ASPHO Board Review Questions – Cancer Predisposition Syndromes

1. You are consulted on a 4-year-old girl who is newly diagnosed with standard-risk pre-B acute lymphoblastic leukemia. After reviewing her previous complete blood examinations, you note she has had a platelet count ranging from 80,000 to 100,000 cells/mcL over the past 2 years. Her father mentions that he has also been told he has mild thrombocytopenia. You suspect the child may have a cancer predisposition syndrome.

Which sample should you send for analysis, and which gene is most likely implicated?

1. Skin fibroblasts to evaluate the *RUNX1* gene
2. Skin fibroblasts to evaluate the *ETV6* gene
3. Buccal swab to evaluate the *RUNX1* gene
4. Buccal swab to evaluate the *ETV6* gene
5. Skin fibroblasts to evaluate the *TP53* gene

**Answer & explanation: B**

The correct sample to analyze for a leukemia predisposition syndrome is cultured skin fibroblasts, making answer choices C and D incorrect. Buccal swabs may contain peripheral blood mononuclear cells, which circulate throughout the mucosa and are also found in saliva. These blood mononuclear cells may provide false positive results, particularly in a patient who is newly diagnosed with leukemia and may have circulating blasts. The correct gene to explain this patient’s phenotype is *ETV6*, making answer B correct. Thrombocytopenia 5, which is caused by germline pathogenic variants in *ETV6*, is the most common leukemia predisposition syndrome linked to pre-B acute lymphoblastic leukemia (ALL) with a preceding history of mild thrombocytopenia. Li-Fraumeni syndrome, caused by pathogenic variants in *TP53*, is associated with development of low hypodiploid pre-B ALL, and typically the family history is positive for solid tumors, not thrombocytopenia. Pathogenic variants in *RUNX1* cause familial platelet disorder with associated myeloid malignancy and are much more commonly associated with the development of acute myeloid leukemia (AML) than ALL.

1. You receive a phone call from a community pediatrician who is caring for a 2-year-old toddler with a cancer predisposition syndrome. The pediatrician describes a child at the 95th percentile for height and weight with a history of corrective oral surgery to reduce a large tongue and a history of an omphalocele in infancy. The pediatrician is currently performing ultrasound of the abdomen and laboratory evaluation for this patient every 3 months.

Which tumor is this patient most at risk of developing?

1. Pleuropulmonary blastoma
2. Hepatocellular carcinoma
3. Cystic nephroma
4. Nephroblastoma
5. Pheochromocytoma

**Answer & explanation: D**

The pediatrician has described a child with Beckwith-Wiedemann syndrome (BWS), which carries an increased risk for hepatoblastoma and nephroblastoma (Wilms’ tumor), making answer choice D the correct answer. Pleuropulmonary blastoma occurs in patients with *DICER1* syndrome, making option A incorrect. Patients with BWS do not develop hepatocellular carcinoma, making option B incorrect. Cystic nephromas develop in patients with *DICER1* syndrome, making choice C incorrect. Pheochromocytomas occur in patients with BWS exceedingly rarely, therefore the child is most at risk for developing Wilms’ tumor, making option E incorrect.

1. You are seeing a 12-year-old boy in the survivorship program who presented at 2 years old with a desmoplastic nodular medulloblastoma. You note the child recently underwent germline genetic testing and was found to have nevoid basal cell carcinoma syndrome.

In which gene is the child most likely to have a pathogenic variant?

1. *PTEN*
2. *CDKN2A*
3. *SUFU*
4. *SMARCB1*
5. *TP53*

**Answer & explanation: C**

Nevoid basal cell carcinoma syndrome, also known as Gorlin syndrome, is caused by a pathogenic variant in either the *PTCH1* or *SUFU* gene. Pathogenic variants in *SUFU* are more commonly linked to the development of desmoplastic nodular medulloblastoma in early childhood, making answer choice C correct. Option A is incorrect because pathogenic variants in *PTEN* are not linked to the development of desmoplastic nodular medulloblastoma. Option B is incorrect because *CDKN2A* is linked to familial melanoma and is unrelated to development of medulloblastoma. Option D is incorrect because pathogenic variants in *SMARCB1* are linked to the development of atypical teratoid/rhabdoid tumor. Option E is incorrect because patients with pathogenic variants in *TP53* are more likely to develop low- or high-grade gliomas.

1. A 10-year-old girl is a long-term survivor of type II pleuropulmonary blastoma (PPB). You suspect she has a cancer predisposition syndrome and perform genetic testing, which confirms she has *DICER1* syndrome.

Which other cancer is she predisposed to?

1. Papillary thyroid cancer
2. Medullary thyroid cancer
3. Pheochromocytoma
4. Renal cell carcinoma
5. Osteosarcoma

**Answer & Explanation: A**

Pleuropulmonary blastoma (PPB) is highly associated with *DICER1* syndrome. Other tumors in this cancer predisposition syndrome include papillary thyroid carcinoma, making A the correct answer. Medullary thyroid cancer is associated with multiple endocrine neoplasia (MEN2), therefore option B is incorrect. Pheochromocytomas are linked to pathogenic variants in the *SHDx* gene family and not associated with *DICER1,* making option C incorrect. Renal cell carcinoma is linked to hereditary leiomyosarcoma and renal cell carcinoma predisposition or Von Hippel-Lindau, making option D incorrect. Osteosarcoma is linked to Li-Fraumeni syndrome, making option E incorrect.

1. A 14-month-old child is diagnosed with hepatoblastoma. Upon review of the family history, the child’s mother had her colon removed at the age of 20 years due to the presence of innumerable polyps.

You suspect this child has a hereditary predisposition to gastrointestinal cancer. For which of the following would you recommend genetic testing?

1. *MLH1*
2. *PMS2*
3. DNA methylation array at chromosome 11p15.5
4. *MUTYH*
5. *APC*

**Answer & Explanation: E**

The child described in this vignette has familial adenomatous polyposis (FAP), based upon the child’s history of hepatoblastoma and the family history of the mother having innumerable colon polyps requiring colectomy in early adulthood, making E the correct answer. Answer choices A and B are incorrect because they describe hereditary non-polyposis colon cancer (Lynch syndrome), which is not linked to the development of hepatoblastoma in childhood, and the parent does not have extensive colonic polyposis. Answer choice C is incorrect because this describes Beckwith-Wiedemann syndrome, which, though linked to hepatoblastoma, is not linked to the development of colon cancer later in life. Answer choice D is incorrect because *MUTYH* is an autosomal recessive colon cancer predisposition syndrome and does not fit with the family history described above.

1. A 2-year-old girl is recently diagnosed with intermediate-risk neuroblastoma. The child is meeting her developmental milestones and has no physical abnormalities. Upon review of the family history, you discover she has an older brother who was diagnosed with high-risk neuroblastoma at the age of 4 years. You offer the family genetic testing for genes that predispose to neuroblastoma.

Which of the following genetic etiologies would explain this child’s diagnosis and family history?

1. Germline inactivating pathogenic variant in the *ALK* gene
2. Germline activating pathogenic variant in the *PHOX2B* gene
3. Germline activating pathogenic variant in the *ALK* gene
4. Two germline inactivating pathogenic variants in the *ALK* gene
5. Germline inactivating pathogenic variant in the *PTPN11* gene

**Answer & Explanation: C**

The *ALK* gene acts as a proto-oncogene, and pathogenic variants activate this gene to predispose a child to neuroblastoma, making answer choice C correct. Answer choice A follows the pathophysiology of a typical tumor suppressor gene, which is not the case for neuroblastoma predisposition due to an *ALK* mutation, making it incorrect. Neuroblastoma predisposition due to a *PHOX2B* mutation follows the classic tumor suppressor model and should be inactivating, making choice B incorrect. Answer choice D describes a recessive disorder, which is incorrect to describe neuroblastoma predisposition, which is autosomal dominant. Answer choice E is incorrect because children with pathogenic variants in *PTPN11* have Noonan syndrome, typically with developmental and facial features.

1. A 15-month-old child is diagnosed with an embryonal rhabdomyosarcoma of the left neck. You review the pathology report, which describes a primitive myoblastic neoplasm with positive immunohistochemical stains for myogenin and desmin. There is diffuse anaplasia. The *PAX-FOXO1* gene rearrangement was negative.

Based upon these pathology findings, for which cancer predisposition syndrome would you offer the family genetic testing?

1. *DICER1*
2. Li-Fraumeni syndrome
3. Von Hippel-Lindau syndrome
4. Rhabdoid tumor predisposition type I
5. Familial adenomatous polyposis

**Answer & Explanation: B**

Anaplastic embryonal rhabdomyosarcoma is associated with Li-Fraumeni syndrome, making answer choice B the correct answer. Anaplastic embryonal rhabdomyosarcoma has not been described in *DICER1* syndrome (option A), rhabdoid tumor predisposition type 1 (option D), Von Hippel-Lindau syndrome (option C), or familial adenomatous polyposis (option E).

1. You are seeing a 12-year-old child who was recently diagnosed with a meningioma. The patient was recently evaluated by an ophthalmologist because of concern for headaches and was noted to have a retinal hamartoma.

For which cancer predisposition syndrome would you offer germline genetic testing?

1. Neurofibromatosis type 1
2. Von Hippel-Lindau syndrome
3. Neurofibromatosis type 2
4. PTEN-hamartoma syndrome
5. Hereditary retinoblastoma

**Answer & Explanation: C**

Retinal hamartoma is a physical exam finding consistent with neurofibromatosis type 2 (NF2), which predisposes a patient to the development of meningiomas, making C the correct answer choice. Neurofibromatosis type 1 (NF1) is associated with the development of hamartomas of the iris (Lisch nodules) and is not linked to the development of meningiomas, making option A incorrect. Von Hippel-Lindau syndrome causes cerebellar and retinal angiomas but not retinal hamartomas, making option B incorrect. PTEN-hamartoma syndrome causes gastrointestinal hamartomas but not retinal hamartomas or meningiomas, so option D is incorrect. Hereditary retinoblastoma syndrome (option E) is incorrect because this predisposes a patient to retinoblastoma but not retinal hamartoma formation and is linked to the development of pineoblastoma, not meningioma.