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Recommendations for Childhood Cancer Screening and Surveillance in DNA Repair Disorders

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Abstract

DNA repair syndromes are heterogeneous disorders caused by pathogenic variants in genes encoding proteins key in DNA replication and/or the cellular response to DNA damage. The majority of these syndromes are inherited in an autosomal recessive manner, but autosomal dominant and X-linked recessive disorders also exist. The clinical features of patients with DNA repair syndromes are highly varied and dependent on the underlying genetic cause. Notably, all patients have elevated risks of syndrome-associated cancers, and many of these cancers present in childhood. While it is clear that the risk of cancer is increased, there are limited data defining the true incidence of cancer and almost no evidence-based approaches to cancer surveillance in patients with DNA repair disorders. This manuscript is the product of the October 2016 American Association of Cancer Research Childhood Cancer Predisposition Workshop which brought together experts from around the world to discuss and develop cancer surveillance guidelines for children with cancer-prone disorders. Herein we focus on the more common of the rare DNA repair disorders: ataxia telangiectasia, Bloom's syndrome, Fanconi anemia, dyskeratosis congenita, Nijmegen breakage syndrome, Rothmund-Thomson syndrome, and xeroderma pigmentosum. Dedicated syndrome registries and a combination of basic science and clinical research have led to important insights into the underlying biology of these disorders. Given the rarity of these disorders, it is recommended that centralized centers of excellence be involved directly or through consultation in caring for patients with heritable DNA repair syndromes.

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Keywords

DNA repair; ataxia telangiectasia; telomere; Dyskeratosis congenita; Fanconi anemia; Bloom syndrome; Nijmegen breakage; xeroderma pigmentosum; Rothmund-Thomson syndrome

INTRODUCTION

Germline pathogenic variants (*i.e.*, mutations) in key components of DNA repair and telomere biology result in a spectrum of heritable disorders usually associated with characteristic physical findings and an elevated risk of specific cancers. In many instances, the DNA repair disorders are diagnosed in childhood, but some, particularly those caused by aberrant telomere biology, may manifest later in life. Dedicated syndrome registries, basic science, and clinical research have provided insights into the treatment and management for individuals with these rare disorders of aberrant DNA repair mechanisms.

This manuscript originates from the October 2016 American Association of Cancer Research Childhood Cancer Predisposition Workshop which focused on reviewing pediatric cancer surveillance guidelines for children with hereditary risk of cancer. Limited data exist to define the true incidence of cancer in the DNA repair disorders and almost no evidence-based approaches exist to evaluate cancer surveillance in patients with DNA repair disorders. Since the comprehensive review of all inherited disorders of DNA repair is beyond the scope of this manuscript and has been done elsewhere, we reviewed the primary clinical manifestations and associated malignancies of these disorders and to provide information on family support groups and/or patient registries as a starting point for clinical management and the future development of evidence-based guidelines (Tables 1 and 2).(1–8) All patients and/or their families are encouraged to promptly report to health care professionals any changes in their health, and physicians should have a low index of suspicion for malignancy in patients with DNA repair disorders. In addition to contacting centers of excellence for these rare disorders, clinicians are referred to <https://clinicaltrials.gov> to help identify ongoing clinical trials for these disorders.

ATAXIA TELANGIECTASIA

Genetic Summary

Ataxia telangiectasia (A-T, Mendelian Inheritance in Man [MIM] 208900) is an autosomal recessive (AR) disorder presenting in childhood due to bi-allelic pathogenic variants in the *ATM* (ataxia-telangiectasia mutated) gene, which encodes a protein belonging to the phosphatidylinositol-3 kinase (PI3) protein family. The incidence of A-T is estimated between 1:40,000 and 1:100,000 people.(9) The ATM protein is a cell cycle checkpoint kinase that functions as a regulator of multiple proteins, including tumor suppressor proteins p53, BRCA1, CHEK2, and NBS1.(10) Pathogenic variants in *ATM* typically decrease the expression and/or function of ATM and prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and contributes to genomic instability and/or cell death. This results in increased sensitivity to ionizing radiation in cells of patients with A-T. (11) Patients with A-T typically develop progressive cerebellar ataxia

between one and four years of age. Conjunctival telangiectasias, oculomotor apraxia, choreoathetosis, and immunodeficiency are often also present.(1) The progressive neurologic symptoms are thought to be due to aberrant DNA repair and neuronal cell death with most children with A-T wheelchair bound by the teen years. Malignancy is reported to develop in up to 40% of patients with A-T and is typically non-Hodgkin lymphoma and acute lymphoid leukemia.(12)

Cancer Screening/Surveillance/Management Protocols

Children with A-T are often diagnosed by a variety of different methods including abnormal newborn screening for reduced T-cell receptor excision circle levels. Other laboratory abnormalities that can be detected in children suspected of having A-T include increased alpha-feto protein (AFP) levels, reduced IgA, IgE, and IgG2 levels, poor antibody response to pneumococcal polysaccharide vaccines, abnormal peripheral blood karyotype analysis including presence of a 7;14 translocation (in 5–15% of patients), and cerebellar hypoplasia on MRI.(1) Increased lymphocyte sensitivity to ionizing radiation is also present.

Patients with A-T require multidisciplinary care including referrals to 1) neurology for progressive cerebellar ataxia, ocular apraxia, and choreoathetosis; 2) immunology/hematopoietic cell transplant (HCT) for management of immunodeficiency; 3) pulmonology for recurrent infections, pulmonary function evaluation, and restrictive lung disease; 4) gastroenterology (GI) for swallow evaluation and nutrition; and 5) oncology for leukemia, lymphoma and solid tumor risks.

Evidence-based standards for cancer screening do not exist for patients with A-T, particularly in childhood. Annual physical exam, complete blood count, complete metabolic profile including lactate dehydrogenase should be considered. As described in another manuscript in this series, considerable debate exists on whether early diagnosis of acute leukemia improves survival (reference – Porter et al, in this issue). It is important for parents and providers to keep in mind that A-T patients are sensitive to ionizing radiation and x-rays, and thus their use should be limited accordingly. Treatment regimens of any incident cancer should be adjusted given the increased risk of treatment related toxicity in children with A-T. Providers and patients should coordinate both acute and chronic care with centers focusing on A-T. The A-T Children's project, <http://www.atcp.org>, has information for families and physicians.

Individuals who are heterozygous for a single pathogenic *ATM* variant have increased risk of adult onset breast, prostate and pancreatic cancer (13–15). This also has implications for cancer screening in affected parents of children with A-T. The adult onset cancer risk in *ATM* carriers continues to be extensively studied but remains beyond the scope of this manuscript.

NIJMEGEN BREAKAGE SYNDROME

Genetic Summary

Nijmegen breakage syndrome (NBS, MIM 251260) is an AR disorder presenting in childhood due to bi-allelic pathogenic variants in nibrin, encoded by the *NBN* gene. Nibrin

belongs to the MRE11/RAD50 double stranded break repair complex. Patients with NBS are characterized by microcephaly, microgenia (small deformed chin), immunodeficiency and “bird like” facies.(16) NBS is estimated to affect one in 100,000 newborns worldwide, but is thought to be more common in Slavic populations of Eastern Europe.(17) Approximately 40% of affected individuals develop malignancies before age 20. T-cell and B-cell lymphomas are the most common NBS-associated malignancies; medulloblastoma, glioma and rhabdomyosarcoma have also been reported.(17)

Laboratory evaluation for NBS shows some similar features as described for children with A-T, including reduced CD3⁺ and CD4⁺ T cells, IgA deficiency (20% of patients), IgG2 and IgG4 deficiency (with normal serum IgG), increased frequency of CD45RO⁺ T cells and simultaneous decrease in naïve CD45RA⁺ T-cells (rare) and the same structural aberrations of chromosome 7 and 14 in cultured lymphocytes as seen in AT. Response to testing of ionizing radiation sensitivity in lymphocytes will be abnormal and demonstrate increased sensitivity. Germline genetic testing reveals loss of function mutations in *NBN* with the Slavic founder mutation being the most common. (6, 17)

Cancer Screening/Surveillance/Management Protocols

Patients with NBS require multidisciplinary care beginning at diagnosis that is tailored to each patient’s specific needs. Patients should be evaluated by an immunologist and for management of immunodeficiency, undergo monitoring by a pulmonologist for recurrent infections, be followed by endocrinology and nutrition evaluations for growth deficiency and by oncology for leukemia, lymphoma and solid tumor risks. Annual CBC is indicated or when symptomatic to assess for hematologic disease. Patients with NBS require often intravenous immunoglobulin therapy for immunodeficiency. (18–21) As described for patients with A-T, children with NBS demonstrate increased sensitivity to ionizing radiation and may require tailored treatment regimens for any malignancy that develops.(22)

Heterozygous carriers of pathogenic variants in *NBN* are at risk for adult onset breast, and prostate cancer. (14, 15, 23)

BLOOM’S SYNDROME

Genetic Summary

Bloom’s syndrome (BS, MIM 210900) is an AR disorder resulting from bi-allelic pathogenic variants in the *BLM* gene encoding the BLM DNA helicase, a member of the RECQ family and sometimes referred to as *BLM*.(24, 25) RECQ helicase enzymes attach and unwind the DNA double helix. BLM maintains genomic stability during the DNA copying process by limiting sister chromatid exchange. Cells from patients with BS with absent BLM activity demonstrate a ten-times higher rate of sister chromatid exchange.

Only a few hundred individuals with BS have been described, and approximately one-third are of Ashkenazi Jewish descent due to a founder allele.(26–28) The classic BS characteristics include pre- and postnatal growth deficiency, short stature, sun-sensitivity, gastroesophageal reflux, recurrent infections, decreased fertility in males, insulin resistance, and cancer predisposition.(4) Two hundred twelve cancers in 136 patients have been

described in the Bloom's Syndrome Registry.(4) Cancers diagnosed during the pediatric period include gastrointestinal, genital and urinary tract carcinoma, lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, sarcoma, Wilms tumor, medulloblastoma, and retinoblastoma.(29) Multiple cancers occur commonly and with a distribution that is similar to cancer that is seen in the general population, but with an earlier onset.

Cancer Screening/Surveillance/Management Protocols

There is no established cancer screening protocol for patients with BS, and the risk for cancer at multiple sites presents a surveillance challenge. Patients and their families should be aware of the signs and symptoms of leukemia and lymphoma, the most commonly encountered malignancies in BS, and patients should be evaluated promptly when recognized. The second most common cancer type is colorectal cancer, with the earliest occurrence being at age 16 years. (28). A reasonable approach to screening includes colonoscopy every 1–2 years and guaiac fecal occult blood testing every 6 months, beginning at age 15 years. Breast cancer was diagnosed in 16 women in the BS Registry at a median age of 35.8 years (range 21 – 48). Based on this information, annual breast MRI scans beginning between ages 20 and 25 is a reasonable surveillance strategy. For the remaining cancers, patients and their families should be aware of the common but nonspecific signs of cancer including unintentional weight loss, unexplained fever, fatigue, changes in bowel or bladder habits, and persistent and unexplained pain. When imaging is used for diagnostic evaluation, ultrasonography and MRI scan are preferred over radiographs or CT scans because of the presumed increased risk for cancer from ionizing radiation. The BS registry has information on various aspects of BS patient care (<http://weill.cornell.edu/bsr/>) as does the Bloom's Syndrome Association (<http://www.bloomssyndromeassociation.org>). Clinicians should consult with experts in BS on the specific areas of clinical management. An international RECQ disorders meeting (RECQ2016) resulted in a recent plan to further develop BS management guidelines.

ROTHMUND-THOMSON SYNDROME

Genetic Summary

Rothmund-Thomson syndrome (RTS, MIM 268400) is a rare disorder with only a few hundred patients described in the literature.(30, 31) Type 2 RTS is associated with an increased cancer risk results due to bi-allelic pathogenic variants in the *RECQL4* DNA helicase.(8) The *RECQL4* protein, like BLM, belongs to the RECQ DNA helicase family. It is a multifunctional protein which participates in several cellular processes, including DNA replication, DNA damage repair, maintenance of telomeres and mitochondrial DNA integrity.(32, 33) A proportion of individuals with a clinical diagnosis of RTS (based on poikiloderma) do not have an identifiable *RECQL4* pathogenic variant (referred to as RTS Type 1) and do not appear to have an increased risk of cancer. The gene for RTS type 1 has not been identified.

Patients with RTS have the characteristic skin finding of poikiloderma (hyper and hypopigmentation, atrophy, and telangiectasias) that starts in infancy and persists throughout life. (34–36) They may also have sparse hair, hyperkeratosis, small stature, skeletal defects

including osteoporosis, dental anomalies, and cataracts.(36–38) RTS patients develop osteosarcoma at an earlier age than the general population (median age 10 years), so any screening could be limited to the first two decades of life. (39) The incidence of OS in patients with no truncating mutations was 0.00 per year (100 person-years of observation), and the incidence of OS in patients with one or two truncating mutations was 0.05 per year (230 person-years of observation) ($P = .037$ using the two-sided log-rank test (40). A smaller number of patients have been described with basal cell carcinoma and skin squamous cell carcinoma (SCC).(40, 41) A specific allele of *RECQL4* associated with a related disorder (RAPADILINO syndrome) is associated with an increased risk of lymphoma.(42) Hematologic abnormalities such as bone marrow failure, myelodysplastic syndrome (MDS), lymphoma, and leukemia have also been reported.(36, 43–47)

Cancer Screening/Surveillance/Management Protocols

Patients with RTS require multidisciplinary care including evaluations by 1) genetics for counseling about cancer risk; 2) dermatology for annual skin exam and skin care; 3) ophthalmology for cataract screening and management; and 4) dentistry for routine care. Patients are cautioned to avoid excessive radiation (UV or IR) exposure, employ sensible sun protection, and monitor skin for lesions. Retinoids may be used to manage hyperkeratosis, and pulsed laser therapy may be used to improve cosmesis of telangiectasias.(48, 49) RTS patients with pathogenic variants in *RECQL4* are recommended to have a skeletal survey before the age of 5 years to identify any underlying skeletal abnormalities; they should receive counseling about the risk of osteosarcoma and be aware of signs and symptoms of osteosarcoma. Should these occur, they should seek immediate medical attention. Any new imaging of affected areas (*e.g.*, x-rays) can be compared to the baseline skeletal survey to determine whether further work-up is warranted. The benefit of routine screening for osteosarcoma has not yet been determined. Factors to consider include timing, length, modality (plain radiographs vs. MRI) and cost of screening.

The RTS Foundation, <http://www.rtsplace.org/>, has patient-centered information.

DYSKERATOSIS CONGENITA

Genetic Summary

Dyskeratosis congenita (DC, MIMs: 127550, 30500, 615190, 613987, 613989) is a telomere biology disorder (TBD) characterized by nail dystrophy, lacy skin pigmentation, and oral leukoplakia.(7, 50) DC is caused by pathogenic variants in genes important in stability and maintenance of telomeres, the nucleoprotein complex essential for chromosomal stability. The mode of inheritance depends on the gene and is X-linked for *DKC1*, autosomal dominant (AD) for *TERC* or *TINF2*, AR for *CTC1*, *NHP2*, *NOP10*, *PARN*, or *WRAP53*, and either AD or AR for *ACD*, *RTEL1*, or *TERT*. The prevalence of DC in the general population is unknown. Diagnosis is made by the presence of telomeres less than the first percentile for age measured by flow cytometry with fluorescent *in situ* hybridization to measure telomere length in white blood cells.(51) Patients with DC are at an increased risk of MDS, bone marrow failure, leukemia, cancers of the head and neck and genitourinary system, as well as pulmonary fibrosis, emphysema, liver fibrosis/cirrhosis.(51–53)

Cancer Screening/Surveillance/Management Protocols

Diagnosis and clinical care guidelines for patients with DC were recently published (<https://www.dcoutreach.org/guidelines>). A bone marrow aspirate and biopsy are recommended after diagnosis of DC to establish a baseline. Due to the risk of developing MDS complete blood counts and bone marrow evaluation should be performed at least annually, but more often if clinically indicated due to signs, symptoms or abnormal complete blood counts consistent with the familial leukemia report in this same series. Patients with DC on androgen therapy for cytopenias should undergo biannual hepatic ultrasounds and liver function tests every three months due to a potential risk of hepatic tumors and elevation of liver enzymes. Patients with DC are at high risk of head and neck squamous cell cancer (HNSCC) and thus should perform monthly oral self-examinations, biannual dental examinations, and have annual HNSCC evaluation by an otolaryngologist experienced in oral cancer beginning by age 16 years. An annual gynecologic examination is recommended for women. Additionally, recommendations for non-malignant sequelae include baseline pulmonary function tests when the patient is old enough to perform them with follow-up testing tailored to the individual patient's needs. A baseline endocrine evaluation for growth is recommended and should be at least annually for patients on androgen therapy. Additional evaluation with developmental pediatricians and neurologists may be required for developmental delays. (5, 54)

Additional resources for patients with DC are available at <https://www.dcoutreach.org>.

FANCONI ANEMIA

Genetic Summary

Fanconi anemia (FA, MIMs: 134600, 227650, 600901, 609054, 605724, 613951, 610832, 614083, 614082, 609053) is a primarily AR disorder with at least 20 associated DNA repair genes. Pathogenic variants in one X-linked recessive gene, *FANCB*, and one AD gene, *FANCR* (RAD51) have been reported(3, 55–58) FA proteins function to maintain genomic stability by repairing DNA inter-strand cross-links (ICLs) and by interacting with other DNA damage response pathways.(59, 60) The screening diagnostic test for FA involves chromosomal breakage assessment after exposure of T-cells to diepoxybutane (DEB) or mitomycin C (MMC).(61, 62)

Although the most common congenital anomalies include short stature, thumb or radii abnormalities, dysmorphic features, skeletal abnormalities, and genitourinary malformations, up to one-third of patients will have no physical anomalies.(63) Approximately 40% of patients with FA develop severe BMF by age 20 years and one-half of all patients with FA develop BMF by age 50. The risks of solid tumors, including HNSCC, or AML by age 50 years in FA are estimated at 30% and 10% respectively. (51, 64–67) The success of HCT for bone marrow failure has led to improved survival in patients with FA but a possible increase in the incidence of HNSCC, kidney and liver tumors, brain tumors, breast cancers, and other tumor types.(67, 68)

Cancer Screening/Surveillance/Management Protocols

The guidelines for diagnosis and management of FA can be found at <http://fanconi.org/index.php/publications/guidelines>. A complete blood count (CBC) and bone marrow aspirate and biopsy is recommended at diagnosis. The bone marrow evaluation should then be repeated annually. The CBC should be monitored more frequently to allow for proactive monitoring for progressive cytopenias and MDS. From the time of diagnosis, patients with FA should perform monthly oral self-examinations (or with parents assistance); have a biannual dental examination (general inspection exam without X-rays unless specific indication), and annual HNSCC evaluation by an otolaryngologist beginning in early adolescence. An annual gynecologic examination is recommended starting in adolescence and the HPV vaccine should be administered per the AAP vaccination schedule for both boys and girls. Clinical management of patients with FA do not include standard myeloablative dosing, these lower dose regimens are designed to be myeloablative in the setting of FA, alternatively, androgen therapy may be tried for FA patients with bone marrow failure, as well as, cancer-specific therapy with avoidance of DNA damaging agents, and supportive care for other complications.(3)

Parents of children with the more common FA subtypes, *FANCA*, *FANCC*, and *FANCG*, do not appear to have an increased cancer risk. However, heterozygous mutations in several of the more rare FA subtype genes: *FANCD1/BRCA2*, *FANCF/BRIP1/BACH1*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCES/BRCA1*, and *FANCU/XRCC2* are associated with moderate adult onset cancer risks, particularly for breast and ovarian cancer. Thus, parents of children with these FA subtypes may benefit from increased cancer screening and prevention strategies. The use of multi-gene panel testing for individuals at risk for hereditary breast/ovarian cancer is increasingly identifying adult carriers who also need to be alerted to their cancer risk as well as their risk for FA in their offspring and options for preconception planning and testing of their partner for the same FA gene. (3, 69).

The FA family support group, Fanconi Anemia Research Fund, www.fanconi.org, has information for patients, clinicians, and researchers.

XERODERMA PIGMENTOSUM

Genetic Summary

Xeroderma pigmentosa (XP, MIMs: 278700, 278720, 278730, 278740, 278750, 610651) is caused by AR inheritance of pathogenic variants in nucleotide excision repair genes, *DDB2*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *POLH*, *XPA*, or *XPC*. Patients with XP have severe sun sensitivity; develop significant skin freckling and skin cancers (basal cell, skin SCC, and melanoma). Other cancers that have been described in XP patients include leukemia, squamous cell carcinoma (common sites face, head and neck), brain and spinal cord tumors, and other solid tumors.(70–74) Eye involvement in XP can be significant with keratitis and lid atrophy. Some patients may have neurologic symptoms including progressive sensorineural hearing loss and cognitive impairment.(70, 75–78) XP is a rare disorder and estimated to affect 1 in 1 million people in the United States and Europe and a slightly increased frequency in the Middle East, Japan and North Africa.(79)

Cancer Screening/Surveillance/Management Protocols

Screening will be most effective when paired with strategies to minimize UV exposure. Patients and families should be educated about limiting UV exposure by protecting all surfaces of the body and the eyes and provided with psychosocial support to help ensure adherence to these measures. Those with XP are most sensitive to UVA and UVB radiation, which come from the sun, but indoor light sources can also produce UV and should be evaluated with a light meter to identify sources of significant UV that could be replaced. (2) Patients with XP require multidisciplinary care including comprehensive dermatologic evaluations at least every 3 months. Close monitoring by ophthalmology for ocular disease, by otolaryngology for hearing loss as well as endocrinology and nutrition for dietary supplementation specifically vitamin D.(2) Additional information for families with XP is available at <http://www.xps.org/>

HETEROZYGOUS CARRIERS OF PATHOGENIC VARIANTS IN DNA REPAIR GENES

The majority of the DNA repair disorders described above are AR syndromes with a few exceptions. Heterozygous carriers of pathogenic variants in DNA repair genes may have an elevated cancer risk, but the data vary by gene and cancer. Parents of children with AR DNA repair disorders should receive genetic counseling and cancer screening in accordance with national guidelines and expert providers.(23, 80)

In addition, non-syndromic children may be heterozygous carriers for DNA damage genes, and recent next generation sequencing studies have identified children with cancer harboring pathogenic variants in these genes.(81–83) At this time it is not clear if these variants are directly connected to the cancer affecting the children in those studies. Providers should tailor their discussions with these families based on comprehensive patient-specific information including: other clinical features of the disorder being present and other biomarker or functional evidence before determining whether testing and/or screening should be considered for unaffected siblings under the age. It should be noted, however, that genetic testing of children for adult onset diseases is generally not recommended. (84)

CONCLUSIONS

DNA repair syndromes manifest from heritable underpinnings and when identified, affected individuals require multidisciplinary care, nuanced therapeutic considerations, and screening (Table 2). Although these syndromes are rare, dedicated syndrome registries, basic science research, and clinical research continue to develop the foundation for the most appropriate treatment and management for individuals with inherent aberrant DNA repair mechanisms. Centralized centers of excellence are highly recommended to be involved directly or through consultation in caring for patients with heritable pediatric DNA damage syndromes. For parents carrying a single mutation in a DNA damage syndrome gene, screening and prevention considerations may be indicated and necessitate genetic counseling and guidance.

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Table 1

Genetic features of DNA repair and telomere biology disorders

Disorder	Biologic Pathway	Inheritance: Gene(s)
Ataxia telangiectasia	DNA repair checkpoints	AR: <i>ATM</i>
Bloom's syndrome	Homologous recombination	AR: <i>BLM</i>
Dyskeratosis congenita	Telomere biology	XLR: <i>DKC1</i> AD: <i>TERC, TERT, TINF2, RTEL1, PARN, NAF1</i> AR: <i>NOP10, NHP2, TERT, RTEL1, PARN, CTC1, STN1, POT1, WRAP53, ACD,</i>
Fanconi anemia	DNA damage response, especially inter-strand crosslink repair	AR: <i>FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI/BRIPI/BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCQ/XPF/ERCC4, FANCR/RAD51, FANCES/BRCA1, FANCT/UBE2T, FANCU/XRCC2</i> <i>REV7/MAD2L2</i> XLR: <i>FANCB</i>
Nijmegen Breakage Syndrome	DNA double strand break repair	AR: <i>NBN</i>
Rothmund-Thomson syndrome	DNA replication/repair helicase	AR: <i>RECQL4</i>
Xeroderma pigmentosum	Nucleotide excision repair	AR: <i>DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA, or XPC</i>

Abbreviations: AD, autosomal dominant; AR autosomal recessive; XLR, X-linked recessive

Table 2

Diagnosis, associated malignancies, and management recommendations for DNA repair and telomere biology disorders

	Diagnostic Testing and Other Biomarkers	Associated Malignancies	Management Recommendations
Ataxia Telangiectasia	Genetic testing Newborn screening: reduced T-cell receptor excision circle levels Elevated alpha fetal protein Karyotype: 7:14 chromosomal translocation Immunoblotting (research) Chromosome breakage studies for radiation sensitivity (research)	Lymphoma, ALL, ovarian cancer, breast cancer, gastric cancer, melanoma, leiomyomas, sarcomas	Hematology-Oncology: History/physical, annual complete blood counts, metabolic profile and lactate dehydrogenase and avoid excessive radiation. Immunology: monitoring of immunoglobulin levels per immunologist recommendation. Dermatology: annual skin exam Pulmonary: baseline and as needed pulmonary function tests. Gastroenterology/Nutrition: baseline and as needed swallowing function and nutritional management Endocrine: annual diabetes screen Neurology: supportive medications Orthopedics: annual scoliosis evaluation Dental: biannual exam
Bloom's Syndrome	Genetic testing Chromosome breakage with DEB and/or MMC abnormal sister chromatid exchange (research)	Lymphoma, AML, ALL, sarcoma, genital and urinary tract carcinoma, medulloblastoma, retinoblastoma	Hematology-Oncology: annual complete blood counts, avoidance of radiation; breast MRI/ultrasound starting between 20–25 years of age, colonoscopy starting at age 15 every 2 years and fecal occult blood every 6 months starting at age 15 Dermatology: annual skin exam, limit sun exposure Pulmonary: pulmonary function tests Gastroenterology/Nutrition: baseline and as needed swallowing function evaluation and nutritional management Endocrine: annual diabetes screen Genitourinary: congenital anomaly evaluation at diagnosis Orthopedics: annual scoliosis evaluation Dental: biannual exam
Dyskeratosis Congenita	Genetic testing Telomere length measurement of leukocyte subsets using flow cytometry with <i>in situ</i> hybridization	Head and neck SCC, AML, MDS, anogenital cancer	Hematology-Oncology: annual CBCs, ~annual bone marrow evaluations based on clinical features, early referral to HCT center, HPV vaccine, annual ENT evaluation beginning in adolescence Immunodeficiency: monitoring of immunoglobulin levels per immunologist recommendation. Dermatology: annual skin exam Pulmonary: baseline pulmonary function tests with routine follow-up Gastroenterology/Nutrition: liver function tests at least annually, more frequent if on androgens Endocrine: annual diabetes screen Neurology: MRI assessment for cerebellar hypoplasia at diagnosis, early intervention for developmental delay Ophthalmology: annual examination, monitoring and early management of lacrimal duct stenosis Orthopedics: evaluation of hip and shoulder avascular necrosis based on symptoms Dental: biannual exam ENT: baseline hearing evaluation
Fanconi Anemia	Genetic testing Chromosomal breakage with DEB and/or MMC	Head and neck SCC, AML, MDS, anogenital cancer	Hematology-Oncology: annual CBCs, ~annual bone marrow evaluations based on clinical features, early referral to HCT center, HPV vaccine, annual ENT evaluation beginning in adolescence Immunology: monitoring of immunoglobulin levels per immunologist recommendation. Dermatology: annual skin exam

	Diagnostic Testing and Other Biomarkers	Associated Malignancies	Management Recommendations
			Pulmonary: baseline pulmonary function tests with follow-up as needed Gastroenterology/Nutrition: annual liver function tests, more frequent if on androgens Endocrine: annual diabetes screen, follow growth trajectory Orthopedics: assessment of radial ray anomalies and management, if needed Genitourinary: baseline evaluation for renal malformations Cardiology: baseline evaluation for heart malformations ENT: annual hearing evaluation, annual cancer screening starting in teenage years Dental: biannual exam
Nijmegen Breakage Syndrome	Genetic testing Chromosomal Breakage with DEB and/or MMC Chromosomal instability involving chromosomes 7 and 14 in PHA stimulated lymphocytes Immunoblotting (research)	Lymphoma, medulloblastoma, glioma, rhabdomyosarcoma	Hematology-Oncology: Hematology-Oncology: History/physical, annual complete blood counts, metabolic profile and lactate dehydrogenase and avoid excessive radiation. Dermatology: annual skin examinations Pulmonary: baseline pulmonary function tests with follow-up as needed, aggressive treatment of recurrent infections Gastroenterology/Nutrition: baseline and as needed swallowing function evaluation and nutritional management Endocrine: monitor growth, assess females assess for ovarian failure Neurology: developmental assessment and early intervention if needed Ophthalmology: annual examination Orthopedics: baseline assessment for anomalies and as needed Dental: biannual exam
Rothmund-Thomson Syndrome	Genetic testing	Osteosarcoma, basal cell carcinoma, skin SCC	Oncology: avoid ionizing radiation, consider imaging for osteosarcoma risk Dermatology: Avoid excessive UV; use sunscreen annual exam and early treatment of lesions Ophthalmology: annual evaluation and cataract treatment as needed Endocrine: management for osteopenia Orthopedics: baseline skeletal survey Dental: biannual evaluation with proper care for hypoplastic teeth, enamel defects
Xeroderma Pigmentosa	Genetic testing	Melanoma, basal cell carcinoma, skin SCC, leukemia, brain and spinal cord tumors	Oncology: beginning at diagnosis - avoid excessive sunlight and ionizing radiation; early identification and treatment of skin lesions; exam for ocular and ENT neoplasms every 6–12 months Dermatology: thorough skin evaluation every 3 months Gastroenterology/Nutrition: evaluate swallowing function, nutritional support, as needed Ophthalmology: exam every 6–12 months Neurology: evaluation for developmental delay or progressive neurologic changes Orthopedics: annual scoliosis evaluation ENT: baseline hearing evaluation and as needed, cancer screening every 6–12 months

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CBC, complete blood count; DEB; diepoxybutane; ENT, ear, nose and throat; IVIg, intravenous immunoglobulin; MDS, myelodysplastic syndrome; MMC, mitomycin C; PHA, phytohemagglutinin; SCC, squamous cell carcinoma