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 L2 hydroxyisocitrate dehydrogenase 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 American Association for Cancer Research.

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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 downslanting 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), AZML1 (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 T73;
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Table 1. Summary of cancer surveillance recommendations

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

Abbreviations:AFP, alpha-fetoprotein; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AP US, abdominopelvic ultrasound; JHCG, 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.

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;
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

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

<table>
<thead>
<tr>
<th>Metabolic pathway/enzyme</th>
<th>Autosomal dominant condition, gene and OMIM ID#</th>
<th>Autosomal recessive condition, gene and OMIM ID#</th>
<th>X-linked condition, gene and OMIM ID#</th>
<th>Associated cancer(s)</th>
<th>Cancer surveillance recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea cycle</td>
<td>Citrullinemia: SLC25A13, #603471</td>
<td>Ornithine transcarbamylase deficiency (OTCD): OTC, #311250</td>
<td>May consider adding AFP to scheduled metabolic bloodwork in those without a liver transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinate dehydrogenase complex</td>
<td>Familial pheochromocytoma and paraganglioma syndrome: SDHA #614165 SDHB #608684 SDHC #606864 SDHD #606864 SDHAF2 #613019</td>
<td>Leigh syndrome: SDHA #600857 SDHB (117)</td>
<td>Associated with autosomal dominant mutations: Pheochromocytoma, paraganglioma, gastrointestinal stromal tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowden syndrome 2: SDHAF2 #612359</td>
<td>Cowden syndrome-associated tumors</td>
<td></td>
<td>See article by Rednam et al. (118) in this series.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-2-hydroxydehydrogenase</td>
<td>L-2-hydroxyglutaric aciduria: L2HGDH #236792</td>
<td>Gliomatosis brain tumors</td>
<td>Clinical/neurologic exam every 3-6 months Annual Brain MRI*(108)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Tyrosinemia: FAH #276700</td>
<td>Hepatocellular carcinoma (risk is reduced with diet and nitisinone treatment)</td>
<td>AFP monthly for the first 6 months of life, then every 6 months (114) Consider baseline US/MRI of liver</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*With contrast for the first study, then without contrast thereafter, unless an abnormality is identified.
develop neoplasms, including ovarian fibromatosis, NBL, acute lymphoblastic leukemia, acute myelogenous leukemia, hematoblastoma, sacroccygeal teratomas, ganglieneuroma, 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 doughty 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 coloboma, 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, choriostoma, 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.

Schinzel–Giedion Syndrome

Individuals with Schinzel–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). Several 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 retropitoneal 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, bHCG) 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 bHCG.

NKX2-1 Syndrome

Loss-of-function mutations in the NKX2-1 gene (also known as TTF-1, TITF1, TEBP), 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 a ectopic or dysgenetic gland (91, 92). Familial non-medullary thyroid carcinoma (FNMTc) 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 FNMTc (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 nitisimone (114). It is noteworthy that AFP can be falselayed 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, L2 hydroxoglyutaric 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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