

Preferred product characteristics of blood-based biomarker diagnostics for Alzheimer disease



World Health
Organization

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Abbreviations and acronyms

Aβ40	Amyloid-beta 40
Aβ42	Amyloid-beta 42
AUC	Area under the curve
CSF	Cerebral spinal fluid
GFAP	Glial fibrillary acidic protein
GDO	Global Dementia Observatory
HICs	High-income countries
LMICs	Low- and middle-income countries
NfL	Neurofilament light
PET	Positron emission tomography
PPC	Preferred product characteristics
p-tau181	Phosphorylated tau 181
p-tau181	Phosphorylated tau 217
p-tau 231	Phosphorylated tau 231
TDP-43	TAR DNA-binding protein-43
WHO	World Health Organization

Photo credit (next page): A woman seated on a chair in front of a red door outside the Reference Health Centre of Ménakam Mali, 2022. © WHO / Fatoumata Diabaté



1. Global context

Dementia is a syndrome consisting of a range of symptoms associated with a variety of diseases that share the development of progressive neurodegeneration and cognitive decline. Dementia is a major cause of disability and is the seventh leading cause of death globally (1). In 2019, over 55 million people were estimated to be living with dementia (1), out of which 60–70% of cases were caused by Alzheimer disease (2). The Global action plan on the public health response to dementia 2017–2025 (3) (herein referred to as “global dementia action plan”) has the goal of improving the lives of people living with dementia, their carers and families, while decreasing the impact of dementia on them as well as on communities and countries. To achieve that, the plan outlines a range of actions across seven strategic areas for WHO’s Member States, the WHO secretariat and international, regional and national partners to address dementia comprehensively and make it a public health priority (3).

Action area 7 of the global dementia action plan addresses dementia research and innovation. To support countries in this area, WHO has published a blueprint for dementia research (4), identifying gaps and outlining strategic goals with actions and timebound milestones to address those gaps. A specific strategic goal of the blueprint (strategic goal 5 – Development of biomarkers) pertains to the need to develop highly sensitive, specific diagnostic biomarkers for dementia that are cost-effective and can distinguish the underlying diseases that cause dementia such as Alzheimer disease (4).

A key action identified in the blueprint to achieve this goal is the definition of preferred product characteristics (PPC) for diagnostic products for Alzheimer disease and (ultimately) other diseases that cause dementia in order to provide guidance to funders, researchers, product developers and regulatory agencies in the development and implementation of diagnostic tools (4).

2. Public health need

A timely and accurate diagnosis is a prerequisite for accessing services – including appropriate treatment and care, advice about the disease and prognosis, as well as support for families and care partners (3). A timely and accurate diagnosis potentially allows for early intervention, action on modifiable risk factors, management of symptoms, planning for the future, maintenance of independence and postponement of institutionalization (5). Currently, a diagnosis of Alzheimer disease (and other diseases that cause dementia) is based on clinical judgment which can be supported by imaging techniques and laboratorial analysis of cerebrospinal fluid (CSF) (6-8). However, there is a global shortage of qualified health professionals to perform extensive clinical evaluations, while access to imaging and CSF analysis is similarly limited due to high associated

costs and lack of infrastructure and workforce capacity. Access to Alzheimer disease diagnostics is even more limited in low- and middle-income countries (LMICs), where the size of the specialized health-care workforce is significantly lower compared to that in high-income countries (HICs) and health system infrastructure and funding are unable to provide such services sustainably to populations (9).

In most countries, primary care facilities are the first point of contact for a person presenting with cognitive complaints. However, given the scarcity of resources and training, 75% of people living with dementia are not diagnosed – a proportion that can reach 90% in some LMICs (5). Indeed, the Global Dementia Observatory (GDO) shows that the action plan's global target of at least 50% of countries reaching a dementia diagnostic

Photo credit: Elderly couple smile and stand beside a car in Rudaki District Primary Health Centre, Tajikistan, 2023. © WHO / Mukhsin Abidzhanov

rate of at least 50% by 2025 is unlikely to be met. According to GDO data, fewer than half of the countries (29/62 or 47%) are able even to report on dementia diagnostic rates, thereby not fulfilling the first condition of the global target (1). This is of concern insofar as countries submitting data to the GDO tend to be more "dementia-ready". Once GDO data collection is expanded to countries that are less dementia-ready, the percentage is likely to decrease. Further, among the 29 countries contributing their diagnostic rate data there is considerable variability by country income, with the median diagnostic rate for HICs being 58% compared with 21% for LMICs (1).

The large diagnostic gap, especially in LMICs, is particularly concerning because the expected global increase in dementia prevalence is heavily driven by an increase of dementia incidence in these countries (10). The large dementia diagnostic gap is a result of the scarcity of a health workforce that is appropriately trained to diagnose dementia (1, 9) and the scarce availability of diagnostic markers for diseases that cause dementia such as Alzheimer disease and other neurodegenerative conditions. As such, building workforce capacity and developing easy-to-use, safe, accessible and reliable biomarkers

will enable countries to respond to the growing need for accurate and timely diagnosis. Recent advances in the identification and measurement of fluid biomarkers are paving the way for the development of new diagnostics (11-13); however, these advances have been limited to fluid biomarkers associated with Alzheimer disease. Biomarkers for other diseases that cause dementia (e.g. dementia with Lewy bodies and neurodegenerative diseases associated with TAR DNA-binding protein-43 [TDP-43]) require further research.

Given the limited evidence on fluid biomarkers for the diagnosis of other diseases that cause dementia, this PPC focuses on the preferred characteristics for the development of diagnostics using fluid biomarkers to aid the diagnosis of Alzheimer disease. Moreover, given the robust performance of tests using blood as preferential fluid for investigation of biomarkers and other associated benefits (see section 5) the focus of this PPC is on the use of blood-based biomarkers for Alzheimer disease.



3. The purpose of WHO preferred product characteristics

WHO PPCs are technical documents that define the preferred attributes of diagnostic products for regulatory purposes, policy and programmatic implementation. PPCs can be used to inform product developers, regulatory agencies, procurement agencies and funders on research and development and public health priorities. PPCs target entities that intend eventually to seek WHO policy recommendation and prequalification for their products. WHO PPCs account for access, equity and affordability at all stages so that future diagnostic products can be used globally, including in LMICs.

WHO PPCs are intended to encourage innovation and promote development of products for use in settings that are most relevant to global unmet public health needs. WHO's objective is to promote the development of diagnostic products with optimal effectiveness and suitability for use in LMICs, recognizing that access, equity and affordability are integral parts of the innovation process and should be considered at all stages.

4. WHO's vision and strategy on the use of blood-based biomarkers for diagnosis of Alzheimer disease and dementia

Evidence suggests that certain diseases that cause dementia such as Alzheimer disease are the consequence of progressive, neurodegenerative processes that start decades before clinical symptoms manifest (4). Consequently, early identification of pathological markers can create opportunities for modification of clinical trajectories. In the future, it is hoped that the use of a single biomarker or a combination of biomarkers can be implemented upon minimally acceptable clinical evaluation, enabling clinicians to distinguish confidently between disease subtypes (e.g. dementia with Lewy bodies, Alzheimer disease, vascular dementia), and that results would also reflect disease progression or severity. Achieving this will require major scientific advances.

Most people living with Alzheimer disease currently reside in LMICs where the health system infrastructure is not prepared to deal with the estimated increased rate of dementia (1). Therefore, developing diagnostic products from an equity perspective means taking into consideration the capacity of different countries to implement such tools, and ensuring that these are not developed on the basis of the capacity in high-resource settings.

In many LMICs, access to a specialized neurological workforce and memory clinics is limited at best and most people who are seen in primary care settings are unlikely to be referred to specialists for further investigation (9). When referrals are possible, waiting times can reach several months or years in many countries (5). It is critical, therefore, to seek to develop diagnostic tools that can support the non-specialized health-care workforce, as well as specialists (e.g. neurologists, geriatricians, old-age psychiatrists), in their clinical decision-making, and that can be readily implemented in low-resource settings. To achieve this, diagnostic products should have the highest possible sensitivity and specificity, allowing health-care providers confidently to rule in patients who are likely to have Alzheimer disease and to rule out those unlikely to have it, ultimately optimizing referral systems and further investigations and decreasing the burden on health systems.

This WHO PPC is a timely publication to promote the development of diagnostic products using emerging technologies and to ensure that these will not only exhibit optimal clinical performance but will also be relevant to different populations, affordable and available to those who need these products. See Annex 1 for a description of the development process of this WHO PPC.

5. State of the art on Alzheimer disease biomarkers

Science supporting the use of fluid biomarkers to aid the diagnosis of Alzheimer disease has rapidly advanced in recent years. Tests involving biomarkers found in the CSF are currently used in some countries, both in memory clinics and research, with some having received regulatory approval (14). To date, biomarkers found in blood – commonly referred as blood-based biomarkers – have demonstrated, in research contexts, that they can accurately identify and quantify markers of pathophysiological processes in disease development (11, 12). Given the strong correlation found in most cases between biomarker measurement in blood and in CSF, the use of blood is preferred over CSF due to its safer sample collection, reduced need for specialized workforce and lower infrastructure requirements (14). Moreover, blood collection is inexpensive, scalable and allows for serial collection if needed (15).

Photo credit: Elderly couple sitting on a sofa in their home in Lima, Peru, 2018.
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This is particularly relevant in the case of widespread implementation in many LMICs where appropriate infrastructure and trained personnel are scarce (1, 9). As such, the following evidence is based on blood/plasma unless there is specific reference to CSF.

Different blood-based biomarkers are currently being explored and are used in research settings. These biomarkers include plasma amyloid-beta 42/40 ($\text{A}\beta_{42}/\text{A}\beta_{40}$), plasma phosphorylated tau (p-tau181, p-tau217 and p-tau 231), plasma neurofilament light (NfL) and plasma glial fibrillary acidic protein (GFAP) (11, 12, 16).

Clinical research suggests that p-tau isoforms show high performance in identifying Alzheimer disease, with p-tau217 showing promising results regarding its association with $\text{A}\beta$ pathology and ability to detect abnormalities sensitively even before imaging techniques such as positron emission tomography (PET) (11, 17). Given its high performance, the measurement of p-tau217 is currently being explored as a means to classify patients accurately and reduce the need for confirmatory PET tests or CSF tests on p-181, $\text{A}\beta_{42}$ and $\text{A}\beta_{40}$ (13, 16).

The use of plasma $\text{A}\beta_{42}/\text{A}\beta_{40}$ has been shown to be effective in measuring $\text{A}\beta$ pathology in individuals at pre-symptomatic stages; however, challenges with small fold changes between $\text{A}\beta$ -positive and $\text{A}\beta$ -negative individuals and difficulty in standardizing and maintaining the stability of such tests over time are barriers to its clinical implementation (12, 16).

Plasma NfL is commonly considered as a nonspecific marker of neurodegeneration. Research suggests that it can potentially be used as a prognostic marker of cognitive decline (15) and may also be relevant to supporting diagnosis

of other diseases, including frontal temporal dementia (18). Nevertheless, more research is needed to understand its specific association with disease development given the multiple potential age-related and neurological changes in people above 70 years of age (16). Additionally, elevated plasma GFAP has been associated with abnormal presence of amyloid plaques and neuronal damage (11, 19).

The performance of specific tests being investigated varies significantly and tests with measurements of certain analytes appear to perform better compared to others. For example, current $\text{A}\beta_{42}/\text{A}\beta_{40}$ assays demonstrate an area under the curve (AUC) associated with amyloid PET status ranging from approximately 0.70 to 0.85 (20, 21). Recent studies have shown that assays based on phosphorylated tau, particularly p-tau217, typically have even better performance, with AUC often well above 0.90 (11, 13, 22).

Despite showing high performance and clear potential benefits for implementation in routine clinical practice, it is important to note that current blood tests for Alzheimer disease are being investigated in highly resourced, carefully controlled clinical settings and in populations with limited diversity (4). The real-world implementation of Alzheimer disease blood tests on a large scale must be validated, especially in view of the varied clinical context in which they will be utilized, particularly in LMICs.

6. Considerations for implementation

6.1 Target population

Prevalence rates of Alzheimer disease increase significantly with age – by a factor of 1.6–1.9 for every 5-year age increment after the age of 60 years (1) – and some groups are at increased risk of developing Alzheimer disease due to exposure to risk factors and genetic backgrounds (23). The lack of workforce capacity to perform comprehensive dementia evaluations, as well as a misconception that early cognitive decline is a normal consequence of biological ageing, makes it imperative to develop tools that can provide quantitative and qualitative evidence to support clinical decision-making.

Primary health-care providers are usually the first point of contact for people with symptoms

of cognitive decline and, given the promising role of blood biomarkers for Alzheimer disease, their development for use in the population seeking such type of care should be a strategic priority.

Considering that current evidence on blood-based biomarkers for Alzheimer disease has been gathered mainly through research cohorts from specific backgrounds (i.e. white populations of European origin), further studies are needed to improve understanding of how they vary in people of different races and ethnicities, including Indigenous peoples and underrepresented groups.

- the cost of equipment and chemical reagents;
- the physical infrastructure;
- transport and distribution systems;
- storage conditions;
- workforce availability and expertise, including clinical and laboratory capacity;
- sample types and their stability;
- accessibility, including availability and affordability; and
- simplicity of use.

Moreover, appropriate technical guidance must be developed and adapted to take account of local contexts.

Ensuring that these tools can be implemented in low-resource settings will contribute to a decrease in the diagnostic gap in underserved communities, promote timely and accurate diagnosis and increase the cost-effectiveness of interventions. These factors reflect a commitment to equitable access to health care that does not depend on the geographical, local and financial situation and that represents a significant step towards a more inclusive and effective approach to supporting people with Alzheimer disease worldwide.

6.2 Global access

It is crucial to develop diagnostic tools for Alzheimer disease that are accessible and can be easily adapted and implemented in LMICs. In fact, over 60% of people currently living with dementia reside in LMICs and this is also where the largest increase in dementia cases is expected (1).

As diagnostic tools are being developed, several technical and practical issues must be considered to avoid limiting the implementation of the tools only to well-resourced settings. Factors that must be considered include:

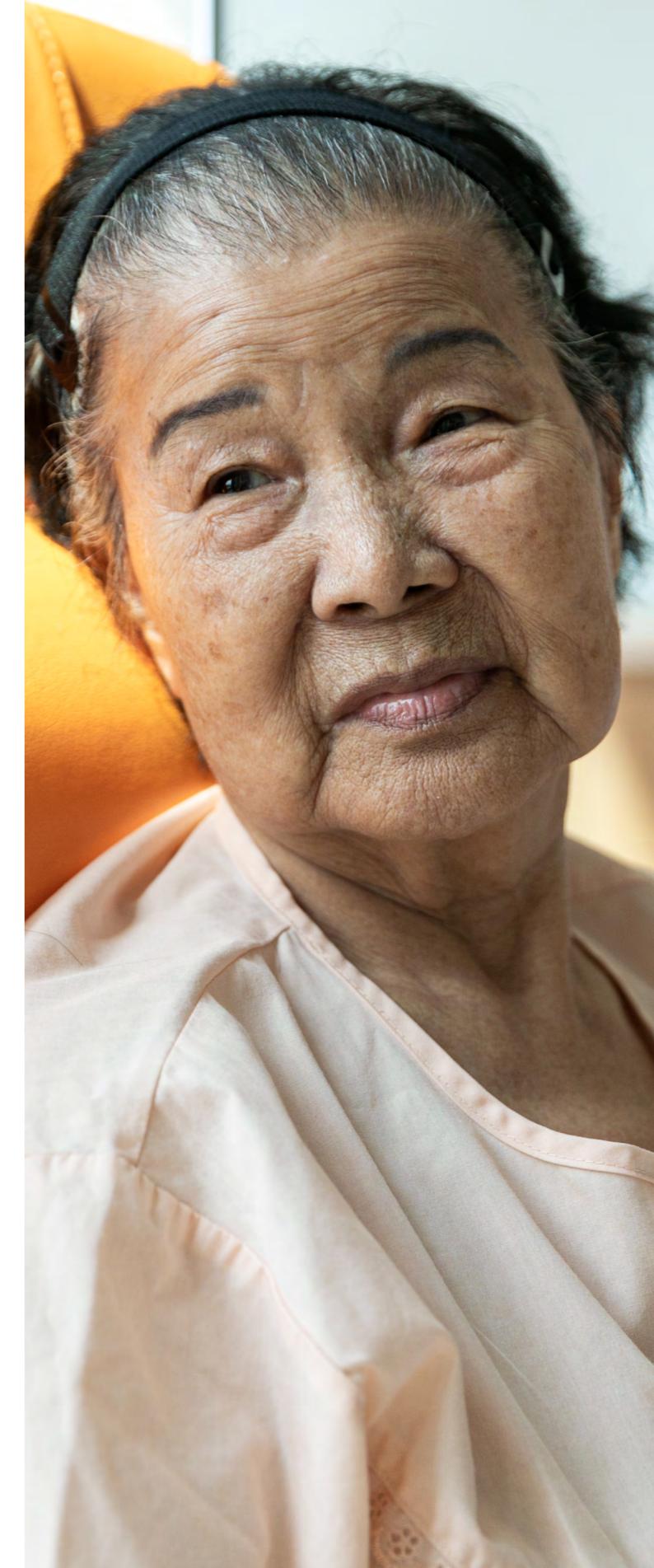


Photo credit:
A serene elderly woman relaxes in an orange chair at the Outram Community Hospital, Singapore, 2021.
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6.3 Post-diagnostic support

With only four medicines currently available internationally for Alzheimer disease (three acetylcholinesterase inhibitors and one N-methyl-D-aspartate receptor antagonist – all symptomatic treatments with no disease-modifying properties), pharmacological treatments for the disease remain limited. Additionally, these medicines are inequitably available around the world with medicines for on-label use being more commonly available and affordable in HICs than in LMICs. According to GDO data, generic versions of medicines for Alzheimer disease are available in most HICs (85%) compared to less than 60% of LMICs (1). The United States Food and Drug Administration's approval of three monoclonal antibodies with disease-modifying properties, with additional medicines in the pipeline, may provide people living with Alzheimer disease with additional options for treatment (24). However, current associated costs and infrastructure needs may increase inequity. At present, given the limited efficacy and accessibility of available medicines, the care of people living with a dementia diagnosis should be focused on maintaining quality of life and ensuring that the person, their family and their carers have the resources and support that they need as the condition progresses (6, 7). Therefore, in line with the global dementia action plan, improving access to diagnostic tools should be paired with increased access to post-diagnostic support (3).

Although there is currently no cure for Alzheimer disease, a timely diagnosis can facilitate access to post-diagnostic support as well as guide family decision-making. Post-diagnostic support can optimize the physical health, cognition and well-being of persons living with dementia, significantly improving the lives of these persons and their caregivers (6). Non-pharmacological interventions can produce positive effects on cognitive function and depressive symptoms as well as on everyday function, quality of life and overall dementia rating/severity with small-to-large magnitude and overall low-to-moderate certainty (7).

When using blood-based biomarkers for the diagnosis of Alzheimer disease, post-diagnostic support should include an explanation of the biomarker results. These should include the interpretation and limitations of blood-based biomarker findings, in addition to following evidence-based recommendations for delivering a dementia diagnosis (e.g. [mhGAP](#) or any other national/international evidence-based dementia guidelines), performing regular medical reviews

and providing ongoing support (e.g. mhGAP intervention guide (6)). Additional post-diagnostic support and care services should be offered across the entire continuum of care, including treatment (pharmacological and non-pharmacological), rehabilitation and palliative care (3).

WHO has developed several tools to support countries in providing post-diagnostic support, as well as resources that can be used by communities, people living with dementia, carers and families.

The tools include the following:

- The mhGAP guidelines and intervention guide includes a specific dementia module that gives evidence-based recommendations for the diagnosis and management of dementia by non-specialist health workers (6, 7).
- Integrated care for older people (ICOPE) toolkit provides guidance for person-centered assessment and pathways in primary care. It helps community health workers to implement the recommendations outlined in the ICOPE guidelines and assists inter alia with screening for loss in a range of domains of intrinsic capacity, including cognitive impairment (25, 26).
- iSupport for dementia provides training to carers on what dementia is and how to respond to common challenges of caregiving (27). iSupport includes five modules on: 1) introduction to dementia; 2) being a caregiver; 3) caring for me; 4) providing everyday care; and 5) dealing with behavior changes.
- The Dementia toolkit for community workers in low- and middle-income countries is a guide for community-based management and care of people with dementia developed by WHO's Regional Office of the Western Pacific (28).
- Towards a dementia-inclusive society: WHO toolkit for dementia-friendly initiatives supports individuals, communities and countries in raising awareness of dementia and empowering people living with dementia to remain in, and be a significant part of, their community. The toolkit provides practical guidance and tools to support efforts, including planning and implementation activities, to create dementia-inclusive societies (29).
- WHO's Package of interventions for rehabilitation outlines the most essential interventions for rehabilitation for 20 health conditions, including dementia, that have high prevalence and high levels of associated disability (30). The package also includes information on workforce needs and the assistive products, equipment and consumables required to deliver the interventions.

7. Perspectives of people with lived experience



Implementation processes should take account of the perspectives of people with lived experience in order to ensure suitability and uptake. Ten individuals living with dementia from Australia, Canada, Germany, Ireland, Namibia, New Zealand, Singapore, and the United States of America were involved in the development of this PPC (see [Annex 1](#)). Their perspectives on the use of blood-based biomarkers are briefly summarized below and may not necessarily reflect or represent the views of all people with lived experience.

Given the sensitivity and potential impact of test results, people living with dementia recommend that the blood test should be offered only to symptomatic individuals and should be used in conjunction with other diagnostic tools. In addition, if third parties (e.g. insurance companies) are granted access to test results, it is imperative to consider how this information could affect a person's livelihood. People living with dementia also shared that the use of blood-based biomarkers could support a timely diagnosis of Alzheimer disease which could greatly benefit a person's quality of life. However, although a dementia diagnosis can support quality of life and access to care, dementia is still highly stigmatized globally. Consequently, people living with dementia recommend that efforts to increase diagnostic rates should be paired with programmes and initiatives to combat stigma and raise awareness about dementia.

To ensure suitability and uptake, people living with dementia recommend that patients should be appropriately supported throughout the diagnostic process, provided with accessible information so that they can make an informed choice about taking the test, and the test should be accessible and affordable to all who are eligible ([Annex 2](#)). Additionally, unless the test is administered by clinicians trained in dementia care and appropriate post-diagnostic services are in place, making blood-based biomarkers for the diagnosis of Alzheimer disease widely available could potentially cause more harm than good. [Annex 2](#) presents additional perspectives and preferences of people living with dementia on the potential use of blood-based biomarkers as well as the need for access to post-diagnostic support.

Photo credit (previous page): A man stands next to his herd of cattle in Kukufami, Kenya, 2022. © WHO / Billy Miaron

8. Preferred product characteristics

Intended use

Preferred characteristic

- Aid the diagnosis of Alzheimer disease

Rationale

- Alzheimer disease is the most common disease that causes dementia. Its characteristic pathophysiology can be detected by blood-based biomarkers.
- The pathology of most other causes of dementia is not yet readily detectable with available blood-based biomarkers.

Notes

- Further guidance may be published for other diseases that cause dementia as scientific knowledge progresses.
- For the purpose of this PPC and diagnostic use case, the test should not be used for: 1) disease staging evaluation; 2) disease-modifying therapy efficacy evaluation; and 3) direct-to-consumer tests.
- Further guidance may be published for other intended uses as scientific knowledge progresses.

Target population

Preferred characteristic

- Individuals with cognitive impairment consistent with the ICD-11 definition¹, established by a trained health-care professional. Cognitive symptoms are progressive and represent a decline from previous cognitive function (see notes for details).
- Exclusion criteria: For this PPC, individuals without established cognitive impairment as described above, as well as individuals undergoing treatment with disease-modifying therapies or participating in clinical trials for such therapies should not be offered the test for the intended use described.
- Tests should be developed in the knowledge that in many LMICs, access to specialists is limited and cognitive assessments will be performed by a non-specialist workforce. Training, expertise, time, and access to validated cognitive assessment tools may vary.

Rationale

- The target population should be offered the test to determine the likelihood of Alzheimer disease pathology.
- Current technologies being investigated in research settings show strong potential to be implemented in this use case, with high accuracy and clear potential to scale up.
- Non-specialist health-care providers should seek to identify possible cases of dementia caused by Alzheimer disease in the primary health-care setting and in the community after

appropriate training and awareness-raising. Brief informant assessment and cognitive tests should first be used to determine whether biomarker testing would be helpful in diagnosis (6, 7).

Notes

- The symptoms consistent with the ICD-11 definition include a slow but steady decline from a previous level of cognitive functioning with impairment across multiple domains, such as memory, executive functions, attention, language, social cognition and judgment, psychomotor speed, visuoperceptual or visuospatial abilities. Alzheimer disease may be accompanied by mental and behavioral symptoms such as depressed mood, apathy, and irritability.
- Guidance on exclusion criteria refers to the use case of this PPC and further guidance may be published if future tests show appropriate performance for the excluded population.
- Current tests still lack thorough validation in LMICs and in populations with diverse genetic backgrounds and different exposures to health determinants.
- The test should be prescribed only by a trained health-care professionals after a clinical evaluation (e.g. following the WHO mhGAP intervention guide (6); it should not be offered without prior clinical assessment as this would affect interpretation of the test (e.g. the predictive value varies by symptom severity).

¹ Other criteria such as the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) criteria may also be considered when relevant.

Accessibility and affordability

Preferred characteristic

- Tests must be easy to use in primary care and community settings (especially in LMICs) and should enable easy interpretation of results.
- Tests must be affordable and cost-effective in comparison with the standard diagnostic workflow in local practice.

Rationale

- Accessing such diagnostic tests should not drive individuals and families into financial hardship – i.e. paying more than they can afford to access a diagnostic service.
- The majority of people with Alzheimer disease currently live in LMICs and the most rapid increase in prevalence will also take place in LMICs.

Notes

- Barriers to access such tests in countries, including HICs, also include the high associated cost. It is vital that prices are affordable across all regions and countries and tests should be cost-effective regardless of where they are being performed.
- Costs of tests should not increase the gap of what can be performed in HICs compared to LMICs.
- Cost-effectiveness calculations should include the capital cost of the platform, revenue kits, associated costs of sample handling and training personnel.

- Serum analysis is possible and can be informative but currently yields lower concentrations for specific analytes.
- In specific cases, where appropriate safety and hygiene are available and trained personnel and infrastructure are in place, CSF and/or

- amyloid PET may be used for confirmatory testing and analysis of additional biomarkers.
- The use of dried blood and plasma spots is a promising alternative but requires extensive development and validation to achieve a performance similar to that achieved by blood/plasma.

Specimen type

Preferred characteristic

- Peripheral blood.
- Dried blood or plasma spots (see notes).

Rationale

- Blood collection is minimally invasive compared to other fluids such as CSF.
- Most health facilities have personnel able to perform blood sample collection.
- Training for sample collection is relatively simple.
- Among the fluid biomarkers available or being investigated, peripheral blood has demonstrated similar performance compared to CSF, which requires a more invasive collection procedure.

- Blood sample collection is inexpensive and serial collection in short intervals is feasible when needed.
- Blood sample collection is scalable.
- Blood samples can be easily stored and transported.
- The use of dried blood spots would not require immediate access to centrifuges and ultra-low-temperature freezers, drastically facilitating and expanding the use of blood-based biomarkers in locations/facilities lacking such infrastructure.

Notes

- Different anti-coagulants should be evaluated and validated for maximum biomarker stability.

Intended user and use setting

Preferred characteristic

- Sample collection and testing should be performed by trained health-care professionals and laboratory technicians.
- Sample analysis should be performed solely by certified laboratories.
- Outcome assessment and advice should be done by a health-care professional who is appropriately trained to interpret results and conduct referrals to a specialist as needed.

Rationale

- Peripheral blood collection is suitable in most, if not all, care settings, including low-resourced primary care.

- Estimated demand is unlikely to require analysis to be performed in all local health facilities (including primary care facilities).

Notes

- Sample analysis is recommended to take place initially in centralized laboratories and coverage should be expanded as demand increases.
- Sample collection should be performed in settings with blood collection capacity with appropriate safety and hygiene conditions, allowing for collection in different settings, including at home, long-term care facilities and other community level facilities.

Reagents characteristics

Preferred characteristic

- Preferably and where possible, reagents should be stable at room temperature and refrigerated conditions, with minimum freezing required for both shipment and storage.
- To the extent possible, reagents should be supplied in individual, self-contained cartridges to avoid spoiling and expiration.

- When possible, reagents for buffers and other components of large volume should be supplied in dried or lyophilized forms for on-demand preparation and reconstitution.
- Ensure stringent reagent quality control measures so that reagent performance does not vary significantly between batches or lots, with effective reagent packaging that promotes reagent stability and prolongs shelf-life.

Rationale

- Many LMICs do not have sufficient infrastructure to transport and maintain appropriately reagents that require refrigerated or extremely low temperatures.
- The demand for tests can vary depending on a country's context and demographics.

Power requirements, stability and storage

Preferred characteristic

- Basic electricity is required for the functioning of equipment, preferably with emergency or back-up batteries.
- Appropriate guidance from manufacturers should inform users about optimal processing steps and stability of samples, as well as storage requirements of processed samples prior to test performance.
- Reagents should be stable at room temperature and refrigerated conditions and minimum freezing required.
- Appropriate logistics for reagent delivery should be made available.

Rationale

- Electricity is required across several steps, from maintenance of reagents and samples to functioning of test equipment.

Notes

- Alternative power sources should be considered (e.g. solar panels in locations with unstable electricity supply).

refrigerated or extremely low temperatures.

- The demand for tests can vary depending on a country's context and demographics.

Training, capacity and mandate for the workforce

Preferred characteristic

- Health-care professionals requesting the tests should have the clinical mandate to do so and should be appropriately trained to determine the target population (see **Target population** above).
- Sample collection must be conducted only by appropriately trained professionals.
- Test performance should require trained laboratory technicians to run the test.
- Health-care professionals disclosing the test results should be appropriately trained and able to discuss the meaning of results as well as to provide post-diagnostic support.

Rationale

- While regulatory requirements may differ between countries, the ordering of tests and patient assessment must be performed by appropriately trained health-care professionals.
- Laboratory procedures for running the tests should require a type of training similar to that required for conventional and routine blood tests to allow for global implementation.

Notes

- Assays should be automated as much as possible to facilitate implementation in low-capacity settings.

Technical support for equipment

Preferred characteristic

- Technical support should not rely on highly specialized staff, and clear guidance should be provided for troubleshooting of equipment.
- Training for basic maintenance should be provided.
- Local and/or remote technical support should be available in different languages and should be easily accessible and affordable.

Rationale

- Field engineers should preferably be available within a week to provide more complex support and maintenance.

Technical guidance

Preferred characteristic

- Technical guidance (clinical and neurochemical) must be provided for the appropriate interpretation of results associated with clinical information of the patient.
- Clear guidance for the interpretation of test outcomes should be provided, including potential variation originating from age, sex, genetic mutations, medications, comorbidities, local/regional factors and disease stage.
- Tests must be validated according to the age range, country/region and sex in which they are being used – with clear understanding of reference values.

Rationale

- Test outcomes should give a clear indication to health-care professionals of the next steps, (e.g. rule in/rule out, need for referral and further investigation). Guidance should be provided by the manufacturer.
- Variations may be observed for several reasons and these need to be evaluated and guidance provided to avoid misinterpretation of results.

Notes

- Web and mobile applications could be available to support test interpretation. If patient information is used on such Web-apps, it must be protected.

Clinical performance

Preferred characteristic

- Minimum sensitivity and specificity of 90% when compared with a valid reference standard (e.g. neuropathology, amyloid PET or approved CSF assays) in the target population and for a diagnostic use case.
- Validation and assessment of clinical relevance and performance of the biomarker tests must be conducted in the intended use setting, especially in LMICs, in addition to studies in more highly controlled environments.
- The assay should minimize, as far as is possible, the proportion of indeterminate and invalid results.

Rationale

- Evidence demonstrates that current methods using blood biomarkers achieve similar outcomes to those of other established

methods using CSF or PET imaging. Therefore, tests using blood biomarkers should have similar performance as demonstrated in the research environment, in diverse, real-world settings (e.g. everyday clinical practice).

- With comparable outcomes of other established methodologies, the use of blood biomarkers presents an unprecedented opportunity to improve access to Alzheimer disease diagnostics globally.

Notes

- Sufficient analytical performance (e.g. in terms of measurement precision, accuracy, reagent stability) needs to be demonstrated according to standard guidelines.



Photo credit (next page): A health worker takes a blood sample at the National Reference Laboratory in Dushanbe, Tajikistan, 2023.
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Annex 1

Development of this preferred product characteristics

Needs assessment and conceptualization of document

This PPC was developed following the WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles: Standard Procedure, second edition, 2024. The need for a PPC was assessed in October 2022 and confirmed within WHO. Following a landscape analysis using robust WHO methodology (1), an initial working draft of the PPC was prepared.

Declarations of interest of the PPC Development group

The WHO Secretariat established a PPC Development Group of 20 leading scientists and experts, with due attention to geographical and gender representation. All members completed the WHO declaration of interests form. WHO processes were used to assess declared interests and to manage any conflicts of interest. Ten experts declared potential competing interests, including unpaid work with nongovernmental organizations, grants for blood-based biomarkers research, non-financial collaboration with pharmaceutical and biotechnology companies and holding intellectual property rights on topics unrelated to this PPC. After review and due diligence by the WHO Secretariat, it was concluded that these interests were relatively minor and did not interfere with the development of this report.

Drafting of document

In December 2023, all members of the PPC Development Group received the working document and met in a virtual expert consultation to discuss the topics related to the PPC. In February 2024, a second expert consultation with the PPC development group was held to continue the discussions on the topics and PPC parameters in order to develop a next draft. In March 2024, all PPC development group members received the proposed next draft and met virtually to define their rating of agreement regarding the preferred characteristics described in section 8 of this document. Rating of agreements followed a scale of: 1, agree; 2, agree with comments/suggestions; 3, disagree; 4, abstain. The level of agreement for each characteristic (considered as all "agree" or "agree with comments/suggestions" votes) was high, averaging 98% and at least 93% for every item. The WHO Secretariat reviewed all comments received by group members and revised the PPC as relevant to address concerns, incorporate suggestions or clarify language to avoid ambiguity or misunderstanding of intent.

Public consultation

Between April and May 2024, the revised draft was posted online for public consultation (2) for over 28 days with announcements on mailing lists and social media by the WHO Secretariat. Anyone could respond by completing a standard WHO submission form, identifying themselves and listing their comments and suggested amendments. A total of 18 individuals or organizations submitted comments (six were from the academic sector, six from non-governmental or not for profit organizations and six from pharmaceutical/biotechnology/private sector). All comments were reviewed by the WHO Secretariat. Inputs were discussed with PPC development group members and revisions to the PPC were made when appropriate and relevant.

Finalization of the document

The proposed revisions to the preferred characteristics were shared with the members of the PPC Development Group before finalizing the document.

Involvement of people with lived experience in the development process

To reflect the views and perspectives of people with lived experience in the document a group of ten individuals living with dementia from primarily high-income countries and English-speaking backgrounds were involved throughout the development of the document, especially section 7 and the recommendations outlined in Annex 2.

Individuals were engaged through focus group meetings where they shared their views about the use of blood samples for the diagnosis of Alzheimer disease; including necessary information to help patients decide whether or not to take such tests if/when they became available; eligibility criteria and important considerations to ensure equitable access to such tests; and information that would be important to include with the test results.

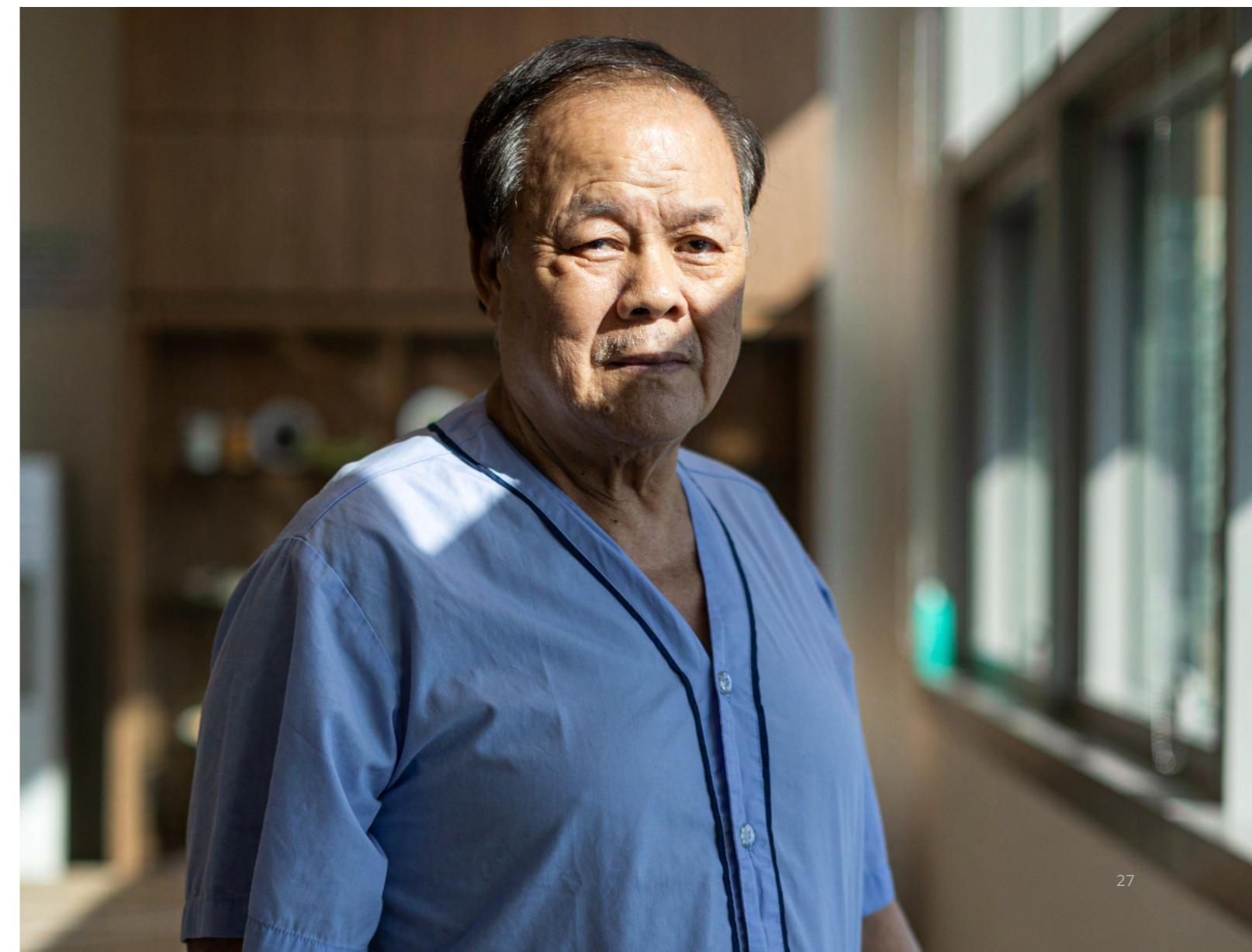
The points raised during the focus group discussions were summarized by the WHO Secretariat in a format suitable for this report. The summary was shared with participants for their review. As requested by participants, another round of focus groups was held to go over the content and refine it. The second draft was reviewed by all participants and feedback was provided via email. All participants approved the third and final draft.

References (Annex 1):

(1) Performing a landscape analysis: understanding health product research and development: a quick guide. Geneva: World Health Organization; 2023 (<https://iris.who.int/handle/10665/372696>, accessed 14 August 2024).

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Photo credit: A senior man at the Outram Community Hospital, Singapore, 2021.
WHO / Blink Media - Juliana Tan



Annex 2

Recommendations for the use of blood-based biomarkers for Alzheimer disease by people living with dementia

These recommendations are based on the experience of the dementia diagnostic process and post-diagnostic support from ten people living with dementia from Australia, Canada, Germany, Ireland, Namibia, New Zealand, Singapore, and the United States of America. Although the group discussed implications for low-and middle-income settings, as most participants were born and reside in high-income countries, the recommendations may be biased towards high-income settings.

Photo credit: A laboratory technician at work in the Diagnostic Laboratory at the Dnipropetrovsk Regional Clinical Hospital, Ukraine, 2023. © WHO / Christopher Black



Appropriate support throughout the diagnostic process

- Clinicians administering and interpreting the test, and the workforce providing post-diagnostic support, should be trained in dementia care.
- When a diagnosis is provided to someone, the test results should be communicated in a way that describes what the test looked for, communicates the clinical assessment along with the test result, expresses empathy, and considers the person's sensitivity and the impact that this information could have. Please make sure that appropriate time is allocated for discussing the test results with the person concerned:
 - For results that indicate the **likely absence of underlying Alzheimer disease pathology (i.e. a negative test)**, provide guidance on the next steps to determine the cause of symptoms. The person should also be provided with support (including mental health support) to manage their symptoms while determining the cause of the symptoms.
 - For results that indicate the **likely presence of Alzheimer disease pathology (i.e. a positive test)**, provide the person with post-diagnostic support including:
 - clarification of the meaning of the test results;
 - education about Alzheimer disease;
 - information about available pharmacological and non-pharmacological interventions; and
 - referral to post-diagnostic support for both the person and their care partner(s). Services may include those of an occupational therapist, physical therapist and a counselor.
 - Regardless of the test outcome, provide the person with information about lifestyle and brain health, and with appropriate support for making lifestyle changes, if needed.

Support for making an informed decision about taking the test

Provide accessible information about:

- the development of the test and whether it has been trialed with persons from diverse backgrounds, including younger persons, and with persons living with other health conditions;
- the accuracy of results, including an explanation of the meaning of a positive and negative result;
- what the test is assessing (e.g. What is it measuring? Is it assessing risk?);
- how the blood sample will be handled, analyzed, stored and discarded;
- how the person's privacy will be protected, including who will have access to the blood sample and test results; and
- how the test supports the diagnostic process, including clear guidance on next steps (e.g. by providing a flowchart outlining how the test supports the diagnostic process).

Global equitable access to this type of testing

- The test should be accessible, affordable and ideally provided for free to all those eligible.
- Consider the unique needs of individuals living in rural communities:
 - How far will they need to travel to be tested?
 - If the test is offered by a "mobile team" (i.e. a team that comes to conduct testing on set dates), will a trained clinician who understands the cultural context be administering the test?

- How, when and by whom will the results be communicated to the person concerned? If it is not possible to provide results in a timely manner, please consider the implications of this on the quality of life of the person and the progression of symptoms.
- Will samples be processed and stored in the same manner as in an urban setting? If not, will this have an impact on the validity of results and the privacy of information?
- What is the local understanding of dementia (e.g. Is dementia recognized as a medical condition? Is there a risk that a diagnosis could result in the person being secluded from their community? If yes, safeguards need to be in place to protect the privacy of the person and/or provide appropriate support.

Overarching considerations

- Blood biomarkers should be used only with symptomatic individuals. They should not be routinely used in non-symptomatic individuals. If no symptoms are present, there is a potential for psychological harm that could result from a positive test.
- Assessments to rule out other causes of the symptoms should be conducted first to determine whether further testing is needed. As symptoms will present differently in each person, the cognitive assessments should assess more than decline in memory.
- Blood biomarkers should be used in conjunction with other diagnostic tools. The test should not be treated as a stand-alone diagnostic for Alzheimer disease.

The background features a stylized, abstract illustration of a brain composed of orange and dark blue organic shapes. Orange nerve-like fibers branch out from the left side towards the center. A large, dark blue, rounded shape is on the right side.

For more information please contact:

Brain Health Unit

Department of Mental Health and Substance Use

World Health Organization

Avenue Appia 20

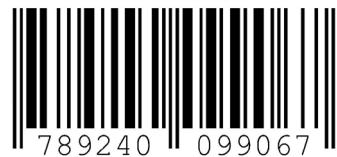
CH-1211 Geneva 27

Switzerland

Email: brainhealth@who.int

Website: <https://www.who.int/health-topics/brain-health>

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