GlycanAge

WHITE PAPER

Glycans as Biomarkers of the Psychoneuroimmunoendocrine Network: Reflections from Practice and Research

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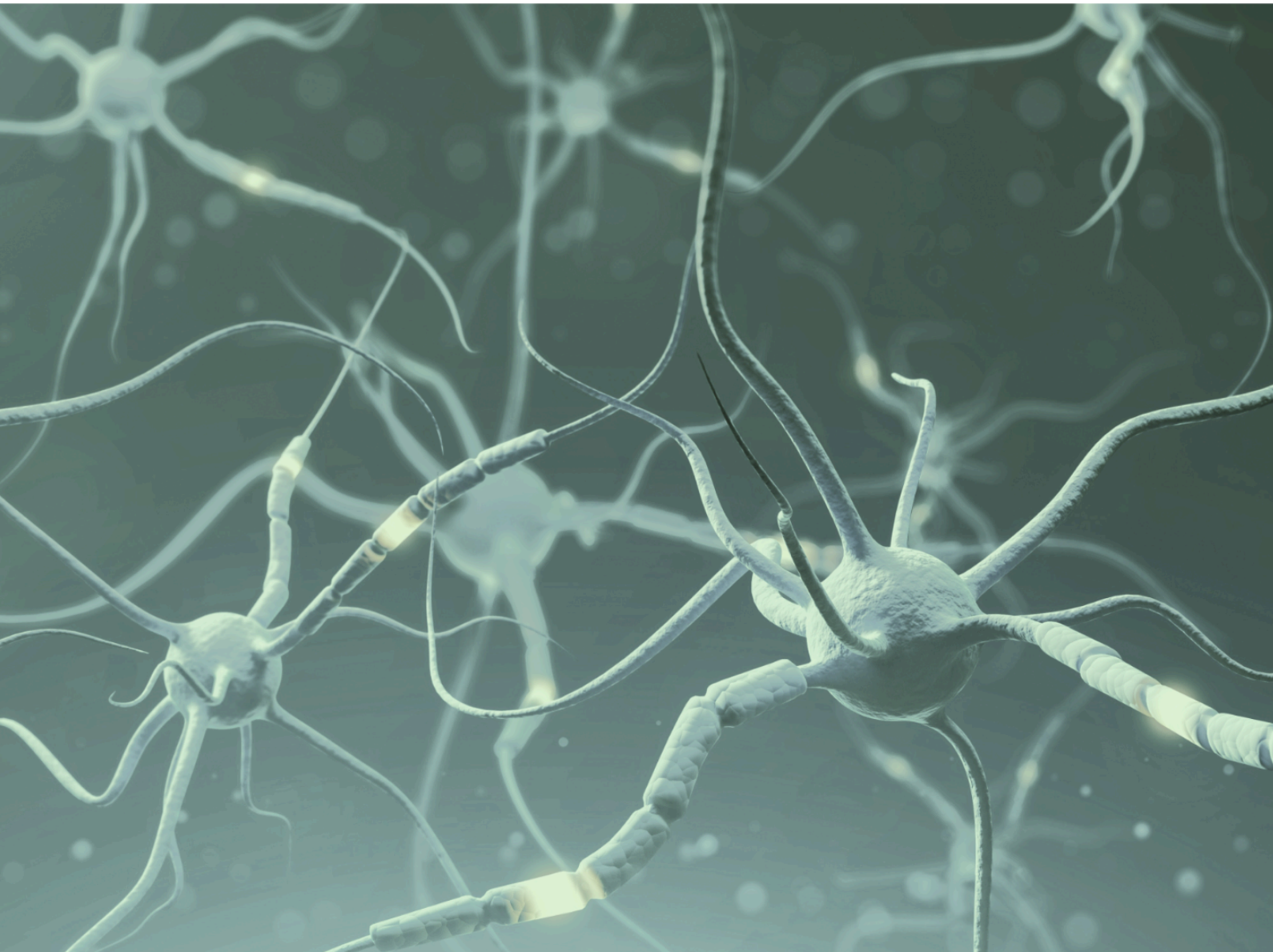

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Insights from GlycanAge specialists

Over the past few years, we have worked with thousands of individuals, helping them understand what their GlycanAge results reveal about the state and age of their immune system. These conversations have shown that our results provide insight far beyond basic biology. They seem to reflect how long-term stress, environmental exposures, and mental health shape immune function and contribute to the biological aging process in ways that are often unexpected.

GlycanAge is a biological age test that assesses immune system aging by analyzing the glycosylation patterns of immunoglobulin G (IgG) antibodies.

These glycan patterns determine how effectively the immune system regulates inflammation. When this regulation becomes less efficient with age, the result is a state known as “inflammaging”.

Inflammaging contributes to the development of chronic diseases and accelerates key hallmarks of aging. This process may naturally intensify with age, but it is further amplified by negative lifestyle factors such as chronic stress, poor diet, lack of physical activity, and poor sleep (1).

Through both research and clinical practice, it has become clear that GlycanAge results often capture the broader physiological impact of lived experience. In this sense, GlycanAge is not just a snapshot of immune aging and biological age, but a potential lens into the dynamic interaction between body, mind, and environment. This white paper explores that possibility and considers how glycans may serve as one of the earliest, most integrative biomarkers of psychoneuroimmunological (PNI) health.

When the GlycanAge results don’t match the lifestyle

One of the most striking patterns we observe involves individuals who, by conventional measures, lead healthy lives. They eat a fairly balanced diet, exercise regularly, and avoid smoking and excessive alcohol. Yet, their GlycanAge profiles reveal an accelerated immune aging.

This apparent mismatch between lifestyle and biological markers initially raised questions. However, as we engaged more deeply with these individuals, a recurring theme became clear: underlying chronic psychological stress, unresolved trauma, or the pressures of demanding, high-stress lives were common factors. These stresses leave subtle yet measurable imprints on the

immune system, driving chronic low-grade inflammation that traditional health assessments often miss.

We've come to refer to this pattern informally as the "manager's profile" *(Figure 1)*.

It is typically marked by:

- A significantly **elevated immune system biological age** compared to the individual's chronological age.
- **Reduced levels of digalactosylated glycans**, which are commonly abundant in younger individuals and are associated with a healthy immune profile. These glycans have anti-inflammatory properties and support the resolution of inflammation. In the commercial report, they are grouped under the Glycan Youth index.
- **Elevated levels of agalactosylated glycans**, which play a pro-inflammatory role and are indicative of immune system aging. In the commercial report, they are grouped under the Glycan Mature index.

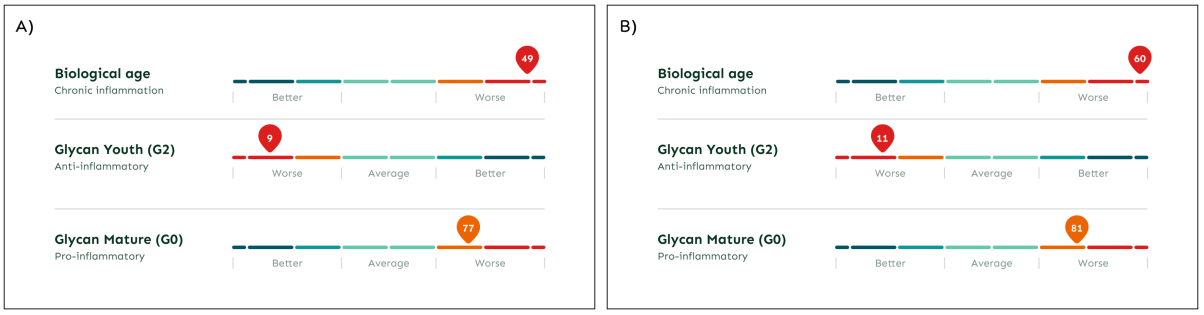

Figure 1: Examples of the "manager's profile" in two individuals aged 32 and 33 (A and B, respectively). Both individuals hold high-responsibility roles with intense workloads, frequent travel, and irregular routines. In addition to the characteristic glycan pattern, both profiles show suboptimal markers linked to metabolic resilience and early signs of frailty, suggesting broader physiological strain beyond immune aging. Biological age is shown in age; the two glycan indexes show percentile values comparing the individual with other individuals in the same chronological age group and biological sex group.

The Glycan signature of purpose, belonging, and recovery

On the other side of the spectrum, some individuals display glycan profiles that reflect immune youthfulness and resilience. These people often describe a strong sense of purpose, meaningful relationships, and emotional stability. Even more compelling are the transformations we've observed when individuals make significant life changes, such as leaving toxic work environments, establishing supportive social connections, or pursuing activities that bring meaning and joy (*Figure 2*). In many such cases, we've seen notable improvements in their glycan profiles within just a few months.

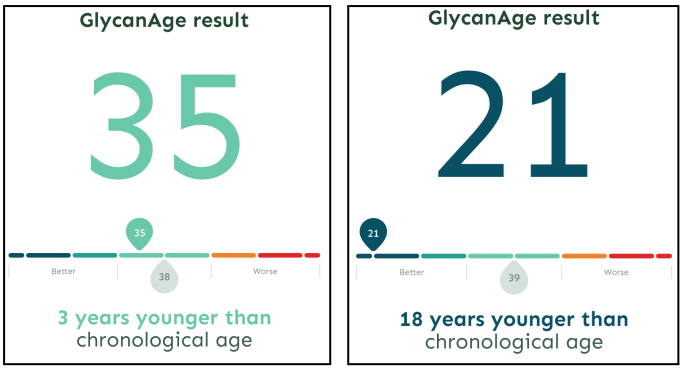

Figure 2. Biological age results of the same individual measured one year apart. After leaving their corporate position to pursue a more fulfilling solo career, their biological age improved significantly to 21, which is 18 years younger than their chronological age of 39.

Glycans reflect reality: Distinguishing true change from noise

A core question when interpreting changes in biological age is whether observed shifts are real or simply a product of measurement noise. This is especially important when we begin to examine how psychological stress, emotional state, and therapeutic interventions can influence immune ageing.

To be clinically meaningful, a biomarker must show two things:

1. **Stability** in the absence of biological change.
2. **Responsiveness** when change does occur.

GlycanAge is uniquely positioned in this regard.

Unlike many popular aging clocks, such as those based on epigenetic markers, GlycanAge shows low intra-individual variability and high technical reproducibility. As illustrated in *Figure 3*, repeated measurements of epigenetic clocks in the same individual can vary by up to 10 years, even when no intervention or major health event has taken place. This high level of analytical noise makes it difficult to discern whether an observed shift reflects a real change in physiology or random fluctuation.

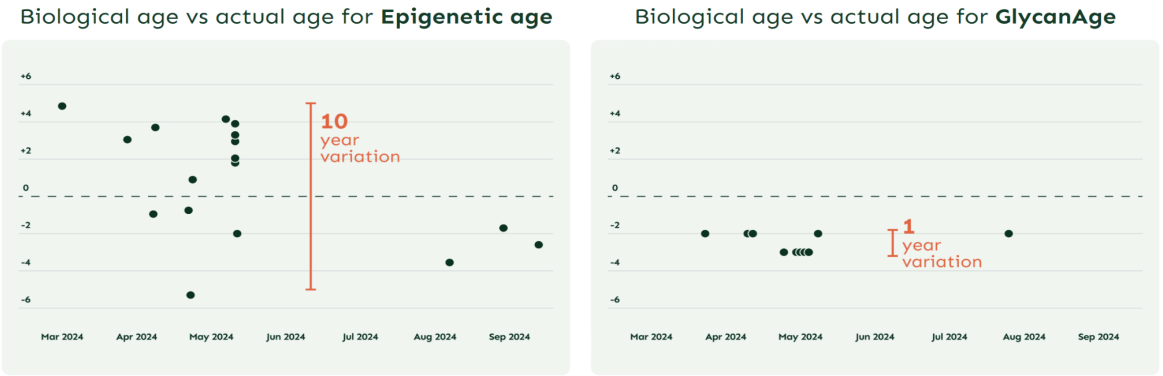

Figure 3. Comparison of biological age variability between epigenetic clocks and GlycanAge. The figure demonstrates the difference in repeat measurement stability between epigenetic age (left) and

GlycanAge (right). While epigenetic clocks showed a variation of up to 10 years in the same individual over a short period, GlycanAge results remained consistent within a 1-year range. This highlights GlycanAge's reliability for tracking true biological change rather than analytical noise. This analysis was conducted by the independent research group Alden Scientific.

By contrast, GlycanAge demonstrates remarkable consistency, with variation in repeat samples limited to approximately 1 year, well below the threshold of most meaningful interventions. This level of stability allows clinicians and clients to interpret glycan changes with confidence, knowing they reflect true underlying biological shifts, not laboratory artifacts (2).

The same study also highlights how this balance of stability and sensitivity plays out in long-term longitudinal data (*Figure 4*). In individuals with no major lifestyle, health, or emotional changes, glycan traits remain stable over time. However, when meaningful physiological events occur, such as recovery from illness, weight loss, initiation of stress-reducing practices, or even major life changes, glycan markers shift in consistent and biologically plausible directions (2).

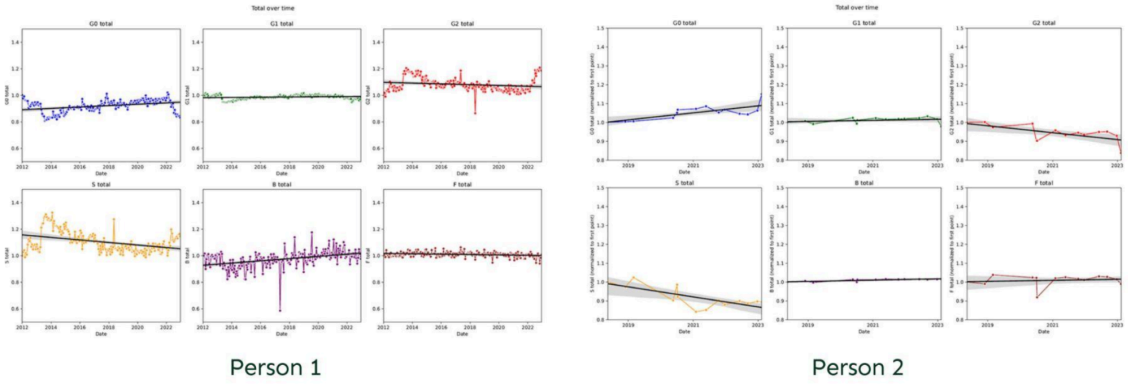

Figure 4. Longitudinal glycan profiles in two individuals. Person 1 (left) demonstrates long-term consistency across all glycan groups with no major lifestyle or health changes. Person 2 (right) shows clear directional shifts, such as increased G0 (Glycan Mature) and decreased G2 (Glycan Youth) and S (Glycan Shield), indicating true biological change. These patterns highlight the high stability of glycan measurements when health status is unchanged, and their sensitivity to detect real physiological shifts when they occur.

Early markers of risk

Numerous longitudinal studies have demonstrated that changes in IgG glycans can appear years in advance, in some cases up to a decade before the clinical onset of chronic conditions such as type 2 diabetes, cardiovascular disease, and autoimmune disorders. The changes in glycan profiles may serve as early markers of disease risk, before symptoms become apparent (*Figure 5*) (3-10).

Glycans predict chronic diseases up to 10 years in advance

Pathology	Model parameters	AUC | HR	Prediction (years)	Study
Menopause	IgG glycans + Age	AUC 0.85	n/a	Deris et al, iScience, 2022
Hypertension	IgG glycans + age + BMI + MAP	AUC 0.983	6.3	Kifer et al, J Hypertens, 2021
Cardiovascular and cerebrovascular events (M=men, W=women)	plasma glycans + AHA score	(M) AUC 0.72	8.3	Wittenbecher et al, Diabetes Care, 2020
	plasma glycans + AHA score	(W) AUC 0.77	8.3	Wittenbecher et al, Diabetes Care, 2020
	IgG glycans + age + sex	(M) HR 1.6	8.3	Birukov et al, Diabetes Care, 2022
	IgG glycans + age + sex	(W) HR 0.74	8.3	Birukov et al, Diabetes Care, 2022
Type 2 diabetes	plasma glycans + GDRS	AUC 0.9*	6.5	Wittenbecher et al, Diabetes Care, 2020
	plasma glycans + BMI	AUC 0.78	7.1	Cvetko et al, BMJ Open Diab Res Care, 2021
	IgG glycans + age + sex	HR 1.21 - 1.49	6.5	Birukov et al, Diabetes Care, 2022
Insulin resistance	plasma glycans + BMI	AUC 0.78	7.1	Cvetko et al, BMJ Open Diab Res Care, 2021
Rheumatoid arthritis	IgG glycans		9.8	Gudelj et al, Bioch Biophys Acta Mol Basis, 2018
	IgG glycans	AUC 0.928		Sebastian et al, OMICS, 2016
Crohn's disease	IgG glycans		6.0	Gaifem et al, Nature Immunology, 2024

Figure 5. Summary of evidence from large cohort studies demonstrating that IgG and plasma glycosylation patterns can predict the onset of chronic diseases years before clinical diagnosis. Glycan-based models consistently achieve strong predictive accuracy (AUC values ranging from 0.72 to 0.98). In several cases, glycan signatures were detectable 6–10 years in advance of disease onset. AUC–Area Under the Curve, HR–Hazard Ratio, IgG–Immunoglobulin G.

Even in individuals who appear clinically healthy, we often see glycan patterns that mirror those found in higher-risk groups. These early changes are commonly observed in people predisposed to rheumatoid arthritis, Crohn's disease, type 2 diabetes, or cardiovascular disease (11).

Importantly, individuals with a history of trauma or chronic stress exposure frequently show similar IgG disruptions, suggesting that these "disease fingerprints" may in fact be early indicators of immune system imbalance that increase long-term risk.

The link between autoimmunity and chronic stress is not a new concept. As early as 1892, the eminent physician William Osler proposed that emotions and stress might be connected to conditions such as systemic lupus erythematosus (SLE). While this perspective was largely set aside in the development of modern treatments, advances in glycoscience now allow us to revisit and reinforce this idea. The idea was never without merit, but until recently, it lacked the tools needed to be quantified and tracked in clinical practice.

GlycanAge as a psychoneuroimmunological biomarker

In the book *When the Body Says No*, Gabor Maté reflects on the work of William Osler and early pioneers of psychoneuroimmunology, a field that explores the intricate connections between psychological states, the immune system, the nervous system, and the endocrine system. He observed that individuals who struggle to set boundaries often show a higher risk of autoimmune disease and even cancer. Early in his career, such ideas were dismissed by the medical community, which was slow to acknowledge that the mind and body are inseparably linked (12).

Advances in glycoscience now provide a framework to revisit these insights with measurable evidence. Glycan research has demonstrated that disease begins far earlier than conventional medicine is able to detect. As mentioned in the chapter above, across decades of studies, IgG glycosylation changes have been shown to predict chronic diseases, including type 2 diabetes, cardiovascular disease, and autoimmune disorders, up to ten years before diagnosis.

This creates a challenge for modern medicine. The current model is reactive: it diagnoses disease once pathology is established and focuses on managing consequences. By this stage, the subtle interactions between mind, body, and environment that contributed to disease onset have already been overlooked. Glycans, however, offer the possibility of detecting these disruptions at their earliest stages, when prevention and intervention are still possible.

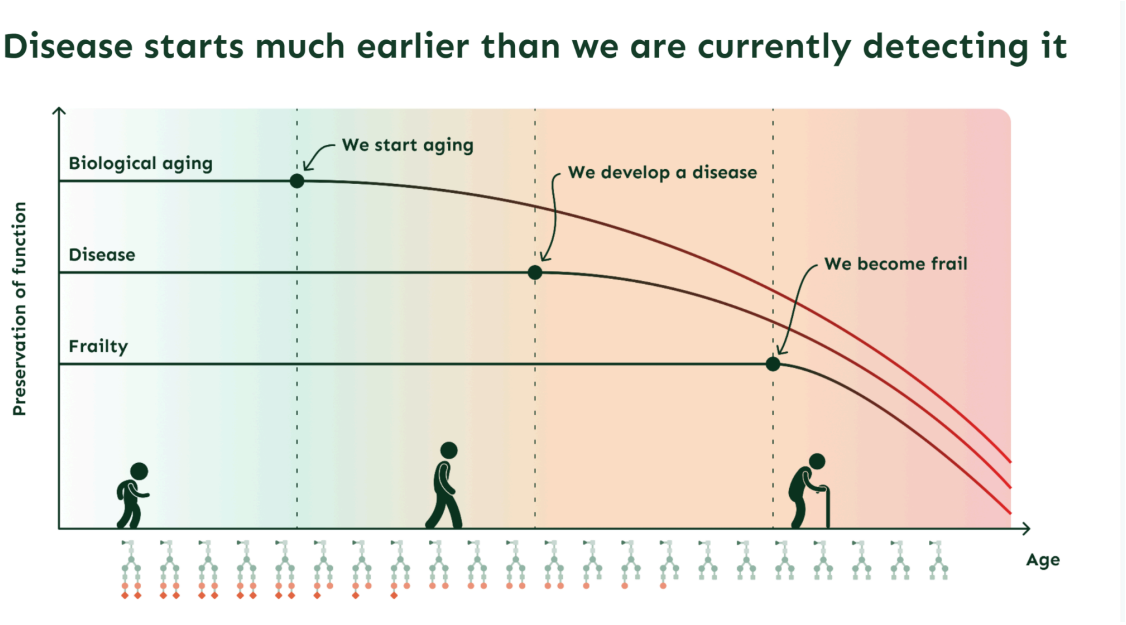

Figure 6. An illustration of how biological aging and immune system changes begin well before the first clinical signs of disease. The top trajectory shows biological aging, with early immune shifts

occurring decades before diagnosis. The middle trajectory marks the point at which disease is typically detected, when significant dysfunction has already accumulated. The lower trajectory represents progression to frailty. Glycan patterns, shown along the bottom axis, provide molecular evidence of these early changes, demonstrating that disease processes start long before they are visible through conventional clinical methods.

Maté argues that recognizing personality traits and unresolved trauma may help prevent disease development. Glycans extend this paradigm: they represent measurable biomarkers of psychoneuroimmunological balance, capable of capturing early immune system disturbances. Because glycans are also dynamic, they allow clinicians to monitor the effectiveness of lifestyle, psychological, or medical interventions in restoring balance.

Psychoneuroimmunology (PNI), sometimes expanded as psychoneuroendocrinoimmunology (PNEI), studies how thought processes, stress responses, and emotional regulation influence the nervous, endocrine, and immune systems. IgG glycans, as part of the immune system's regulatory machinery, provide a clear molecular endpoint for this interaction. If the mind shapes immunity, it will inevitably alter the resolution of inflammation, and glycans directly encode that signal.

The interconnectedness of this "super-system" means that influence flows in many directions. For example, during perimenopause, the loss of sex hormones accelerates immune system aging and disrupts anti-inflammatory glycan production. Women can biologically age by 7–10 years in just a few months during this transition, a change accompanied by nervous system instability and increased vulnerability to both physical and mental health disorders (13).

Taken together, glycans provide one of the first practical tools to quantify what psychoneuroimmunology has long proposed: that the mind, body, and environment function as an integrated whole, and that disruptions in this balance can be detected, and potentially addressed, before disease takes hold.

Glycans and stress-related conditions

Although still a developing field, our research group and collaborators have already provided some of the first direct evidence that glycans are altered in stress-related psychiatric conditions. These studies, spanning both human cohorts and animal models, demonstrate that glycosylation patterns capture aspects of stress vulnerability, immune dysregulation, and therapeutic response, laying the groundwork for glycans as biomarkers of the psychoneuroimmunological network.

Major Depressive Disorder (MDD).

In one of the exploratory studies, plasma and IgG N-glycans were profiled in patients with major depressive disorder before and after antidepressant treatment. Glycan traits correlated with the severity of depressive symptoms and certain glycan features predicted response to treatment. Notably, these effects showed gender-specific differences, with female patients demonstrating the clearest associations. The glycan alterations paralleled those seen in chronic inflammation and immune aging, supporting the concept that depression carries a biological signature of accelerated immune decline (14,15).

Post-Traumatic Stress Disorder (PTSD) in humans.

In a large-scale study of 543 Croatian war veterans, it has been demonstrated for the first time that PTSD is accompanied by distinct plasma glycan alterations. Six plasma N-glycans were consistently different between PTSD cases and controls across both discovery and replication cohorts, underscoring the robustness of the finding. Interestingly, these glycan shifts were not tied to symptom severity, suggesting that they may reflect underlying biological vulnerability rather than momentary distress. The altered glycan structures overlapped with those observed in other inflammatory and neuropsychiatric conditions, highlighting common pathways of stress-related immune dysregulation (16).

Post-Traumatic Stress Disorder in animal models.

To further test the relationship between trauma and glycosylation, our collaborators employed a rat model of PTSD. This work showed that glycan patterns could distinguish resilient from vulnerable animals, even before trauma exposure. Following trauma, susceptible animals displayed consistent shifts toward pro-inflammatory glycosylation in plasma and in brain regions such as the prefrontal cortex. These results mirror the alterations seen in human PTSD and provide mechanistic evidence that glycans are involved in the stress response rather than being secondary bystanders (17).

Together, these studies illustrate a consistent narrative:

- Glycan alterations are present in major stress-related disorders such as MDD and PTSD.
- Certain glycan traits can serve as predictors of vulnerability, resilience, or treatment response.
- Changes are reproducible across species, observed in both plasma and brain tissue, and align with known pathways of immune and inflammatory dysregulation.

While this body of work represents only the first steps, it provides strong support for glycans as promising biomarkers of the psychoneuroimmunological network. The challenge now is to expand to larger, longitudinal cohorts and to determine whether psychological, pharmacological, or lifestyle-based interventions can shift glycan profiles back toward health.

Looking ahead

The emerging body of evidence shows that glycans are not just markers of biological age, but also sensitive indicators of how stress, trauma, lifestyle, and environment shape the psychoneuroimmunoendocrine network. Our work across large population cohorts, patient groups, and animal models consistently demonstrates that glycan patterns reflect vulnerability, resilience, and the early molecular fingerprints of disease, often years before clinical symptoms appear.

For clinicians, this offers a new perspective. Glycans bridge disciplines: they capture how the immune system communicates with the nervous, endocrine, and psychological domains. They provide measurable, dynamic signals that can be monitored in the same way we now track blood pressure, lipids, or glucose. Unlike static risk factors, glycans can shift in response to interventions, making them uniquely positioned to inform prevention and guide treatment.

At this stage, the field is still young. More work is needed to refine reference ranges, validate markers in diverse populations, and embed glycan analysis into everyday clinical workflows. Yet the early results are clear: glycans are among the most promising biomarkers for capturing the lived reality of patients, bridging mind and body in a way few other measures can.

We invite colleagues across disciplines, including immunology, psychiatry, psychology, endocrinology, or preventive medicine to explore the potential of glycans within their own practice and research. Collaboration is essential to accelerate translation. By working together, we can move from proof-of-concept toward clinical utility, and in doing so, open new pathways for earlier detection, achieve true personalized, preventative care, and improved outcomes for our patients.

About the author

Paula Francekovic is a health professional with a background in Human Nutrition and extensive experience in preventative and longevity-focused health. As Education Manager at GlycanAge, she develops clinical resources and programs that help healthcare professionals integrate biological age testing into practice. Paula specializes in interpreting complex biomarker data and translating it into actionable strategies to improve healthspan and patient outcomes.

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