytology
4. Bone marrow aspirate and biopsy
5. Ga 68-DOTATATE PET/CT
6. MRI of the brain

**Explanation**

Ga 68 dotatate is a radioisotope that binds to the somatostatin receptor. Based on the intensity of signals detected, PET images obtained using Ga 68 dotatate indicate the presence and density of somatostatin receptors in tissues. In 2016 the FDA approved Ga 68-DOTATATE PET for adult and pediatric patients with somatostatin positive neuroendocrine tumors (NETs), including pheochromocytoma and paraganglioma. Ga 68-DOTATATE PET is now the gold standard imaging modality for NETs. 123I-MIBG scans can also be used for the staging of pheochromocytoma and paraganglioma. Lumbar puncture, bone marrow aspirate and biopsy, and MRI of the brain are not indicated in the routine staging of these diseases. Although bone scan can detect bony metastases in pheochromocytoma and paraganglioma, Ga 68-DOTATATE PET is both more sensitive and specific.

1. Your patient with relapsed high-risk neuroblastoma returns to your care after travelling to an outside institution for 131I-MIBG therapy. In the weeks following 131I-MIBG therapy, what adverse events directly attributable to this therapy will the patient most likely encounter?
	1. Myelosuppression requiring growth factor and blood product support
	2. Severe mucositis
	3. Hemorrhagic cystitis
	4. Symptomatic hypothyroidism
	5. Renal failure

**Explanation**

The correct answer is A, myelosuppression requiring growth factor and blood product support. The need for blood product support (both packed red blood cells [PRBC] and platelets) and growth factor support in the weeks following 131I-MIBG therapy is very common and expected. Many heavily pretreated patients require autologous stem cell infusion following 131I-MIBG therapy. Severe mucositis and hemorrhagic cystitis are not commonly associated with 131I-MIBG therapy. Although renal failure could be attributed to 131I-MIBG therapy, it is rare. Hypothyroidism is a very common finding but typically does not occur acutely. Evidence of effects on the thyroid is often based on laboratory studies, and many patients are asymptomatic.

1. An otherwise healthy 18-year-old female is diagnosed with high-risk neuroblastoma after presenting with fatigue and bony pain. Imaging findings demonstrate a left adrenal mass with multiple osseous metastases. She successfully completes standard therapy for high-risk neuroblastoma, but experiences several episodes of disease recurrence and ultimately dies of her disease 10 years after her initial diagnosis. During her treatment, her tumor was sent for molecular analysis. Of the following, what molecular aberration was most likely to have been detected?
	1. *ETV6-NTRK3* gene fusion
	2. *PTPN11* mutation
	3. *ATRX* mutation
	4. *WT1* mutation
	5. *MYCN* amplification

**Explanation**

Inactivating mutations in the *ATRX* chromatin remodeling gene are found in 14% of patients with high-risk neuroblastoma and in 44% of adolescent and adult patients with metastatic neuroblastoma. In addition to the association with older age at diagnosis, this mutation is associated with an indolent disease course and poor overall survival, as is seen in this patient’s case. *ETV6-NTRK3* gene fusions are characteristic of infantile fibrosarcoma and cellular congenital mesoblastic nephroma. Although *NTRK* aberrations can be seen in neuroblastoma, this specific fusion product is not. *PTPN11* mutations are seen in neuroblastoma, particularly in patients with a germline mutation and phenotypic evidence of Noonan’s syndrome. These mutations are also not associated with older age or an indolent disease course. *WT1* mutations are not associated with neuroblastoma. *MYCN* amplification is incorrect because the incidence of *MYCN* amplification is low in older patients with neuroblastoma (approximately 3%), whereas the incidence of *ATRX* mutations is higher. Of note, *ATRX* mutations are mutually exclusive of *MYCN* amplification in neuroblastoma.

1. You have been asked to see a 10-month-old boy with irritability, periorbital ecchymoses, and proptosis. Head imaging shows a soft-tissue mass arising from the zygomatic arch and displacing the orbit. A large, locally invasive retroperitoneal mass that encases abdominal vasculature is also detected. MIBG scan also shows multiple sites of osteomedullary disease throughout the body. Tumor biopsy confirms poorly differentiated neuroblastoma with *MYCN* amplification. Bilateral bone marrow aspirates and biopsies are positive for tumor cells.

Which statement is most accurate regarding this patient?

* 1. The patient has high-risk neuroblastoma and should receive neoadjuvant chemotherapy followed by a single cycle of myeloablative chemotherapy and autologous stem cell rescue. The primary tumor should be resected, but radiation and immunotherapy should not be administered because of the patient’s young age.
	2. The patient has high-risk neuroblastoma and should undergo immediate resection of the tumor, followed by chemotherapy and radiation therapy to primary tumor and metastatic disease sites.
	3. The patient has intermediate-risk disease and should receive neoadjuvant chemotherapy followed by surgical resection of the primary tumor and radiation therapy to the primary tumor bed, regardless of extent of resection.
	4. The patient has intermediate-risk disease and should receive neoadjuvant chemotherapy followed by surgical resection of the primary and radiation only to residual tumor.
	5. This patient has high-risk disease and should receive induction therapy that includes neoadjuvant chemotherapy and surgical resection of the primary tumor. This should be followed by tandem myeloablative chemotherapy and autologous stem cell rescue, external beam radiotherapy, and immunotherapy/cis-retinoic acid.

**Explanation**

This 10-month-old has INSS stage 4/INRG stage M neuroblastoma with *MYCN* amplification and thus has high-risk neuroblastoma even though he is very young. Current standard-of-care therapy for high-risk neuroblastoma in North America includes induction (chemotherapy and surgical resection), consolidation (tandem myeloablative chemotherapy followed by stem cell rescue and external beam radiotherapy), and post-consolidation therapy (immunotherapy plus cis retinoic acid).

1. A 3-year-old female is referred to you from rheumatology, where she was being evaluated for hip pain and fevers. MRI of her pelvis showed diffuse but heterogenous marrow replacement. Her complete blood count (CBC) reveals very mild leukopenia and thrombocytopenia. Given the MRI and CBC findings, you proceed with a bone marrow aspirate and biopsy. The hematopathologist tells you that, on preliminary evaluation, the marrow appears to be infiltrated with a malignant solid tumor. Immunostains are positive for S100, synaptophysin, and neuron-specific enolase. Given these findings, cross-sectional imaging is performed, but the radiologists are unable to locate a primary tumor. In the absence of a tumor biopsy, what additional finding will confirm a definitive diagnosis of neuroblastoma?
	1. Elevated serum alpha fetoprotein (AFP)
	2. Elevated urine catecholamines (HVA/VMA)
	3. Elevated ferritin
	4. Elevated lactate dehydrogenase (LDH)
	5. PET/CT demonstrating numerous osseous metastases

**Explanation**

Elevated urine catecholamines are present in about 90% of neuroblastoma cases. A diagnosis of neuroblastoma can be made if elevated catecholamines are detected and bone marrow pathology is consistent with neuroblastoma. However, a tumor biopsy for molecular analysis should be performed whenever possible. Serum alpha fetoprotein (AFP) is elevated in hepatoblastoma and germ cell tumors but not neuroblastoma. Elevated ferritin, lactate dehydrogenase (LDH), and PET/CT demonstrating numerous osseous metastases can all be seen in neuroblastoma; however, they are non-specific findings and cannot confirm the diagnosis.

1. A toddler presents with secretory diarrhea, hypokalemia, and abdominal pain. Exam reveals abdominal distension and a questionable mass. Subsequent anatomical imaging demonstrates a retroperitoneal infiltrative soft tissue mass.

What is the most likely etiology of the patient’s diarrhea?

a. Neuroblastoma with diarrhea caused by infiltration of mesenteric vasculature

b. Neuroblastoma with diarrhea caused by tumor-related catecholamine secretion

c. Neuroblastoma with diarrhea caused by vasoactive intestinal peptide

d. Neuroblastoma with diarrhea caused by concurrent infectious gastroenteritis

**Explanation**

Secretory diarrhea is a rare syndrome associated with neuroblastoma, usually occurring in toddlers with retroperitoneal mass. The syndrome is caused by tumor secretion of vasoactive intestinal peptide (VIP). VIP acts on the intestinal epithelial cells via the blood circulation, causing excessive secretion of intestinal fluid, promoting pancreatic juice and bile secretion and exacerbating the loss of water and electrolytes. Although rare, neuroblastoma should be in the differential diagnosis for etiology of noninfectious severe secretory diarrhea.

1. Tumor histologic classification is an important prognostic factor for neuroblastoma. Which of the following determines this classification?

a. Age, tumor cell apoptosis, and *MYCN* amplification

b. Age, tumor cell differentiation, and mitosis-karyorrhexis index

c. Age, tumor cell differentiation, and necrosis

d. Age, tumor alveolar histology, and DNA index (ploidy)

**Explanation**

Independent prognostic variables for neuroblastoma include age, stage, histology, MYCN amplification, and DNA index. Histology is graded according to the International Neuroblastoma Pathology Classification, which evaluates for degree of tumor cell differentiation and mitosis-karyorrhexis index as related to age (younger than or older than 18 months) to define favorable or unfavorable histology. Alveolar histology is a histologic subtype of rhabdomyosarcoma.

1. A 9-month-old previously healthy infant presents with abdominal distension. Physical exam is otherwise unremarkable. Radiographic imaging reveals bilateral adrenal masses. Family history is notable for diagnosis of neuroblastoma in the maternal aunt and maternal grandfather.

Which germline genetic abnormality is most likely to be present?

a. *NF1* mutation

b. *PHOX2B*

c. *ALK*

d. *TP53*

**Explanation**

Neuroblastoma usually arises sporadically in infancy and young childhood. About 1% to 2% of children with neuroblastoma have familial neuroblastoma with autosomal dominant inheritance, with the most common germline mutations in *ALK* or *PHOX2B*. *ALK* is a tyrosine kinase receptor that has a role in cell proliferation; germline *ALK* mutations are often associated with bilateral or multifocal disease. *PHOX2B* germline mutations are typically associated with additional neurologic abnormalities, including Hirschsprung disease and central hypoventilation, and therefore are unlikely in this scenario.