HEALTHCARE REVIEW: LONGEVITY

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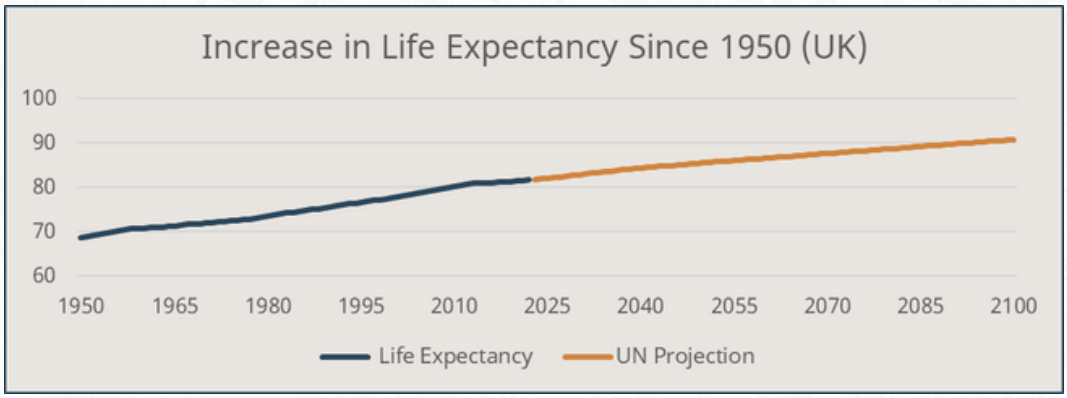
THE PURPOSE OF THIS REPORT

What is a long life? In 1950's England, you did well to see 70. An increasing number of scientists now believe humans could live to 150

The quest for longer life is as old as humanity itself. Despite the failure to discover an elixir of life, progress has been substantial, with no slowing of this trend in sight. As a result of this success, age-related diseases are increasingly common, limiting both length and quality of life.



Life expectancy from birth in the United Kingdom (MacroTrends, 2023)

The economic value of extending human life is immense; Scott, Ellison and Sinclair conclude that a slowdown in aging that increases life expectancy by one year is worth $38 trillion, and by ten years $367 trillion (Scott et al., 2021).

It is no surprise that the worlds of medicine, academia, and commerce are increasingly invested in this area. This report stands as a review of two key areas of progressive research, each of which stands to be revolutionary if it lives up to the promises of its proponents.

DIGITAL TWINS: REVOLUTIONIZING HEALTHCARE

SIMON F. WASLANDER

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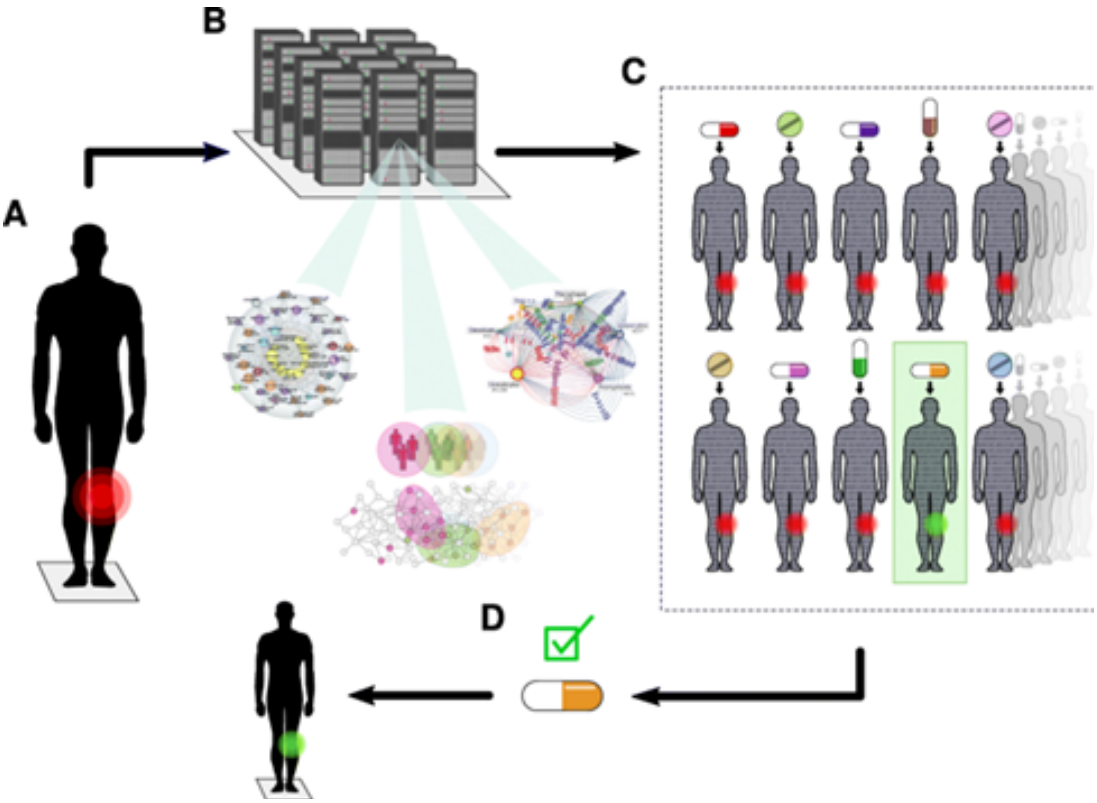
DIGITAL TWINS: REVOLUTIONIZING HEALTHCARE

- **Recent advancements in underlying technologies have advanced the clinical relevance of Digital Twins to the near future**
- **This technique brings tremendous potential benefits to patients, medics, pharmaceutical companies and society at large**



Digital Twins will allow pesonalization of medicine (Björnsson *et al.*, 2023)

Executive Summary

Driven by advancements in sensors, data gathering, laboratory diagnostics and Artificial Intelligence, creating personalized Digital Twins of patients is a near-term possibility. With the potential to profoundly affect the entire healthcare sector, this technique aims to reduce human suffering and address the high workload on the increasingly scare and most valuable resource in healthcare - human doctors. Society can benefit economically, with billions of dollars of savings and productivity benefits.

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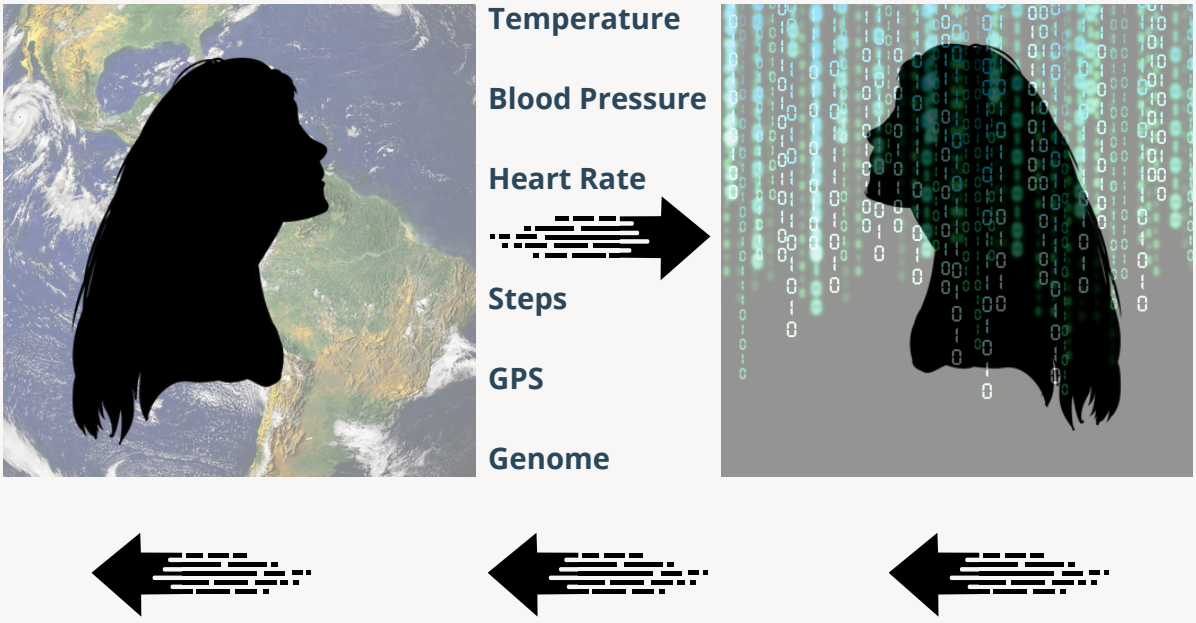
THE MEANING OF THE 'DIGITAL TWIN'

"A digital twin is a virtual model of a physical entity, with dynamic, bi-directional links between the physical entity and its corresponding twin in the digital domain. Digital twins are increasingly used today in different industry sectors. Applied to medicine and public health, digital twin technology can drive a much-needed radical transformation of traditional electronic health/medical records (focusing on individuals) and their aggregates (covering populations) to make them ready for a new era of precision medicine and public health. Digital twins enable the discovery of new knowledge, new hypothesis generation and testing, and in silico *experiments and comparisons." (Boulos, 2023)*



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THE ENDLESS POTENTIAL FOR HEALTHCARE

The most obvious area where Digital Twins can revolutionize healthcare is by enabling the era of true precision medicine.

Most patients in non-academic hospitals are treated and prescribed medication via clinical guidelines, themselves based on double-blind randomized clinical trials.

This ignores many of the unique features of each individual and does not deliver uniform results across the patient population.

With Digital Twins, treatments can be customized, predicting which medication, dosage, and time schemes will work best for each patient, preventing unwanted and often dangerous side effects and increasing efficacy. This reduces human suffering, time spent by medical professionals, and overall healthcare costs.

Potential treatments tested *in silico*, on multiple instances of Digital Twins, allowing safe and effective methods to be used *in vivo*

Digital Twins have been used by medical professionals as far back as 2010, as illustrated in the following table.

CASE STUDIES: DIGITAL TWINS IN USE

Year	Team	Applications of DT in medical field	The characteristics of DTs in medical field
2011	Niederer et al.	Using mechanical models to investigate the dependence of the CRT efficacy on cellular-scale mechanisms and organs	It was used to predict that a patient will respond less to CRT treatment and identify novel patient selection criteria
2017	Cone Health Team	The HeartFlow Analysis combined the information of CT, AI, cloud computing and computational physiology	The non-invasive diagnostic test helped physicians identify the impact that blockages have on blood flow to the heart
2018	The Philips	The Philips HeartNavigator tool combines CT images in a single image of the patient's heart anatomy	It provided real-time 3D insight into the positioning of devices during surgery, which can simplify the prior procedure planning
2019	Chakshu et al.	They built a DT model coupled with blood flow and head vibration to develop diagnostic tools	Comparing the in vivo vibration against the virtual data to detect the severity of carotid stenosis from a video of a human face
2020	Croatti et al.	They integrated agents and multi-agent system technologies together with DT on trauma patients	It is the first application of agent-based DT on severe traumas and realised personalised management
2020	Subramania n et al.	They built a DT that integrated scientific information and clinical source information	It helped drug research, bio-markers identification, test development, screening and clinical trial optimisation
2021	Golse et al.	They built a model of entire blood circulation which is automatically calibrated based on patients	The DT model was demonstrated to predict post-operative portal hypertension through estimated hepatic flow rate
2022	Aubert et al.	They created a DT with the help of 3D X-ray images of patient to simulate the scenarios of bone healing	The risk of recurrent fractures was assessed by applying the maximum load during gait
2022	FEops	They transformed cardiac images into DT and combined with AI-enabled anatomical analyses to generate data-driven insights	It provided physicians with unique digital tools to treat the right patients with the right technology at the right time

The concept of the Digital Twin is already seen in medicine (Sun *et al.*, 2023)

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DIGITAL TWINS AND DRUG DISCOVERY

Digital Twins can be leveraged by pharmaceutical and biotech companies in the design of novel treatments. Reducing the time of the drug development pipeline translates to hundreds of billions in aggregate savings for the healthcare sector.

> *"Using our PandaOmics and Chemistry42 platforms built on AWS, we were able to bring a fibrosis drug candidate from target discovery to compound validation in under 18 months for just $2.6 million."*
>
> Petrina Kamya, Global BDD, Chemistry42

This technology will be an essential component of delivering future healthcare. As an increasing number of conditions are understood on a genetic level, truly personalized treatments will be increasingly required. The development of *in silico* testing can meet this need within the constraints of the resources available.

Simon F. Waslander

Simon is Strategic Engagement Partner at Swire Consulting, focused on establishing links from within his deep science networks. His multifaceted expertise drives him to explore intersections between scientific advancement and business opportunities, shaping the future of both healthcare and consulting landscapes.

He is Chief Operating Officer at Teleios Health, an innovative start-up poised to transform healthcare by pioneering digital twins through cutting-edge quantified-self methodologies.

Simon holds a BSc. in Medicine from the University of Groningen, complemented by an MSc. in Healthcare Management, Policy and Innovation from Maastricht University.

Björnsson B;Borrebaeck C;Elander N;Gasslander T;Gawel DR;Gustafsson M;Jörnsten R;Lee EJ;Li X;Lilja S;Martínez-Enguita D;Matussek A;Sandström P;Schäfer S;Stenmarker M;Sun XF;Sysoev O;Zhang H;Benson M; ; (no date) Digital Twins to personalize medicine, Genome medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/31892363/ (Accessed: 30 August 2023).

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ADVANCED NEXT-GEN HEALTH MARKERS: MITOCHONDRIAL DNA METHYLATION

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MITOCHONDRIA: THE POWERHOUSE OF THE CELLS

A sequence of chemical processes known as cellular respiration converts glucose and fat, from food, into ATP (adenosine triphosphate; a type of energy package), which can then be used as energy for bodily functions. Glycolysis, the citric acid cycle, and oxidative phosphorylation are the three basic processes that occur during cellular respiration. This process takes place in the mitochondria, therefore the mitochondria are referred to as the "powerhouse" of all cells in the body.

Oxidative phosphorylation takes place through the transfer of electrons via several complexes situated in the mitochondria, the so called electron transport chain. During this process ATP is generated (Figure 1).

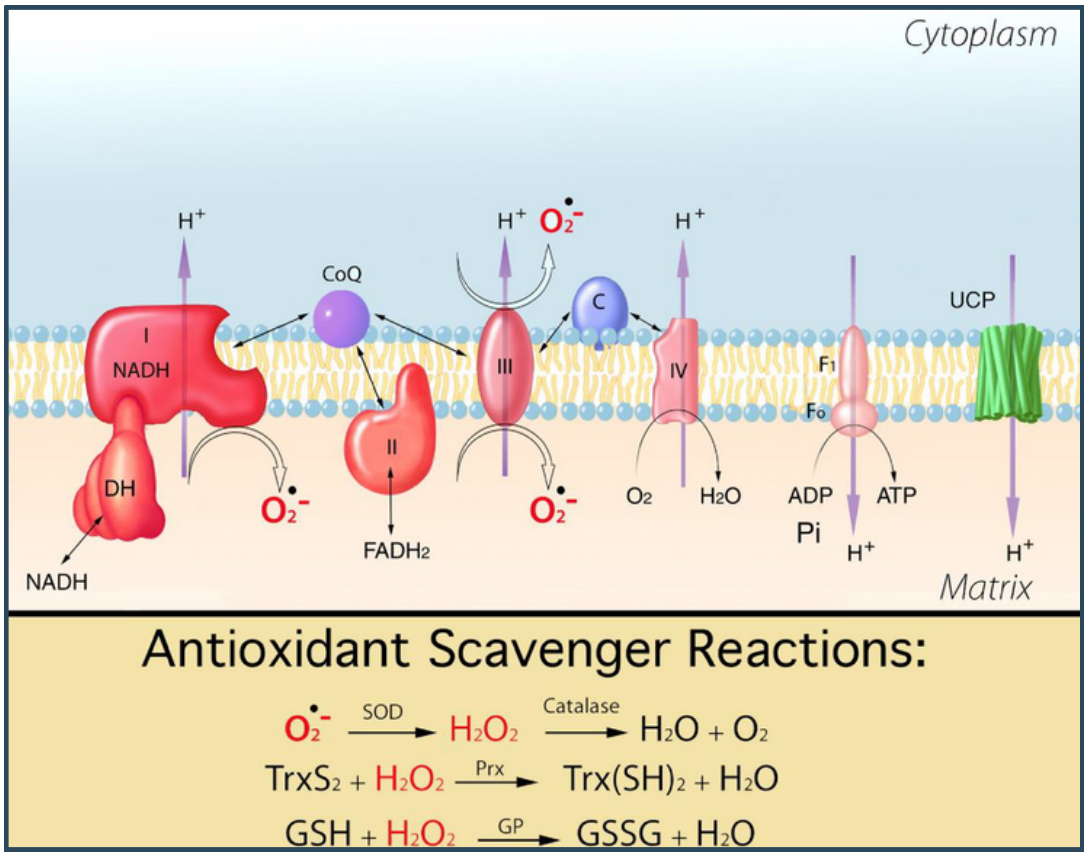

Figure 1. Schematic model of reactive oxygen species (ROS) production in mitochondria.
The main sites of superoxide anion production and the main pathways of ROS elimination have been identified at Sites I and III. Antioxidant enzymes include various isoforms of peroxiredoxin (Prx), superoxide dismutase (SOD), and glutathione peroxidase (GP). At the first step, break down of toxic, charged oxygen molecules called superoxide radicals takes place. In the second step, cellular dithiol proteins, such as thioredoxin (TrxS2), are required for the peroxiredoxin family's scavenging reaction. During aging, muscle Trx contents increase. In the third step of the reaction the glutathione/oxidized glutathione (GSH/GSSG) ratio maintains intracellular redox homeostasis (Robert S Balaban, 2005).

According to the free radical theory of aging, the formation of intracellular reactive oxygen species (ROS) is the most important driver of life span (Robert S Balaban, 2005).

This hypothesis proposes that mitochondrial oxidative damage accumulates with aging as a result of ROS formation during electron transport for ATP synthesis. As a result of this process, mitochondrial dysfunction worsens because ROS are extremely reactive and break down macromolecules like proteins, lipids, and DNA. Because of this, cells and organisms age and eventually die as their functions decline over time. An increasing collection of research supports this notion by indicating that changes to mitochondrial function affect how quickly organisms age (Dimitry A. Chistiakov, 2014).

An increasing collection of research supports this notion by indicating that changes to mitochondrial function affect how quickly organisms age

In addition to other tasks, the mitochondria participate in the synthesis of antioxidants to neutralize ROS through the antioxidant scavenger reaction, as depicted in Figure 1. By doing this the oxidant/antioxidant balance is maintained.

Due to the lack of histone protection (Figure 2) and an ineffective DNA repair system, the mitochondria are particularly susceptible to oxidative damage (Matilainen et al., 2017).

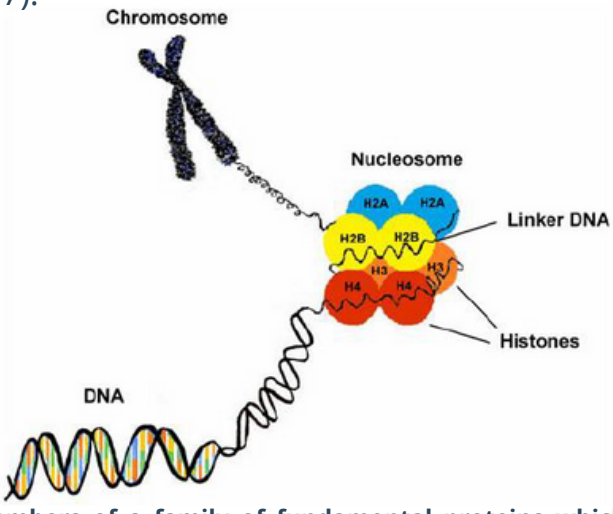

Figure 2. Histones are members of a family of fundamental proteins which interact with DNA in the nucleus to help it condense into chromatin. Nuclear DNA is extremely compressed and wrapped around histones in order to fit inside the nucleus and participate in the creation of chromosomes. It does not exist as free linear strands (Creative Proteomics Blog, 2023)

Disruption of the oxidant/antioxidant balance leads to many pathologies, including diabetes, neurodegenerative diseases, atherosclerosis, heart disease, inflammation, and cancer.

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THE DIFFERENCE BETWEEN AGING AND LONGEVITY

Only recently have significant advances in sequencing technologies and analytical techniques enabled the differentiation of aging and longevity.

These definitions are crucial for enhancing aging and longevity, and for living longer, healthier, and more energetic lives. Although there are several accurate definitions of aging, in general biological aging can be characterized as the progressive, event dependent loss of the capacity to maintain biochemical or physiological function. The length of a life unaffected by biological aging is what is meant by longevity. Although people are living longer, they are also suffering from age related chronic diseases for a greater period of time. In other words, we are experiencing more years of illness rather than gaining more years of vigor and excellent health (Roger B. McDonald, 2011). This definition of longevity provides the basis for extensive biomarker research to be better validated as predictors of disease risk.

Why and Which Markers for Health?

Many health issues manifest as changes in specific markers long before we experience physical symptoms. Spotting these changes early enables treatment or lifestyle changes, as appropriate, and prevents more significant repercussions. The markers that should give insight are the markers for glucose metabolism (glycated haemoglobin (HbA1c)), kidney function (creatinine and urea), lipid profile (HDL and LDL cholesterols), pituitary gland (TSH), total blood count, minerals (calcium, magnesium, iron profile), and vitamins (vitamin B12, folic acid, vitamin D).

These markers give some insight. However, because of the work of the Human Genome Organization (HUGO) project, the multilayer control of the human genome is better understood, and this has increased our understanding of the environmental, dietary, and epigenetic risk factors for human disease (Laura S. Rozek, 2014).

mtDNA METHYLATION AS AN ADVANCED MARKER

Less than 1% of the total cellular DNA is made up of mitochondrian DNA (mtDNA). Normal cellular function requires that mtDNA as well as nuclear DNA (nDNA) regulates mitochondrial activity and biogenesis to meet the cellular needs. The human mtDNA encompasses 16,569 base pairs, is circular, and double stranded. Its inheritance is through the mother.

Methylation is a chemical process (Figure 3), and is one of the epigenetic changes of DNA that can affect gene expression without changing the sequence of that gene.

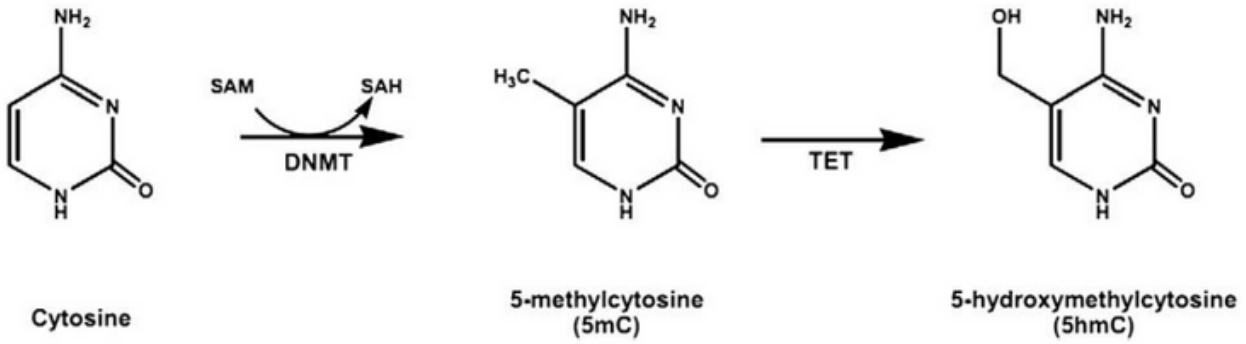

Figure 3. The methylation and hydroxymethylation of cytosine. SAH; S-adenosylhomocysteine, SAM; S-adenosyl methionine, DNMT; DNA methyltransferase, TET; ten-eleven translocation (partly adapted from Vito Iacobazzi, 2013).

It was previously thought that the mtDNA methylation machinery was absent in mitochondria. However, novel methodological approaches reveal that mtDNA could occur at much lower levels than in the nucleus. An approximate range of 1-20% methylation could be detected. It remains a matter of debate whether mtDNA methylation is present. This debate is driven by variation in measurements depending on the detection method employed. In our hands, the Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) is a powerful analytical and sensitive technique to detect low levels of mtDNA methylation in various samples. The LC-MS-MS machine combines the separating power of liquid chromatography with the highly sensitive and selective mass analysis capability of triple quadrupole mass spectrometry.

More evidence highlights the existence of mtDNA epigenetic regulation in normal and pathological conditions. Global methylation levels, as measured by 5mC and 5hmC, in a range of clinical and physiological situations have been determined in various tissues.

Cancer, diabetes, cardiovascular disease, HIV/AIDS, multiple sclerosis, Alzheimer's, Parkinson's, and Huntington's disease, aging and schizophrenia are just a few of the human disorders that have been linked to mitochondrial dysfunction (Amanda L. Morin, 2022). This mitochondrial DNA variation is associated with epigenomic changes at specific locations in the genome and influences gene expression. Mitochondrial function is strongly correlated with both disease and aging.

Individuals with a higher degree of methylation showed a higher risk of mortality

Individuals with a higher degree of methylation showed a higher risk of mortality than others, suggesting that methylation of some of the analyzed locations in the genome might reflect cell or organism survival status. We can conclude that there is significant evidence that connects mtDNA and mitochondrial function with cellular metabolism and the epigenome.

This is a rationale for follow up studies, particularly for additional epigenomic modifications that are not studied as extensively as DNA methylation. Research into these associations could reveal new pathogenic pathways and allow for the research of treatments. The research will be related to the pathophysiology of many diseases, particularly age-related complex disease, and will add to growing body of longevity research.

Klary Niezen-Koning PhD

Klary is a Clinical Biochemical Geneticist at UMC Groningen, Netherlands. She is focused on diagnostics and research of Inherited Metabolic Disorders.

She had the opportunity to found a department dedicated to the detection of these disorders on genetic and protein level, as is founder of the Case Data Base of Inherited Metabolic Disorders, a platform that can be used as a global shared educational resource.

Klary is Chief Scientific Officer at Teleios Health, a forward thinking start-up poised to revolutionize healthcare by developing digital twins using cutting edge quantified-self techniques, and holds a PhD in Medicine from the University of Groningen.

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SWIRE CAPITAL: WHAT WE DO

Swire Consulting

Preparing for Investment

The journey to delivering health benefits is complex. Swire aims to remove as many distractions as possible, supporting you in developing commercial strategy, and preparing financial models and pitch.

Finding the Right Capital

Securing the right capital is crucial for your project's success. Our expert team will diligently identify and connect you with the ideal capital sources or execution partners tailored to your specific needs. Our fee structure is designed with your long-term success in mind.

Swire Capital

Succession Planning

Planning for the future is essential. Swire Capital offers guidance and solutions for effective succession planning, ensuring a smooth transition and sustainable growth for your business.

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LET'S WORK TOGETHER

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