HHS Public Access

Author manuscript

Am J Med Genet C Semin Med Genet. Author manuscript; available in PMC 2023 December 19.

Published in final edited form as:

Am J Med Genet C Semin Med Genet. 2022 December ; 190(4): 530–540. doi:10.1002/ajmg.c.32018.

Cancer incidence and surveillance strategies in individuals with RASopathies

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Abstract

RASopathies are a set of clinical syndromes that have molecular and clinical overlap. Genetically, these syndromes are defined by germline pathogenic variants in RAS/MAPK pathway genes resulting in activation of this pathway. Clinically, their common molecular signature leads to comparable phenotypes, including cardiac anomalies, neurologic disorders and notably, elevated cancer risk. Cancer risk in individuals with RASopathies has been estimated from retrospective reviews and cohort studies and have found clear associations with some RASopathies and increased cancer incidence. For example, in Costello syndrome, cancer incidence is significantly elevated over the general population, largely due to solid tumors. In some forms of Noonan syndrome, cancer risk is also elevated over the general population and is enriched for hematologic malignancies. Thus, cancer surveillance guidelines have been developed to monitor for the occurrence of such cancers in individuals with some RASopathies. These include abdominal ultrasound and urinalyses for individuals with Costello syndrome, while complete blood counts and splenic examination are recommended in Noonan syndrome. Improved cancer risk estimates and refinement of surveillance recommendations will improve the care of individuals with RASopathies.

Keywords

RASopathy; cancer predisposition; screening

The importance of the RAS pathway in cancer

RAS/MAPK signaling is involved in nearly every facet of cell biology, and it is therefore not surprising that pathogenic variants disrupting these vital cellular processes have potent

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effects on disease development. Mutations in the RAS/MAPK pathway are among the most common oncogenic variants detected across a range of both adult and pediatric cancers, in some cases approaching 90% (Kamisawa, Wood et al. 2016, Grobner, Worst et al. 2018, Ma, Liu et al. 2018). Germline pathogenic variants in the RAS/MAPK pathway give rise to a spectrum of clinical syndromes called RASopathies, which can affect multiple organ systems, including cardiac, skeletal and neurologic. Given the importance of the RAS pathway in somatic cancer development, germline RAS signaling pathway hyperactivation predisposes some of these individuals to cancer. Care of these high-risk individuals is challenging, and one could consider tumor surveillance as part of their routine care. However, recommendations for screening vary across professional opinions and depends not only on the specific RASopathy but also the specific variant of that individual. Thus, careful consideration is needed and is likely unique for each patient. Successful treatment of individuals with a RASopathy and cancer is likely dependent on the ability to identify them early, as has been shown in other tumor predisposition syndromes, such as Li-Fraumeni (Ballinger, Best et al. 2017). Therefore, having detailed knowledge of the incidence of cancer, and cancer type, in each of the RASopathies to inform recommended screening protocols is crucial for the optimal clinical management of these patients.

In this article, we undertook a librarian-informed comprehensive literature review of what is known, and remains unknown, about cancer incidence in the non-neurofibromatosis type 1 (NF1) RASopathies and discuss current recommendations for cancer surveillance.

Methods

A biomedical librarian conducted a literature search in the PubMed (US National Library of Medicine) and Embase (Elsevier) citation and abstract databases in August 2022. Two search strategies were created with input from the authors to find articles on 1) clinical management of all RASopathies and 2) cancer incidence of non-NF1 RASopathies in humans. The search strategies incorporated both keywords and controlled vocabulary terms (i.e., MeSH (PubMed) and EMTREE (Embase)) for the specified RASopathies and concepts of interest (*i.e.,* clinical management and cancer incidence). Key articles identified by the authors were reviewed to further identify keywords for the searches. The searches were not limited by language nor publication year but were limited to exclude animal studies and specific article types (*e.g.,* conference abstracts, conference proceedings, letters, editorials, commentary, case reports, case series, corrigenda, errata, protocols). See Supplemental Materials for final search strategies used. All search results from each database were exported to EndNote 20 (Clarivate Analytics) and duplicates identified and removed. Two reviews in Covidence (Veritas Health Innovations, Ltd.) were setup and used to screen and select relevant articles from the unique search results.

A total of 1289 unique articles were retrieved on clinical management of all RASopathies and 375 on cancer incidence of non-NF1 RASopathies. One author screened each article to determine its relevance to the specific questions. Each reviewer assessed the title and abstract returned during the search to determine appropriateness for inclusion. After abstract review, a final list of references was obtained and a second examination by the same reviewer was conducted using full-text to determine relevance to manuscript content.

Costello Syndrome

Costello syndrome is a RASopathy with a reported prevalence of 1:380,000 live births (Gripp and Rauen 1993). The majority of individuals with Costello syndrome carry an *HRAS* p.G12S variant, and therefore represent a large percentage (~80%) of this population (Gripp, Morse et al. 2019). Given the identification of the causative gene for Costello syndrome, genotype-phenotype correlations have been noted, including *HRAS* p.G12D, *HRAS* p.G12V, *HRAS* p.G12C and *HRAS* p.G12E, which often have a severe presentation early in life, most often cardiac in origin (Gripp, Morse et al. 2019). Although rare, less severely affected genotype-phenotypes have been associated with other *HRAS* variants, such as *HRAS* p.G60D (Gripp, Sol-Church et al. 2015).

Cancer Incidence

Despite its low prevalence, there are clear data indicating that individuals with Costello syndrome have increased cancer risk. Previous analyses of cancer cases among 735 individuals with a germline variant in a RASopathy gene showed a cancer incidence roughly 40-fold higher in Costello syndrome than in the general population (Kratz, Franke et al. 2015) and represents an estimate of cancer incidence based on existing data. For specific *HRAS* variants, such as *HRAS* p.G12A, cancer incidence may be even higher (Gripp, Morse et al. 2019) (Table 1). These more recent observations remain consistent with the earliest cancer estimates in Costello syndrome, where the solid tumor incidence was initially 17% (Gripp, Scott et al. 2002) and add further observations regarding potential genotype-phenotype associations. The cancers reported in Costello syndrome are largely early-onset solid tumors, such as rhabdomyosarcoma (highest risk until age 6), neuroblastoma (also in early childhood) and bladder cancer in childhood and adolescence (Gripp, Scott et al. 2002, Villani, Greer et al. 2017) (Figure 1). In a study of pediatric patients enrolled in Children's Oncology Group trials for rhabdomyosarcoma, about 7% had an underlying cancer predisposition syndrome (Li, Sisoudiya et al. 2021). Of those, 11% had a pathogenic/likely pathogenic germline variant in *HRAS*, representing 1.4% of all individuals with embryonal rhabdomyosarcoma (Li, Sisoudiya et al. 2021).

In addition to rhabdomyosarcoma, individuals with Costello syndrome are at high risk for a range of other solid tumors. In childhood, individuals with Costello syndrome are at increased risk of neuroblastoma, with an incidence close to 1% (Kratz, Franke et al. 2015). Similar to rhabdomyosarcoma, risk for neuroblastoma tends to occur early in infancy and young childhood, consistent with non-syndromic neuroblastoma diagnoses (Kratz, Rapisuwon et al. 2011). In parallel to the high frequency of somatic *HRAS* mutations reported in bladder cancer, individuals with germline *HRAS* variants are also at elevated risk (Kompier, Lurkin et al. 2010, Kratz, Franke et al. 2015, Yee, Zheng et al. 2019). Notably, unlike non-syndromic bladder cancer, which often occurs after age 60, increased bladder cancer risk begins at age 10 years in Costello syndrome (Gripp 2005, Beukers, Hercegovac et al. 2014, Villani, Greer et al. 2017, Gripp, Morse et al. 2019). Furthermore, while the majority of those diagnosed with bladder cancer are > 10 years of age, bladder cancer in CS has been detected in much younger patients (Yu, Luk et al. 2019). Despite the well-characterized increased solid tumor risk, hematologic malignancies in Costello

syndrome are likely rare, although myeloproliferative disorders have recently been newly described (Pabari, Chun et al. 2022)

Surveillance Guidelines

Given the high risk of cancers in these younger populations and well-defined cancer types, tumor surveillance recommendations exist for Costello syndrome. The most recent consensus recommendations for screening were detailed by Villani et al in 2017 and include physical exam and abdominal ultrasound with or without a chest radiograph every 3-4 months for patients under 10 years old, and annual urinalysis for those ≥ 10 years (Table 1). The recommendation to include a chest radiograph for the surveillance of neuroblastoma was added by Villani, et al to align with other recommendations for individuals at high risk for developing neuroblastoma (Kamihara, Bourdeaut et al. 2017). Given the frequency with which chest radiographs are recommended and exposure to radiation, the interval between chest radiographs and their completion should be a shared decision between caregivers and providers. The first set of tumor surveillance recommendations for Costello syndrome were proposed by Gripp et al in 2002 and included: 1) routine ultrasounds of the abdomen and pelvis through 10 years of age to screen for rhabdomyosarcoma and abdominal neuroblastoma, 2) urine catecholamines and metabolites every 6-12 months until 5 years old for neuroblastoma and 3) urinalysis for assessment of hematuria annually starting at 10 years old (Gripp, Scott et al. 2002). Subsequent to this proposal, it was found that patients with Costello syndrome have a baseline increase in urinary catecholamines without the presence of neuroblastoma and therefore the recommendation for routine urinary catecholamine screening was rescinded (Gripp 2005).

In addition to the consensus recommendations by Villani et al, several single center cohort studies have led to additional surveillance considerations in these patients. These are not consensus recommendations and should therefore be utilized and considered on a case-by-case basis. In 2010, Ahmadi et al recommended nasal endoscopy and ear examination including tympanography every 4-6 months to screen for nasopharyngeal rhabdomyosarcoma (Ahmadi and Harley 2010). In 2022, Leoni et al reported that 10 of 13 asymptomatic patients were found by cystoscopy to have bladder lesions that were not identified by ultrasound or urinalysis, and therefore recommended that cystoscopy every 12-24 months be added as a routine screening in patients with Costello syndrome > 10 years old (Leoni, Paradiso et al. 2022). Given the invasiveness and unclear benefit of these procedures, additional studies are needed to determine if these screening methodologies will provide clinically meaningful improvement in outcomes for these patients.

Noonan Syndrome

Noonan syndrome, similar to other RASopathies, is characterized by multi-system involvement with characteristic cardiac defects and short stature (Roberts, Allanson et al. 2013). The estimated incidence of Noonan syndrome is around 1:2500 live births, however, it is thought that the incidence may be higher due to under- or unrecognized mild phenotypes. About half of all individuals with a diagnosis of Noonan syndrome have a

pathogenic or likely pathogenic variant in *PTPN11*, which leads to increased cancer risk, as discussed below.

Cancer Incidence

Studies evaluating cancer risk in Noonan syndrome are overwhelmingly derived from *PTPN11*-positive individuals, while cancer predisposition is less often reported in rarer Noonan-associated genes. For example, a recent Noonan syndrome study showed that individuals with a *PTPN11* variant have a high risk of malignancy (~10%), however this is likely an overestimate as about half of those individuals developed juvenile myelomonocytic leukemia (JMML)-like myeloproliferation and not frank JMML (Li, Yao et al. 2019). Importantly, specific variants have been associated with a higher risk of myeloproliferative disorders and JMML, notably variants at codon 61 or T73I in *PTPN11* and T58I in *KRAS* (Kratz, Niemeyer et al. 2005, Schubbert, Zenker et al. 2006, Strullu, Caye et al. 2014). However, this list is likely not exhaustive and, as more is learned about cancer risk and genetics of individuals with RASopathies, new associations with high-risk or low-risk features will likely be uncovered. Overall, when excluding patients diagnosed with Noonan syndrome because of a JMML-like myeloproliferative condition, childhood cancer risk in individuals with Noonan syndrome due to any pathogenic/likely pathogenic variant is roughly 8-fold increased when compared to the general population (Kratz, Franke et al. 2015). Notably, literature-reported cases of Noonan syndrome with cancer have been examined, with cancer incidence estimated at 4% by age 20 (Kratz, Rapisuwon et al. 2011). However, this may be an overestimate of true cancer risk as ascertainment bias is likely when evaluating clinical phenotypes reported rather than examining the entire population that carries a genetic diagnosis.

Dysregulation of the RAS/MAPK pathway is common in pediatric hematologic malignancies and is often associated with somatic or germline variants in the pathway (Tartaglia, Niemeyer et al. 2003, Bolouri, Farrar et al. 2018, Ma, Liu et al. 2018). Within the hematopoietic stem cell compartment, hyperactive RAS signaling leads to clonal expansion and hematopoietic progenitor survival, most often skewing towards a myeloid phenotype (Li, Bohin et al. 2013, Ney, Yang et al. 2021). Thus, the elevated risk for development of hematologic cancers and myeloproliferative neoplasms is plausible. In this vein, studies of infantile cancers over a 14-year period in France observed 50 individuals with JMML, of whom 10 were in individuals with Noonan syndrome (Desandes, Faure et al. 2020). Additionally, JMML-like myeloproliferation occurs in a high percentage of individuals with germline *PTPN11* variants and can be self-limited (Niemeyer 2014). However, a small percentage (~10%) of these individuals can progress to frank JMML and connects the increased risk of JMML to Noonan syndrome (Tartaglia, Niemeyer et al. 2003, Niemeyer 2014, Locatelli and Niemeyer 2015). Although spontaneous regression of JMML and JMML-like myeloproliferation in Noonan syndrome are common and the majority of myeloid disorders occur in pediatric patients with Noonan syndrome, adults with acute myeloid leukemia (AML) and germline variants in *PTPN11* have been reported (Yang, Long et al. 2022). Cancer risk in adults with Noonan syndrome remains largely unknown. Finally, while dysregulated RAS signaling within the hematopoietic system favors clonal expansion within the myeloid compartment, hyperdiploid acute lymphoblastic leukemia (ALL) has

been reported in 0.5% and 2% of patients with a germline pathogenic/likely pathogenic variant in *PTPN11* and *SOS1*, respectively (Cave, Caye et al. 2016)

While the highest risk of cancer in Noonan syndrome is for hematologic malignancies, cases of solid tumors have also been commonly described (Jongmans, van der Burgt et al. 2011, Kratz, Franke et al. 2015). Similar to Costello syndrome, cases of neuroblastoma and rhabdomyosarcoma have been reported in Noonan syndrome, typically in younger children (Jung, Bechthold et al. 2003, Li, Yao et al. 2019). An analysis of the German Childhood Cancer Registry showed an approximately 8-fold increased cancer risk in patients with Noonan syndrome, of which there were three Noonan children with a germline *PTPN11* variant and a solid tumor: one neuroblastoma, one pilocytic astrocytoma and one dysembryoplastic neuroepithelial tumour (Kratz, Franke et al. 2015) (Figure 1). Furthermore, multiple literature cases exist describing individuals with Noonan syndrome and solid tumors including rhabdomyosarcoma, brain tumors and neuroblastoma (Khan, McDowell et al. 1995, Lopez-Miranda, Westra et al. 1997, Jung, Bechthold et al. 2003, Sherman, Ali-Nazir et al. 2009, Hastings, Newbury-Ecob et al. 2010, Jongmans, Hoogerbrugge et al. 2010, Rankin, Short et al. 2013, Garavelli, Cordeddu et al. 2015, Harms, Alawi et al. 2018, Boonyawat, Charoenpitakchai et al. 2019, El-Ayadi, Ansari et al. 2019, Garren, Stephan et al. 2020). While these reports suggest a possible association, a definitive, quantitative analysis of solid tumor risk is still needed to understand its true incidence in Noonan syndrome.

Surveillance guidelines

The risk of hematologic disorders in Noonan syndrome is most notably increased in those patients with specific *PTPN11* (e.g., variants at codon 61 or T73I) and *KRAS* (e.g., T58I) variants (Kratz, Niemeyer et al. 2005, Schubbert, Zenker et al. 2006). Therefore, the most recent consensus by Villani et al recommends those patients with higher risk germline pathogenic variants undergo a physical exam (with assessment of spleen) and complete blood count (CBC) with a differential every 3–6 months until 5 years of age (Villani, Greer et al. 2017) (Table 2). Of note, although this group did not recommend specific surveillance for those with other germline variants causing Noonan syndrome (*e.g., SOS1, NRAS, RAF1, BRAF, SHOC2*), several other groups have recommended that these patients get a baseline CBC as part of their initial RASopathy evaluation and, if diagnosed in infancy, at least one additional CBC after one year of age. In addition, routine physical exams should include evaluation for hepatosplenomegaly and a low threshold for additional work-up, such as a bone marrow aspirate/biopsy if any abnormalities are found on CBC (Roberts, Allanson et al. 2013, Porter, Druley et al. 2017). As expected, recommendations are concentrated on the well-defined hematologic malignancy risk in Noonan syndrome, but strategies for solid tumor surveillance do not exist because of anecdotal and descriptive associations reported in the literature. Thus, screening individuals with Noonan syndrome for solid tumors relies on joint decision-making between the primary physician and families.

Noonan syndrome with multiple lentigines (NSML) and Noonan syndrome with loose anagen hair (NSLH)

Noonan-like spectrum disorders, NSML and NSLH, have overlapping features with classic Noonan syndrome such as cardiac anomalies but also distinctive characteristics (e.g., many lentigines in NSML and slow-growing hair in NSLH). NSML is a Noonan-like disorder due to pathogenic germline variants in *BRAF, MAP2K1*, *PTPN11*, and *RAF1* (Gelb and Tartaglia 1993) and can be mistaken for classic Noonan syndrome in childhood if lentigines are not present and molecular testing is unknown or not pursued (Sarkozy, Digilio et al. 2008). NSLH, also a rare Noonan-like spectrum disorder, is caused by pathogenic germline variants in *SHOC2* (most common) and *PPP1CB* (Cordeddu, Di Schiavi et al. 2009, Gripp, Aldinger et al. 2016).

Cancer incidence

The majority of cancers described in NSML and NSLH have been case reports and therefore specific estimates of cancer incidence are not well described. Rare hematologic malignancies, such as myelofibrosis and T-cell lymphoma, have been reported in NSLH (Gripp, Zand et al. 2013, Avery, Metcalf et al. 2022). Additionally, there have been cases of neuroblastoma in individuals with *SHOC2* variants (Garavelli, Cordeddu et al. 2015). In NSML, five cases of cancer were observed in 296 individuals with NSML in a literature review, estimating cancer incidence just above 1% (Kratz, Rapisuwon et al. 2011). Several cases of leukemia (ALL and AML) have been reported in NSML (Ucar, Calyskan et al. 2006, Laux, Kratz et al. 2008) Additional case reports in NSML include melanoma, which is perhaps not surprising given the skin lesions associated with NSML (Garcia-Gil, Alvarez-Salafranca et al. 2020). These reports suggest a possible association between Noonan-like syndromes and cancer, but the lack of epidemiologic data in these disorders remains problematic to conclusively define cancer risk and propose surveillance guidelines.

Road to discovery: *LZTR1* and *SPRED2* in Noonan Syndrome

With improving and evolving genetic sequencing efforts, new genes are being discovered as causative for RASopathies, including Noonan syndrome. *LZTR1* and *SPRED2* are two such examples (Johnston, van der Smagt et al. 2018, Motta, Fasano et al. 2021). *LZTR1*, most often associated with autosomal dominant schwannomatosis (Piotrowski, Xie et al. 2014), has been identified as causative for both autosomal dominant and autosomal recessive Noonan syndrome (Roberts, Adam et al. 1993, Johnston, van der Smagt et al. 2018). Given the known association with schwannomatosis risk, individuals with *LZTR1*-associated Noonan syndrome may also be at increased risk for cancer. Case reports in *LZTR1*-Noonan syndrome have described Grade II-III oligoastrocytoma and ALL (Johnston, van der Smagt et al. 2018, Jacquinet, Bonnard et al. 2020), however the relative novelty of this gene/syndrome association means there is uncertainty regarding cancer risk. In *SPRED2*-associated Noonan syndrome, first described in 2021, even less is known about clinical phenotype (Motta, Fasano et al. 2021). In functional laboratory studies, similar to *SPRED1*, *SPRED2* acts as a tumor suppressor gene (Kachroo, Valencia et al. 2013,

Jiang, Liu et al. 2016). Thus, one could postulate an increased cancer risk for individuals who carry a pathogenic/likely pathogenic germline variant. However, given the redundancy and nuances of the RAS pathway, prospective studies must be done to define true cancer incidence in these individuals.

CBL Syndrome

CBL syndrome, first described in 2010 as a disorder with similarities to Noonan syndrome, is due to germline pathogenic/likely pathogenic variants in *CBL*, a negative regulator of receptor tyrosine kinase activity (Niemeyer, Kang et al. 2010). Thus, CBL works upstream of the Ras protein to impact its downstream signaling cascades.

Cancer incidence

Individuals with germline variants in *CBL* are enriched in cohorts of JMML patients, suggesting there is an increased risk for JMML development (Niemeyer, Kang et al. 2010, Perez, Mechinaud et al. 2010). Importantly, loss of heterozygosity was often observed in individuals with *CBL* germline variants, suggesting it is directly involved in tumorigenesis (Locatelli and Niemeyer 2015) (Figure 1). Initially, and similar to individuals with *PTPN11* variants, germline *CBL* variants detected in JMML samples were believed to be associated with a less aggressive clinical course (Stieglitz, Mazor et al. 2017). However, recent data points to a more unpredictable course in *CBL*-associated JMML (Hecht, Meyer et al. 2022). Thus, given the recent description of CBL syndrome, additional data will be needed to fully ascertain cancer risks and genotype-phenotype correlations (Martinelli, Stellacci et al. 2015).

Even less clear than the role of CBL in hematologic malignancies is its role in solid tumors. Of children with pediatric rhabdomyosarcoma enrolled in Children's Oncology Group studies with a cancer predisposition syndrome (~7% of all cases), 4% harbored a pathogenic/likely pathogenic germline variant in *CBL*, suggesting there is an additional solid tumor risk (Li, Sisoudiya et al. 2021). Therefore, longitudinal studies and systematic retrospective reviews are needed to better define these solid tumor risks for patients with germline *CBL* variants (Ji, Navid et al. 2019, Kim, Light et al. 2021).

Surveillance guidelines

Patients with CBL syndrome have an increased risk of JMML/myelodysplastic syndrome (MDS) that is similar to patients with high-risk Noonan genotypes (such as variants at codon 61 or T73I in *PTPN11* or T58I in *KRAS*) (Roberts, Allanson et al. 2013). Therefore, similar screening guidelines are recommended, including physical exams (with assessment of spleen) and CBC with differential every 3–6 months until 5 years of age (Villani, Greer et al. 2017), when the risk for JMML is diminished (Table 2).

Cardiofaciocutaneous syndrome (CFC)

Cardiofaciocutaneous syndrome (CFC) is a rare condition, with the best estimates placing prevalence around 1:810,000 individuals in Japan (Abe, Aoki et al. 2012), although confirmatory national and international epidemiologic studies are lacking. CFC syndrome, like many of the other RASopathies, is characterized by distinct cardiac and facial

anomalies, neurocognitive/developmental disorders, and skin manifestations due to germline variants in *BRAF, MAP2K1, MAP2K2* and *KRAS* (Rauen, Adam et al. 1993).

Cancer incidence

Assessing true cancer risk in CFC syndrome is challenging due to the limited number of individuals reported with this condition (Table 1). Nonetheless, individual cases of ALL, non-Hodgkin lymphoma, B-cell lymphoma and hepatoblastoma have been reported in patients with CFC (Pierpont, Magoulas et al. 2014). A literature-based review identified eight cases of cancer among 226 individuals with CFC (3.5%) which was close to the estimated incidence of cancer in Noonan syndrome (Kratz, Rapisuwon et al. 2011). However, more recent retrospective oncology studies did not identify individuals with a concurrent diagnosis of CFC and cancer (Kratz, Franke et al. 2015), making it unclear if clinical (rather than genetic) diagnoses of CFC contributed to this discrepancy (Bisogno, Murgia et al. 1999). Additional support for non-elevated cancer risk in CFC come from ALL and rhabdomyosarcoma studies, where individuals with concurrent cancer and CFC diagnosis were not identified (Cave, Caye et al. 2016, Li, Sisoudiya et al. 2021). Although not malignant per se, pathogenic/likely pathogenic germline variants in *BRAF, MAP2K1, MAP2K2* are associated with a higher incidence of melanocytic nevi in CFC patients and could serve as an initiating event in melanoma tumorigenesis, although melanoma risk remains unknown (Kiuru, Urban et al. 2020).

Surveillance guidelines

A recent 2016 consensus conference of the American Association for Cancer Research recommended that screening guidelines should be established for syndromes when known cancer risk exceeds 5% in the first 20 years of life (Brodeur, Nichols et al. 2017). Thus, given the uncertainty of cancer incidence in CFC syndrome, tumor surveillance guidelines do not currently exist, and further longitudinal and genetic studies are needed to precisely define the genotype-cancer phenotypes.

Legius syndrome

Legius syndrome, a RASopathy with phenotypic overlap with neurofibromatosis type 1, is due to *SPRED1* variants (Legius, Messiaen et al. 2021). Pathogenic germline variants in *SPRED1* activate RAS/MAPK signaling through effects on neurofibromin (Yan, Markegard et al. 2020). However, despite the clinical similarities with NF1, individuals with Legius syndrome have a cancer incidence similar to the general population (Legius, Stevenson et al. 1993, Yan, Markegard et al. 2020) and thus diverges from NF1 in this very important phenotype. Hence, tumor surveillance is not recommended at this time.

Future of Screening and Surveillance in RASopathies

Early tumor detection is key to improved outcomes. In RASopathies, there are multiple potential avenues to achieve this goal. Annual whole-body MRI screening has been effective in Li-Fraumeni syndrome but remains unstudied in the RASopathies (Ballinger, Best et al. 2017). Improvements in clinical phenotyping and pre-natal screening may permit earlier

RASopathy testing and thus identification of these patients and better surveillance starting at birth (Sinajon, Chitayat et al. 2020). Assay of circulating tumor DNA to perform “liquid biopsies” from blood samples as a screening or surveillance tool for cancers may soon be a reality (Sundby, Pan et al. 2022). For example, in NF1, circulating tumor DNA can distinguish between the malignant and benign peripheral nerve sheath tumors that can develop (Szymanski, Sundby et al. 2021, Mattox, Douville et al. 2022). If similar results could be achieved in other RASopathies, it could address ongoing concerns about limited availability of advanced imaging modalities and, in some cases, radiation associated with CT and/or radiograph. Though additional validation is needed, and evaluation of its broad clinical use is unknown, there may be significant promise in this type of technology.

Knowledge of cancer incidence and best practices for cancer surveillance in RASopathy patients remains relatively limited. Thus, prospective natural history studies are needed to help further quantify cancer incidence in these conditions. These studies will provide the longitudinal data needed to understand acute and long-term cancer risk and help inform surveillance guidelines and improve outcomes in the future.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and the Center for Cancer Research of the National Cancer Institute, Bethesda, MD. CPK has been supported by the German Childhood Cancer Foundation (DKS 2021.02).

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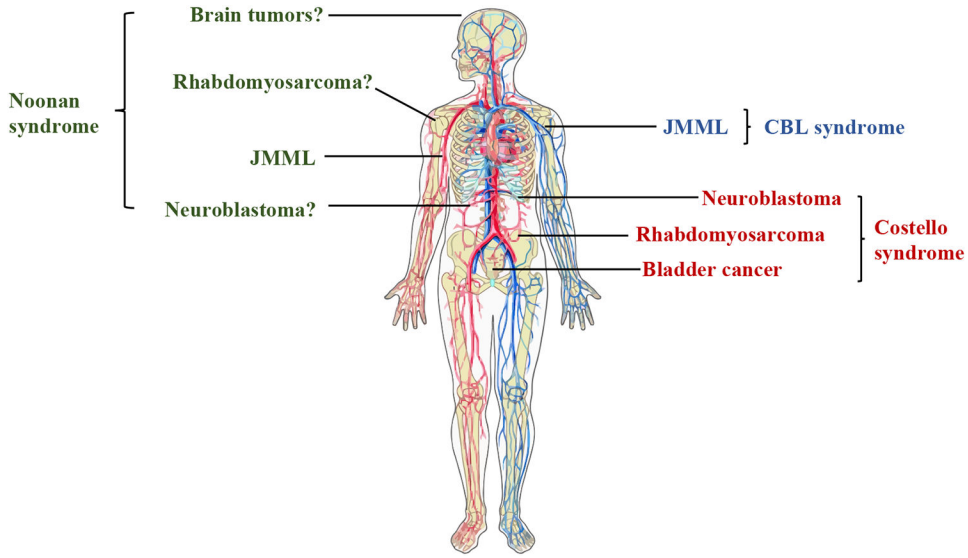

Figure 1:

Common cancer associations across the RASopathies. JMML: Juvenile myelomonocytic leukemia. Blue= CBL syndrome; Green= Noonan syndrome; Red= Costello syndrome. Image created with ChemDraw.

Table 1:

Incidence of Specific Cancer Types in RASopathies. ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; JMML: Juvenile myelomonocytic leukemia

RASopathy	Most Common Cancer Type(s)	Approximate Incidence
Costello syndrome (*HRAS*)	General	~40-fold increase over general population
	Bladder cancer	~1.5%
	Neuroblastoma	~2%
	Rhabdomyosarcoma	~7%
Noonan syndrome (*PTPN11; e.g.,***codon 61 or T73I**), (*KRAS; e.g.,* T58I)	JMML, rhabdomyosarcoma, ALL, neuroblastoma, brain tumors	~8-fold increase over general population
Noonan syndrome (*SOS1, RAF1, RIT1, SOS2, RRAS, LZTR1, BRAF*)	Case reports of ALL, neuroblastoma, rhabdomyosarcoma	Unclear risk
Noonan syndrome with multiple lentigines (*PTPN11, RAF1, BRAF, MAP2K1*)	Case reports of AML, ALL, neuroblastoma, melanoma	Possibly mildly elevated, although unclear how much so
Noonan syndrome with loose anagen hair (*PPPC1B, SHOC2*)	Case reports of neuroblastoma, myelofibrosis, t cell lymphoma	Possibly mildly elevated, although unclear how much so
CBL syndrome*(CBL)*	JMML	Elevated, but unclear how much so
Cardiofaciocutaneous syndrome (*BRAF, MAP2K1, MAP2K2, KRAS*)	Case reports of rhabdomyosarcoma, ALL, lymphoma	Possibly mildly elevated, although unclear how much so
Legius syndrome (*SPRED1*)	Case reports of pediatric leukemias	Not believed to be elevated

Table 2:

Summary of Published Surveillance Guidelines in RASopathies

RASopathy	Cancer Surveillance Recommendations	Source	Source Details
Costello syndrome (*HRAS*)	0 to 8–10 yrs: Physical exam and abdominal ultrasound +/− Chest radiograph every 3–4 months Age 10+: Annual urinalysis	(Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
	0 to 8–10 yrs: Physical examination plus abdominal and pelvic ultrasounds are suggested every 3 months Age 10+: Annual urinalysis	(Gripp, Morse et al. 2019)	Expert opinion[B]
	Nasal endoscopy and ear examination including tympanography every 4-6 months	(Ahmadi and Harley 2010)	Expert opinion[B]
	Age 10+: Cystoscopy every 12-24 months	(Leoni, Paradiso et al. 2022)	Expert opinion[B]
Cardiofaciocutaneous syndrome (*BRAF, MAP2K1, MAP2K2, KRAS*)	No routine surveillance*	(Rauen, Adam et al. 1993, Pierpont, Magoulas et al. 2014, Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research) & Expert opinions
Noonan syndrome with specific high-risk mutations (*PTPN11; e.g., codon 61 or T73I),* (*KRAS; e.g.,* T58I)	0 to 5 years: Physical exam (with assessment of spleen) and CBC with differential every 3–6 months	(Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
	CBC with differential at baseline evaluation and then as clinically indicated; physical exam with evaluation for hepatosplenomegaly	(Porter, Druley et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
Noonan syndrome; no high risk variant (*SOS1, RAF1, RIT1, SOS2, RRAS, LZTR1, BRAF,* non high-risk *PTPN11, KRAS*)	No routine surveillance*	(Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
	CBC with differential at diagnosis and after 6–12 months of age if initial screen performed in infancy	(Romano, Allanson et al. 2010)	Interdisciplinary Expert Panel[A] (Noonan Syndrome Support Group)
	CBC with differential at diagnosis and repeat at least once after >1 year old, then as clinically indicated; physical exam with evaluation for hepatosplenomegaly	(Roberts, Allanson et al. 2013)	Expert opinion[B]
CBL syndrome*(CBL)*	0 to 5 years: Physical exam (with assessment of spleen) and CBC with differential every 3–6 months	(Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
	CBC with differential at baseline evaluation and then as clinically indicated; physical exam with evaluation for hepatosplenomegaly	(Porter, Druley et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)
	CBC with differential at baseline evaluation and at least once after > 1 year old, then as clinically indicated; physical exam with evaluation for hepatosplenomegaly	(Roberts, Allanson et al. 2013)	Expert opinion[B]
Noonan syndrome with multiple lentigines (*PTPN11, RAF1, BRAF, MAP2K1*)	No routine surveillance*	(Villani, Greer et al. 2017)	Consensus Recommendations[A] (American Association for Cancer Research)

RASopathy	Cancer Surveillance Recommendations	Source	Source Details
Noonan syndrome with loose anagen hair (*PPPC1B, SHOC2*)	No routine surveillance *	(Villani, Greer et al. 2017)	Consensus Recommendations A (American Association for Cancer Research)
Legius Syndrome	No routine surveillance *	(Villani, Greer et al. 2017)	Consensus Recommendations A (American Association for Cancer Research)

* For patients with these conditions, there should still be increased awareness and low threshold for investigating new potential tumor-related symptoms (Villani, Greer et al. 2017).

A Consensus recommendations are defined as widely accepted guidelines from disease-specific experts in the field.

B Expert opinion is defined as a recommendation based on individual subspecialist or single institution study. These opinions are not widely accepted in the RASopathy community but are included in this review for completeness.