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Pediatric Buccal Epigenetic (PedBE) and Neonatal Epigenetic Estimator of Age (NEOage) Clocks: A Focus on Pediatric Oncology

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Abstract
The Pediatric Buccal Epigenetic (PedBE) and Neonatal Epigenetic Estimator of Age (NEOage) clocks provide a novel method for assessing the biological age of young individuals, enhancing our comprehension of their health and development. By analyzing DNA methylation patterns, these clocks identify risk factors for various health conditions and guide personalized interventions to promote optimal growth in children and infants. With ongoing research and validation, PedBE and NEOage could revolutionize pediatric and neonatal healthcare by facilitating early detection of age-related changes and targeted interventions to improve long-term outcomes. In pediatric oncology, PedBE is particularly promising for evaluating biological age in children with cancer, as it accurately estimates DNA methylation age in buccal cells, revealing the effects of cancer and its treatments on biological aging. Additionally, PedBE can detect DNA methylation changes associated with environmental exposures and childhood adversities, making it a valuable tool for studying the impact of cancer on the epigenetic age of pediatric patients. The NEOage clock, designed to predict gestational age in newborns, complements the PedBE clock, offering a comprehensive assessment of biological age from infancy to adolescence, which is vital for understanding pediatric oncology's influence on aging. This paper examines the complexities of both clocks, highlighting their potential for accurately determining the age of children and infants through DNA methylation analysis.
Keywords: Biological Variation, DNA Methylation, Gestational Age, Oncology, Pediatric

Introduction

Epigenetic clocks have emerged as reliable tools for assessing biological age by examining DNA methylation profiles, enabling the evaluation of age across diverse tissue types (1, 2). Currently, they exhibit superior precision in predicting actual chronological age compared to transcriptomic and proteomic data, as well as telomere length measurements (3). These clocks show precision in age prediction across tissues and cell types, supporting aging interventions and mortality risk assessment (4). By examining specific CpG sites, epigenetic clocks provide accurate age predictions with strong correlation values,

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outperforming previous models (5). Changes in methylation status at these sites as age progresses allow for precise calculation of biological age (6). The Hannum et al. clock, one of the earliest reported examples of epigenetic clock, was trained and tested on DNA derived from blood samples. It was composed of 71 CpG sites selected from the Illumina 450k array, effectively capturing alterations in chronological age, influenced in part by age-related changes in blood cell composition (7). In contrast, the Horvath clock was developed across various tissues, incorporating blood data from the Samoilova et al. study, aiming to serve as a universal "pan-tissue" timekeeper of chronological age. It was designed to detect common epigenetic changes independent of tissue type, utilizing 353 CpGs present on the earlier Illumina 27k array (8). These differences in training datasets resulted in conflicting reported associations between the two clocks. Knight et al. created an epigenetic clock for gestational age (GA) using cord blood and blood spot samples from 1434 newborns (9). Clocks like HannumEAA, IEAA, PhenoEAA, GrimEAA, and DunedinPACE have mainly been developed for individuals of European or Hispanic descent (10–12). The concept of epigenetic clocks has expanded beyond human studies, as seen in the identification of an epigenetic clock in the model insect Nasonia vitripennis, suggesting promising avenues for further research on aging interventions. Additionally, epigenetic clocks have been successfully established for various mammalian species, including domestic dogs, highlighting their evolutionary conservation and broad applicability across different organisms. These findings demonstrate the evolution and diversification of epigenetic clocks across species and their significance in estimating biological age, providing valuable insights into human biology, aging, and healthspan extension (2, 13–15). By exploring the applicability of these clocks across diverse species, scientists can gain a deeper understanding of the fundamental processes underlying aging and longevity (16–18). The development of epigenetic clocks for non-human organisms opens up new avenues for comparative studies, shedding light on the evolutionary conservation of aging processes and potential strategies for promoting healthy aging. As research in this field continues to advance, epigenetic clocks may prove to be valuable tools for personalized medicine and targeted interventions to improve health and quality of life across species (13, 19, 20). The use of buccal epithelial cells in pediatric epigenetic research is gaining attention for reflecting methylation patterns in non-blood-related diseases, especially epithelial disorders (7, 21). Recent studies suggest that buccal cells may be a more informative tissue for epigenome-wide association studies (EWAS) of non-blood-related diseases like pediatric eosinophilic esophagitis. Research has also explored the link between intragenic DNA methylation in buccal cells and intellectual performance in pediatric groups, particularly males with fragile X syndrome (22, 23). Specific epigenetic clocks tailored for buccal cells have been developed which offer greater precision for the pediatric age group, as compared to adult clocks. Further investigation into the use of buccal epithelial cells in pediatric epigenetic research has revealed promising potential for understanding the underlying mechanisms of various childhood disorders (7, 24, 25). Studies have shown that buccal cells can provide valuable insights into the epigenetic changes associated with conditions such as autism spectrum disorder, attention deficit hyperactivity disorder, and childhood obesity. By focusing on the unique methylation patterns present in buccal

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cells, researchers hope to uncover new biomarkers and therapeutic targets for these complex pediatric conditions (26–28). Additionally, the development of advanced sequencing technologies and bioinformatic tools has enabled more comprehensive analysis of the buccal cell epigenome, paving the way for future breakthroughs in pediatric epigenetic research (29, 30). The aim of this review was to provide a comprehensive analysis of the Pediatric Buccal Epigenetic (PedBE) and Neonatal Epigenetic Estimator of Age (NEOage) clocks. This review examines the development, validation, and potential applications of these epigenetic clocks in pediatric and neonatal populations. Additionally, we discuss the current challenges and future directions for utilizing these clocks in clinical practice and research.

PedBE Clocks

The PedBE clock is a useful tool for evaluating children's biological age by examining DNA methylation in buccal epithelial cells, showing promise in understanding pediatric development (24, 31, 32). It provides a non-invasive method to accurately determine age in pediatric samples, aiding in the study of how environmental factors influence DNA methylation patterns during child development and their significance for children's health (33, 34). The PedBE clock has been trained on a dataset of 1032 children aged 0-19 years, highlighting its relevance in this particular age bracket (7). Studies suggest that epigenetic aging, as determined by the PedBE clock, is connected to neonatal brain growth, delayed brain development, and adverse neurodevelopmental outcomes in very preterm neonates (35). Additionally, epigenetic modifications in buccal samples have been associated with such metabolic disorders as obesity, with specific CpG sites indicating links to BMI, insulin resistance, and leptin levels (36). Studies have found epigenetic markers in buccal cells that may predict preterm birth, with distinct DNA methylation patterns linked to this outcome in mothers and their children. Research using the PedBE clock has examined how critical illness and nutritional interventions in the Pediatric Intensive Care Unit (PICU) affect epigenetic age in previously hospitalized patients (31, 37). Based on the findings, older patients experienced a deceleration in epigenetic age during illness, which was correlated with impaired height growth (38, 39). Studies on extremely premature neonates using the PedBE clock have investigated the relationship between epigenetic aging, brain development and neurodevelopmental outcomes. As the findings revealed, epigenetic aging in neonates was associated with reduced brain volumes, slower brain growth, and poorer neurodevelopment (33, 35, 40). However, challenges remain in accurately characterizing and integrating epigenetic age assessments across different developmental stages, as current clocks focus mainly on cord blood for estimating gestational age or peripheral blood/buccal cells in childhood and adolescence (41, 42). Researchers have investigated how critical illness and early parenteral nutrition affect the deviation of epigenetic age in former PICU patients. They found that buccal cells could provide insights into the long-lasting effects of severe illness in children (41, 43). Abnormal DNA methylation patterns in genes related to steroid production have been identified in these former critically ill children, which correlate with issues like stunted growth. This highlights the significance of buccal cells in studying the prolonged consequences of pediatric critical illness (44, 45). Table I outlines the main characteristics, uses, correlations, and accuracy metrics of the PedBE epigenetic clocks, which are vital for evaluating biological age and health outcomes in pediatric oncology and neonatal care.

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Accuracy of PedBE

The PedBE clock has been extensively studied for its accuracy in estimating DNA methylation age in pediatric buccal cells (35). Developed based on DNA methylation patterns from individuals aged 0-20 years, the PedBE clock has demonstrated high accuracy in age prediction, achieving a median absolute error of just 0.35 years in validation studies (24, 33). It has also been associated with various obstetric outcomes, performed well in longitudinal data analysis, and shown reliability in tissues other than buccal cells. Accelerated epigenetic aging as measured by the PedBE clock has been correlated with reduced brain volumes, slower brain growth, and poorer neurodevelopmental outcomes in extremely premature infants (46, 47). Despite the lower quantity and purity of genomic DNA obtained from buccal swabs compared to blood samples, studies have shown a 100% genotype call rate and reliable genotyping results (35, 48). The PedBE clock shows promise for estimating biological age in children, and buccal swab collection presents a feasible alternative to invasive blood sampling for genetic research in pediatric populations (24). Saliva and buccal specimens are frequently utilized in epigenome-wide association studies (EWAS) due to their ease of collection, with methods like the EpiDISH algorithm validated for estimating cellular heterogeneity in this context (11, 49). Furthermore, the epigenetic aging measured by the PedBE clock has been associated with brain growth and neurodevelopmental outcomes in extremely premature infants, indicating its potential as a predictor for these outcomes (7, 35, 50). Comparisons of genome-wide DNA methylation patterns between pediatric buccal epithelial cells and peripheral blood mononuclear cells have revealed differences in variability and agreement, which can have implications for epigenetic investigations in pediatric populations (51–53). Various epigenetic clocks tailored for pediatric samples have been assessed in multiple tissues such as blood, saliva, buccal specimens, and brain tissue, with clocks trained on pediatric samples proving to be most accurate across all tissues tested (54). The skin and blood clock has exhibited the strongest correlation with chronological age in blood samples, while the PedBE clock has emerged as the most precise for saliva and buccal specimens (55). The Horvath clock is acknowledged as the most accurate measure for brain tissue. In pediatric brain tumors, the Horvath methylation age was discovered to be advanced, with subtype-specific acceleration seen in atypical teratoid rhabdoid tumor (ATRT), ependymoma, medulloblastoma, and glioma (54). Therefore, As a result, methylation age serves as a predictive marker for pediatric brain tumors (54). The PedBE clock is notable for its precision in estimating DNA methylation age in pediatric buccal cells, rendering it a significant tool in research related to children and providing insights into age-related alterations influenced by various factors (24).

NEOage Clocks

Epigenetic clocks based on DNA methylation have been developed to accurately predict chronological age and capture biological aging (24). Numerous studies have concentrated on creating epigenetic clocks tailored for various tissue types and age ranges; however, there is a notable absence of clocks designed specifically for preterm infants. Recent research has introduced epigenetic clocks which aim at assessing neonatal aging in preterm infants and demonstrate strong correlations between the predicted ages and the actual reported ages, suggesting their accuracy (31, 56). Moreover, epigenetic clocks that utilize DNA

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methylation have proven to be precise and accurate in estimating gestational age at birth, surpassing older models. In addition, a specialized epigenetic gestational age clock created from umbilical vein endothelial cells has shown a stronger correlation with clinical gestational age than those derived from blood samples of newborns with European ancestry (57, 58). NEOage clocks estimate the age of newborns based on DNA methylation patterns, using samples from racially and ethnically diverse populations, such as umbilical vein endothelial cells. The epigenetic gestational age, calculated using these clocks, is highly correlated with clinical gestational age in newborns (56, 59). Birth weight and NICU admission are associated with epigenetic gestational age acceleration. Accurate epigenetic predictors of chronological age and biological age have been identified through the use of large-scale EWAS studies and integration of multiple datasets (60, 61). Epigenetic clocks serve as valuable instruments for assessing biological age and estimating lifespan and mortality risk. They evaluate DNA methylation patterns, which can be affected by a variety of factors, such as lifestyle and environmental influences (62). This suggests that by altering these factors, it might be possible to positively impact the aging process. Additionally, researchers have developed epigenetic clocks for various fish species, which can facilitate effective fishery management and help estimate the age classes of endangered species, thereby enhancing conservation efforts. (24). Epigenetic age acceleration (EAA) and epigenetic gestational age acceleration (EGAA) are biomarkers of physiological development and may be influenced by the perinatal environment. Overall, studies demonstrate the accuracy and utility of neonatal epigenetic clocks in estimating age and gestational age in preterm infants and newborns (42, 63, 64). Research on buccal epigenetics in newborns has revealed a significant connection between accelerated epigenetic aging—assessed by the PedBE clock—and decreased brain volume, slower brain development, and poorer neurodevelopmental outcomes in very preterm infants at 18 months (35, 54). Another study compared DNA quality from buccal swabs in neonates immediately extracted versus after storage and found comparable DNA yield and purity in both cases, suggesting that buccal swabs can be stored for two weeks without affecting DNA quality (65). A third study assessed the quantity, purity, and genotyping efficiency of genomic DNA from neonatal buccal swabs, indicating lower DNA concentration and yield, compared to blood samples, but still obtaining reliable genotyping results (66, 67). A study explored how DNA methylation in buccal cells relates to neurobehavioral traits in very preterm infants. It revealed that those with well-regulated profiles had an epigenetic age that was older, while those with atypical profiles exhibited variations in methylation at specific CpG sites (68). Epigenetic clocks using DNA methylation can reliably predict chronological age and indicate biological aging. However, such clocks tailored for preterm infants have yet to be developed (56). Several epigenetic clocks have been tailored for preterm infants, utilizing buccal cells or placental tissue as DNA sources. These clocks have demonstrated a high correlation with actual gestational age, showing precision and accuracy. Compared to other methods like clinical estimation or blood samples, epigenetic clocks have proven more accurate in estimating gestational age in preterm infants (31, 58, 69). However, it's crucial to acknowledge that epigenetic clocks designed for other populations, such as adults or newborns of European descent may not be as precise in estimating gestational age in preterm infants (58, 70). Hence, the use of specific epigenetic

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clocks developed for preterm infants is recommended for accurate gestational age estimation in this group. A recent study aimed to bridge this gap by establishing epigenetic clocks tailored for evaluating neonatal aging in preterm infants (56, 71). The study showed strong correlations between predicted and actual ages, suggesting that neonatal aging epigenetic markers in preterm infants could be valuable for assessing biological maturity and its associations with neonatal and long-term health issues. Buccal epigenetics could provide a new approach to identifying fetal growth restriction (FGR) with brain-sparing (35, 72). Richter et al. discovered that children with FGR showing brain-sparing mechanisms had increased methylation of certain genes associated with neurotrophic pathways. This suggests potential early epigenetic changes influenced by oxygen availability due to hemodynamic shifts in FGR, which can impact neurodevelopmental outcomes later in life (73). Studies show that epigenetic markers of inflammation, such as DNA methylation patterns, can indicate innate immunity in neonatal health and help identify factors influencing neurodevelopmental differences (74, 75). Benítez-Marín et al. suggested that brain sparing in FGR may not provide complete protection and could be associated with decreased cognitive function and lower IQ scores (76). Conole et al. further advocated for the use of inflammation-related DNAm assessments to capture the allostatic load of inflammatory stress in preterm infants and to investigate neurodevelopmental differences (77). Neonatal epigenetics may provide valuable insights into infant neurobehavior, with well-regulated neurobehavioral profiles associated with a higher epigenetic age. Moreover, variations in neonatal epigenetics may provide insights into infant neurobehavior, with well-regulated profiles linked to a higher epigenetic age compared to other infants. Additionally, changes in DNA methylation of several genes have been associated with atypical neurobehavioral patterns in preterm infants. These findings indicate that epigenetic factors, including PedBEs, could impact the NICU environment and serve as potential indicators for neurodevelopmental outcomes in preterm infants. (68, 78).

Accuracy of NEOage

Neonatal epigenetic estimators, such as the NEOage clocks, have demonstrated high accuracy in predicting post-menstrual and postnatal age in premature infants, with strong correlations ranging from 0.93 to 0.94 and minimal root mean squared errors between 1.28 and 1.63 weeks (56). Epigenetic clocks designed for gestational age, using DNA methylation data from the Illumina MethylationEPIC 850K array, have shown precision and accuracy in forecasting gestational age, surpassing previous models with an R2 value of 0.724 and a median absolute deviation of 3.14 days (61). DNA methylation in umbilical cord blood has proven to be a reliable method for estimating gestational age at birth, displaying predictive accuracy comparable to such traditional techniques as ultrasound (9). Neonatal epigenetic clocks have shown remarkable accuracy in predicting health outcomes, especially in models tailored for premature infants like NEOage, demonstrating strong correlations between predicted and actual ages (56). Epigenetic clocks developed by individuals of European or Hispanic descent, such as DunedinPACE have been observed to reflect Taiwanese physiological conditions and health outcomes, including conditions like obesity, diabetes, and dyslipidemia (10, 79). Associations have also been found between EAA and EGAA with perinatal variables, child gender, and ethnic backgrounds. These findings suggest potential implications for pediatric

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epigenetic aging and long-term health and development (42). Furthermore, sociodemographic characteristics of participants significantly influence clock precision, and this can highlight the importance of diverse representation in training data. Epigenetic clocks specifically designed for premature infants can evaluate their biological maturity and predict long-term health outcomes, which is particularly important in epidemiological research (16). Furthermore, studies have found a correlation between accelerated epigenetic aging at birth and child behavior, suggesting a potential link to developmental pathways. The creation of a dedicated epigenetic gestational age clock for the EPIC array underscores the accuracy of DNA methylation in determining gestational age. This is vital for monitoring neonatal development in both infants conceived through assisted reproductive technology (ART) and those conceived naturally (80).

PedBEs in Oncology

Epigenetic alterations are fundamental in the pathogenesis and advancement of childhood malignancies through the modulation of gene expression independent of DNA sequence modifications (81). These changes, which encompass DNA methylation, modifications of histones, and disruptions in non-coding RNA activity, can lead to the activation of oncogenes while inhibiting tumor suppressor genes, and thus can facilitate the development of tumors. Pediatric cancers, noted for their relatively low mutation rates, are especially vulnerable to epigenetic modifications that interfere with normal cellular functions critical for growth and maturation during fetal development. The influence of epigenetic alterations in childhood brain tumors is well-established, contributing to unique molecular traits in individuals and providing potential targets for personalized therapies, such as DNA methyltransferase and histone deacetylase inhibitors (82–84). Understanding and accurately targeting these epigenetic modifications is crucial for advancing treatment and improving outcomes in pediatric oncology patients. The emergence of the PedBE and NEOage clocks has facilitated a precise assessment of biological age in pediatric populations, especially in premature infants. These epigenetic clocks are important tools for examining biological maturation and its relationship with both neonatal and long-term health challenges, which are potentially significant in pediatric oncology (85). The PedBE clock, designed for individuals from birth to 20 years, uses DNA methylation profiles from buccal epithelial cells to determine biological age with considerable accuracy (54). In contrast, the NEOage clock, which focuses on extremely premature newborns, has identified associations between accelerated epigenetic aging and negative neurodevelopmental outcomes, which can highlight its importance in understanding the effects of biological aging on pediatric health. Incorporating these epigenetic clocks into pediatric oncology could provide valuable insights into the biological age of young cancer patients and its impact on treatment success and long-term survival rates (56). Epigenetic clocks are essential in assessing the risk of childhood cancers by providing precise estimates of methylation age in children and identifying potential prognostic biomarkers in pediatric brain tumors (86). Studies indicate that clocks specifically designed for pediatric samples yield more accurate methylation age predictions, which can underscore the importance of tailored models for this age group. In the context of pediatric brain tumors, accelerated Horvath methylation age has been noted, particularly in specific subtypes such as atypical teratoid rhabdoid tumor (ATRT), ependymoma,

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medulloblastoma, and glioma (54, 87). This acceleration correlates with poorer prognostic outcomes in ATRT, ependymoma, and glioma and can suggest that methylation age could serve as a valuable prognostic biomarker in these tumors. Further investigation into epigenetic clocks in pediatric cancers may pave the way for effective pre-diagnostic or cancer risk assessments for this vulnerable demographic group. While these clocks show potential as biomarkers of aging, their reliability can be hindered by technical noise (54). Recent studies have evaluated the role of liquid biopsies in children with brain tumors, showing that these methods are viable for tumor detection and monitoring. Specifically, liquid biopsies analyzing cerebrospinal fluid and serum have successfully identified tumor-specific copy number variations and elevated levels of circulating tumor DNA in cerebrospinal fluid, and can offer a comprehensive approach to genetic and epigenetic profiling (88, 89). This non-invasive technique facilitates early detection and monitoring of pediatric cancers, and provides critical insights into tumor development and supporting personalized medicine strategies for young oncology patients. Specialized devices, such as the PedBE clock, have shown great precision when measuring buccal samples, and can help in understanding the epigenetic modifications linked to pediatric cancers (7). There is a connection between epigenetic age acceleration (EAA) and various factors, including treatment history, lifestyle choices, and chronic health issues in survivors of childhood cancer, which can indicate that EAA could serve as a prognostic marker for pediatric brain tumors. Early indications of epigenetic aging in young individuals correspond to chronic health issues and increased risk of early mortality. This can underscore the necessity for targeted interventions to improve long-term outcomes for childhood cancer survivors (90, 91). The NEOage clocks demonstrate potential applications in oncology that extend beyond their initial use in neonatal assessments, with studies suggesting that EAA may serve as a valuable prognostic marker in pediatric brain tumors, and with implications that vary depending on the tumor subtype. Epigenetic clocks have been examined in childhood cancer survivors, and have shown connections between EAA and the early onset of chronic health conditions, as well as with mortality that is postponed (54, 56). The Levine and GrimAge clocks have been found to be associated with early-onset obesity, the seriousness of chronic health conditions, and delayed mortality. This can highlight the predictive significance of EAA for survivors of childhood cancer. These findings highlight the potential of epigenetic clocks, such as the NEOage clocks, in oncology for assessing cancer risk and prognosis (85).

Advantages and Disadvantages

Table II demonstrates that the PedBE Clock is a valuable and simple-to-use, non-invasive tool for assessing epigenetic aging in children via buccal swabs. It provides insights into developmental milestones and health concerns, facilitates early intervention in cases of accelerated biological aging, particularly for children aged 0-19, and holds promise for predicting negative neurodevelopmental outcomes in vulnerable populations like very preterm infants. Despite its precision, the PedBE Clock has significant limitations, such as a lack of comprehensive validation across diverse demographic groups, which raises concerns about its reliability. The interpretation of differences in epigenetic age can be complex, and genetic testing costs may not be covered by insurance, creating accessibility issues. Ethical

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considerations regarding the genetic privacy of minors also merit careful consideration. Similarly, the NEOage Clock offers early assessments of biological age in newborns, and shed light on overall health and potential risks linked to abnormal aging. It is particularly beneficial in research settings for understanding the impacts of prenatal and perinatal conditions on long-term health. Designed for preterm infants, the NEOage Clock outperforms the existing methods in estimating both post-menstrual and post-natal ages, and in identifying health risks and demonstrating strong predictive capabilities. However, it faces challenges such as the logistical difficulties of obtaining appropriate neonatal samples and the highly variable nature of biological aging during the neonatal period, which can complicate interpretation of results. As a newer technology, it may encounter resistance in clinical settings, and ethical issues related to family planning and healthcare access for biological age assessments in newborns remain a concern, too. While the predictive potential of the NEOage Clock is encouraging, further validation is necessary to ensure its reliability for long-term health predictions, especially considering the complexities of biological aging among preterm infants.

Table I. Summary of PedBE and NEOage Clocks.

Clock Type	Key Features	Applications	Correlations	Accuracy Metrics
PedBE Clocks	Utilizes DNA methylation from buccal epithelial cells to evaluate biological age in children (0-19 years); non-invasive method.	Studying environmental impacts on child development and health outcomes; predicting metabolic disorders and neurodevelopmental outcomes.	Epigenetic aging linked to brain growth, delayed development, metabolic disorders (obesity), and neurodevelopmental outcomes in preterm neonates.	Median absolute error of 0.35 years; 100% genotype call rate; strong in longitudinal data.
NEOage Clocks	Specifically developed for preterm infants; estimating chronological and gestational ages using DNA methylation.	Accurate assessment of age and gestational age in neonatal populations; understanding long-term health risks.	High correlation with clinical gestational age, birth weight, and NICU admissions.	R2 value of 0.724 for gestational age prediction; accuracy of 1.28 - 1.63 weeks in age predictions.

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Table II. Comparing the advantages and disadvantages of PedBE Clock and NEOage Clock.

Clock Type	Advantages	Disadvantages
PedBE Clocks	- High Accuracy - Non-invasive Sampling - Potential Prognostic Tool: May link accelerated epigenetic aging to negative neurodevelopmental outcomes. - Development Insights - Facilitation of Early Interventions - Research Opportunities	- Limited Applicability: Not suitable for all age groups or conditions. - Complexity of Interpretation: The biological implications of age differences are intricate and under ongoing research. - Limited validation - High costs - Ethical dilemmas
NEOage Clocks	- Tailored for Preterm Infants - Enhanced Predictive Accuracy: Surpasses existing epigenetic clocks in forecasting post-natal and post-menstrual age. - Valuable for Health Outcomes: Identifies early life risks for morbidities and neurodevelopmental issues. - Early Assessment - Risk Prediction - Research Utility	- Developmental Limitations: Long-term predictive capabilities need further validation. - Biological Aging Complexity: Distinct aging processes in preterm infants complicate interpretation. - Challenges in Sample Collection - Developmental Variability - Emerging Technology - Societal and Ethical Concerns

Conclusion

Epigenetic clocks serve as essential instruments for determining the biological age of individuals, and offer valuable insights into their health, aging processes, and potential diseases. The PedBE and NEOage clocks are specifically designed to evaluate the biological age of children and newborns, respectively. The PedBE clock utilizes DNA methylation patterns found in buccal cells to estimate a child's developmental age and progression. On the other hand, the NEOage clock is aimed at neonates, and aids researchers and clinicians in understanding the epigenetic modifications that occur in early life. These epigenetic clocks have a range of applications in pediatrics, such as identifying developmental abnormalities, assessing the influence of environmental factors, and detecting early indicators of age-related conditions. By estimating the biological age of children and infants, healthcare practitioners can customize interventions and preventive measures to enhance health and wellness. This non-invasive method also facilitates the continuous monitoring of epigenetic age throughout cancer treatments, allowing healthcare professionals to observe real-time changes in a patient's epigenetic age. In the field of pediatric oncology, these clocks are vital for grasping how cancer and its treatments impact the evolving epigenome, as they have been specifically tailored for the needs of young patients.

Availability of Data and Materials

Not Applicable

Ethics Approval

This article does not include any studies involving human participants or animals conducted by the authors.

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Author’s contribution

Seyedeh Elham Shams, Reza Bahrami, and Mohammad Golshan-Tafti conceptualized the study and designed the methodology. Seyedeh Alireza Dastgheib, Maryam Sadat Yazdanparast, and Mahsa Danaie

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conducted the data collection and performed the analyses. Ali Masoudi, Amirhossein Omidi, and Maryam Aghasipour assisted in interpreting the results and reviewing the literature. Kazem Aghili and Mahmood Noorishadkam contributed to statistical analysis and data interpretation. Hossein Neamatzadeh provided critical revisions and oversight throughout the study. Amirhossein Omidi and Amirmasoud Shiri reviewed and approved the final manuscript.

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Conflict of interest
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