Update on Pediatric Cancer Surveillance Recommendations for Patients with Neurofibromatosis Type 1, Noonan Syndrome, CBL Syndrome, Costello Syndrome, and Related RASopathies

Melissa R. Perrino[1]; Anirban Das[2]; Sarah R. Scollon[3]; Sarah G. Mitchell[4]; Mary-Louise C. Greer[5]; Marielle E. Yohe[6]; Jordan R. Hansford[7]; Jennifer M. Kalish[8]; Kris Ann P. Schultz[9]; Suzanne P. MacFarland[10]; Wendy K. Kohlmann[11]; Philip J. Lupo[12]; Kara N. Maxwell[10,13]; Stefan M. Pfister[14]; Rosanna Weksberg[15]; Orli Michaeli[16]; Marjolijn C. J. Jongmans,[17]; Gail E. Tomlinson[18]; Jack Brzezinski[2]; Uri Tabori[2]; Gina M. Ney[19]; Karen W. Gripp[20]; Andrea M. Gross[21]; Brigitte C. Widemann[21]; Douglas R. Stewart[19]; Emma R. Woodward[22]; and Christian P. Kratz[23]

[1]Department of Oncology, St Jude Children's Research Hospital, Department of Oncology, Memphis, Tennessee, United States

[2]Division of Paediatric Haematology & Oncology, Hospital for Sick Children, University of Toronto, Canada

[3]Department of Pediatrics, Texas Children's Cancer and Hematology Center, Baylor College of Medicine, Houston, Texas, United States

[4]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, United States

[5]Department of Diagnostic and Interventional Radiology, The Hospital for Sick Children, Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada

[6]Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, United States

[7]Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital; South Australia Health and Medical Research Institute; South Australia ImmunoGENomics Cancer Institute, University of Adelaide, Adelaide, Australia.

[8]Division of Genetics and Center for Childhood Cancer Research Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

[9]Cancer and Blood Disorders, Children's Minnesota, Minneapolis, Minnesota, United States

[10]Division of Oncology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States

[11] VA Medical Center, National TeleOncology Clinical Cancer Genetics Service, Durham NC; University of Utah Huntsman Cancer Institute, Salt Lake City, Utah, United States

[12]Division of Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States

[13]Medicine Service, Corporal Michael Crescenz Veterans Affairs Medical Center, Philadelphia, Pensylvannia, United States

[14]Hopp Children´s Cancer Center Heidelberg (KiTZ), Division Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg University Hospital and National Center for Tumor Diseases (NCT), Heidelberg, Germany

[15]Division of Clinical and Metabolic Genetics, Dept Pediatrics, Hospital for Sick Children and University of Toronto, Toronto, Canada

[16]Division of Hematology/ Oncology, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

[17]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands.

[18]University of Texas Health Science Center at San Antonio, Department of Pediatrics, Division of Hematology-Oncology and Greehey Children's Cancer Research Institute, San Antonio, Texas, United States

[19]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland, United States

[20] Division of Medical Genetics, Nemours Children's Hospital, Wilmington, Delaware, United States

[21]Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, United States

[22]University of Manchester and Manchester Centre for Genomic Medicine, Manchester, United Kingdom

[23]Hannover Medical School, Pediatric Hematology and Oncology, Hannover, Germany

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Corresponding Author: Melissa R. Perrino

St Jude Children's Research Hospital

262 Danny Thomas Pl, Mail Stop 1170

Memphis, TN 38105

E-mail: Melissa.perrino@stjude.org

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Abstract:
Neurofibromatosis type 1 (NF1), Noonan syndrome and related syndromes, grouped as the RASopathies, result from dysregulation of the RAS-MAPK pathway and demonstrate varied multisystemic clinical phenotypes. Together the RASopathies are among the more prevalent genetic cancer predisposition syndromes and require nuanced clinical management. When compared to the general population, children with RASopathies are at significantly increased risk of benign and malignant neoplasms. In the last decade, clinical trials have shown that targeted therapies can improve outcomes for low-grade and benign neoplastic lesions but have their own challenges, highlighting the multi-disciplinary care needed for such individuals, specifically those with NF1. This perspective, which originated from the 2023 AACR Childhood Cancer Predisposition Workshop, serves to update pediatric oncologists, neurologists, geneticists, counselors, and other healthcare professionals on revised diagnostic criteria, review previously published surveillance guidelines, and harmonize updated surveillance recommendations for patients with NF1 or RASopathies.

Introduction:

Neurofibromatosis type 1 (NF1), Noonan syndrome (NS) and related RASopathies, including Costello syndrome (CS), Cardiofaciocutaneous (CFC) syndrome and Legius syndrome (LS) are genetic conditions caused by dysregulation of the RAS-mitogen activated protein kinase (MAPK) pathway. People with these germline genetic changes face variable neurologic, cardiac, skeletal, and other medical challenges from an early age. With the exception of LS, children with RASopathies are at significantly increased cancer risk compared to the general population(1-6). Advances in genotype-phenotype correlation have led to diagnostic updates and improved management of individuals with these syndromes. Molecular therapeutics inhibiting the RAS-MAPK pathway now expand the treatment options for patients with NF1 and symptomatic, unresectable plexiform neurofibroma or glioma, which is promising to reduce and prevent severe tumor burden and subsequent morbidity(7-9). As diagnostic and treatment modalities evolve, surveillance recommendations must be amended to optimize patient care and stay true to the pillars of surveillance: early tumor detection with potential for intervention while minimizing the risks of surveillance when possible(4,10-15). In this effort, we present updated consensus cancer surveillance recommendations for patients with NF1, NS, CS, and other RASopathies.

Neurofibromatosis Type 1

NF1 incidence, genetic etiology, and updates to the clinical criteria:

NF1 is among the most common cancer predisposition syndromes (CPS) and has a birth prevalence of 1/2,000-1/3,000 persons(16). It is an autosomal dominant syndrome resulting

from pathogenic variants (PV) in the gene *NF1*, encoding neurofibromin, a key negative regulator in the RAS-MAPK pathway.

Approximately half of NF1 cases occur *de novo* and penetrance is generally complete with variable expressivity(17). Somatic mosaicism is well-documented in NF1, and mosaic individuals may have variable to few clinical features(18-20). Genotype-phenotype associations have been described, but for the majority of variants, the expressivity cannot be predicted based on the specific variant(20-22). Currently, there is no recommendation to change NF1 tumor surveillance recommendations in the setting of mosaicism or for genotypes with stronger phenotype correlation.

In 2021, Legius et al., revised the diagnostic criteria for NF1, with a specific focus on differentiating it from Legius syndrome, a RASopathy caused by *SPRED1* PV, which features the most phenotypic overlap with NF1(23). This clinical update represented the first significant alteration to the clinical diagnostic criteria since they were introduced in 1987(24). Moreover, when a patient is suspected to have NF1 but does not meet full clinical criteria and has negative *NF1* testing, other conditions with overlapping features such as Legius syndrome (*SPRED1*), other (mosaic) RASopathies (e.g. *KRAS), CDKN2A*-Related Melanoma-Astrocytoma Syndrome (*CDKN2A*), and constitutional mismatch repair deficiency (*PMS2, MLH1, MSH2, MSH6*) should be considered.

Tumor Risk and Natural history in NF1

In individuals with NF1, most neoplasms involve the nervous system, including gliomas, benign neurofibromas, borderline and malignant peripheral nerve sheath tumors (MPNST). Furthermore, *NF1*-associated tumors are age-dependent. Optic pathway gliomas (OPG)

present early in childhood. Other cancers, including juvenile myelomonocytic leukemia (JMML), rhabdomyosarcoma (RMS), and neuroblastoma (NB), though rare, can develop early in childhood at higher frequencies than in the general population. Plexiform neurofibromas (PN) are likely congenital but grow in the first two decades of life, and atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) are pre-malignant tumors that typically develop within, or nearby, a known PN in the second to third decades of life(25-27). Meanwhile, MPNST, pheochromocytomas, gastrointestinal stromal tumors (GIST), and breast cancers usually develop in adults, though many are diagnosed at significantly younger ages than in the general population(6).

Central Nervous System Tumors

The most common central nervous system tumor type in NF1 is low-grade glioma (LGG; ~20%), frequently affecting the optic pathway (OPG) and presenting at age <8 years (median: 4-5 years). The vast majority of NF1-related OPGs will not progress after their initial diagnosis, and may follow an indolent course with the potential for spontaneous growth arrest. However, 15-20% of these tumors progress, result in visual deterioration, strabismus, proptosis, papilledema, and nystagmus, and require intervention. Patients with radiological involvement of the posterior optic tracts, age <2 years, and of female sex may be at increased risk of progression(28,29). Irradiation is usually avoided in NF1-associated gliomas due to vascular and other complications. Chemotherapy is traditionally the mainstay of therapy though response to targeted therapies including MEK-inhibitors is promising with multiple studies underway(30,31) (NCT04923126; NCT03326388; NCT03871257).

Pilocytic and diffuse astrocytomas may occur as focal brainstem enlargement in <10% of individuals with NF1[37]. Mean age of presentation is 7 years and <5% tumors identified require treatment(32),(33). Treatment may ultimately be necessary in patients with neurological deterioration and a biopsy may be required prior to treatment as these lesions have the potential to transform from low to high-grade.

Malignant transformation of pre-existing LGG is rare in NF1, but well-recognized. Anaplastic transformation of some LGG may be independent of radiation therapy. Such grade 3 and 4 diffuse astrocytomas do not occur in the optic pathway, but may develop in the hemispheres, thalamus, cerebellum, and spinal cord and harbor aberrations in *ATRX*, *TP53* and *CDKN2A/2B* (while lacking histone or *IDH* mutations)(34).

Peripheral Nerve Sheath Tumors

PNs are histologically benign tumors seen in ~50% of patients with NF1 and develop following somatic loss of the remaining wild-type allele in Schwann cells. These lesions are likely congenital, have faster growth in young children, and may cause pain, disfigurement, and compression symptoms. Clinically meaningful, and durable, benefit from MEK-inhibitors in younger children has led to FDA approval of selumetinib for children ≥ age 2 years with symptomatic, inoperable PNs(7-9). Trametinib, another MEK-inhibitor, can be effective in the management of PNs where selumetinib is not available(35,36). In addition, the receptor tyrosine kinase inhibitor cabozantinib has shown activity in the treatment of patients with NF1 PN ≥ 16 years old(37). It is not known whether the risk of transformation to ANNUBP or MPNST is modified by targeted therapies, mandating the need for close attention to clinical changes throughout the duration of therapy(8,38).

Peripheral nerve sheath tumors with atypical growth patterns, symptoms, or imaging characteristics from an underlying PN should raise suspicion for ANNUBP. These tumors are thought to be pre-malignant lesions, although the timeline for malignant transformation remains unclear. They are often characterized by magnetic resonance imaging (MRI) findings of distinct nodular lesions (DNL), a >3 cm nodule within or nearby a known PN with loss of a central "target sign", and grow faster than the surrounding PN(26,27,39,40). ANNUBP are defined by histological features and genomic studies identified additional biallelic somatic loss of *CDKN2A/B* (25). While *TP53* and PRC2 genes including *EED* and *SUZ12* are common variants seen in MPNST, these have not been identified in ANNUBP to date. ANNUBP should be considered for surgery with gross total resection using a nerve-sparing approach without wide-margins at a center with surgeons familiar with NF1 whenever feasible(41-43).

Full malignant transformation of PN into MPNST occurs in 8-16% of NF1 patients. This is rare in childhood and peak incidence is in the 3rd-4th decade. Risk factors for MPNST development in individuals with NF1 include those with microdeletion involving *SUZ12*, *NF1* missense variants affecting codons 844-848, previous ANNUBP, neuropathy, previous radiation, and an NF1-relative with MPNST(44-49). In individuals with a known PN, rapid growth of a DNL, intra-tumoral cystic changes, and evidence of necrosis on imaging are concerning for 'high-risk' pathological features, and combined use of MRI- and 18F-fluorodeoxyglucose positron-emission (18F-FDG PET)-based imaging may facilitate accurate and timely diagnosis of MPNST. Primary resection with wide negative margins, if feasible, is strongly recommended(50).

Other malignancies and young adult considerations

While a diagnosis of NF1 is enriched among JMML patients, the estimated risk in patients with NF1 is <1%(11). Fusion-negative embryonal RMS has an overall risk of <1% but is enriched in males and demonstrates a predilection for the genitourinary system(51-54). Clinical education should be provided to patients and families regarding the increased risk of these tumors, but surveillance is not indicated.

While the focus of these recommendations is for childhood surveillance, it is important to recognize increased adult malignancies. Many individuals are not the first in their family with the cancer predisposition syndrome highlighting the need for awareness and family care. Further, preparation for the transition into adulthood has many nuances, but adult surveillance is vital for adolescents to understand prior to their transition from pediatrics. Detailed adult surveillance recommendations have been previously published(55). Specifically, individuals with NF1 being born female are at increased risk for young-onset breast cancer (56). Breast cancer screening with mammography and consideration of breast MRI should be discussed between starting around age 30 years(55,57). Small imaging studies suggest that females with NF1 may have greater breast density and breast MRI, when available, should be incorporated into screening when mammograms cannot be adequately interpreted(58). Surveillance for tumors other than breast cancer is not currently recommended in adulthood. Education regarding additional adult cancer risk should be considered for the adolescent individual. Pheochromocytomas and paragangliomas have been reported in 1–5% of patients with NF1, diagnosed at a median age of 40–50 years(59). In adults, undifferentiated pleomorphic sarcoma is seen at increased rates and with inferior outcomes compared to sporadic cases(6). Glomus tumors of the digits are small benign tumors that present with localized tenderness,

severe paroxysmal pain and sensitivity to cold(60). Patients with NF1 have a 200-fold increased risk of developing GISTs, which present around age 50 years and typically lack alterations in *KIT* or *PDGFRA*. Melanoma is reported in <1% of individuals with NF1 but has an overall higher association and inferior survival as compared to sporadic cases(6).

Proposed tumor surveillance updates for pediatric patients with Neurofibromatosis Type 1

OPG: In individuals with confirmed NF1, those with pending testing and a family history, or if NF1 is clinically suspected, ophthalmology surveillance should start at age 6-8 months (Table 1). An ophthalmologic exam by a trained pediatric ophthalmologist or neuro-ophthalmologist is recommended for age-appropriate, comprehensive evaluation with visual acuity and visual fields. Optical coherence tomography may be utilized if available at an experienced center but does not replace standard visual exams. Visual assessment continues annually, if exams remain normal, until age 8 years, then every other year to age 18 years (**Table 1**). If an exam is concerning for visual compromise, a MRI of the brain and orbits should be obtained and follow up for close visual monitoring should occur within 3 months. If a tumor is identified, but vision remains stable, close monitoring without therapeutic intervention is warranted. As the visual exam guides intervention and often can be completed without sedation, many groups have removed imaging from surveillance of asymptomatic patients for OPG(11,12,61,62). However, a highly trained pediatric ophthalmologist or neuro-ophthalmologist is not always accessible and if visual assessment is unreliable or inconsistent ≥ age 2 years, an MRI should be obtained(11,63). Caution should be used in interpreting an MRI without visual changes to avoid increased surveillance imaging studies, sedation, and treatment in patients that may

never become symptomatic. Importantly, a normal MRI does not abrogate the recommendation for continued visual exams.

PN: Surveillance for PN has typically not been recommended, as interventions for asymptomatic PN were contraindicated. With the success of, and increasing access to, MEK-inhibitors, early treatment may be considered for patients at high risk of developing PN-related morbidity(7-9). In this regard, a clinical trial is currently underway to determine whether surveillance and treatment initiation for asymptomatic, but high-risk due to location, PN will be beneficial (NCT06188741). Outside of a clinical trial, imaging in asymptomatic patients is not yet warranted (**Table 1**). If imaging is obtained due to another cause and internal tumors are identified incidentally, referral should be made to a pediatric oncology center with expertise in the care of NF1 patients with PN. If future growth of the tumors may interfere with vital organ function or cause acute neurologic complications, further dedicated imaging may guide interventions.

ANNUBP/DNL: In general, if a patient has a biopsy-proven ANNUBP, the current recommendation is for resection with a narrow margin if this can be achieved without significant morbidity. Additional consensus is needed for the recommended monitoring for ANNUBP that are not resected, but these lesions should be considered at increased risk for malignant transformation. For new or increasing symptomatic lesions, or rapidly growing lesions in older adolescence, imaging should be completed and if a DNL is detected in the area of symptoms, even with classically ‘benign’ features on imaging, marginal resection should be considered if feasible without significant morbidity. If resection is not feasible, image-guided biopsy should be completed with subsequent somatic testing for *CDKN2A*/*2B* loss.

MPNST: Whole-body MRI (WBMRI) has been recommended after puberty, in late adolescence when benign PN growth rates slow considerably, as a baseline for overall tumor burden prior to adulthood, and this recommendation remains unchanged (**Table 1**)(26,55,64-67). This is used to stratify risk for development of MPNST and educate patients to seek early medical attention for any change in symptoms at known tumor locations. A PN tumor burden >300mL or DNL should prompt closer clinical follow-up and education regarding symptoms of malignant transformation(26,67,68). Caution should be taken for patients with high-risk genotypes including an *NF1* microdeletion involving *SUZ12*, patients with a high tumor burden of PN in childhood, and patients with a personal or family history of MPNST, ANNUBP, or DNL(11,13,44). 18F-FDG PET/CT should remain reserved for patients with lesions concerning for MPNST such as painful or growing tumors and can be combined with dedicated regional MRI, including diffusion weight imaging (DWI) to use apparent diffusion coefficient (ADC) mapping for increased specificity and sensitivity in determining the most likely area of malignant transformation to target for biopsy or resection(11,67). Circulating tumor, or plasma cell-free DNA methods are currently still under investigation but are hoped to play a pivotal role in surveillance and early detection for ANNUBP and MPNST in high-risk patients in the future. In fact, individuals with NF1 may serve as exceptional models for circulating tumor DNA surveillance as imaging continues to be difficult to determine malignancy risk with both high sensitivity and specificity, and the secondary genetic drivers of these tumors have been well characterized(25,40,69,70).

If targeted MEK-inhibitor therapy is started for any reason in a patient with NF1, consider a WBMRI if available, or similar thick section MRI limited to the neck, chest, abdomen

and pelvis (NCAP-WBMRI) prior to initiation as a baseline to better understand and monitor potential non-target tumor response (**Table 1**). Additional work through the AACR-Cancer Predisposition Working Group highlights radiologic detail and variations of WBMRI and can be found in a collaborating manuscript.

Noonan syndrome and CBL syndrome

Noonan syndrome incidence, genetic etiology, and clinical spectrum

NS is an autosomal dominant (with the rare exception of recessive *LZTR1* or *SPRED2* variants) condition with an estimated prevalence of 1 in 1,000 to 2,500 live births(71,72). Knowledge of the molecular basis of NS has increasingly evolved with variants in *PTPN11, SOS1, RAF1, RIT1, LZTR1, KRAS, SOS2, NRAS, RRAS, RRAS2, MRAS*, and *SPRED2* currently associated with disease(73-75). Individuals with a PV in *PTPN11* represent nearly half of NS cases and, therefore, the majority of data on cancer incidence is based on *PTPN11* cases. Clinically, NS is characterized by facial dysmorphisms, short stature, developmental delays, congenital heart defects (most often pulmonary valve stenosis, typically with dysplasia), hypertrophic cardiomyopathy, and increased cancer risk[(76,77)].

Cancer risk in Noonan syndrome

The relative childhood cancer risk in NS is estimated to be increased approximately 8-fold over the general population(5). Due to the low baseline cancer risk in children, the high relative risk leads to a moderate absolute cancer risk(5). The spectrum of cancer types is broad and includes myeloid and lymphoblastic leukemia, RMS, NB, and glioma, among others(2,4,5,78-81).

Specific *PTPN11* variants are associated with the development of an often-self-limiting myeloproliferative disorder (MPD)(4,82,83). This MPD can undergo transformation into JMML, although – apart from somatic events such as monosomy 7 - strong predictors for which individuals' MPD will self-resolve, and which will transform, are not yet known(84).

CBL syndrome

CBL syndrome has features overlapping with NS, including growth and developmental delays, hypertrophic cardiomyopathy, and vasculitis. This syndrome is diagnosed in an individual with a germline PV in *CBL*. Patients with CBL syndrome have an increased risk for JMML, associated with loss of heterozygosity in the bone marrow. The severity of CBL-related JMML is variable with both aggressive cases and those resolving without treatment(85,86). Unique to CBL syndrome, a patient's clinical course may be complicated by arteritis(85).

Proposed tumor surveillance updates for Noonan syndrome and CBL syndrome

While some individuals with NS first present with JMML, many first present with less-aggressive MPD, and there is no evidence to predict which patients' disease will spontaneously resolve and which will have frank transformation into JMML. Similarly, CBL syndrome patients can present with a less clinically aggressive form of JMML, and clinical management now recommends watchful waiting(87). Nevertheless, all patients with suspected MPD should be evaluated and followed by a pediatric hematologist/oncologist. There is no evidence that in otherwise healthy children with NS or CBL syndrome, surveillance with complete blood counts (CBC) is beneficial. Therefore, routine CBC has been removed from

surveillance, in alignment with other CPS predisposing to leukemia (See related manuscript through the AACR-Cancer Predisposition Working Group specific to leukemia surveillance). Clinical exam remains the mainstay of early intervention, and all patients, regardless of genotype, are recommended to have close monitoring including physical examination for hepatosplenomegaly especially during infancy and early childhood (**Table 2**). The absolute cancer risk for non-hematologic malignancies is not sufficiently high to warrant radiologic or laboratory surveillance. However, education of patients and families on the signs and symptoms of RMS, gliomas, and NB can be considered. Finally, there has been no evidence supporting the notion that use of growth hormones increases the risk or rate of tumor growth. Therefore, in patients with NS, and other RASopathies, we do not advise against the use of growth hormone therapy, if indicated clinically without other contraindications. Outside of a clinical trial, a brain MRI is not recommended in an asymptomatic child prior to starting growth hormone therapy.

Costello syndrome

Costello syndrome incidence, genetic etiology, and clinical spectrum

CS is characterized by heterozygous disease-causing variants in *HRAS* and is the RASopathy with the highest risk for malignancy. With a lower birth prevalence, at 1:380,000 births, it is much less common than NF1(88). Despite being an autosomal dominant condition, most patients with CS have a *de novo* variant as individuals with CS rarely have biological children, making inheritance of this syndrome rare.

Tumor spectrum and natural history in Costello syndrome

CS has an estimated 13% risk (95% CI: 9-16) of malignancy by age 20 years(3). This is predominantly due to an increased risk for RMS, NB, and transitional cell carcinoma of the bladder (TCC). Due to the high absolute cancer risks during the pediatric age range (**Table 3**), surveillance is recommended for these malignancies in all patients with CS(3,5,89). Genotype-phenotype cancer risk correlations showed that *HRAS* p.Gly12Cys (37.5% cancer incidence) and *HRAS* p.Gly12Asp (38.7%) have higher risks of malignancy compared to the more common *HRAS* p.Gly12Ser (9.2%)(3). However, as *HRAS* p.Gly12Ser is found in over 80% of CS patients, it is difficult to provide reliable cancer risk estimates for non-p.Gly12Ser variants. To our knowledge, there have been no malignancies reported in rare patients with CS due to *HRAS* non-p.Gly12 substitution variants(2,3,5,15,90). These possible genotype-cancer risk associations should be discussed with the parents/guardians of an affected child with CS but do not currently change recommended surveillance strategies.

Proposed tumor surveillance updates for Costello syndrome

Rhabdomyosarcoma

RMS is diagnosed in children with CS at similar young ages compared to sporadic RMS and has not been diagnosed after age 14 years. RMS is most often found in the abdomen/pelvis (80% of patients with CS and known tumor location)(3). While sporadic RMS also occurs in the head and neck region in 35% of cases and in the extremities in 13% of cases, this appears less frequently in CS (one patient each with: orbital, sphenoid, foot, and chest location)(89,91)·(92) Therefore, imaging surveillance efforts focus on the abdomen and pelvis for early identification and rely on physical exam for tumors arising outside of the abdomen/pelvis(89,91). Abdominopelvic ultrasound (US) should be started as early as a

disease-causing *HRAS* variant is identified and continue until age 14 years (**Table 3**). Due to US techniques and potential limitations relating to body habitus, sensitivity may decrease in older children and a dedicated, regional MRI should be pursued if US is considered non-diagnostic, or in patients with symptoms. Due to comorbidities and potential increase in repeated sedation for individuals with CS, MRI is not recommended as first line for screening.

Neuroblastoma

Young patients with CS are also at higher risk to develop NB. The age of diagnosis and location of NB do not differ from the general population, although data are limited. Screening should begin as early as an *HRAS* variant is identified, and continue until age 6 years, then with decreasing frequency from 6-10 years (**Table 3**). Not specific to CS, over 80% of NB occur in the adrenal glands and paraspinal sympathetic chain. As such, abdominopelvic US is the primary method for surveillance(14,89,93). The remainder of NB diagnoses primarily occur in the thoracic region, however, given the low estimated absolute risk of thoracic NB of <1%, chest radiograph is not generally recommended. Urine catecholamines levels are not a useful surveillance method for patients with CS, as these individuals have variable and elevated levels at baseline(94).

Bladder carcinoma

TCC of the bladder has been seen in up to 2.2% of patients with CS and shows the highest relative cancer specific risk increase because it is rarely diagnosed in the general pediatric population(2,3). In contrast to RMS and NB, TCC is rarely seen in infancy and more often occurs after age 10 years with an elevated risk throughout adolescence and adulthood.

Surveillance for TCC remains challenging as sensitive measures, such as cystoscopy, are highly invasive and typically require in-hospital anesthesia. Surveillance cystoscopies could be considered for effective surveillance every 2 years starting at age 10, with a role for patient and family shared decision making due to the invasive nature of the procedure **(Table 3)**(95). Urinalysis (UA) has previously been recommended to evaluate for hematuria due to its minimally invasive nature, although data are limited on sensitivity and specificity of this method(14,89),(95). Less invasive testing, such as urine cytology, may be most effective but should be done in the context of a clinical trial to understand concerning features that would prompt further work-up.

Adult tumors: Aside from TCC, there is not an identified increased incidence for common adult malignancies. This may be due to early non-malignancy related deaths in patients with CS, and likely does not reflect true risk. Annual clinical exams remain important throughout life and cancer surveillance recommendations for the general population should be followed(90).

Other RASopathies and their associated cancer risk

NS with multiple lentigines (NSML), previously referred to as multiple lentigines syndrome or LEOPARD syndrome, is associated with distinct disease-causing variants in the *PTPN11* gene (the most common being Y279C and T468M), *RAF1, MAP2K1,* and *BRAF*(96-100). Clinical features of NSML include hypertrophic cardiomyopathy, pulmonary valve stenosis, short stature, pectus deformity, and dysmorphic facial features including widely spaced eyes and ptosis. Lentigines appear predominantly around age 4-5 years as hypertrophic, black-brown

macules occurring on the face, neck and upper trunk(101). Cancers reported in association with NSML include leukemia, neuroblastoma, and melanoma(2,102).

Cardiofaciocutaneous (CFC) syndrome is currently estimated to affect 1 in 800,000 newborns and is caused by germline disease-causing variants in *BRAF, MAP2K1*, *MAP2K2*, and more rarely *KRAS* and *YWHAZ(103).* Individuals with CFC syndrome have been reported with leukemia, lymphoma, RMS, and hepatoblastoma, however, whether an increased cancer incidence in CFC syndrome exists remains unknown given limited cases(2,104).

Legius syndrome (LS) is caused by PVs in *SPRED1* and was first identified in individuals meeting previous diagnostic criteria for NF1 in the absence of *NF1* PV(105). Pigmentary changes similar to those seen in NF1, including café au lait macules and skin fold freckling, are a common feature of LS. However, tumor risks including neurofibromas and optic gliomas are absent(106). While cancers have been reported in individuals with *SPRED1* PVs, it is unknown whether these were related to the *SPRED1* variants or occurred by chance(105,107,108). Given the phenotypic overlap between LS and NF1, it is important to differentiate the two conditions in individuals presenting with café au lait macules as it can have significant impact on screening recommendations(23).

Tumor surveillance in other RASopathies

We recommend that in patients with NSML and CFC syndrome, the surveillance guidelines for NS are followed (**Table 2**). In NSML, the skin should be examined at least annually, and a dermatologist should be involved if there are specific concerns(102). No cancer surveillance is recommended in LS.

Discussion and Future Directions:

Improved understanding of the genetic basis to these syndromes, genotype-phenotype correlations, and the natural history of at-risk cancers will continue to advance surveillance recommendations. Refining surveillance techniques is necessary to provide the most impact on improving patient outcomes while decreasing ineffective surveillance. Further, enrollment of these individuals in a cancer predisposition or disease-specific registry is recommended to gain the necessary data and advance recommendations. Shared decision making is needed between healthcare providers and families. As many of these tumors present in adolescence and young adulthood, a smooth transition of healthcare should be emphasized, and young adults are encouraged to take an active role in their health. Guidelines for surveillance will continue to develop as novel germline associations are elucidated, identifiable somatic drivers are discovered, and treatment modalities improve. Future AACR-CPWG meetings will continue to be convened for up-to-date surveillance and intervention recommendations.

Table 1: Childhood Cancer Surveillance for Neurofibromatosis Type I (NF1)

Tumor/ Cancer Type	Cumulative Tumor Risk	Screening/ Management Method	Starting Age	Frequency	Comment
Optic pathway glioma (OPG)	20%	Visual assessment: Fundoscopy Visual acuity Visual fields	6-8 months	Yearly if normal until age 8	Continue visual assessment every other year from 8 years until transition to adulthood.
		Optic coherence tomography		When feasible	Stop at age 8 years if normal.
		Obtain brain/orbit MRI	If unreliable or inconsistent visual exam in a patient ≥2y	Once	Continue to obtain visual exams as able regardless of imaging results.
Plexiform neurofibroma (PN)	30-50%	2-plane spinal MRI pre-operatively	If surgery for scoliosis is needed	Once for baseline	
		WBMRI	Post-pubertal/ prior transition to adulthood	Once	Evaluate asymptomatic tumors for risk of ANNUBP and future MPNST.
			Prior to starting MEK-inhibitor therapy	If needed, once	Consider a limited NCAP-WBMRI prior to starting MEK-inhibitor therapy if WBMRI is not readily available*.
Atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP)	Unknown	Regional MRI-DWI and 18F-FDG PET/MRI or 18F-FDG PET/CT	For clinical signs/symptoms: change in neurological function, pain or rapid growth of a PN in an adolescent or young adult.		
Malignant peripheral nerve sheath tumor (MPNST)	8-13%				
Non-OPG Brain Tumor	5-fold increase from general population	None indicated unless patient is symptomatic			
Leukemia	≤ 2%	Physical exam by general physician	Birth, or at diagnosis	Yearly	
Pheochromocytoma	≤ 5%	Blood pressure monitoring	Birth, or at diagnosis	Yearly	Consider renal artery stenosis if hypertensive in the absence of other symptoms of pheochromocytoma
Rhabdomyosarcoma (RMS)	≤ 1%	None indicated unless patient is symptomatic.			
***NCAP-WBMRI: neck, chest, abdomen, and pelvis MRI imaging with thick slices (see related manuscript through the AACR-Cancer Predisposition Working Group specific to whole-body MRI surveillance)**					

Table 2: Childhood Cancer Surveillance for Noonan syndrome, CBL syndrome, CFC syndrome and NSML

Tumor/ Cancer Type	Cumulative Tumor Risk	Screening/ Management Method	Starting Age	Frequency	Comment
MPD (regardless of genotype)	Depending on underlying PV	Physical exam with evaluation for hepatosplenomegaly and clinical concern for leukemia	Birth, or at diagnosis	Every 3 months through age 1y, then at every well child visit until age 5y, and as needed for clinical symptoms.	If abnormal consult hematologist with experience in MPD due to RASopathies - CBC if ill or hepatosplenomegaly on exam. - No bloodwork is recommended for an asymptomatic/healthy child
Brain Tumors	<1%	No surveillance unless clinical symptoms.			
Lentigines	Nearly 100%	Skin Exam	Birth	Yearly	For individuals with NSML

Abbreviations: CFC - Cardiofaciocutaneous syndrome, NSML - Noonan syndrome with multiple lentigines, MPD: myeloproliferative disorder, CBC – complete blood count

Abbreviations: DWI – diffusion weighted imaging, MRI – magnetic resonance imaging, 18F-FDG PET/CT or PET/MRI – 18F-fluorodeoxyglucose positron emission tomography and computed tomography or magnetic resonance imaging, WBMRI – whole-body magnetic resonance imaging

Table 3: Childhood Cancer Surveillance for Costello syndrome

Tumor/ Cancer Type	Cumulative Tumor Risk*	Screening/ Management Method	Starting Age	Frequency	Comment
Rhabdomyosarcoma (RMS)	7 %	Abdominopelvic US	Birth, or at diagnosis	Specific for RMS: Every 3 months until age14y	Sensitivity of US may decrease in older patients, consider MRI for indeterminant US.
Neuroblastoma (NBL)	2 %			Specific for NBL: Every 6-12 months until age 10y	Screening catecholamines are not recommended
Transitional Cell Carcinoma of the Bladder (TCC)	2.2 %	Urinalysis with cytology$^{\Delta}$	10y	Annual	If micro/macroscopic hematuria, pursue cystoscopy. $^{\Delta}$Routine cytology is encouraged to be done in the setting of research study if available.
		Consider cystoscopy		Every 2 years if negative	

*****Malignancies have been reported in CS patients with a PV in *HRAS* predicting p.Gly12 substitutions only. Cancer appears to be less common in rare CS patients with other *HRAS* PVs.

Abbreviations: MRI- magnetic resonance imaging; US- ultrasound; Y- years of age

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