INPLASY

INPLASY2025120081

doi: 10.37766/inplasy2025.12.0081

Received: 22 December 2025

Published: 23 December 2025

Telomerase Activity in Melanoma: impact on cancer cell proliferation kinetics, tumor progression, and clinical therapeutic strategies – A Scoping Review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025120081

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 December 2025 and was last updated on 23 December 2025.

INTRODUCTION

Review question / Objective Does the direct quantification of telomerase enzymatic activity levels correlate with measured cancer cell population doubling time in TERT promoter-mutated melanoma cells, and can variant-specific TERT mutations (C250T vs. C228T) predict differential proliferation kinetics independent of telomere length maintenance?

Background Melanoma remains a significant global health challenge, with incidence rates stead-ily rising worldwide [1]. Recent epidemiology data indicate that melanoma accounts for approximately 1.5% of all newly diagnosed cancer, with age-adjusted incidence rates in-creasing from 15.1 per 100,000 in 1999 to 23.0 per 100,000 in 2021 [1]. As of 2025, mela-noma represents one of the most prevalent cancers, with over 816,580 individuals living with a melanoma diagnosis in the United States alone [2]. A defining molecular characteristic of melanoma is the aberrant activation of telomerase, with 69-82 % of cutaneous melanoma exhibiting detectable telomerase activity [3, 4]. This activation is predominantly mediated by telomerase reverse transcriptase (TERT) promoter mutations [5, 6] which occur at frequencies ranging from 50% to 82% in melanoma cases, representing the most common noncoding mutation in this malignancy [7, 8].

Telomerase activation represents a critical mechanism enabling replicative immortality in melanoma cells, directly facilitating sustained cancer cell proliferation and tumor progression [9, 10]. The enzyme complex maintains telomere length at chromosomal ends, thereby bypassing cellular senescence and apoptosis pathways that normally limit cell division [3, 4, 11]. The most prevalent TERT promoter mutations (C228T and C250T, located at 124 and 146 pb from the ATG start site) generate de novo binding sites for ETS (Erythroblast Transformation Specific) transcription factors, resulting in 2- to 4-fold in-creases in TERT mRNA expression and telomerase activity [6-8].

This heightened telomerase activity correlates strongly with cancer cell proliferation rates, telomere length maintenance, and population doubling capacity [12-15]. Importantly, telomerase activity levels in melanocytic lesions demonstrate progressive elevation from benign nevi to primary melanomas and metastatic disease [4], suggesting a direct relationship with disease progression. Furthermore, telomerase activation has been implicated in therapeutic resistance to BRAF and MEK inhibitors [16] , contributing to treatment failure and poor clinical outcomes [17].

Despite the well-established prevalence of telomerase activation in melanoma, several critical knowledge gaps persist regarding the relationship between telomerase activity levels and cancer cell population doubling time in melanoma [18, 19]. Additionally, although telomerase inhibitors have demonstrated preclinical efficacy, their clinical translation has been limited by delayed cytotoxic effects and therapeutic resistance mechanisms that remain poorly understood [18-20]. Currently no scoping review has systematically mapped the evidence linking telomerase activity to melanoma cell proliferation kinetics and doubling time. More literature about immunity and telomerase will be included in the results section.

While this review focuses on melanoma, TERT promoter mutations represent a hallmark of telomerase activation across multiple human malignances. Similar mutations occur in approximately 70-80 % of melanomas, 40-70% of gliobalstomas,60% of bladder cancers, and 50% of squamous cell carcinomas, suggesting conserved mechanisms of telomerase reactivation in cancer progression [6,41,42]. Understanding telomerase biology in melanoma thus provides insights applicable to other UV- exposed and non-UV ex-posed cancers.

This scoping review aims to identify key studies by comprehensively synthesizing current knowledge and highlighting existing gaps. In doing so, the review will provide a foundation for future research directions and inform the development of telomerase-based strategies. The research team is notable for its international representation, comprising experts in oncology, basic science, nursing, and pharmacy. This work will serve as a valuable reference for clinicians and researchers in the future. Drawing from the example of arsenic, when it was first submitted for publication, few believed that such an apparently irrelevant emerging drug would one day become the cornerstone of leukemia treatment. Time will tell whether telomerase can become a useful target for refractory cases of melanoma once current well-known treatments have been exhausted.

Rationale

1. Knowledge Gap in Literature

Current literature lacks precise quantitative correlations between telomerase enzymatic activity levels and measured cell population doubling times in melanoma. Most studies use surrogate markers (e.g., Ki-67) rather than directly measuring proliferation kinetics.

2. Clinical Relevance

Direct measurement of doubling times would identify high-risk patients requiring aggressive treatment protocols and enable personalized prognostic predictions based on individual telomerase activity levels.

3. Variant-Specific Mechanistic Understanding

Although C250T TERT mutations demonstrate worse clinical outcomes than C228T variants, the underlying mechanistic basis remains unclear. Determining whether this difference reflects accelerated proliferation rates versus alternative resistance mechanisms is essential for targeted therapeutic development.

4. Feasibility and Future Direction

This research question is actionable through: (a) prospective clinical trials with direct cell population doubling time measurements, (b) in vitro assays quantifying telomerase activity alongside proliferation kinetics, and (c) comparative analysis of proliferation rates between TERT variant carrier.

METHODS

Strategy of data synthesis

Data extracted from eligible studies were synthesized using a thematic analysis approach organized into four interconnected domains:

1. Telomerase Molecular Mechanisms

TERT promoter mutations (C228T vs. C250T variants) and their prevalence in melanoma

Mechanisms linking TERT activation to telomere length maintenance and replicative immortality

Extratelomeric TERT functions beyond telomere biology

2. Proliferation Kinetics and Biomarkers

Quantitative associations between telomerase activity levels and cancer cell population doubling times

Biomarkers correlating with proliferation rates (telomere length, TERRA expression, Ki-67 positivity)

Disease progression patterns from benign nevi to primary melanomas to metastatic disease

3. Therapeutic Targeting and Resistance Mechanisms

Telomerase inhibitors and their mechanisms of action (Imetelstat, BIBR1532, nucleotide incorporation)
Immunotherapeutic approaches (peptide vaccines, dendritic cell vaccines, CAR-T cells)
Alternative telomere maintenance (ALT) pathways as resistance mechanisms

4. Clinical-Prognostic Correlations
Associations between telomerase activity/TERT mutations and survival outcomes
Predictive value of telomerase biomarkers for treatment response
Correlations with stage, grade, and metastatic potential
Synthesis Method: Findings were compared across study designs (primary research vs. reviews) and organized chronologically to identify emerging trends, knowledge gaps, and inconsistencies in the literature. Particular attention was given to studies reporting quantitative doubling time data and variant-specific differences in proliferation kinetics.

Eligibility criteria

Inclusion Criteria
(1) Primary Research Studies:
Quantitative, qualitative, or mixed methods primary research on telomerase activity in melanoma and its role in cancer cell proliferation and doubling time
Published in English
Published primarily between 2020-2025, with select key studies from 2015-2019 included where they provide essential mechanistic insights
(2) Review Articles:
Systematic and narrative review articles on telomerase in melanoma

Published in English
Any published date (no time restriction)
Rationale: Select studies from 2015-2019 were retained because they elucidate important mechanisms of telomerase biology, drug resistance pathways, and therapeutic approaches that remain clinically relevant and are not superseded by more recent literature.

Exclusion Criteria
Studies unrelated to telomerase activity or function
Studies published in languages other than English
Review articles published before the inclusion window (before 2015) that do not provide critical mechanistic or clinical synthesis
Studies that do not address melanoma or telomerase function
Study Selection Process
Two independent reviewers (O.A. and P.T.) reviewed eligible studies
First step: Title and abstract screening
Second step: Full-text assessment
Resolution: Any disagreements resolved through discussion and re-examination. A third researcher (D.A.) was available to arbitrate if consensus could not be reached.

Source of evidence screening and selection

Search Strategy
A comprehensive search was conducted across four major electronic databases:
Scopus
ScienceDirect
MEDLINE/PubMed
CINAHL (Cumulative Index to Nursing and Allied Health Literature)
Search Keywords: "telomerase," "melanoma," "cancer," "cell proliferation," and "doubling time"
Screening and Selection Process
Stage 1: Initial Search Results
Total records identified: 195 studies
Duplicates removed: 50 records
Records for title and abstract screening: 145
Stage 2: Title and Abstract Screening
Records excluded (not related to telomerase): 113
Full texts assessed for eligibility: 32
Stage 3: Full-Text Assessment
Reports excluded (not meeting inclusion criteria): 16
Studies included in review: 16 studies
Selection Criteria Applied During Screening
Screeners: Two independent reviewers (O.A. and P.T.) evaluated each study against predefined inclusion/exclusion criteria:
Relevance to telomerase and melanoma
Language (English only)
Publication date alignment (primarily 2020-2025, with select key studies from 2015-2019)
Study design quality and peer-review status
Presence of data on cell proliferation, doubling time, or telomerase activity
Conflict Resolution: Any disagreements between reviewers were resolved through discussion and re-examination of articles. A third researcher (D.A.) was available to arbitrate if consensus could not be reached.
PRISMA Flow Diagram
The selection process followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses- scoping review (PRISMA -ScR)) guidelines, as documented in Figure 1 of your manuscript.

Data management

Data were extracted from each included study (n=16) using a standardized data extraction form capturing:

Study Characteristics:

Author(s) and publication year

Study design (primary research vs. review article)

Geographic location/institution

Sample size (if applicable)

Content-Specific Data:

TERT promoter mutation types and frequencies (C228T vs. C250T)

Telomerase activity levels (quantitative measurements)

Cancer cell population doubling times (when reported

Telomere length measurements

TERRA expression levels

Biomarkers associated with proliferation (Ki-67, mitotic index)

Therapeutic targets and mechanisms of action

Treatment outcomes and resistance mechanisms

Survival data and prognostic correlations

Quality Assessment

While formal quality assessment tools (e.g., MMAT or ROBIS) are typically reserved for systematic reviews, this scoping review evaluated source credibility based on:

Study design rigor

Peer-review status

Methodological transparency

Sample size and representativeness (where applicable)

Note: Narrative and systematic reviews were assessed for synthesis quality, mechanistic clarity, and citation of primary evidence

Data Organization and Synthesis

Extracted data were organized into three core thematic categories:

(1) TERT Promoter Mutations and Proliferation Markers

TERT mutation prevalence and distribution

Correlations between TERT mutations and telomere length

Associations with cancer cell proliferation rates

(2) Therapeutic Targeting of Telomerase

Telomerase inhibitors (enzyme inhibitors, nucleotide incorporation, telomere destabilization)

Immunotherapeutic approaches (peptide vaccines, dendritic cell vaccines, CAR-T cells)

Resistance mechanisms and alternative telomere maintenance (ALT)

Extratelomeric TERT functions as therapeutic targets

(3) Clinical-Prognostic Correlations

Associations between telomerase activity and disease stage, grade, and survival outcomes

Biomarker value for prognosis and treatment prediction

Patterns of disease progression (benign nevi → primary melanoma → metastatic disease)

Data Analysis Approach

Thematic Analysis Method: Findings were synthesized qualitatively using thematic analysis, comparing:

Quantitative associations across studies

Temporal trends (chronological analysis 2015-2025)

Consistency vs. inconsistencies in reported findings

Identification of knowledge gaps regarding specific cell proliferation doubling times

Variant-specific differences in proliferation kinetics (C250T vs. C228T)

Comparison Across Study Types: Primary research findings were contrasted with narrative and systematic reviews to identify emerging trends and validate mechanistic insights.

Reporting results / Analysis of the evidence

Overview of Included Studies

The scoping review included 16 studies published between 2017 and 2025, comprising:

11 narrative/systematic reviews synthesizing telomerase biology, therapeutic strategies, and clinical implications

5 primary research studies including retrospective cohorts, preclinical experimental studies, bioinformatics analyses, and translational investigations

Geographic distribution spanned North America, Europe, and Asia, with studies originating from major cancer centers and research institutions.

Thematic Analysis Results

Theme 1: TERT Promoter Mutations and Proliferation Markers

Key Findings:

TERT promoter mutations (C228T and C250T) represent the most frequent noncoding alterations in melanoma, occurring in 50-82% of cases

C250T variant demonstrates 5.7-fold increased TERT expression compared to C228T and is associated with significantly poorer prognosis (PFS: 5 months, OS: 36 months vs. C228T: PFS: 23 months, OS: 106 months)

Telomerase activity levels show progressive elevation from benign nevi → primary melanoma → metastatic disease

The EXTEND algorithm (13-gene signature) outperforms TERT expression alone in predicting telomerase enzymatic activity across >9,000 tumors

Quantitative correlations between telomerase activity and specific cell population doubling times

remain sparsely reported and inconsistently measured across studies
Evidence Gaps Identified:
Direct measurement of cancer cell population doubling times in relation to telomerase activity levels
Variant-specific proliferation kinetics (C250T vs. C228T) in controlled experimental settings
Standardized methodologies for quantifying telomerase activity and proliferation rates
Theme 2: Therapeutic Targeting of Telomerase
Key Findings:
Enzyme Inhibitors:
Imetelstat (telomerase inhibitor) and BIBR1532 show preclinical efficacy but limited clinical translation due to delayed cytotoxicity
6-thio-dG (telomerase-targeted nucleoside) induces telomere dysfunction, apoptosis, and tumor control in therapy-resistant melanoma
Immunotherapeutic Approaches:
Telomerase-specific CD4 T-cell immunity occurs naturally in melanoma patients
Universal telomerase-based cancer vaccines combined with ipilimumab show 5-year survival benefits in metastatic melanoma
CAR-T cell therapies and dendritic cell vaccines targeting telomerase demonstrate emerging potential
Resistance Mechanisms:
Alternative Lengthening of Telomeres (ALT) pathway activation confers resistance to telomerase inhibitors
ALT-high/TEL-high phenotypes correlate with worse overall survival across 33 cancer types
TERT overexpression induces resistance to BRAF/MEK inhibitors by reactivating MAPK pathway independently of telomere maintenance
Novel Strategies:

TICCA concept (Transient, Immediate, Complete, and Combinatory Attack) integrates CRISPR/Cas9, telomere deprotection, and hybrid inhibitors for improved long-term control

G-quadruplex stabilizers and antisense oligonucleotides represent emerging therapeutic candidates

Evidence Gaps Identified:

Limited clinical trial data on telomerase inhibitors in melanoma-specific populations

Mechanisms underlying variant-specific (C250T vs. C228T) therapeutic responses

Optimal combination strategies with immunotherapy and targeted agents

Theme 3: Clinical-Prognostic Correlations
Key Findings:

High telomerase activity correlates with advanced disease stage, higher grade, and metastatic potential

TERT promoter mutations serve as prognostic biomarkers with C250T associated with poorest survival outcomes

TPP1 promoter mutations cooperate with TERT mutations, synergistically lengthening telomeres and promoting melanoma progression

TERT expression independently predicts reduced response to BRAF/MEK inhibitors in BRAF-mutated melanoma

Pan-cancer analysis reveals five distinct telomere maintenance mechanism (TMM) phenotypes with ALT-high/TEL-high showing worst survival

Evidence Gaps Identified:

Prognostic value of dynamic telomerase activity changes during treatment

Variant-specific (C250T vs. C228T) prognostic models incorporating doubling time kinetics

Clinical validation of EXTEND algorithm specifically in melanoma cohorts

Synthesis and Critical Analysis
Strengths of Current Evidence:
Consistent mechanistic understanding of TERT promoter mutations driving telomerase reactivation

Strong prognostic associations established, particularly for C250T variant

Multiple therapeutic modalities identified with preclinical validation

International collaboration and large-scale bioinformatics analyses (TCGA, 11,123 samples)

Limitations and Inconsistencies:
Methodological heterogeneity in measuring telomerase activity and proliferation rates

Scarce quantitative data on cell population doubling times

Limited clinical translation of telomerase inhibitors due to delayed effects and resistance

Conflicting reports on universal prognostic utility of telomerase across different tumor contexts

Absence of standardized reporting for telomerase activity and proliferation kinetics

Critical Knowledge Gaps:
Direct correlation studies linking telomerase enzymatic activity levels with measured doubling times in melanoma

Variant-specific proliferation kinetics (C250T vs. C228T) in controlled experimental and clinical settings

Dynamic biomarker models incorporating telomerase activity changes during treatment

Mechanistic basis for differential clinical outcomes between TERT promoter variants

Optimal integration of telomerase-targeted therapies with current standard-of-care (immunotherapy, BRAF/MEK inhibitors)

Implications for Future Research
The evidence synthesis reveals that while telomerase is a validated therapeutic target and prognostic biomarker in melanoma, critical gaps persist in:

Quantitative kinetic studies measuring proliferation rates

Variant-specific mechanistic investigations

Clinical trial development for telomerase inhibitors

Combination therapy strategies overcoming resistance

Addressing these gaps through prospective studies with standardized methodologies will be essential for translating telomerase biology into personalized therapeutic strategies for melanoma patients.

Presentation of the results

Domain 1: TERT Mutation Prevalence and Variant-Specific Outcomes
Primary Finding:

TERT promoter mutations present in 50-82% of melanomas

C250T variant (most prevalent hotspot):

Associated with 5.7-fold higher TERT expression than C228T

Median PFS: 5 months vs. C228T: 23 months

Median OS: 36 months vs. C228T: 106 months

Biomarker Performance:

EXTEND algorithm (13-gene signature) predicts telomerase enzymatic activity across >9,000 tumors with superior accuracy vs. TERT expression alone

Domain 2: Telomerase Activity and Disease Progression
Progressive Elevation Pattern:

Benign nevi: Minimal/absent telomerase activity

Primary melanoma: Intermediate telomerase activity

Metastatic disease: Maximal telomerase activity

Mechanism of Replicative Immortality:

C228T and C250T mutations generate de novo ETS transcription factor binding sites

Results in 2-4 fold increases in TERT mRNA expression[6-8]

Maintains telomere length, bypassing senescence and apoptosis

Domain 3: Therapeutic Response and Resistance
Immunotherapy Outcomes:

Telomerase-based vaccines + ipilimumab: 5-year survival benefit in metastatic melanoma

Targeted Therapy Resistance:

High TERT expression: Reduced response to BRAF/MEK inhibitors

TERT overexpression reactivates MAPK pathway independently of telomere length

Alternative Lengthening of Telomeres (ALT):

ALT-high/TEL-high phenotype: Worst overall survival across 33 cancer types

ALT pathway activation major mechanism of telomerase inhibitor resistance

Domain 4: Clinical Prognostic Biomarkers
Survival Associations:

TERT mutations = independent prognostic factor for worse outcomes

TPP1 promoter mutations = synergistic effect with TERT mutations

Telomerase activity levels correlate with:

Disease stage and grade

Metastatic potential

Treatment response prediction

Evidence Synthesis Across Study Designs
Narrative Reviews (n=9)
Contribution: Comprehensive mechanistic synthesis, therapeutic drug development summaries, clinical application frameworks

Primary Research Studies (n=5)
Retrospective Cohort (n=1): Variant-specific prognostic stratification

Bioinformatics Analysis (n=1): Pan-cancer TMM phenotyping

Preclinical Experimental (n=1): Telomerase inhibitor efficacy

Translational/In Vitro (n=1): TERT expression and BRAF/MEK inhibitor resistance

Mechanistic Review (n=1): UV-driven TERT/TPP1 cooperation

Critical Data Gaps in Current Evidence
Gap Impact Recommended Approach
Quantitative doubling time data Cannot correlate telomerase activity with proliferation kinetics
Prospective cell proliferation assays with standardized doubling time measurements
Variant-specific kinetic studies C250T vs. C228T mechanistic basis unclear Comparative in vitro and in vivo studies measuring doubling times by variant
Standardized telomerase activity measurement
Methodological heterogeneity limits comparisons
Develop consensus protocols for telomerase enzymatic activity quantification
Dynamic biomarker changes during treatment
Cannot assess prognostic utility of real-time telomerase monitoring Longitudinal studies tracking telomerase activity during therapy

Clinical telomerase inhibitor trials in melanoma
Limited evidence for clinical translation Phase II/III trials combining telomerase inhibitors with immunotherapy
Visual Summary: Study Characteristics and Distribution
Geographic Distribution:

North America: 4 studies

Europe: 7 studies

Asia: 4 studies

International collaborations: 1 study

Publication Timeline:

2017-2019: 1 study

2020-2021: 2 studies

2022: 4 studies

2023: 5 studies

2024: 4 studies

Study Design Distribution:

Narrative/Systematic Reviews: 11 studies (69%)

Primary Research: 5 studies (31%)

Retrospective cohort: 1

Preclinical experimental: 1

Bioinformatics: 1

Translational: 1

Mechanistic: 1

Integration with Research Question
The systematic analysis of 16 studies reveals that current evidence provides strong support for telomerase as a prognostic biomarker and therapeutic target, yet critical quantitative gaps persist regarding:

Direct correlation between telomerase enzymatic activity and measured cell population doubling times

Variant-specific proliferation kinetics (C250T vs. C228T) with explicit doubling time measurements

Standardized methodologies for quantifying both parameters simultaneously

These gaps directly align with your research question and provide the evidence base for future prospective studies measuring proliferation kinetics in relation to telomerase activity levels and TERT promoter variants.

Language restriction
Inclusion Criteria:

All studies included in this scoping review were published in English only

Rationale:
The restriction to English-language publications was implemented to ensure:
Direct comprehension of methodology, findings, and conclusions without translation errors
Standardized interpretation of technical terminology and scientific concepts
Feasibility for the international research team (comprising members from Jordan, Belgium, Palestine, Kosovo, Canada, USA, Germany, China)
Consistency with PRISMA guidelines for systematic and scoping reviews
Limitation Acknowledged:
This language restriction may introduce language bias by potentially excluding relevant high-quality research published in other languages (e.g., French, German, Spanish, Chinese, Arabic). Studies published in non-English languages addressing telomerase, melanoma, and proliferation kinetics may exist but were not captured in this review.

Country(ies) involved Jordan. Nursing Department, Al-Zaytoonah University, Airport Street, Amman.

Keywords cell proliferation, doubling time, telomerase, scoping review, survival, prognosis, out-come, resistance, target, melanoma.

Dissemination plans Academic publication
The primary dissemination route will be submission of the full scoping review manuscript to a peer-reviewed oncology or cancer biology journal with international readership, ensuring open-access publication where possible to maximize global visibility and citation potential.
Conference presentations
Key results will be presented at national and international conferences in oncology, radiation oncology, dermatology, and translational cancer research, using oral and poster formats to reach clinicians, researchers, and trainees.
Local and institutional sharing
Findings will be shared within participating institutions (universities, oncology centers, and research groups) through grand rounds, departmental seminars, and teaching sessions to inform clinical decision-making and stimulate further research on telomerase-targeted strategies in melanoma.

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