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Inherited Telomere Biology Disorders: Pathophysiology, Clinical Presentation, Diagnostics, and Treatment

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Abstract
Background: Telomeres are the end-capping structures of all eukaryotic chromosomes thereby protecting the genome from damage and degradation. During the aging process, telomeres shorten continuously with each cell division until critically short telomeres prevent further proliferation whereby cells undergo terminal differentiation, senescence, or apoptosis. Premature aging due to critically short telomere length (TL) can also result from pathogenic germline variants in the telomerase complex or related genes that typically counteract replicative telomere shortening in germline and certain somatic cell populations, e.g., hematopoetic stem cells. Inherited diseases that result in altered telomere maintenance are summarized under the term telomere biology disorder (TBD). ***Summary:*** Since TL both reflects but more importantly restricts the replicative capacity of various human tissues, a sufficient telomere reserve is particularly important in cells with high proliferative activity (e.g., hematopoiesis, immune cells, intestinal cells, liver, lung, and skin). Consequently, altered telomere maintenance as observed in TBDs typically results in premature replicative cellular exhaustion in the respective organ systems eventually leading to life-threatening complications such as bone marrow failure (BMF), pulmonary fibrosis, and liver cirrhosis. ***Key Messages:*** The recognition of a potential congenital origin in approximately 10% of adult patients with clinical BMF is of utmost importance for the proper diagnosis, appropriate patient and family counseling, to prevent the use of inefficient treatment and to avoid therapy-related toxicities including appropriate donor selection when patients have to undergo stem cell transplantation from related donors. This review summarizes the current state of knowledge about TBDs with particular focus on the clinical manifestation patterns in children (termed early onset TBD) compared to adults (late-onset TBD) including typical treatment- and disease course-related complications as well as their prognosis and adequate therapy. Thereby, it aims to raise awareness for a disease group that is currently still highly underdiagnosed particularly when it first manifests itself in adulthood.

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Introduction

The end structure of all chromosomes was identified in 1938 by Hermann Mueller as "telomeres" in flies and a little later by Barbara McClintock in corn [1, 2]. McClintock also recognized the importance of proper telomere maintenance

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for chromosomal stability by demonstrating that telomeres are required to prevent (otherwise free) chromosome ends from fusion with each other [1]. It took almost four decades until the underlying tandem repeat sequence of telomeres was first described by Elizabeth Blackburn in 1978 [3]. This noncoding, three-dimensional telomeric loop structure organizes and protects genetic information encoded in subtelomeric DNA [1, 4]. In the course of this review, we will (1) introduce the structure of the telomere complex including telomere-associated proteins as well as telomerase, (2) describe diseases that are thought to result from impaired telomere maintenance, (3) focus on the differential symptomology associated with early onset (classical "dyskeratosis congenita," DKC) as well as late-onset (so-called cryptic) telomere biology disorders (TBDs), and finally, (4) explain existing diagnostic and therapeutic options for patients with TBD.

Structure of Telomeres and Telomerase

The typical $(TTAGGG)^n$ telomere repeat sequences at the 192 ends of the 48 chromosomes of a human cell are organized by a sophisticated interplay between different proteins and nucleic acids that build various complexes essential for proper telomere maintenance and protection [4]. The most important complexes are the shelterin complex, telomerase and associated modifiers, the CST, cytoplasmic iron-sulfur assembly, and the Apollo complexes [4–8].

The shelterin complex contributes essentially to the formation of the T-loop end structure of the chromosomes and is comprised of proteins such as telomeric repeat binding factor 1 (TERF1), TERF2, TERF1 interacting nuclear factor 2 (TINF2) (=TIN2), repressor/activator protein 1 (RAP1), adrenocortical dysplasia protein homolog (TPP1), and protection of telomeres 1 (POT1) [6, 9]. The complex functionally constitutes a protective cap around the telomeres thereby protecting them from degradation and from being (mis)recognized as a double-strand break by the DNA repair machinery (shown in Fig. 1) [6, 9].

The telomerase complex consists of the proteins telomerase reverse transcriptase (TERT) with the corresponding telomerase RNA component (TERC), the protein dyskerin (DKC1), the H/ACA ribonucleoprotein complex subunit 2 (NHP2), the nucleolar protein 10 (NOP10), GAR1 ribonucleoprotein (GAR1), and the WD repeat containing antisense to TP53 (TCAB1) [4, 5]. The complex is of particular importance in germline and certain somatic (stem) cell populations and promotes the active lengthening or net stabilization of telomeres, e.g., in highly proliferative organs (shown in Fig. 1) [4, 5].

The CST complex includes the CST telomere replication complex component 1 (CTC1), the TEN1 subunit of CST complex (TEN1) and the STN1 subunit of CST complex (STN1) and is essential for telomere maintenance especially under conditions of replicative stress [6, 10]. There are also other complexes described as the cytoplasmic iron-sulfur assembly complex and the Apollo complex (contains the protein DNA cross-link repair 1B, DCLRE1B, = Apollo) [7, 11, 12]. Both complexes play a fundamental role in DNA repair and protection of telomeric DNA [7, 11, 12].

In general, many of the proteins involved in telomere regulation are important for DNA integrity, intracellular signaling cascades, and ribosomal function [8, 13, 14]. These proteins protect the telomeric region and regulate its tertiary and quaternary structure thereby avoiding genetic instability leading to end-to-end fusions, unbalanced translocations, and eventually loss of chromosomal DNA [8].

Telomeres and Telomerase Activity

In most somatic cells, telomeres shorten with each cell division due to the so-called "end replication problem" [1]. This physiological mechanism leads to age-related telomere length (TL) shortening thereby limiting the lifespan of cellular organisms [1, 15, 16]. Cells that reach critically short TL undergo replicative senescence and/or apoptosis [17]. Non-replication dependent reduction of TL can also occur due to oxidative damage [18, 19] or increased activity of the telomeric zinc finger-associated protein (TZAP) that can actively trim telomeres [20]. TL shortening can both act as an efficient regulator of cell proliferation as well as a tumor preventive mechanism by limiting the number of cell divisions a somatic cell can undergo under normal circumstances, a condition first described in 1961 as the so-called Hayflick limit. For most somatic cell types, the Hayflick limit is assumed to be reached after around 50–80 mitoses in somatic cells [21]. With increasingly critical shortness, telomeres can destabilize DNA leading to increased DNA degradation, increased fusion between different chromosomes, eventually resulting in dicentric chromosomes, chromosomal breakage, or aneuploidy [8].

The inverse correlation between an individual cell's TL and its lifespan was suggested to act in the sense of a biological clock [1, 17]. Nevertheless, some cellular compartments are capable to counteract replicative TL shortening via various mechanisms. In 1985, the telomerase complex that enables the elongation of the telomere repeat sequence was first discovered [22]. Telomerase is primarily recruited to the telomeric region by interacting with proteins of the shelterin complex [4, 8, 9]. Embryonic stem cells, sperm cells, but also some adult cell populations (e.g., hematopoietic stem cells [HSCs], epidermal cells, and activated (B-)lymphocytes) are able to (re)express and actively use the function of this protein [8]. Nevertheless, in steady-state, most somatic cells do not express telomerase which means that telomeres require special protective mechanisms [4]. Apart from telomerase activity, other

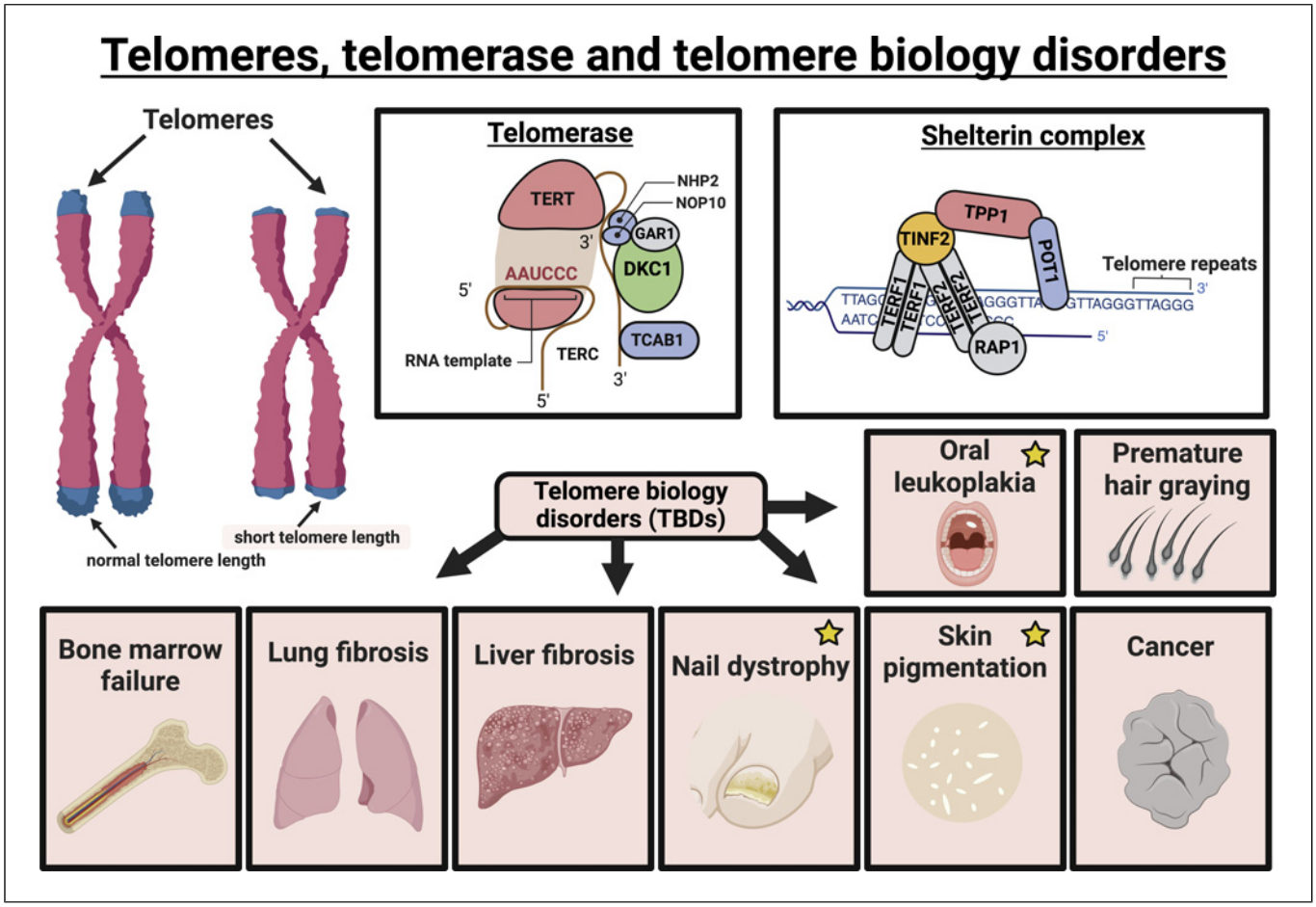

Fig. 1. Telomeres, telomerase, and TBDs. The figure shows parts of the telomerase and shelterin complex and their interaction with the telomere repeat region. The components are shown in different colors depending on the described disease-causing heritability. Red indicates components that are inherited in an autosomal dominant (and/or autosomal recessive) manner. Blue indicates components that are mostly inherited in an autosomal recessive manner. Green indicates the x-linked inheritance of *DKC1*, orange shows *TINF2* (often de novo), and gray indicates components for which the current literature is sparse or not present. Potential symptoms of telomere biology disorders (TBDs) are indicated in the bottom part of the figure. The classical triad of dyskeratosis congenita (DKC) is marked with a yellow star. Adapted from "Telomeres and Telomerase," by BioRender.com (2024). Retrieved from "https://app.BioRender.com/biorender-templates".

mechanisms known to be able to sustain and increase TL are summarized under the term "alternative lengthening of telomeres" (ALT) [23].

Brief Introduction into TBDs

Historically, DKC was first described on the basis of skin manifestations such as leukoplakia and nail dystrophy by the dermatologist Zinsser [24], as well as Engman [25] and Cole [26]. One of the first systematic reviews of dyskeratosis congenita was published by Costello and Buncke [27] in 1956 and later reports expanded the spectrum of clinical symptoms related to dysfunction of other organ systems such as bone marrow failure (BMF) [28, 29]. Only in 1998, the connection between a defective telomerase component leading to prematurely shortened telomeres was discovered, thereby proving the causal link between a pathogenic variant in a single gene and the multisystem pathophysiology of DKC [30, 31]. In the following years, techniques to routinely measure TL in the peripheral blood of normal individuals and patients with HSC-associated disorders were developed [32–35] enabling the functional screening of patients for an underlying TBD as practiced today [36, 37].

Whereas accelerated telomere shortening had first been described in blood cells from patients with acquired aplastic anemia in 1998 [38], this was initially suspected to be a secondary phenomenon, i.e., to result from increased stem cell turnover of residual HSCs as a response to continuous autoimmune-mediated damage to the stem cell compartment [39]. Subsequently, in 2005 it was

Table 1. Genes that have been proven to cause telomere biology disorders (TBDs)

Gene	Protein	Function	Potential consequence of pathogenic variants	Estimated proportion of all TBDs, *n* (%)	Year reported (clinical condition)	Nature of inheritance
Adrenocortical dysplasia protein homolog (*ACD*) (=*TPP1*) [46, 47]	TPP1 (not (!) tripeptidyl peptidase 1)	• Part of the shelterin complex (Capping/ Bridging shelterin) • Bridging component • Recruits POT1 and telomerase • Binds to the POT1 protein, TINF2, and the ataxia telangiectasia and Rad3-related protein (ATR) • Regulates TL and supports stability • Regulates DNA repair	• Decreased recruitment of the telomerase	1.5	2014	Autosomal dominant or autosomal recessive
CST telomere replication complex component 1 (*CTC1*) [48, 49]	CTC1	• Part of the CST complex • Replication of the telomere repeats • Stimulation of DNA polymerase α-primase	• Instable telomeres • Impaired replication of the telomere repeats • Sometimes less prominent/no change in TL	3	2012	Autosomal recessive
DNA cross-link repair 1B (*DCLRE1B*) (=*SNM1B*) (=*Apollo*) [11, 50]	Apollo	• Interacts with TERF2 • Protects telomeres during and after replication • Function in DNA repair • Overhang processing	• Genetic instability • Often with normal TL (in some cases very short telomeres were only detected by using more sensitive methods)	<1	2010	Autosomal recessive
Dyskerin pseudouridine synthase 1 (*DKC1*) [30]	Dyskerin	• Part of the telomerase complex • Stabilization of TERC	• Reduced telomerase activity • Instability of TERC	25	1998	X-linked
MDM4 regulator of p53 (*MDM4*) [51]	MDM4	• Regulates and degrades TP53	• Increased TP53 activity • Short TL	<1	2020	Autosomal dominant
Nuclear assembly factor 1 ribonucleoprotein (*NAF1*) [52]	NAF1	• Regulation of telomerase • Enables protein binding and binding of TERC • Stabilization of TERC and H/ACA small ribonucleoproteins (chaperon function) • Important factor for the biosynthesis of ribosomes	• Reduced telomerase activity • Instability of TERC	<1	2016	Autosomal dominant

Table 1 (continued)

Gene	Protein	Function	Potential consequence of pathogenic variants	Estimated proportion of all TBDs, *n* (%)	Year reported (clinical condition)	Nature of inheritance
H/ACA ribonucleoprotein complex subunit 2 (*NHP2*) (=*NOLA2*)	NHP2	• Part of the telomerase/dyskerin complex • (Non-catalytic) component of H/ACA small nucleolar ribonucleoproteins • Biogenesis of telomerase • Stabilization of TERC • Essential for the biogenesis of ribosomes	• Reduced telomerase activity • Instability of TERC	<1	2008	Autosomal recessive
Nucleolar protein 10 (*NOP10) (=NOLA3)* [53, 54]	NOP10	• Part of the telomerase/dyskerin complex • Biogenesis of telomerase • Stabilization of TERC	• Reduced telomerase activity • Instability of TERC	<1	2007	Autosomal recessive
Nucleophosmin 1 (*NPM1*) [55]	NPM1	• Modifying rRNA (for example regulating ribosomal RNA 2′-O-methylations (2′-O-Me)) • Interacts with NHP2 and NOP10	• Impaired ribosome function by aberrant 2′-O-Me on rRNA residues	<1	2019	Autosomal dominant
Poly(A)-specific ribonuclease (*PARN*) [56–60]	PARN	• Processing of TERC • Stabilization of TERC	• Reduced telomerase activity • Instability of TERC • Sometimes only with subtle change in TL (close to the 10% percentile)	>1% (especially in patients with idiopathic PF)	2015	Autosomal dominant or autosomal recessive
Protection of telomeres 1 (*POT1*) [61, 62]	POT1	• Part of the shelterin complex • Binds to telomeres (3′ overhang) and interacts with the CST complex • Binds to TPP1 • Binds to ATR and inhibits ATR-mediated DNA damage response • Inhibits end-to-end fusion/protects the G-strand	• Impaired replication of the telomere repeats • Dysfunctional regulation of the telomerase • Defective binding to the telomere overhang	<1	2016	Autosomal recessive
Replication protein A1 (*RPA1*) [63]	RPA1	• Important for DNA replication and telomere maintenance • Functions in DNA repair • Binds single-stranded DNA and protect its structure	• Increased amount of unfolded telomeres • Increased binding affinity to single-stranded and telomeric DNA (gain of function)	<1	2022	Autosomal dominant

Table 1 (continued)

Gene	Protein	Function	Potential consequence of pathogenic variants	Estimated proportion of all TBDs, *n* (%)	Year reported (clinical condition)	Nature of inheritance
Regulator of telomere elongation helicase 1 (*RTEL1*) [64–68]	RTEL1	• Replication of the telomeres • Dissociation and stability of T-loops • Target of the cytosolic iron-sulfur protein assembly (CIA) complex • Prevents loss of telomeres	• Decreased/ impaired telomere replication • Decreased telomere stability	10	2013	Autosomal dominant or autosomal recessive
STN1 subunit of CST complex (*STN1*) [69]	STN1	• Part of the CST complex • Important for telomere replication	• Decreased/ impaired telomere replication	<1	2016	Autosomal recessive
Telomerase RNA component (*TERC*) [70]	TERC	• Part of the telomerase complex • Elongation of telomeres	• Reduced telomerase activity	10	2001	Autosomal dominant
Telomerase reverse transcriptase (*TERT*) [40, 41]	TERT	• Part of the telomerase complex • Recruitment of telomerase • Elongation of telomeres • Impacts the Wnt signaling pathway • Might promote pluripotency and mobilization of stem cells	• Reduced telomerase activity • Impaired telomerase recruitment	7	2005	Autosomal dominant or autosomal recessive
TERF1 interacting nuclear factor 2 (*TINF2*) (=*TIN2*) [71, 72]	TIN2	• Part of the shelterin complex (bridging shelterin) • Stabilizes the shelterin complex • Protects telomeres and regulates TL • Recruits and regulates telomerase • Binds to TPP1, TERF1, and TERF2. Stabilizes TERF1/ TERF2 interaction • Inhibits PARsylation of TERF1	• Impaired telomere maintenance	20	2008	Autosomal dominant (often as a de novo mutation)

Table 1 (continued)

Gene	Protein	Function	Potential consequence of pathogenic variants	Estimated proportion of all TBDs, *n* (%)	Year reported (clinical condition)	Nature of inheritance
WD repeat containing antisense to TP53 (*WRAP53*) (=*TCAB1*) [73, 74]	TCAB1	• Associated with the telomerase complex • Facilitates (physiological) protein-protein and protein-RNA interactions • Interacts with Dyskerin, TERT, and TERC • Recruits telomerase to the telomeres • Recruits proteins to the sides of Cajal bodies and sides of DNA damage • Transcript regulates levels of *TP53* RNA	• Impaired trafficking and recruitment of telomerase	<1	2011	Autosomal recessive
Zinc finger CCHC-type containing 8 (*ZCCHC8*) [75]	ZCCHC8	• TERC processing and maturation	• Decreased/ impaired telomerase function • Accumulation of extended TERC/ decreased maturation of TERC	<1	2019	Autosomal dominant
Unknown [17, 45]				≈20		

The table summarizes genes with the respective protein name and function that might harbor pathogenic variants that lead to impaired telomere maintenance and clinical manifestations. Potential consequences of pathogenic variants, the estimated proportion of pathogenic variants in this gene among all telomere biology disorders (TBDs), the year of the first clinical description and the suspected inheritance pattern are shown [43, 45, 76, 77].

shown that pathogenic germline variants in the telomerase reverse transcriptase (*TERT*) gene can be detected in adult patients with aplastic anemia thereby defining the so-called late-onset, adult TBDs [40, 41]. Due to the rapid development of sequencing techniques, a larger number of other genes with pathogenic variants were detected in juvenile and adult TBD patients in the following years, such as variants in the regulator of telomere elongation helicase 1 (*RTEL1*) or the poly(A)-specific ribonuclease (*PARN*) in patients with interstitial lung disease [42].

At the moment, there is sufficiently strong evidence that certain variants of the following genes might cause a clinically relevant TBD phenotype (see Table 1): adrenocortical dysplasia protein homolog (*ACD*) (=*TPP1*), CST telomere replication complex component 1 (*CTC1*), DNA cross-link repair 1B (*DCLRE1B; =SNM1B*; = *Apollo*), dyskerin pseudouridine synthase 1 (*DKC1*), MDM4 regulator of p53 (*MDM4*), nuclear assembly factor 1 ribonucleoprotein (*NAF1*), H/ACA ribonucleoprotein complex subunit 2 (*NHP2*) (=*NOLA2*), nucleolar protein 10 (*NOP10*) (=*NOLA3*), nucleophosmin 1 (*NPM1*), *PARN*, protection of telomeres 1 (*POT1*), replication protein A1 (*RPA1*), *RTEL1*, STN1 subunit of CST complex (*STN1*), telomerase RNA component (*TERC*), *TERT*, TERF1 interacting nuclear factor 2 (*TINF2*) (=*TIN2*), WD repeat containing antisense to TP53 (*WRAP53*) (=*TCAB1*), and zinc finger CCHC-type containing 8 (*ZCCHC8*) [17, 43–45].

While initially DKC was considered an appropriate term for all telomere-related diseases, it later became clear that on the one hand side, certain pediatric forms such as the Revesz syndrome, the Hoyeraal-Hreidarsson syndrome, or the Coats plus syndrome are characterized by a strikingly more severe phenotype and earlier disease onset clearly distinct from classical DKC [48, 64, 78]. On the other hand, adult-onset forms of TBDs sometimes only manifest themselves beyond 40 years of age, often lacking a skin phenotype and displaying distinct and highly variable organ system manifestations from classical DKC [36, 45].

Consequently, in parallel to the identification of a growing number of disease-causing genes, there was also a change in nomenclature [7, 44]. For instance, some patients with a Coats plus syndrome harbor a pathogenic variant in a gene important for telomere maintenance and show a TBD phenotype, but do not have shorter TL [43, 48, 61]. This led to the change in terminology away from the term telomeropathy or telomere disease to the currently used term TBD [17, 43].

The main clinical symptoms and diagnostic of TBDs are shown below. We proceed chronologically according to age of first disease manifestation. TBDs that will be discussed include early pediatric forms, and classical adolescence DKC, but the focus of this review is on different forms and manifestations of late-onset (previously called "cryptic") TBDs.

Diagnostics

In general, there are several techniques available to measure TL [33, 36, 37]. The current standard for clinical detection of shortened TL is the combination of a quantitatively telomere-binding FISH probe in combination with flow cytometry (flow-FISH) [32, 33]. This method was developed for the analysis of clinical specimen, i.e., to allow for high cell numbers (see telomere Q-FISH for comparison [79]) in high throughput and to be able to analyze at the same time different blood cell subpopulations involved in disease pathophysiology [34, 39, 80–82]. Interestingly, lymphocyte TL measured via flow-FISH is sensitive and highly specific and was empirically shown to be superior for diagnosis of inherited TBD over granulocyte TL probably because the latter population is more directly involved in the disease course of AA itself (see above) while lymphocyte TL more specifically reflects the hereditary "telomere genotype" [15, 43, 83]. In analogy to percentile-based growth curves that are used to track physical development in children, TBDs can be identified on the basis of differences in TL from age-adapted percentiles [36, 83]. Thereby, TL in the peripheral blood shows a negative correlation with age and it follows an at least bi-phasic kinetic [33]. The most frequently used diagnostic threshold for TBDs is currently a TL value below the 1% percentile of normal individuals measured by flow-FISH in lymphocytes. Due to the substantially larger "diagnostic window" in children, conventional methods for TL measurement like PCR with lower sensitivity are still being used in pediatric patients [37]. In borderline cases or in scenarios with a high degree of clinical suspicion for an underlying TBD (e.g., due to family history, clinical phenotype or other aspects), detection of TL in lymphocyte subsets might also help increase sensitivity and specificity [15, 43, 83]. Although overall lymphocyte TL is the most established marker to diagnose TBDs, more recent publications indicate that the simultaneous detection of lymphocyte and granulocyte TL should be preferred [43, 84]. In case of short TL below the 1% percentile, subsequent genetic testing is recommended to test for disease causing germline variants in so-far known TBD-related genes [36, 37, 83]. However, based on current knowledge a pathogenic variant cannot be detected in all clinical TBD cases primarily suggesting that not all gene alterations involved in telomere maintenance are yet known and secondly, highlighting the diagnostic value of TL measurements as the yet only functional test available for primary screening of TBDs [17, 45].

Early Severe Pediatric Forms of TBDs

Early severe pediatric forms of TBDs with often characteristic underlying genetic variants are the Revesz syndrome, the Hoyeraal-Hreidarsson syndrome, and the Coats plus syndrome [45, 64, 69, 78]. Revesz and Hoyeraal-Hreidarsson syndrome are characterized by a severe disease course, very short telomeres (considerably below the 1% percentile), and a disease onset in the early childhood [45, 65, 78]. In comparison, the Coats plus syndrome does not necessarily have to be accompanied by short TL (in this rare case of a TBD leading to a limited diagnostic value of TL screening) but otherwise shows classical signs of TBD [61, 69, 76]. All three forms overlap clinically with classical DKC and are associated with significantly reduced survival [45, 85].

Revesz syndrome typically features bilateral exudative retinopathy, intracranial calcification, cerebellar hypoplasia thereby causing ataxia, (intrauterine) growth restriction, general developmental delay, and fine hairs. Affected patients have a high risk for BMF. It is often caused by variants in the *TINF2* gene [78, 77].

Hoyeraal-Hreidarsson syndrome, on the other hand, shares some signs of Revesz syndrome such as cerebellar hypoplasia and intrauterine growth restriction, but can also present with progressive immunodeficiency, microcephaly, and moderate to severe mental retardation. Also, progressive pancytopenia (early onset) is frequently observed. In many cases, pathogenic germline variants in the *DKC1* gene are detected as the underlying cause of the syndrome [11, 64, 65, 86, 73].

Characteristic findings of Coats plus syndrome are exudative retinopathy, cerebroretinal microangiopathy with concomitant brain calcifications, brain cysts, loss of the white matter (leukodystrophy), gastrointestinal bleedings, and bone abnormalities (e.g., osteopenia). Abnormalities of the skeletal system are often accompanied by impaired bone healing. The leukodystrophy can lead to a progressive cognitive decline [48]. Also, anemia and thrombocytopenia (with or without BMF) are common symptoms. Variants in the genes *CTC1*, *STN1* and *POT1* are frequently found in patients with Coat plus syndrome [48, 61, 69].

Table 2. (Inherited) telomere biology disorders (TBDs) together with accompanying symptoms

Disease	Genes that might harbor pathogenic variants	Clinical manifestations
(Classical) Dyskeratosis congenita (DKC) (=Zinsser-Engman-Cole syndrome) [30, 49, 53, 55, 56, 66, 67, 70, 71, 74] (Manifestation: childhood or (early) adolescence)	*DKC1*, *TERT*, *TERC*, *TINF2*, *RTEL1*, *NOP10*, *NHP2*, *CTC1*, *ACD* (=*TPP1*), *PARN*, *RPA1*, *WRAP53* (=*TCBA1*), *DCLRE1B* (*Apollo*), *NPM1*	• Dystrophic nails* • Skin pigmentations* (e.g., hyper/hypopigmented areas, often with a reticular pattern) • Oral leukoplakia*(potential precancerous) • BMF • Gray hairs and alopecia • Palmoplantar hyperkeratosis and hyperhidrosis • Short stature and osteoporosis • Avascular necrosis (e.g., hip or shoulder) • Lung fibrosis and emphysema • (Pulmonary) arteriovenous malformations • Liver fibrosis, liver cirrhosis, and various other liver diseases • (Gastro)intestinal diseases • Neurological symptoms • Visual disorders • Hypogonadism • Increased watering of the eyes due to lacrimal duct atresia • Dental caries • Esophageal strictures • Stenosis of the urethra • Increased cancer and leukemia risk
Hoyeraal-Hreidarsson syndrome [11, 64, 65, 73, 86] (severe phenotypic variant of DKC) (Manifestation: early childhood)	*DKC1*, *TERT* (autosomal recessive), *TINF2*, *PARN*, *WRAP53* (=*TCBA1*), *ACD* (=*TPP1*), *RTEL1*, *NHP2*, *DCLRE1B* (*Apollo*)	• Possible overlap with most characteristics of DKC • Cerebellar hypoplasia and microcephaly • Immunodeficiency (progressive) • (Intrauterine) growth restriction • Mental retardation • BMF (early onset and progressive) • Mucocutaneous lesions (e.g., hyper/hypopigmentation, nail dystrophy, and premalignant leukoplakia [oral + gastrointestinal]) • Higher risk of cancer and PF
Revesz syndrome [71] (severe phenotypic variant of DKC) (Manifestation: early childhood)	*TINF2*	• Bilateral exudative retinopathy • Skin hyper/hypopigmentation • Nail dystrophy • Oral leukoplakia • Fine and sparse hairs • Intracranial calcifications • Balance problems/ataxia • (Intrauterine) growth restriction • High risk of BMF • Risk of liver and lung fibrosis • High risk of cancer (e.g., leukemia)
Coats plus syndrome [48, 61, 69] (Manifestation: (early) childhood or (early) adolescence)	*CTC1*, *STN1*, *POT1*	• Dilatation of blood vessels in the retina (exudative retinopathy/cerebroretinal microangiopathy) • (Brain) calcifications • (Brain) cysts • Gastrointestinal bleedings • Bone abnormalities (e.g., osteopenia) • Impaired bone healing • Leukodystrophy/leukoencephalopathy

Table 2 (continued)

Disease	Genes that might harbor pathogenic variants	Clinical manifestations
		• Ataxia, seizures, spasticity, and cognitive decline • Anemia and thrombocytopenia • Changed skin pigmentations (café-au-lait spots) • Malformations of the nails • Prematurely gray hairs • Portal hypertension • Often without short TL
"**Cryptic**" **DKCs/TBDs** (**Manifestation**: **adolescence or (late) adulthood**)		
BMF/aplastic anemia [41, 46, 50, 51, 55, 58, 63, 72]	*DKC1*, *TERT*, *TERC*, *NOP10*, *NHP2*, *RTEL1*, *ACD* (=*TPP1*), *DCLRE1B* (*Apollo*), *TINF2*, *NPM1*, *MDM4*, *RPA1*	• Pancytopenia (anemia, thrombocytopenia, neutropenia) • Hypocellular BM • Increased bleeding tendency • Increased susceptibility to infections
Idiopathic PF, interstitial lung diseases, emphysema [42, 47, 52, 54, 59, 62, 63, 75, 86, 89, 90]	*DKC1*, *TERT*, *TERC*, *NOP10*, *NHP2*, *ACD* (=*TPP1*), *RTEL1*, *PARN*, *RPA1*, *NAF1*, *TINF2*, *ZCCHC8*, *POT1*	• (Progressive) shortness of breath • Shallow and fast breathing • (Dry) cough – increased fatigue • (Unintended) weight loss • Clubbing of the finger tips (and toes)
Idiopathic liver cirrhosis/nodular regenerative hyperplasia/liver disease [68, 91, 92]	*TERT*, *TERC*, *RTEL1*, *TINF2*, *DKC1*, *NHP2*, *NOP10*, *NAF1*, *WRAP53* (=*TCBA1*)	• Increased fatigue • Increased bleeding tendency/bruising • Nausea and decreased appetite • (Unintended) weight loss • Edema • Jaundice of the skin and eyes • Itchy skin
Head and neck cancer (HNSCC), squamous cell carcinoma (e.g., anogenital cancer, skin, or esophagus) and other cancers [51, 93–100]	*TERT* (but also *TERT* promoter**), *TERC*, *CTC1*, *MDM4*, *NAF1*, *POT1****	• Cancer at a young age • Absence of risk factors • Family history of cancer or symptoms typical of TBD • Increased therapy-related toxicity
Others: MDS/hematopoietic diseases (e.g., *TERT*, *TERC*, *RPA1*, *NAF1*) [52, 63, 101, 102], immunodeficiencies/(auto)inflammation (e.g., *TERT*, *TERC*, *DKC1*, *RTEL1*) [84, 103, 104], and inflammatory bowel diseases/gastrointestinal manifestations [105, 106]		

Shown are different manifestations of telomere biology disorders (TBDs) and clinical symptoms which fall within the spectrum of a TBD. The table demonstrates potential clinical manifestations as well as genes that were predominantly described in the literature for different variants of TBD. The table shows diseases that often manifest in the early childhood (Revesz and Hoyeraal-Hreidarsson syndrome), childhood and early adolescence (DKC and Coats plus syndrome) and during late adulthood (cryptic TBDs). Important clinical features are printed in bold. *Classical DKC triad. **Associated with longer TL. ***Might also cause longer telomeres.

Adolescence or Young Adults: Classical DKC

The paradigmatic TBD is DKC or Zinsser-Engman-Cole syndrome. Classical DKC can be caused by different genetic variants in genes affecting telomerase function, telomere maintenance, and telomere interaction. Classical DKC is often diagnosed during childhood or early adolescence. In classical DKC pathogenic variants are found in genes such as *DKC1*, *TERT*, *TERC*, *TINF2*, *RTEL1*, *NOP10*, *NHP2*, *CTC1*, *ACD* (=*TPP1*), *PARN* and *WRAP53* (=*TCBA1*) [30, 49, 53, 56, 66, 67, 70, 71, 74]. Most variants lead to reduced telomerase activity and increased telomere erosion [15, 83]. More recent reports indicate that variants in *RPA1*, *STN1*, *DCLRE1B* (*Apollo*), and *NPM1* can also cause (classical) DKC [50, 55, 63].

Classical DKC shows severe manifestations early in life and the typical mucocutaneous triad with leukoplakia, reticulated skin pigmentations and nail dystrophy (classical DKC, shown in Fig. 1) [44, 83, 85]. Apart from the mucocutaneous triad, the characteristic clinical disease course includes an increased risk for BMF and cancer development [43, 44]. Additional symptoms reflecting the multi-systemic nature of TBDs include early hair

graying and alopecia, palmoplantar hyperkeratosis and hyperhidrosis, short stature and osteoporosis, avascular bone necrosis, lung fibrosis and lung emphysema, liver disease including liver fibrosis and liver cirrhosis, arteriovenous malformations, hypogonadism, different gastrointestinal diseases, neurological symptoms, visual disorders, atresia of the lacrimal duct, severe dental caries, esophageal strictures, and stenosis of the urethra (shown in Fig. 1; Table 2) [15, 44, 72, 83, 85, 87, 88].

About 80% of all cases show signs of BMF leading to significantly increased mortality. Especially patients with hematopoietic insufficiency experience a substantially increased risk of developing secondary hematopoietic malignancies such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) [85]. The cumulative risk of developing a secondary malignancy by the age of 50 years is about 40–50% [85]. As a result, median overall survival for patients with DKC was shown to be reduced to about 42 years in two independent cohorts [85].

Late-Onset Adult TBDs or Cryptic TBDs

In addition to TBDs first manifesting themselves in childhood or adolescence, there is nowadays increasing awareness about so-called late-onset TBDs also referred to as cryptic TBDs or adult-onset TBDs [36, 91]. Despite of this increasing perception as an important clinical subgroup, e.g., of patients with aplastic anemia (and/or liver cirrhosis and/or lung fibrosis), adult-onset hereditary syndromes in general and TBDs in particular are still severely underdiagnosed presumably because non-pediatricians are simply not as sensitized for a hereditary disease manifesting itself for the first time in adulthood [45]. What also contributes to this underdiagnosis is the fact that clinical symptoms are often subtle and highly variable between individuals as well as heterogeneously distributed over the organ systems involved [36, 43, 45]. The age of first manifestation depends very much on the respective genetic alteration and its respective impact on telomere biology (with or without the influence of additional external factors) [43, 76, 77]. Furthermore, TBDs are characterized by disease anticipation, i.e., age of critical telomere shortening and as a consequence, clinical onset of symptoms tends to decrease with consecutive generations [43, 44]. First manifestations often take place in middle-aged adulthood [36, 91]. The spectrum of cryptic TBDs might also include individuals who remain oligo- to even asymptomatic for most of their lives. Symptoms are often unspecific, making it very challenging to accurately diagnose a TBD [36, 91]. Cryptic TBD patients can present with only a single manifestation typically affecting lung, bone marrow, liver, or other TBD-associated symptoms [36, 45, 57, 91]. The four quantitatively most important clinical manifestations are given below.

BMF or MDS as a Manifestation of a Cryptic TBD

Due to the high cell turnover of the hematopoietic system with daily blood cell productions exceeding 10^{12} cells in steady-state [107], blood and bone marrow cells are particularly susceptible toward defects in telomere maintenance genes [17, 45]. It is assumed that critically short telomeres functionally impact the individual bone marrow replicative capacity until eventually, the bone marrow function exhausts due to HSCs depletion [17]. TL can therefore be used as a (bio-)marker to approximate the degree of replicative exhaustion of the HSC compartment (very short TL indicates long-lasting and intensive compensatory proliferation of the residual HSC compartment) and/or severity of the underlying genetic defect. Pathogenic variants in *DKC1*, *TERT*, *TERC*, *NOP10*, *NHP2*, RTEL1, *ACD* (=*TPP1*), *DCLRE1B* (*Apollo*), *TINF2*, *RTEL1*, *NPM1*, *MDM4*, and *RPA1* have been described in patients showing signs of BMF or aplastic anemia [41, 46, 50, 51, 55, 58, 63, 72]. Furthermore, pathogenic variants in *TERT*, *TERC*, *RPA1*, and *NAF1* have been recently associated with MDS-typical changes in the bone marrow [52, 63, 101, 102]. Ineffective hematopoiesis and an increased risk of malignant transformation can therefore be considered a consequence of telomere-mediated genetic instability [41, 108].

Due to the fact that many TBD-associated diseases may lead to cytopenia and BMF, exclusion of a TBD is part of the comprehensive diagnostic assessment in every newly diagnosed case of BMF [43, 109]. In particular, the clarification of the family history, examination of the patient for TBD-typical stigmata (see Fig. 1) and TL measurement are indispensable (see Fig. 2) [43]. The assessment of TL represents a relatively cheap and essential (pre)screening tool which should be followed (in case of significantly shortened TL) by a further work-up with a next-generation sequencing approach that focuses on pathogenic variants in genes that are involved in telomere maintenance (Fig. 2).

Correct identification of TBD patients is of utmost importance as patients with TBDs typically show no relevant clinical response to standard treatment for aplastic anemia like antithymocyte globulin, cyclosporine A, or eltrombopag [110]. In addition, TBDs are characterized by a significantly poorer outcome after allogeneic stem cell transplantation (allo-SCT) [111, 112]. Especially, the choice of a potentially affected family donor with the same genetic aberration should be avoided due to an increased risk of complications after allo-SCT (graft-failure, accelerated telomere shortening, and graft-versus-host disease) [112, 113]. A very careful donor selection, an adapted therapy

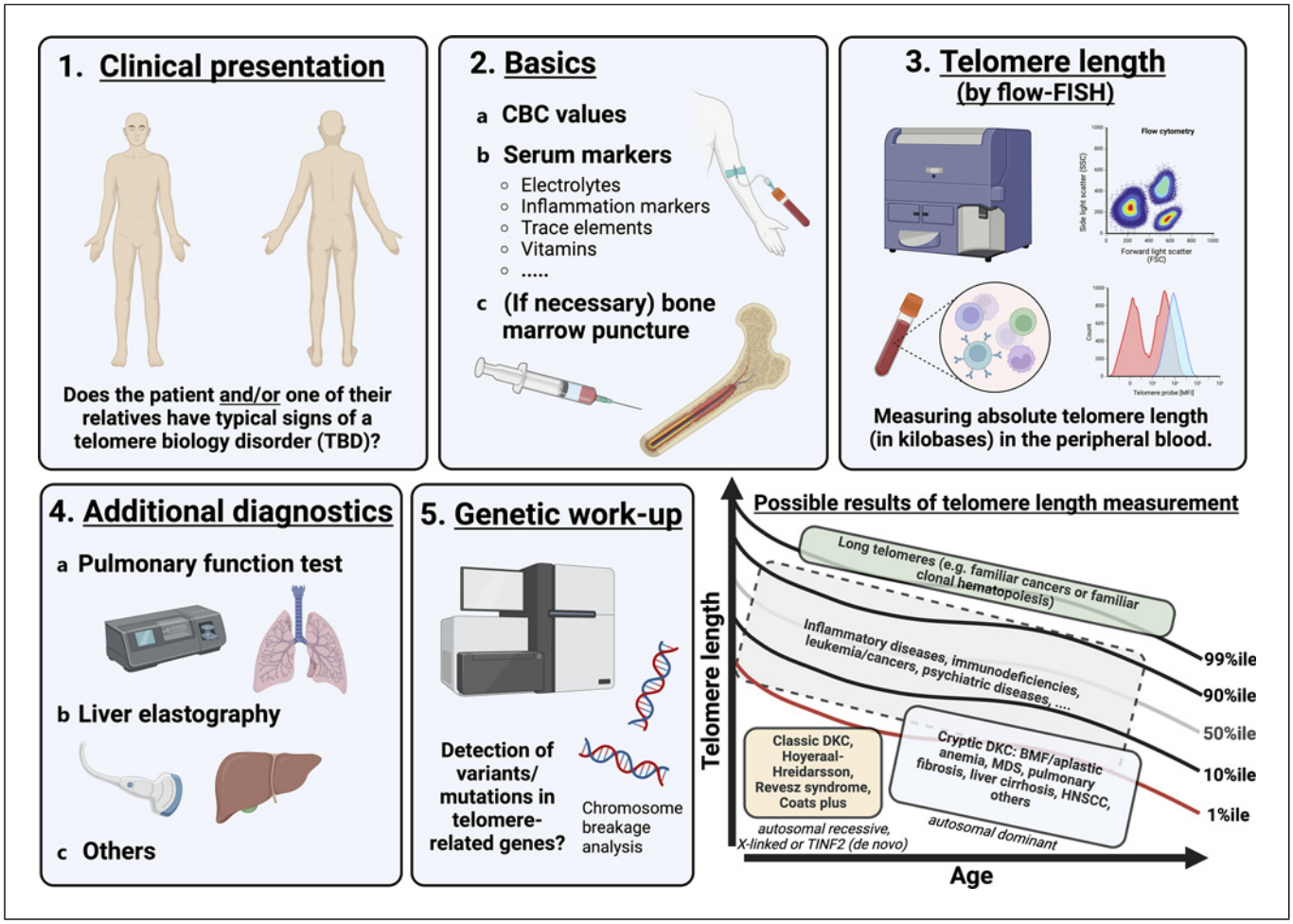

Fig. 2. Diagnostic procedures to confirm a suspected telomere biology disorder (TBD). The step-by-step diagnostic algorithm for proper identification of a telomere biology disorders (TBD) is shown as follows: (1) clinical presentation + basic diagnostics: the clinical appearance is often the first and sometimes the only indicator for a present TBD; (2) basic diagnostics such as a routine laboratory work-up mainly serve to exclude other causes that explain the patient's phenotype; (3) flow-FISH diagnostic: to measure the absolute telomere length (TL) in peripheral blood lymphocytes and granulocytes; (4) advanced diagnostics: variable and highly dependent on the clinical presentation of the patient. Complications such as PF or liver fibrosis/liver cirrhosis can be diagnosed and quantified; (5) genetic work-up: NGS diagnostic, whole exome or whole-genome sequencing to detect a genetic cause of TBD. A chromosome breakage analysis should be performed to rule out other differential diagnoses that might lead to chromosomal instability and (secondary) telomere shortening (especially Fanconi anemia). Graph: possible results of telomere measurements and typical results for various diseases. Created with "BioRender.com."

regime and (if possible) avoidance of radiotherapy due to the increased risk of secondary malignancy as well as the development of fatal interstitial lung diseases are preferable for TBD patients [111, 113, 114]. In addition, special check-ups as well as follow-ups after treatment are recommended in order to recognize common secondary diseases (e.g., secondary malignancies) [44]. Moreover, the introduction of affected patients to a specialized center for a second opinion, study inclusion, and inclusion in central registries should be standard of care. There are a few registries worldwide that systematically collect patient data, document the disease course of TBD patients and systematically archive patient material (see Acknowledgment).

Pulmonary Fibrosis as a Manifestation of a Cryptic TBD

Pulmonary fibrosis (PF) is a disease characterized by progressive scar formation and thickening of the tissue around the alveoli in the lung thereby impairing the vital process of gas exchange [115]. The disease can be caused by external factors like air pollution, or previous medical treatments as radiation therapy or drugs with pulmonary toxicity (e.g., bleomycin, busulfan, and several other medications) [111, 116]. Some cases remain etiologically unclear and are therefore described as idiopathic [59, 115]. Usually, PF occurs in middle-aged and older

individuals so that young patients with a family history raise a strong suspicion that the disease might be caused by pathogenic germline variants [115]. However, in analogy to inherited BMF, there are also reports indicating that even older patients suffering from PF might harbor pathogenic variants in TBD-associated genes that are inherited in an autosomal dominant manner [89]. Several studies showed that idiopathic PF can be caused by pathogenic variants in TBD-associated genes such as *DKC1*, *TERT*, *TERC*, *NOP10*, *NHP2*, *ACD* (=*TPP1*), *RTEL1*, *PARN*, *RPA1*, *NAF1*, *TINF2*, *ZCCHC8*, *POT1*, *RPA1* [42, 47, 52, 54, 59, 62, 63, 75, 86]. It has also been shown that genetically impaired telomere maintenance is associated with several other interstitial lung diseases [59]. Symptom severity and type of manifestation differed greatly between patients with TBD-associated PF, but for all patients a continuously progressive disease course was observed [59].

Cryptic Liver Cirrhosis as a Manifestation of a Cryptic TBD

Liver diseases are an increasing problem in the Western world with a significantly rising number of cases with non-alcoholic fatty liver disease and nonalcoholic steatohepatitis [117, 118]. In around 5% of all cases with liver cirrhosis, the underlying etiology cannot be identified, leading to the fact that these cases being classified as cryptogenic cirrhosis [118]. In TBD patients, a hepatic involvement is common (in some cohorts 40% of all TBD patients [119]), difficult to specifically detect [91] and contributes to mortality to a highly variable degree [91, 119]. Interestingly, the presence of a TBD-causing pathogenic variant was a risk factor for the progression from liver fibrosis to liver cirrhosis [120]. Studies in patients with liver cirrhosis who undergo liver transplantation have shown that cryptic TBD can be the cause of isolated liver fibrosis/liver cirrhosis [68, 92, 120]. It was demonstrated that aberrations in telomere maintenance genes such as *TERT*, *TERC*, *RTEL1*, *TINF2*, *DKC1*, *NHP2*, *NOP10*, *NAF1*, and *WRAP53* (=*TCBA1*) were able to cause severe hepatic manifestations [68, 91, 92, 121].

Solid Cancers as a Manifestation of a Cryptic TBD

Even though the risk for many cancers including head and neck squamous cell carcinoma (HNSCC) are associated with somatic *TERT* promoter and *POT1* variants leading to longer TL [93, 94, 122], there are also indications that pathogenic germline variants in TBD-associated genes promote cancer development [17, 45]. Many tumor types that occur in the context of TBDs also show a higher incidence in the presence of (very) short telomeres in the general population [85, 108, 123–125]. For example, variants in *TERT*, *TERC*, *CTC1*, and *MDM4* lead to a higher risk for HNSCC and other squamous cell carcinomas (SCCs) (unpublished data) [51, 95, 126].

Patients with DKC have hundreds-fold greater risk of developing HNSCCs, SCCs of the skin and the anogenital region [85, 108]. 30% of the macroscopic oral leukoplakia in TBD patients might transform to HNSCC [108, 127]. Also, a higher risk of stomach cancer, lung, esophagus, and colon cancer is described in DKC patients [85]. Even the risk for AML development, Hodgkin's disease as well as non-Hodgkin lymphoma was found to be increased [108]. Future studies are needed to address the question whether the increased susceptibility toward carcinogenesis in TBDs is explained by increased genetic instability only and/or by impaired tumor surveillance by the immune system [103]. Importantly, treatment of TBD-associated malignancies is expected to result in increased treatment-related toxicities due to a higher risk of functional organ damages, secondary BMF and increased mortality [87, 111, 116, 128]. For this reason, adapted therapy regimes (and components) including potential dose reductions in TBD patients suffering from cancer should be discussed individually with specialized TBD centers.

Treatment of TBDs

Androgen derivatives as cyclostragenol, oxymetholone, and danazol are molecules that may increase telomerase activity [129–131]. The first case of a patient with AA who continuously showed in vivo multi-lineage telomere elongation in peripheral blood cells associated with transfusion independence following androgen treatment was published in 2012 [132]. For various androgen derivatives such as oxymetholone and danazol, elongation of TL in the peripheral blood was shown for TBD patients [109, 132–136]. About 69% of all patients had a hematologic response to oxymetholone treatment [135], but side effects such as liver toxicity and virilization were frequent and were primarily observed in female patients [109, 135]. For danazol, on the other hand, side-effects were less frequent and about 50–100% of all TBD patients had at least a short-term response in the sense of an increase in blood counts [109, 135, 136]. Previous data showed that androgens are intracellularly converted to estrogens acting on the estrogen sensitive promotor of the telomerase gene resulting in an increased telomerase activity [129]. In line with this mechanism, an increased telomerase activity was observed after androgen treatment [129, 135]. Another study demonstrated that 11/12 patients under danazol treatment gained TL (mean increase of 386 bp) and 83% showed a hematologic response after 24 months [134].

Even though allo-SCT can reconstitute cytopenias in the hematopoietic system in TBD-associated BMF, long-term survival remains low in TBD patients with only 23% after 10 years [112]. One frequent long-term complication for TBD patients after allo-SCT was progressive PF [111, 112]. Due to the fact that increased (therapy-related) toxicity in TBD patients has been described [112], it was shown that a non-myeloablative protocol with reduced intensity and the avoidance of radiation were able to improve overall outcome [113, 114]. There are some indications that allo-SCT should not be enforced in patients with pre-existing organ damages, whereby patients with progressive BMF more likely benefit from the procedure [111, 113].

In the future, telomerase gene therapy represents a highly promising potential therapeutic strategy for patients with TBDs especially in patients with early BMF. Even though this concept is still experimental, first studies have already been carried out (NCT04211714). In line with this, in telomere-deficient mice that recapitulated the phenotype of BMF/aplastic anemia, cytopenias were successfully treated by using a *Tert* gene therapy system that was based on an adeno-associated virus serotype 9 (AAV9) vector [137]. Also, as another promising therapeutic approach, it was shown that PAPD5 inhibitors are able to restore telomerase activity in stem cells thereby implying that these drugs might be useful to restore the replicative capability of stem cells in TBD patients [138].

Conclusion

TBDs are characterized by impaired telomere maintenance that is often caused by pathogenic variants in various telomere-associated genes. Most patients with TBDs are prone to develop premature and eventually functional telomere shortening. Even though classical TBDs are very rare, the number of unreported cases of adult-onset TBDs is expected to be higher and every physician and particularly hematologist, hepatologist and pulmonologist should be aware of the classical symptom complexes and particularly, the heterogeneity of this hereditary disease group. TL screening by flow-FISH represents a sensitive and cost-effective method to functionally identify patients with suspected TBDs. This is of high importance as TBD patients require specific and individual treatment decisions, are prone to (often immediately life-threatening) complications and careful follow-up care concepts are needed to detect secondary (particularly malignant) disorders at the earliest possible time point (e.g., where they are still locally resectable). Furthermore, adequate counseling is of utmost importance in affected families. Inclusion into innovative clinical trials and registries including proper biobanking as well as connection of the patients with specialized patient support groups (see Acknowledgment) should be offered, e.g., with the help of a specialized tertiary hematology center.

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Conflict of Interest Statement

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Author Contributions

B.R. and T.H.B. conceptualized the project, designed and wrote the manuscript. B.R. has created the figures by using "BioRender.com." M.T., M.K., R.M., and F.B. provided scientific input, revised, and updated the manuscript, figures, and tables accordingly. All authors approved the final version of the manuscript including figures and tables.

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