

Recommendations for Cancer Surveillance in Individuals with RASopathies and Other Rare Genetic Conditions with Increased Cancer Risk



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Abstract

In October 2016, the American Association for Cancer Research held a meeting of international childhood cancer predisposition syndrome experts to evaluate the current knowledge of these syndromes and to propose consensus surveillance recommendations. Herein, we summarize clinical and genetic aspects of RASopathies and Sotos, Weaver, Rubinstein-Taybi, Schinzel-Giedion, and NKX2-1 syndromes as well as specific metabolic disorders known to be associated with increased childhood cancer risk. In addition, the expert panel reviewed whether sufficient data exist to make a recommendation that all patients with these disorders be offered cancer surveillance. For all syndromes, the panel recommends increased awareness

and prompt assessment of clinical symptoms. Patients with Costello syndrome have the highest cancer risk, and cancer surveillance should be considered. Regular physical examinations and complete blood counts can be performed in infants with Noonan syndrome if specific *PTPN11* or *KRAS* mutations are present, and in patients with CBL syndrome. Also, the high brain tumor risk in patients with L-2 hydroxyglutaric aciduria may warrant regular screening with brain MRIs. For most syndromes, surveillance may be needed for nonmalignant health problems. *Clin Cancer Res*; 23(12); e83–e90. ©2017 AACR.

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Introduction

A number of rare syndromes are known to be associated with increased risk of cancer. In contrast with high cancer risk syndromes such as Li-Fraumeni syndrome or constitutional mismatch repair deficiency, others are associated with a mildly to moderately increased cancer risk. Herein, we concisely review the clinical features, genetic basis, and cancer association of several rare syndromes and discuss the need for cancer surveillance as part

of clinical management. A summary of these recommendations is presented in Tables 1 and 2.

The RASopathies

The RASopathies are a group of disorders that are characterized by (i) constitutional dysregulation of the Ras signaling pathway, and (ii) a phenotype resembling Noonan syndrome (NS; refs. 1–3). NS features include abnormal growth (proportionate short stature and relative or absolute macrocephaly), congenital heart defects (most commonly pulmonary stenosis or hypertrophic cardiomyopathy), dysmorphism (hypertelorism with down-slanting palpebral fissures; ocular ptosis; low-set, posteriorly rotated ears; broad neck with low hairline; and thorax deformity), and abnormal skin and adnexa. Additional features may include learning difficulties, ocular anomalies, feeding problems in infancy, cryptorchidism, disorders of pubertal timing, lymphatic anomalies, bleeding diathesis, and increased cancer risk. The group of RASopathies are described in detail below (1–3). Among these are neurofibromatosis type 1 (NF1); cancer surveillance in persons with NF1 is discussed in the CCR Pediatric Oncology Series article by Evans and colleagues (4).

NS is caused by germline mutations of *PTPN11* (50%; ref. 5); *SOS1* (13%; refs. 6, 7); *RAF1* (5%; refs. 8, 9); *RIT1* (5%; ref. 10); or more rarely, *KRAS* (11), *NRAS* (12), *BRAF* (13), *MAP2K1* (14), *RRAS* (15), *RASA2* (16), *A2ML1* (17), *SOS2* (18), or *LZTR1* (18). Children with NS are at an approximately 8-fold increased risk for a spectrum of different cancers (19). These include (but are not limited to) gliomas such as dysembryoplastic neuroepithelial tumors, acute lymphoblastic leukemia, neuroblastoma (NBL), and rhabdomyosarcoma (19–22). Specific mutations of *PTPN11* (most commonly, but not exclusively at codon 61 or T73I;

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Table 1. Summary of cancer surveillance recommendations

Syndrome	Childhood cancer risk	Surveillance guidelines
I. Surveillance warranted		
Costello syndrome	15% by 20 yrs: ERMS, NBL, bladder cancer	0 to 8–10 yrs: physical exam and AP US ± CXR q 3–4 mths From 10 yrs: annual urinalysis
NS—specific <i>PTPN11</i> or <i>KRAS</i> mutations	High risk of myeloproliferative disorder/JMML	0 to 5 yrs: physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
CBL syndrome	High but not precisely defined JMML risk; more rarely other neoplasms	0 to 5 yrs: Physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
SGS—mild	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider periodic AP US, AFP/βHCG
II. Baseline only		
SGS—severe	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider addition of AFP/βHCG to baseline bloodwork for SGS
III. No surveillance		
For all of the following:	<5% or unknown but low likelihood	No routine surveillance Increased awareness and low threshold for investigating new potential tumor-related symptoms
NS (non-high risk mutations)	Dysembryoplastic neuroepithelial tumors, ALL, NBL, RMS, others	
NSLAH	e.g., NBL, myelofibrosis	
NSML	e.g., acute leukemias	
CFCS	e.g., ALL, NHL	
Legius syndrome	Few cancers reported to date	
Sotos syndrome	e.g., NBL, ALL, AML, HBL, SCT, etc.	
Weaver syndrome	e.g., NBL, hematologic malignancies	
Rubinstein–Taybi syndrome	e.g., HBL, NBL, RMS, CNS tumors, carcinomas, etc.	
NKX2-1 syndrome	No evidence for cancer predisposition	

Abbreviations: AFP, alpha-fetoprotein; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AP US, abdominopelvic ultrasound; βHCG, beta human chorionic gonadotrophin; CBC, complete blood count; CFCS, cardiofaciocutaneous syndrome; CNS, central nervous system; CXR, chest x-ray; ERMS, embryonal rhabdomyosarcoma; HBL, hepatoblastoma; JMML, juvenile myelomonocytic leukemia; mths, months; NBL, neuroblastoma; NHL, non-Hodgkin lymphoma; NS, Noonan syndrome; NSLAH, Noonan syndrome-like with loose anagen hair; NSML, Noonan syndrome with multiple lentigines; PNET, primitive neuroectodermal tumor; q, every; RMS; rhabdomyosarcoma; SC-GCT, sacrococcygeal germ cell tumor; SCT, sacrococcygeal teratoma; SGS, Schinzel-Giedion syndrome; yrs, years.

refs. 23–26) or *KRAS* (T58I; ref. 11) are associated with a myeloproliferative disorder (NS/MPD) resembling juvenile myelomonocytic leukemia (JMML). NS/MPD occurs in neonates and young infants, starts as a polyclonal disease, and typically resolves over time. However, some neonates or infants with NS develop an aggressive monoclonal disease that may be lethal, especially if left untreated (27, 28).

NS-like with loose anagen hair (NSLAH) is caused by germline mutations of *SHOC2* (29) or more rarely, *PPP1CB* (30) and is characterized by NS features, darkly pigmented skin, and ectodermal anomalies. Cancer risk appears to be mildly increased based on a few reports of myelofibrosis and NBL among the small group (<50) of NSLAH patients described previously (31).

NS with multiple lentigines (NSML) is typically caused by specific mutations of *PTPN11* (T468M and Y279C; ref. 32; other rare mutations have been reported; ref. 33), and affected individuals show an NS phenotype with multiple lentigines, frequent hypertrophic cardiomyopathy, and deafness. As in classic NS, childhood cancer risk is mildly increased; acute leukemias and a few other cancers have been reported in approximately 2% of cases (19).

Cardiofaciocutaneous syndrome (CFCS) is due to germline mutation of *KRAS* (11, 34), *MAP2K1* (35), *MAP2K2* (35), or *BRAF* (34, 35). Affected persons have NS features and tend to have significant mental and neurologic impairment, more severe ectodermal involvement, and characteristic facies. Several cases of childhood cancer have been reported, and the cancer risk may be mildly increased (19, 20).

Costello syndrome (CS) is due to germline mutations of *HRAS* (36). In addition to NS features, CS patients have mental deficits, poor feeding, hypertrophic cardiomyopathy, tachycardia, typical skin and hair, a coarse face, and a high childhood cancer risk, especially for embryonal rhabdomyosarcoma (ERMS), NBL, and early-onset bladder cancer. The cumulative incidence of cancer is 15% by age 20 years (19, 20, 37, 38). The *HRAS* G12A mutation appears to be associated with the highest cancer risk (39).

Legius syndrome (LS) is due to germline *SPRED1* mutations (40). Affected individuals show café-au-lait macules with or without freckling but lack neurofibromas or NF1-associated tumors. They may demonstrate an NS appearance and/or learning difficulties. The childhood cancer risk is unclear, but occasional neoplasms in patients have been reported (40).

Germline mutations of the *CBL* gene cause CBL syndrome (CBLs), a variable phenotype characterized by a relatively high frequency of neurologic features/vasculitis, mild NS features, and high JMML risk (41). Other cancers [e.g., acute myelogenous leukemia (AML) and glioma] have also been reported (41, 42).

Proposed Surveillance for Patients with RASopathies

With a few exceptions, patients with RASopathies have a mildly increased cancer risk justifying increased awareness and prompt assessment when suspicious clinical symptoms are present. Given that childhood cancer risk falls below 5% in most of these syndromes, routine cancer surveillance is probably not warranted;

Table 2. Summary of neoplastic features and surveillance recommendations for selected metabolic disorders

Metabolic pathway/ enzyme	Autosomal dominant condition, gene and OMIM ID#	Autosomal recessive condition, gene and OMIM ID#	X-linked condition, gene and OMIM ID#	Associated cancer(s)	Cancer surveillance recommendations
Urea cycle	n/a	Citrullinemia: <i>SLC25A13</i> , #603471 Argininosuccinate lyase deficiency: <i>ASL</i> , #207900 Arginase deficiency: <i>ARG1</i> , #207800	Ornithine transcarbamylase deficiency (OTCD): <i>OTC</i> , #311250	Associated with OTCD: Hepatocellular carcinoma (116)	May consider adding AFP to scheduled metabolic bloodwork in those without a liver transplant
Succinate dehydrogenase complex	Familial pheochromocytoma and paranglioma syndrome: <i>SDHA</i> #614165 <i>SDHB</i> #606864 <i>SDHC</i> #606864 <i>SDHD</i> #606864 <i>SDHAF2</i> #613019 Cowden syndrome 2: <i>SDHB</i> #612359	Leigh syndrome: <i>SDHA</i> n/a #600857 <i>SDHB</i> (117)	n/a	Associated with autosomal dominant mutations: Pheochromocytoma, paranglioma, gastrointestinal stromal tumor Cowden syndrome– associated tumors	See article by Rednam et al. (118) in this series.
L-2- hydroxydehydrogenase	n/a	L-2- hydroxyglutaric aciduria: <i>L2HGDH</i> #236792	n/a	Gliomatosis brain tumors	Clinical/neurologic exam every 3–6 months Annual Brain MRI ^a (108)
Tyrosinemia	n/a	Tyrosinemia: <i>FAH</i> #276700	n/a	Hepatocellular carcinoma (risk is reduced with diet and nitisinone treatment)	AFP monthly for the first 6 months of life, then every 6 months (114) Consider baseline US/MRI of liver

Abbreviations: AFP, alpha-fetoprotein; n/a, not applicable; US, ultrasound.

^aWith contrast for the first study, then without contrast thereafter, unless an abnormality is identified.

however, surveillance may be justified for nonmalignant complications (e.g., heart defects, vasculitis, endocrine disturbances). In patients with CBLS or patients with NS due to specific *PTPN11* or *KRAS* mutations known to be associated with MPD/JMML (see above), 3 to 6 monthly physical exams with spleen size assessment and complete blood counts with differential should be considered starting at birth (or diagnosis) and continuing until age 5 years. There are no data indicating that this strategy leads to a survival advantage, but the sometimes more aggressive course of the MPD/JMML in patients with specific RASopathies may justify this recommendation in selected patients. Treatment may be necessary for patients with symptoms due to the hematologic complications and should be discussed with JMML experts.

The high cancer risk in individuals diagnosed with CS (19) supports cancer surveillance, although its benefit remains to be proven. For patients with CS, based on previous recommendations (43), we propose increased awareness and prompt assessment of new symptomology, 3 to 4 monthly physical exams, and abdominal and pelvic ultrasound examinations to screen for rhabdomyosarcoma and NBL until age 8 to 10 years, and annual

urinalysis for evidence of hematuria to screen for bladder cancer beginning at age 10 years (43). Of note, we suggest avoiding urinary vanillylmandelic acid/Homovanillic acid (VMA/HVA) for NBL screening in CS due to the high false positive rate in this population (44). As described in the CCR Pediatric Oncology Series article on NBL predisposition by Kamihara and colleagues (45), chest X-ray is a recommended surveillance tool for patients with a high NBL risk. Although chest X-ray was not part of previous recommendations for patients with CS (43), inclusion of chest X-ray in the surveillance may be discussed with the family as an option.

Sotos and Weaver Syndromes

Sotos syndrome is caused by heterozygous germline mutations in *NSD1* and is characterized by a distinctive facial appearance, height and head circumference >97th percentile, advanced bone age, and developmental delay (46, 47). Although the childhood cancer risk is not known, it is likely to be mildly elevated (<5%). Multiple individuals with Sotos syndrome have been reported to

develop neoplasms, including ovarian fibromatosis, NBL, acute lymphoblastic leukemia, acute myelogenous leukemia, hepatoblastoma, sacrococcygeal teratomas, ganglioneuroma, small cell lung cancer, ganglioglioma, gastric carcinoma, and testicular cancer (48–60). Although awareness of cancer risk is important, routine surveillance is not recommended.

Weaver syndrome is characterized by overgrowth (tall stature), distinct facial features (hypertelorism, broad forehead, almond-shaped eyes, pointed chin with horizontal crease, large and fleshy ears), and variable cognitive disability. Other common characteristics of Weaver syndrome include doughy skin, camptodactyly, poor coordination, umbilical hernia, hoarse cry, advanced bone age, and hyper- or hypotonia (61). The syndrome is caused primarily by heterozygous missense mutations in *EZH2* (62, 63). Somatic *EZH2* mutations, both activating and inactivating, have been identified in hematologic malignancies and in solid tumors (64). Tumors have been reported in individuals with germline *EZH2* mutations, albeit infrequently. One mutation-positive individual developed lymphoma at age 13 years, another developed NBL and acute lymphoblastic leukemia at age 13 months, and a third was diagnosed with NBL at age 4 years. The risk for developing NBL may be slightly increased in individuals with Weaver syndrome, but currently, the numbers are too small to calculate the absolute risk. There is no recommendation for tumor surveillance at this time, but clinical vigilance and workup of potential tumor-related symptoms, especially for NBL, are suggested (61, 65).

Rubinstein-Taybi Syndrome

Rubinstein-Taybi syndrome (RSTS) is characterized by facial features, including down-slanting palpebral fissures, low columella, high palate, grimacing smile, and talon cusps, broad thumbs and great toes, short stature, and intellectual disability (66, 67). RSTS is inherited in an autosomal dominant manner, but mutations usually occur *de novo*. The incidence is approximately one in 100,000 to 125,000 (68, 69). RSTS is caused by germline mutations of *CREBBP* (40%–50%; ref. 70) or *EP300* (3%–8%; ref. 71), both affecting a pathway that is also implicated in cancer (72). Several case reports indicate that individuals with RSTS are at increased risk of developing cancer, but the cancer risk is unknown and may be only moderately increased. Different cancers have been reported in patients with RSTS, including hepatoblastoma, ovarian and endometrial carcinomas, NBL, medulloblastoma, meningioma, oligodendroglioma, pheochromocytoma, rhabdomyosarcoma, leiomyosarcoma, seminoma, and embryonal carcinoma. They may also develop benign tumors, such as odontoma, choristoma, dermoid cyst, and pilomatricomas (73–81). Because of the unknown cancer risk, firm cancer surveillance recommendations cannot be made at this time, but prompt assessment of any new or persistent symptoms is warranted.

Schinz-Giedion Syndrome

Individuals with Schinz-Giedion syndrome (SGS) have severe developmental delay, distinctive facial features, and multiple congenital anomalies (particularly skeletal, genitourinary/renal, and cardiac); most patients die from the condition in the first decade of life (82). The disorder is caused by *de novo* mutations of *SETBP1* (83), an important gene implicated in myeloid malignancies (84). Surprisingly, no SGS patients with myeloid neoplasms have been reported. However, a number of patients

have developed cancer, including sacrococcygeal germ cell tumors (85–88); sacrococcygeal primitive neuroectodermal tumors (82), an ependymal tumor with myxopapillary and ependymoblastic differentiation (89); hepatoblastoma; and a malignant retroperitoneal tumor arising in a multicystic dysplastic kidney (90). The cancer risk is unknown but is likely to be high based on the number of reported tumors in patients with this condition (approximately 10 tumors in 70 cases). Families should be made aware of the increased risk for tumors. The merits of surveillance need to be weighed against the severity of the patient's clinical condition. We recommend close attention for the presence of congenital tumors on baseline diagnostic investigations for SGS (which may include imaging of the spine and abdomen/pelvis for skeletal/neurologic and renal workup, respectively). Baseline germ cell and hepatoblastoma tumor markers (alpha-fetoprotein—AFP, β HCG) with other baseline syndrome-related bloodwork can be considered. For milder cases, clinicians may consider ongoing screening with periodic abdominal and pelvic ultrasound and periodic measurements of serum AFP and β HCG.

NKX2-1 Syndrome

Loss-of-function mutations in the *NKX2-1* gene (also known as *TTF-1*, *TITF1*, *T/EBP*), located at 14q13.3, are associated with the "Brain-Lung-Thyroid syndrome (BLTS)," which is characterized by (i) benign hereditary chorea (BHC); (ii) infantile respiratory distress syndrome, which may be fatal; and (iii) congenital hypothyroidism, which may present with an ectopic or dysgenetic gland (91, 92). Familial non-medullary thyroid carcinoma (FNMTTC) represents roughly 5% of thyroid malignancies, and no reproducible susceptibility genes have been consistently associated with the diagnosis (93–95). Given the role of *NKX2-1* in thyrocyte differentiation, proliferation, and survival (96), germline mutations in *NKX2-1* have been postulated to play a role in predisposition to thyroid malignancies (97–99). A single case series demonstrated a recurrent loss-of-function variant of *NKX2-1* (p.A339V) in four of 20 independent kindreds affected by both papillary thyroid carcinoma (PTC) and multinodular goiter (MNG; ref. 100). In only one of these families did PTC segregate with the variant. Further studies have failed to show germline variants of *NKX2-1* in 38 kindreds affected by FNMTTC (101). Similarly, genome-wide association studies have failed to demonstrate linkage to the *NKX2-1* locus on 14q (93, 102). Thus, it is plausible that the effect of *NKX2-1* mutation identified by Ngan and colleagues (100) is more tightly associated with the MNG phenotype than with PTC.

Although *NKX2-1* is reported to be overexpressed in small cell and adenocarcinoma of the lung, and although there are rare reports of lung carcinoma arising in individuals with components of the BLTS (103, 104), the association with germline *NKX2-1* mutation has not been established. At present, the available data do not support a strong role for *NKX2-1* in predisposition to hereditary lung or thyroid malignancy, thus we do not recommend screening *NKX2-1* mutation carriers for lung or thyroid cancer.

Metabolic Disorders/Genes

L-2-hydroxyglutaric aciduria is a recessive neurometabolic disorder characterized by the presence of high levels of L-2-hydroxyglutaric acid in urine, plasma, and cerebrospinal fluid. The condition is caused by mutations of *L2HGA* and clinically

associated with progressive ataxia, mental impairment, subcortical leukoencephalopathy, and cerebellar atrophy (105). Despite the rarity of the condition, several cases of brain tumors have been associated with the disease, including ependymoma, primitive neuroectodermal tumor, low- and high-grade glioma, medulloblastoma, and oligodendroglioma (106, 107). Nephroblastoma has been reported in one patient (108). Although the cancer risk is not currently known, the relatively large number of reported brain tumors suggests that cancer surveillance with 3 to 6 monthly clinical and neurologic assessments and annual brain MRI may be warranted (using contrast enhancement for the baseline MRI only). Notably, D-2-hydroxyglutaric aciduria is due to germline mutations of *IDH2* (109). Although somatic *IDH1* and *IDH2* mutations occur in brain and other cancers (110, 111) and somatic mosaic mutations of these genes lead to the Maffucci syndrome and Ollier disease (which are also associated with cancer), there does not appear to be documentation of an increased cancer risk in individuals with germline mutations of *IDH2* (112, 113).

There are other metabolic conditions that are associated with an increased cancer risk, including tyrosinemia type I (hepatocellular carcinoma; ref. 114). The risk warrants consideration for baseline liver imaging along with regular AFP measurements but is dramatically reduced when children are treated with nitisinone

(114). It is noteworthy that AFP can be falsely elevated in this population due to liver adenomas and regeneration (115). A summary of these recommendations and those for selected other metabolic disorders is provided in Table 2.

Conclusions

For most of the syndromes discussed in this article, cancer risk does not justify routine cancer surveillance. However, exceptions include CS, CBLS, NS with specific high-risk mutations, L-2 hydroxyglutaric aciduria, and tyrosinemia type I (Tables 1 and 2). It will be important to assess more precise cancer risks and cancer types by enrolling affected individuals in cancer predisposition syndrome registries. In addition, for patients in whom surveillance is currently recommended, its benefits, psychosocial implications for the patient and family, as well as cost, need to be carefully considered. Finally, cancer prevention strategies remain an objective for future research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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