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# An ethical framework for the clinical use of Alzheimer's disease biomarker testing



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This paper proposes a conceptual ethical framework to guide decision-making around blood-based biomarker (BBM) testing for Alzheimer's disease in primary care, where patients often present with cognitive impairment and multiple chronic conditions. Grounded in current evidence and ethical principles, it addresses clinical benefit, patient values, risk, and justice. Developed by a multidisciplinary team, the framework is illustrated through real-world case scenarios and highlights future research needs to support ethical implementation.

The emergence of blood-based biomarkers (BBMs), alongside the availability of disease-modifying therapies (DMTs), is poised to transform the diagnostic and therapeutic landscape of Alzheimer's disease (AD)[1]. Under recently updated diagnostic criteria, BBMs are expected to play a central role in identifying individuals who may benefit from treatment[2–4]. Compared to cerebrospinal fluid (CSF) and PET biomarkers, BBMs are more scalable and less invasive, enabling potential use beyond specialty centers, including in primary care[3].

However, while clinical adoption of BBMs is advancing, a critical gap remains in ethical guidance. Current recommendations focus on BBM use in specialized care settings and emphasize analytical validity, performance thresholds, and appropriate diagnostic contexts[2,5–7]. BBMs are commercially available as clinician ordered Laboratory Developed Tests (LDTs) and, in some cases, through consumer-initiated pathways (e.g., Direct to Consumer Testing). Emerging reports suggest BBM is being selectively adopted in primary care and other nonspecialist settings, signaling a real-world shift that outpaces current guidance[8–10]. Recently, the first BBM testing, Elecsys pTau181, has been FDA cleared for use in primary-care settings[11,12]. While BBM offers significant benefits for improving patient care and are central to accessing DMT, ethical guidance is needed to support responsible use of BBMs. This is particularly important for primary care, where most older adults with dementia are diagnosed[7]. In these settings, clinicians may be challenged to manage complex clinical scenarios that include multiple chronic conditions, prognostic uncertainty, and limited access to follow-up diagnostic resources[7].

This manuscript introduces an ethical framework to guide decision-making around AD BBM testing, with a focus on primary care settings. It integrates anticipated benefits, patient-centered goals, potential harms/risks, and justice. Importantly, the framework considers medical futility as an ethical boundary for when testing is unlikely to offer meaningful benefit. By aligning testing decisions with clinical complexity, patient values, and evolving evidence, this framework aims to support ethically sound and person-centered use of BBMs that reflect the realities of clinical care.

## Framework development

This ethical framework was developed within the Alzheimer's Diagnosis in Older Adults with Chronic Conditions (ADACC) Network (NIH/NIA U24AG082930). The ADACC Ethics Working Group meets monthly to identify and evaluate ethical challenges associated with diagnosis, detection, and treatment of Alzheimer's disease in the context of persons with co-morbidities and chronic conditions.

The Working Group identified a need for a framework to evaluate responsible use of BBMs in primary care settings. To develop the framework, the group conducted a literature review across four domains: (1) evidence on the clinical utility and performance of BBMs; (2) emerging data on stakeholder experiences and ethical concerns; (3) complexity of diagnosing cognitive impairment in real-world primary care; and (4) the concept of medical futility as applied to BBM testing. Drawing from this review, the group used an iterative, consensus-based process to define the framework's core components.

To reinforce its clinical relevance, the framework was applied to case scenarios inspired by real-world dilemmas and refined through discussion with experienced dementia clinicians and scientists with expertise in dementia care, bioethics, and implementation research. These illustrative cases served to validate and shape the framework, ensuring it was conceptually sound, ethically grounded, and applicable to clinical practice.

## Evidence of clinical utility and performance of BBM testing

AD BBMs are now clinically available in the U.S.[13]. Among BBMs, plasma p-tau217, used alone or in combination with the Aβ42/40 ratio, has

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demonstrated strong diagnostic performance[1,6,12,13,14]. It also shows high discriminative accuracy in differentiating AD from other neurodegenerative conditions, such as progressive supranuclear palsy[15], supporting its potential clinical utility. In May 2025, the Lumipulse G p-tau217/β-amyloid 1-42 plasma ratio test became the first BBM to receive FDA 510(k) clearance for clinical use in AD diagnosis[16].

Current evidence and guidelines recommend BBM testing by specialists for patients with objectively confirmed cognitive impairment[2,7]. The guidelines distinguish the use of BBMs for "triage" versus "confirmatory" purposes[2]. The evidence establishes performance thresholds, approximately 90% sensitivity and specificity, for BBMs to be considered confirmatory tools and emphasizes the importance of interpreting results within the context of a comprehensive evaluation and high pretest probability of AD pathology[2,5,6].

However, commercial tests such as $C_2$N's PrecivityAD® and Quest AD-Detect™ are increasingly available as LDTs through clinician-ordered pathways, specific laboratories or networks, and are not subject to formal FDA oversight[17]. These tests are already being used selectively in non-specialist settings, including primary care, driven by their accessibility and appeal as less invasive diagnostic tools, particularly where CSF or PET-based diagnostics are impractical[8–10]. In addition, Elecsys pTau181 has recently been cleared for use in primary-care settings to aid in assessment of Alzheimer's-related amyloid pathology[15,16]. This real-world expansion introduces ethical challenges not addressed by existing guidelines. These concerns are now increasingly reported by clinicians, patients, and caregivers with direct experience of BBM use.

## Stakeholders' experiences and ethical concerns

While emerging empirical studies highlight the perceived utility of BBMs across stakeholder groups, they also reveal several ethical concerns related to their clinical use. Caregivers and older adults report value of BBMs for facilitating health planning and early decision-making, but report concerns about psychological distress, privacy, and potential insurance discrimination[18–20]. Clinicians, particularly in primary care, echoed these concerns and expressed additional uncertainty about the interpretability of results, clinical utility in non-specialist settings, and the risk of unintended consequences such as overdiagnosis or financial strain on patients[21]. The Alzheimer's Association's 2025 guidelines similarly emphasize ethical challenges, including informed consent, result communication, and equitable access[2]. These findings underscore the need for ethical guidance that addresses the nuanced realities of BBM use, especially in cases complicated by multimorbidity, prognostic uncertainty, or diverse patient goals of care.

## Complexity of diagnosing cognitive impairment in real-world primary care

Despite advances in AD biomarker development, BBMs should not be used in isolation. A positive result may suggest underlying AD pathology but must be interpreted within a comprehensive clinical evaluation that includes cognitive, neuropsychiatric, and functional assessment, and medical history[7]. This is especially critical in adults over 80, who often present with mixed or non-AD neuropathology, where a biomarker-positive result may not fully explain symptoms. In some cases, prioritizing interventions such as vascular risk management, sleep disorder treatment, depression care, or lifestyle modification may offer greater clinical value than BBM-driven diagnostics alone.

Patients in primary care are generally older, with an average diagnosis age of 83[22], and typically present multiple chronic conditions. Over 95% of individuals with AD have at least one other chronic condition, and over 60% have three or more[23–25]. Common coexisting diagnoses, such as hypertension, heart disease, kidney disease, and diabetes, may influence cognitive decline or confound biomarker interpretation values[26–29]. Depression, alcohol use disorder, sleep-related issues, and polypharmacy may further impair cognition and obscure diagnostic clarity[30–33]. As a result, 50–70% of individuals with AD are undiagnosed or misdiagnosed in primary care[3].

## The concept of medical futility as applied to BBM testing

Medical futility offers a useful ethical boundary for identifying when BBM testing may be inappropriate, particularly in clinical contexts marked by multimorbidity, uncertainty, or limited benefit. Quantitative futility refers to situations in which a test is unlikely to yield a technically valid or actionable result, such as when comorbidities interfere with biomarker accuracy[34,35]. Qualitative futility applies when results would not improve quality of life, inform care decisions, or support a patient's goals. For example, testing may be considered qualitatively futile for a patient with limited life expectancy or when testing would not meaningfully change diagnosis, management, or help achieve patient goals[34,35].

## Practical ethical framework for BBM use

The proposed framework (Table 1) is intended primarily for clinicians who care for older adults with cognitive impairment in primary care and other community-based settings, where access to specialists and advanced diagnostic tools may be limited. It may also inform efforts by health systems leaders, implementation researchers, and policymakers working to integrate BBMs ethically into routine care. By addressing ethical challenges that extend beyond specialty memory clinics, the framework supports more equitable, context-sensitive, and patient-centered decision-making.

**Table 1 | Proposed framework for medical futility decision-making of AD BBMs testing**

| Ethical considerations | Key questions | Follow-up questions |
|---|---|---|
| Potential benefit or values | Context of use: Is the biomarker test being used for screening (to be followed by a second test if positive) or confirmation (no further testing needed)?<br>• Personal utility: Is there a personal utility for biomarker testing (e.g., the patient "just wants to know" their diagnosis)?<br>• Diagnostic evaluation: Is biomarker testing likely to affect further diagnostic testing, especially if the result is negative?<br>• Treatment: Is the biomarker test used for the purpose of confirming eligibility for disease-modifying treatments?<br>• Monitoring: Is the biomarker test being used for monitoring disease or treatment monitoring? | If used for screening, is a confirmatory test available (e.g., CSF or PET)?<br>If used for confirmation, will insurance pay for treatment based on a BBM test? |
| Reduction of potential benefits | Do patient-specific factors (e.g., chronic conditions, age, or polypharmacy) reduce test utility? | Would another biomarker modality be more appropriate? |
| Potential harms | Could testing or disclosure of results lead to significant risks (e.g., discrimination, psychological distress, or unnecessary interventions)? | Do the benefits of testing outweigh potential risks? |
| Justice Considerations | Do any factors, including futility, risk exacerbating disparities or disproportionately burden sub-populations? | What resources are available to provide appropriate care?<br>Do socioeconomic or geographic barriers limit access to follow-up testing or care? |

The proposed framework harnesses four key ethical norms, including anticipated benefits, patient-centered goals, potential harms or risks, and justice. We provide a flexible structure that encourages thoughtful clinical judgment and shared decision-making with patients, supported by current criteria and guidelines[7]. Within this structure, we highlight responsible use and a patient-centered approach to biomarker testing.

The first consideration is the potential benefit or value of BBM testing. The concept of "benefit" as a *prima facia* consideration is well established in ethical frameworks across domains and applications[36–38]. Broadly, BBMs may improve diagnostic accuracy and timeliness. However, benefits at an individual level may differ and depend on the potential uses or values of results for a patient. Clinicians may consider various factors, including:

- The purpose of the biomarker testing (screening, confirmation, or to determine eligibility for treatment).
- The availability of follow-up testing for the patient for this specific patient, including access to confirmatory testing.
- Treatment options for the patient.
- Non-treatment clinical benefits for this patient or personal utility[39], including benefits of a definitive diagnosis or advanced care planning.

Patients' goals of care and values may significantly inform the potential benefit that could be accomplished from testing (e.g. diagnostic clarity or planning for the future), even in the absence of treatment options[2,34,40,41]. Pre-test counseling is important to determine if an individual patient will benefit from testing. During counseling, if clinicians and patients do not identify a benefit, it is ethically justifiable to decline testing.

The second consideration involves patient-specific factors that affect the usefulness or reliability of BBM testing. Patient specific factors may range from clinical status (e.g., other chronic conditions), age, psychosocial factors, and patient values. A patient's pre-existing clinical status, including co-morbidities and other chronic conditions, may affect the potential usefulness of biomarker testing results[2]. As highlighted above, some clinical patients may have chronic conditions associated with aging. The presence of other chronic conditions may cause cognitive symptoms unrelated to AD pathology (e.g., co-pathologies, multiple chronic conditions, polypharmacy, lifestyle or other factors). Underlying chronic conditions may also affect testing outcomes or treatment options. For example, impaired kidney function could affect test results and impede accurate interpretation[42]. This could undermine the value of testing, and it may be ethically justifiable to not offer BBM testing due to medical futility or to offer a different biomarker modality. Similarly, it may be justifiable to decline testing if a patient's primary goal is to access DMT, but they are not a candidate due to other factors (e.g., a high number of microhemorrhages)[43].

It is unethical to decline biomarker testing based on psychosocial factors (e.g., financial status). Yet, psychosocial factors may be relevant to broader decision-making (e.g., insurance status). If the patient's primary goal of testing is to determine eligibility for DMT and their insurance coverage would not cover testing or treatment, clinicians should discuss the economic consequences of testing and barriers[44]. This should be a joint decision, and patient-financial factors are not determinative.

A third consideration is the potential for risks or harm to a patient following AD BBM testing and disclosure of the results. While physical risks of BBM testing are minimal, potential risks may include distress, discrimination, stigma, and financial distress[45–48]. These consequences could outweigh its potential value[49]. This may be particularly true for patients who remain employed[45]. BBM testing should not be performed if the patient does not wish to know their AD status given these risks. Additionally, testing may not be appropriate if patients or family members misinterpret the meaning of results. For example, if patients request testing to understand potential genetic or familial risk. Clinical counseling and education pre and post testing are important to avoid misinterpretation of the results. Identifying the potential risks relevant to an individual patient is critical to understanding whether the benefits of testing outweigh the risks.

A final consideration, justice, evaluates whether benefits or risks of testing could disproportionately affect sub-populations. This is particularly true if patient-level factors inadvertently serve as a discriminatory proxy for race, ethnicity, or socio-economic status. These factors could directly or indirectly increase barriers to testing and the benefits of testing to sub-populations. For example, some clinics may have limited access to DMTs, thereby reducing potential benefits of testing. Not performing BBM testing in this setting, with the rationale that treatments are not readily available, could exacerbate disparities in AD diagnosis and treatment.

This framework encourages clinicians to evaluate BBM testing through the intersecting lenses and centering patient values and goals relevant to testing. As an iterative process, the framework supports ongoing reflection to ensure that decisions remain responsive to evolving clinical circumstances and patient preferences. When such an assessment reveals that testing is unlikely to meaningfully inform care or align with what matters to the patient, it may be ethically inappropriate and constitute medical futility.

## Application of the framework: case scenarios

The framework is not intended as a rigid algorithm but as a dynamic process that supports ethical deliberation. Clinicians are encouraged to iteratively consider the relevant ethical standards as they reassess decisions over time in response to changing patient needs, values, and prognoses. To support structured clinical reasoning, we synthesize these considerations into a proposed conceptual decision pathway that illustrates how empirical constraints, contextual factors, and ethical considerations interact to determine when blood-based biomarker testing is ethically justified or futile (Fig. 1). The following case scenarios illustrate its application across common primary care contexts.

### Patient one: a 72-year-old man with very mild but increasing forgetfulness over the past 18 months and multiple morbidities who wants to know whether he has AD. His stated goals are to access AD DMTs and use biomarkers for disease monitoring

Biomarker testing is ethically justifiable in a cognitively impaired patient with a strong desire to learn whether AD is the likely etiology of their symptoms. However, additional considerations warrant exploration, including whether the patient would be eligible for DMT. First, it is ethically important to evaluate the impact of the patient's comorbidities. Co-morbidities may be a source of cognitive impairment, impede accurate biomarker testing results, or affect DMT eligibility. Therefore, co-morbidities may affect whether the BBMs would be beneficial to this patient. While not determinative, it is important to verify insurance coverage for BBM testing and treatment options. If coverage gaps exist, these should be communicated along with other risks. If any of these factors negatively affect the potential benefits of testing, it is important to reassess whether testing is appropriate.

The patient's stated goal relevant to disease monitoring may not be sufficient to warrant testing. Despite other potential benefits associated with BBMs, existing data does not provide sufficient evidence that serial testing (e.g., annual BBM testing) offers clinical value to individual patients for monitoring purposes[2,50]. Additionally, in a clinical trial of an anti-amyloid antibody that used amyloid PET to monitor amyloid clearance, there were only modest correlations between individual rates of change in BBM levels and amyloid PET values[51]. This suggests that BBM tests cannot currently monitor anti-amyloid treatment effects for individuals. Accordingly, if the patient is found ineligible for treatment, testing may be discouraged due to misalignment with the patient's goal. Alternative monitoring approaches should be explored.

### Patient two: a frail, 91-year-old woman accompanied by her caregiver, who is concerned about her declining cognition and functional status over the past three years

The ethical justification for BBM testing in a nonagenarian with cognitive impairment depends on whether it offers meaningful benefit (e.g., diagnostic value, treatment or non-treatment implications, or personal utility). Given the high pre-test probability of AD pathology in the oldest-old, testing would mainly reinforce clinical suspicion. However, the prevalence of

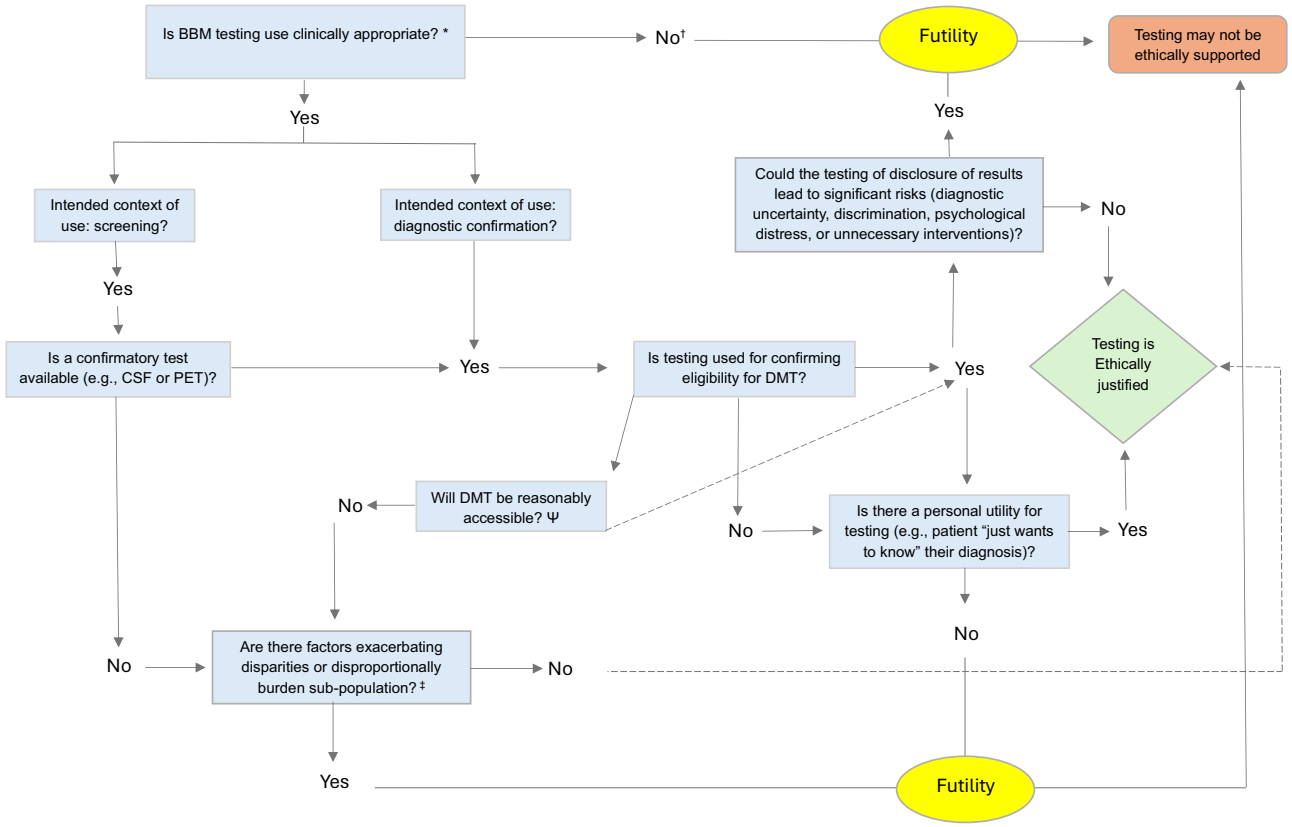


**Fig. 1 | A proposed conceptual decision pathway for determining ethical use or futility of Alzheimer's disease blood-based biomarker testing in primary care.** This proposed conceptual framework illustrates a structured decision pathway designed to support clinicians in synthesizing empirical evidence, clinical context, and ethical considerations when evaluating the use of Alzheimer's disease blood-based biomarkers in primary care. The pathway integrates assessment of clinical appropriateness, test interpretability, intended context of use (screening versus diagnostic confirmation), availability of confirmatory testing, implications for disease-modifying therapy eligibility and reasonable accessibility, potential risks and harms, equity considerations, and patient-centered values. Within this framework, determinations of clinical or ethical futility emerge as the outcome of sequential empirical and contextual assessments rather than as a priori value judgments. The pathway is intended as a decision-support model rather than a prescriptive algorithm and is designed to complement, not replace, clinical judgment and shared decision-making. * This includes cognitive symptoms or evaluation context consistent with current appropriate-use recommendations; patient-specific factors (such as chronic conditions, polypharmacy, age) do not impede testing interpretation. † consider another more appropriate biomarker modality (e.g., CSF, PET). Ψ Reasonable accessibility refers to the plausibility of timely and equitable access to disease-modifying therapy and required downstream care in a given clinical context. ‡ including insurance coverage, access to confirmatory testing and downstream care.

comorbid conditions, polypharmacy, and mixed neuropathology (e.g., vascular pathology, TDP-43) increases the likelihood multifactorial cognitive impairment. Consequently, if amyloid pathology is present, it may not be the primary cause. Relying solely on BBM results may underappreciate other contributing conditions, including treatable polypharmacy. In poor health, limited diagnostic value may be further reduced by short life expectancy, as BBM utility in this group remains unclear[2].

If the goal of testing is to determine eligibility for DMTs, other eligibility factors must be considered. A 91-year-old patient is likely to have comorbidities that would be contradictions for DMT treatment. For example, multiple previous strokes would indicate that the individual is ineligible for current treatments[43]. A patient with significant frailty (e.g., functional dependence, weight loss, or limited physiological reserve) may be less able to tolerate the burden of treatment (e.g., regular infusions and multiple MRI scans)[52]. Finally, it is unknown whether treatments have similar safety and efficacy in nonagenarians.

If the BBM test is unlikely to impact diagnosis, guide further evaluation, or treatment and management plan, it may be deemed futile. In this case, testing may impose additional burdens on patients and their caregivers without benefits and therefore, would be ethically inappropriate.

Non-treatment benefits, such as life planning, must also be considered. Testing may aid advance planning, legal and financial decision-making, or caregiver preparation. However, if these have already been addressed, AD diagnosis may not change care. Depending on the patient's health status, priorities may center on symptom management and quality of life, including emotional and social engagement. If, for example, the patient's main goal is maintaining a positive mood and family connection, testing decisions must align accordingly.

### Patient three: a 78-year-old woman with moderate dementia who lives in an assisted living facility, is seen due to worsening delusions and agitation

In a patient with more advanced dementia, determining the etiology may not change the diagnosis, testing, or the management plan. The patient would not be a candidate for DMTs, and other considerations are less likely to be relevant (e.g., advance care planning). Biomarker testing is unlikely to meet the patient's current needs and is likely to be deemed futile. It is ethically justifiable to decline BBM testing given a lack of a clear benefit to the patient. Testing to provide information not directly valuable to the patient should be avoided. This includes testing requested by family members to infer their own risks. This indicates a significant misinterpretation of the meaning of individual biomarker results, which do not provide information on genetic risk for disease. Accordingly, BBM testing is not likely ethically justified.

## Conclusion

The advancements associated with BBM testing in recent years are laudable with significant benefits that will advance clinical care of patients affected by AD. However, ethical clarity and guidance are increasingly needed to support the responsible use of BBMs as they move beyond specialist environments. This manuscript introduces an ethical framework for BBM testing. Although conceptually grounded, the framework is designed to be practical and responsive to the complexities of the primary care context. Its application to case scenarios drawn from real-world dementia practice, refined with input from interdisciplinary experts, demonstrates its relevance to common dilemmas in BBM decision-making. We also incorporated insights from emerging empirical literature on stakeholder concerns, including psychological, financial, and interpretive challenges identified by patients, caregivers, and primary care clinicians. While the framework is not yet empirically tested, it offers an actionable tool for guiding BBM use in ethically complex cases. Future work should assess its feasibility, acceptability, and outcomes through implementation studies in diverse care environments, particularly in resource-constrained and underserved settings. Anticipated implementation challenges include variability in clinician preparedness, lack of clear decision algorithms, and unequal access to follow-up testing and treatment in primary care. To address these barriers, implementation efforts should include the development of decision aids and training toolkits to support ethical, evidence-informed use of BBMs. Additionally, policy action is needed to address access and affordability concerns, ensuring that AD BBM testing and subsequent testing (e.g., PET) and treatments do not leave underserved groups behind. This framework presents an initial step toward bridging ethical gaps, supporting alignment between emerging diagnostic innovations and the complexities of everyday clinical practice.

## Data availability

No datasets were generated or analysed during the current study.

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## Author contributions

C.E.A.S. and J.J.A. conceptualized the manuscript. C.E.A.S. conducted the literature synthesis and drafted the initial version. J.J.A. provided critical guidance on the ethical framework and supervised the project. M.M.M., A.C.R., and S.E.S. contributed to the clinical and scientific interpretation of biomarker evidence and critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

## Competing interests

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## Additional information

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