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REVIEW ARTICLE

Personalized prevention of neurodegenerative diseases: scoping review and evidence gap map

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Abstract

Neurodegenerative diseases represent a major public health challenge due to their high prevalence and poor prognosis. Identifying biomarkers to stratify individuals by their risk of developing these diseases may help to define new personalized prevention interventions. The objective of this study was to conduct a scoping review of biomarkers for primary and secondary personalized prevention of neurodegenerative diseases. The search targeted biomarkers in adults or high-risk subpopulations in clinical or public health settings for Alzheimer's disease, vascular dementia, Lewy body disease,

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frontotemporal dementia, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis. Ultimately, 286 papers were included in the review and the interactive gap map. There is a strong focus on Alzheimer's disease, and most papers included -omics-based biomarkers and/or used artificial intelligence. Genetics/genomics are at the forefront of current scientific research, although there is a notable gap in studying gene–environment interactions, and studies in clinical settings are still scarce.

KEYWORDS
biomarker, dementia, multiple sclerosis, neurodegenerative disease, personalized prevention

Highlights

- Research indicates a strong focus on Alzheimer´s disease and limited research in other diseases.
- Genetics and genomics are at the forefront of current scientific research.
- We found biomarkers for predicting progression in mild cognitive decline.
- There is a notable gap in studying gene-environment interactions.
- Studies investigating biomarkers in a clinical context are still scarce.

1 | INTRODUCTION

Neurological diseases are among the most challenging public health problems. In terms of disability-adjusted life years (DALYs), the burden of disease due to these pathologies increased by around 18% from 1990 to 2021 worldwide.[1] Even though a significant part of this trend could be considered a result of increased life expectancy, it is also undeniable that neurological diseases, and in particular neurodegenerative diseases, are currently an important cause of disability and one of the leading causes of death worldwide.[2] In 2021, neurodegenerative diseases were responsible for nearly 45 million DALYs globally.[1] Within this group, dementia was the single largest contributor, accounting for about 36.3 million DALYs that year, underscoring its role as the main driver of disability among neurodegenerative disorders.[3] This large burden, together with the limited therapies available for many of these pathologies, highlights the urgent need to improve primary and secondary prevention.[4]

In this connection, many authors are searching for risk factors of these diseases in order to formulate prevention strategies,[2,5] paying special attention to those modifiable risk factors where intervention is possible, such as tobacco smoking, sleep, diet, physical activity, hypertension, dyslipidemia, or diabetes, among others.[5,6] However, these factors do not fully explain the significant interindividual heterogeneity recognized by clinicians in neurodegenerative diseases in terms of incidence, evolution, and prognosis.

In recent years, innovative health research has produced and given access to many new sources and amounts of data, creating new opportunities to learn about chronic diseases etiology and progress, integrating information from areas such as biology, epidemiology, sociodemographics, or environment science. According to the *European Council Conclusion on personalized medicine for patients* (2015/C421/03), the term "personalized medicine" defines a medical model that involves characterizing the genotypes, phenotypes, lifestyle, and environmental exposures of individuals in order to (1) tailor the right therapeutic strategy to the right person at the right time, (2) determine disease predisposition, and (3) provide timely and targeted prevention.[7]

The emerging concept of "personalized medicine" entails enhancing subgroup categorization to individual-based tailored interventions for complex disorders like neurodegenerative diseases.[8] Within this framework, "personalized prevention" seeks to avoid or delay the onset, progression, and recurrence of illnesses by incorporating a diverse array of individualized data.[7] The purpose is to provide timely and effective interventions to allow a better course of the pathology in terms of health and economic costs, although its translation into clinical practice represents a major challenge for health systems.[9]

Technological advances that can promote personalized prevention of neurodegenerative diseases include the identification and validation of available or developing biomarkers that can help stratify individuals into subgroups according to their risk of disease. Stratification of individuals into subgroups includes, for example, the definition of risk groups based on their genetic profiles. We need to know and understand the scope and focus of recent biomarker research to inform and define what the main lines of future research in this field should be. However, to reach its true potential, personalized prevention must also be able to incorporate individual data on lifestyle or environmental exposures with those obtained from biomarkers. Tools such as wearable technologies and artificial intelligence (AI) are increasingly being explored as means to collect and analyze such data, potentially enhancing the personalization of preventive approaches. Delving deeper into the interaction between biomarkers and these factors is crucial to identifying high-risk individuals who could benefit most from personalized prevention strategies.

In this study, we present the results of a scoping review and its interactive evidence gap map (EGM), providing a global view on the status and gaps in current scientific literature on available biomarkers or those under development that may be useful for personalized primary and secondary neurodegenerative prevention strategies in clinical or public health settings. We developed a conceptual framework to classify and evaluate all available biomarkers – both in current use and under development – for their potential role in personalized primary and secondary prevention of neurodegenerative diseases. The framework is structured along three main dimensions: (1) biomarker type, categorized by its biological or technological nature (e.g., genetic, proteomic, imaging, digital, environmental); (2) its added value in relation to modifiable risk factors, based on an assessment of whether the biomarker contributes new predictive or stratifying information beyond what is already known about lifestyle or behavioral risk factors; and (3) the availability of stratified data for known risk groups. This framework allows for a structured appraisal of the usefulness of biomarkers not only in mapping current evidence but also in identifying those with the greatest potential to enhance precision prevention strategies. Ultimately, it emphasizes that biomarkers must go beyond replicating existing knowledge and instead offer added value to support personalized decision-making.

This research is part of the "PeRsOnalized Prevention roadmap for the future HEalThcare" (PROPHET) project, funded by the European Union's Horizon Europe research and innovation programme and is linked to the International Consortium for Personalized Medicine (https://www.icpermed.eu/). The PROPHET project seeks to highlight the gaps in current personalized preventive approaches to develop a Strategic Research and Innovation Agenda (SRIA) for the European Union.

2 | METHODS

2.1 | Study design

This review constituted the first phase of the PROPHET project and was intended to provide an evidence base that would allow progress in its remaining phases. In line with the broad scope and following recommendations from the Cochrane Rapid Review Methods Group, a rapid scoping review was identified as the most suitable methodological approach to produce the project deliverable within the time available.[10] The PROPHET project protocol specified the investigation of biomarker research for personalized prevention for neoplasms, cardiovascular, and neurodegenerative diseases. We performed three scoping reviews in parallel using a common protocol, available in the Open Science Framework [11] and published in a peer-reviewed scientific journal for public consultation.[12]

This report presents the review and results for neurodegenerative diseases and is focused on those with the greatest impact worldwide. We included dementias – Alzheimer's disease (the most prevalent neurodegenerative disease), vascular dementia, frontotemporal dementia, and Lewy body disease – as well as Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.[2,4]

The methodology used followed the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards based on the population, concept, and context (PCC) framework.[13,14] The PRISMA for Scoping Reviews (PRISMA-ScR) checklist was followed during the review process (available in Supplementary File S1).

Population: We looked for biomarkers measured in the general adult population (≥18 years). In addition, we looked for biomarkers that could stratify individuals into subgroups of adults with higher risk of developing these diseases, based on the available literature, namely, family history/high genetic risk,[15,16] apolipoprotein E (*APOE*)genotype,[17,18] obesity,[19,20] arterial hypertension,[19,20] diabetes mellitus,[19,20] dyslipidemia,[20] alcohol consumption,[21,22] tobacco smoking,[19,20,23,24] and hearing loss.[25,26]

Concept: For this review, a biomarker was understood to be a substance, structure, characteristic, or process (or a combination of them) that can be objectively measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure.[27,28] Biomarkers were classified as molecular, cellular, imaging, physiological, and anthropometric types, each of which has different subtypes (available in Supplementary File S2). Biomarker types and each of their different subtypes were collected during data extraction. Also, to be included in this review, biomarkers should be useful for personalized primary or secondary prevention. Studies were classified as primary prevention if biomarkers aimed at preventing or delaying neurodegenerative disease onset and as secondary prevention if they focused on early detection. Tertiary prevention was not included. Regarding personalization, biomarkers were considered useful for personalized prevention when they enabled risk stratification. In primary prevention, this referred to classifying healthy individuals into distinct risk groups. In secondary prevention, it involved using novel biomarkers or data combinations to improve stratification, supporting more tailored screening and follow-up strategies. Each neurodegenerative disease type was assessed individually.

Context: This review searched for biomarkers that could be applied in clinical or public health settings.

We also had additional inclusion criteria: In terms of study design, we considered all those articles with original research, among which we included umbrella reviews, systematic reviews, meta-analyses, scoping reviews, randomized controlled trials, non-randomized controlled trials, before and after studies, interrupted time series, cohort studies, case-control studies, and analytical/descriptive cross-sectional studies. Editorials and narrative reviews were excluded. Studies should be published in English, and no limitation was defined in terms of geographical region. All the eligibility criteria are available in Supplementary File S3.

2.2 | Data sources and search strategy

The databases searched were Medline and Embase, via Ovid, for articles published between January 1, 2020 and February 21, 2023. Embase preprints via Ovid were also searched between January 1, 2021 and February 21, 2023. The Centers for Disease Control and Prevention (CDC)-authored genomics and precision health publications databases (2023) were also searched.

To optimize the search matrix and select search terms, the freely accessible tools SR-Accelerator and Polyglot Search Translator,[29,30] Citationchaser,[31,32] and Yale Mesh Analyzer[33] were used. Keywords and thesaurus terms were identified, and a pilot study was conducted to refine the search strategy as well as test the literature review software Covidence.[34] Additionally, we consulted experts in the field of neurodegenerative diseases and librarians. Their input helped ensure comprehensive coverage of all relevant terms, publications, and diseases within our study. The complete search matrix is presented in Supplementary File S4.

2.3 | Screening and data extraction

A pilot study was performed to enhance the search strategy, refine selection criteria, and optimize the data extraction sheet. Citations were uploaded into Covidence software,[34] which automatically removed duplicates. To ensure consistency in the interpretation of the criteria, two reviewers screened the titles and abstracts of the first 10% of articles. The remaining articles were screened by a single reviewer. The full-text screening was also conducted by a single reviewer. In contrast, the data extraction phase was carried out by two reviewers for 100% of the records.

The data extraction sheet was developed based on JBI recommendations, including the following information: methods, biomarkers, clinical utility, use of AI, radiomics, digital technology, diseases, prevention type, population in which the research was done, and observations (other lifestyles mentioned, different populations, countries, ethnicity).[35] The concept of AI was constrained to its application in the medical field, mainly encompassing image processing and tools such as machine learning. Additionally, wearable technologies were considered, which refers to personal sensors or computing devices embedded in accessories to provide health-related information about the individuals wearing them.

For primary prevention studies, we also collected information on whether the study accounted for known lifestyle factors (diet, alcohol, air pollution, immunization, obesity, and preventive drugs). The full data extraction sheet is available as Supplementary File S5.

The databases with the results of the review processes were exported as .csv files for subsequent analysis in R (version 4.3.0)[36] to create descriptive maps (bubble plots). The objective was to provide a summary of the integration of biomarkers with lifestyle-related factors in primary prevention studies for the diseases investigated, as well as their presence in studies involving high-risk subpopulations for both types of prevention. In the interest of transparency and open science, the R codes to generate these tables and bubble plots are accessible via https://github.com/phg-foundation/PROPHET.

Summary interactive EGMs were also created using EPPI-Mapper and Python programming language.[37] They are available in the Open Science Framework (https://osf.io/48g5p/), in Repisalud (http://hdl.handle.net/20.500.12105/19630) where they must be downloaded and used following the corresponding instruction, and in Biodama (https://biodama.isciii.es/prophet/) where they can be accessed and used directly online.

3 | RESULTS

The results of the search and the study inclusion process are reported in a flow diagram following the PRISMA-ScR recommendations (Figure 1).[13] The search yielded 2066 articles (2014 studies identified in the bibliographic databases and 52 references from CDC databases and Embase preprints). After removing duplicates, title and abstract screening was done in 1650 papers, of which 458 were selected for full-text review. Finally, a total of 286 papers were selected for inclusion in the scoping review.

The main results are summarized in Table 1. Overall, 79% of the studies reported biomarkers for Alzheimer's disease, 12% for Parkinson's disease, and 8% for multiple sclerosis. For the remaining pathologies, results were scarce. In a Sankey diagram (Figure 2), we provide a general overview of the research on biomarkers for personalized prevention in neurodegenerative diseases and illustrate the over-representation of research on Alzheimer's disease. It is also noteworthy that the body of research is relatively well balanced between primary and secondary prevention. In the case of primary prevention, genetic approaches are particularly prominent, whereas in secondary prevention, imaging techniques tend to assume a more central role. With regard to the field of prevention, 120 papers focused on primary prevention, 149 on secondary prevention, and 17 on both types. While in Alzheimer's disease the total number of secondary prevention studies was higher than primary prevention, in the other neurodegenerative diseases there were more primary prevention papers (Figure 3).

3.1 | Primary prevention

In primary prevention, the most investigated biomarker types were *molecular* biomarkers, with genetic/genomic biomarkers being the most common among them (Table 1). Also, protein-based biomarkers were represented in nearly a quarter of all studies, usually amyloid types and ratios in blood samples (i.e., free, total, and bound amyloid beta (Aβ) 42 and Aβ40 in plasma; Aβ42/40 ratio; total tau (t-tau); and tau phosphorylated at threonine 181 (p-tau181) as surrogates for more expensive or invasive tests. *Imaging* biomarkers ranked second in number of results, with those derived from magnetic resonance imaging (MRI) and positron emission tomography (PET)/single-photon emission computed tomography (SPECT) being the most commonly reported. *Cellular* biomarkers appeared in a single paper, focused on Alzheimer's

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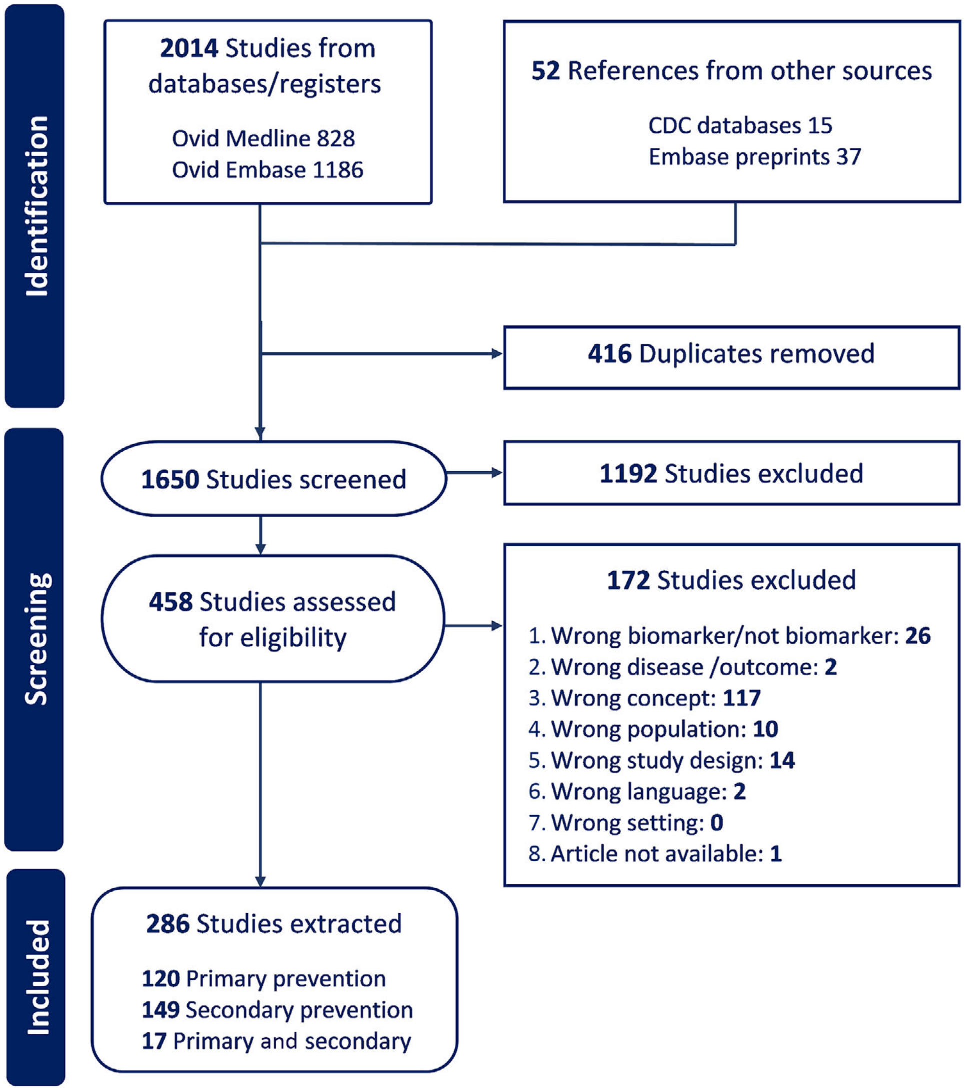

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Of the 2066 articles identified (2014 from Ovid Medline-Embase and 52 references from other databases), 416 duplicates were eliminated. A total of 1650 articles were reviewed based on their titles and abstracts, of which 458 were included. After reviewing the full text, 172 papers were excluded, resulting in a final selection of 286 articles.

disease, which referred to leukocyte cell surface biomarkers as possible biomarkers for both primary and secondary prevention.[38] *Physiological* and *anthropometric* biomarkers had 18 and 15 results, respectively; the commonest were blood pressure and body mass index (BMI), which were often included in predictive models.

In the biomarker review, the majority of the papers took into account known risk factors for these diseases either as possible confounders or – less frequently – as possible effect modifiers. Lifestyle factors were included in 55% of all the papers analyzed; tobacco smoking, alcohol, diet, physical activity, and obesity were often examined together and across various neurodegenerative diseases (Supplementary File S6). Additional factors considered were hearing loss, sleep patterns or disturbances, family history, and air pollution. Limited results were found for Lewy body disease, which primarily focused on the effects of alcohol consumption and tobacco smoking.[39]

With regard to the population in which the research was done, almost 68% of the studies investigated biomarkers in a general population (Supplementary File S7). Additionally, we identified research focused on high-risk populations, including those with diabetes, obesity, and a family history of related conditions. In studies of Alzheimer's disease and vascular dementia, 16% of these considered the *APOE* genotype and the biomarker to stratify individuals based on estimates of their risk for developing the disease.

3.2 | Secondary prevention

In secondary prevention, Alzheimer's disease remained the most studied pathology. Molecular and imaging biomarkers were predominant, mainly those derived from MRI and PET/SPECT for early diagnosis, typ-

TABLE 1 Number of papers found for primary and secondary prevention by biomarker category and neurodegenerative disease.

Biomarker category	Primary prevention								Secondary prevention							
	Total	Alzheimer's disease	Vascular Dementia	Lewy body disease	Fronto-temporal dementia	ALS	Multiple sclerosis	Parkin-son's disease	Total	Alzheimer's disease	Vascular dementia	Lewy body disease	Fronto-temporal dementia	ALS	Multiple sclerosis	Parkin-son's disease
Total	137	90	10	1	0	10	21	23	166	149	1	1	2	2	2	12
Molecular	**122**	**77**	**7**	0	0	**10**	**21**	**22**	**97**	**86**	**1**	0	**2**	**1**	**2**	**7**
Genetics	**94**	**54**	**4**	0	0	**8**	**20**	**18**	**45**	**39**	**1**	0	**1**	**1**	0	**4**
Epigenetics	**1**	**1**	0	0	0	0	0	0	**0**	0	0	0	0	0	0	0
Transcriptomics	**8**	**5**	0	0	0	**1**	**1**	**1**	**8**	**6**	0	0	0	0	0	**2**
Biochemistry	**24**	**22**	**3**	0	0	**1**	**1**	**3**	**21**	**18**	0	0	**1**	0	**1**	**2**
Metabolomics	**6**	**6**	**2**	0	0	0	0	0	**8**	**8**	**1**	0	0	0	0	0
Proteomics	**18**	**14**	**2**	0	0	**1**	**1**	**1**	**51**	**48**	**1**	0	**2**	0	**1**	**1**
Microbiomics	**4**	**3**	0	0	0	0	0	**1**	**1**	**1**	0	0	0	0	0	0
Cellular	**1**	**1**	0	0	0	0	0	0	**2**	**1**	0	0	0	0	**1**	0
Cytology	**1**	**1**	0	0	0	0	0	0	**2**	**1**	0	0	0	0	**1**	0
Hystology	**0**	0	0	0	0	0	0	0	**0**	0	0	0	0	0	0	0
Imaging	**25**	**22**	**3**	**1**	0	**1**	**1**	**3**	**90**	**83**	0	**1**	0	**1**	**1**	**5**
Scan	**1**	0	**1**	0	0	0	0	0	**2**	**1**	0	0	0	0	0	**1**
MRI	**19**	**16**	**1**	**1**	0	0	0	**2**	**74**	**69**	0	**1**	0	**1**	**1**	**3**
PET	**8**	**8**	0	0	0	0	0	0	**25**	**23**	0	0	0	0	0	**2**
Spectrometry	**0**	0	0	0	0	0	0	0	**1**	**1**	0	0	0	0	0	0
Ultrasound	**2**	**2**	**1**	0	0	0	0	0	**1**	**1**	0	0	0	0	0	0
X-rays	**1**	**1**	**1**	0	0	**1**	**1**	**1**	**0**	0	0	0	0	0	0	0
Other	**0**	0	0	0	0	0	0	0	**2**	**1**	0	0	0	**1**	0	0
Physiology	**18**	**15**	**3**	0	0	**1**	**1**	**3**	**19**	**15**	0	0	0	0	0	**4**
Blood pressure	**16**	**13**	**2**	0	0	**1**	**1**	**3**	**7**	**4**	0	0	0	0	0	**3**
Electromyography	**0**	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	**1**
EEG	**0**	0	0	0	0	0	0	0	**9**	**8**	0	0	0	0	0	**1**
Other	**5**	**4**	**1**	0	0	0	0	**1**	**4**	**3**	0	0	0	0	0	**1**
Anthropometry	**15**	**10**	**4**	0	0	**2**	**2**	**3**	**9**	**7**	0	0	0	0	**1**	**1**
BMI	**12**	**7**	**3**	0	0	**2**	**2**	**3**	**9**	**7**	0	0	0	0	**1**	**1**
Body perimeters	**2**	**1**	0	0	0	0	0	**1**	**2**	**1**	0	0	0	0	0	**1**
Other	**3**	**2**	**1**	0	0	0	0	**1**	**2**	**1**	0	0	0	0	0	**1**

Note: The overall sum of the numbers in different categories does not match the total because a single study may assess more than one type of biomarker or cover more than one disease.
Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body max index; EEG, electroencephalogram;MRI, magnetic resonance imaging; PET, positron emission tomography.

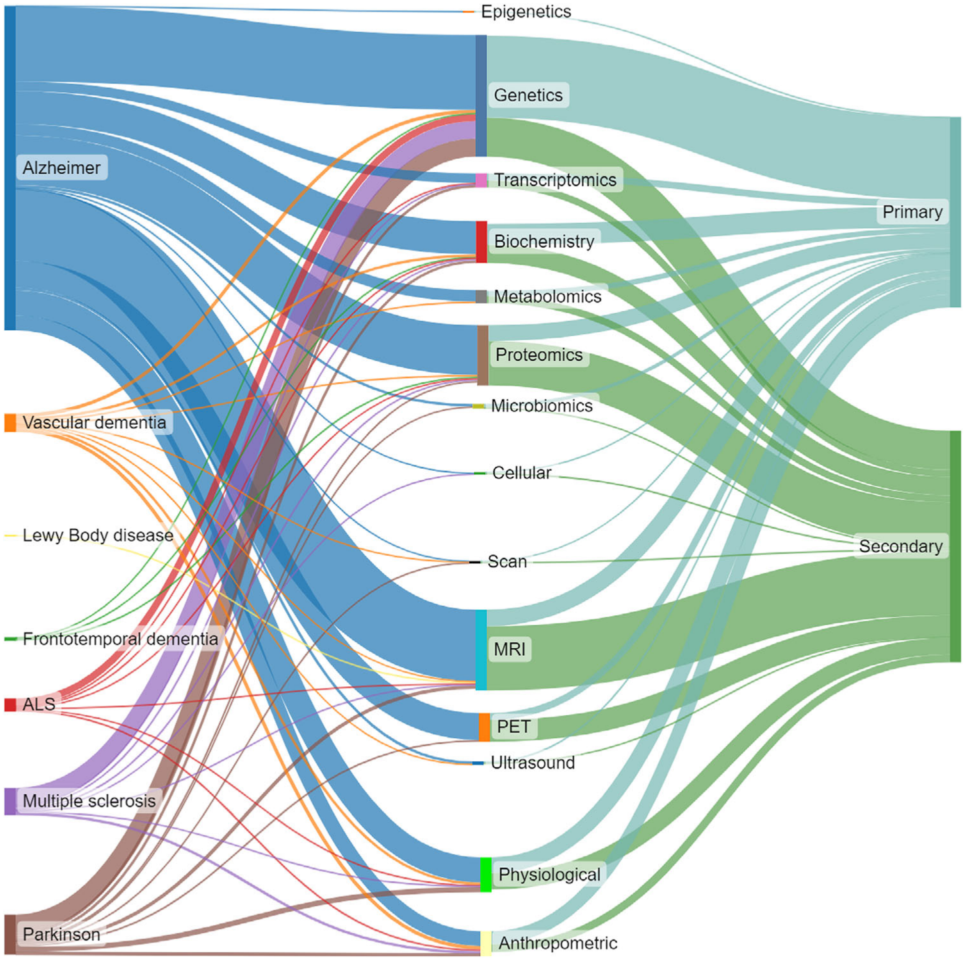

FIGURE 2 Sankey diagram. Biomarkers used in primary and secondary prevention by disease. The nodes on the left correspond to the studied diseases; the nodes in the center are biomarkers categories, and those on the right show the type of prevention. The figure incorporates independent nodes for the main subtypes of molecular and imaging biomarkers, while for the rest a single node represents the whole category. The Sankey diagram reflects the extensive research on Alzheimer's disease compared to other neurodegenerative diseases, as well as the large number of studies focused on genetics and different imaging techniques.

ically included in algorithms, sometimes with AI models.[40] There was still a considerable number, 97 to be precise, of papers that studied molecular biomarkers, in which proteins and genetics/genomics were again the prominent subtypes (Table 1).

In terms of physiological biomarkers, electroencephalogram information was used for the early detection of Alzheimer's and Parkinson's diseases and electromyography in Parkinson's disease.[41–43] Other physiological biomarkers (i.e. blood pressure, BMI, and body perimeters) were also taken into account, but typically just as part of multivariate prediction models.[44]

Almost 76% of the studies were done in the general population (Supplementary File S8), although, as in primary prevention, some authors provided risk estimates of biomarkers within high-risk populations (i.e. those with family history of neurodegenerative diseases, specific *APOE* genotypes or diabetes). In Alzheimer's disease, a large number of papers used biomarkers in subpopulations with mild cognitive impairment (MCI) or subjective cognitive decline (SCD), considered prodromal stages of the disease, with the aim of developing predictive models to detect individuals in whom the disease might progress or to provide an earlier diagnosis.

3.3 | Wearable technology and AI

Regarding wearable technology in primary and secondary prevention, three papers mentioned the use of accelerometers, although only one of them proposed a biomarker based directly on measurements extracted from the device itself (movement pattern, sleep) for a preventive purpose.[45]

AI was widely used – 23.4% of all the included papers – and was mostly applied to imaging biomarkers for both types of prevention, although it was more common in secondary prevention (Table 2). In most cases, authors used AI to develop and improve models for the prediction and early detection of these diseases, which were particularly relevant when there was a well-defined prodromal stage. The use of AI was particularly valuable in this context, as it could analyze large

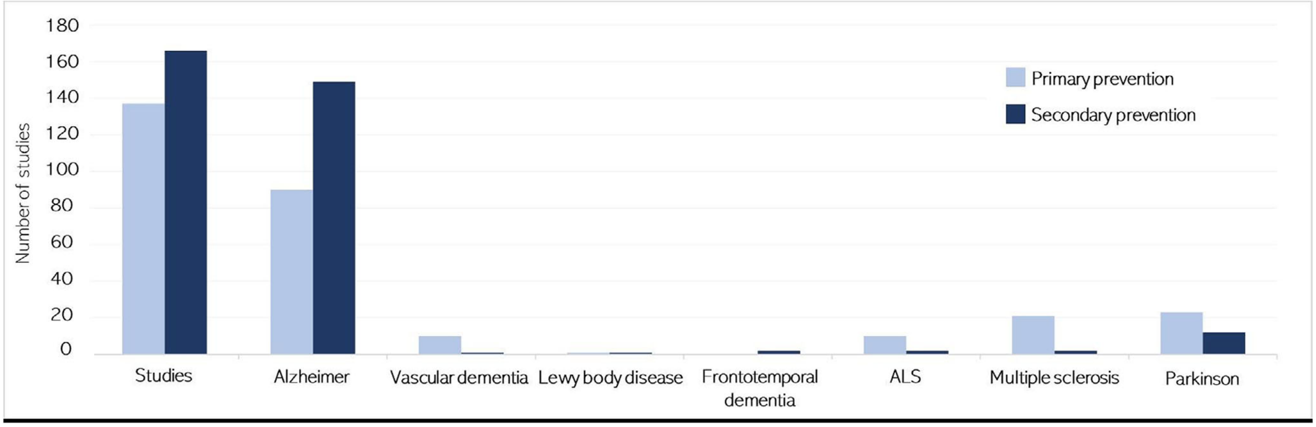

FIGURE 3 Number of studies – primary and secondary prevention – included in the data extraction process, for all neurodegenerative diseases together and for each individual disease. The figure shows that in Alzheimer's disease there are more studies focused on secondary prevention, while in most other neurodegenerative diseases there is more research focused on primary prevention.

and complex datasets to uncover early signals that often go undetected with conventional approaches.

3.4 | Interactive EGMs

We integrated the detailed results of this scoping review for neurodegenerative diseases into three interactive EGMs, which complete the presentation of the results of this work. We present in Figure 4 a snapshot of one of the three EGMs, while their full version can be freely downloaded at http://hdl.handle.net/20.500.12105/19630 and https://biodama.isciii.es/prophet/. The first EGM shows biomarker research (and its gaps) in personalized primary prevention of neurodegenerative diseases, allowing the viewer to see which studies took into account lifestyle-related factors/family risk within the framework. The other two EGMs – one for primary and the other for secondary prevention – also present biomarker research for personalizing prevention and its gaps, but in these cases, reports are classified by the risk subpopulation in which the biomarker has been evaluated, corresponding to the same population groups included in Supplementary Files S7 and S8.

The purpose of these EGMs is to provide a valuable reference tool for researchers in the field. Not only do they offer a graphical overview of research on biomarkers for personalized prevention, they also allow filtering of the results by disease, type of biomarker, or type of study. Additionally, they provide easy access to all the data collected for this study, including the complete bibliographical information of the selected papers, which can be easily downloaded in RIS format directly from the maps.

4 | DISCUSSION

Biomarker research in neurodegenerative diseases has grown substantially in recent years, yet significant gaps remain, particularly for less-studied disorders and high-risk subpopulations. This review provides a global overview of the recent research on biomarkers – both available or under development – for the primary and secondary personalized prevention of neurodegenerative diseases. The scoping review included 286 studies, with the vast majority focusing on Alzheimer's disease, followed by Parkinson's disease and multiple sclerosis, while evidence for other neurodegenerative disorders was scarce. The research was relatively balanced between primary and secondary prevention: In primary prevention, genetic and protein-based biomarkers predominated, whereas secondary prevention relied more on imaging and molecular markers, particularly in prodromal stages such as MCI or SCD. Lifestyle and established risk factors were frequently considered, often as confounders, and some studies targeted high-risk subgroups defined by genotype, comorbidities, or family history. Physiological measures, including blood pressure and BMI, were mainly incorporated into multivariate prediction models, while wearable technologies were rarely explored. AI was applied in almost a quarter of the studies, mostly to enhance imaging-based prediction and early detection models.

To synthesize these findings, three interactive EGMs were created, which highlight key patterns in the literature. The EGMs show that Alzheimer's disease dominates biomarker research, particularly in secondary prevention, whereas other neurodegenerative diseases, such as ALS, frontotemporal dementia, and Lewy body disease, remain largely understudied. Genetic and molecular biomarkers are most frequently investigated in primary prevention, whereas imaging biomarkers predominate in secondary prevention. High-risk subpopulations – such as individuals with specific genotypes, comorbidities, or family history – are examined in only a minority of studies, indicating gaps in targeted prevention research. Lifestyle factors, although frequently considered, are inconsistently integrated into predictive models across diseases. These findings allow readers to grasp key patterns and research gaps directly from the narrative without accessing the interactive maps. While the article draws conclusions from the aggregated evidence, the EGMs remain openly accessible, enabling other researchers to

TABLE 2 Number of studies found using artificial intelligence for primary and secondary prevention by biomarker category and neurodegenerative disease.

	Primary prevention								Secondary prevention							
Biomarker type	Total	Alzheimer's disease	Vascular Dementia	Lewy body disease	Fronto-temporal dementia	ALS	Multiple sclerosis	Parkin-son's disease	Total	Alzheimer's disease	Vascular dementia	Lewy body disease	Fronto-temporal dementia	ALS	Multiple sclerosis	Parkin-son's disease
Molecular	15	13	1	0	0	0	0	1	25	24	0	0	0	0	0	1
Cellular	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Imaging	9	8	0	0	0	0	0	1	58	54	0	0	0	1	0	3
Physiological	2	2	0	0	0	0	0	0	7	6	0	0	0	0	0	1
Anthropometric	2	2	0	0	0	0	0	0	2	2	0	0	0	0	0	0

Abbreviation: ALS, amyotrophic lateral sclerosis.

interrogate the same dataset, explore gaps, and identify priority areas for future biomarker research and tailored prevention strategies.

Building on the evidence highlighted in the EGMs, several clear research gaps emerge. Despite the concentration of studies on Alzheimer's disease, other neurodegenerative disorders remain understudied. Studies integrating multi-modal biomarkers across primary and secondary prevention are scarce. High-risk subpopulations remain underrepresented, and the integration of lifestyle and environmental factors with biomarker data in predictive models is limited. Addressing these gaps should be a priority in future research to enable more comprehensive and equitable strategies for personalized prevention.

Taken together, these findings provide an integrated perspective on biomarkers for the personalized primary and secondary prevention of neurodegenerative diseases. A study may support personalized prevention by using biomarkers to define risk groups – helping to tailor primary prevention efforts. In secondary prevention, the use or combination of new biomarkers can enable improved risk stratification, guiding more targeted screening and follow-up strategies. Within this framework, the role of biomarkers in personalized prevention should not be seen in isolation but integrated with existing knowledge, adding to what we already know.

The most notable finding was the high concentration of research on Alzheimer's disease compared to other neurodegenerative diseases, likely due to its higher prevalence. This imbalance in favor of Alzheimer's disease was even more pronounced in secondary prevention research. In contrast, our results show that there are few biomarkers under investigation for the prevention of diseases such as ALS and frontotemporal dementia, highlighting the need for additional research. In fact, further investigation into their common genetic background could lead to common preventive strategies.[46]

In terms of biomarker type, molecular and, more specifically, genetic/genomic biomarkers were the most investigated. Single nucleotide polymorphisms (SNPs) and polygenic risk scores (PRSs) played a prominent role in the research and were frequently included in multivariable prediction models, usually combined with lifestyle factors, to potentially enhance their performance. We also identified genome-wide association studies (GWAS) aimed at confirming or discovering new genetic factors related to these diseases. In addition, mendelian randomization studies were used to evaluate the potential causal role of several lifestyle-related factors in neurodegenerative diseases such as tobacco smoking for multiple sclerosis[47] or Parkinson's disease,[48] alcohol intake for Parkinson's disease,[48] coffee for Alzheimer´s disease,[49] and other dietary factors for Alzheimer's disease, Parkinson's disease, and ALS.[50–52]

However, there was a notable research gap in the study of gene–environment interactions, as well as in the study of other omics such as the identification of epigenomic or metabolomic biomarkers. Research in these areas could also provide potential biomarkers for the personalized approach to prevention in the future. Image biomarkers were also very relevant for these diseases, in many cases linked to AI-based approaches. In particular, a new term, radiomics,[53] has been coined to describe the extraction of quantitative metrics – so-called radiomic features – typically from raw medical imaging data, which yield new

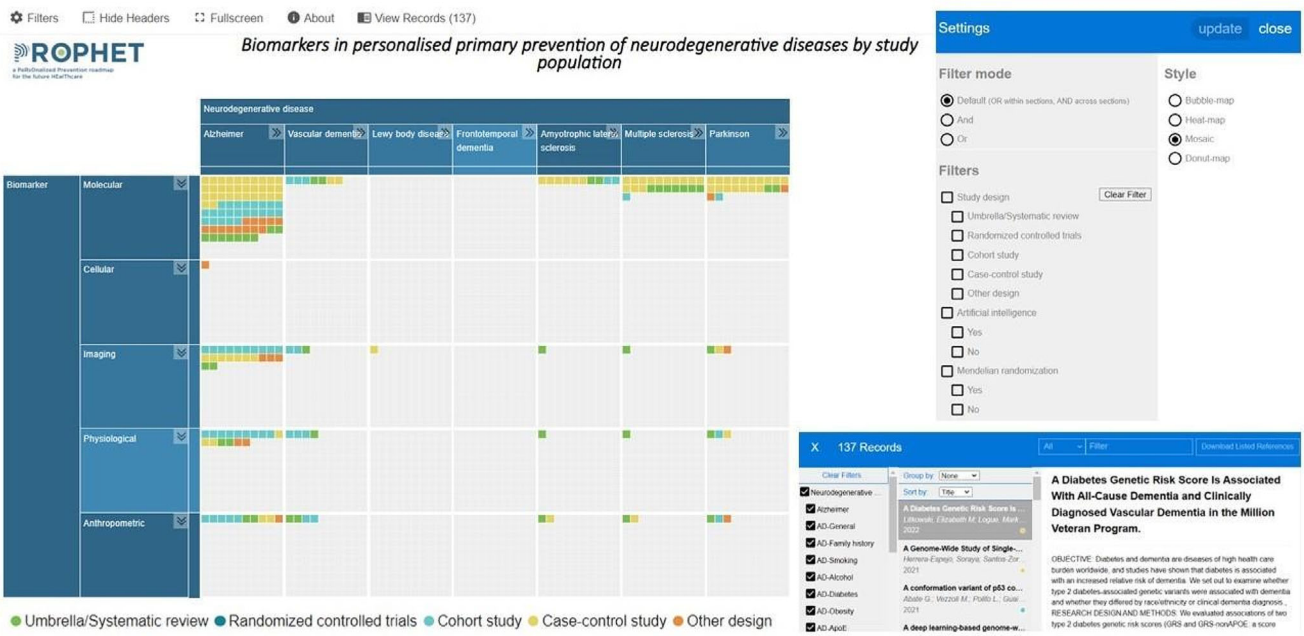

FIGURE 4 Snapshot of one of the three Evidence Gap Maps (EGMs): biomarkers in personalized primary prevention of neurodegenerative diseases by study population. The settings enable filtering by study design, use of artificial intelligence, and mendelian randomization.

features or patterns that are not visible to humans. This approach may help to improve predictive models or to get much more accurate early diagnosis, although there are still limitations that need to be resolved that restrict their use in clinical practice.[54]

It is worth noting that recent research has identified blood biomarkers as possible game changers in the early detection of neurodegenerative diseases, especially Alzheimer's disease. These biomarkers have great potential – in some cases they might provide information comparable to more invasive or expensive standard tests like cerebrospinal fluid analysis and PET – and their possible scalability for wide and effective use could help to improve prevention strategies. However, our search revealed that still very few studies exist exploring the feasibility of their use in a clinical setting, much less their application as tools to personalize prevention; this reflects that there is still a long way to go to translate research into clinical practice.

This review is specifically focused on biomarkers that can be used to personalized prevention. In this sense, biomarkers that help to refine subclassification of individuals within well-known very high-risk populations are especially interesting. For Alzheimer's disease, our research found biomarkers intended to differentiate risk of progression among individuals in prodromal stages – MCI and SCD[55] – but also to subclassify risk among diabetics, who have been identified as another relevant subgroup; some authors even refer to Alzheimer's as Type 3 diabetes because several mechanisms involving impaired glucose metabolism play a role in the etiology and progression of the disease.[56] Similarly, we identified biomarkers that could complement the information provided by *APOE* genotype and family history in Alzheimer's and other dementias. In the context of Parkinson's disease, biomarkers – predominantly genetics and imaging – were sometimes used in subgroup analyses involving idiopathic rapid eye movement sleep behavior disorder.[57]

Classifying biomarker studies into primary and secondary prevention categories has been challenging. Studies investigating specific genetic variants associated with a disease in particular populations have typically been classified as primary prevention. However, the identification of subgroups with varying genetic risks is increasingly being integrated into secondary prevention (early detection). Additionally, biomarkers that help to evaluate the progression of prodromal stages of a disease, such as MCI, could also be considered part of tertiary prevention.

Primary prevention is particularly relevant in neurodegenerative diseases, as treatment options are scarce. Even though the causes of neurodegenerative diseases remain largely unknown, there is evidence that environmental or lifestyle factors – most of them actionable and common to other chronic diseases – may influence their onset.[6,58] Based on this knowledge, classic prevention strategies, such as programs to quit smoking or to maintain an adequate weight, can also be considered "neuropreventive." However, biomarker information – including genetics – when integrated with sociodemographic, lifestyle, and behavioral information, could tailor preventive interventions to help identify individuals in whom the risk of developing a particular disease is increased.

Another important issue in this field of research is external validity. According to our review, most studies were done in a single country; in many cases, this also implies a particular ethnic distribution. Other studies were carried out in a specific hospital and sometimes in specific age/sex subgroups. In many cases, whether the results can be extrapolated to other populations remains a challenge.

Our scoping review has allowed us to provide structured quantitative data on biomarker research in the field of primary and secondary prevention for neurodegenerative chronic diseases for the last 3 years.

Among the strengths of this study we can highlight the EGMs, which allow researchers to access study results interactively and download the literature included in the review in a usable format, the detailed search strategy, reviewed by librarians to ensure robustness, and the incorporation into the analysis of known risk factors and risk groups to obtain a better picture of the possible added value of the studied biomarkers in personalizing prevention. However, some of the variables collected during our data extraction, such as ethnicity or country of origin, age, and gender, were not recorded systematically but only as observations, which could be relevant for personalization. Furthermore, by integrating the EGMs and the scoping results into the narrative, we emphasized the most relevant research gaps and patterns in the evidence, allowing readers to understand key findings without needing to access the maps, while still retaining the option to explore the full data and bibliographic details. Moreover, other important factors, such as education, were not captured at all, which represents a limitation in addressing social determinants of health. Additionally, although we gathered information on the inclusion of lifestyle-related risk factors in the studies, we did not delve into the details of how these factors were integrated into the analysis, but rather only noted their inclusion in the study. Moreover, at this stage, our objective was to map and summarize the landscape of biomarkers applied in personalized prevention, regardless of their clinical utility, something that belonged to the objective of the second phase and, therefore, was not covered in this part.

Scoping reviews are intended to provide a general overview of a field and to highlight gaps, but they do not assess the quality or biases of the included studies or the relative importance of the risk factors explored, and this limitation also applies to our study. Due to time constraints, we conducted a rapid scoping review for which we followed the Cochrane Rapid Review Methods Group's guidelines.[59] In this case, this implied limited double-checking and a relatively short timeframe (2020–2023). However, we believe that this period may effectively have allowed us to explore recent research. In addition, the review included key biomarkers from previous years through the information available in the systematic reviews.

5 | CONCLUSION

There is a pressing need to expand biomarker research beyond Alzheimer's disease to encompass a broader spectrum of neurodegenerative disorders, addressing the critical gaps identified in less-studied conditions such as ALS, frontotemporal dementia, and Lewy body disease. Research should also devote more attention to primary prevention, as well as the integration of lifestyle and environmental factors with genetic and molecular biomarkers, to enhance personalized risk stratification. Investigating gene–environment interactions remains paramount for advancing personalized epidemiological prevention strategies. Biomarker research, particularly in genetics/genomics and imaging techniques, including applications of AI and radiomics, shows substantial promise for both early detection and risk prediction. Future studies should prioritize filling these gaps and developing tailored prevention strategies for complex, chronic neurodegenerative diseases, leveraging tools such as EGMs to guide research priorities, and facilitate access to existing evidence.

AUTHOR CONTRIBUTIONS

Cristina Barahona-López and Elena Plans-Beriso elaborated the first draft. Cristina Barahona-López, Paul Diez-Echave, Orlando Hernández, Chantal Babb-de-Villiers, and Elena Plans-Beriso developed the search strategy. Beatriz Perez-Gomez, Elena Plans-Beriso, and Cristina Barahona-López coordinated and managed the development of this work. All authors reviewed the content, commented on the methods, provided feedback, contributed to drafts, and approved the final manuscript. Beatriz Perez-Gomez and Mark Kroese supervised and led the PROPHET project work package in which this paper is included.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

The data supporting this scoping review are derived from previously reported studies and datasets, which have been cited.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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