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Retinoblastoma and Neuroblastoma Predisposition and Surveillance

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Abstract

Retinoblastoma (RB) is the most common intraocular malignancy in childhood. Approximately 40% of retinoblastomas are hereditary and due to germline mutations in the *RB1* gene. Children with hereditary RB are also at risk for developing a midline intracranial tumor, most commonly pineoblastoma. We recommend intensive ocular screening for patients with germline *RB1* mutations for retinoblastoma as well as neuroimaging for pineoblastoma surveillance. There is an approximately 20% risk of developing second primary cancers among individuals with hereditary RB, higher among those who received radiotherapy for their primary RB tumors. However, there is not yet a clear consensus on what, if any, screening protocol would be most appropriate and effective. Neuroblastoma (NB), an embryonal tumor of the sympathetic nervous system, accounts for 15% of pediatric cancer deaths. Prior studies suggest that about 2% of patients with NB have an underlying genetic predisposition that may have contributed to the development of NB. Germline mutations in *ALK* and *PHOX2B* account for most familial NB cases. However, other cancer predisposition syndromes, such as Li–Fraumeni syndrome, RASopathies, and others, may be associated with an increased risk for NB. No established protocols for NB surveillance currently exist. Here, we describe consensus recommendations on hereditary RB and NB from the AACR Childhood Cancer Predisposition Workshop.

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Introduction

In October 2016, the American Association of Cancer Research (AACR) sponsored the AACR Childhood Cancer Predisposition Workshop. A group of international experts from the fields of pediatric oncology, genetics, genetic counseling, radiology, and other affiliated fields convened to discuss and to propose consensus recommendations for surveillance in cancer predisposition syndromes that affect children [see *CCR* Pediatric Oncology Series article by Brodeur and colleagues (1)]. Although retinoblastoma (RB) and neuroblastoma (NB) are both embryonal tumors, the evidence for and approaches to screening differ significantly. Herein, we present a literature review and consensus recommendations resulting from the AACR-sponsored workshop, with a focus on genes predisposing to these cancers and the surveillance recommendations from this expert panel.

Hereditary RB: Introduction

RB is the most common intraocular malignancy in childhood. It is a rare pediatric cancer with an age-adjusted incidence rate of about three to five per million children in the United States and Europe, although considerable geographic variation has been reported (2, 3). It is a disease of young children, with almost two thirds of cases diagnosed before the age of 2 years, and 95% diagnosed by age 5 (2). RB typically occurs in two forms: hereditary and nonhereditary (sporadic). In hereditary cases, a germline mutation in the *RB1* gene predisposes to the development of RB, requiring only one additional somatic hit in the remaining *RB1* allele for tumor formation, whereas two independent somatic mutations or epigenetic silencing through methylation is required in nonhereditary cases. About1%of RB (usually unilateral) is due to somatic *MYCN* amplification rather than loss of *RB1* function (4). Another study demonstrated three RBs with focal chromothripsis in the tumor tissue disrupting the *RB1* locus, suggesting that somatic acquisition of these complex structural rearrangements can play a role in *RB1* tumor-suppressor inactivation (5).

About 40% of RBs are hereditary, about 80% of which arise from *de novo* germline mutations in the absence of a known family history (6). The majority of hereditary cases have bilateral or multifocal ocular involvement, but about 10% to 15% of children with unilateral, unifocal RB also have hereditary disease (7). Bilateral RB typically presents earlier than unilateral RB, with a median age of diagnosis of approximately 10 months compared with 24 months, respectively (8, 9).

Children with hereditary RB are also at risk for developing a midline intracranial primitive neuroectodermal tumor (PNET), in addition to unilateral or bilateral RB (trilateral RB). These are most commonly pineoblastomas, but tumors of the suprasellar or parasellar regions may also occur (10, 11). More than 95% of these tumors are diagnosed by 5 years of age (12, 13). Among asymptomatic pineal trilateral RB cases found by neuroimaging, 60% are diagnosed within 1 year from the intraocular RB diagnosis (11). Although previous estimates were higher, a more recent meta-analysis found a 5.3% chance of developing trilateral RB among individuals with bilateral disease, or a 4.1% chance with the inclusion of presumed hereditary unilateral cases (12). Previous external beam radiation therapy (EBRT) is thought to contribute to this risk, and others have cited a decrease in incidence to as low as

<2% when radiotherapy is no longer used for intraocular disease (14). It is possible that further reduction in risk may be attributable to the use of systemic chemotherapy for intraocular disease, although this remains controversial (14–16).

In developed countries where early detection and multimodality therapy are readily available, >95% of patients survive intraocular RB (17). However, individuals with hereditary RB continue to have a higher risk of developing a second primary tumor, some of which may arise as a result of treatment (18). Individuals are especially at risk for developing osteosarcomas and soft-tissue sarcomas, as well as tumors of the nasal cavities, eye, and orbit (19–21). Increased risks of skin cancers, especially melanomas, as well as brain tumors have also been described (19, 21). The median age of a second primary tumor is between 15 and 17 years old (20, 22). However, increased risks of adult tumors such as epithelial cancers of the lung, bladder, and breast as well as uterine sarcomas have also been described (23, 24).

Prospective follow-up of a large cohort of patients with hereditary RB demonstrated that the cumulative probability of developing a second cancer was 38% by age 50 among patients who received radiation (90% received EBRT, whereas 1% received brachytherapy and 9% received both) compared with 21% among nonirradiated patients (19). A recent study demonstrated an increased risk of second cancers in the setting of EBRT plus chemotherapy (40-year cumulative incidence of 54.2% vs. 37.1% with EBRT alone; ref. 25). In contrast, brachytherapy did not change the incidence ratio of second cancers compared with enucleation or other focal treatments alone. Early data from patients treated with proton radiotherapy suggest a lower risk of second malignancies compared with conventional photon radiotherapy, with a 10-year cumulative incidence of second cancers in the radiation field of 0% versus 14%in the proton versus photon groups ($P = 0.015$). Although these data are encouraging, longer follow-up is needed (26). Another study demonstrated increased risk of bone tumors and leiomyosarcoma for those treated with alkylating agent chemotherapy plus radiotherapy (including ERBT and brachytherapy) versus radiotherapy alone (27). Together, these studies demonstrate the importance of surveillance for second primary tumors among patients with hereditary RB, and the need to better understand the relationship of specific therapies and clinical risk factors associated with these malignancies.

Hereditary RB: The *RB1* Gene and Genotype–Phenotype Correlations

Knudson analyzed the age of onset of tumor formation in hereditary versus nonhereditary cases of RB in 1971, and this led to the "two-hit hypothesis," providing a description of one of the most fundamental mechanisms of tumorigenesis (7). In 1986, the RB gene *RB1* was identified, and somatic inactivation of both *RB1* alleles appeared to be necessary and sufficient for the development of RB (28, 29). The protein product of *RB1*, pRB, is a nuclear phosphoprotein belonging to the family of pocket proteins, with roles in growth, differentiation, and apoptosis. pRB features prominently in cell-cycle control, preventing progression through the G_1 phase of the cell cycle via its interactions with the family of E2F transcription factors (30).

Hereditary RB is inherited in an autosomal dominant fashion, with *de novo* mutations in the child with RB as the most common presentation. The majority of germline mutations lead to 90% to 95% penetrance, and germline carriers usually develop bilateral or multifocal tumors (6). Nonsense and frameshift mutations in exons 2 to 25 almost always lead to highly penetrant bilateral RB, and they are the most frequent types of mutations found among familial cases (31–33). The high penetrance is likely due to posttranscriptional nonsense-mediated decay, leading to degradation of truncated mRNA transcripts (32). Lower penetrant mutations with variable expressivity have also been described. These include missense and promoter mutations, as well as some splice site mutations, in particular those at less well-conserved residues (32, 33). Intra- and interfamily variation in phenotypic expressivity suggests there may be other modifying factors (32, 33). In a large retrospective cohort of RB survivors, individuals with lower penetrance mutations were also found to have a lower risk of second primary malignancies (34).

A small subset of individuals with RB have a full gene deletion due to germline 13q deletions. Although data are limited, the outcome of RB appears to be the same, and pineoblastoma has also been reported in this context (35, 36). Individuals with these cytogenetic deletions may have dysmorphic facial features (most commonly anteverted ears, broad forehead, long philtrum) as well as varying levels of neurologic impairment, but the extent and severity of the abnormalities are likely due to the additional gene(s) encompassed by the germline deletion (35, 37). In addition, germline mosaicism for *RB1* mutations has been estimated to occur in approximately 6% of unilateral cases (38). These patients are at risk not only for RB but also in transmitting this predisposition to offspring. Testing by next-generation sequencing will likely increase the rate of detection of germline mosaicism (31, 38–40).

Hereditary RB: Recommended RB Surveillance Protocol

Expert consensus recommendations

The following recommendations for tumor surveillance of *RB1* mutation carriers are based upon review of the literature, discussion with ocular oncologists, and consensus from the expert panel at the AACR Childhood Cancer Predisposition Workshop. In development of these recommendations, the committee considered available evidence, median age of onset of tumors/second primary cancers, potential benefits of early detection, and risks of surveillance modalities.

Genetic counseling and testing

Genetic counseling plays a critical role in the care of RB patients (41). Genetic testing provides families with recurrence risk information and allows guidance for appropriate screening recommendations of patients and siblings. Furthermore, education regarding the age-related risks of developing second primary cancers can be pursued along with discussion regarding potential surveillance programs. Counseling should also be revisited among adult RB survivors when they reach childbearing age given the very young age at which tumors are diagnosed.

Intraocular screening for carriers of pathogenic *RB1* mutations

Given the high risk of tumor development among carriers of pathogenic *RB1* mutations and the positive impact that early detection may have for better visual outcomes, early and intensive intraocular screening is recommended. Abramson and colleagues demonstrated significantly better ocular preservation among individuals with positive family history who underwent intensive surveillance from birth compared with those who did not receive screening (67.7% vs. 38.2% at 5 years; $P < 0.001$; ref. 42). In one Dutch cohort, early diagnosis and intensive screening led to almost 90% of patients with a visual acuity of 20/20 to 20/40 (43). The importance of early detection is especially important among younger infants, as the earliest RB develops at or near the fovea or macula with more significant consequences on central vision, whereas tumors diagnosed later tend to form in the periphery.

For specific intraocular screening, institutional practices as well as previously published recommendations from France, the Netherlands, New York, and Canada for individuals with known *RB1* mutations were reviewed and considered (43–47). Overall, the approaches to RB screening were very similar among these different programs. Common themes emerging from these recommendations include an ophthalmic exam at or within 1 to 2 weeks of birth, usually without anesthesia, then frequent eye exams every 2 to 4 weeks until at least 3 months of age, often without anesthesia. A retrospective review demonstrating tumor detection as early as 2 weeks after an initial negative exam supports this early frequency (47). Thereafter, most of these recommendations begin exams under anesthesia (EUA) around 3 months, progressively spacing out exams thereafter. The end point of EUA screening varies but typically continues until about 5 years of age, although some have reported that screening beyond the age of 4 may not be necessary (48).

As screening for primary ocular tumors is generally performed by ophthalmologists or ocular oncologists, the expert panel, in consultation with representatives from these groups, presents here intraocular screening guidelines based on the forthcoming consensus recommendations for ophthalmic surveillance from the American Association of Ophthalmic Oncologists and Pathologists (Table 1; A.H. Skalet; personal communication). In concert with previously published guidelines, these recommendations begin with intensive surveillance from birth with progressively spaced EUAs until age 5, although more frequent surveillance may be appropriate in individual cases. Of note, these guidelines are meant for *RB1* mutation carriers who have not yet developed RB. Subsequent schedules will depend on findings and ongoing treatment at the discretion of the treating provider.

Dilated eye exams are generally performed as EUAs, although some practitioners perform nonsedated exams when the child is able to remain still for full visualization of the retina. This has become especially relevant in light of the December 2016 FDA drug safety communication warning that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years … may affect the development of children's brains" (49). Although early studies in children suggest an association between repeated or prolonged exposure to anesthesia and subsequent learning disabilities, the underlying indications for surgery/anesthesia may also lead to potential confounders, and further studies are underway (50, 51). As these data continue to emerge,

future guidelines may affect the frequency of EUAs among children with RB, and the recommendations as included here may evolve. For now, we continue to encourage the use of non-sedated exams when the child is able to cooperate, balancing the potential long-term risks of anesthesia with needed sensitivity for early tumor detection.

Prenatal detection of RB

The uses of maternal ultrasound (US) and fetal MRI have both been described for prenatal detection of RB in at-risk infants (52, 53). Indeed, some groups may recommend earlyterm delivery to minimize loss of central vision, as small lesions may not be detectable using current prenatal imaging (54, 55). However, upon review of these data and current practices, the expert panel concluded that more data are needed to better understand the risks and benefits of early delivery for vision sparing. The early age of tumor formation also highlights the importance of genetic counseling for adult RB survivors who are of childbearing age, so that an appropriate plan for testing and ophthalmic surveillance can be rapidly implemented. For fetuses that are at 50% risk of developing hereditary RB, or who are known to carry a germline *RB1* mutation, some centers recommend prenatal surveillance with US and/or MRI at 34- to 38-week gestation. If a tumor is detected, early-term delivery may be considered after multidisciplinary discussion to determine the best timing to balance the potential benefits of increased central visual sparing while minimizing risks of early delivery. If a tumor is not detected prenatally, or if prenatal surveillance is not pursued, the first ophthalmologic exam should be performed within 24 hours after birth, as current prenatal imaging modalities may not detect the smallest tumors.

Screening for trilateral RB in hereditary RB

Small pineoblastoma tumors are associated with better prognosis, suggesting a role for early detection (13). Recommendations have ranged from a single MRI at diagnosis of RB to every-6-month screening until age 5 (45, 56, 57). As above, there is a less than 2% to 5% risk of pineoblastoma among individuals with hereditary RB, although this risk may be further reduced by the use of systemic chemotherapy (12, 14–16). Therefore, we recommend a brain MRI at the time of diagnosis of RB. However, there was debate among the panel regarding whether or how often to perform repeat brain MRI. The practice among groups in the United States is to perform periodic brain MRIs every 6 months until 5 years of age (Table 1), whereas the practice among other groups in Europe is not to perform surveillance MRIs after the one at diagnosis unless the patient received previous EBRT. This remains an area of ongoing investigation.

Second malignant neoplasms among *RB1* mutation carriers

The risk of second malignant neoplasms is about 20% in individuals with hereditary RB who have not received radiotherapy and substantially higher (40%–50%) in those that have been irradiated (19, 25). We, therefore, recommend consideration of second primary tumor surveillance for all carriers of pathogenic *RB1* germline mutations regardless of previous radiation. No established screening protocols exist for early detection of second primary tumors in hereditary RB, but this remains an area of great interest. The wide range of tumors across a broad age range contributes to the complexity of designing such a protocol. As above, the median age of second primary tumor ranges from 15 to 17 years, warranting

screening beginning in childhood (20, 22). In one study of 488 survivors with known pathogenic *RB1* germline mutations, the cumulative incidence of second primary malignancy was 5.2% [95% confidence interval (CI), 1.7–8.7] at age 10 years, with a standardized incidence ratio (SIR) of 147 for sarcoma (95% CI, 39.8–378.9) and an SIR of 41 for leukemia (95% CI, 11.1–106; ref. 58).

Melanomas have been reported both within and outside the field of radiotherapy, and among both irradiated and nonirradiated patients (19, 23). In one meta-analysis, the median age was reported at 27 years (range, 9.2–37 years; ref. 59). Among a cohort of 816 RB survivors, most of whom received EBRT, tumors affecting the skin of the face and neck (presumably within the radiation field) occurred at a median age of 23 years (range, 6–43 years), whereas those below the neck occurred at an older age (median, 28 years; range, 16–50 years; ref. 60). Data from the Dutch RB registry demonstrated an SIR of 77.9 in the 20- to 29-year-old age range (95% CI, 25.3–181; ref. 23). We recommend that pediatricians are informed about risks of second primary skin cancers in hereditary RB and perform skin exams during routine well child visits. These should be continued on an annual basis from age 18, either by the primary care physician or by a dermatologist as the child enters adulthood and approaches the median age of onset for melanoma in hereditary RB.

Given the increased risks for bone and soft-tissue sarcomas, we recommend an annual physical exam, potentially through a long-term survivor clinic, as well as education about signs and symptoms. Some also recommend considering whole-body MRI (WBMRI) annually, which (if done) the expert panel felt would be most appropriate after age 8 to 10, when the child is able to tolerate the study without the risks of general anesthesia. This should be performed in the context of a prospective study when feasible, as further data are needed to understand the value of this modality in surveillance among RB survivors. The feasibility of WBMRI for this population was demonstrated by a small retrospective pilot study (61). The most effective screening strategy for second primary malignancies in RB survivors remains an area of active research.

Hereditary RB: Conclusions and Future Directions

Treatment of RB has led to a >95% long-term survival of intraocular disease where multimodality therapies are readily available. Therefore, current work focuses on the early detection of tumors, allowing clinical treatment choices that promote vision sparing, minimize toxicity, and reduce second tumor risk. Genetic testing and counseling are integral components to the care of RB patients and their families, and they can provide information on recurrence risk, the importance of early testing and detection, and screening recommendations for patients and other family members. However, for individuals with *RB1* germline mutations, intraocular RB is just the beginning, and a high risk of second primary malignancies ensues over the lifetime of the individual. The need to understand the best modalities and timing of surveillance for these subsequent malignancies remains great. Further understanding of risk modifiers, advances in imaging, and international collaborative efforts to define best surveillance practices will inevitably shape the future care of individuals with hereditary RB.

Hereditary NB: Introduction

NB, an embryonal tumor of the sympathetic nervous system, accounts for 15% of pediatric cancer deaths (62). At least 1% to 2% of individuals with NB exhibit features suggestive of a hereditary predisposition, such as a family history of NB, bilateral/multifocal primary tumors, and earlier median age of diagnosis (NB susceptibility, OMIM #613014). On the basis of early studies of large kindreds with multiple cases of NB, Knudson and Strong predicted that hereditary predisposition to NB would follow an autosomal dominant pattern of inheritance with a penetrance of about 63% (63). Notably, they postulated that NB, like RB, would follow a two-hit model explaining hereditary and sporadic cases. Pedigrees show considerable heterogeneity in the type of neuroblastic tumors that arise in families with NB, because benign ganglioneuromas (GN) and malignant NBs have been reported in the same families, and some families show incomplete penetrance (64, 65). However, because of the lethality of NB before reproductive age, previous genetic linkage studies were underpowered, and results have been difficult to replicate (66–68).

In most cases of hereditary NB, no specific clinical features characterize individuals with predisposition. However, a small proportion of patients with NB have a clinically recognizable genetic syndrome that has been associated with NB. In general, these are characterized as disorders of neural crest development and include congenital central hypoventilation syndrome (CCHS), aganglionosis of the colon (Hirschsprung disease), ROHHAD syndrome (rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysfunction), RASopathies such as Costello syndrome, Noonan syndrome, neurofibromatosis type 1, and epigenetic syndromes such as Beckwith–Wiedemann syndrome (BWS, including hemihypertrophy, or 11p overgrowth). Finally, NBs have been seen in patients with germline mutations in other cancer predisposition syndromes, such as Li–Fraumeni syndrome (LFS), hereditary pheochromocytoma/paraganglioma syndrome, and others. The expert committee participating in the AACR Childhood Cancer Predisposition Workshop reviewed the literature on the genetics of NB predisposition and reached a consensus on recommended guidelines for NB surveillance in predisposed individuals.

Hereditary NB: Genes Responsible for NB Predisposition

Activating mutations in the *ALK* gene

The gene(s) responsible for hereditary NB remained elusive for a long time. However, in 2008, SNP-based linkage studies were undertaken that led to the identification of activating mutations in the Anaplastic Lymphoma Kinase (*ALK*) receptor tyrosine kinase as the major familial NB gene (69–72). Germline mutations in *ALK* encode for single-base substitutions in key regions of the kinase domain that result in constitutive activation of the kinase, with the R1275Q mutation most frequently observed (Table 2). These families demonstrated incomplete penetrance of developing NB, possibly due to the lack of acquisition of a second genetic event, or to spontaneous regression following malignant transformation. The overall penetrance of germline *ALK* mutations was estimated at about 50% across these families, although this estimate is based upon a relatively small number of families overall (69–74). Patients with germline *ALK* mutations do not appear to develop NB earlier than the general population. *ALK* is also commonly activated by somatic mutation or amplification in 8% to

10% of sporadic NBs without a germline mutation, which further supports the biological importance of *ALK* in NB pathogenesis (69–72).

Inactivating mutations in *PHOX2B*

NB can occur in association with disorders related to neural crest development, including CCHS and Hirschsprung disease (OMIM #603851; refs. 75–78). These clinical observations suggested that a gene or genes implicated in the genesis of Hirschsprung disease or CCHS may confer a predisposition to develop NB (79, 80). *PHOX2B* is a homeobox gene that is a master regulator of autonomic nervous system development. A very strong genotype–phenotype association exists between the type of *PHOX2B* variant and the clinical presentation of the child. The majority of *PHOX2B* mutations in CCHS insert 5 to 13 alanines in the 20 polyalanine repeat domain, and larger polyalanine expansions are associated with worse hypoventilation and with NB or related tumors, including maturing ganglioneuroblastomas (GNB) and GNs. Missense, frameshift, or truncating mutations in *PHOX2B* (nonpolyalanine repeat mutations, or NPARM) predispose a small subset of these patients to develop NB or related tumors (refs. 79–85; Table 2). The risk for a neural crest tumor for individuals with NPARMs is about 45%, whereas the risk for individuals with PARMs is about 1% to 2%, and essentially all of those with tumors had large PARMs (30–33 repeats; ref. 84). Larger PARMs would be detected by whole-exome sequencing, but may not be detected by gene panels. Although *PHOX2B* mutations are most often associated with CCHS and/or Hirschsprung disease, germline *PHOX2B* mutations have also been observed in some patients with NB in the absence of CCHS and/or Hirschsprung disease (86).

A rare syndrome, ROHHAD, has overlapping features with CCHS and has also been associated with the development of neuroblastic tumors, such as GNB or GN (87, 88). The absence of *PHOX2B* mutations in individuals with ROHHAD, despite its clinical similarity to CCHS, suggests that other genes or regulatory sequences may be associated with autonomic function and NB pathogenesis (89).

RASopathies

In addition to *ALK* and *PHOX2B*, NB has been reported in individuals with germline mutations in genes involved in the RAS pathway (RASopathies). This includes Costello syndrome (*HRAS* gene), Noonan syndrome (*PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, MEK1*, and *RIT1* genes), neurofibromatosis type 1 (NF1), and others (90–96). Indeed, homozygous inactivation of the *NF1* gene has been described in primary NBs (97, 98), although the overall prevalence of *NF1* mutations in NBs is very low. Given the relative prevalence of NF1 and NB, the reported cases with both diagnoses may be attributed to fortuitous coincidence, so risks for NB may not be increased sufficiently in individuals with NF1 to warrant surveillance (99). However, the frequency of NB may be sufficiently high in individuals with Costello syndrome and perhaps some forms of Noonan syndrome to warrant surveillance. It should be noted that patients with Costello syndrome may have elevated urinary catecholamine metabolites without a catecholamine-secreting tumor, which is relevant for the recommended NB surveillance protocol (see below; ref. 92).

LFS and other cancer predisposition syndromes

Several cases of NB have been reported in patients with LFS and germline mutations of *TP53*, especially the R337H mutation (refs. 100–102; Table 2), although NB is not generally considered a classic LFS tumor. In addition, patients with BWS due to mutations in *CDKN1C* have a 2% to 5% risk of developing NB (103, 104), which is sufficiently high to warrant NB screening in these patients. Furthermore, several large studies looking broadly at somatic and germline mutations in children with cancer identified germline mutations in several other genes, including *SDHB, APC, BRCA1*, and *BRCA2*, in children with NB (105–107). At present, the prevalence of NB in children harboring germline mutations in these other genes is unclear, but emerging data on individual genetic associations may result in consideration of NB screening among these populations in the future. Finally, *GALNT14* gene mutations have been associated with NB predisposition in three individuals from two families (108). Aberrant function of galactosaminyltransferases has been associated with tumor aggressiveness in various cancers, suggesting that *GALNT14* may be involved in NB predisposition or pathogenesis.

In summary, mutations in *ALK* and *PHOX2B* account for the majority of familial NB, and some additional cases may be associated with germline mutations in RAS pathway and other known cancer predisposition genes (e.g., *TP53* and *CDKN1C*). Nevertheless, the hereditary basis and molecular pathogenesis of NB are incompletely understood, and the causal gene in a small subset of families with NB (~15%) remains unknown. Although the monogenic basis of *ALK* and *PHOX2B* hereditary NB is driven by highly penetrant mutations in single genes, these mutations act in the context of a haplotypic background, and the key modifiers of phenotype and penetrance have not been defined (73). Genetic testing for mutations in genes known to be associated with NB predisposition should be considered in any individual diagnosed with NB who has a family history of NB, features suggesting predisposition such as bilateral or multifocal primary tumors, or clinical features associated with these other predisposition genes. For individuals with NB who have either a strong family history of NB among first-degree relatives, or clear bilateral, multifocal, or metachronous primary NB, we also recommend NB surveillance even in the absence of an identifiable germline mutation.

Hereditary NB: Recommended NB Surveillance Protocol

Individuals with highly penetrant, heritable *ALK* or *PHOX2B* (NPARM) mutations have a significant risk (45%–50%) to develop one or more tumors, especially in infancy and childhood. In addition, we recommend NB surveillance for individuals with the following disorders: (i) LFS and germline *TP53*-R337H mutations; (ii) BWS with germline *CDKN1C* mutations; (iii) Costello syndrome with *HRAS* mutations; and (iv) those with NB and a strong family history of NB, or clearly bilateral/multifocal NB. The age at diagnosis does not appear to be different in these syndromes, although the data addressing this issue are limited. NBs can be present at birth, so screening should be started as soon as a germline predisposition mutation is identified. The median age at diagnosis for NBs that present clinically is approximately 20 months based on a series of 3,666 cases reported by the Children's Oncology Group (109). In this cohort, 80% were diagnosed by age 6 and 98%

were diagnosed by 10 years of age. Therefore, we recommend screening more frequently up to age 6 years, less frequently from ages 6 to 10, and then stop.

No surveillance protocol for individuals with NB predisposition has been proposed for early detection of tumors, which would likely improve their prognosis. In Japan, North America, and Europe, mass NB screening of normal infants by measuring urinary catecholamine metabolites (110–113) was shown to be effective for detecting NBs before they produced clinical symptoms. This resulted in a dramatically increased incidence of NB in the screened population, without an expected decrease in NBs in patients over 1 year of age. This suggested that mass screening is not appropriate for infants at average risk. However, this is a simple technique that can be used to detect tumors early and should be useful in the high-risk population of children with hereditary NB. The majority of NBs arise in the abdomen, especially the adrenal glands, so diagnostic imaging using US should be an effective approach for early detection of tumors before they cause clinical symptoms, especially for nonsecreting tumors. However, about 20% of primary NBs arise in the chest, so a simple screening test of the chest is warranted.

A surveillance protocol for patients with LFS and germline *TP53* mutations resulted in a substantially improved outcome compared with patients with clinically detected tumors, demonstrating the value of cancer surveillance (114, 115). However, no such protocol exists for individuals with NB predisposition. Therefore, we recommend that the following testing be done for individuals who are genetically at increased risk to develop NB, as described above: (i) an abdominal US; (ii) quantitative, normalized assessment of urinary catecholamine metabolites [such as vanillylmandelic acid (VMA) and homovanillic acid (HVA)] by gas chromatography and mass spectroscopy (GC-MS); and (iii) a chest radiograph as NB surveillance tests. This should begin at birth or at diagnosis of NB predisposition and be continued every 3 months until 6 years of age, and then continued every 6 months until 10 years of age (and then stop; Table 3). A 24-hour urine collection is not necessary, as a random urine normalized to urine creatinine is sufficient (116). It should be noted that patients with Costello syndrome can have elevated urinary VMA and HVA in the absence of a catecholamine-secreting tumor (92), so only very high levels or significantly rising levels would prompt further investigation beyond the abdominal US and chest radiograph (CXR). The cost and radiation exposure of a periodic chest radiograph are small, but there was some concern among the expert panel about the sensitivity of chest radiography to detect small tumors, so this will need to be evaluated prospectively. Nevertheless, we recommend periodic CXR, as above, except for patients with LFS, in whom even low levels of radiation exposure should be avoided when possible.

Hereditary NB: Conclusions and Future Directions

For individuals with a mutation in a known NB predisposition gene, we recommend biochemical and radiographic surveillance for early detection of tumors in the first 10 years of life, avoiding the need for general anesthesia and minimizing radiation exposure. Given that the predisposition genes described above do not account for all the families with hereditary NB, or all the cases of bilateral/multifocal or metachronous primary NBs, additional genes are likely to be identified (117). It is unclear whether individuals with other

TP53 mutations besides R337H are at increased risk for NB, but that should become clear over time. Similarly, in addition to Costello syndrome, individuals with other RASopathies may also be at significantly increased risk for NB. Finally, it is unclear currently if individuals with germline mutations in *SDHB, GALNT14*, or other predisposition genes would benefit from NB screening. For individuals with germline *ALK* or *PHOX2B* mutations, it is unclear if these genetic changes confer an increased risk of other tumors in childhood or adulthood, but germline *ALK* mutations may account for some cases of NB in adults (69–72). As we learn more about genotype–phenotype correlations, modifiers of penetrance, and life-long risk for NB and potentially for other cancers, we may advocate for modifications of the surveillance recommendations presented here.

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Table 1

Hereditary RB surveillance protocol

Age	Frequency
Surveillance for intraocular RB[a]	
Birth to 8 weeks	Nonsedated exams every 2 to 4 weeks
8 weeks to 12 months	EUA monthly
12 to 24 months	EUA every 2 months
24 to 36 months	EUA every 3 months
36 to 48 months	EUA every 4 months
48 to 60 months	EUA every 6 months
5 to 7 years[c]	Nonsedated exams every 6 months
Surveillance for trilateral RB	
Brain MRI at the time of RB diagnosis; some centers recommend a brain MRI every 6 months until 5 years old	
Surveillance for second primary tumors	
Education regarding second primary tumor risks and close attention to any new signs/symptoms	
Skin exam by the pediatrician during well child visits, to continue annually by the primary care physician or dermatologist for melanoma from age 18	
Some consider WBMRI annually after age 8, but no consensus[b]	

Abbreviation: WBMRI, whole-body MRI.

[a] On the basis of consensus recommendations of the American Association of Ophthalmic Oncologists and Pathologists.

[b] Or later, when the child is able to tolerate WBMRI without anesthesia.

[c] Some suggest continuing exams every 1 to 2 years after age 7.

Table 2

Mutations in genes that predispose to NB

Gene[a]	Mutation/alteration	Domain	Reference(s)
ALK	R1275Q	Kinase	69–73
	L1204F	Kinase	
	R1192P	Kinase	
	I1183T	Kinase	
	T1151R	Kinase	
	G1128A	Kinase	
PHOX2B	676delG	NPARM	79, 80, 83, 85, 86
	R100L	NPARM	
	R141G	NPARM	
	G197D	NPARM	
	PARM-28–33+	PARM	
TP53	R337H, (other?)	NLS domain-1	102
CDKN1C	Inactivating	Nonfocal	103, 104
RASopathies[b]	Activating	Hotspots	90–96

Abbreviations: NLS, nuclear localization sequence; NPARM, nonpolyalanine repeat mutation; PARM, polyalanine repeat expansion mutation.

[a]Other genes have been implicated in NB predisposition, including *GALNT14* and *SDHB*, but the data on prevalence and relative risk are limited at this time.

[b]Costello syndrome is cause by mutations in *HRAS*, and Noonan syndrome is caused by mutations in *PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF*, or *MEK1*. Costello syndrome is the only RASopathy that warrants NB screening at the present time. However, patients with Costello syndrome may have elevated catecholamine metabolites, so only very high levels or significantly rising levels would warrant further evaluation for NB (92).

Table 3

Recommended surveillance for individuals with NB predisposition

Age	Surveillance studies	Frequency
0–6 yr.	Abdominal US, Urine VMA and HVA, CXR	Every 3 mo.
6–10 yr.	Abdominal US, Urine VMA and HVA, CXR	Every 6 mo.
>10 yr.	No screening recommended	

Abbreviations: CXR, chest radiograph [postanterior (PA) and lateral]; mo., months; yr., years.