TECHNOLOGY REVIEW (MINI-HTA)

HAIR FOLLICLES AS EPIGENETIC BIOMARKERS FOR ASSESSING WELLBEING

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
011/2024

IPT Mark
Mini-HTA
INAHTA

DISCLAIMER

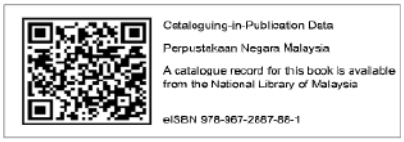
This technology review (mini-HTA) is prepared to assist health care decision-makers and health care professionals in making well-informed decisions related to the use of health technology in health care system, which draws on restricted review from analysis of best pertinent literature available at the time of development. This technology review has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since the completion of this technology review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

Please contact htamalaysia@moh.gov.my if further information is required.

EVIDENCE INFORMED DELIBERATIVE PROCESS

This Technology Review underwent evidence informed deliberative process during the Health Technology Assessment (HTA) Technical Advisory Committee meeting, chaired by the Director, Medical Development Division, MOH. Then it was endorsed in the HTA-CPG Council meeting chaired by the Director General of Health.

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229
Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my


Cataloguing-in-Publication Data
Perpustakaan Negara Malaysia
A catalogue record for this book is available from the National Library of Malaysia
eISBN 978-967-2887-88-1

eISBN: 978-967-2887-88-1

SUGGESTED CITATION: Aidatul Azura AR, Ahmad Tasnim M and Izzuna MMG. Hair Follicles as Epigenetic Biomarkers for Assessing Wellbeing. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2024. 63 p. Report No.: 011/2024.

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

AUTHORS (HTA EXPERTS)

Dr. Aidatul Azura binti Abdul Rani
Medical Officer
Senior Principal Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

Dr. Ahmad Tasnim bin Muslim
Medical Officer
Senior Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

Information Specialist:
Madam Zamilah binti Mat Jusoh @ Yusof
Head of Information Specialist
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

REVIEWERS (HTA EXPERT)

Dr. Izzuna Mudla binti Mohamed Ghazali
Public Health Physician
Deputy Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

EXTERNAL REVIEWERS

Dr. Ngu Lock Hock
Consultant Clinical Geneticist and Paediatrician
Head of Genetic Department
Hospital Kuala Lumpur

EXECUTIVE SUMMARY

Background

The genomics field has advanced rapidly since the human genome was mapped, leading to significant progress in epigenetics. Epigenetics studies heritable changes in gene expression influenced by external factors, without altering the DNA sequence. Key mechanisms—DNA methylation, histone modification, and non-coding RNA molecules—play key roles in regulating gene expression during development and in response to environmental factors such as diet, stress, and exposure to pollutants. DNA methylation, a primary epigenetic process, controls gene activity by adding methyl groups to DNA. It is essential for normal development but can also contribute to diseases like cancer when abnormal patterns occur. Histone modifications and non-coding RNAs also regulate gene expression and have been linked to conditions such as neurodegenerative and cardiovascular diseases.

Epigenetics has practical applications in healthcare, as it shows how lifestyle and environmental factors can influence gene expression. For example, nutrients like folate and vitamin B12 affect DNA methylation, and physical exercise can influence epigenetic changes in various tissues. This knowledge helps guide preventive healthcare strategies and improve health outcomes. Epigenetic clocks based on DNA methylation patterns have been developed to estimate biological age, which is a better predictor of age-related diseases than chronological age. Earlier clocks like Horvath and Hannum were designed to estimate chronological age. Newer models, such as PhenoAge and GrimAge, provide insights into disease risk and mortality, helping to personalise healthcare.

In light of these advances, a new health screening procedure has emerged utilising a portable device, which analyses hair samples. This assessment was prepared in response to a request by the Director of Medical Practice Division, Ministry of Health Malaysia, to provide comprehensive information on the effectiveness and recognition of this procedure in clinical practice.

Objective/ aim:

The objectives of this technology review are:

i. To evaluate the effectiveness of epigenetic hair analysis in predicting health status in healthy adults.
ii. To assess the safety aspects of epigenetic hair analysis and epigenetic testing.
iii. To examine the economic, social, ethical, and organisational implications related to epigenetic testing.

Results and conclusion

Search results

A total of **1,631** records were identified through the Ovid and PubMed, with **10** more from other sources. After removing duplicates, **1,631** titles were screened using inclusion and exclusion criteria, leading to **24** relevant abstracts that were retrieved in full text. Of these, **nine** full-text articles were selected, including **one** systematic review, **one** scoping review, **one** randomised controlled trial, **two** cohort studies, **one** pilot study, and **three** in-vitro studies. All the included studies were published in English between 2012 and 2023, with the majority conducted in the United States of America (five studies). Additionally, one study each was conducted in the United Kingdom, France, Germany, and China.

Effectiveness

From the systematic review, the outcomes were categorised as follows:

1. **Hair Follicles and Signature Wave Technology**
    - There was no retrievable evidence on the hair follicles analysis utilising wave resonance and vibrational analysis to decode epigenetic information.

2. **Hair Follicles and DNA methylation**

    Three in-vitro studies analysed the anagen phase of hair follicles using DNA methylation techniques, yielding the following results:

    - Individuals with the 5-HTTLPR S/S genotype and low SLC6A4 methylation had higher hair cortisol levels (β=0.83, p=0.049), indicating increased sensitivity to stress.
    - DNAm methylation of scalp hair follicles can predict age, with a mean absolute deviation (MAD) of 3.68 years.
    - Hair follicles-derived induced pluripotent stem-cells (HF-iPSCs) demonstrated differentiation into the three embryonic germ layers and neuronal cells, offering potential for neurodevelopmental disorder research.

3. **DNA methylation as a blood-based biomarker in assessing wellbeing**

    DNA methylation analysis is emerging as a valuable tool in understanding how various factors, such as social determinants and lifestyle, influence biological aging and wellbeing.

    Methylation patterns influenced by social determinants like trauma and socioeconomic status can reflect biological aging, with neighbourhood environment impacting epigenetic age. Positive factors like greenness slow aging, while negative ones accelerate it. Lifestyle interventions, such as diet and exercise, alter DNA methylation linked to immunity, tumour suppression, and ageing. Epigenetic clocks like GrimAge and DunedinPoAm predict disease risks for COPD, diabetes, heart disease, and mortality. Higher cardiovascular

health scores and lower GrimAge acceleration associated with reduced risk for cardiovascular disease and cognitive decline.

Safety

There was no retrievable evidence on the adverse events or complications related to the use of the portable device or the sample collection process for analysis. The procedure is non-invasive, using hair plucking, and generally considered low-risk.

Organisational

The device is easy to use in clinical settings but raises concerns about data privacy and security. Organisations need strong cybersecurity measures to protect personal health data and comply with data protection laws.

Economic implication

No evidence on cost-effectiveness is available. The device itself priced between USD 3,500 and USD 4,000 depending on the provider.

Legal

The reviewed device has several international certifications: Conformité Européenne (CE) mark, Electrical Testing Laboratories (ETL), Federal Communications Commission (FCC) approval, and China Quality Certification (CQC), but it is not registered as a medical device in Malaysia.

Conclusion

Epigenetic modifications, particularly DNA methylation, are a valuable tool for understanding the relationship between environmental factors, aging, and disease risk. Most current studies primarily analyse DNA samples from peripheral blood, buccal swabs, and saliva. Research on DNA methylation from hair follicles remains limited, with **no evidence supporting the use of wave resonance and vibrational analysis for decoding epigenetic information**. The epigenetic signatures associated with human wellbeing have not been scientifically established for routine use in risk prediction, prognosis, or diagnosis beyond the scope of research. It should not be used for profit-driven initiatives until its scientific use is well proven. Epigenetic profiles are highly cell-type specific. Analysing only the hair follicle cells is unlikely to be a representative epigenetic profile for an individual.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® ALL 1946 to June 28, 2024, EBM Reviews - Cochrane Central Register of Controlled Trials June 2024, EBM Reviews - Database of Abstracts of Reviews of Effects - 1st Quarter 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 28, 2024, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in Pubmed, US FDA and INAHTA websites. Google was used to search for additional web-based materials and information. The search was limited to articles on human. There was no language limitation in the search. Additional articles were identified from reviewing the references and bibliographies of the retrieved articles. The last search was conducted on 28th June 2024.

TABLE OF CONTENTS

ABBREVIATION

DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
mRNA	Messenger RNA
ncRNAs	Non-coding RNAs
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CpG	Cytosine/guanine pair refers to regions of DNA where a cytosine (C) nucleotide is followed by a guanine (G) nucleotide in the linear sequence of bases, with the "p" representing the phosphate group that links them together.
HFSCs	Hair follicle stem cells
HF-iPSCs	Hair follicle-derived induced pluripotent stem cells
HR	Hazard ratios
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MaHTAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
US FDA	United States Food and Drug Administration
WHO	World Health Organization

1.0 BACKGROUND

The field of genomics has experienced remarkable advancements since the advent of human genome mapping. This has spurred substantial growth in research and fostered rapid technological innovation, particularly in epigenetics. Epigenetic mechanisms are closely linked to human health and diseases, as they regulate gene expression without altering the underlying deoxyribonucleic acid (DNA) sequence.

Epigenetics, a term introduced in the 1940s, explains how different phenotypes can arise from a single genotype due to changes in gene expression induced by external factors. This field focuses on heritable changes in gene expression that occur without alterations to the underlying DNA sequence.[1-3] These epigenetic modifications, which are reversible, occur throughout all stages of development and in response to environmental factors.[4]

Epigenetic modifications occur in response to lifestyle and environmental factors, such as diet, stress, pollution, and certain drugs exposure.[1] These modifications are primarily driven by three main mechanisms: **DNA methylation, histone modification, and non-coding RNA molecules**. These mechanisms regulate gene expression across various cellular processes, including cell differentiation, embryogenesis, and genomic imprinting.[4]

a. DNA methylation

DNA methylation involves the addition of a methyl group at the C5 position of cytosine within CpG (cytosine/guanine) pairs in DNA, mediated by enzymes called DNA methyltransferase (DNMTs). This process generally blocks transcriptional machinery and prevents the gene from being transcribed into RNA.[4]

- Role in development and disease: DNA methylation is crucial for normal development and is involved in processes such as X-chromosome inactivation, genomic imprinting, and suppression of transposable elements. Aberrant DNA methylation patterns are associated with diseases, including cancer.[4]
- The methylation levels at CpG sites are important for predicting a person's age. In forensic science, researchers have developed models to estimate a person's age based on DNA methylation patterns found in blood, saliva, and semen.[5]

b. Histone modification

Histones are proteins that DNA wraps around, forming structures called nucleosomes. These nucleosomes are organised into chromatin, the building block of chromosomes. Reversible and site-specific histone modifications occur at multiple sites through acetylation, methylation and phosphorylation.[2] The most common modifications are the methylation of arginine or lysine residues, and the acetylation of lysine.[4] These

modifications can either activate or suppress gene expressions, depending on the specific modification.[1]

- Role in development and disease: Histone modifications are dynamic and reversible, playing critical roles in gene regulation during development and differentiation. Abnormal histone modification patterns are linked to various diseases, including cancer and neurodegenerative disorders.

c. Non-coding RNA molecules

Non-coding RNAs (ncRNAs) are RNA molecules that are not translated into proteins. A key player in the epigenetic landscape is microRNA (miRNA), a group of short (~22 nucleotides), single stranded, non-coding RNAs that regulate the expression of other protein-coding gene at the post-transcriptional level. These miRNAs bind to complementary sequences on messenger RNA (mRNA) molecules, leading to mRNA degradation or inhibition of translation.

- Role in development and disease: ncRNAs are essential for normal cellular function and development. Dysregulation of ncRNAs is implicated in a range of diseases, including cancer, cardiovascular diseases, and neurological disorders.

Clinical Applications of Epigenetics

Epigenetics provides evidence that health can be improved through diet, stress management, and disease prevention. These inheritable and potentially reversible epigenetic effects influence gene expression, affecting metabolism and disease susceptibility. One area of application, *nutri-epigenetics*, explores how dietary interventions can impact epigenetic modification. For example, DNA methylation relies on the intake of micronutrients like folate, vitamin B12, methionine, betaine, and choline. Additionally, research shows that epigenetic changes in tissues such as adipose, brain, blood, and skeletal and cardiac muscle respond to aerobic and resistance exercises.[1]

These modifications play an essential role in normal development and cellular differentiation. However, abnormal epigenetic changes can lead to conditions, such as cancer and neurological disorders. Understanding epigenetic mechanisms offers promising opportunities to enhance health and wellbeing through targeted lifestyle and dietary choices.[1] The field of epigenetics serves as a bridge between genetics and environmental factors. A new paradigm for understanding how nutrition, stress, toxins, environmental, and other lifestyle factors influence health, disease, and even the health of future generations.

Epigenetic Age and its Implications

Advancing age is a key factor in age-related conditions. However, emerging evidence suggests that biological age – especially epigenetic age – might be a better predictor of age-related morbidity. Epigenetic age reflects the cumulative impact of environmental factors on cellular and molecular functions over time, offering insights into potential disease risk.

Various methods, or "clocks", have been developed to estimate an individual's epigenetic age based on DNA methylation patterns. While earlier clock like Horvath and Hannum were designed to predict chronological age, newer models such as PhenoAge, GrimAge and DunedinPoAm looks further. PhenoAge estimates an individual's phenotypic age, GrimAge predicts mortality and age-related conditions like cardiovascular disease, and DunedinPoAm measures the 'Pace of Aging (PoA)', reflecting how quickly a person is ageing. These clocks provide valuable insights into health span and age-related diseases.[6]

In forensic science, DNA methylation patterns have been used to create age prediction models for tissues such as blood, saliva, and semen. However, age prediction methods for other tissues, like hair, exfoliated cells, are still under development.[5] Currently, DNA for these analyses is typically sourced from peripheral blood (81%), buccal swabs or saliva (10%), tumour tissues (3%), and a combination of blood with other tissues like saliva, brain, or adipose tissue (6%).[7]

The following related terms are important to distinguish:

a. **Chronological age (chAge)** refers to the passage of time or the amount of time a person has lived.[6]
b. **Biological age** refers to physiological characteristics that reflect functional decline of the body. Advancing biological age may be a more useful indicator for assessing disease risk.[6]
c. **Epigenetic age (eAge)** is a measure of biological age that captures the impact of environmental factors over time on cellular and molecular functions, and consequently, on potential disease risk.[6]
d. **Epigenetic age acceleration (EpAA)** occurs when an individual's epigenetic age progresses more rapidly than their chronological age. EpAA may serve as a biomarker for the extent of wear and tear the body has endured. It has been identified as a strong predictor of age-related conditions and all-cause mortality.[6]
e. **Social genomics** studies how fixed biological traits affect health outcomes influenced by social factors (socially influenced health outcomes).[7]
f. **Social epigenetics** examines how social factors impact biological processes and lead to different health outcomes.[7]

Reasons for Request

A new health screening procedure has emerged, utilising a portable device. This technology claims to analyse hair samples to predict a patient's health status over the next five years. Given the rapid advancements in genomic and epigenetic research, it is essential to thoroughly evaluate new technologies that facilitate health screening and disease prediction in terms of its scientific validity, clinical effectiveness, and overall benefit to patient.

This assessment was prepared in response to a request made by the Director of Medical Practice Division, Ministry of Health Malaysia, to provide comprehensive information on the effectiveness and recognition of this procedure within the field of practice.

2.0 OBJECTIVE

The objectives of this technology review are:

i. To evaluate the effectiveness of epigenetic hair analysis in predicting health status in healthy adults.
ii. To assess the safety aspects of epigenetic hair analysis and epigenetic testing.
iii. To examine the economic, social, ethical, and organisational implications related to epigenetic testing.

3.0 TECHNICAL FEATURES

This S-Drive epigenetics technology originates from Germany and retrieves information through its website.[8]

Adult Hair Follicle Homeostasis: Key Concepts [9]

Adult hair follicles undergo repeated cycles of growth (anagen), regression (catagen) and quiescence (telogen). During the telogen phase, primed hair follicle stem cells (HFSCs) form a compact structure in the hair germ, beneath quiescent HFSCs in the bulge area. Signals from mesenchymal cells in the dermal papilla activate these primed HFSCs, initiating the transition from telogen to anagen. The activated HFSCs rapidly proliferate and expand, forming matrix progenitor cells in early anagen. These matrix cells then differentiate to form the inner root sheath (IRS), cortex, and hair shaft during anagen. Following this, the differentiated cells undergo systematic cell death during the catagen phase (**Figure 1**).

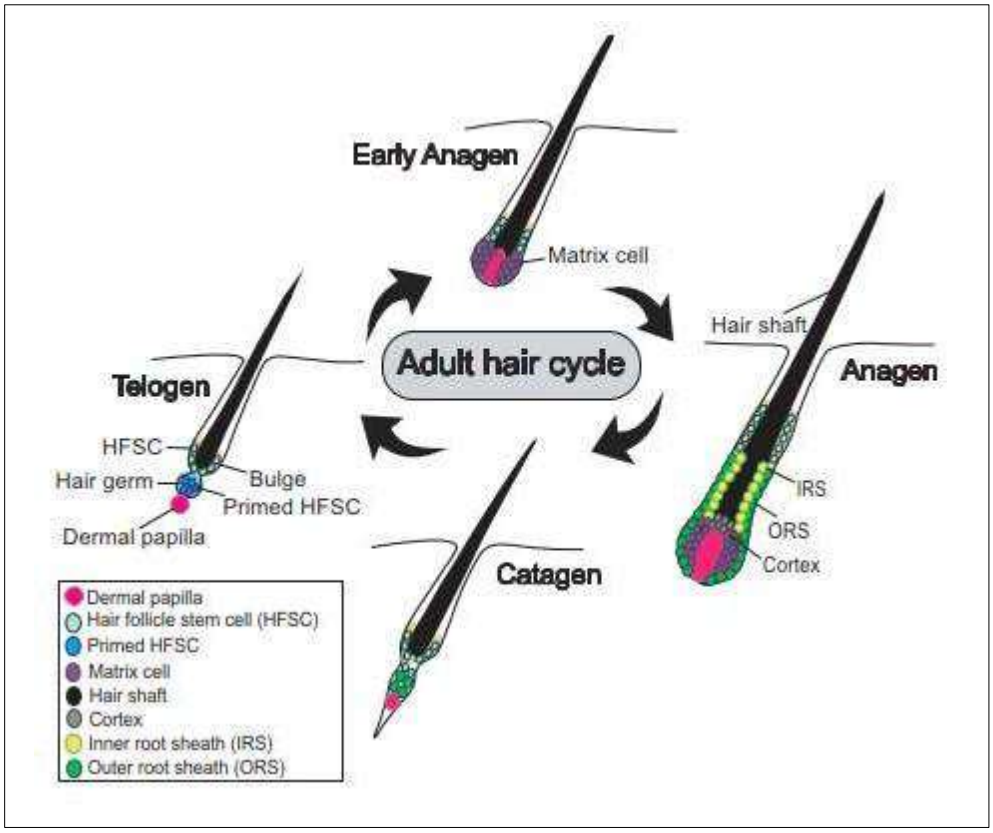


Figure 1: Adult hair cycle[9]

Hair follicle stem cells (HFSCs) function through both the cell-intrinsic mechanisms and cell-extrinsic signals from their microenvironment. HFSCs are essential not only for hair growth, but also for skin wound healing. They play a significant role in organising various skin components

around the hair follicle, acting as a central hub for maintaining adult skin homeostasis. Recent reviews highlight advancements in understanding the cell-intrinsic mechanisms of HFSC homeostasis, which include transcription factors, histone modifications, DNA regulatory elements, non-coding RNAs, cell metabolism, cell polarity and post-transcriptional mRNA processing. HFSCs also secrete molecules that guide the organisation of skin components such as nerves, the erector pili muscle, and vasculature around the hair follicle. Progress in this field aims to generate a comprehensive map of molecular interactions, providing a theoretical foundation for applications in treating hair and skin diseases, as well as ageing.

The Hair Bulb as an Epigenetic Marker

Hair has an embryological origin from the ectoderm, similar to the nervous system, and its ability to self-regulate and replicate. The hair bulb acts as an antenna constantly sensing environmental signals through the erector pili muscle, which reacts to stimuli like changes in temperature, atmospheric pressure, vibration, and frequencies. Environmental impacts on the body are reflected in hair bulb epigenetic information, which claimed can be analysed using epigenetic technology to understand environmental and nutritional impacts.[10]

The S-Drive Epigenetics Technology[10-12]

The S-Drive technology functions as a digital peripheral linked to secure servers in Germany, serving as a wellness tool. It is utilised by various practitioners and organisations in fields such as fitness, sports, beauty, nutrition, and preventive healthcare. Compact and portable, the device features a spectrum coil at its centre (**Figure 2**). Four strands of hair with their bulbs intact, plucked from the occipital area of the skull, are analysed by the S-Drive device. It captures information from hair roots, acting as an in-vivo biomarker reflecting environmental influences and body conditions.

This information is then securely transmitted to servers in Germany, where advanced algorithms analyse it to reveal underlying metabolic and nutritional conditions affecting wellness. By digitising data from the hair strands and their bulbs, the technology offers real-time personalised insights into one's health status. The technology's intelligent mapping system in Germany decrypts and decodes the data, mapping biological information and presenting it in a user-friendly format. Comprehensive reports are returned to operators within 15 minutes, with the most common report generated being the *90-Day Optimize Immunity and Wellbeing* (**Figure 3**) including the epigenetic indicators (**Figure 4**). Epigenetic mapping covers various categories including vitamins, minerals, amino acids, fatty acids, anti-oxidants, toxins, microbiology, electromagnetic fields, gut health, and food intolerances, and potential environmental impact information. These insights remain relevant for 90 days, considering the constantly changing epigenetic influences.

The company affirms that client personal data remains on the local S-Drive licensed computer and is not stored on the German facility's external databases. The intended purpose of the

device is to support general health by detecting epigenetic signals influencing gene expression, enabling adjustments to diet, nutrition, and lifestyle to promote optimal physiology and performance. This is achieved without involving invasive procedures or posing safety risks. The company emphasises that the device is not intended to diagnose, treat, cure, or prevent disease. Furthermore, the company declares that the device is fully compliant with US FDA guidance 1300013 – General Wellness: Policy for Low Risk Device (UCM429674).

Figure 2: S-Drive device

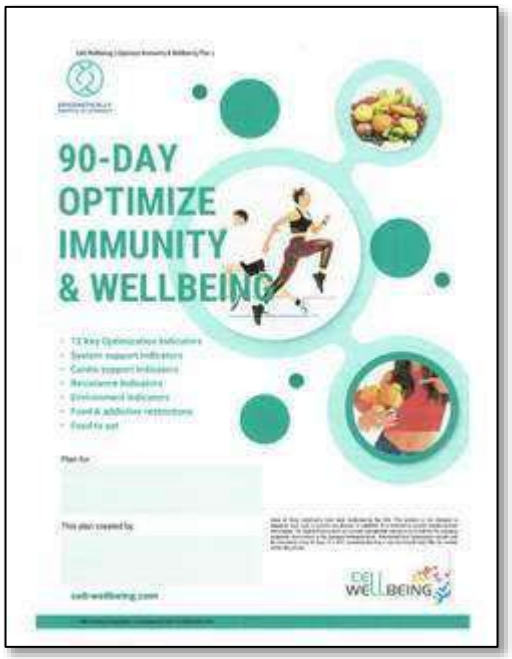


Figure 3: The generated cover report

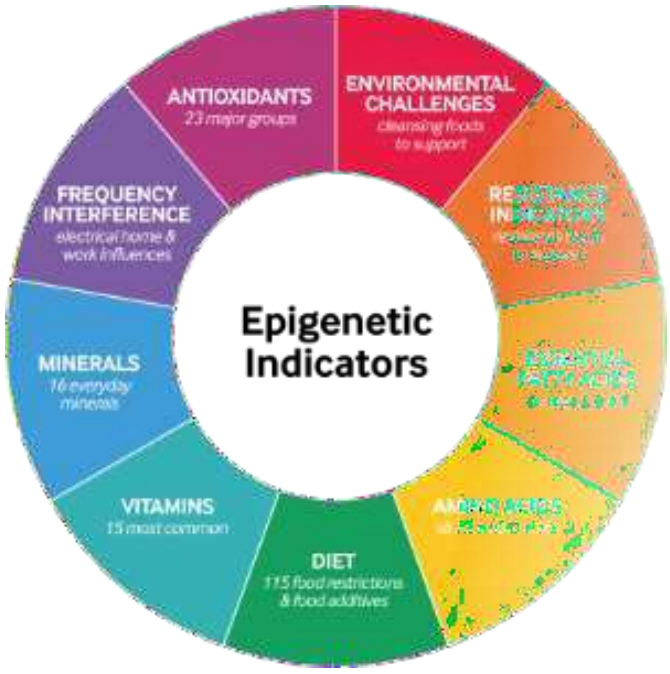


Figure 4: The epigenetic indicators

The S-Drive Principle and Its Connection to Epigenetics and the Signature Wave

The S-Drive operates on the principle of the signature wave, an individualised characteristic resembling to a fingerprint, which contains epigenetic information. This distinct signature present in hair carries a rich array of epigenetic data reflective of daily haemodynamic activities. As hair, skin, and brain share an ectodermic origin and serve as sensory organs sensitive to environmental signals, they are the key sources for such data. Through the utilisation of the vibrational resonance principle, the S-Drive decodes and digitalises this epigenetic information. Subsequently, this data is transmitted to a facility in Germany, for analysis and interpretation. The decoding process relies on wave equations, mirroring the harmonic resonance found in quantum physics, where vibrations between waves of the same frequency and amplitude influence one another. Thus, this technology presents a pathway for accessing and understanding individualised epigenetic information through the resonance of the signature wave.[3]

4.0 METHODS

4.1 SEARCHING

4.1.1 Literature Search Strategy

A systematic review was conducted, with the review protocol and search strategy developed by the main author and an Information Specialist. The literature search focused on published articles related to the analysis of hair follicles epigenetics in the context of health screening and wellbeing.

The following electronic databases were searched through the Ovid interface:

- Ovid MEDLINE® ALL (1946 to June 28, 2024)
- EBM Reviews - Cochrane Central Register of Controlled Trials (June 2024)
- EBM Reviews - Cochrane Database of Systematic Reviews (2005 to June 28, 2024)
- EBM Reviews - Database of Abstracts of Reviews of Effects (1st Quarter 2016)
- EBM Reviews - Health Technology Assessment (4th Quarter 2016)
- EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016)

Other databases:

- PubMed
- Other websites: US FDA, INAHTA database

General databases, including Google, were used to identify additional web-based materials and information. The search was limited to articles on human subjects with no language restrictions applied. Detailed search strategies are provided in **Appendix 2**. The last search was performed on 28th June 2024. Additional relevant articles were identified by reviewing the references and bibliographies of the retrieved articles.

4.2 SELECTION

4.2.1 Study Selection

Two reviewers (AA and AT) independently screened the titles and abstracts based on the inclusion and exclusion criteria outlined below. They then evaluated the selected full-text articles to determine the final article selection. Any disagreements were resolved through discussion.

Inclusion criteria:

a.	**Population**	Healthy adult (≥ 18 years old)
b.	**Interventions**	Epigenetics, S-Drive technology
c.	**Comparators**	Standard care, placebo, no treatment
d.	**Outcomes**	Effectiveness: i. Social determinants of health ii. Epigenetic age iii. Epigenetic markers iv. Hair cortisol analysis v. Clinical application Safety: i. Side effects/adverse events ii. Complications iii. Mortality Organisational issues: i. Length of follow up ii. Patients satisfaction Economic implications: i. Cost-effectiveness/cost-utility/cost-analysis
e.	**Study design**	Health Technology Assessment (HTA) reports, systematic review (SR) with/out meta-analysis, randomised controlled trial (RCT), non-RCT, case control study, diagnostic, cohort, pre- and post-intervention study, cross sectional, laboratory study, and economic evaluation studies.
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case series, case report, survey, anecdotal, animal study, narrative review
b.	Non-English full text articles	

4.2.2 Critical Appraisal and Risk of Bias Assessment

Relevant articles were then critically appraised. The risk of bias or quality assessment of all retrieved literature was assessed depending on the type of the study design; using the relevant checklist including the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS)[13] for Systematic Review and Meta-analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials[14], and Critical Appraisal Skill Programme (CASP)[15] for Cohort Study.

4.2.3 Analysis and Synthesis of Evidence

Data extraction strategy

Data were extracted from included studies by a reviewer (AT) using a pre-designed data extraction form (*Evidence Table* as shown in **Appendix 3**) and checked by another reviewer (AA). Disagreements were resolved by discussion. The data extracted was as follows:

i. Details of methods and study population characteristics;
ii. Detail of intervention and comparators; and
iii. Details of individual outcomes specified.

Methods of data synthesis

Data on the accuracy, effectiveness, safety, and cost-effectiveness associated with the analysis of hair follicles epigenetics in relation to health screening and wellbeing were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

5.1 SEARCH RESULTS

5.1.1 Selection of Included Studies

An overview of the systematic search and selection of the studies are illustrated in **Figure 5.** A total of **1,631** records were identified through the Ovid interface and PubMed while **10** were identified from other sources. After removing **10** duplicates, **1,631** titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, **24** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **24** full-text articles, **nine** were included. **Twenty-four** articles were excluded as those were narrative reviews (n=10), a mini-review article (n=1), wrong intervention (n=7), irrelevant population (n=2), trial registries (n=3), and a conference proceedings (n=1).

The **nine** full-text articles selected for this review included **one** systematic review, **one** scoping review, **one** randomised controlled trial, **two** cohort study, **one** pilot study, and **three** in-vitro studies. All the included studies were published in English between 2012 and 2023, with majority conducted in the United States of America (five studies). Additionally, one study each was conducted in the United Kingdom, France, Germany, and China. **Table 1** summarised the characteristics of the included studies.

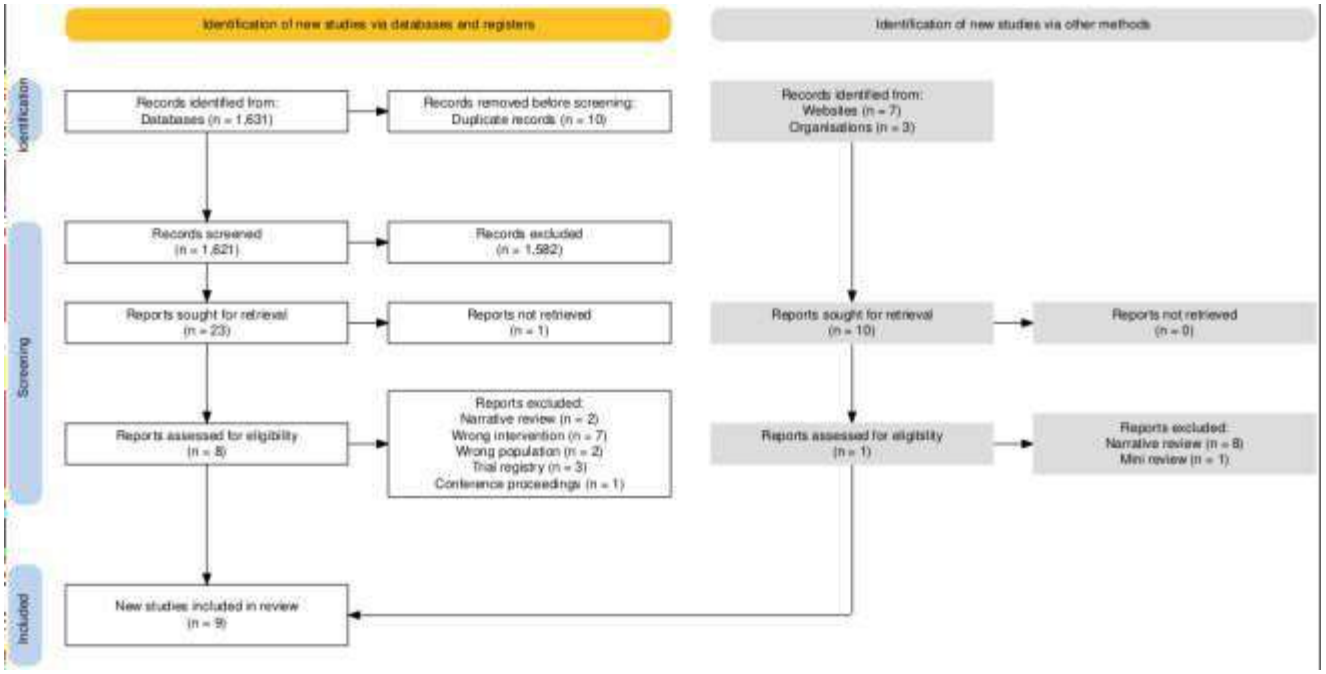


Figure 5: PRISMA 2020 flow diagram[16] of retrieval articles used in the results

Table 1: Characteristics of the included studies

Author	Study design	Study objectives	Sample size	Intervention	Comparator	Key findings
Evans L et al. (2021) **USA**	Systematic review 67 empirical studies • 60 longitudinal cohorts' studies • 5 case-control studies • 2 studies combination of both study designs	To evaluate the integration of the SDOH framework into social epigenetic research.	N = 51,408 - Ranging from 34 to 8,397 participants	Exposure (SDOH) • Social & political context • Structural stratification processes • Material & socioemotional resources • Proxies for structural "stratifiers"	-	Future social epigenetics research should focus on larger, more diverse populations and utilise the SDOH framework to better understand how social factors like early-life socioeconomic exposure, trauma, and environmental influences impact gene expression, disease development, and health disparities.
Jackson P et al. (2023) **USA**	Scoping Review 9 studies • 7 cross-sectional studies • 2 longitudinal studies	To describe on the relationship between neighbourhood environmental characteristics and epigenetic age.	N = 7,074 - Ranging from 100 to 2,630 participants <u>Population</u>: • Adults - 7 studies • Adolescents -1 • Children -1 study	Neighbourhood characteristics	Epigenetic age calculator • Hannum (Ha) • Horvath (Ho) • PhenoAge (P) • GrimAge (G) • DunedinPoAm (D) • Author-developed epigenetic mortality risk score (eMRS)	• Epigenetic age is influenced by neighbourhood socioeconomic and physical characteristics. • This association may vary depending on the specific epigenetic clock used, with Hannum's clock being most commonly utilised.
Hao T et al. (2021) **China**	In vitro study	To investigate the relationship between DNA methylation patterns at specific age-related CpG sites in hair follicles and construct an age prediction model with high accuracy.	166 hair samples	SNaPshot assay	-	• Both human identification and age information can be obtained from scalp hair follicles using DNA methylation analysis. • The MLR model provided the most accurate age prediction, with a MAD of 3.68 years.
Petit I et al. (2012) **France**	In vitro study	1. To establish the feasibility of utilising hair follicles as a source of reprogrammable cells for generating patient-specific neurons, and 2. To demonstrate that hair follicle-derived induced pluripotent stem cells (HF-iPSCs) can differentiate into functional neuronal cell types, providing a non-invasive method for modelling psychiatric and neurodevelopmental disorders.	Hair follicles in anagen phase from two healthy individuals	Reprogrammed keratinocytes to pluripotent iPSC	Neural lineages	Hair follicles are a viable and accessible source of reprogrammable cells for generating patient-specific neurons, making them valuable for modelling psychiatric and neurodevelopmental disorders.

Author	Study design	Study objectives	Sample size	Intervention	Comparator	Key findings
Alexander N et al. (2019) **Germany**	In vitro study	To investigate the endocrine correlates of SLC6A4 DNA methylation in an adult sample by utilising hair cortisol concentrations (HCC).	200 hair strands and blood samples from healthy participants • 17 samples excluded (8.5%)	• Hair cortisol concentration analysis for hair strands • Methylation analysis for whole blood samples	-	• A negative association between SLC6A4 DNAm and HCC. • A significant interaction between the 5-HTTLPR genotype and SLC6A4 DNAm in assessing long-term stress responses.
Hibler E et al. (2019) **USA**	RCT	To examine the impact of the Make Better Choices 2 (MBC2) healthy diet and activity intervention on patterns of epigenome-wide DNA methylation.	68 participants • 204 whole blood samples (68 x 3 time points) for DNA methylation analysis	1. Increase MVPA, improve fruits or vegetables intake and sedentary leisure. (simultaneous group; n=25) 2. Improve fruits or vegetables and sedentary leisure first, followed by MVPA (sequential group; n=31)	3. Improve stress and sleep. (Control group, n=12)	• Lifestyle improvements (diet and physical activity) was associated with changes in DNAm in regions related to immune cell metabolism, tumour suppression, and aging. • Positive health behaviour changes were linked to pathways involving immune cell adhesion and other pathways essential for normal cell function and cancer prevention. • DNAm could be a biomarker for identifying population that may benefit from health behaviour changes.
Hillary RF et al. (2020) **UK**	Cohort study	To test the association between the six epigenetic measures of ageing and the prevalence and incidence of the ten leading causes of disease burden and mortality in high-income countries.	Discovery cohort: ($n_{discovery}$ = 4,450) Replication cohort: ($n_{replication}$ = 2,578)	DNA methylation (from blood samples)	Biological age	Epigenetic measures of ageing may have utility in clinical settings to complement gold-standard methods for disease assessment and management.
Joyce BT et al. (2021) **USA**	A prospective longitudinal cohort study	1. To investigate the association between GrimAge acceleration (GrimAA) and cardiovascular health (CVH). 2. To explore whether GrimAA mediates the established relationship between CVH and coronary artery calcium.	CARDIA study (n = 1,999) FHS (n = 2,106)	GrimAA (DNA methylation from blood samples)	CVH score according to AHA Life's Simple 7 metrics	• Accelerated GrimAge was associated with decline in CVH from a young age. • GrimAge has potential as a biomarker for cardiovascular disease (CVD) risk. • It plays a role in linking age-related decline in CVH to CVD.
Vyas CM et al. (2023) **USA**	Pilot study	To explore the relationship between DNA methylation, and cognitive and neuropsychiatric symptoms in older adults.	45 participants	DNA methylation (from blood samples)	Cognitive and neuropsychiatric symptoms	• Chronological age showed a strong correlation with DNAmGrimAge and a moderately correlation with DNAmPhenoAge and DNAmTL. • Significant associations between changes in DNAm markers and global cognition.

SDOH: social determinants of health; MLR model: Multiple linear regression model; MAD: mean absolute deviation; MVPA: Moderate-vigorous physical activity; CARDIA study: Coronary Artery Risk Development of Young Adults study; FHS: Framingham Heart Study.

5.1.2 Quality Assessment of the Studies

The risk of bias in the included studies were assessed using the domain-based evaluation. Tools that are being used to assess the risk of bias are Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) for Systematic Review and Meta-analysis,[13] a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials,[14] and Critical Appraisal Skill Programme (CASP) for Cohort Study.[15] These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement on the risk of bias as either:

X	High
-	Unclear
+	Low
?	No information

The included studies in this review exhibit varying levels of risk of bias. One systematic review had an unclear risk of selection and reporting bias, while another scoping review was rated as having a high risk of selection, publication and reporting bias. Among the primary studies, one randomised controlled trial was assessed with some concerns regarding bias. Two cohort studies demonstrated a low risk of bias, providing more reliable evidence. Additionally, two laboratory studies showed strong control over potential biases, though one of them had limitations due to a small sample size. The spectrum of bias levels should be considered when interpreting the overall findings of the review. The results of risk of bias of included studies are summarised in **Figure 6.1 to 6.3.**

Risk of bias assessment included systematic review and meta-analysis

Two studies were included in this assessment. One SR was judged to have an unclear risk of bias, while one scoping review had an overall high risk of bias (**Figure 6.1**).

Evans L et al. (2021) were rated as having an unclear risk of bias. They conducted electronic searches in PubMed and Scopus for English-language studies published up to March 2020. Their review followed predefined clinical questions and inclusion criteria, with an initial independent screening of 20% of publications by a three-member team. Disagreements were resolved by consensus or with guidance from a senior author. The remaining articles were screened based on inclusion/exclusion criteria, with one of the principal investigators periodically checked the review process. However, the review lacked a formal quality assessment, resulting in an unclear risk of bias. Due to study heterogeneity in exposure types, measurement of DNAm, and study designs, a meta-analysis was not conducted, and the results were analysed descriptively.

The scoping review by Jackson P et al. (2023) was rated to have an overall high risk of bias. They performed electronic searches across three databases, covering data up to January 16, 2022, limited to full-text articles available in English. Their review had predefined clinical questions, as well as specific inclusion and exclusion criteria to determine study eligibility. However, there were concerns with the review process which were not address by the authors, including the potential for missing studies and absence of a formal quality assessment. The results were analysed descriptively.

		Risk of bias				
		D1	D2	D3	D4	Conclusion
Study	Evans L et al.[7]	+	+	-	-	-
	Jackson P et al.[6]	+	x	x	x	x

D1: Concerns regarding specification of study eligibility criteria.
D2: Concerns regarding methods used to identify and/or select studies.
D3: Concerns regarding methods used to collect data and appraise studies.
D4: Concerns regarding the synthesis and findings.
CONCLUSION: Risk of bias in the review.

Judgement

x	High
-	Unclear
+	Low
?	No information

Figure 6.1: Risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCT

		Risk of bias					
		D1	D2	D3	D4	D5	Overall
Study	Hibler E et al.[19]	-	-	+	-	+	-

D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

x	High
-	Some concerns
+	Low

Figure 6.2: Risk of bias assessment for RCT using RoB 2.0

Hibler E et al. (2019) was assessed to have some concern regarding bias, particularly related to the assignment to intervention and assessment processes. Although study participants were randomly allocated to one of the three groups, the methods of randomisation and allocation concealment was not adequately reported. Due to the

nature of the study, it was impossible to blind both the investigators and participants, and there was no mention of blinding for the outcome assessors. All participants received the designated interventions, and assessments were conducted at similar time across all groups. The risk of bias from selective reporting was considered low, as all pre-specified outcomes were reported and analysed (**Figure 6.2**).

Risk of bias assessment for included cohort study

		Risk of bias					
		D1	D2	D3	D4	D5	Overall
Study	Hillary RF et al.[20]	+	+	+	+	+	+
	Joyce BT et al.[21]	+	+	+	+	+	+

D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

x	High
-	Some concerns
+	Low

Figure 6.3: Risk of bias assessment for cohort study using CASP checklist

The risk of bias for the cohort studies conducted by Joyce BT et al. (2021) and Hillary RF et al. (2020) is assessed as low, based on the CASP checklist. Both studies utilised robust data sources – Joyce from the CARDIA study and Hillary from the Generation Scotland study. In both cases, exposures were measured accurately, ensuring the reliability of the data. Similarly, outcomes were carefully measured to minimise the potential for bias. Key confounding factors were identified and appropriately accounted for in the analysis, further reducing the risk of bias. Follow-up periods were sufficiently long to observe relevant outcomes, with Joyce's study spanning 15, 20, and 25 years, and Hillary's study providing up to 13 years of follow-up. This comprehensive and long-term data collection ensured that the studies were able to capture relevant health outcomes and supporting that both studies have a low risk of bias (**Figure 6.3**).

5.2 EFFICACY/ EFFECTIVENESS

5.2.1 Hair Follicles and Signature Wave Technology

There was no retrievable evidence on the hair follicles analysis utilising wave resonance and vibrational analysis to decode epigenetic information.

5.2.2 Hair Follicles and DNA Methylation

Three in-vitro studies analysed the anagen phase of hair follicles using DNA methylation techniques, yielding the following results:

a. Hair cortisol concentration and DNA methylation

In a 2019 study, Alexander N et al. explored **the relationship between DNA methylation in the serotonin transporter gene (SLC6A4) and hair cortisol concentrations (HCC) as a measure of long-term cortisol levels**. They recruited 200 healthy adults, screened them for psychiatric disorders, chronic diseases, and life stressors, and collected **hair and blood samples** for analysis. **Hair cortisol concentrations** were measured from strands cut as close to the scalp as possible at the posterior vertex position. The analysis focused on the 3 cm segment most proximal to the scalp, representing cumulative cortisol secretion over the 3-month period prior to sampling. Liquid chromatography coupled with tandem mass spectrometry was used for this analysis. **Whole blood samples** provided genomic DNA for the quantitative methylation analysis of 83 CpG sites within a 799-bp promoter-associated CpG island in SLC6A4. The DNA was bisulfite-treated and analysed by pyrosequencing. All participants were genotyped for the serotonin transporter polymorphism (5-HTTLPR). A total of 183 participants were included in the final analysis, with the mean age of 23.8 ± 2.8 years; 47.5% were women, 35.0% were smokers, and 31.0% of the women used oral contraceptives. The study found that SLC6A4 DNAm levels and HCC were unrelated to sex, smoking, oral contraceptives use, alcohol consumption, childhood maltreatment, or recent trauma (all p-values > 0.05). Additionally, HCC levels were not influenced by hair-related factors such as the frequency of hair washing per week, presence of curls, hair colouration, or permanent waves (all p-value > 0.05). The study reported the following associations between SLC6A4 DNAm, the 5-HTTLPR genotype, and HCC:

i. **SLC6A4 DNAm and HCC:** Linear regression analysis revealed a negative association between SLC6A4 DNAm and HCC (β= -0.15, p=0.045). Further analysis identified 8 specific CpG sites where DNAm levels were negatively correlated with HCC, especially in regions with high inter-individual variation in DNAm.

ii. **5-HTTLPR Genotype and HCC:** No significant effect of the 5-HTTLPR genotype on HCC was found.

iii. **Interaction of SLC6A4 DNAm and 5-HTTLPR on HCC:** A significant interaction between SLC6A4 DNAm and 5-HTTLPR genotype on HCC was observed (β=0.83, p=0.049). Specifically, low SLC6A4 DNAm levels led to higher HCC in individuals with the S/S genotype. This genotype-dependent effect was absent in cases where SLC6A4 DNAm was high. These results are consistent with previous clinical research indicating that the combination of 5-HTTLPR S/S genotype and lower SLC6A4 DNAm may predict increased sensitivity to stress at both behavioural and psychological levels.

Hence, the study highlights the importance of considering both genetic and epigenetic factors when assessing long-term stress responses.[17]

b. DNA methylation patterns in hair follicles for age prediction

A study by Hao T et al. (2021) was conducted to investigate **the relationship between DNA methylation patterns at specific age-related CpG sites in hair follicles and construct an age prediction model with high accuracy**. The study utilised a multiplex methylation SNaPshot assay method to assess the methylation status of these CpG sites. A total of 166 unrelated **hair samples** were collected from individuals of a Han population residing in the Shanxi Province, northern China. The samples consisted of 130 scalp hairs from donors aged 1 to 86 years, six pairs of black and white scalp hairs, and 24 hairs from different body areas (including calf, pubic area, and armpit). The hair samples were plucked and stored at -80°C for a maximum of two months before DNA extraction. DNA was extracted using a DNeasy Blood & Tissue Kit (Qiagen, USA), with five hair follicles used for scalp hair and 10-20 follicles for hair from other body parts. The quantity of extracted DNA was measured using an Invitrogen Qubit 4 device (Thermo Fisher Scientific, USA). Approximately 300 ng of extracted DNA was treated with bisulfite using an EpiTect Fast DNA Bisulfite Kit (Qi-agen) for further analysis.

Out of 21 potential CpG sites analysed, 10 were identified as reliable age indicators – within the LAG3, SCGN, ELOVL2, KLF14, C1orf132, SLC12A5, GRIA2, and PDE4C genes. These sites demonstrated a statistically significant correlation with age in the 130 scalp hair samples ($p<0.05$). There were no significant differences in methylation levels between male and female samples ($p>0.01$ for each CpG site). To develop an age prediction model, four different statistical approaches were applied: multiple linear regression (MLR), backward stepwise regression (BSR), multilayer perceptron (MLP), and radial basis function (RBF). The MLR model, which consisted of the 10 identified CpG sites, provided the most precise age prediction, with a mean absolute deviation (MAD) of 3.68 years and a root-mean-square error (RMSE) of 5.06 years (**Table 2**). The model was particularly accurate for individuals

under 20 years of age (MAD of 3.25 years) compared to those over 60 years of age (MAD of 4.68 years) (**Table 3**). There were no significant differences in the methylation between black and white hairs, nor among hairs from different body regions. The 10 CpG sites were human-specific and could be distinguished from animal hair. This study demonstrated that both human identification and age information can be obtained from scalp hair follicles using DNA methylation analysis. The methylation patterns of 10 specific CpG sites were consistent across different sexes, hair types, and hair colours, making them reliable markers for age prediction. The MLR model showed to be the most accurate, with a MAD of 3.68 years, indicating its potential utility in evaluate chronological age based on hair samples.[5]

Table 2: Test the performance of different models.[a]

Different models	Training group		Testing group	
	MAD(years)	RMSE(years)	MAD(years)	RMSE(years)
Multiple linear regression model	3.6835	5.0589	4.1508	4.9174
Backward regression model	3.9356	5.2252	4.2190	5.0698
Multilayer perceptron model	3.8073	4.8534	4.5526	5.6699
Radial basis function model	5.5774	7.8420	6.3824	9.0214

[a] MAD: mean absolute deviation, RMSE: root mean square error.

Table 3. The prediction performance of multiple linear regression model composed of 10 CpG sites for different age groups.[a]

Age	Training group (N=90)				Testing group (N=40)			
	No.	MAD(years)	RMSE(years)	±1 RMSE(No.(%))	No.	MAD(years)	RMSE(years)	±1 RMSE(No.(%))
<20	22	3.2486	4.2967	16(72.73%)	9	3.6811	4.3502	6(66.67%)
20-39	36	3.2629	4.2603	26(74.29%)	16	3.7666	4.4040	9(56.25%)
40-59	24	4.3800	6.0463	16(66.67%)	11	4.0731	4.8153	6(54.54%)
>=60	8	4.6826	6.7677	6(75%)	4	6.9583	7.6080	3(75%)
Total	90	3.6835	5.0589	68(75.56%）	40	4.1508	4.9174	26(65%)

[a] MAD: mean absolute deviation, RMSE: root mean square error, No.(%): number and percentage of individuals with the prediction error between ±1.0 RMSE

c. Utilising hair follicles-derived induced pluripotent stem-cells (HF-iPSCs) for modelling neurodevelopmental disorders

Induced pluripotent stem cells (iPSCs) are particularly useful for studying neuropsychiatric disorders because they allow for the generation of affected neuronal cells that are otherwise inaccessible. Traditionally, iPSCs are derived from fibroblasts obtained through skin biopsies. However, **hair follicle-derived keratinocytes** offer an alternative, as they originate from the same ectodermal embryonic layer as neurons and may retain similar epigenetic markers.

In 2012, Petit I et al. conducted an in vitro study to explore the feasibility of using **hair follicles** as a non-invasive source of reprogrammable cells for generating

patient-specific neurons. Hair follicles from two healthy individuals were collected, processed, and cultured to obtain keratinocyte colonies, which appeared after 7-10 days. The pluripotency of the resulting iPSC colonies was confirmed by immunofluorescence and quantitative real-time PCR. These colonies were further cultured in differentiation medium to form embryoid bodies (EBs). The study demonstrated that as few as 10 anagen-phase hair follicles can provide sufficient keratinocytes for reprogramming into iPSCs. These hair follicles can be stored for up to 48 hours at room temperature without losing cell viability. The reprogramming efficiency was significantly increased by 3.5 fold ($p=0.04$) by using a combination of 2 µM SB431542 (Sigma), 3 µM CHIR99021 (AxonMedchem, Groningen, the Netherlands), 3 µM Parnate (P8511, Sigma) and 5 µM PS48 (Stemgent, Cambridge, MA, USA).

The hair follicle-derived iPSCs (HF-iPSCs) were confirmed to be pluripotent by the expression of markers such as Pou5F1 (Oct3/4), Sox2, Nanog and DNMT3B, as well as TRA-1-81, SSEA-4, and alkaline phosphatase activity. These HF-iPSCs were capable of differentiating into the three embryonic germ layers and various types of neuronal cells. The study concluded that hair follicles are a viable and accessible source of reprogrammable cells for generating patient-specific neurons, making them valuable for modelling psychiatric and neurodevelopmental disorders.[18]

5.2.3 DNA Methylation as a Blood-based Biomarker in Assessing Wellbeing

DNA methylation analysis is emerging as a valuable tool in understanding how various factors, such as social determinants and lifestyle, influence biological aging and wellbeing. Below are key findings from recent studies:

a. Social Determinants of Health and DNA Methylation

Evans L et al. (2021) systematically reviewed the literature on social epigenetics, focusing on how empirical research has conceptualised and operationalised social determinants of health (SDOH). Social epigenetics is a subfield of genomics that investigates whether and how exposures to the physical and social environment influence differential gene expression. The World Health Organization's Global Commission on Social Determinants of Health defined SDOH as the structural determinants and conditions of daily life which are responsible for a major part of health inequities between and within countries. This review specifically focused on studies examining **the impact of SDOH on DNA methylation (DNAm)**.

The review included English-language studies published up to March 2020 from PubMed and Scopus databases, involved human participants. These studies focused on DNAm in adulthood as the outcome and examined the impact of

upstream SDOH at any point in the participants' life. The DNAm had to be measured when participants were 18 years or older. A total of 67 studies met the inclusion criteria, comprised of 60 longitudinal cohorts' studies, five case-control studies, and two studies combining both study designs, published between 2000 and 2020. Sample sizes ranged from 34 to 8,397 participants, with half having 300 or less participants. Most studies (67%) involved middle-aged adults (35-60 years). North America studies predominantly involved monoracial Black/African-American participants, while European studies mostly included monoracial White, non-immigrant samples.

DNA methylation was mainly analysed through epigenome-wide methylation assessments (51%), followed by CpG-specific methylation (33%), global methylation alone, and a combination of global and CpG-specific methylation. Thirteen studies quantified methylation patterns across the genome to measure accelerated ageing, using the Horvath clock (31%), the Hannum clock (15%), or both (54%). **Most DNA samples were collected from peripheral blood (81%), while others were obtained from buccal cheek swabs, saliva, and other tissues**. The main methods for quantifying DNA methylation were microarray-based techniques and pyrosequencing.

The review identified **four key challenges**: limited racial, ethnic and geographic diversity in samples; high dependence on convenience sampling; an overemphasis on sociodemographic characteristics as proxies for stratification processes; and a focus on downstream SDOH and individual experiences with social stressors. Commonly studied SDOH included early life socioeconomic exposure, early life trauma, and place-based social exposures. These factors were linked to outcomes such as socioeconomic status (SES), early-life adversity, and environmental and psychosocial exposures. The authors suggest that future social epigenetics research should utilise larger, more diverse populations and apply the comprehensive SDOH framework to better understand how social factors biologically influence gene expression, disease development, and health disparities. This approach could provide deeper insights into the biological pathway through which social determinants affect health throughout the lifespan.[7]

b. Neighbourhood-level environmental characteristics (both physical and social) and epigenetic age

Jackson P et al. (2023) conducted a scoping review to examine on the relationship between neighbourhood environmental characteristics and epigenetic age. The authors searched three electronic databases and included only articles published in English with full-text availability up to January 16, 2022. They focused on peer-reviewed primary studies involving human subjects that investigated **the relationship between neighbourhood-level environmental characteristics**

(both physical and social) and epigenetic age. The review included nine studies: seven cross-sectional (with sample sizes ranging from 100 and 2,630) and two longitudinal, involving a total of 7,074 participants. Among these studies, seven used samples from adults, one from adolescents, and one from children. Commonly studied **neighbourhood characteristics** include household composition, income, education, employment status, and physical attributes (such as sidewalks conditions, presence of graffiti, noise levels, and the presence of large mature trees). Most of the studies (7 out of 9) used a multivariate index to assess the relationship between epigenetic age and neighbourhood characteristics. Only two studies used single indicator, which showed some variability in the results. The findings showed that both socioeconomic and physical characteristics of a neighbourhood influenced epigenetic age. Negative factors, such as neighbourhood deprivation, were associated with accelerated epigenetic ageing, while positive factors, like residential greenness, were linked to slower epigenetic ageing. The review found consistent associations across different age groups, including children and adolescents, as well as various ethnicities. Six different **epigenetic clocks** (Hannum, Horvath, PhenoAge, GrimAge, DunedinPoAm, and author-developed epigenetic mortality risk score [eMRS]) were used to measure this relationship, with Hannum's clock being the most utilised. However, results varied depending on the epigenetic clock used. All studies that used the Hannum clock and GrimAge, and three of four studies using PhenoAge, reported associations with neighbourhood characteristics. There is currently no gold standard for measuring epigenetic age, and further research is needed to fully understand how environmental factors impact epigenetic age.[6]

c. Effects of Healthy Diet and Activity on Epigenome-Wide DNA Methylation Patterns

Hibler E et al. (2019) conducted a 9-month randomised controlled trial between 2012 and 2014 to investigate the effects of the "Make Better Choices 2" (MBC2) **healthy diet and activity intervention on epigenome-wide DNA methylation patterns**. The study included adults aged 18-65 years with suboptimal levels in four lifestyle behaviours: fruits and vegetables intake, saturated fat consumption, sedentary leisure screen time, and moderate-to-vigorous physical activity (MVPA). Participants were randomly assigned into one of the three 12-week treatment groups each utilising a smartphone application and remote coaching:

a. A simultaneous group (n = 25) focusing on increasing MVPA, while improving fruit/vegetable intake and reducing sedentary leisure time.
b. A sequential group (n = 31) initially targeting improvements in fruit/vegetable intake and sedentary leisure time, followed by an increase in MVPA
c. A control group (n = 12) that concentrated on improving stress management and sleep quality.

Whole blood samples were collected from participants to analyse DNA methylation patterns, with profiling performed at baseline, 3 months, and 9 months. At baseline, no differentially methylated regions were found when comparing controls with pooled samples from the sequential and simultaneous intervention groups. However, by 3 months, 154 differentially methylated regions were identified and by 9 months, this number had increased to 298. Gene ontology analysis revealed two terms related to haemophilic cell adhesion and cell-cell adhesion. Additionally, pathways analysis identified pathways related to immune function and carcinogenesis.[19]

In conclusion, this study demonstrates that 12 weeks of lifestyle improvements, focusing on diet and physical activity were linked to change in DNA methylation in regions associated with immune cell metabolism, tumour suppression, and ageing. Moreover, the positive changes in health behaviours were also associated with pathways related to immune cell adhesion and several pathways critical for normal cell function and cancer prevention. These findings suggest that DNA methylation may serve as a biomarker for identifying populations that may benefit from incorporating health behaviour changes into precision prevention strategies.[19]

d. Epigenetic Age and Disease Prediction

Hillary RF et al. (2020) investigated the relationship between six epigenetic measures of ageing and the prevalence and incidence of the ten leading causes of mortality and disease burden (as measured by disability-adjusted life years; DALYs). The study analysed DNA methylation array data and electronic health record from a Scottish cohort, Generation Scotland (GS): Scottish Family Health Study. It consisted of 23,960 individuals' health and lifestyle information. This study involved two cohorts: (i) the discovery cohort, consisting of 4,450 unrelated GS participants with genome-wide methylation data (56.3% female, mean age of 51.4 ± 13.2 years), and (ii) the replication cohort, which included 5,087 GS participants with genome-wide DNA methylation measured separately, including 2,578 unrelated individuals (61.4% female, mean age: 50.0 ± 12.5 years), used for cross-sectional analyses. DNA methylation levels from **blood samples** were assessed using the Illumina HumanMethylation EPIC BeadChip Array. Six epigenetic predictors of ageing were evaluated: Horvath Age, Hannum Age, DNAm PhenoAge, DNAm GrimAge, DNAm Telomere Length, and DunedinPoAm. Health record linkage was available for up to 13 years of follow-up, with a median time-of-onset from baseline of 5.75 years (ranging from less than 1 month to 13 years). Key findings included:

- **DNAm GrimAge** predicted the incidence of clinically diagnosed chronic obstructive pulmonary disease (COPD), type II diabetes and ischaemic heart disease (IHD) after 13 years of follow-up (hazard ratios (HR)=2.22, 95% CI: 1.81 to 2.72; HR=1.52, 95% CI: 1.20 to 1.90; and HR=1.41, 95% CI: 1.18 to 1.68; respectively).

- **DunedinPoAm** predicted the incidence of COPD and lung cancer (HR=2.02, 95% CI: 1.59 to 2.57; and HR=1.45, 95% CI: 1.18 to 1.79; respectively).
- **DNAm PhenoAge** predicted incidence of type II diabetes (HR=1.54, 95% CI: 1.21 to 1.97).
- **DNAm Telomere Length** was associated with a lower risk of IHD (HR=0.80, 95% CI: 0.69 to 0.92).
- **Accelerated DNAm GrimAge** was associated to all-cause mortality, independent of lifestyle risk factors (HR=2.10, 95% CI: 1.36 to 3.25).

These associations remained significant after adjusting for potential confounders, including alcohol consumption, body mass index, deprivation, education and tobacco smoking. This study demonstrated that epigenetic measures of ageing could be valuable in clinical settings, complementing gold-standard methods for disease assessment and management.[20]

e. Epigenetic age and cardiovascular health

Joyce BT et al. (2021) conducted a prospective longitudinal cohort study to investigate **the association between GrimAge acceleration (GrimAA)**, a measure of epigenetic ageing, **and cardiovascular health (CVH) from a young age**. The study also aimed to explore whether GrimAA mediates the established relationship between CVH and coronary artery calcium (CAC), a marker of cardiovascular disease (CVD). The researchers hypothesised that better CVH would be associated with slower GrimAA, as GrimAA is derived from blood protein markers and designed to predict lifespan. Cardiovascular health (CVH) scores were assessed using the American Heart Association (AHA) Life's Simple 7 metrics, which include four health factors (blood pressure, total cholesterol, body mass index, and fasting blood glucose) and three health behaviours (smoking, physical activity, and diet). Epigenetic age acceleration, which reflects the risk of age-related diseases, is calculated from **DNA methylation in blood leukocytes**. The study focused on three measures: (i) extrinsic epigenetic age acceleration (EEAA) that derived from Hannum's DNA methylation age that is sensitive to environment and age-related changes in blood cell composition; (ii) intrinsic epigenetic age acceleration (IEAA) that measure cell ageing derived from Horvath's DNA methylation age; and (iii) GrimAge acceleration (GrimAA). GrimAA integrates chronological age, sex, DNA methylation, and smoking history, and has the ability to predict mortality and other health outcomes.

Data were drawn from two cohort studies: the CARDIA study (Coronary Artery Risk Development of Young Adults), which included 1,999 participants, and the Framingham Heart Study (FHS) with 2,106 Offsprings participants. The CARDIA study analysed samples at Year 15 (Y15; 2000-2008) and Year 20 (Y20; 2005-2006),

while the FHS cohort which had DNA methylation measured at exam 8 (2005-2008). DNA methylation samples were collected at two time points (Y15 and Y20), and then combined models using generalised estimating equations (GEEs). The findings were validated in the FHS cohort, and GEE models were applied for stratified and sensitivity analyses (**Figure 7**). Mediation analyses were performed to assess CVH and GrimAA separately for each cohort and time point. The CARDIA cohort consisted of 59.3% White and 51.3% female participants, with an average age of 40.9 years at Y15. The FHS cohort was 100% White and 54.4% female, with an average age of 66.2 years.

The study found that higher CVH scores were consistently associated with lower GrimAA across multiple time points in both cohorts. In the CARDIA study, higher CVH score was linked to significantly lower GrimAA at Y15 (β range, -0.28 to -0.21 years per 1-point increase in CVH; p range, < 0.01) and Y20 (β range, -0.41 to -0.31 years per 1-point increase in CVH; FDR all < 0.01), with no significant differences by race or sex. These associations were confirmed in combined models for both clinical CVH scores (β range, -0.29 to -0.24 years per point increase in CVH; p and FDR < 0.01 for all) and full CVH scores (β range, -0.67 to -0.65 years per point increase in CVH; p and FDR < 0.01 for all). The results were validated in the FHS cohort, where higher clinical and full CVH scores were also significantly associated with lower GrimAA (clinical score: β range, -0.51 to -0.54 years; p < 0.01 for all; full score: β range, -0.76 to -0.83 years; p < 0.01 for all). Mediation analysis demonstrated that GrimAA partially mediated the effect of CVH scores on CAC in both studies, suggesting that epigenetic ageing may play a role in the relationship between CVH and CVD. Additionally, a significant correlation (r = -0.53) was found between GrimAA and smoking in the CARDIA cohort. In conclusion, the study indicates that accelerated GrimAge is associated with a decline in cardiovascular health from a young age, highlighting its potential as a biomarker for CVD risk and its role in linking age-related cardiovascular health decline to cardiovascular disease.[21]

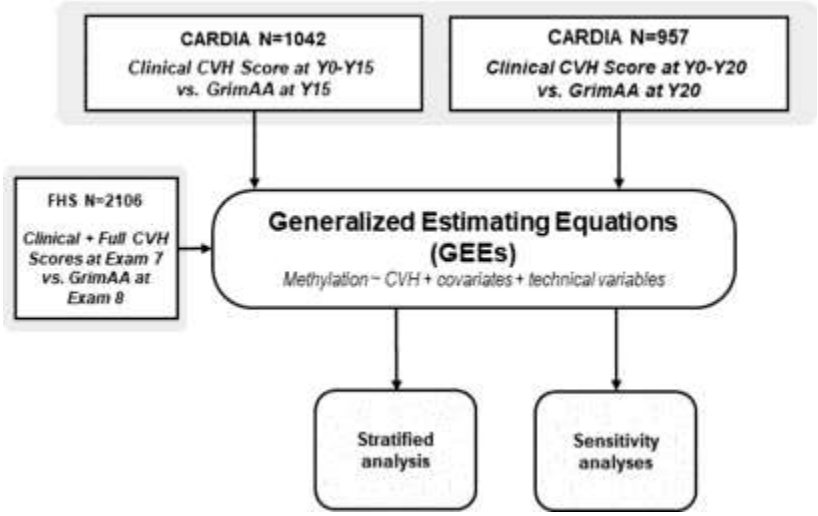


Figure 7: The study design

f. Epigenetic age as a biomarker for cognitive and neuropsychiatric symptoms

Vyas CM et al. (2023) conducted a pilot study to explore **the relationship between DNA methylation and cognitive and neuropsychiatric symptoms in older adults**. The study included 45 participants, with a mean age of 69.8 (SD=5.5) years and 48.9% were female. These participants were randomly selected from the VITAL-DEP (VITamin D and OmegA-3 TriaL-Depression Endpoint Prevention) cohort, and consisted of healthy, high-functioning men and women aged 60 or older with either normal cognition or mild cognitive impairment. They underwent comprehensive neuropsychiatric assessments and provided **blood samples** at baseline and after two years for DNA methylation analysis. The prevalence of neuropsychiatric symptoms (NPS); defined by an Neuropsychiatric Inventory (NPI) severity score of 2 or higher, was 28.9% in this sample.

The study found no significant differences in DNAm-based epigenetic markers when comparing different cognitive groups. However, DNAmGrimAge and AgeAccelGrim were negatively correlated with global cognitive scores (Spearman's rho (ρ) = -0.36, p = 0.04; ρ = -0.40, p = 0.02, respectively), suggesting that higher levels of these markers are associated with lower cognitive performance. There were also negative correlations between these markers and executive function/attention (ρ = -0.32, p = 0.07; ρ = -0.38, p = 0.03, respectively), but no significant associations with verbal memory. Longitudinal analysis revealed that changes in DNAm markers were linked to changes in global cognition over two years. A 1-year increase in DNAmGrimAge was associated with a faster decline in global cognitive score [adjusted β (95% CI): -0.09 (-0.15 to -0.02); p = 0.02], while a 100-base pair increase in DNAmTL was linked to an improvement in global cognitive score [adjusted β (95% CI): 0.15 (0.03 to 0.28); p = 0.02]. Over two years, an increase in DNAmGrimAge was linked to a decline in global cognitive scores, while an increase in DNAmTL was associated with improved cognitive scores. No significant changes were found with DNAmPhenoAge or in specific cognitive functions like verbal memory.[22]

In conclusion, the study suggests that DNAGrimAge and AgeAccelGrim are associated with lower cognitive function, particularly global cognition and executive function/attention. Changes in DNAGrimAge over time were linked to a decline in cognitive performance, while changes in DNAmTL were associated with improvements. These findings indicate potential longitudinal relationship between specific DNAm markers and cognitive outcomes, providing preliminary evidence for further investigation into the role of epigenetic markers in cognitive ageing.[22]

5.3 SAFETY

The S-Drive Epigenetic technology has not been linked to any documented safety concerns, as no specific studies have evaluated its safety profile. The procedure involves plucking of hair, which is generally considered non-invasive and poses minimal risk to individuals. Moreover, the analysis is performed on an outpatient basis, further indicating the low risk associated with the process. While the procedure is generally safe, caution may be advisable for certain individuals.

5.4 ECONOMIC IMPLICATION

No retrievable evidence regarding the cost-effectiveness of S-Drive Epigenetic technology was found in medical databases. The device is priced between USD 3,500 and USD 4,000, depending on the provider and any additional services included with the purchase. It is primarily used by wellness practitioners to generate epigenetic reports from hair follicle samples.[8,24]

5.5 ORGANISATIONAL

Although no specific studies have been conducted on the organisational challenges related to S-Drive Epigenetic technology, several considerations arise in its practical application. The procedure itself is non-invasive, and the device can be easily operated in clinical settings by wellness practitioners. However, the handling of sensitive personal and health data presents potential organisational concerns. The S-Drive system decodes and digitalises epigenetic information, which is then transmitted to a facility in Germany, for further analysis and interpretation. Once processed, the results are transferred back to the operating centres.

This transfer of personal data raises important questions about data security, privacy, and the potential misuse of sensitive health information. As the data crosses international borders, cybersecurity measures must be robust to prevent unauthorised access or breaches. Organisations using the technology need to ensure compliance with data protection regulations and implement strong cybersecurity protocols to safeguard client information. Additionally, concerns about the ethical handling and storage of personal health data must be addressed to build trust among clients and maintain the integrity of the process.

5.6 SOCIAL, ETHICAL AND LEGAL ISSUES

This technology have obtained several key certifications including: Conformité Européenne (CE) mark, Electrical Testing Laboratories (ETL), Federal Communications Commission (FCC) approval, and China Quality Certification (CQC). Their technology extends across numerous countries including Australia, New Zealand, Albania, Czech Republic, Denmark, Germany, Italy, Kosovo, Portugal, Spain, Sweden, Switzerland, the Netherlands, UK, USA, Canada,

Mexico, Argentina, Brazil, Hong Kong, India, Indonesia, the Philippines, Singapore, and Thailand. Moreover, they are supported by a growing network of distributors, who provide sales, support and training services. The S-Drive technology is utilised in various industries such as wellness, retail nutrition, professional sports clubs, fitness centres, beauty and spa resort, fresh juicing bars, and has recently expanded into the equine market.[8]

However, in Malaysia, this device is not included in the registered medical device list of the Medical Device Authority, Ministry of Health Malaysia.

5.7 LIMITATION

We acknowledge several limitations in our review that should be considered when interpreting the results. Although there were no language restrictions during the search, only full text articles published in English and peer-reviewed journals were included, which may have excluded relevant studies and further limited the number of studies included. A key limitation was the methodological quality of the included studies, particularly with regard to heterogeneity and risk of bias. No studies directly assessed hair follicles utilised the wave resonance and vibrational analysis to decode epigenetic information. Instead, the findings were inferred from studies on hair follicles and whole blood, focusing on DNA methylation analysis and its association with epigenetic age.

6.0 DISCUSSION AND CONCLUSION

Epigenetics has commonly been studied as a result of health outcomes rather than as a predictor.[7] However, epigenetic mechanisms play an essential role in regulating gene expression without altering the underlying DNA sequence. External factors such as lifestyle, environment, and age can influence these processes, impacting human health and disease development. DNA methylation, histone modifications, and non-coding RNA molecules are particularly responsive to environmental triggers like diet, stress, pollution, and drug exposure. These mechanisms act as molecular mediators, translating environmental inputs into heritable changes in gene expression, which can either contribute to either disease development or provide protective effects.

DNA methylation, in particular, is one of the most studied epigenetic modifications and has become a focus in aging and age-related disease research. Evans L et al. (2021) and Jackson P et al. (2023) provided valuable insights into how DNA methylation patterns are influenced by social determinants of health (SDOH). Their findings highlight the significant link between environmental factors, such as early-life trauma and socioeconomic status, and DNA methylation changes that may accelerate biological aging. These changes, in turn, increase the risk for various diseases.

A key advancement in the field has been the development of epigenetic clocks, which estimate biological or "epigenetic" age based on DNA methylation patterns.[20-22] These clocks, including the well-known Horvath and GrimAge clocks, provide a more precise assessment of how environmental exposures and lifestyle factors impact aging at a molecular level. Epigenetic age, as determined by these clocks, has proven to be a better predictor of age-related morbidity compared to chronological age. The GrimAge clock, for example, has shown strong associations with cardiovascular disease (CVD), cognitive decline, and overall mortality, making it a powerful tool for predicting disease risk and identifying individuals at higher risk.

Moreover, Jackson P et al. (2023) demonstrated that neighbourhood and environmental factors, such as socioeconomic deprivation and access to green spaces, can either accelerate or decelerate biological aging. These findings align with the concept that epigenetic age reflects the cumulative effect of lifetime exposures, making it a valuable marker for understanding health disparities and informing public health strategies.

The utility of hair follicles in DNA methylation studies marks a significant advancement in the field. Hair follicle-derived DNA methylation patterns have been shown to be able to estimate an individual's biological age, particularly in those under 20 years old, with a mean absolute deviation (MAD) of 3.25 years.[5] Furthermore, these studies have expanded possibilities for exploring psychiatric disorders[17, 18] and long-term stress responses[17]. Research shows that individuals with the SLC6A4 gene and the S/S genotype demonstrate increased sensitivity to

stress when DNA methylation levels are low,[17] highlighting the value of epigenetic analysis in the context in precision medicine. However, no evidence was retrieved regarding the use of wave resonance and vibrational analysis of hair follicles analysis for decoding epigenetic information.

CONCLUSION

Epigenetic modifications, particularly DNA methylation, are a valuable tool for understanding the relationship between environmental factors, aging, and disease risk. Most current studies primarily analyse DNA samples from peripheral blood, buccal swabs, and saliva. Research on DNA methylation from hair follicles remains limited, with **no evidence supporting the use of wave resonance and vibrational analysis for decoding epigenetic information**. The epigenetic signatures associated with human wellbeing have not been scientifically established for routine use in risk prediction, prognosis, or diagnosis beyond the scope of research. It should not be used for profit-driven initiatives until its scientific use is well proven. Epigenetic profiles are highly cell-type specific. Analysing only the hair follicle cells is unlikely to be a representative epigenetic profile for an individual.

.0 REFERENCES

1. Horowitz S. Epigenetics and its clinical applications. Alternative and Complementary Therapies. 2015;21(6):269-275.
2. Rodenhiser D, Mann M. Epigenetics and human disease: translating basic biology into clinical applications. Cmaj. 2006;174(3):341-348.
3. Orozco C. Quantum Mechanics The Wave Equation, The Signature Wave Entanglement and the S Drive. Cell Wellbeing Ltd. Available at https://www.thequietcone.com.au/uploads/1/9/5/5/19557321/the-wave-equation-and-signature-wave-by-carlos-orozco-feb-2106.pdf (Accessed on 13 February 2024).
4. Moltrasio C, Romagnuolo M, Marzano AV. Epigenetic mechanisms of epidermal differentiation. International journal of molecular sciences. 2022;23(9):4874.
5. Hao T, Guo J, Liu J, et al. Predicting human age by detecting DNA methylation status in hair. Electrophoresis. 2021;42(11):1255-1261.
6. Jackson P, Kempf MC, Goodin BR, et al. Neighborhood Environment and Epigenetic Age: A Scoping Review. Western Journal of Nursing Research. 2023;45(12):1139-1149.
7. Evans L, Engelman M, Mikulas A, et al. How are social determinants of health integrated into epigenetic research? A systematic review. Social Science & Medicine. 2021;273:113738.
8. Cell Wellbeing. S-Drive Technology. Available at https://www.cell-wellbeing.com/en/s-drive-technology (Accessed on 13 February 2024).
9. Lee SA, Li KN, Tumbar T. Stem cell-intrinsic mechanisms regulating adult hair follicle homeostasis. Experimental dermatology. 2021 Apr;30(4):430-447.
10. Cell Wellbeing. Epigenetics: The key to healthy living. Available at https://cell-wellbeing.com/en/science-epigenetics (Accessed on 13 February 2024).
11. Cell Wellbeing. 90-Day Optimize Immunity and Wellbeing Plan. Available at https://www.harmonizingcare.com/uploads/5/0/8/7/50872843/adult_immunity_and_wellbeing.pdf (Accessed on 13 February 2024).
12. Harmonizing Healthcare. Epigenetic Mapping Scan with the S Drive. Available at https://harmonizingcare.com/epigenetic-mapping-scan-with-s-drive/ (Accesses on 29 April 2024).
13. ROBIS: Risk of Bias in Systematic Reviews. Available at https://www.bristol.ac.uk/population-health-sciences/projects/robis/ (accessed on 20th February 2024)
14. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. Available at https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (accessed on 20th February 2024)
15. Critical Appraisal Skills programme. Available at https://casp-uk.net/casp-tools-checklists/ (accessed on 20th February 2024)

16. Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230
17. Alexander N, Illius S, Stalder T, Wankerl M, Muehlhan M, Kirschbaum C. Serotonin transporter gene methylation predicts long-term cortisol concentrations in hair. Psychoneuroendocrinology. 2019;106:179-182.
18. Petit I, Kesner NS, Karry R, et al. Induced pluripotent stem cells from hair follicles as a cellular model for neurodevelopmental disorders. Stem cell research. 2012;8(1):134-140.
19. Hibler E, Huang L, Andrade J, et al. Impact of a diet and activity health promotion intervention on regional patterns of DNA methylation. Clinical Epigenetics. 2019;11:1-12.
20. Hillary RF, Stevenson AJ, McCartney DL, et al. Epigenetic measures of ageing predict the prevalence and incidence of leading causes of death and disease burden. Clinical epigenetics. 2020; 12:1-12.
21. Joyce BT, Gao T, Zheng Y, et al. Epigenetic age acceleration reflects long-term cardiovascular health. Circulation research. 2021; 129(8):770-781.
22. Vyas CM, Sadreyev RI, Gatchel JR, et al. Pilot study of second-generation DNA methylation epigenetic markers in relation to cognitive and neuropsychiatric symptoms in older adults. Journal of Alzheimer's Disease. 2023;93(4):1563-1575.
23. Harmonizing Healthcare. Epigenetic mapping. Available at: https://www.harmonizingcare.com/epigeneticmapping.html/ (accessed on 13 February 2024).
24. For Healthy Cells. Available at: https://forhealthycells.com/offerings/ (accessed on 13 February 2024).

APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomised controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomisation.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

1. HEALTH/
2. health.tw.
3. (individual adj1 health).tw.
4. normal*.tw.
5. HEALTH STATUS/
6. ((general or overall or status) adj1 health).tw.
7. (general adj2 health level*).tw.
8. ((general or overall) adj2 health status).tw.
9. (health adj1 level*).tw.
10. health screening.tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. EPIGENETICS/
13. epigenetic*.tw.
14. S-DRIVE TECHNOLOGY/
15. S-Drive technology.tw.
16. 12 or 13 or 14 or 15
17. 11 and 16
18. limit 17 to (humans and "all adult (19 plus years)" and last 5 years)

TECHNOLOGY REVIEW (MINI-HTA) : HAIR FOLLICLES AS EPIGENTIC BIOMARKERS FOR ASSESSING WELLBEING

e ISBN 978-967-2887-88-1

MAHTAS
(online)