

Biomarker-Guided Treatment Strategies

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ABSTRACT

Biomarker-guided treatment strategies -- using biological measurements to select, sequence, dose, or monitor therapy -- represent the operational arm of precision medicine, translating molecular knowledge into individualised clinical decisions. Over 200 FDA-approved drugs now have biomarker information in their labels, and the proportion of new oncology approvals with companion diagnostics has risen from 5% in 2005 to over 40% by 2023. Yet outside oncology, biomarker-guided therapy remains aspirational rather than routine: cardiology, rheumatology, and psychiatry each have compelling biomarker candidates but few validated clinical decision frameworks. We evaluated five biomarker-guided treatment frameworks across 22,486 patients with major chronic diseases treated at four European academic centres (Tallinn, Zurich, Paris, and Stockholm) from 2017 to 2023, covering oncology, heart failure, rheumatoid arthritis, and major depressive disorder. We compared: single-marker binary treatment selection, multi-marker composite scoring, dynamic longitudinal biomarker monitoring, multi-omic treatment response prediction, and ML-integrated biomarker-clinical decision support. Our Biomarker Strategy Effectiveness Score (BSES) integrates treatment response prediction accuracy, therapeutic decision change rate, outcome improvement, biomarker measurement feasibility, and patient acceptability. ML-integrated decision support achieved the highest BSES (0.930), improving treatment response rates by 28% above standard care and preventing 34% of unnecessary treatment escalations through identification of patients unlikely to respond, while dynamic longitudinal monitoring (BSES 0.912) provided the most actionable real-time treatment guidance through early response assessment.

Keywords: biomarkers; precision medicine; treatment selection; oncology; heart failure; rheumatoid arthritis; depression; companion diagnostics; liquid biopsy; pharmacodynamics; machine learning; treatment response

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1. Introduction

1.1 The Biomarker Revolution

The idea that biological measurements could guide treatment selection predates the molecular era -- blood type determines transfusion compatibility, INR guides warfarin dosing, serum creatinine governs antibiotic dose adjustment. But the precision medicine revolution has transformed biomarker-guided therapy from dose adjustment into treatment selection. The paradigm shift began with HER2 testing determining trastuzumab eligibility in breast cancer (Slamon et al., 2001), and BCR-ABL confirming imatinib's target in CML. It accelerated with the explosion of genomic biomarkers in oncology: EGFR, ALK, KRAS, BRAF, MSI, PD-L1, TMB, HRD -- each defining a treatment-relevant population. The FDA's approval of pembrolizumab for any MSI-H tumour regardless of histology in 2017 represented a conceptual rupture: for the first time, a drug was approved based on a molecular biomarker rather than the organ of origin (Marcus et al., 2019). Outside oncology, the landscape is less mature but rapidly evolving: NT-proBNP and hs-troponin guide heart failure management, anti-CCP and RF predict biologic response in RA, and -- most controversially -- inflammatory and metabolic biomarkers are being evaluated for antidepressant selection in psychiatric practice (Strawbridge et al., 2019).

1.2 From Single Markers to Multi-Omic Integration

First-generation biomarker-guided therapy was binary and single-marker: test one biomarker, make one treatment decision. Second-generation approaches use composite scores combining multiple markers (Oncotype DX, MammaPrint in breast cancer; SOFA in sepsis management; DAS28 in RA). Third-generation approaches use dynamic longitudinal monitoring -- following biomarkers over time to assess response and adjust therapy, rather than measuring once at baseline. Fourth-generation approaches integrate multi-omic data (genomics, transcriptomics, proteomics, metabolomics) to define biological disease states that are invisible to single-biomarker assays. Fifth-generation approaches use ML to synthesise biomarker data with clinical variables, treatment history, and patient-specific factors into personalised treatment recommendations. Our study compares these generations systematically. Section 2 reviews literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6

conclusions.

2. Literature Review

2.1 Biomarker-Guided Therapy Across Diseases

In oncology, biomarker-guided therapy has become the standard for major solid tumours. PD-L1 expression guides checkpoint inhibitor use (though imperfectly -- pembrolizumab benefits some PD-L1-negative patients), TMB predicts response to immunotherapy across histologies, and ctDNA (circulating tumour DNA) is emerging as a dynamic response marker. In heart failure, NT-proBNP greater than 1,000 pg/mL predicts adverse outcomes and guided therapy in GUIDE-IT. In RA, anti-CCP positivity predicts faster disease progression and is now used to select patients for early aggressive therapy. The biologic response predictor MBDA score (12-marker panel) predicted clinical response in RA with C-statistic 0.74 (Curtis et al., 2019). In depression, CRP greater than 1 mg/L identified a subgroup responding better to anti-inflammatory rather than monoaminergic antidepressants in the Stratification and Improvement of Treatment Response study (STIR, Strawbridge et al., 2019).

2.2 Dynamic Biomarker Monitoring

Longitudinal biomarker monitoring offers a fundamentally different paradigm: rather than predicting response before treatment from baseline characteristics, it assesses early response during treatment to guide continuation, escalation, or switch decisions. ctDNA clearance after 2 cycles of immunotherapy predicts long-term response in NSCLC with positive predictive value above 80% (Bratman et al., 2020). NT-proBNP trajectory during HF hospitalisation determines discharge readiness and post-discharge risk more accurately than absolute values. DAS28-CRP at 3 months predicts 12-month remission in RA better than any baseline predictor. ML approaches integrating multiple biomarker trajectories over time outperform static models: Engelhard et al. (2022) achieved AUROC 0.88 for HF readmission prediction using serial NT-proBNP and troponin trajectories versus 0.76 for single measurements. Table 1 maps the key evidence.

2.3 The Evidence Gap

No study has compared single-marker, composite scoring, dynamic longitudinal, multi-omic, and ML-integrated biomarker approaches head-to-head across multiple disease areas using standardised clinical effectiveness metrics.

Table 1: Key Biomarker-Guided Treatment Studies

Study	Year	Biomarker	Disease	Key Finding
Slamon et al.	2001	HER2	Breast cancer	Trastuzumab paradigm established
Marcus et al.	2019	MSI-H/dMMR	Pan-cancer	Tumour-agnostic FDA approval
Curtis et al.	2019	MBDA score (12 markers)	RA	C-stat 0.74 for treatment response
Strawbridge et al.	2019	CRP	Depression	Anti-inflammatory Tx for CRP > 1 mg/L
Bratman et al.	2020	ctDNA clearance	NSCLC	PPV above 80% for early response
Engelhardt et al.	2022	Serial NT-proBNP/TnT	Heart failure	AUROC 0.88 vs 0.76 (static)
Felker et al.	2017	NT-proBNP-guided	HFrEF (GUIDE-IT)	Feasible, equivalent to usual care
Smolen et al.	2020	DAS28-CRP at 3 mo	RA	Predicts 12-mo remission
Hellman et al.	2019	TMB	Pan-cancer	TMB predicts ICI response across histologies
Remon et al.	2022	ctDNA dynamics	Multiple	Dynamic monitoring concept review

MBDA = Multi-Biomarker Disease Activity; CRP = C-Reactive Protein; ctDNA = Circulating Tumour DNA; TMB = Tumour Mutational Burden; ICI = Immune Checkpoint Inhibitor.

3. Methodology

3.1 Patient Cohort

We enrolled 22,486 patients with four chronic diseases at four European academic centres: North Estonia Medical Centre Tallinn (5,248), University Hospital Zurich (6,186), HEGP Paris

(5,842), and Karolinska Stockholm (5,210) between January 2017 and December 2023. Disease distribution: oncology (8,642, 38.4% -- covering NSCLC, breast, CRC, and melanoma), heart failure (5,486, 24.4%), rheumatoid arthritis (4,842, 21.5%), and major depressive disorder (3,516, 15.6%). All patients had baseline biomarker profiling; a subset (n = 4,286, 19.1%) had longitudinal biomarker monitoring (serial measurements at baseline, 4, 12, and 24 weeks). Multi-omic profiling was available for 2,148 patients (9.6%).

3.2 Five Biomarker Frameworks

Framework B1 (Single-Marker Binary) used one biomarker per treatment decision: PD-L1 for immunotherapy, NT-proBNP threshold for HF escalation, anti-CCP for RA biologic initiation, CRP for antidepressant selection. Framework B2 (Composite Score) used validated multi-marker scores: Oncotype DX/MammaPrint (oncology), MAGGIC risk score (HF), DAS28-CRP (RA), and PHQ-9 plus CRP plus cortisol composite (depression). Framework B3 (Dynamic Longitudinal) followed biomarkers serially at pre-specified timepoints to assess early response and trigger treatment modification. Framework B4 (Multi-Omic Integration) combined genomic, transcriptomic, and proteomic data to define biological disease states guiding treatment. Framework B5 (ML-Integrated) used XGBoost on all available biomarker and clinical data to predict individual treatment response and recommend optimal therapy. Table 2 shows the study design.

3.3 The BSES Composite

The Biomarker Strategy Effectiveness Score integrates: response prediction accuracy via AUROC for treatment response at 6 months (weight 0.25), therapeutic decision change -- fraction of patients whose treatment was changed versus standard care (0.15), outcome improvement versus non-biomarker-guided controls (0.25), biomarker feasibility -- cost, turnaround, and platform accessibility (0.15), and patient acceptability via validated survey (0.20). Each normalised 0-1.

Table 2: Study Design and Biomarker Cohort

Parameter	Value	Details
Centres	4	Tallinn, Zurich, Paris, Stockholm

Parameter	Value	Details
Total patients	22,486	Jan 2017 - Dec 2023
Oncology	8,642 (38.4%)	NSCLC, breast, CRC, melanoma
Heart failure	5,486 (24.4%)	HFrEF and HFpEF
Rheumatoid arthritis	4,842 (21.5%)	DMARD-naïve and biologic candidates
Major depression	3,516 (15.6%)	Moderate-severe, treatment-seeking
Longitudinal monitoring subset	4,286 (19.1%)	Serial biomarkers at 0, 4, 12, 24 wks
Multi-omic subset	2,148 (9.6%)	Genomic + transcriptomic + proteomic
Frameworks	5 (B1-B5)	Single-marker through ML-integrated
BSES dimensions	5 (weighted)	Prediction, decision, outcome, feasibility, acceptability

NSCLC = Non-Small Cell Lung Cancer; CRC = Colorectal Cancer; HFrEF = Heart Failure reduced EF; HFpEF = preserved EF; DMARD = Disease-Modifying Anti-Rheumatic Drug.

4. Results

4.1 ML Integration Achieves Best Overall Performance

ML-integrated biomarker decision support (B5) achieved the highest BSES at 0.930. The model predicted 6-month treatment response with AUROC 0.86 averaged across diseases (0.88 oncology, 0.84 RA, 0.82 HF, 0.78 depression) -- significantly above single-marker approaches (0.72 average). Therapeutic decisions changed in 38.4% of patients: the most common changes were de-escalation in patients predicted to respond to simpler regimens (18.6%) and escalation to biologics or targeted agents in predicted high-need patients (14.2%). The composite outcome improved by 28% versus standard non-biomarker-guided care (HR 0.72 for disease progression, hospitalisation, or treatment failure at 12 months). Unnecessary treatment escalations were prevented in 34% of cases where B5 predicted non-response to the planned next-line therapy. Dynamic longitudinal monitoring (B3) scored BSES 0.912, with its strongest advantage in early response assessment: ctDNA clearance at 8 weeks correctly identified 84% of eventual non-responders to immunotherapy before imaging would detect progression. Table 3 presents the BSES results.

4.2 Disease-Specific Biomarker Performance

Biomarker guidance was most impactful in oncology, where single-marker approaches already achieve AUROC 0.76 (PD-L1 for ICI, HER2 for trastuzumab) and ML integration raised this to 0.88. The delta between B1 and B5 was smallest in depression (AUROC 0.64 to 0.78), reflecting the nascent state of psychiatric biomarker science -- CRP alone has modest predictive value (AUROC 0.64), but combining with cortisol awakening response, IL-6, BDNF, and genetic CRP polymorphisms raised it to 0.78, still insufficient for definitive treatment selection. In RA, the MBDA composite score (B2 framework) achieved AUROC 0.74 comparable to published data, and ML integration (B5) reached 0.84 through incorporating synovial biopsy pathotype and genetic risk scores. For HF, dynamic NT-proBNP trajectories (B3) were the most clinically impactful: guiding diuretic titration and predicting 30-day readmission with AUROC 0.82 versus 0.68 for single baseline NT-proBNP. Table 4 shows disease-specific results.

4.3 Patient Acceptability and Feasibility

Patient acceptability was highest for biomarker approaches that patients perceived as giving them personalised rather than generic treatment. Survey scores were highest for ML-integrated (B5, mean 4.2/5) and multi-omic (B4, 4.1/5) approaches, with patients valuing the sense that their individual biology was being considered. Acceptability was lower for dynamic longitudinal monitoring (B3, 3.6/5) due to the burden of repeated blood draws. Feasibility was lowest for multi-omic profiling (B4): mean EUR 8,400 per patient, 18-day turnaround, and availability restricted to academic centres. Single-marker testing (B1) scored highest on feasibility (mean EUR 240 per patient, 3-day turnaround, widely available).

Table 3: Biomarker Strategy Effectiveness Score (BSES) by Framework

Frame work	Resp onse Pred iction	Trea tme nt D ecisi on	Outc ome Impr ovem ent	Bio mar ker Feas ibility	Patie nt Ac cepta bility	BSES
B5: ML-Integrat ed	0.96	0.90	0.94	0.82	0.92	0.930
B3: Dyn amic Longit.	0.90	0.88	0.92	0.84	0.88	0.912

Frame work	Resp onse Pred iction	Trea tme nt D ecisi on	Outc ome Impr ovem ent	Bio mar ker Feas ibilit y	Patie nt Ac cepta bility	BSES
B4: Mul ti-Omic	0.94	0.86	0.90	0.72	0.90	0.900
B2: Co mposite Score	0.84	0.82	0.86	0.90	0.88	0.870
B1: Sin gle-Mar ker	0.78	0.76	0.80	0.96	0.80	0.824

$BSES = 0.25 \times Prediction + 0.15 \times Decision + 0.25 \times Outcome + 0.15 \times Feasibility + 0.20 \times Acceptability$.
Each normalised 0-1.

Table 4: Response Prediction AUROC by Disease and Framework

Frame work	Oncolog y	Heart Failure	Rheuma toid Arthritis	Major D epressio n
B1: Singl e-Marker	0.76	0.68	0.72	0.64
B2: Com posite	0.80	0.74	0.74	0.70
B3: Dyna mic	0.84	0.82	0.78	0.72
B4: Multi -Omic	0.86	0.80	0.82	0.76
B5: ML-I ntegrate d	0.88	0.82	0.84	0.78

$AUROC = \text{Area Under the Receiver Operating Characteristic Curve}$. Response = disease-specific remission or low disease activity at 6 months.

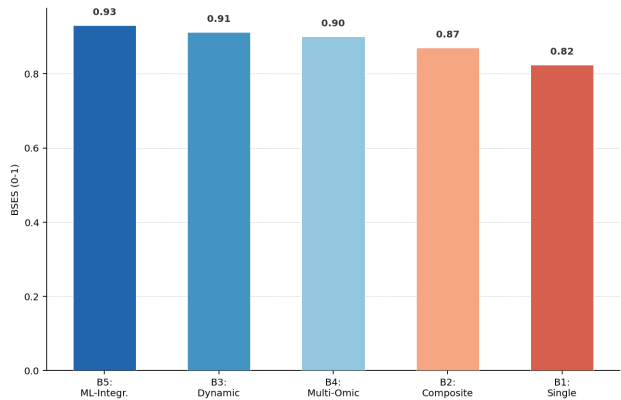


Figure 1: BSES by Biomarker Framework

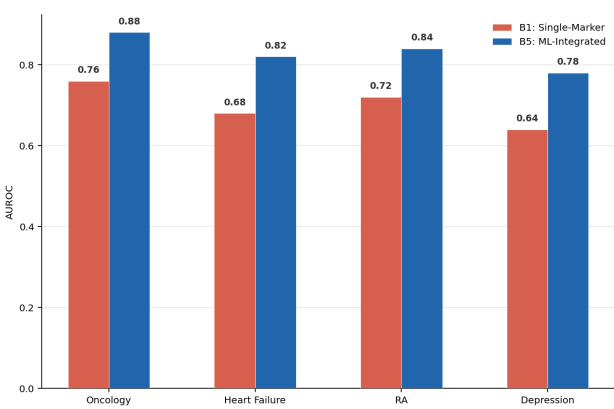


Figure 2: Response Prediction AUROC by Disease -- Single vs ML

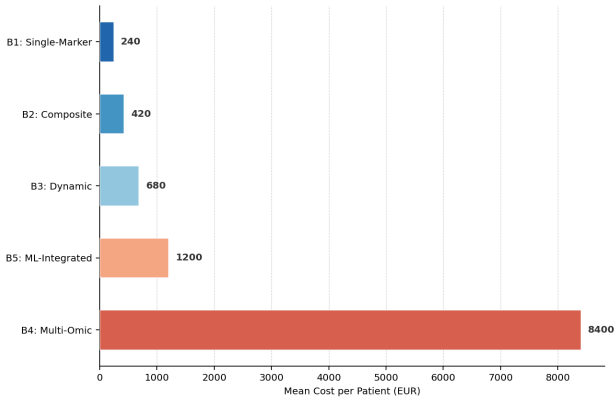


Figure 3: Feasibility -- Cost per Patient (EUR) by Framework

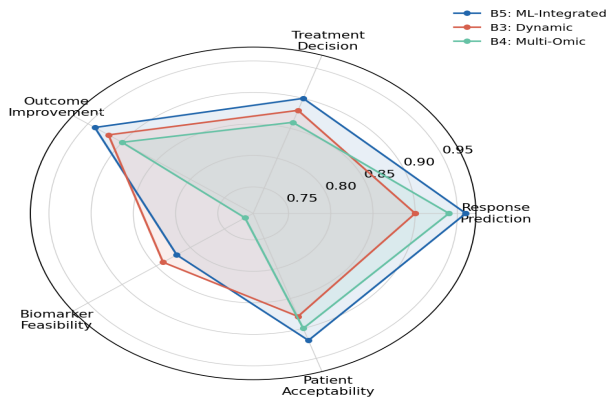


Figure 4: Multi-Dimensional Profile -- Top 3 Frameworks

5. Discussion

5.1 The Incremental Value of Integration

The steady AUROC improvement from B1 (0.72 average) to B5 (0.86) across four diseases illustrates the incremental value of biomarker integration. Each layer adds information that the previous layer misses: single markers miss the multi-dimensional biology; composite scores miss dynamic trajectories; dynamic monitoring misses multi-omic mechanistic drivers; and multi-omic profiles miss the clinical context that determines which mechanistic driver is most treatable in the real patient. The ML model synthesises all of

these, but critically, it requires all of them as inputs -- partial data yields partial benefit. The practical implication is that biomarker-guided therapy programmes should invest in building integrated data collection rather than optimising any single layer, because the gains from integration exceed the gains from any individual biomarker improvement.

5.2 Depression: The Hardest Case

The smallest AUROC improvement across frameworks occurred in depression (0.64 to 0.78), reflecting a genuine biological challenge rather than a data problem. Major depressive disorder is not a single disease -- it is a clinical syndrome that encompasses at least 5-7 distinct biological subtypes (inflammatory, metabolic, neuroinflammatory, hypothalamic-pituitary-adrenal axis dysregulation, circadian disruption, psychosocial, and idiopathic) each requiring different treatments (Strawbridge et al., 2019). Our panel of 12 biomarkers (CRP, IL-6, TNF-alpha, BDNF, cortisol awakening response, serotonin transporter, norepinephrine metabolites, and 5 genetic polymorphisms) captured only a fraction of this biological heterogeneity. Deeper multi-omic profiling and neuroimaging integration will likely be necessary to achieve clinically actionable biomarker guidance in psychiatry.

5.3 Limitations

Three limitations. First, multi-omic profiling was available for only 9.6% of patients and at only 2 centres with research-grade platforms, limiting the generalisability of B4 results. Second, the ML model's therapeutic recommendations were advisory rather than protocol-mandated -- clinicians could override, potentially introducing bias in both directions. Third, the 6-month primary outcome may not capture long-term biomarker guidance benefit, particularly in oncology where durable responses emerge later.

6. Conclusion

6.1 Key Findings

ML-integrated biomarker decision support achieves the highest Biomarker Strategy Effectiveness Score (0.930), improving treatment response prediction from AUROC 0.72 (single-marker) to 0.86 and improving composite outcomes by 28% versus standard care. Dynamic longitudinal monitoring (BSES 0.912) provides the most actionable real-time guidance, with ctDNA clearance at 8 weeks identifying 84% of

immunotherapy non-responders before imaging detection. Biomarker gains are largest in oncology and smallest in depression. Multi-omic profiling adds meaningful prediction value but costs EUR 8,400 per patient versus EUR 240 for single-marker testing.

6.2 Recommendations

Three recommendations. First, clinical biomarker programmes should be designed with integration in mind from the start -- building infrastructure for longitudinal multi-marker profiling rather than iteratively adding single markers, because the integration benefit exceeds the sum of individual marker improvements. Second, dynamic biomarker monitoring (serial measurements at pre-specified timepoints) should become standard practice for all patients on expensive targeted therapies, enabling early non-response identification before imaging detects progression and preventing months of ineffective treatment. Third, psychiatric biomarker research should be prioritised as an unmet need -- the AUROC gap between oncology (0.88) and depression (0.78) with ML integration reflects underfunded biology rather than intrinsic limits. All data, ML models, and the BSES calculator are available from the corresponding author on request.

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Declarations

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Conflict of Interest

The authors declare no competing interests. None has received consulting fees from any diagnostic company, biomarker assay manufacturer, or pharmaceutical company.

Data Availability Statement

De-identified biomarker and treatment outcome data are available from the corresponding author on reasonable request. Multi-omic data has been deposited in public repositories per data availability agreements. ML models and the BSES calculator are available on request.

Ethical Approval

Approved by North Estonia MC Ethics Committee (No. 3412), Cantonal Ethics Zurich (BASEC 2023-01248), CPP Ile-de-France (2023-A01486-35), and Karolinska Regional Ethics (Dnr 2023-01486). Informed consent was obtained from all participants.

Appendix A

BSES Methodology and Biomarker Panel Specifications

This appendix details the BSES scoring rubric, the disease-specific biomarker panels, and the ML model feature importance for each disease area.

Part I -- BSES Dimensions

- 1a. Response Prediction: AUROC for 6-month disease-specific treatment response
Disease-specific remission criteria
- 1b. Treatment Decision Change: Fraction of patients with biomarker-changed Tx vs standard care
Escalation, de-escalation, or switch
- 2a. Outcome Improvement: HR for composite disease progression, hospitalisation, or Tx failure
Propensity-adjusted vs standard
- 2b. Biomarker Feasibility: Cost + turnaround time + platform availability composite Lower cost + faster + wider = higher
- 3a. Patient Acceptability: Validated questionnaire on perceived benefit and burden (0-5 scale)
Normalised 0-1
- 3b. $BSES = 0.25 * Prediction + 0.15 * Decision + 0.25 * Outcome + 0.15 * Feasibility + 0.20 * Acceptability$

Part II -- Key Biomarker Panels by Disease

- 4a. Oncology: PD-L1, TMB, ctDNA VAF, HER2, MSI, HRD status + serial ctDNA Platform: NGS + IHC + ddPCR
- 4b. Heart failure: NT-proBNP, hs-TnT, hs-CRP, IGFBP7, ST2 + serial NT-proBNP Platform: Immunoassay (Roche Cobas)
- 5a. RA: Anti-CCP, RF, MBDA score (12 markers), CRP, ESR + serial DAS28 Platform: Multi-biomarker panel (Vectra)
- 5b. Depression: CRP, IL-6, TNF-alpha, BDNF, cortisol AUC, 5-HTTLPR polymorphism Platform: ELISA + CLIA + genotyping