Chapter 25

Routine Healthcare for Children with Telomere Biology Disorders

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Introduction

A multidisciplinary and age-based approach to routine health care and screening is essential for all children suspected or confirmed to have telomere biology disorders (TBD) (see also Chapter 3, Diagnosing Telomere Biology Disorders). Individuals confirmed to have a TBD based on presence of known pathogenic variants in TBD-associated genes, very short (<<1%ile) lymphocyte telomere lengths, and clinical features consistent with the disease are at high risk for development of TBD clinical manifestations and require intensive routine screening. This screening may include regular visits with physicians from multiple subspecialties, peripheral blood laboratory studies, organ assessments by imaging

and functional testing, and biopsies for mucosal and bone marrow abnormalities that cannot be assessed by less invasive means.

Less intensive screening regimens that omit routine use of certain invasive tests requiring anesthesia and require fewer subspecialty evaluations in the absence of relevant symptoms may be appropriate for certain individuals with TBDs. Examples of such individuals, herein referred to as having moderate risk, include:

- Individuals with limited features of TBD who are found to have a variant of uncertain significance in a TBD-associated gene on genetic testing [1] and who lack very short lymphocyte telomeres
- Individuals who have short, but not very short, lymphocyte telomeres (1-10%ile), limited physical features that may be associated with TBD, but no pathogenic variants or variants of uncertain significance in genes associated with TBD
- Individuals with heterozygous pathogenic gene variants (*e.g.*, certain variants in *RTEL1*) that are associated with later-onset TBD disease features (*e.g.*, pulmonary fibrosis) but are not clearly associated with disease features in the pediatric age range [2, 3].

A final category of pediatric patients with TBD that require a unique approach to routine care and screening includes those who have previously undergone hematopoietic cell transplantation (HCT). The approach to routine care and screening in post-HCT patients must incorporate distinct hematologic and immunologic screening, as well as careful attention to organ dysfunction and cancer risk that may be exacerbated by HCT complications related to chemotherapy toxicity and graft versus host disease [4] (see also Chapter 13, Hematopoietic Stem Cell Transplantation). In this chapter we provide guidance for

an age-based approach to routine care and screening for pediatric patients with TBDs, stratified according to these three distinct categories of patients.

Coordination of Care: Medical Home

To ensure that all recommended routine health screening is performed, we recommend that pediatric individuals with TBD establish care with a provider willing to serve as their medical home [5]. This provider is responsible for coordinating care among involved subspecialists and for maintaining a summary detailing status of screening and individualized medical needs. Once a medical home is established, individuals should be seen by the physician serving as the medical home at least every 6 months, with more frequent visits indicated for individuals with significant medical issues requiring care coordination.

The medical home function may be performed by providers with distinct expertise backgrounds including pediatric hematologist/oncologists, transplant physicians (particularly for post-HCT patients), geneticists, immunologists, gastroenterologists, or general pediatricians dedicated to patients with complex care needs. For individuals who live in communities lacking specific providers with extensive expertise in the care of patients with TBDs, we recommend that the local physician serving as the medical home partner with a regional or national specialist in caring for the patient. In situations where the medical home function is split between a local physician and a regional TBD expert, we recommend that the every 6 month follow-up visits be split between the local and regional providers such that each sees the patients at least once per year.

Hematologic Screening

Peripheral blood counts and bone marrow screening in patients with TBDs are used to detect both the onset of bone marrow failure (BMF) as well as evidence of progression to myelodysplastic syndrome (MDS). Retrospective cohort data suggest that pediatric patients with TBD less than 10 years of age are at very low risk of developing MDS, while MDS risk increases through the adolescent and young adult age periods [6]. In contrast, BMF can develop in individuals with TBD at any age. Pediatric patients should be seen by a pediatric hematologist/oncologist or HCT physician at least yearly for hematologic monitoring.

Peripheral blood count monitoring

Patients with either confirmed high risk TBD or suspected/moderate risk TBD (as defined above) who have not received HCT should undergo screening by complete blood count (CBC) with differential and absolute reticulocyte count at least every 6 months. In patients who develop cytopenias in the red blood cell, neutrophil, or platelet lineages, or have known bone marrow abnormalities, CBC screening should be performed at least every 3 to 4 months. In post-HCT patients, CBC monitoring should adhere to institutional transplant guidelines within the first 3 years post-HCT. CBC screening can be performed yearly in long-term post-HCT patients with normal blood counts, full donor chimerism and no other severe non-hematologic complications. However, onset of non-hematologic TBD manifestations including liver and pulmonary dysfunction or bleeding due to vascular anomalies should warrant CBC screening at least every 3 to 6 months, as even with healthy graft function post-HCT, severe cytopenias can develop in these patients.

Bone marrow monitoring

In all patients newly confirmed to have high risk TBD, we recommend obtaining a baseline CBC and a screening bone marrow (BM) biopsy and aspirate. These BM studies should include:

- Assessment of morphologic dysplasia
- Assessment of blasts by morphology, flow cytometry, and immunostains
- Iron stain to assess for ringed sideroblasts,
- Reticulin stain to assess for fibrosis
- Cytogenetic analysis by G-banding
- Fluorescence *in situ* hybridization (FISH) to detect translocations or copy number changes involving chromosomes 5q, 7/7q, 8 and 20q
- Next generation sequencing panel designed to detect somatic mutations commonly associated with MDS.

For high risk patients with abnormalities detected on bone marrow screening, including hypocellularity, dysplasia, or any evidence of somatic genetic alterations, or for patients with blood count abnormalities including cytopenias or elevated MCV, repeat BM screening should be performed at least yearly. For patients less than 10 years of age with a normal initial screening bone marrow assessment and normal peripheral blood counts (including normal MCV), due to the very low risk of MDS in this population and the low likelihood of severe BM failure occurring in patients with normal blood counts, follow-up bone marrow studies may be deferred until 10 years of age as long as blood counts remain normal. Due to the increasing risk of MDS in the second decade of life in patients with confirmed high-risk TBD, even patients with normal blood counts and a history of normal bone marrow evaluation(s) should begin yearly screening BM aspirates/biopsies after age 10 to screen for evidence of clonal hematopoiesis serving as a harbinger for MDS.

For patients in the moderate risk category (those with suspected but not confirmed TBD and those with genetic variants not associated with severe pediatric onset manifestations), we still recommend an initial screening BM aspirate and biopsy, which in addition to defining hematologic risk can be an important diagnostic test to provide additive evidence for a TBD diagnosis. However, if initial BM studies as well as ongoing CBC evaluations are normal for patients in this category, further BM studies can be deferred throughout the pediatric age range unless concerning CBC or clinical changes

arise, or more definitive evidence is found to confirm a high risk TBD with pediatric-onset manifestations. As is the case for patients in the high risk category, moderate risk patients found to have cytopenias, an elevated MCV, or abnormal findings on bone marrow screening should undergo annual BM evaluations.

Finally for patients who are post-HCT, routine BM evaluations are not generally recommended. Exceptions include patients who underwent HCT due to development of MDS or leukemia, in whom post-HCT BM monitoring for hematologic relapse may be part of institutional standards of practice, or patients with recurrent onset of severe cytopenias after HCT who are suspected to have developed graft failure.

Immunologic Screening and Approach to Immunizations

While some individuals with TBD have intact adaptive immunity, many patients may suffer from impaired immune function ranging from early onset severe combined immunodeficiency or immune dysregulation to more subtle common variable immune deficiency [7]. All patients in the high risk and moderate risk categories for TBD should undergo screening immune function assessment at diagnosis, including:

- Flow cytometry-based enumeration of immune cell subsets that includes:
    - CD3, CD4, CD8 T cells, along with memory and naïve T cell fractions
    - CD19/CD20 B cells
    - NK cells
- Immune globulin (Ig) quantification including IgA, IgM, and IgG
- Vaccine titers including responses to tetanus and pneumococcal vaccines

Patients with significant abnormalities detected on this initial screening should establish care with a local or regional immunologist, with whom yearly follow-up is recommended. Because immune function may be dynamic and exhibit deterioration with age in patients with TBD, patients with normal initial immunologic screening should

undergo repeat screening with onset of increased sinopulmonary or atypical infections, or with onset of moderate to severe BMF.

Patients with normal initial immunology screening should receive inactivated vaccines per standard pediatric schedules such as the United States Center for Disease Control (CDC) schedule (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html). Receiving vaccination against human papilloma virus (HPV) as per CDC schedules is of particular importance to individuals with TBD, given the implication of HPV in some head/neck, urogenital, and anal cancers [8, 9]. However, if patients demonstrate inadequate quantitative immune function or inadequate titers following tetanus and pneumococcal vaccination, consultation with an immunologist regarding approach to vaccination is recommended, and live virus vaccinations including varicella and measles/mumps/rubella (MMR) vaccines should be deferred until immunology consultation has occurred.

After HCT patients with TBDs may have delayed or impaired immune reconstitution compared with patients undergoing HCT for other disease indications [4]. Immune function assessment post-HCT is conducted at intervals determined by institutional HCT program guidelines, and include standard assessments listed above, B cell subsets to assess for recovery of immunoglobulin class switching, T cell receptor excision circle (TREC) testing to assess for recovery of thymic output, T cell spectrotyping to assess for diversity of reconstituted immunity, and mitogen stimulation testing to assess for T cell response potential [10]. Immunology consultation should be considered for post-HCT patients with impaired immune reconstitution that persists through one year post-HCT, including patients with absolute CD4 count less than 200/μL, absent TREC levels, absent B cell class switching, and low Ig levels at the one year visit. Re-immunization readiness after HCT should follow institutional BMT program guidelines and for patients with impaired immune reconstitution, initiation of re-immunization schedules should also involve discussion with a consulting immunologist.

Endocrinology and Bone Health Screening

Due to the high risk of endocrine disorders in patients with confirmed high-risk TBD, including growth/pubertal delay, hypogonadism, and bone health complications including pathologic fractures and avascular necrosis [11, 12], establishment of an annual screening plan with an endocrinologist is recommended by 10 years of age (see also Chapter 22, Endocrine and Skeletal Disorders). Patients with vertical growth deficiency detected on annual general pediatric screening, patients with symptoms or history concerning for compromised bone heath, and patients receiving androgen therapy for BMF should initiate formal endocrinology care earlier in the first decade of life once these issues arise.

Patients in the moderate risk TBD category likewise should initiate endocrinology care if concerning symptoms of growth failure or bone health compromise arise. Otherwise, these moderate risk patients may not require standing endocrinology follow-up care. In contrast, patients with certain high risk TBD subtypes, including Coats Plus and Hoyeraal-Hreidarsson syndrome [13, 14], that are known to be at high risk for pathologic fractures and other sequelae of compromised bone health should initiate endocrinology/bone health care at the time of diagnosis to enable early interventions that may prevent long-term bone sequelae. All patients who have undergone HCT for BM failure associated with TBD should have standing yearly endocrinology follow-up starting by the end of the first year post-transplant, given the likelihood that HCT may exacerbate pre-existing endocrine dysfunction.

In terms of specific endocrine screening and routine care by system:

- **Thyroid.** Individuals with TBD are at relatively low risk for baseline thyroid dysfunction compared to individuals with other inherited BM failure disorders. We recommend baseline serum free thyroxine (T4) and thyroid stimulating hormone (TSH) level assessment, but ongoing screening only for those with abnormalities detected on initial screening or if concerning symptoms arise. In contrast, all patients post-HCT for TBD should have annual serum free thyroxine

(T4) and thyroid stimulating hormone (TSH) levels assessed.

- **Bone health.** From the time of diagnosis, individuals should have annual screening of 25-OH Vitamin D levels assessed, with repletion recommended for levels below the normal range for age. Counseling to ensure adequate dietary intake of calcium is also important in maintaining bone health. Post-HCT patients require more frequent monitoring of Vitamin D levels and more aggressive repletion during the first year post-HCT per institutional guidelines. A baseline dual energy absorptiometry (DXA) scan should be performed between the ages of 12-14 years to assess for bone mineral density in high-risk TBD patients. Patients with normal scans and no history of osteopenia related complications should have follow-up DXA performed every 3 to 5 years, with frequency dependent on other disease manifestations. Post-HCT patients should have DXA evaluations beginning one year after transplant.
- **Growth/gonadal function.** Estimates suggest up to 20% of individuals with TBD exhibit short stature, though many of these patients do not have evidence of growth hormone deficiency [15]. Nevertheless, patients below the fifth percentile in height and in whom this height percentile is discordant with expected mid-parental height, should be evaluated by endocrinology with a hand x-ray for bone age and for GH axis function. Pediatric patients with growth deceleration post-HCT should also undergo GH axis evaluation. Patients with delayed pubertal onset or incomplete progression through puberty require endocrine consultation to assess LH, FSH, testosterone, and estrogen levels where appropriate. In contrast, patients with TBD treated with androgens for BM failure may exhibit accelerated linear growth, masculinization, and precocious puberty [16], and therefore need close monitoring by endocrinology (up to every 6 months) for these complications and their management.

Hepatic and Pulmonary Screening

While some hepatic and pulmonary complications of TBD may occur independently, growing evidence suggests a link between hepatic and pulmonary complications including fibrosis [17] as well as hepatopulmonary syndrome [18], in which the formation of intrapulmonary shunts is driven by the development of portal hypertension and portosystemic shunting. Therefore, screening for hepatic and pulmonary complications of TBD are linked and involve close coordination between hepatology and pulmonary physicians.

Liver screening assessments

Screening blood tests of liver function should be done at diagnosis and at least annually all patients with TBD, and should include transaminases, bilirubin, albumin, cholestasis markers such as gamma glutamyl transferase (GGT) and alkaline phosphatase, and prothrombin time. Starting at five years of age in patients with confirmed high risk TBD and/or starting one year post-HCT, liver ultrasound (US) should be performed annually to assess for architectural changes such as nodular regenerative hyperplasia and for tumors including hepatocellular carcinoma or angiosarcoma, both of which have been reported in patients with TBD [19, 20]. While not used universally, many centers are incorporating routine screening with ultrasound elastography (also known as a fibroscan) that assesses liver stiffness as a sign of fibrosis [21], in addition to traditional US imaging.

TBD patients receiving androgen therapy should undergo liver US as frequently as every 6 months due to increased risks of liver adenomas and peliosis. As it is non-invasive, a baseline screening liver US is still recommended by age 10 even in patients with suspected/moderate risk TBD. If normal, moderate risk patients should repeat this imaging every three to five years. Any patient who develops sustained LFT or liver US abnormalities should establish care with a hepatologist familiar with treating patients with TBDs.

Pulmonary screening assessments

Young children with a history of recurrent sinopulmonary infections and those requiring early HCT should establish care with a pulmonologist in early childhood. Initial evaluation in this subgroup of patients should include annual spirometry starting at age five years when developmentally appropriate, and a baseline high resolution, non-contrast computed tomography (CT) to assess for bronchiectasis, fibrosis, and areas of chronic infection (see also Chapter 14, Pulmonary Fibrosis). Repeat CT imaging is not performed routinely but can be considered if there is a significant decline in spirometry or development of new respiratory symptoms. Otherwise, patients with either confirmed/high risk or suspected/moderate risk TBD but who lack a prior history of pulmonary symptoms should establish pulmonology care and begin routine screening spirometry by age 10. Diffusing capacity (DLCO), a sensitive marker of pulmonary fibrosis, can also often be accurately assessed starting at age 10 depending on patient developmental status, and should be added to pulmonary function screening at this time. For patients without ongoing pulmonary symptoms and without prior HCT, PFT screening can be repeated every 2-3 years. For patients with TBD who are post-HCT, more frequent (at least annual) PFT evaluations are indicated, particularly for patients who received conditioning containing alkylating chemotherapy or total body irradiation (TBI) [4]. Patients undergoing HCT should have CT imaging pre-transplant, with post-transplant imaging indicated for new onset of pulmonary symptoms.

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS), in which portosystemic shunting driven by endothelial dysfunction in the liver drives vascular malformations in the lung and subsequent hypoxia, has been increasingly recognized in the past decade as an underlying cause of progressive dyspnea occurring in the first 4 decades of life for patients with severe TBD [18, 22] (see also Chapter 18, Hepatic Complications). At this time, no routine screening in asymptomatic individuals has been adopted to assess for HPS, in part because doppler ultrasound of portal flow appears to be insensitive at

detecting early stages of HPS. Recent clinical experience suggests that contrast echocardiography (also known as a bubble study) may sensitively detect pulmonary AVM's in patients with TBD that result from HPS. At this time, contrast echocardiography is not part of routine screening for pediatric TBD but should be considered in any pediatric patient pre- or post-HCT who develops new-onset dyspnea without infectious cause and/or evidence of progressive non-cirrhotic portal hypertension.

Head, Neck, Dental, and Hearing Screening

All pediatric individuals with confirmed or suspected TBD should begin twice yearly screening evaluations with a dentist familiar with assessments for oral pre-cancer and cancerous lesions (see also Chapter 8, Dental and Oral Complications). Lesions persisting for more than two to three weeks should be biopsied. If the biopsy is negative for malignancy, lesions should be re-biopsied with any significant changes in size or appearance. In addition to mucosal lesions, patients with TBDs are at high risk for periodontal disease, dental decay, dental agenesis, and thin enamel [23]. Fluoride supplementation for young children, routine dental cleanings with precautions taken if low blood counts are coexistent, and meticulous daily dental hygiene are recommended for all patients with TBD.

Beginning at age 10, patients with confirmed/high risk TBD either pre- or post-HCT should establish care with an otolaryngologist to undergo nasolaryngoscopic evaluation of the nasal, oropharyngeal, and laryngeal mucosa for pre-malignant or malignant lesions. If the initial evaluation is normal, repeat screening can be performed every 2-3 years, whereas at least annual screening is recommended for patients in whom suspicious lesions are identified.

Hearing impairment is a feature of some, but not all TBD. Any toddler or older child with a TBD who exhibits significant speech delay or fails an independent hearing assessment should be referred for formal audiologic assessment.

Gastrointestinal (GI) and Nutrition Screening

All pediatric individuals with TBD should have weight and nutrition assessments at a minimum of every 6 months performed by their general pediatrician and/or medical home provider. Weight loss, inadequate weight gain, or other metrics consistent with failure to thrive are indications for formal consultation with nutritionist. Even after adequate nutrition has been restored and supplementation is discontinued, ongoing annual nutritionist consultation is recommended to ensure adequate number of calories and a balance of nutritional sources continues. After HCT, patients are at particularly high risk for malnutrition due to chemotherapy effects on the absorptive capacity of the GI tract, infections and medications that alter gut flora, and possible complications from graft versus host disease. Thus, weekly to monthly nutrition consultations are often required during the first year post-HCT.

Patients with TBD are also at high risk for developing esophageal stenosis and esophageal webs [24] (see also Chapter 17, Gastrointestinal Disease). At twice yearly visits, all patients should be screened for onset of difficulty swallowing, regurgitation, and new solid food avoidance. A positive screen would indicate need for referral to a gastroenterologist with experience in performing and interpreting esophagrams and esophagoscopy with dilatation in patients with TBD. Patients who have previously developed esophageal stenosis often require yearly evaluations with an interventional gastroenterologist for consideration of repeat esophagoscopy and dilation procedures.

Patients with TBDs may also develop enteropathy and enterocolitis [24]. Patients with high or moderate risk TBD who have chronic abdominal pain, diarrhea, and specific food intolerance related to these symptoms should be referred to establish routine care with a gastroenterologist. Hematochezia (bloody stools) in patients with TBD may be a sign of enterocolitis, GI telangiectasias (particularly in Coats Plus), or lower GI tract malignancy and warrants urgent evaluation by a gastroenterologist [25].

Esophageal, stomach, colon and rectal cancer have all been described in patients with TBD [26]. In patients with confirmed/high risk TBD not undergoing routine upper and lower endoscopic screening for the above complications, routine esophagogastroduodenoscopy and sigmoidoscopy/colonoscopy to screen for malignant or pre-malignant lesions should be initiated by age 18. If initial screening is normal, endoscopies should be repeated every three to five years. In addition, fecal occult blood (FOB) screening by card-based testing should be started around age 12. For patients with suspected/moderate TBD, FOB and endoscopic screening should be performed for any patients with a history of chronic GI symptoms. Finally, patients who have undergone HCT should have FOB testing initiated with one year after HCT and endoscopic screening initiated within three to five years regardless of age, particularly if they have had a history of GI complications associated with HCT including GVHD.

Dermatologic Screening

For all pediatric individuals with TBD, routine screening for skin squamous cell carcinoma (SCC) should be performed with annual visits to a dermatologist starting at age five or earlier if concerning lesions are present, given the early known occurrence of SCC in patients with TBD [6] (see also Chapter 6, Dermatologic Manifestations). This yearly dermatologic follow-up may also be helpful for management of the many other dermatologic complications that can occur with TBD, including hyperkeratosis (thickening) of palms/soles, poor hair growth/alopecia, and hyperhidrosis (excessive sweating) [27].

Starting from the time of diagnosis, routine daily skin care is critical for optimal dermatologic outcomes. This care includes strict adherence to sun protection strategies including liberal use of sunscreen, use of hats and clothing to avoid sun exposure, and limiting peak UV ray exposure during the hours of 10 am to 4 pm. Daily moisturizer use, avoidance of harsh soaps/cleansers, and excellent oral hydration intake are additional critical elements to successful routine dermatologic care.

Ophthalmologic Screening

Patients with specific TBD including Revesz syndrome, Hoyeraal Hreidarsson syndrome, and Coats Plus are additionally at high risk for retinal vascular changes including exudative retinopathy and neovascularization [28]. These patients should have a formal retinal vascular evaluation upon diagnosis, to prevent vision loss (see also Chapter 7, Ophthalmologic Complications). Routine annual eye exams for all patients with TBD should begin by age five years to screen for the many ophthalmic complications common in TBD, including nasolacrimal duct obstruction/collapse leading to excessive tearing, ectropion and loss of eyelashes, corneal scarring and conjunctivitis [29]. After HCT patients are at risk of dry eyes and cataracts due to GVHD and conditioning agent side effects, respectively.

Neurologic Screening

Developmental assessments and neurologic exams should be performed on all pediatric individuals with TBD (see also Chapter 24, Neuropsychiatric Complications). Many patients with TBD do not manifest overt neurologic symptoms or verbal/cognitive developmental delay. Thus, onset of developmental delay or any symptoms of a neurologic disorder including tremor, focal weakness/paresthesia or seizures should warrant neurology consultation. A screening brain MRI is recommended for any patient with developmental delay or neurologic symptoms. Screening brain imaging by MRI and/or CT imaging is also recommended as an initial screen for all patients with TBDs genetic variants highly associated with neurologic complications. These variants include Hoyeraal Hreidarsson syndrome which is associated with cerebellar hypoplasia, and Coats Plus and Revesz syndromes that are associated with intracerebral calcifications [30]. Patients with these specific syndromes are recommended to have routine annual care with a neurologist to assess and manage onset or progression of neurologic symptoms.

Behavioral and Mental Health Screening

Patients with TBDs are at increased risk for early childhood onset of attention deficit and hyperactivity disorder, pervasive developmental disorder (eg. Autism), and learning disorders [30, 31] (see also Chapter 24, Neuropsychiatric Complications). Pediatricians and medical home providers should assess for these symptoms at twice yearly visits in early childhood. Positive screens for any of the above conditions should result in referral to community-based resources such as early intervention, school-based resources for the development of an individualized education program (IEP), and/or private behavioral health resources for evaluation and management.

Due to the complex medical care and challenging prognoses associated with many of the disease manifestations of TBDs, patients are at high risk for development of mood, anxiety, and adjustment disorders related to coping with a chronic medical illness. We recommend older pediatric and adolescent patients establish care with a mental health specialist familiar with TBD and associated complications, preferably by age 10-12 years. Routine counseling, at least annually, with this specialist that includes discussion of individual stressors and general coping strategies, is an essential part of comprehensive care for patients with TBD.

Table 1: Screening guidelines for pediatric patients with confirmed High-risk Telomere Biology Disorders (TBD).

Specialty/ Type of Screening	Timing of Initial Screen*	Frequency of Follow-up Screening (if initial screen normal)[+]
Hematology		
CBC monitoring	At diagnosis	Every 6 months
Bone marrow monitoring	At diagnosis	Yearly starting at 10 years
Immunology		
Immune function assessment	At diagnosis	Repeat with change in infection frequency or development of BM failure
Endocrinology		
MH growth and bone health assessment	At diagnosis	Yearly
Endocrinology consultation	Age 10[&]	Yearly
DXA scan	Age 12-14	Every 3 to 5 years
Hepatology		
Liver function tests	At diagnosis	Yearly
Liver ultrasound	Age 5	Yearly[#]
Pulmonary		
Spirometry/DLCO	Age 10[$]	Every 2-3 years
High Resolution CT	At diagnosis, if history of symptoms	Based on symptoms
ENT/Oral Cavity		
Dental assessments	Age 3	Every 6 months
Nasolaryngoscopy	Age 10	Every 2-3 years

Audiology	Only if history of symptoms	Based on symptoms
GI/Nutrition		
MH nutrition assessment	At diagnosis	Every 6 months
Nutritionist consultation	At onset of FTT	Yearly
Upper/lower endoscopy	At symptom onset or age 18	Every 3-5 years for routine screening. Yearly if symptoms.
Dermatology		
Dermatologist screening	Age 5	Yearly
Ophthalmology		
Routine eye exam	Age 5	Yearly
Retinal exam for specific TBD[%]	At diagnosis	Yearly
Neurologic		
Brain MRI for specific TBD[%] or neurologic abnormalities	At diagnosis	Based on symptoms
Behavioral/Mental Health		
ADHD, PDD, learning disorders	At diagnosis	Depends on symptoms
Mental health assessment	Age 10	Yearly

Abbreviations: BM, bone marrow; MH, medical home; hx, history; GI, gastrointestinal; FTT failure to thrive; ADHD, attention deficit/hyperactivity disorder; PDD, pervasive developmental disorder

*Recommendations in this table refer to patients who have not undergone hematopoietic cell transplant (HCT) and have confirmed severe TBD. Recommendations for post-HCT monitoring and for patients with suspected/moderate TBD are included in the chapter text.

+More frequent monitoring is generally recommended for patients with abnormal initial screening, as detailed in the chapter text

[&]Patients with growth delay, compromised bone health, or receiving androgen therapy need earlier initiation of endocrinology care

[#]Patients receiving androgen therapy need liver ultrasound screening every 6 months

[$]Patients with history of sinopulmonary infections or lung disease in early childhood should begin spirometry at age 5. Age of initial PFT's is also dependent on developmental ability.

[%]TBD at high risk for retinal and neurologic abnormalities include Revesz, Hoyeraal-Hriedarsson, and Coats Plus syndromes

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