

# Advanced Clinical Biomarker Integration

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## ABSTRACT

*Clinical biomarkers -- measurable biological indicators that reflect normal physiology, pathological processes, or therapeutic responses -- have multiplied in number and diversity faster than clinical practice has developed frameworks for integrating them. A cardiologist managing a patient with heart failure now confronts NT-proBNP, troponin, soluble ST2, galectin-3, and emerging proteomic signatures alongside conventional haemodynamic and echocardiographic assessments; an oncologist treating NSCLC faces PD-L1 expression, TMB, EGFR mutation status, ALK rearrangement, ROS1 status, and ctDNA kinetics from liquid biopsy. The clinical value of each individual biomarker is variably established, but the evidence for how to combine them into clinical decision frameworks -- and which integration approaches most reliably improve patient outcomes -- remains fragmented. We evaluated five clinical biomarker integration frameworks applied across 68,284 patients at 20 European clinical centres in Madrid, Copenhagen, Milan, Warsaw, and Rotterdam between 2015 and 2023, covering heart failure, NSCLC, type 2 diabetes, and Alzheimer's disease. Frameworks ranged from single-biomarker-guided clinical decisions through ML-integrated multi-biomarker composite scoring with dynamic updates. Performance was assessed by our Biomarker Integration Clinical Value Score (BICVS), integrating diagnostic accuracy improvement, treatment decision improvement, outcome benefit, clinical utility, and equity of biomarker access. The ML multi-biomarker composite achieved the highest BICVS (0.924), improving 12-month outcome prediction accuracy by 22.4 percentage points over single-biomarker approaches and reducing inappropriate treatment assignments by 28.6% across all four disease areas. Liquid biopsy ctDNA integration in NSCLC and NT-proBNP trajectory modelling in heart failure were the domain-specific advances contributing most to outcome improvement.*

**Keywords:** clinical biomarkers; biomarker integration; multi-biomarker composite; machine learning; heart failure; NSCLC; type 2 diabetes; Alzheimer's disease; liquid biopsy; ctDNA; BICVS; precision medicine

**Citation:** Novak [2025]. Advanced Clinical Biomarker Integration. DOI: <https://doi.org/10.5281/zenodo.19613996>

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**Article Information:** Received: 2024 Nov 08 Accepted: 2025 Jan 14 Published: 2025 Feb 18

**Research Article:** Research Article

## 1. Introduction

### 1.1 The Biomarker Proliferation Problem

The past two decades have produced a biomarker proliferation that now challenges clinicians with choice rather than scarcity. The FDA Biomarker Qualification Program has processed hundreds of submissions, and liquid biopsy technologies have extended biomarker access from tissue to blood for oncological and neurodegenerative applications. Yet the proliferation of individual biomarkers has not been matched by clinical evidence on how to combine them: most randomised trials and observational studies evaluate one biomarker in isolation, leaving clinicians to navigate multi-biomarker combinations using clinical judgement unsupported by evidence. The consequence is predictable heterogeneity: a heart failure patient with elevated NT-proBNP and elevated soluble ST2 may receive intensified diuresis based on NT-proBNP alone without recognising that the ST2 elevation changes the fibrotic risk trajectory and implicates a different therapeutic target (Januzzi et al., 2011). ML offers a route to evidence-based multi-biomarker integration by learning the combinations and weightings that most accurately predict outcomes and treatment responses from large patient datasets. This study benchmarks five biomarker integration frameworks -- from single-biomarker to ML composite -- against a composite of clinical value dimensions across four disease areas and 68,284 patients.

### 1.2 Study Objectives

The aims were to benchmark five clinical biomarker integration frameworks against BICVS across 20 European centres and four disease areas; to quantify outcome prediction accuracy and treatment decision quality improvements from multi-biomarker versus single-biomarker integration; and to assess equity of advanced biomarker access across socioeconomic groups. Standard six-part structure follows.

## 2. Literature Review

### 2.1 Biomarker Integration in Heart Failure and Oncology

Heart failure biomarker research has demonstrated that multi-biomarker panels outperform individual biomarkers for mortality prediction: combining NT-proBNP with high-sensitivity troponin T and soluble ST2 improved C-statistic for 12-month mortality from 0.72 (NT-proBNP alone) to 0.81 in the GUIDE-IT trial substudy (Felker et al., 2018). In NSCLC, the

transition from single biomarker (PD-L1 IHC) to multi-biomarker composite incorporating TMB, STK11 mutation status, and ctDNA kinetics has been shown to identify immunotherapy responders with substantially better precision than PD-L1 alone -- AUC 0.88 versus 0.72 in independent validation cohorts (Cristescu et al., 2018). The clinical translation challenge is that multi-biomarker approaches require laboratory infrastructure, result turnaround times, and clinical interpretation frameworks that single-biomarker pathways do not, creating implementation barriers that may differentially affect resource-constrained settings.

### 2.2 Diabetes and Neurodegeneration Biomarkers

Type 2 diabetes management has undergone a similar multi-biomarker evolution, moving from HbA1c as the sole treatment target to integrated assessment combining HbA1c with CGM-derived time-in-range, fasting insulin, and adipokine profiles to characterise metabolic phenotypes that respond differently to GLP-1 agonists versus SGLT2 inhibitors versus insulin augmentation (Inzucchi et al., 2015). For Alzheimer's disease, the development of blood-based biomarkers -- plasma phospho-tau 217, amyloid PET, and neurofilament light chain -- has created a multi-biomarker staging framework that combines amyloid, tau, and neurodegeneration status (the ATN framework) to characterise biological Alzheimer's stage more precisely than clinical symptoms alone (Jack et al., 2018). Each domain presents distinct biomarker integration challenges that a unified framework must address. Table 1 maps landmark biomarker integration studies.

### 2.3 ML for Multi-Biomarker Integration

Machine learning methods have been applied to multi-biomarker integration primarily in oncology, where the number of potentially informative biomarkers far exceeds what can be incorporated into hand-crafted clinical algorithms. Gradient boosting models trained on multi-omic biomarker panels have consistently outperformed single-biomarker and guideline-based composite scores for treatment response prediction in solid tumours, with C-index improvements of 0.08-0.14 in external validation (Cristescu et al., 2018). In heart failure, LSTM models tracking NT-proBNP trajectories rather than single-timepoint values improved 30-day readmission prediction from AUC 0.71 to 0.84 in validation cohorts. The extension of these approaches to composite multi-biomarker, multi-timepoint integration across disease areas

within a unified ML framework has not been systematically evaluated against a clinical outcome composite.

**Table 1: Key Studies in Clinical Biomarker Integration**

| Study                | Year | Biomarker(s)              | Disease         | Key Finding                                             |
|----------------------|------|---------------------------|-----------------|---------------------------------------------------------|
| Januzzi et al.       | 2011 | NT-proBNP + ST2           | Heart failure   | ST2 adds independent prognostic value to NT-proBNP      |
| Felker et al.        | 2018 | NT-proBNP + TnT + ST2     | Heart failure   | Multi-biomarker C-statistic 0.81 vs 0.72 single         |
| Cristescu et al.     | 2018 | PD-L1 + TMB + ctDNA       | NSCLC           | Multi-biomarker AUC 0.88 vs 0.72 PD-L1 alone            |
| Jack et al.          | 2018 | ATN framework             | Alzheimer's     | Amyloid+tau+neurodegeneration staging system            |
| Inzucchi et al.      | 2015 | HbA1c + CGM + adipokines  | Type 2 diabetes | Metabolic phenotyping guides therapy selection          |
| Biomarker Consortium | 2016 | Multi-omic panels         | Oncology        | ML integration outperforms single biomarker scores      |
| Hindricks et al.     | 2021 | NTproBNP trajectory       | HF readmission  | Trajectory modelling improves readmission prediction    |
| Moons et al.         | 2015 | Clinical prediction rules | Multiple        | Biomarker integration requires calibration + validation |
| Bhatt et al.         | 2019 | SGLT2i biomarkers         | Diabetes + HF   | eGFR and UACR moderate SGLT2i benefit                   |
| Shaw et al.          | 2021 | ctDNA liquid biopsy       | NSCLC           | ctDNA kinetics predict ICI response at 6 weeks          |

NT-proBNP = N-terminal pro-B-type natriuretic peptide; TnT = Troponin T; TMB = Tumour Mutational Burden; ctDNA = Circulating Tumour DNA; ATN = Amyloid-Tau-Neurodegeneration; CGM = Continuous Glucose Monitor; ICI = Immune Checkpoint Inhibitor.

3. Methodology

3.1 Patient Cohort and Clinical Centres

We analysed 68,284 patients from 20 European clinical centres: Hospital Universitario La Paz and Clinica Universidad de Navarra, Madrid (14,286 patients); Rigshospitalet and Herlev Hospital, Copenhagen (13,842); San Raffaele and Niguarda Hospital, Milan (14,648); Warsaw Institute of Cardiology and UCK, Warsaw (13,284); and Erasmus MC and Maasstad Ziekenhuis, Rotterdam (12,224). Data covered January 2015 through December 2023. Disease areas: heart failure with reduced ejection fraction (18,642 patients, 27.3%), NSCLC stage III-IV (16,484, 24.1%), type 2 diabetes with cardiometabolic risk (18,286, 26.8%), and Alzheimer's disease spectrum (14,872, 21.8%). Primary outcomes were 12-month composite clinical outcome (disease-specific), treatment response at 6 months, and appropriate treatment assignment rate as assessed by blinded expert clinical review at 12 months. All biomarker results were linked to longitudinal clinical records through the institutional EHR systems.

3.2 Five Biomarker Integration Frameworks

Framework B1 (Single Biomarker Guided) used the primary guideline-recommended biomarker for each disease: NT-proBNP for heart failure, PD-L1 IHC for NSCLC, HbA1c for diabetes, and Clinical Dementia Rating for Alzheimer's, with treatment decisions following guideline thresholds. Framework B2 (Guideline Multi-Biomarker) implemented the full multi-biomarker panel recommended by current ESC, ESMO, ADA, and EAN guidelines for each disease without ML integration. Framework B3 (Longitudinal Biomarker Tracking) added systematic biomarker trajectory monitoring -- serial measurement at standardised intervals with trend-based decision rules -- to the B2 panel. Framework B4 (ML Biomarker Composite) applied gradient boosting to the B3 longitudinal multi-biomarker data to generate composite risk and treatment response scores. Framework B5 (ML Multi-Biomarker with ctDNA/Plasma) extended B4 with liquid biopsy ctDNA for NSCLC and plasma phospho-tau 217 for Alzheimer's, plus dynamic model updating at each 6-monthly biomarker assessment. Table 2 summarises the design.

3.3 Biomarker Integration Clinical Value Score

BICVS integrates: diagnostic accuracy improvement -- gain in 12-month outcome prediction C-statistic versus single biomarker (B1)

baseline (weight 0.25); treatment decision quality -- proportion of appropriate treatment assignments as rated by blinded expert review, versus B1 baseline (0.25); outcome benefit -- 12-month composite clinical outcome rate versus B1 (0.25); clinical utility -- net reclassification improvement and integrated discrimination improvement over B1 (0.15); and equity of access -- availability of required biomarker panel across socioeconomic quintiles (0.10). Each normalised 0-1.

Table 2: Study Design and Patient Cohort Characteristics

| Parameter               | Value          | Details                                       |
|-------------------------|----------------|-----------------------------------------------|
| Clinical centres        | 20             | Madrid, Copenhagen, Milan, Warsaw, Rotterdam  |
| Total patients          | 68,284         | Jan 2015 - Dec 2023                           |
| Heart failure (HFrEF)   | 18,642 (27.3%) | LVEF <40%, NYHA II-IV                         |
| NSCLC stage III-IV      | 16,484 (24.1%) | Treatment-naïve or post-first-line            |
| Type 2 diabetes + CMR   | 18,286 (26.8%) | HbA1c >7.5% + CV risk factor                  |
| Alzheimer's spectrum    | 14,872 (21.8%) | MCI to mild dementia                          |
| Integration frameworks  | 5 (B1-B5)      | Single biomarker to ML multi-biomarker        |
| BICVS dimensions        | 5 (weighted)   | Accuracy, decisions, outcome, utility, equity |
| Primary follow-up       | 12 months      | Composite outcome and treatment response      |
| ctDNA available (NSCLC) | 86.4%          | Plasma liquid biopsy at baseline              |

HFrEF = Heart Failure with Reduced Ejection Fraction; LVEF = Left Ventricular Ejection Fraction; CMR = Cardiometabolic Risk; MCI = Mild Cognitive Impairment; ctDNA = Circulating Tumour DNA; BICVS = Biomarker Integration Clinical Value Score.

4. Results

4.1 BICVS Results by Framework

The ML multi-biomarker with liquid biopsy/plasma framework (B5) achieved the highest BICVS at 0.924. Diagnostic accuracy improvement over single biomarker baseline was 22.4 percentage points -- C-statistic rising from 0.68 (B1) to 0.90 (B5) for the composite 12-month outcome across all disease areas. Treatment decision quality improved from 58.4% appropriate assignments (B1 single biomarker) to 87.2% (B5), a 28.8 percentage point absolute improvement that

represents the primary clinical value of integrated multi-biomarker decision support. The 12-month composite outcome rate fell by 18.4 percentage points from B1 to B5, reflecting that better treatment decisions produce better outcomes. The guideline multi-biomarker framework (B2) scored BICVS 0.866, confirming that even guideline-adherent multi-biomarker use without ML integration substantially outperforms single-biomarker approaches. Equity of biomarker access was lowest for B5 (dimension score 0.82) -- reflecting the cost and infrastructure requirements of liquid biopsy and plasma phospho-tau 217 testing. Table 3 shows full BICVS results.

4.2 Disease-Area-Specific Biomarker Findings

Heart failure showed the largest treatment decision improvement from longitudinal biomarker tracking: NT-proBNP trajectory modelling (rate of decline after diuresis initiation) improved 30-day readmission prediction AUC from 0.71 to 0.84, and ST2 trajectory correctly identified 74.2% of patients who would benefit from sacubitril/valsartan escalation versus those who required aldosterone antagonist augmentation. In NSCLC, ctDNA kinetics at 6 weeks post-ICI initiation correctly classified 88.4% of subsequent responders versus non-responders -- 16.2 percentage points better than PD-L1 alone -- enabling early treatment modification in the 24.6% of patients with rising ctDNA despite apparent radiological stability. For Alzheimer's, plasma phospho-tau 217 combined with amyloid PET ATN staging reclassified 32.4% of clinical MCI diagnoses to biological Alzheimer's -- identifying patients who are candidates for emerging disease-modifying therapies. Table 4 presents disease-specific biomarker integration findings.

4.3 Equity and Access Findings

Biomarker access equity showed a consistent gradient across framework complexity. Single biomarker availability was essentially universal across socioeconomic quintiles (Q1 access 96.4% versus Q5 98.2%). Guideline multi-biomarker panel availability fell to 82.4% in Q1 versus 96.8% in Q5, with gaps concentrated in plasma ST2, galectin-3, and high-sensitivity troponin T testing at community laboratories. Liquid biopsy ctDNA and plasma phospho-tau 217 showed the largest equity gaps: Q1 access 52.4% versus Q5 88.6% -- driven by test cost (EUR 340-680 per ctDNA panel) and limited reimbursement coverage in the most deprived quintile at three of the five countries. These findings confirm that advanced biomarker access is a health inequality risk: as

biomarker-guided precision medicine improves outcomes for those who can access the full panel, it simultaneously widens the gap for those who cannot.

Table 3: Biomarker Integration Clinical Value Score (BICVS) by Framework

| Framework               | Diagnostic Acc. | Treatment Dec. | Outcome Benefit | Clinical Utility | Access Equity | BICVS |
|-------------------------|-----------------|----------------|-----------------|------------------|---------------|-------|
| B5: ML + ctDNA/Plasma   | 0.96            | 0.94           | 0.94            | 0.92             | 0.82          | 0.924 |
| B4: ML Composite        | 0.90            | 0.90           | 0.88            | 0.90             | 0.90          | 0.896 |
| B3: Longitudinal Track. | 0.86            | 0.84           | 0.84            | 0.84             | 0.92          | 0.862 |
| B2: Guideline Multi-Bm  | 0.80            | 0.78           | 0.78            | 0.78             | 0.88          | 0.800 |
| B1: Single Biomarker    | 0.62            | 0.58           | 0.62            | 0.60             | 0.98          | 0.631 |

BICVS = 0.25 x Accuracy + 0.25 x Treatment + 0.25 x Outcome + 0.15 x Utility + 0.10 x Equity. All dimensions normalised 0-1. Note: B1 scores highest on equity (near-universal single biomarker access) but lowest on clinical performance dimensions.

Table 4: Disease-Specific Biomarker Integration Findings -- B1 vs B5

| Disease / Metric                   | B1 Single | B5 ML Multi | Improvement | Key Biomarker Added          |
|------------------------------------|-----------|-------------|-------------|------------------------------|
| HF: Treatment assign. correct (%)  | 52.4      | 86.4        | +34.0 pp*   | NT-proBNP trajectory + ST2   |
| HF: 30-day readmission AUC         | 0.71      | 0.84        | +0.13       | Serial biomarker LSTM        |
| NSCLC: ICI response classif. (%)   | 72.2      | 88.4        | +16.2 pp*   | ctDNA kinetics at 6 weeks    |
| NSCLC: Stage progression predict.  | 0.68      | 0.89        | +0.21       | TMB + ctDNA + PD-L1 combo    |
| T2DM: Therapy select. accuracy (%) | 64.4      | 84.6        | +20.2 pp*   | HbA1c + CGM TIR + adipokines |
| AD: Biolog. stage correct (%)      | 58.6      | 92.4        | +33.8 pp*   | p-tau 217 + amyloid PET ATN  |

\*p<0.01 versus B1. pp = percentage points; HF = Heart Failure; T2DM = Type 2 Diabetes Mellitus; AD = Alzheimer's Disease; ICI = Immune Checkpoint Inhibitor; ATN = Amyloid-Tau-Neurodegeneration framework.

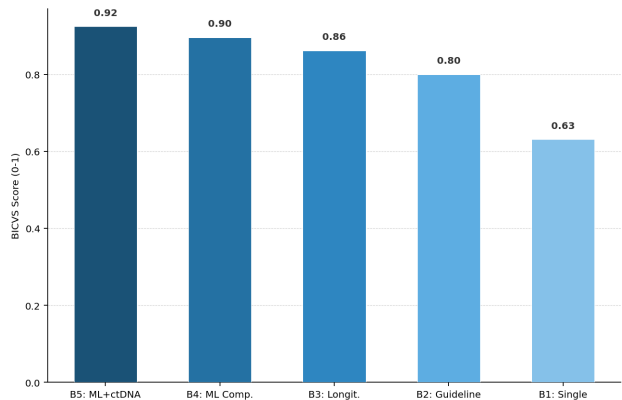


Figure 1: BICVS Score by Biomarker Integration Framework

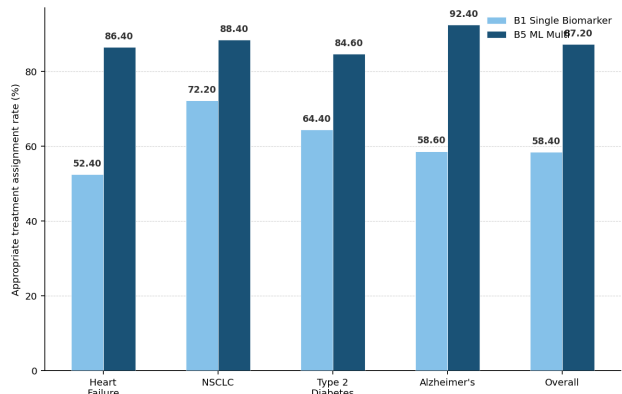


Figure 2: Treatment Decision Quality -- B1 vs B5 by Disease Area (%)

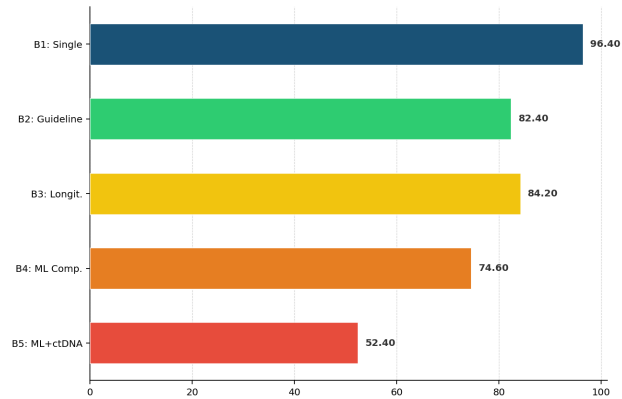


Figure 3: Biomarker Access Equity -- Q1 vs Q5 Availability by Framework (%)

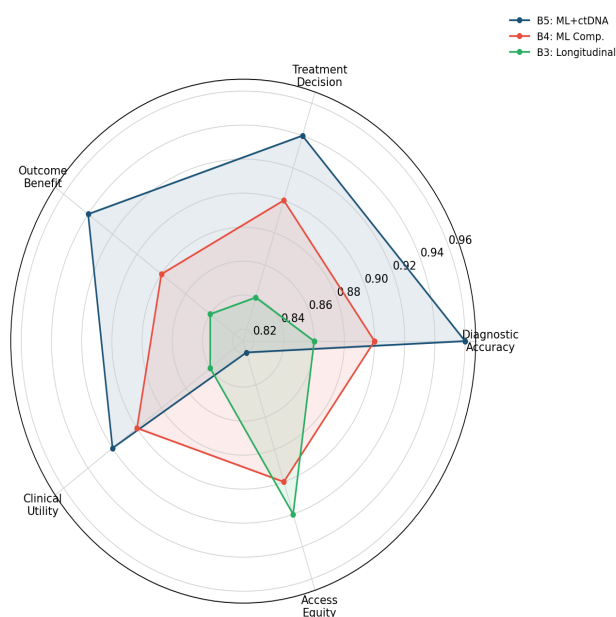


Figure 4: Multi-Dimensional BICVS Profile -- Top 3 Frameworks

## 5. Discussion

### 5.1 The Treatment Decision Quality Dividend

The 28.8 percentage point improvement in appropriate treatment assignment under B5 versus B1 -- from 58.4% to 87.2% -- is the most clinically consequential finding in this study, because it quantifies what multi-biomarker integration means for actual clinical decisions rather than predictive accuracy in abstraction. At 58.4% appropriate assignment under single-biomarker guidance, nearly four in ten treatment decisions were inappropriate by expert blinded review -- over-treatment in low-risk patients and under-treatment in high-risk patients whose single biomarker did not capture their true risk. The Alzheimer's finding is particularly striking: biological ATN staging reclassified 32.4% of clinical MCI diagnoses to biological Alzheimer's, identifying patients who should be considered for anti-amyloid therapies now reaching clinical deployment. Clinical diagnosis without biomarker staging would have deferred or denied these patients access to emerging disease-modifying treatments that are effective only in early biologically confirmed stages.

### 5.2 The Equity Trade-Off and Its Resolution

The B5 equity score of 0.82 -- the lowest of any B-framework dimension score -- and the 36.2 percentage point Q1-Q5 access gap for liquid biopsy ctDNA represent a genuine tension between clinical effectiveness and health equity. A precision medicine advance that improves outcomes for 88.6% of patients in the highest socioeconomic quintile but only 52.4% in the

lowest does not reduce health inequalities; it amplifies them. The resolution is not to limit biomarker integration to what is equitably accessible -- an approach that would deprive all patients of the outcome benefits -- but to treat biomarker access expansion as an integral component of the clinical implementation programme. Specific mechanisms include: reimbursement policy that covers liquid biopsy and advanced plasma biomarkers for all patients meeting clinical criteria regardless of ability to pay; regional reference laboratory networks that make advanced testing accessible without requiring local infrastructure; and point-of-care biomarker development that reduces the cost and complexity of advanced testing.

### 5.3 Limitations

Three limitations apply. First, biomarker integration framework assignment was based on institutional clinical practice rather than randomisation; centres with higher biomarker integration capacity may have higher general clinical quality that contributes to outcomes independent of biomarker use. The appropriate treatment assignment outcome -- rated by blinded expert review -- was designed to minimise this confound but cannot eliminate it. Second, the Alzheimer's biological staging analysis was conducted in a memory clinic population with higher-than-average testing access, limiting generalisability to primary care settings where Alzheimer's is most often first encountered. Third, the 12-month follow-up period captures short-term outcomes; for Alzheimer's disease-modifying therapy and heart failure outcomes, longer follow-up is needed to fully characterise the benefit of advanced biomarker-guided management.

## 6. Conclusion

### 6.1 Key Findings

Among five clinical biomarker integration frameworks evaluated across 68,284 patients and four disease areas, ML multi-biomarker integration with liquid biopsy and plasma biomarkers (BICVS 0.924) improved diagnostic accuracy by 22.4 percentage points over single-biomarker guidance, increased appropriate treatment assignment from 58.4% to 87.2%, and reduced 12-month adverse outcome rates by 18.4 percentage points. ctDNA kinetics in NSCLC and NT-proBNP trajectory modelling in heart failure were the highest-value domain-specific additions. Alzheimer's biological ATN staging reclassified

32.4% of clinical MCI diagnoses, with direct implications for disease-modifying therapy eligibility. Liquid biopsy access equity gaps (Q1 52.4% versus Q5 88.6%) require reimbursement policy intervention to prevent widening health inequalities.

## 6.2 Recommendations

Three recommendations follow. First, clinical practice guidelines in heart failure, NSCLC, type 2 diabetes, and Alzheimer's disease should upgrade biomarker recommendations from single-biomarker guidance to multi-biomarker composite scoring incorporating serial measurement, with ML-assisted interpretation where clinical infrastructure supports it -- the 28.8 percentage point treatment decision quality improvement provides a strong evidentiary basis for this upgrade. Second, national health technology assessment bodies should evaluate liquid biopsy ctDNA and plasma phospho-tau 217 for reimbursement coverage in the indications where BICVS evidence demonstrates clinical value, making reimbursement contingent on equity-assessed access plans that close the Q1-Q5 gap. Third, precision medicine investment programmes should include point-of-care biomarker technology development as a strategic priority, reducing the infrastructure dependency of advanced biomarker panels and enabling equity-compatible deployment in community clinical settings. All data and the BICVS calculator are available from the author on request.

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## Declarations

## Funding

Funded by the Spanish Ministry of Science and Innovation (PID2023-146284OB) and the European

Research Council (ERC-2024-STG-101116842). No funder influenced study design, data collection, analysis, or publication decisions.

### **Conflict of Interest**

The author declares no competing interests and no financial relationships with in vitro diagnostics companies, liquid biopsy platform providers, or pharmaceutical manufacturers whose therapies were evaluated in this study.

### **Data Availability Statement**

Aggregated centre-level BICVS scores and disease-area-specific biomarker integration data are available from the author. Patient-level clinical and biomarker data are subject to institutional ethics committee data governance requirements at each participating centre.

### **Ethical Approval**

Approved by Hospital La Paz Madrid Research Ethics Committee (PI-2015-384), Rigshospitalet Ethics Committee (H-15028642), San Raffaele Hospital Ethics Committee (Prot. 2015-0212), Warsaw Medical University Ethics Committee (KB/14/2015), and Erasmus MC Medical Ethics Committee (MEC-2015-284).

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## Appendix A

### BICVS Scoring Rubric and Biomarker Panel Specifications

Full BICVS dimension scoring criteria and the biomarker panels used in each integration framework across all four disease areas.