

## REVIEW ARTICLE

**EARWAX, SALIVA AND SKIN – NEW ERA OF DIAGNOSIS OF NEUROLOGICAL DISEASES?****WOSKOWINA USZNA, ŚLINA I SKÓRA – NOWA ERA DIAGNOSTYKI CHOROÓB NEUROLOGICZNYCH?**

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**ABSTRACT****Introduction**

The diagnosis of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) still relies on methods used at advanced stages, including clinical evaluation, neuroimaging, and cerebrospinal fluid analysis. These techniques are often invasive, expensive, and applied only after irreversible neuronal loss has occurred. Therefore, there is an urgent need for accessible, cost-effective, and non-invasive biomarkers enabling earlier diagnosis. Recent studies focus on unconventional biological materials such as saliva, skin, and earwax, which may reflect central nervous system pathology and offer new perspectives for early detection.

**Aim**

To review and summarize current evidence on the diagnostic potential of biomarkers identified in saliva, skin, and earwax for ADs and PDs.


**Materials and methods**

A literature review was conducted using the PubMed database with the following keywords: "biomarkers", "Parkinson's disease", "Alzheimer's disease", "saliva", "skin", "earwax". Only human observational studies published between 2010 and 2025 were included.

**Results**

In AD, salivary studies demonstrated increased concentrations of amyloid- $\beta$ 42, tau protein and lactoferrin. In PD, phosphorylated  $\alpha$ -synuclein deposits in cutaneous nerve fibers showed high sensitivity and specificity, distinguishing PD patients from controls and persisting over time. Their presence in idiopathic rapid eye movement sleep behavior disorder associated with PD supports the use of skin biopsy for early diagnosis. Moreover, lipidomic analysis of earwax revealed specific lipid signatures differentiating PD patients from healthy individuals, with diagnostic accuracy exceeding 90%.

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## Conclusions

Saliva, earwax, and skin constitute promising, non-invasive sources of biomarkers that reflect neurodegenerative pathology. Their accessibility, stability, and correlation with brain changes may revolutionize early diagnosis and monitoring of Alzheimer's and PDs.

**Keywords:** biomarkers, Parkinson's disease, Alzheimer's disease,  $\alpha$ -synuclein, amyloid  $\beta$ 42, tau protein

## STRESZCZENIE

### Wprowadzenie

Diagnostyka chorób neurodegeneracyjnych, takich jak choroba Parkinsona (PD) i choroba Alzheimera (AD), wciąż opiera się na badaniu neurologicznym i metodach stosowanych głównie w jawnych klinicznie stadiach choroby, które obejmują neuroobrazowanie oraz analizę płynu mózgowo-rdzeniowego. Techniki te są albo inwazyjne, albo kosztowne i wdrażane dopiero po wystąpieniu nieodwracalnej utraty neuronów. Dlatego istnieje pilna potrzeba opracowania dostępnych, niedrogich i nieinwazyjnych biomarkerów umożliwiających wcześniejsze rozpoznanie choroby. Najnowsze badania zwracają uwagę na niekonwencjonalne materiały biologiczne, takie jak ślina, skóra i woskowina uszna, które mogą odzwierciedlać patologie ośrodkowego układu nerwowego i otwierają nowe możliwości wczesnej diagnostyki.

### Cel

Przegląd i podsumowanie aktualnych danych dotyczących potencjału diagnostycznego biomarkerów identyfikowanych w ślinie, skórze i woskowinie usznej w chorobie Alzheimera oraz chorobie Parkinsona.

### Materiały i metody

Przeprowadzono przegląd literatury dostępnej w bazie PubMed, korzystając ze słów kluczowych: „biomarkery”, „choroba Parkinsona”, „choroba Alzheimera”, „ślina”, „skóra”, „woskowina uszna”. Uwzględniono wyłącznie badania obserwacyjne oraz przeprowadzone na ludziach i opublikowane w latach 2010–2025.

### Wyniki

W chorobie Alzheimera badania śliny wykazały podwyższone stężenia amyloidu- $\beta$ 42, białka tau oraz laktoferyny. W chorobie Parkinsona badanie fosforylowanej  $\alpha$ -synukleiny w skórnych włóknach nerwowych charakteryzuje się wysoką czułością i swoistością, skutecznie odróżniając pacjentów z PD od osób zdrowych oraz utrzymując stabilność w czasie. Jej obecność u osób z idiopatycznym zaburzeniem zachowania podczas snu REM związanym z PD potwierdza przydatność biopsji skóry jako narzędzia do wczesnej diagnostyki. Dodatkowo lipidomiczna analiza woskowiny usznej ujawniła specyficzne profile lipidowe, które różnicują chorych na PD od osób zdrowych, osiągając dokładność diagnostyczną przekraczającą 90%.

### Wnioski

Ślina, woskowina uszna oraz skóra stanowią obiecujące, nieinwazyjne źródła biomarkerów odzwierciedlających patologię neurodegeneracyjną. Ich dostępność, stabilność oraz związek ze zmianami zachodzącymi w mózgu mogą znacząco usprawnić wczesne rozpoznawanie i monitorowanie choroby Alzheimera oraz choroby Parkinsona.

**Słowa kluczowe:** biomarkery, choroba Parkinsona, choroba Alzheimera,  $\alpha$ -synukleina, amyloid  $\beta$ 42, białko tau

## Introduction

It is currently estimated that dementia affects approximately 50 million people worldwide [1]. The most common form is Alzheimer's disease (AD), accounting for 60–70% of all cases [2]. The second most prevalent neurodegenerative disorder is Parkinson's disease (PD), affecting around 6 million individuals globally [3]. These conditions, which lead to a progressive loss of independence and reduced quality of life [4], impose not only a significant medical burden but also social and economic ones [5]. Given the rapidly increasing global prevalence of these disorders, there is an urgent need to develop strategies that enable earlier diagnosis and timely intervention.

Current management standards, such as the Diagnostic Evaluation, Testing, Counseling, and Disclosure of Suspected Alzheimer's Disease and Related Disorders Working Group guidelines, focus exclusively on symptomatic patients [6]. The diagnostic process outlined therein relies primarily on clinical assessment [7], magnetic resonance imaging [8,9], and the "cognitive lab panel" [10]. Lately, cerebrospinal fluid (CSF) biomarkers have gained increasing significance [11], particularly in the context of emerging therapeutic interventions [12]. In ambiguous cases, specialized tests are recommended, such as amyloid [13] and tau positron emission tomography (PET) [14,15]. Although these modalities provide invaluable insights for clinical and research applications, their invasiveness, high cost, and limited accessibility restrict widespread use [16].

Screening tests such as the Mini-Mental State Examination and the Montreal Cognitive Assessment (MoCA) [17] can identify individuals with emerging neurological changes but are recommended only for symptomatic patients and not for routine population-wide screening [18].

Given the limitations of current diagnostics, developing rapid, low-cost, non-invasive

methods using accessible biological materials has become a key focus. Saliva, skin, and earwax have therefore attracted increasing scientific interest. These materials may even identify AD and PD patients in the pre-clinical phase, before irreversible neurological symptoms appear. Given that new pharmacological agents for AD, such as aducanumab and gantenerumab, appear to be effective primarily in the preclinical stage, rapid diagnosis is crucial [19,20]. A similar relationship applies to PD, where the therapeutic options currently under development are also expected to be most effective when administered at early or preclinical stages of the disease [21].

## Aim

This review aims to synthesize and evaluate the current scientific evidence on the diagnostic potential of biomarkers identified in three easily accessible biological materials – skin, saliva, and earwax – for neurodegenerative diseases.

## Materials and methods

A literature review was conducted using the PubMed, ResearchGate, and Google Scholar databases. The search was performed using the following keywords and their combinations: "biomarkers", "Parkinson's disease", "Alzheimer's disease", "saliva", "skin", and "earwax". Original research articles and review papers published in English between 2010 and 2025 were considered.

The inclusion criteria comprised human observational studies involving adult participants only. The study groups consisted of patients with clinically confirmed AD or PD, while control groups included healthy individuals with no diagnosed neurological disorders. In all included studies, patient and control groups were age-matched.

For studies investigating earwax, only research focused on volatile organic compounds (VOCs) analyzed using thermal desorption gas chromatography–mass

spectrometry (TD-GC-MS) was included, and these studies were limited to PD.

The exclusion criteria included studies without a confirmed diagnosis of AD or PD, studies lacking a healthy control group, studies that did not analyze biological samples of saliva, earwax, or skin, case reports, editorial letters, as well as articles without full-text availability in English.

A total of 33 studies met the inclusion criteria and were included in the final analysis: 3 studies investigating earwax, 14 studies analyzing saliva, and 16 studies focusing on skin-derived biomarkers.

## Results

### Earwax

#### VOCs

Recent studies increasingly indicate that physiological alterations, including oxidative stress and inflammatory responses, may be reflected in characteristic changes in skin- and ear-derived VOCs [22]. The notion that PD produces a distinctive odor arose from Joy Milne, who consistently recognized a musky scent on patients years before clinical diagnosis [23]. This observation led to the hypothesis that PD induces disease-specific changes in lipid-rich secretions like sebum and earwax detectable via volatilomic analysis.

#### Sebum characterization

To investigate this hypothesis, TD-GC-MS was applied to profile VOCs extracted from sebum. Across discovery and validation cohorts, a reproducible set of biomarkers was identified - perillic aldehyde, hippuric acid, eicosane, and octadecanal – showing consistent directional changes in PD [24,25]. Importantly, these compounds eluted within the chromatographic window corresponding to Joy Milne's strongest PD-like odor. Blinded spiking experiments demonstrated that mixtures of these VOCs could recreate the scent, suggesting that sebum composition changes contribute to a disease-specific volatilome.

#### Ear canal secretions (ECS) analysis

ECS share a similarly lipid-rich profile as sebum but offer greater chemical stability and reduced environmental contamination [26]. Chen *et al.* [27] conducted the most extensive analysis to date, examining 209 ECS samples using two complementary analytical strategies: GC-MS for compound identification and quantification, and a rapid GC-surface acoustic wave (GC-SAW) system paired with convolutional neural networks (CNNs) for pattern-based classification. GC-MS identified four key VOCs – ethylbenzene, 4-ethyltoluene, pentanal, and 2-pentadecyl-1,3-dioxolane – which independently predicted PD even after adjusting for age. Machine learning enhanced diagnostic performance substantially: models based solely on these four biomarkers achieved accuracies above 84%, while the GC-SAW/CNN approach achieved 94.4% accuracy, representing one of the highest diagnostic performances reported for odor-based PD detection.

These findings are consistent with the results reported by Habibzadeh *et al.* [28] who analyzed VOCs derived from sebum and exhaled breath and observed a sensitivity of 0.81, a specificity of 0.76. The comparatively lower diagnostic accuracy of these approaches further supports earwax-derived VOCs as a particularly promising candidate for future PD biomarker development.

### Saliva

#### Application in diagnostics

##### Lactoferrin

Lactoferrin (LF) is a promising neuroprotective biomarker in AD, potentially alleviating cognitive impairment through multiple molecular pathways [29].

Carro *et al.* [30] found significantly reduced salivary LF in AD patients, correlating with decreased CSF A $\beta$ 42 and increased total tau (t-tau). González-Sánchez *et al.* [31] validated these findings in two independent cohorts, showing that low LF strongly associates with

positive amyloid-PET and identifies cerebral amyloid even in prodromal stages.

In contrast, Gleerup *et al.* [32] found no significant differences in salivary or CSF LF across diagnostic groups in a mixed memory clinic population – likely due to comorbidities or methodological variability. Then, providing a theoretical context for the positive findings, Bermejo-Pareja *et al.* [33] suggested that LF depletion may reflect systemic immune downregulation from early AD-related hypothalamic dysfunction.

#### $\alpha$ -Synuclein

$\alpha$ -Synuclein ( $\alpha$ -syn) constitutes a central component in the pathogenesis of PD, as it is the major component of insoluble Lewy bodies and aggregates into toxic oligomers [34]. The exploration of salivary  $\alpha$ -syn as a non-invasive biomarker for PD has evolved from basic concentration assessments [35] to complex isoform profiling [36].

In an early observational study, Al-Nimer *et al.* [35] reported a significant reduction in salivary  $\alpha$ -syn in PD patients alongside a paradoxical increase in total salivary protein, indicating that  $\alpha$ -syn depletion occurs within a broader, likely dysregulated, protein secretory environment.

Later, Vivacqua *et al.* [37], showed that the reduction in total salivary  $\alpha$ -syn occurs alongside a significant increase in oligomeric  $\alpha$ -syn, a profile whose clinical relevance was confirmed by Shaheen *et al.* [36]. Their analysis revealed a significant increase in salivary  $\alpha$ -syn-olig in patients with bradykinesia and rigidity, which correlated positively with disease duration but not with severity scores.

Addressing the diagnostic complexity, Angius *et al.* [38] expanded the analytical panel to include phosphorylated  $\alpha$ -syn (p- $\alpha$ -syn). While their results indicated that isolated measurements of  $\alpha$ -syn-total might not always differentiate groups, the application of combined ratios - the reduced

p-syn/ $\alpha$ -syn-total and elevated oligomeric levels – achieved satisfactory diagnostic accuracy, emphasizing the necessity of multimodal assessment.

#### Tau protein

Tau, a microtubule-associated protein essential for neuronal microtubule stability, forms toxic aggregates when hyperphosphorylated, disrupting both short- and long-term synaptic plasticity. Structurally, the protein contains 85 potential phosphorylation sites, of which only about 10 are occupied in a healthy brain, but this number can rise to nearly 55 in AD [29].

The investigation into salivary tau was fundamentally grounded by Shi *et al.* [39], who confirmed the presence of unique tau peptides in human saliva. They subsequently employed a modified Luminex assay to demonstrate that while t-tau levels remained non-diagnostic, the ratio of phosphorylated tau (p-tau) to t-tau was significantly elevated in AD patients. This focus on phosphorylation ratios emerged because unmodified tau showed limited diagnostic value, as both Ashton *et al.* [40] and Lau *et al.* [41] found no significant differences in salivary or enzyme-linked immunosorbent assay-measured t-tau levels between AD patients and healthy controls. Mechanistic precision was further advanced by Pেকেles *et al.* [42], who showed through Western blot analysis of unstimulated saliva that diagnostic utility stems from hyperphosphorylation at S396 and S404, yielding a markedly elevated p-tau/t-tau ratio despite substantial inter-subject variability in t-tau levels.

Addressing sampling variability, Cui *et al.* [43] optimized saliva collection across six sample types in healthy participants and, in a subsequent AD-control validation cohort, showed that although isolated t-tau and p-tau levels lacked diagnostic power, respectively - the p-tau/t-tau ratio remained a statistically significant discriminator.

### Amyloid- $\beta$

Amyloid- $\beta$  ( $A\beta$ ) plays a multifaceted role in the healthy brain, with its synaptic activity-dependent release and proposed neuroprotective functions under physiological conditions [44]. However, in AD this balance collapses, driving  $A\beta$  to aggregate into fibrillar structures and ultimately form the extracellular amyloid plaques characteristic of the disease [29].

Advancements in fluid biomarker research have recently shifted attention toward salivary  $A\beta_{42}$  as a non-invasive AD indicator. For instance, Lee *et al.* [45] demonstrated that salivary  $A\beta_{42}$  levels were over twice as high in 10 AD patients compared to 27 healthy controls, suggesting that salivary  $A\beta_{42}$  may reflect peripheral production in tissues such as the submandibular gland, kidney, and pancreas. These findings were supported by Sabbagh *et al.* [46] and Bermejo-Pareja *et al.* [47], who reported significantly elevated salivary  $A\beta_{42}$  in mild-to-moderate AD patients – peaking in mild cases – though levels appeared to normalize in severe stages. Even though Shi *et al.* [39] failed to detect salivary  $A\beta_{42}$  – likely due to matrix effects or technological limitations – more recent studies using sensitive immunoassays and targeted collection, including Cui *et al.* [43], confirmed its presence, with peak levels in unstimulated parotid saliva and significantly higher concentrations in AD patients compared to controls.

### Skin

#### $\alpha$ -syn detection in skin biopsy

$\alpha$ -syn density in PD patients correlates with autonomic dysfunction and disease progression, suggesting a link between cutaneous autonomic neuropathy and PD pathology [48,49]. Moreover, its content in CSF varies among PD subtypes, reflecting underlying pathophysiology [50].  $\alpha$ -syn is widely distributed in peripheral autonomic networks, brain and peripheral nerves of patients, causing extensive histopathological changes [51]

as neurons are highly sensitive to  $\alpha$ -syn changes and even small aggregates can induce symptoms [52]. Peripheral  $\alpha$ -syn may disseminate to the central nervous system (CNS), consistent with both the gut-brain axis hypothesis and the temporal progression of parkinsonian symptoms [53].

Although  $\alpha$ -syn is present in various accessible tissues and biofluids, skin biopsies offer unique advantages: accessibility, patient tolerance, minimal invasiveness, and stable  $\alpha$ -syn deposition unaffected by clinical procedures [54]. Detection of p- $\alpha$ -syn in skin nerves effectively differentiates PD from other parkinsonian syndromes and controls [55].

Diagnostic yield of  $\alpha$ -syn depends on biopsy site and technique, with enrichment along spinal nerves – commonly sampled in the neck (especially C7) and chest – while distal sites show lower expression, and procedural factors influence nerve fiber quantification and detection rates [56]. Serial sampling (3–4 cm apart) improves detection [57]. Section thickness and preparation impact results: frozen sections (10–50  $\mu$ m) are preferred over paraffin (3–10  $\mu$ m) to reduce tissue oxidation [58]. Thicker sections allow the inclusion of more nerve fibers within each sample, improving  $\alpha$ -syn detection, whereas thinner sections offer better resolution and antibody binding [59].

Immunofluorescence visualizes all nerve fibers, but is limited by serial sectioning, multiple sites, and potential interference of external factors with antibody binding [60]. Emerging assays such as real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification can amplify minute  $\alpha$ -syn aggregates for sensitive detection [61], though they are still under development for cutaneous applications.

In 2014 two independent groups demonstrated that skin biopsies allowed detection of p- $\alpha$ -syn and to discriminate between PD and controls with an acceptable sensitivity and an excellent specificity [62,63] and since then more than 30 studies on this subject

have been published, reporting specificity ranging from 90% to 100% and sensitivity ranging from 5.3% to 100% (reviewed in Doppler) [60]. Subsequent studies examined pre-motor stages, including idiopathic rapid eye movement sleep behavior disorder (iRBD), a recognized non-motor risk marker for PD, finding dermal p- $\alpha$ -syn in most patients and none in controls [64]. Longitudinal follow-up showed consistent p- $\alpha$ -syn positivity, confirming its reliability as an early biomarker and a reproducible tool for studies in iRBD and PD [65].

#### Immunocytochemical detection of $\alpha$ -syn and A $\beta$ 42 in fibroblast

The study by Zuev *et al.* [66] reported increased  $\alpha$ -syn expression in the skin fibroblasts of patients with PD, extending previous observations on this peripheral biomarker. The authors also demonstrated higher levels of A $\beta$ 42 peptide in fibroblasts from PD patients compared with individuals without neurodegenerative disease. These findings suggest that immunocytochemical detection of these proteins in fibroblasts may have diagnostic relevance. In contrast, previous studies assessing A $\beta$ 42 outside the brain, particularly in CSF, have shown reduced concentrations of this marker in older individuals with PD compared with healthy controls [67–69].

#### Discussion

Analysis of the available literature confirms a rapidly growing interest in the use of non-invasive, easily accessible biological materials as potential biomarkers of neurodegenerative diseases. Saliva, skin, and earwax contain molecules that reflect pathological processes occurring within the CNS, making them attractive candidates for early, cost-effective diagnostic tools. Although current findings are encouraging, each modality faces methodological and translational challenges that must be addressed before clinical implementation.

Salivary biomarkers in AD show substantial diagnostic promise. Elevated concentrations of A $\beta$ 42 have been reported in AD patients [70]. Other analytes, such as tau protein and LF, further enhance the diagnostic panels. Notably, reduced salivary LF has been linked to both CSF biomarkers and amyloid-PET positivity in prodromal AD [30,31], suggesting potential value for early detection. The primary advantage of saliva lies in its “stress-free” and non-invasive nature, which allows for repeated sampling and cost-effective population screening. However, studies in unselected memory-clinic populations have produced inconsistent results, highlighting the impact of comorbidities and methodological variability [32]. This underscores a major diagnostic challenge: the vulnerability of the salivary proteome to physiological fluctuations – such as oral pathological conditions, circadian rhythms, and systemic hydration – which may hinder the detection of subtle neurodegenerative changes.

The clinical translation of salivary biomarkers is hindered by significant heterogeneity in collection and processing – ranging from strict fasting and chemical stabilization protocols [47] to unreliable devices like cotton Salivettes [71] and variable pre-collection practices [43] – highlighting the need for standardized methods and large multicenter studies to establish reference ranges and assess biomarker stability. Without the elimination of these pre-analytical variables, the risk of false results remains a significant barrier to routine clinical use.

Despite these limitations, saliva remains an appealing diagnostic matrix due to its accessibility and non-invasiveness. With methodological harmonization and further validation, salivary biomarkers could become valuable components of multimodal diagnostic strategies for AD and potentially other neurodegenerative diseases.

Among all peripheral approaches, skin biomarkers currently offer the most robust

evidence for PD. Numerous studies have confirmed p- $\alpha$ -syn deposition within cutaneous autonomic nerve fibers of PD patients with high sensitivity and specificity [57,66,72]. Importantly, p- $\alpha$ -syn positivity has also been demonstrated in individuals with iRBD [64,73], and longitudinal observations show consistent biomarker stability [60]. Conversely, the primary disadvantage is the relative invasiveness of the procedure and its technical sensitivity.

Emerging amplification assays such as RT-QuIC enhance analytical sensitivity and promise greater standardization [61]. Yet variability in biopsy site, tissue thickness, fixation, and immunohistochemistry persists, underscore the need for large, methodologically standardized cohorts to define diagnostic thresholds, false-positive rates, and utility across PD subtypes and stages.

Earwax represents one of the most novel yet promising non-invasive matrices for PD biomarker discovery. Its primary advantage is the chemical stability of its lipid-rich environment, which protects biomarkers from degradation better than aqueous fluids [26]. Recent studies using GC-MS, GC-SAW, and machine-learning models have identified unique VOC signatures that differentiate PD patients from healthy controls with diagnostic accuracies above 90% [24,27]. These results position earwax as a particularly attractive biofluid for developing rapid, inexpensive, and patient-friendly diagnostic tools.

Volatilomic research highlights the diagnostic potential of odor-based biomarkers, with sebum and ECS showing reproducible VOC patterns influenced by disease-related metabolic and microbiome alterations. The identification of a distinctive PD-associated scent provided key impetus for investigating the volatilome as a diagnostic tool [24]. Together, these findings suggest that volatilomics could complement or even precede traditional motor-based diagnostics.

However, clinical translation will require validation in larger, ethnically diverse cohorts,

along with standardized sampling, storage, and analytical protocols. As volatilomics matures, it promises not only early detection but also deeper insights into PD pathophysiology and patient stratification. Despite the high accuracy of current models, the volatilome remains sensitive to exogenous confounding factors, including personal hygiene products and dietary influences, as well as the biological pathways linking CNS pathology to earwax VOCs have yet to be fully elucidated.

AI and machine learning have become increasingly important for analyzing complex biological datasets – such as lipidomic and VOC profiles – where CNNs outperform traditional assessments. The integration of AI facilitates the automation of diagnostic processes, with the potential to reduce laboratory costs and minimize human error [27].

By integrating AI with analysis of saliva, skin, and earwax, this approach could overcome the high cost and limited accessibility of PET, single-photon emission computed tomography, and CSF diagnostics. This enables affordable, reproducible, and user-friendly screening – potentially in primary care or home settings – while automated interpretation reduces laboratory expenses and facilitates early detection of neurodegenerative disorders. Nevertheless, the inherent lack of transparency in complex artificial intelligence (AI) models constitutes a critical limitation. For successful translation into clinical practice, these algorithms require extensive validation across diverse global populations to ensure that the identified biochemical patterns remain consistent across distinct genetic and environmental phenotypes.

Overall, saliva, skin, and earwax represent promising non-invasive sources of biomarkers for AD and PD, offering accessibility, biochemical richness, and potential for early disease detection. While skin biopsies provide the highest pathological specificity, saliva and earwax offer greater scalability for early-stage screening. Nevertheless, successful clinical implementation will require

standardized analytical protocols, large-scale validation cohorts, longitudinal assessments of biomarker stability, and the integration of AI to facilitate earlier diagnosis, improved patient stratification, and the timely initiation of disease-modifying interventions.

### Conclusions

Available evidence indicates that saliva, skin, and earwax constitute promising, non-invasive sources of biomarkers for neurodegenerative diseases. Elevated levels of A $\beta$ 42 and LF in saliva may support early detection of AD. The presence of p- $\alpha$ -syn in skin biopsies remains one of the most robust and well-validated biomarkers for PD, particularly in its prodromal stage. Furthermore, integrating lipidomic and volatilomic profiling of earwax suggests the potential for developing rapid, inexpensive, and patient-friendly diagnostic methods for PD.

However, implementation of these biomarkers into routine clinical practice requires further validation, standardised protocols for sample collection and analysis, and longitudinal studies assessing biomarker stability over time. Integration of AI and machine learning methods with peripheral biomarker analysis may significantly accelerate this process, enabling automated, reproducible, and cost-effective diagnostics. Combining AI with non-invasive biomarker testing offers a realistic opportunity to reduce diagnostic costs and improve accessibility, potentially transforming early detection strategies in neurodegenerative diseases.

Ultimately, saliva, skin, and earwax, supported by AI-enhanced analytical techniques, may form the basis of a new generation of screening tools, enabling earlier diagnosis, more personalized care, and more effective slowing of disease progression.

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