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Diagnosis and management of adult telomere biology disorders

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Title: Diagnosis and management of adult telomere biology disorders

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Abstract

Telomere biology disorders (TBDs) comprise a heterogenous group of inherited conditions characterized by impaired telomere maintenance, resulting in abnormal telomere lengths and/or telomere dysfunction. The clinical spectrum of TBDs is broad, spanning bone marrow failure, pulmonary fibrosis, liver disease, and an increased predisposition to malignancy, complicating timely diagnosis and management. In this review, we explore the evolving clinical landscape and diagnostic strategies for TBDs, while highlighting the diverse phenotypic presentations. We further examine the role of telomere dysfunction in driving cancer development and clonal hematopoiesis. Finally, we discuss current and emerging therapeutic approaches for TBDs, emphasizing the need for individualized and multidisciplinary management to optimize patient outcomes.

Located on the ends of human chromosomes are specific DNA codes, called telomeres. Originating from the Greek expressions *telos*, meaning "end," and *meros*, meaning "part," the term “telomere” was coined in the 1930s by American geneticist Herman J. Müller from his work investigating radiation effects on chromosomes [1]. Half a century later, groundbreaking research involving the ciliate *Tetrahymena* expanded our understanding of the function of telomeres and telomerase, leading to the receipt of the 2009 Nobel Prize in *Physiology or Medicine* by Drs. Blackburn, Greider, and Szostak [2]. Telomere biology disorders (TBDs) are a spectrum of conditions resulting in abnormal telomere function and length. TBDs manifest in a wide array of clinical phenotypes, making diagnosis and prompt management challenging. In this review, we discuss clinical presentations and treatment options for TBDs, highlighting new and emerging technologies.

1. Introduction to the telomere apparatus

1.1. Discussion of telomere structure and the telomerase complex

Telomeres are represented by strings of nucleotide repeats, specifically 5′-(TTAGGG)n-3′, which play a crucial role in safeguarding chromosomes and maintaining the integrity of their DNA during cellular division [3, 4]. As cells divide, the DNA gradually loses nucleotides over time due to the end replication problem. Telomeres function as a buffer to protect important genetic information and allow for natural cellular replication throughout life.

The telomere maintenance apparatus includes an enzymatic complex called telomerase, and a combination of protective proteins known as the shelterin complex, among others (**Figure 1**) [4]. Telomerase is the enzyme that lengthens telomeres by synthesizing new end TTAGGG repeats in the sequence [5]. The telomerase complex docks at the end of a chromosome and interfaces directly with the single-stranded 3’ overhang at the terminal end of the telomere [5]. From there, telomerase reverse transcribes the RNA molecule TERC that is complementary to the DNA telomeric nucleotide repeats [5]. This telomerase complex is composed of six subunits with two copies of the following: TERT (Telomerase Reverse Transcriptase), TERC (Telomerase RNA Component), and the protein, Dyskerin. The proteins NOP10 and NHP2 are involved in the assembly of telomerase, while Poly (A)-specific ribonuclease (PARN), telomerase Cajal body protein 1 (TCAB1/WRAP53), and Zinc Finger CCHC-Type Containing 8 (ZCCHC8), each have specialized roles essential for the function of telomerase at the G-rich (3’ overhang) leading strand and in *TERC* maturation (**Figure 2**) [6].

The shelterin complex shields the ends of the chromosomes and ensures the stability of the telomeres [4]. This structure specifically targets telomeric DNA through recognition of the TTAGGG nucleotide repeats in order to bind to the telomeres [4]. This shelterin to telomere binding promotes the formation of telomere loops, or T-loops as seen in **Figure 1** [7]. These DNA-protein loops shield the 3’ overhang, thereby preventing their exposure to the DNA damage repair pathway [8]. The shelterin complex includes six protein subunits: RAP1, TRF1, TRF2, TIN2, TPP1, and POT1. These proteins function together as a unit and the complexes are

found abundantly in telomeres. The components, TRF1/TRF2 and POT1 are most important for shelterin binding to telomeres. TIN2 (encoded by *TINF2*) is part of the core scaffolding of the shelterin complex, with binding sites for the subunits TRF1, TRF2, and TPP1 (encoded by *ACD*).

There are additional proteins involved in the telomere apparatus, including the heterotrimeric CST complex (composed of CTC1, STN1, and TEN1) and related components (Apollo (DCLRE1) and POLA2) [7]. The CST protein complex functions in a regulatory manner – to maintain telomere homeostasis and prevent undesired overextension – as well as in the interaction and recruitment of DNA polymerase α-Primase (composed of *POLA1*, *POLA2*, *PRIM1*, and *PRIM2*), stabilizing DNA replication forks, and maintaining the double stranded nature of telomeres [9-12]. Apollo (encoded by *DCLRE1*) is a shelterin accessory component that directly interacts with TRF2 and is recruited to telomeres to aid in the protection of telomere ends generated by leading-strand synthesis [13].

Finally, there are other important components that help to regulate telomere replication of both strands, including Regulator of Telomere Elongation Helicase 1 (RTEL1), Replication protein A (composed of RPA1-3), and thymidylate synthase (TYMS). RTEL1 allows for the unwinding of the T-loops to allow the telomerase complex to access the end of the telomeres. RPA helps to stabilize single-stranded telomeric DNA during replication and prevents formation of impeding secondary structures (unfolds G-quadruplexes) at telomeres [14]. TYMS is an enzyme critical for DNA synthesis and repair by controlling thymidine nucleotides and ensuring sufficient dTTP [15]. A glossary is provided below to define specialized terms in telomere biology (**Table 1**).

1.2. Telomere physiology

Telomeres measure approximately 10 kilobases on average at the time of birth (evaluated with techniques such as quantitative PCR and southern blot), although this can vary between individuals [16-18]. Telomere length (TL) is heterogenous and varies within tissues of the same individual [19]. Telomere shortening occurs with normal aging but can also be impacted by various genetic and environmental factors [20-22]. These genetic factors include pathogenic variants in genes integral to telomere regulation, while the environmental factors include inflammation, oxidative stress, smoking, physical inactivity, among others [21]. In normal somatic cells, telomeres are reduced up to 200 base pairs on average (data from study involving fibroblasts) with each DNA replication and cellular division [23]. At the end of life, telomeres are significantly shortened, typically measuring around 5 kilobases [24]. While telomeres do not disappear completely in old age, there is an increased frequency of ultra-short telomeres in elderly individuals, usually measuring less than 1.6 kilobases [25-27]. Individuals with an increased proportion of ultra-short telomeres have an increase in the hallmark processes of aging, such as cellular dysfunction [25, 26, 28]. Acknowledging the crucial link between

shortened telomeres and heightened chromosomal instability—thereby influencing aging, disease, and cancer—is critical for exploring effective strategies to counteract these processes.

2. Diagnosis of telomere biology disorders

2.1. Discussion regarding the classification of short and long telomere conditions

Telomere dysfunction encompasses a spectrum of disorders, ranging from short telomere syndromes to those associated with excessively long telomeres. Although both categories involve disordered telomere maintenance, it has been proposed that the term telomere biology disorders (TBDs) be applied specifically to syndromes characterized by critically short telomeres [29]. In contrast, conditions associated with abnormally long telomeres are more accurately described as cancer predisposition with long telomeres (CPLT) [29]. In this review, we adopt this nomenclature: "TBD" will refer to short telomere syndromes, while "CPLT" will denote disorders involving long telomere-associated cancer risk. A detailed examination of the molecular and clinical distinctions between these entities will be provided in the sections that follow.

2.2. Methods of TBD diagnosis

There are many avenues from which a TBD diagnosis can initially be suspected and pursued, from identification of clinical manifestations to genetic screening in relatives of affected individuals. TL testing is an important component and can be performed through various methods (**Table 2**). To date, the only test validated for clinical use is flow cytometry combined with fluorescent *in situ* hybridization (flow FISH) [30, 31]. This test measures the average TLs in peripheral blood leukocytes, after sorting for myeloid cells (CD33+) and lymphoid cells (CD3+). These hematopoietic lineages are sorted to achieve cell-specific analysis, avoiding cross-contamination and confounding factors, and ultimately optimizing data interpretation for ideal reproducibility and reliability [32]. Notably, some flow FISH screening lab tests can extend sorting further, to report TL for lymphocytes, granulocytes, B-cells, naïve and memory T-cells, and NK cells, with a six-cell panel assay thought to be potentially more informative than just measuring TL in total lymphocytes and granulocytes [33]. Categories of methods to measure TL include hybridization-based methods, qPCR-based methods, and computational-based methods, with the caveat that these are currently restricted to research settings [30].

Previously, the gold standard method of measurement was terminal restriction fragment (TRF), due to its ability to provide detailed, highly accurate information about TL distribution. It uses Southern blotting techniques and therefore requires a significant amount of high-quality genomic DNA [1-5 micrograms], time, and effort [34, 35]. As previously noted, flow FISH is routinely utilized in clinical settings due to its scalability and high sensitivity and specificity [80% and 85% respectively when detecting TL < 10^{th} percentile]; however, it remains a limited test, as it can only be performed on peripheral blood samples, provides average TLs and cannot be used in patients with significant leukopenia [30, 36]. Due to these pitfalls, newer methods of

analyzing telomere length are emerging. This includes Telomere Shortest Length Assay (TeSLA) and long-read sequencing, which are advanced methodologies that have improved our ability to characterize telomere length dynamics [27, 37]. TeSLA can detect the shortest telomeres at single-chromosome resolution, providing a more clinically meaningful telomere analysis compared to older methods that provide telomere length averages [27, 38]. Similarly, long-read sequencing technologies can be used to directly measure individual telomere lengths, aiding diagnosis and research purposes [37]. These advanced methods offer a lot of promise, however, they are still in early stages of development and further validation is needed. Other important methods of telomere length measurement can be found in **Table 2** [30, 34, 36, 39].

In addition to assessing TL, a crucial aspect of diagnosing TBDs involves genetic testing to identify pathogenic gene variants that contribute to clinical presentation. This can be accomplished through gene-targeted testing using a multigene panel of known TBD-related mutations or through comprehensive genomic sequencing [40]. It has been seen that approximately 20-40% of adult patients with TBD will not have an identifiable germline pathogenic variant, as all genetic (coding and non-coding variants) and epigenetic mechanisms have not been completely identified [21, 41]. However, this data inherently has great variability, as the various cohorts that have been studied have fundamentally distinct characteristics (mix of adults vs. pediatric patients, etc.).

3. Long and short telomere syndromes

Telomere dysfunction can occur in both long (CPLT) and short (TBD) telomere syndromes.

3.1. Long telomere syndromes (CPLT- cancer predisposition with long telomeres)

Long telomere syndromes are a collection of genetic variants that result in abnormally elongated telomeres (*POT1, TINF2, ACD, TERF2IP, TERF1*) [29, 42, 43]. Originally, it was hypothesized that there might be some advantage to having longer telomeres, as this may reverse the effects of aging or normal shortening of telomeres due to environmental or lifestyle factors [44, 45]. Recent studies, however, have associated long telomere syndromes with an elevated risk of developing certain cancers, as the extended telomeres enable cells to proliferate in an uncontrolled fashion [29, 42, 43, 46]. The spectrum of neoplasms seen in patients with CPLT include melanomas, sarcomas, gliomas, thyroid cancer, and lymphoproliferative disorders [29, 42, 43, 46, 47]. In addition to increased cellular proliferation, long telomere syndromes also contribute to telomere fragility, genomic instability and clonal hematopoiesis [42]. The 2023 study by DeBoy et al. highlighted the association between *POT1* mutations (CPLT) and a familial predisposition to CH, mediated by somatic driver mutations (such as *DNMT3A* and *JAK2*) [42].

3.2. Short telomere syndromes (TBDs)

TBDs, also known as short telomere syndromes, are characterized by phenotypic features resembling accelerated aging. Patients typically present with lymphocyte TLs < 1st percentile for their age, which makes this cutoff value the most sensitive and specific for diagnostic purposes [33]. However, patients with TLs < 10th percentile for their age, especially at advanced ages, might still be regarded as having abnormal telomere biology. The global prevalence of TBD is unclear; estimations for the prevalence of dyskeratosis congenita (DC) (prototypical TBD subtype) cases are around 1 per million, but this does not encompass the full scope of TBD [48, 49]. Common clinical features most relevant to adult patients with short telomere syndromes include bone marrow failure, interstitial lung disease/pulmonary fibrosis, non-cirrhotic portal fibrosis, nodular regenerative hyperplasia of the liver, and an increased incidence of certain visceral and hematological neoplasms [50].

Currently, pathogenic variants in at least 16 genes have been associated with a short telomere phenotype as seen in **Table 3** [16 according to GeneReviews and 18 according to the American Society of Hematology] [48]. Molecular mechanisms that lead to telomere dysfunction vary and can include disruption of any component involved in a normal, working telomere apparatus (components involved in telomerase, shelterin, trafficking, binding, docking, etc.). For example, certain mutations, in *TERT, TERC, DKC1, NOP10, NHP2, WRAP53* (TCAB1), *PARN, ZCCHC8* can lead to defective extension of the G-rich strand by telomerase. Mutations in *TERT*, specifically, can impact the activity level of the telomerase complex, whereas other mutations [*WRAP53* (TCAB1) and *DKC1* (Dyskerin)] primarily affect the stability and protein maturation of telomerase [20]. Furthermore, mutations in the shelterin genes, *ACD* (TPP1) and *TINF2* (TIN2), affect telomerase docking and recruitment, respectively. This impacts appropriate shelterin functioning and trafficking of telomerase to the telomere [20]. Dysfunction in other associated structures, such as the CST-Pola-related components (*CTC1, STN1, TEN1, DCLRE1*, and *POLA2*), can impair the C-strand fill-in process at telomeres, compromising the regulation and maintenance of the 3' G-overhang length [51]. In addition, genes that act in concert to ensure replication of leading and lagging telomeric DNA (*RTEL1, RPA1,* and *TYMS)* play a vital role in maintaining telomere integrity [14, 15]. This underscores the complexity of TL regulation.

4. Clinical manifestations of telomere biology disorders

4.1. *General manifestations of telomere biology disorders*

DC, one of the most extensively studied telomere biology disorders, was initially linked to mutations in *DKC1*. Since its discovery, this list has been expanded upon to include many other genes that disrupt the function of the telomerase and shelterin complexes (*TERC, TERT, TINF2*, etc.). DC usually presents in children with the classical mucocutaneous triad: reticulated skin pigmentation, nail dystrophy, and oral leukoplakia [52]. These features are not always all present but one or more of them can be seen in most patients [pediatric populations], with a large number developing concomitant bone marrow failure [52]. Other clinical features include

lacrimal ductal stenosis, urethral stenosis, esophageal stenosis, interstitial lung disease [in 20% patients] and liver fibrosis with portal hypertension [more common in adolescents and young adults] [53, 54].

Other manifestations of adult-onset TBDs encompass a spectrum of conditions, from premature aging and short stature to multi-organ complications. Patients can notice early development of gray hair (< 20 years in Caucasians and < 30 years in African Americans), dental caries, missing teeth, osteoporosis, retinopathies, growth restrictions, among others [21]. As previously mentioned, pulmonary fibrosis is highly prevalent in this population, often diagnosed later in life. In some cases, it may be the sole presenting manifestation [55, 56]. Liver problems, ranging from nodular regenerative hyperplasia to hepatic fibrosis with portal hypertension can be seen [57]. A 2023 study found that 72.4% of patients had evidence of liver abnormality, through imaging findings or liver enzyme elevation in their cohort of 58 patients with TBDs [57]. However, only 17.2% of all patients progressed to clinically significant liver disease [57].

4.2. Genetic anticipation and phenocopying

A key feature of TBDs is genetic anticipation. Genetic anticipation is the concept that a disease will clinically manifest earlier in successive generations, as well as present with increased severity. In TBDs specifically, this means that successive generations with be born with shorter baseline TLs [21, 58-60]. For example, an affected individual's child might develop more severe phenotypes of pulmonary fibrosis and bone marrow failure at an earlier age than their parent. The mechanism behind genetic anticipation in TBDs is thought to be the haploinsufficiency of telomerase, but further research has highlighted the complexity of this topic [58].

Another concept in TBD is phenocopying, wherein an individual presents with a clinical phenotype similar to those caused by telomere biology mutations but is actually driven by factors unrelated to any known pathologic variants [59]. These factors include environmental stressors as well as completely different genetic mutations (as in mutations leading to TBD phenotypes, without involving the telomere regulation pathway: e.g. *MUC5B, SFTPC, DSP* mutations can result in pulmonary fibrosis.). Additionally, a patient with a clinically similar TBD phenotype may have shortened telomeres relative to the age-adjusted average, but they may not have a known TBD causing pathogenic variant.

4.3. Spectrum of solid cancers

Patients with TBDs have an increased risk for certain solid and hematologic malignancies [61]. [62, 63]. Prior cohort data has suggested that affected patients with short telomeres have a three-fold higher risk of developing cancer than the general population, although this is still under investigation [61]. This cancer risk has been shown to be associated with specific TBD inheritance patterns, with pronounced cancer risk in patients with autosomal recessive or X-linked disease [61]. The solid-tumor cancers most prevalent in prior literature include squamous

cell carcinomas (SCC) of the head and neck, as well as the anogenital region [61]. More research is needed in this field to better understand the specific solid-tumor cancer risks associated with TBDs and how to best screen and manage these patients. See **Table 4** for observed/expected ratios for cancer risk in relevant TBD cohorts.

4.4. Hematologic manifestations and associated malignancy risks

4.4.1. Bone Marrow Failure

Bone marrow failure is a hallmark feature of TBD [50]. The underlying mechanism involves impaired proliferative capacity of hematopoietic stem and progenitor cells due to critically shortened telomeres and corresponding telomere dysfunction [50]. This can progress over time into marrow hypoplasia and decreased blood counts. This intrinsic process differs from bone marrow failure conditions that arise in the setting of extrinsic (viral, nutritional, toxin or drug induced) or systemic (immune-mediated) pressures, such as immune-mediated aplastic anemia. Bone marrow failure at times can be one of the first presenting signs of TBD, and manifests with progressive cytopenias and bone marrow hypocellularity [52]. It has been observed as the most common hematologic manifestation in various TBD cohort studies, but can also vary depending on TBD genotype [64]. The management of TBD-related bone marrow failure requires a nuanced, individualized approach, as will be explored in subsequent sections.

4.4.2. Clonal hematopoiesis and clonal cytopenias of undetermined significance

Context relevant clonal hematopoiesis (CH) and clonal cytopenias of undetermined significance (CCUS) are important concepts in TBDs. CH refers to the clonal expansion of hematopoietic stem and progenitor cells (HSPC) resulting from somatic mutations that confer an adaptive advantage to the fitness constraints within the bone marrow [65]. In patients with TBD, these constraints are compounded by progressively shortening TLs resulting in unique stressors and therefore, a unique spectrum of CH [42, 66, 67]. Clonal cytopenias are defined as persistent unexplainable cytopenias seen in the context of CH mutations (**Table 1**).

While true somatic genetic reversion events have been observed in individuals with TBD, they are not common. On the other hand, individuals with TBD are more likely to develop somatic CH mutations in comparison to non-TBD individuals of the same age. CH in TBD patients can either have adaptive outcomes, counteracting the inherent telomere dysfunction and phenotype (e.g. promotor *TERT*, *POT1* and *TERFPI2* mutations), or maladaptive outcomes, partially compensating the phenotype but potentially increasing the risk for hematological malignancy (e.g. *U2AF1*, *PPM1D*, *TP53* mutations, etc.) [68]. **Figure 3** demonstrates the various pathways leading to each outcome in TBD, demonstrating how CH is a compensatory mechanism whereby somatic mutations in certain genes/pathways can improve the ability of the HSPCs to survive inherent fitness constraints and/or avoid

cellular senescence induced by a pathogenic TBD variant, critically shortening TL [66]. In the case of adaptive outcome CH, these mechanisms of aiding cellular survival and function and/or avoidance of cell death, result in preservation of hematopoiesis. Mechanisms that lead to this are back mutations (somatic reversion) or copy neutral loss of heterozygosity (CN-LOH) seen in **Figure 3**. Another example is the acquisition of promoter *TERT* mutations [C228T (c.-124C>T) and C250T (c.-146C>T)], that lead to increased expression of the wild type TERT allele, resulting in a compensatory increased telomerase activity and telomere lengthening [66].

In contrast, maladaptive outcome CH occurs when somatic mutations lead to aberrant cellular proliferation and increased risk of hematologic malignancy. These mutations result in the activation of cellular pathways that promote tumorigenesis. In a 2024 study investigating the role of CH in TBDs, $U2AF1^{S34}$ and *TP53* pathway mutations were especially important in cancer development [66]. Notably, $U2AF1^{S34}$ mutations leading to maladaptive outcomes (myeloid neoplasms) have been found to be recurrent in TBDs and are highly favored, in comparison to the other well-known *U2AF1* hotspot mutation seen in several myeloid neoplasms and infrequently in age related CH ($U2AF1^{Q157}$) [66]. This points to downstream molecular alterations specific to *U2AF1* S34 pathogenic variants that attempt to overcome fitness constraints on the HSPCs in TBD patients [69]. In another example, truncating mutations in *PPM1D* (all in exon 6 of the gene) have been implicated in maladaptive clonal expansion, with potential contributions to myeloid malignancy and chemoresistance through disruption of DNA damage response and repair pathways; however, this association is still being investigated (**Figure 3**) [66]. Finally, in TBD patients, a diagnosis of CCUS is difficult to establish, as peripheral blood cytopenias in the context of CH mutations could be secondary to progressive marrow failure and not necessarily due to the impact of the CH mutations themselves [70]. Further terms that describe the various terms of mechanisms involved in TBDs, including the previously described back mutations, CN-LOH, and more can be found in **Table 1** for reference.

4.4.3. MDS/AML

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are hematologic malignancies with an increased incidence in patients with TBDs. While AML is a blood cancer resulting in the proliferation of myeloblasts, MDS is a disorder of ineffective hematopoiesis, maturation and resultant cytopenias [71, 72]. The mechanism driving the association between TBDs and MDS/AML involves genomic instability that results from profound telomere dysfunction [73]. As with most genetic mutations that lead to issues with cellular machinery, pathogenic variants in telomere regulation can induce a DNA damage response within cells [73]. Furthermore, these variants lead to impaired cell regeneration and differentiation.

Chromosomal alterations can drive the progression to MDS/AML in TBD patients, such as in the case of chromosome 1q gain (Chr1q+) [68]. In chromosome 1q gain, the enhanced survival of dysfunctional HSPCs can lead to clonal expansion; a notable example is the overexpression of MDM4 (located on 1q32.1) which attenuates p53 activity, facilitating the emergence of CH and pre-malignant states [74]. Moreover, important genetic alterations leading to MDS/AML span multiple categories, including mutations in spliceosome genes (e.g. *U2AF1*^{S34}, *SF3B1*) and DNA damage response (DDR) pathways (such as *TP53*) in the setting of telomere dysfunction [68, 73].

In TBDs, it has been seen that MDS is more commonly diagnosed at initial presentation compared to AML [64]. This is supported by a 2024 French cohort study that reported 17.3% of patients had MDS at initial TBD diagnosis, whereas only 1.6% had AML [64]. Additionally, in a study by Schratz et al., it was found that the combination of MDS and AML attributed to 75% of the cancer cases in their cohort, with MDS being observed at a higher rate [75]. The observed/expected (O/E) ratio for MDS in patients with DC was shown to be as high as 578, denoting a greater than 500-fold risk of this malignancy [76]. Similarly, the O/E ratio for risk of AML in the same study was approximately 73, although other literature focused on TBDs more broadly have put this ratio closer to 20-50 [O/E was 21 in Schratz et al. and 49.5 in Niewisch et al.] [61, 75, 76]. These findings underscore the considerable risk faced by patients with TBDs, emphasizing the importance of frequent monitoring for AML and MDS. Given the aggressive nature of these conditions and the challenges involved in their effective treatment, vigilant surveillance is essential.

5. Clinical management of telomere biology disorders

There is no universally established algorithm for the management of all TBDs; however relevant research has initiated a dialogue toward developing general guidelines and practices for affected individuals.

5.1. Androgenic therapy

Androgens are steroid sex hormones including testosterone and related products. This drug class works by enhancing telomerase activity and is thought to be effective in reducing the telomere attrition rates [77-79]. Danazol is a synthetically derived androgen that has been used in TBD [80]. In Townsley et al., the use of danazol in patients with known TBD led to telomere elongation after 24 months, with a mean increase of 386 base pairs, although variability in TL due to qPCR utilization was a limitation to this study [80]. Contrasting literature, such as the 2018 retrospective observational study by Khincha et al., noted that there was no statistical difference in TL between danazol treated and untreated patients with DC [median of 3 years of treatment] [81]. Other androgens that have been studied in the context of TBD are oxymetholone and nandrolone [79]. These derivatives work in a similar way to Danazol and were seen to significantly increase TL *in vitro* in bone marrow derived mononuclear cells after a 7-day course

of therapy [79]. The mix of outcomes in these studies indicate that the consensus on danazol and androgen therapy is not entirely clear in the context of TBD and warrants further investigation [50]. The NIH currently has a low dose danazol study (400 mg) that is recruiting patients with TBD (ClinicalTrials.gov ID NCT03312400).

Things to consider when initiating androgen therapy for the treatment of TBDs include the side effect profile of these agents and the long-term treatment goal. In a study investigating the side effects of danazol in patients with DC, it was found that all treated patients had abnormalities in their lipid panels and 50% of treated patients had liver enzyme elevations, although there was no clear statistical significance in this value [82]. Other adverse events from this study included development of hypoechoic liver lesion [1 individual], splenic peliosis complicated by rupture [2 individuals], accelerated growth [6 pre-pubertal individuals], bone fractures [3 individuals in treated group, 2 individuals in untreated group], and various endocrine abnormalities (decrease in thyroid binding globulin [10 individuals], masculinizing effects, priapism/hirsutism) [82].

5.2. Transplant in telomere biology disorders

Organ transplantation is an important consideration for TBD patients, with organs most commonly requiring transplantation including the lungs, liver, and bone marrow, with transplantation serving as the sole curative option for end-stage organ dysfunction [41]. In patients affected by short-telomere-related pulmonary fibrosis, lung transplantation has provided a long-term survival benefit in certain cases [83, 84]. Recent literature has indicated that the one-year post-transplant survival rate in patients with interstitial lung disease exceeds 80%, irrespective of the presence of telomere dysfunction [85]. However, reports also highlight increased post-transplant complications leading to poor outcomes, with chronic rejection rates notably higher and an adjusted hazard ratio of 2.88 for lung allograft dysfunction in TBD patients [86]. In the case of hepatic dysfunction, liver transplantation in patients with TBD-related advanced cirrhosis has shown improvement in survival by age, with one-year post-transplant survival rates at 73% [20 patients, median age at transplant 27] and acute or chronic rejection only occurring in 10% [2 out of 20] of the transplanted cohort in a 2024 study [87]. Like lung or liver transplantation, HSCT can be pursued in individuals with bone marrow failure or other hematologic malignancies and also has been seen to improve survival rates and reduce disease progression in TBD patients [one-year post-transplant survival rate 86.2% in Nichele et al. (2023)] [88, 89].

The clinical approach for transplant in TBD patients includes: (1) a comprehensive, multidisciplinary pre-transplant evaluation with a tailored conditioning regimen, and (2) a post-transplant monitoring plan to watch for TBD-specific complications. For the pre-transplant evaluation, it is important to anticipate potential complications and involve insight from hematology, genetics, pulmonology, hepatology, among others. Additionally, when implementing a transplant conditioning regimen in TBD patients, healthcare providers must

account for the heightened sensitivity to the toxic effects of standard regimens in this population [89]. This can be achieved by pursuing standard reduced-intensity conditioning (RIC) regimens or an alternative approach, such as alemtuzumab plus fludarabine – radiation and alkylator free approach [89-91].

Finally, frequent follow-up and vigilant monitoring is important to promptly recognize post-transplant outcomes. There are considerable challenges with any organ transplantation, including organ rejection, immunosuppression and subsequent infection, complications due to conditioning regimens, or post-transplant malignancy [90]. For example, TBD patients have an increased risk of developing life-threatening hematologic complications after a transplant, so adjustments may be needed to transplant immunosuppression to minimize bone marrow failure and severe cytopenias [92, 93]. Furthermore, there is a higher frequency of both acute and chronic renal disease seen in multiple studies following lung transplantation in patients with various forms of TBD [94, 95]. Finally, patients with TBD have an increased risk of certain malignancies, such as SCC, before and after transplant [61].

5.3. Screening and preventative testing: The Mayo Clinic Experience

As discussed earlier, patients affected by TBDs have a higher risk for certain conditions, such as pulmonary fibrosis, bone marrow failure and malignancy [61]. Research efforts in the field have led to the development of informal screening guidelines for TBD patients to initiate prompt intervention when necessary. Current screening recommendations at our institute include: frequent complete blood counts (at baseline and annually unless cytopenias are present), annual bone marrow aspirate and biopsies with cytogenetics and molecular genetics to evaluate for bone marrow failure, somatic mosaicism (Mayo Clinic TBD research NGS (next-generation sequencing) panel including adaptive and maladaptive CH variants with error correction - see supplemental material **Table 1S** for details) and/or hematologic malignancy; for cancer risk, monthly self-exams (skin and breast) and annual screenings by an otolaryngologist for head and neck cancer (flexible laryngoscopy), annual dermatologist assessed skin cancer screens, and periodic gynecological screening visits for anogenital cancers. We also continue to strongly endorse general age-appropriate cancer screening guidelines (breast, colon, and prostate). Additionally, we recommend annual pulmonary function testing (ideally starting at time of diagnosis); annual liver function testing at baseline followed by periodic assessments for liver fibrosis and nodular regenerative hyperplasia of the liver, using either Fibroscan (ultrasound based) or MR Elastography (our preferred modality to assess liver and spleen stiffness); and routine dental screening [all these recommendations are also consistent with Team Telomere guidelines]. Additional screening and preventive measures include periodic assessments for bone health (bone density) and ensuring that immunizations are up to date. More research is needed in the field to better refine and validate these screening guidelines to create robust algorithms for TBD patients. [https://teamtelomere.org/diagnosis-management-guidelines/].

5.4. Specialized TBD Clinics and advocacy groups

With the rising awareness and interest in the field of TBDs, an increasing number of resources have become accessible to affected individuals and their families. Specialized clinics, renowned for their expertise in managing all aspects of TBDs have significantly transformed the care and support available for these rare conditions. As an example, the TBD Clinic at Mayo Clinic aims to provide comprehensive care for patients from initial diagnosis to long-term management. The clinic provides multidisciplinary expertise from physicians, pharmacists, geneticists, and molecular biologists to deliver personalized care for these complex, multisystem conditions.

In addition to the telomere-focused clinics across the country, there have also been great strides taken by Team Telomere, which is an organization dedicated to patients affected by TBDs and their families. Team Telomere serves to address the complex needs of TBD patients, including offering financial assistance for families as well as providing support, education, research, and advocacy [96].

6. Future directions for treatment

6.1. Genetic editing and potential gene-based therapies

The emergence of targeted molecular therapies holds the potential to transform the clinical management of TBD patients. One of the rising gene therapies in this field involves targeting the Zinc Finger and SCAN Domain Containing 4 (*ZSCAN4*) gene, due to its role in telomere maintenance and regulation [97-99]. Specifically, *ZSCAN4* could be utilized to counteract telomere shortening that occurs in TBDs, as it is integral to telomere elongation [97, 98]. The mechanism behind *ZSCAN4* in telomere maintenance is multifaceted, involving activation of telomere recombination [upregulation of homologous recombination genes], inducing global DNA demethylation [downregulation of Uhrf1/Dnmt1], and mediating TL through interactions with shelterin complex components [TRF1, RAP1] [97, 98, 100]. Transient expression of ZSCAN4 is critical for genomic stability and can be a powerful tool for genetic editing.

Another target for genetic therapy is *TINF2*, the gene responsible for coding one of the shelterin complex proteins. In a 2022 study by Choo et al., frameshift mutations were edited into HSPCs of a TBD patient with a *TINF2* pathogenic variant, thereby rendering the faulty allele ineffective and restoring TL in stem cells [101]. In addition to repairing TL deficits, hemizygous editing of *TINF2* also led to an increase in the proliferative capacity of cells [101] without further risk for transformation. This once again highlights the translational work that could provide an innovative solution to DC and other TBD phenotypes.

However, with the introduction of these novel therapies comes new concerns. Challenges include off-target effects, inadvertently promoting oncogenesis, and igniting an adverse immune response. In the case of *ZSCAN4*, this gene has been linked to cancer progression due to its regulatory effects on cancer stem cells [102]. When thinking more broadly, any genetic

modulation that leads to unregulated telomerase reactivation and overexpression could potentially lead to development of cancer [103]. TERT upregulation is an important strategy to achieve immortality for cancer cells and has been seen in approximately 90% of all human cancers [104-106].

6.2. Clinical trials

With the continued interest in novel therapies for treating TBDs, clinical trials are now available for patients to participate in. In terms of potential pharmacologic targets, ongoing research is exploring PAPD5/7 inhibition and GSK3 inhibition for the treatment of TBD-related disease. PAPD5 and PAPD7 are polymerases involved in RNA processing functions. Chemical inhibition of this with RG7834 has led to restoration of TL and TERC levels, specifically in the setting of *DKC1_A353V* variant cells [107]. Similarly, chemical inhibition of the protein kinase, GSK3, with CHIR99021 has shown promise [108]. This inhibition enhances telomerase activity and corrects telomere dysfunction specifically in lung-based, type II alveolar epithelial cells [108].

As for the gene-based trials, one ongoing phase I/II, open label, single center study at Cincinnati Children's Hospital Medical Center is investigating the use of EXG34217 in bone marrow failure patients with TBDs. This trial is with the previously described ZCAN4 protein product, utilizing the viral vector, EXG-001, for cellular entry (ClinicalTrials.gov ID NCT04211714). Published in 2025 by Myers et al., this trial reported successful *ex vivo* telomere elongation in CD34+ cells (HSPCs), although there was no significant increase in TL in the patient peripheral blood samples at the 2 year endpoint following infusion [99]. However, it was suggested that there was a rise in cell subpopulations with increased TL in peripheral blood samples from the treated individuals [2 total] and overall change in TL distribution [99].

Another new phase I interventional study out of Boston Children’s Hospital is investigating enteral nucleoside treatment in TBD patients with deoxycytidine and deoxythymidine. The idea behind this therapeutic approach is to elongate telomeres by introducing two nucleosides that have been shown to play an integral role in telomere maintenance (ClinicalTrials.gov.ID: NCT06817590). Although early on in development, these clinical trials offer the potential to translate years of lab-based scientific research into tangible solutions and life-changing therapeutics for TBDs.

7. Conclusions

TBDs represent a heterogeneous group of conditions that give rise to a broad spectrum of clinical features and systemic effects. While these conditions remain relatively rare, it is essential for healthcare providers to recognize the hallmark signs of TBD disease to enable timely, targeted, and multidisciplinary care. Emerging research underscores the intricate challenges associated with the prompt diagnosis and effective management of these patients. Continued research in this field is essential for developing strategies to better approach the care of TBD patients and their families.

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Table 1. Telomere biology glossary of important terms.

Term	Definition
Back mutations	Reversion of the original germline pathogenic variant to potentially restore normal gene function.
Clonal Cytopenia of undetermined significance	Persistent unexplainable cytopenias seen in the context of clonal hematopoiesis.
Clonal hematopoiesis of indeterminate potential	The clonal expansion of hematopoietic stem and progenitor cells resulting from somatic mutations that confer an adaptive advantage to the fitness constraints within the bone marrow.
Copy neutral loss of heterozygosity	Occurs when one allele is lost and replaced by a duplicate of another, without changing total DNA content.
Genetic Anticipation	A phenomenon where certain genetic disorders become more severe or appear at an earlier age in successive generations.
Haploinsufficiency	A condition in which a single functional copy of a gene is insufficient to maintain normal function, leading to disease or abnormal phenotype when the other copy is defective or deleted.
Phenocopying	The phenomenon where a phenotype resembling TBD can occur in the absence of pathogenic genetic variants due to the inheritance of short telomeres.
Senescence	The irreversible arrest of cell division that occurs when telomeres shorten beyond critical length, contributing to aging and tissue dysfunction.
Shelterin	A protein complex that specifically binds to telomeres, protecting them from being recognized as DNA damage and regulating telomere length and stability.
Somatic genetic reversion (rescue)	The correction of a pathogenic variant in somatic cells via secondary mutations or genetic events, mitigating effects of original mutation and potentially restoring partial function.
Telomerase complex	Complex composed of subunits TERT, TERC, and DKC1, responsible for synthesizing repetitive DNA sequences to telomeres, thereby elongating telomeres and helping to maintain chromosomal integrity. Assembled with the help of NOP10 and NHP2.
Telomeres	Protective caps at the ends of chromosomes that prevent loss of genetic material and help to maintain genomic stability.

Table 2. Methods of telomere length measurement.

Method	Description	Pros	Cons	CLIA certified
Quantitative Fluorescence in Situ Hybridization (Q-FISH) / Fluorescence in Situ Hybridization (Flow-FISH)	Uses fluorescent probes that bind to their target (such as telomeric repeats) to visualize and quantify telomere lengths.	Can be performed in tissues and cells. Highly reproducible.	Need previously stablished standards to infer telomere length from relative fluorescence units.	Yes
Quantitative Polymerase Chain Reaction (qPCR)	Measures ratio of telomere repeat copy number to a single-copy gene using PCR.	Easy to perform. Does not require large amounts of DNA.	Large variation among laboratories. Only average telomere length is provided as a relative ratio.	No
Telomere Restriction Factor (TRF)	Uses southern blotting techniques after restriction enzyme digestion of genomic DNA.	Reproducible within the same laboratory and able to detect and distinguish a wide range of telomere lengths.	Requires large amount of starting DNA. High variability between laboratories.	No
Single Telomere Length Analysis (STELA)	Selectively amplifies individual telomeres w/ PCR using ligated oligonucleotide adapters.	Detects the shorter telomeres at individual chromosome ends. XpYp and 17p are the most commonly tested through STELA, although other arms like 2p, 11q and 21q have also been tested in some published work.	Low throughput and labor intensive.	No
Telomere Shortening Localized Amplification (TeSLA)	Combines ligation-mediated PCR and southern blotting to amplify telomeres.	Measures all telomeres less than 1kb and up to 18 kb.	Low throughput and labor intensive.	No
High-Throughput Single Telomere Length Analysis (HT-STELA)	Utilizing techniques (automation platforms) for rapid analysis – a high-throughput version of STELA.	Higher throughput than STELA.	Labor intensive and limited number of chromosome arms.	No
Telomere Chromosome Analysis (TCA)	Various cytogenetic techniques that visualize and quantify telomeres on individual chromosomes.	Measures all telomeres less than 1kb and up to 18 kb and can be automated.	Needs specialized equipment; is time-consuming and expensive. Lack of standardization.	No
Optical mapping	Fluorescent imaging maps telomeric and sub telomeric regions after labeling of DNA molecule sequence motifs.	High throughput and characterizes large DNA molecules to infer length and structure of individual telomeres.	Needs specialized equipment and may miss certain telomeres.	No
Single Telomere Analysis by Resequencing (STAR)	Captures individual telomeric regions via targeted enrichment and resequencing.	Measures all telomeres equal to 2kb and up to 320 kb. High throughput, fast, and requires small DNA sample.	Recent technology still lacking additional external, independent validation and limited cross-laboratory data to assess reproducibility.	No
DNA Methylation of Telomere Length (DNAmTL)	Estimates TL using DNA methylation patterns at specific CpG sites.	Robust and high throughput.	Estimates telomere length indirectly. Only for lymphocyte telomere length measurement.	No
Short read sequencing	Uses whole genome sequencing data and counts telomeric repeat-containing reads.	High throughput and can be used on existing datasets.	Reports only average telomere lengths. Results may vary with use of next generation sequencing.	No

Long read sequencing	Sequences ultra-long DNA fragments and directly measures entire telomeric regions.	High throughout and provides full telomere/sub telomere sequence	Expensive, requires large DNA samples, still in early development.	No

CLIA, Clinical Laboratory Improvement Amendments; DNAmTL, DNA Methylation of Telomere Length; Flow-FISH, Fluorescence in Situ Hybridization; HT-STELA, High-Throughput Single Telomere Length Analysis; Q-FISH, Quantitative Fluorescence in Situ Hybridization; qPCR, Quantitative Polymerase Chain Reaction; STAR, Single Telomere Analysis by Resequencing; STELA, Single Telomere Length Analysis; TCA, Telomere Chromosome Analysis; TeSLA, Telomere Shortening Localized Amplification

Table 3. Genes associated with short and long telomere syndromes.

	Gene	Gene product	Chromosomal location	Mode of inheritance	Biology	Associated disorder(s)
Short telomere syndromes (TBDs)	*ACD*	TPP1	10q21.3	AD, AR	Component of the shelterin complex that docks with telomerase	Similar to DC
	CTC1	CTC1	17q25.3	AR	Aids in telomere extension with the synthesis of the CCCTAA strand	DC, CP
	DKC1	Dyskerin	Xq28	XLR	Component of telomerase; first identified pathogenic variant of DKC1	DC, HHS
	MDM4	MDM4	1q32.1	AD	Contributes to telomere associated regulation of p53	Similar to DC, PF
	NAF1	NAF1	3q21.3	AD	Involved in telomerase assembly	PF
	NHP2	NHP2	1q41	AR, AD	Involved in telomerase assembly	DC, PF
	NOP10	NOP10	1q42.12	AR	Involved in telomerase assembly	DC
	PARN	PARN	16p13.13	AR, AD	Helps to control the level of hTR and aids in hTR maturation	DC, HHS, PF
	POT1	POT1	7p22.1	AR	Component of the shelterin complex	CP, Familial melanoma
	RTEL1	RTEL1	20q13.13	AR, AD	Involved in telomere replication by unwinding G-quadruplex structures so that telomeres can be copied	DC, HHS, PF, MDS, LC
	STN1	STN1	6q21	AR	Involved in telomere extension	CP
	TERC	hTR	3q26.2	AD	Component of telomerase (the telomerase RNA molecule)	DC, AA, MDS, PF
	TERT	hTERT	5p15.33	AD, AR	Telomerase component involved in reverse transcription	DC, AA, MDS, PF, LC
	TINF2	TIN2	14q12	AD	Component of the shelterin complex	DC
	WRAP53	TCAB1	17q21.32	AR	Aids with transportation of telomerase to the telomere	DC
	ZCCHC8	ZCCHC8	5p15.33	AD	Involved in hTR maturation	PF
Long telomere syndromes (CPLT)	*ACD*	TPP1	16q22.1	AD, AR	Component of the shelterin complex that docks with telomerase	Familial melanoma
	POT1	POT1	7q31.33	AD	Component of the shelterin complex	Familial melanoma/glioma, CLL, B/T-cell lymphoma, clonal hematopoiesis
	TERF1	TERF1	8q21.11	AR	Shelterin component; ds-telomeric DNA binder and telomerase inhibitor	Familial melanoma/sarcoma

	TERF2IP	RAP1	16q23	Unclear; likely AD/monoallelic	Shelterin protein, binds directly to TRF2.	Familial melanoma, sarcoma
	TINF2	TIN2	14q12	AD	Component of the shelterin complex	Cancer predisposition, melanoma, sarcoma

AA, aplastic anemia; AD, autosomal dominant; AR, autosomal recessive; CP, Coats Plus Syndrome; DC, dyskeratosis congenita; HHS, Hoyeraal-Hreidarsson Syndrome; LC, liver cirrhosis; MDS, myelodysplastic syndrome; PF, pulmonary fibrosis; XLR, X-linked recessive. References: short telomere syndromes [48] and long telomere syndromes [29, 42, 43].

Table 4. Spectrum of solid and hematologic malignancy in TBDs.

Malignancy type	Specific cancer	Observed/Expected	95% CI	Prevalence among TBD patients
Hematologic malignancies	Acute myeloid leukemia	73[1]	23-169	1.6% at diagnosis[3]
	Myelodysplastic syndrome	578[1]	343-914	17.3% at diagnosis[3]
	Non-Hodgkin lymphoma	11[1]	2-30	Not specified
Solid neoplasms	Head and neck squamous cell carcinoma	74[1]	37-133	Not specified
	Tongue	216[1]	94-427	Not specified
	Cervical cancer	5[2]	0-30	Not specified
	Esophagus	44[2]	9-129	Not specified
	Anorectal cancers	24[2]	1-134	Not specified

Data obtained from the following: [1]Alter et al., Haematologica. 2018; [2]Niewisch et al., JAMA Netw Open. 2024; [3]Maillet et al., British Journal of Haematology. 2024. In (1), there were approximately 197 patients with dyskeratosis congenita evaluated and observed/expected ratios were calculated by taking the observed number of cancer cases divided by the number of expected cancers in the general population (age controlled) using the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER, https://seer.cancer.gov/). In (2), 230 individuals with TBD (confirmed pathogenic variant) were evaluated and observed/expected ratios were also calculated by dividing the number of cancer cases in TBD cohort by the SEER data (SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2019) database). For data in the last column (3), this is derived from a French nationwide retrospective multicentric study, with all data obtained from the French National Reference Centre for Aplastic Anemia between January 2003 and December 2022.

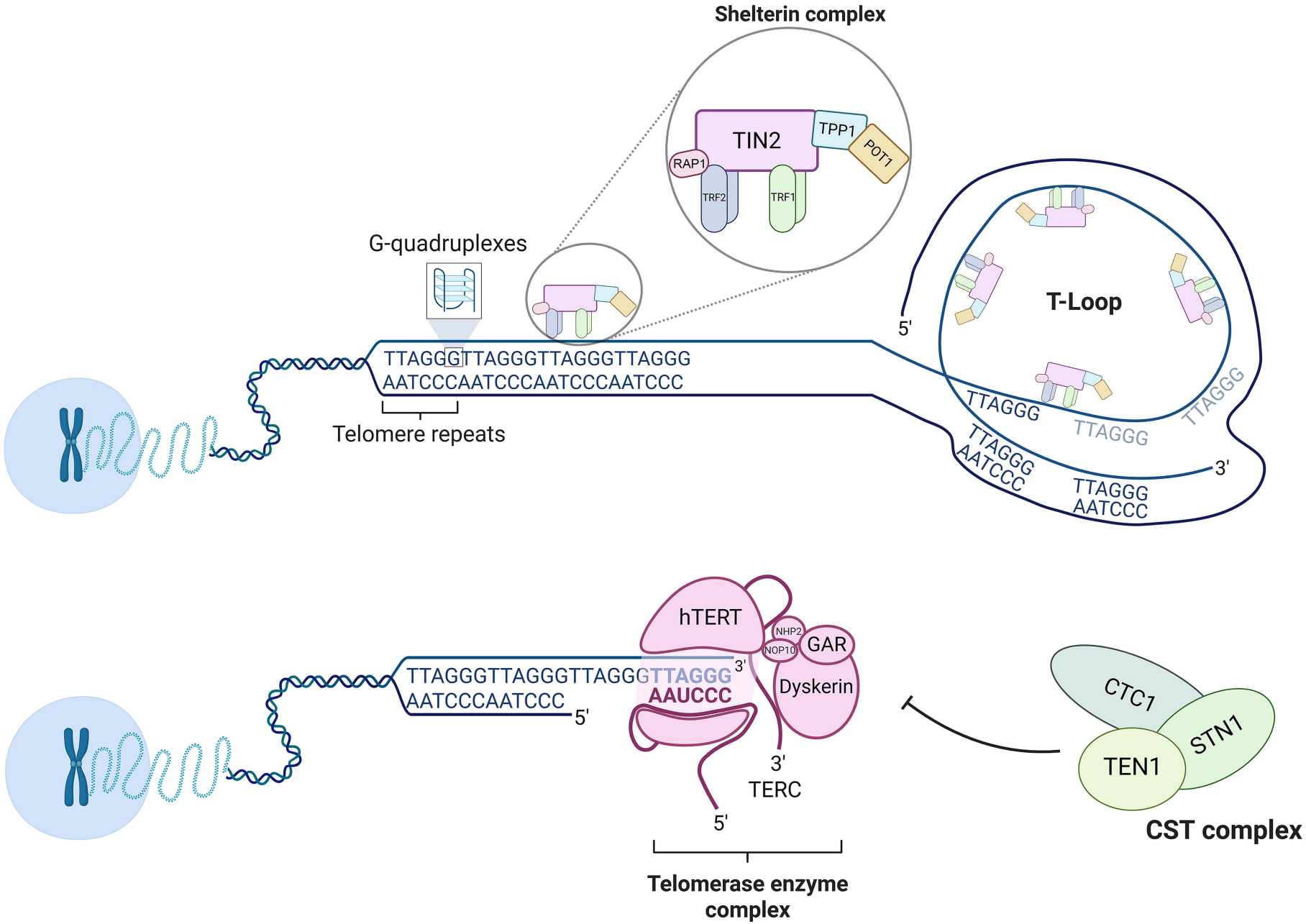
Figures

Figure 1. The telomere apparatus. The telomere interfaces with the shelterin complex and resulting T-loop (top). As seen in this figure, the telomere apparatus is comprised of the telomeres, an enzyme called telomerase and its subunits, and a combination of specialized proteins known as the shelterin complex, which includes six protein subunits: RAP1, TRF1, TRF2, TIN2, TPP1, and POT1. These proteins function together as a unit and the complexes are found amply at telomeres. The components, TRF1/TRF2 and POT1 are most important for the binding shelterin to telomeres. This unique binding mechanism promotes the formation of T-loops. The telomerase complex docks at the end of a chromosome and interfaces directly with the single-stranded 3' overhang at the terminal end of the telomere (bottom). This process is inhibited by the CST complex. The CST protein structure is composed of CTC1, STN1, and TEN1 and functions by halting telomerase activity and thereby stopping telomere extension. [Created in BioRender. Franke, M. (2025) https://BioRender.com/72f23am]

Figure 2. The assembly of telomerase. The active telomerase enzyme complex is composed of six subunits with two copies of the following: TERT, TERC, and the protein, Dyskerin. The proteins, NOP10 and NHP2 are involved in the assembly of telomerase. Other components are involved, such as PARN, TCAB, ZCCHC8, etc. and each have specialized roles essential for the function of telomerase. This telomerase complex is shown interfacing with shelterin via TCAB1. [Created in BioRender. Franke, M. (2025) https://BioRender.com/d74crky].

Figure 3. Mechanisms of clonal hematopoiesis in TBD. [Created in BioRender. Franke, M. (2025) https://BioRender.com/dwvjutv]. This figure demonstrates the various pathways contributing to either adaptive, potentially maladaptive, or maladaptive outcomes. The start of the figure displays the HSPC, or a hematopoietic stem/progenitor cell, with a germline TBD-related variant. The top pathway demonstrates somatic reversion, whereby somatic mutations (in *TERC*, *TERT*, etc.) can improve the ability of the HSPCs to survive inherent fitness constraints through mechanisms like copy-neutral loss-of-heterozygosity and back mutations. These mechanisms both lead to the restoration of normal hematopoiesis. Alternatively, the bottom pathway demonstrates somatic compensation, which can branch into adaptive somatic compensation or potentially maladaptive somatic compensation. This is where there are certain somatic mutations that aim to try and compensate for the germline pathogenic variant dysfunction, rather than restore original functionality. Adaptive somatic compensation is demonstrated by the middle pathway, where an activating mutation in the promoter *TERT* region leads to increased expression of the wild type *TERT* allele, resulting in a compensatory increased telomerase activity and telomere lengthening. The bottom pathway demonstrates somatic changes in various genes that can partially compensate for the phenotype (shortened telomeres)

but potentially increase the risk for hematological malignancy (seen in the case of *TP53* and *U2AF1*). The bottom pathway highlights the example mechanism of a germline *TERT* mutation accompanied by a somatic mutation in *PPM1D*. This same mechanism occurs in the other mutations *TP53, U2AF1,* and *ATM* which have different outcomes (progression to hematologic malignancy or unclear outcomes to be determined).


Shelterin complex
TIN2
TPP1
POT1
RAP1
TRF2
TRF1
G-quadruplexes
T-Loop
5'
TTAGGGTTAGGGTTAGGGTTAGGG
AATCCCAATCCCAATCCCAATCCC
Telomere repeats
TTAGGG
TTAGGG
TTAGGG
TTAGGG
AATCCC
TTAGGG
AATCCC
3'
hTERT
NHP2
NOP10
GAR
Dyskerin
TTAGGGTTAGGGTTAGGGTTAGGG
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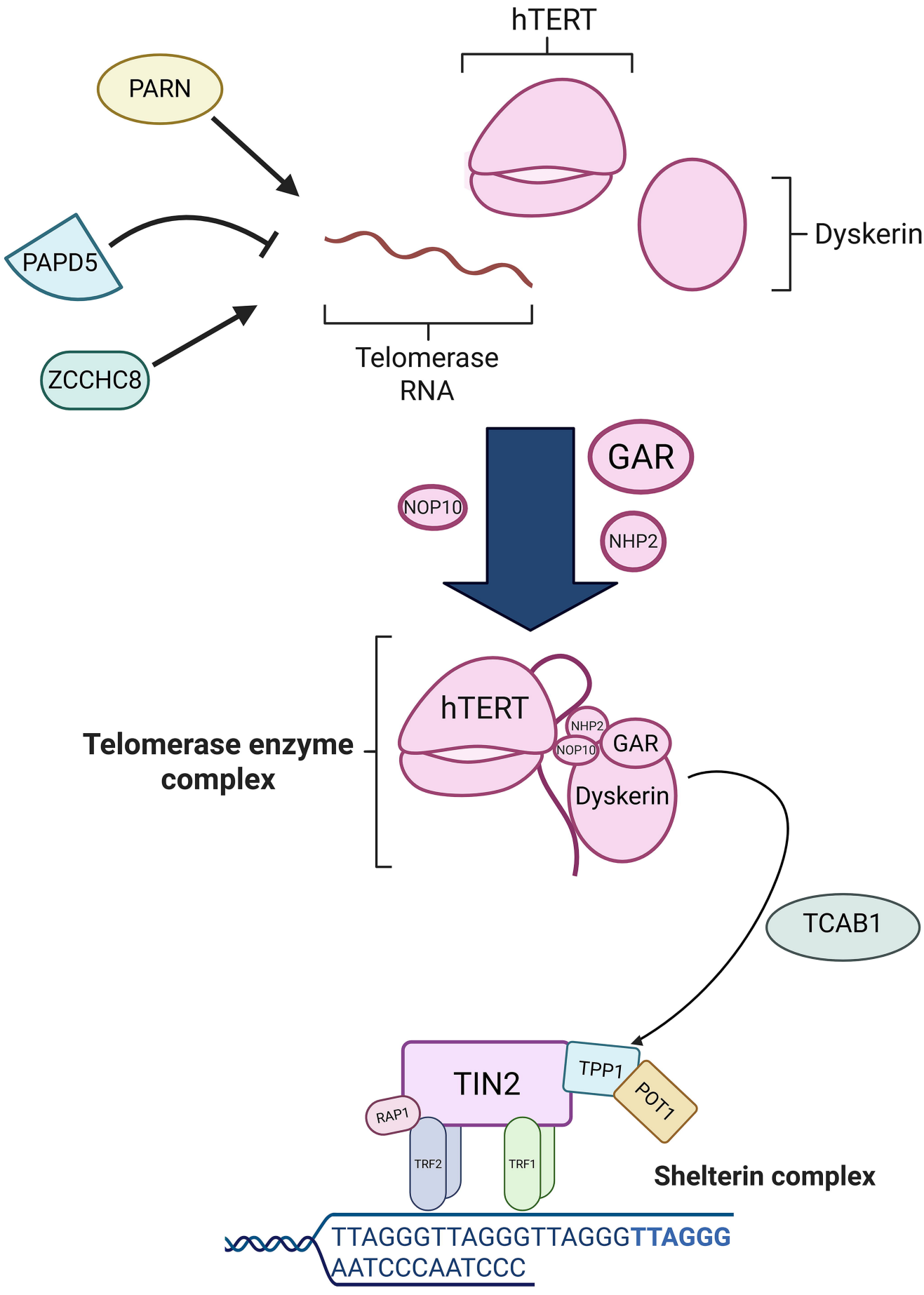
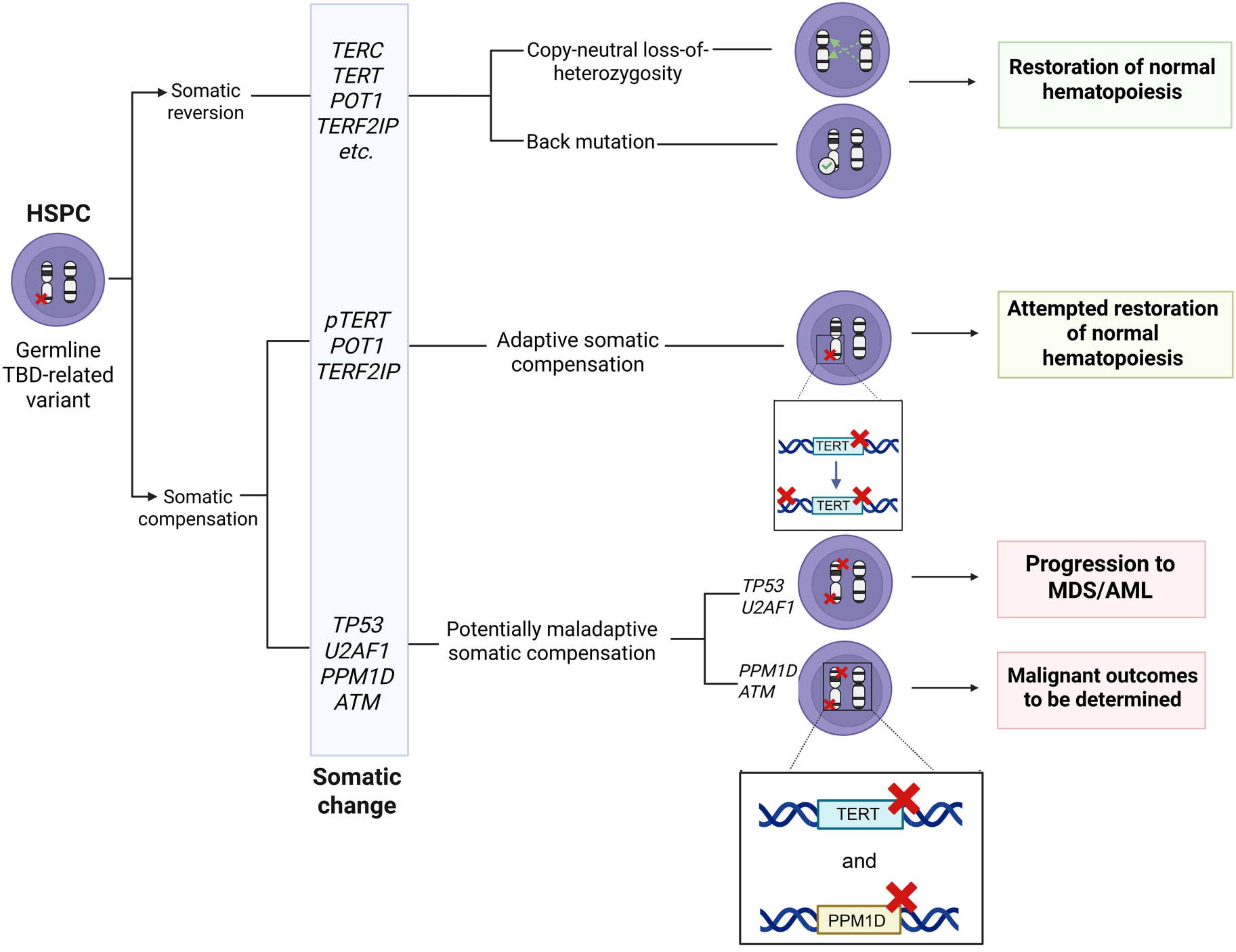
AAUCCC
3'
5'
3'
TERC
5'
Telomerase enzyme complex
CTC1
STN1
TEN1
CST complex


hTERT
PARN
PAPD5
ZCCHC8
Dyskerin
Telomerase
RNA
GAR
NOP10
NHP2
Telomerase enzyme complex
hTERT
NHP2
NOP10
GAR
Dyskerin
TCAB1
TIN2
TPP1
POT1
RAP1
TRF2
TRF1
Shelterin complex
TTAGGGTTAGGGTTAGGGTTAGGG
AATCCCAATCCC


HSPC
Germline TBD-related variant
Somatic reversion
Somatic compensation
TERC
TERT
POT1
TERF2IP
etc.
pTERT
POT1
TERF2IP
TP53
U2AF1
PPM1D
ATM
Somatic change
Copy-neutral loss-of-heterozygosity
Back mutation
Adaptive somatic compensation
Potentially maladaptive somatic compensation
TP53
U2AF1
PPM1D
ATM
TERT
TERT
TERT
and
PPM1D
Restoration of normal hematopoiesis
Attempted restoration of normal hematopoiesis
Progression to MDS/AML
Malignant outcomes to be determined

Supplementary material

Table 1S: *In-house designed Telomere Biology Disorder somatic panel*. Mayo Clinic TBD research NGS panel including adaptive and maladaptive clonal hematopoiesis variants with error correction. This panel covers all exons and relevant promoter regions (i.e. *TERT*) with a read depth between 5000X to 7000X.

Telomere Biology Disorder somatic panel genes					
ACD	***DNMT3A***	***NOP10***	***RTEL1***	***TEN1***	***USB1***
ASXL1	***ETV6***	***NPM1***	***RUNX1***	***TERC***	***WRAP53***
ATRX	***EZH2***	***NRAS***	***SETBP1***	***TERF1***	***ZC3H18***
BCOR	***GATA1***	***PABPN1***	***SF3B1***	***TERF2***	***ZCCHC8***
CBL	***IDH1***	***PAPD5***	***SH2B3***	***TERT***	***ZRSR2***
CHEK2	***IDH2***	***PARN***	***SKIV2L2***	***TET2***	
CTC1	***MDM4***	***PIK3CA***	***SMC1A***	***TINF2***	
DAXX	***MXRA5***	***POT1***	***SRSF2***	***TP53***	
DIS3	***NAF1***	***PPM1D***	***STAG2***	***TPP1***	
DKC1	***NHP2***	***RBM7***	***STN1***	***U2AF1***	