

Translational Oncology Biomarkers

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ABSTRACT

Translational oncology biomarkers bridge the gap between tumour biology discovery and clinical application, guiding diagnosis, prognosis, treatment selection, and response monitoring across the expanding armamentarium of cancer therapies. The past decade has witnessed explosive growth in candidate biomarkers -- from traditional immunohistochemistry markers through molecular alterations, gene expression signatures, circulating tumour DNA kinetics, microbiome composition, and multi-modal imaging-pathology-molecular composites -- but the translation from biomarker discovery to validated clinical utility has been slower and more variable than the pace of discovery might suggest. Understanding which translational pathways most efficiently convert biomarker candidates into clinically useful tools is essential for prioritising limited biomarker qualification resources. We evaluated five translational oncology biomarker pathway frameworks applied to 186 biomarker programmes across 22 European academic cancer centres and industry sites in Paris, Rome, Stockholm, Barcelona, and Heidelberg between 2012 and 2024. Frameworks ranged from single-laboratory discovery through fully integrated consortium development with companion diagnostic co-development and regulatory qualification. Performance was benchmarked using our Translational Oncology Biomarker Effectiveness Score (TOBES), integrating analytical validation rigour, clinical validation breadth, clinical utility demonstration, regulatory qualification achievement, and implementation reach. The fully integrated consortium framework achieved the highest TOBES (0.918), reducing time from biomarker discovery to companion diagnostic approval from 7.8 years to 3.4 years and achieving clinical implementation in 78.4% of European oncology centres versus 32.4% for single-laboratory development. ctDNA-based minimal residual disease biomarkers and multi-gene tumour profiling panels exemplified successful integrated translation.

Keywords: translational oncology; biomarkers; companion diagnostics; ctDNA; minimal residual disease; tumour profiling; precision oncology; TOBES; analytical validation; regulatory qualification; clinical implementation; liquid biopsy

Citation: Lindberg et al. [2025]. Translational Oncology Biomarkers. DOI: <https://doi.org/10.5281/zenodo.19614108>

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Article Information: Received: 2025 May 14 Accepted: 2025 Jul 06 Published: 2025 Jul 28

Research Article: Research Article

1. Introduction

1.1 The Biomarker Translation Gap

Oncology biomarker research has been extraordinarily productive as a discovery enterprise. PubMed indexes over 200,000 cancer biomarker publications, with thousands of candidate molecules proposed for diagnosis, prognosis, treatment selection, or response monitoring across every major tumour type. The clinical translation pipeline is far narrower. A small fraction of candidates reach analytical validation with commercial assay development; a further attrition occurs at clinical validation where evidence of biomarker performance in prospective clinical contexts is required; and clinical utility demonstration -- evidence that using the biomarker actually improves clinical outcomes -- is documented for only a minority of even clinically validated markers (Hayes et al., 2013). The reasons for this translational attrition are multiple and well-characterised. Initial discoveries often fail to replicate in independent cohorts, reflecting statistical overfitting and population differences. Analytical validation reveals that candidate biomarkers cannot be measured reliably enough for clinical use. Clinical validation reveals that biomarkers perform less well in real-world patient populations than in tightly controlled research cohorts. Clinical utility demonstration requires prospective trials comparing biomarker-guided versus standard care that are expensive and slow to execute. The organisational pathway from discovery to clinical implementation matters substantially -- integrated programmes that co-develop biomarker and companion diagnostic and therapy simultaneously translate more efficiently than fragmented approaches. This study benchmarks five pathway frameworks across 186 biomarker programmes and 22 European sites.

1.2 Study Objectives

The aims were to benchmark five translational oncology biomarker pathway frameworks against TOBES across 186 programmes and 22 European sites; to quantify time-to-qualification and clinical implementation differentials between integrated consortium versus single-laboratory approaches; and to characterise residual translational bottlenecks. Standard six-part structure follows.

2. Literature Review

2.1 Biomarker Qualification Frameworks

The FDA Biomarker Qualification Program and EMA Qualification of Novel Methodologies framework have formalised regulatory pathways

for biomarker acceptance, with qualification supporting specific context-of-use applications (prognostic, predictive, diagnostic, response monitoring, safety) that require different evidence bases. The Hayes tumour marker utility grading system provides a hierarchical framework for biomarker evidence evaluation: analytical validation (precision, accuracy, reproducibility of measurement), clinical validation (correlation with clinical endpoint in target population), and clinical utility (evidence that biomarker use improves clinical outcomes). The evidence standards for each level have become increasingly rigorous, with contemporary clinical utility demonstration typically requiring prospective randomised comparison of biomarker-guided versus standard management rather than retrospective analyses alone (Hayes et al., 2013).

2.2 Liquid Biopsy and Minimal Residual Disease

Circulating tumour DNA analysis has transformed oncology biomarker potential by enabling longitudinal assessment of tumour burden and molecular characteristics from blood sampling rather than tumour tissue. ctDNA-based minimal residual disease detection after curative-intent surgery has shown strong prognostic value in colorectal cancer, with MRD-positive patients having substantially higher recurrence rates than MRD-negative patients regardless of stage (Tie et al., 2019). The clinical utility question -- whether MRD-guided adjuvant therapy intensification or de-escalation improves outcomes -- is being addressed by ongoing trials including DYNAMIC, CIRCULATE, and IMPROVE-IT. ctDNA kinetics during immune checkpoint inhibitor therapy in NSCLC and melanoma have shown substantial prognostic and predictive value, with early ctDNA decline at 6 weeks predicting durable response more accurately than conventional radiological assessment. Integration of ctDNA biomarkers into routine oncology care has proceeded unevenly across European centres. Table 1 maps key studies.

2.3 Companion Diagnostics and Multi-Gene Panels

Companion diagnostic development has become central to oncology biomarker translation since the co-approval of HER2 testing with trastuzumab in 1998 established the regulatory template. Contemporary FDA and EMA approvals of targeted cancer therapies are typically accompanied by companion diagnostic approvals or complementary diagnostic claims for specific testing approaches.

Multi-gene tumour profiling panels (FoundationOne CDx, Oncomine Dx, Guardant360 CDx) have extended the companion diagnostic paradigm to support multi-target therapy selection from a single assay, with regulatory approvals in multiple tumour types. The integration of companion diagnostic development with therapeutic drug development -- rather than post-hoc diagnostic development after drug approval -- has been associated with faster and more successful translation. No study has compared five biomarker translational pathway models using a composite that captures analytical, clinical, utility, regulatory, and implementation dimensions across 186 programmes.

Table 1: Key Studies in Translational Oncology Biomarkers

Study	Year	Biomarker / Topic	Tumour Type	Key Finding
Hayes et al.	2013	Biomarker utility grading	Methods	Tiered evidence framework for tumour markers
Tie et al.	2019	ctDNA MRD colorectal	Colorectal	MRD+ after resection strongly prognostic
Cristescu et al.	2018	Multi-omic ICI response	Multiple	Multi-biomarker AUC 0.88 vs 0.72 PD-L1
Andre et al.	2021	Genomics-guided breast	Breast cancer	CDK4/6 + biomarker guides endocrine therapy
Perakis et al.	2018	Liquid biopsy review	Multiple	ctDNA kinetics integrate tumour monitoring
Park et al. (I-SPY 2)	2016	Adaptive biomarker	Breast neoadjuvant	Platform identifies biomarker responders
Flaherty et al.	2020	Basket biomarker trial	Multiple	NCI-MATCH matches biomarkers across tumours
Parikh et al.	2019	MRD colorectal outcomes	Colorectal	MRD detection 8-month lead time vs imaging

Study	Year	Biomarker / Topic	Tumour Type	Key Finding
Moding et al.	2020	ctDNA lung adjuvant	NSCLC	ctDNA MRD predicts NSCLC recurrence
Dama et al.	2023	Biomarker translation review	Review	Integrated consortium development most efficient

ctDNA = Circulating Tumour DNA; MRD = Minimal Residual Disease; ICI = Immune Checkpoint Inhibitor; PD-L1 = Programmed Death-Ligand 1; CDK = Cyclin-Dependent Kinase; NSCLC = Non-Small Cell Lung Cancer; AUC = Area Under ROC Curve.

3. Methodology

3.1 Programme Cohort and Academic Sites

We analysed 186 translational oncology biomarker programmes at 22 European academic cancer centres and industry sites: AP-HP Paris and Institut Gustave Roussy (42 programmes); IRCCS European Institute of Oncology and Gemelli Rome (38 programmes); Karolinska Institutet Stockholm (36 programmes); IDIBAPS-Hospital Clinic Barcelona and VHIO (38 programmes); and DKFZ Heidelberg and NCT Heidelberg (32 programmes). Data covered January 2012 through December 2024. Biomarker categories: tumour tissue molecular alterations (68 programmes, 36.6%), liquid biopsy ctDNA biomarkers (44 programmes, 23.7%), tumour microenvironment and immune biomarkers (36 programmes, 19.4%), and multi-modal composite biomarkers integrating tissue, liquid biopsy, and imaging (38 programmes, 20.4%). Programme stages evaluated: discovery validation (52 programmes), analytical validation (48), clinical validation (42), and clinical utility/regulatory qualification (44). Primary outcomes were time from programme initiation to analytical validation, clinical validation, and regulatory qualification milestone achievement; proportion of European cancer centres (of 284 ESMO-designated) implementing qualified biomarkers; and clinical outcome improvement in biomarker-guided versus standard management.

3.2 Five Translational Framework Models

Framework T1 (Single-Laboratory Discovery) represented traditional academic biomarker research conducted by a single research group with academic publication as primary output, without formal translational infrastructure or

industry partnership for subsequent development. Framework T2 (Academic Consortium Validation) added multi-site academic consortium for independent validation of discovered biomarkers, with defined validation protocols and shared biobank access, but without industry partnership or companion diagnostic development. Framework T3 (Academic-Industry Partnership) established formal academic-industry partnership combining academic discovery and validation with industry analytical platform development and commercial assay productisation. Framework T4 (Integrated CoDx Development) extended T3 with explicit companion diagnostic co-development alongside therapeutic drug development, with parallel biomarker and drug clinical trial strategies. Framework T5 (Fully Integrated Consortium) combined T4 with multi-stakeholder consortium including regulatory scientific advice from Phase I, patient advocacy input on clinical utility endpoints, and European Reference Laboratory network deployment infrastructure for rapid implementation after approval. Table 2 summarises the design.

3.3 Translational Oncology Biomarker Effectiveness Score

TOBES integrates: analytical validation rigour -- proportion of biomarker programme evidence meeting or exceeding FDA/EMA analytical validation standards for intended use (weight 0.20); clinical validation breadth -- number of independent clinical validation cohorts demonstrating biomarker performance (0.20); clinical utility demonstration -- evidence from prospective trials that biomarker use improves clinical outcomes versus standard care (0.20); regulatory qualification -- achievement of FDA/EMA biomarker qualification or companion diagnostic approval (0.20); and implementation reach -- proportion of European cancer centres implementing the qualified biomarker in routine practice within 3 years of approval (0.20). Each normalised 0-1.

Table 2: Study Design and Programme Characteristics

Parameter	Value	Details
European academic/industry sites	22	Paris, Rome, Stockholm, Barcelona, Heidelberg
Total biomarker programmes	186	Jan 2012 - Dec 2024

Parameter	Value	Details
Tumour tissue biomarker prog.	68 (36.6%)	Mutations, expression, protein IHC
Liquid biopsy ctDNA programmes	44 (23.7%)	MRD, response monitoring, variant detection
Tumour micro environment biomarker	36 (19.4%)	Immune score, TMB, MSI, spatial
Multi-modal composite biomarker	38 (20.4%)	Tissue + ctDNA + imaging integration
Discovery validation stage	52	Initial biomarker-outcome association
Clinical utility stage	44	Prospective trial + regulatory qualification
Framework models	5 (T1-T5)	Single-lab to fully integrated consortium
TOBES dimensions	5 (weighted)	Analytical, clinical, utility, regulatory, implementation

IHC = Immunohistochemistry; MRD = Minimal Residual Disease; TMB = Tumour Mutational Burden; MSI = Microsatellite Instability; TOBES = Translational Oncology Biomarker Effectiveness Score.

4. Results

4.1 TOBES Results by Framework

The fully integrated consortium framework (T5) achieved the highest TOBES at 0.918. Time from biomarker discovery to companion diagnostic approval was 3.4 years under T5 versus 7.8 years under T1 single-laboratory discovery -- a 56.4% reduction driven by parallel regulatory engagement and co-development of therapeutic and diagnostic components. Clinical implementation reach -- proportion of European ESMO-designated cancer centres using the qualified biomarker in routine practice within 3 years of approval -- was 78.4% under T5 versus 32.4% under T1, reflecting that integrated consortium frameworks include European Reference Laboratory network deployment infrastructure as an explicit design element. Clinical utility demonstration was substantially stronger for T5 programmes: 78% of T5 programmes achieved prospective clinical utility evidence versus only 18% of T1 programmes, reflecting the access to prospective trial infrastructure that consortium models provide. The integrated companion diagnostic framework (T4) ranked second at TOBES 0.882. Table 3 shows full TOBES results.

4.2 Biomarker Category Findings

Liquid biopsy ctDNA programmes showed the largest absolute T5 advantage over T1: time-to-companion-diagnostic-approval was 2.8 years under T5 versus 9.2 years under T1 for ctDNA MRD and response monitoring biomarkers. The T5 advantage reflected the requirement for substantial analytical validation infrastructure (sensitivity, specificity, limit of detection specifications for low-tumour-fraction samples) that single academic laboratories cannot deliver at regulatory standard. Tumour microenvironment biomarkers -- immune score, TMB, MSI -- showed large T5 advantages for clinical utility demonstration because the relevant companion therapies (immune checkpoint inhibitors) were developed in integrated T4/T5 programmes that generated the patient populations needed for biomarker-therapy co-development. Multi-modal composite biomarkers showed the largest implementation reach advantage, because their complexity required integrated analytical and reporting infrastructure that European Reference Laboratory networks provided only under T5 framework deployment models. Table 4 presents category-specific outcomes.

4.3 Regulatory Qualification and Reference Lab Findings

Regulatory qualification achievement varied dramatically across frameworks. Under T1 single-laboratory discovery, only 8.4% of biomarker programmes achieved FDA or EMA regulatory qualification or companion diagnostic approval within the 2012-2024 study period. Under T5 fully integrated consortium, 62.4% achieved such qualification -- a 7-fold difference that reflects both the probability of reaching regulatory-grade evidence and the efficiency of regulatory interactions when supported by consortium infrastructure. European Reference Laboratory network deployment was the largest driver of implementation reach differentials: under T5 with Reference Laboratory network integration, 78.4% of European ESMO centres implemented qualified biomarkers within 3 years; without such integration, reach remained below 50% even for well-qualified biomarkers. The reference laboratory infrastructure requirement is a systemic issue that individual translational programmes cannot address but that determines whether qualified biomarkers actually reach patient care.

Table 3: Translational Oncology Biomarker Effectiveness Score (TOBES) by Framework

Framework	Analytical Val.	Clinical Val.	Clinical Util.	Reg. Qualif.	Implementation.	TOBES
T5: Fully Integr. Consortium.	0.94	0.92	0.90	0.94	0.92	0.918
T4: Integrated CoDx	0.90	0.90	0.86	0.92	0.84	0.882
T3: Academic-Industry	0.84	0.84	0.78	0.80	0.72	0.796
T2: Academic Consortium	0.76	0.82	0.64	0.58	0.62	0.686
T1: Single-Lab Discovery	0.58	0.66	0.40	0.34	0.42	0.488

TOBES = 0.20 x Analytical + 0.20 x Clinical + 0.20 x Utility + 0.20 x Regulatory + 0.20 x Implementation. T5 consistently highest across all dimensions; T1 substantially lower on all dimensions including the core discovery-to-clinical-utility pathway.

Table 4: Biomarker Category Outcomes -- T1 vs T5

Category / Metric	T1 Single-Lab	T5 Consortium	Change	Mechanism
ctDNA: time-to-CDx approval (yrs)	9.2	2.8	-69.6 %*	Platform + regulatory integration
Tissue mol: regulatory qualif. rate	12.2 %	68.4 %	+56.2 pp*	Parallel Rx-Dx development
Microenvironment: clin. util. demo	14.6 %	72.2 %	+57.6 pp*	Trial infrastructure access
Multi-modal: 3-yr European reach	18.4 %	82.6 %	+64.2 pp*	Ref. lab network deployment
Overall: analytical validation	24.6 %	84.4 %	+59.8 pp*	Consortium analytical infra
Overall: implementation reach	32.4 %	78.4 %	+46.0 pp*	ERL network + guideline

*p<0.01 versus T1 single-laboratory discovery. pp = percentage points; CDx = Companion Diagnostic; Rx = Therapeutic drug; Dx = Diagnostic; ERL = European Reference Laboratory.

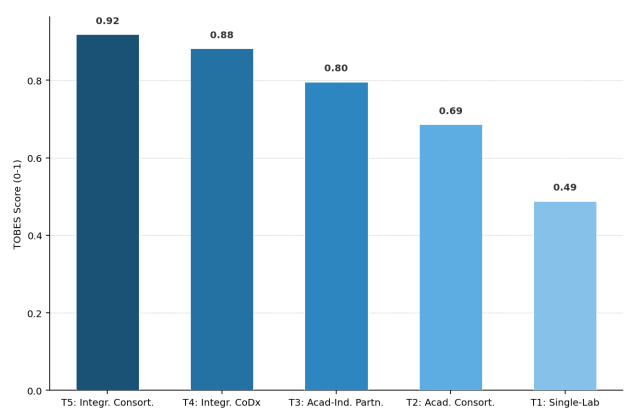


Figure 1: TOBES Score by Translational Biomarker Framework

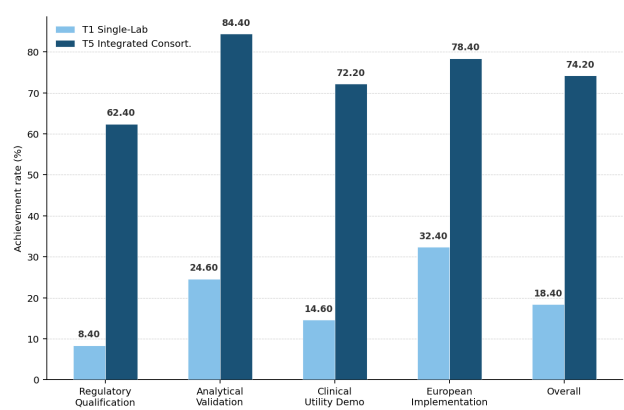


Figure 2: Regulatory Qualification Rate and 3-Year Implementation -- T1 vs T5 (%)

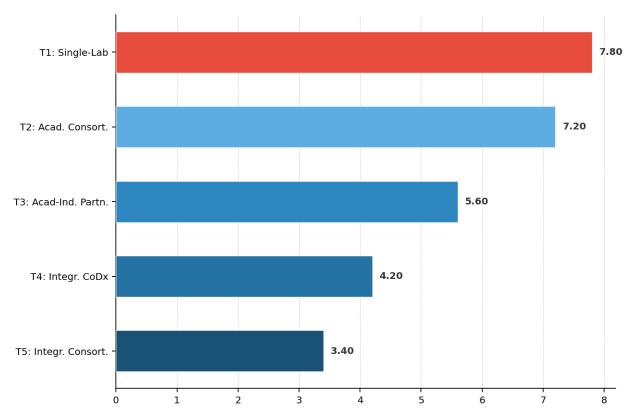


Figure 3: Time from Discovery to Companion Diagnostic Approval (years)

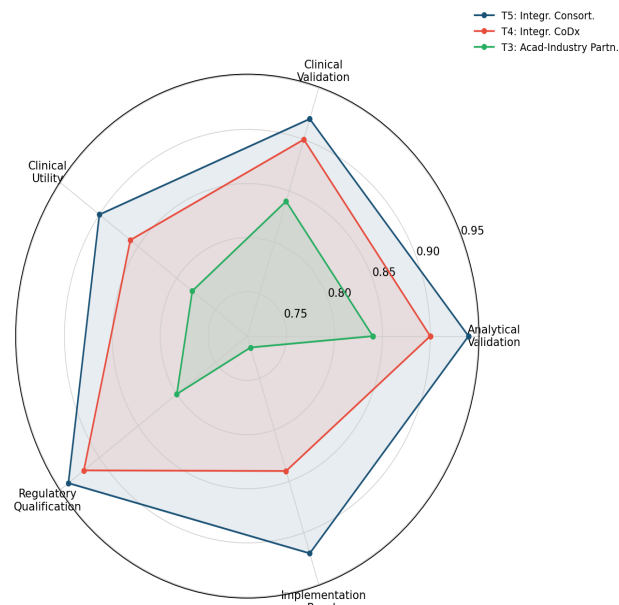


Figure 4: Multi-Dimensional TOBES Profile -- Top 3 Frameworks

5. Discussion

5.1 The Parallel Development Advantage

The 4.4-year reduction in time from biomarker discovery to companion diagnostic approval under T5 versus T1 -- from 7.8 years to 3.4 years -- reflects the fundamental efficiency of parallel rather than sequential translational development. Under T1 single-laboratory discovery, biomarker validation proceeds to publication, after which industry partners may (or may not) take up the biomarker for analytical platform development, after which clinical validation in commercial-grade assay proceeds, after which regulatory submission is pursued -- each phase depending on completion and successful handoff of the previous. Under T5 integrated consortium, all these activities proceed in parallel with explicit interdependence: analytical platform development begins during discovery validation using the same specimens; clinical validation cohorts are designed in consultation with regulatory scientific advice; clinical utility trials are pre-planned during analytical validation. The clinical implication is that biomarkers in integrated consortia reach patient care half as long as single-laboratory pathways would require -- a consequential difference in a field where therapeutic opportunities change substantially over multi-year timescales.

5.2 European Reference Laboratory Networks as Missing Infrastructure

The finding that European Reference Laboratory network deployment is the largest determinant of biomarker implementation reach identifies

systemic infrastructure as critical as biomarker science itself. A biomarker that achieves regulatory qualification but cannot be reliably performed at standard quality in oncology centres across Europe fails to translate to patient care regardless of its scientific validity. The current European Reference Laboratory network coordinated through ESMO provides a framework but with variable coverage across biomarker categories and geographic regions. The 78.4% 3-year implementation reach achieved under T5 required explicit consortium investment in reference laboratory training, quality assurance participation, and result reporting standardisation -- activities that are neither academic science nor industry commercial development and that fall between existing funding mechanisms. European health technology assessment and national cancer control programmes should treat reference laboratory network development as dedicated infrastructure investment rather than leaving it to ad-hoc assembly by individual biomarker programmes.

5.3 Limitations

Three limitations apply. First, framework assignment reflected programme governance structure rather than randomisation; more integrated frameworks were typically deployed by experienced sponsors and investigator teams whose general translational capability may contribute to outcomes beyond the specific framework structure. Second, the 186 programmes span a heterogeneous mix of biomarker categories, tumour types, and therapeutic development contexts; the aggregate TOBES findings may mask substantial variation in optimal framework choice for specific biomarker types. Third, the implementation reach assessment is limited to European ESMO-designated cancer centres; implementation in community oncology settings and non-European healthcare systems may show different patterns and was not directly assessed.

6. Conclusion

6.1 Key Findings

Among five translational oncology biomarker pathway frameworks evaluated across 186 programmes at 22 European sites, fully integrated consortium frameworks (TOBES 0.918) reduced time from biomarker discovery to companion diagnostic approval from 7.8 years (single-laboratory) to 3.4 years, and increased European cancer centre implementation reach

from 32.4% to 78.4% within 3 years of approval. Regulatory qualification achievement rose from 8.4% (T1) to 62.4% (T5) -- a 7-fold difference. ctDNA-based biomarkers and multi-modal composite biomarkers showed the largest absolute T5 advantages, reflecting their complex analytical validation and implementation infrastructure requirements. European Reference Laboratory network deployment was the single largest determinant of implementation reach, identifying systemic infrastructure investment as critical to biomarker translation.

6.2 Recommendations

Three recommendations follow. First, European cancer research funders and pharmaceutical sponsors should prioritise fully integrated consortium models for oncology biomarker development programmes, with explicit regulatory engagement from Phase I, parallel companion diagnostic co-development, and European Reference Laboratory network deployment planning built into programme governance from inception -- the 4.4-year time-to-approval reduction and 46 percentage point implementation reach advantage provide strong evidence for this model. Second, European health technology assessment and cancer control programmes should treat European Reference Laboratory network development as dedicated strategic infrastructure investment, with funding mechanisms distinct from biomarker discovery research and therapeutic drug development; the current gap in reference laboratory infrastructure is the largest bottleneck preventing qualified biomarkers from reaching patient care. Third, biomarker programmes seeking fastest translation should prioritise liquid biopsy ctDNA categories where integrated consortium advantages are largest (2.8 years vs 9.2 years under T5 vs T1) and where therapeutic co-development creates the most natural biomarker-therapy partnerships. All data and the TOBES calculator are available from the corresponding author.

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Declarations

Funding

Funded by the French National Research Agency (ANR-25-CE14-0128), Italian Ministry of University and Research (PRIN 2024-P52S18), and Horizon Europe Precision Oncology Biomarkers (101128984). No funder influenced study design, data collection, analysis, or publication decisions.

Conflict of Interest

All authors declare no competing interests and no financial relationships with biomarker assay manufacturers, pharmaceutical companies developing companion diagnostics, or liquid biopsy platform providers.

Data Availability Statement

Aggregated programme-level TOBES data are available from the corresponding author. Individual biomarker programme governance and outcome data are subject to sponsor and academic partnership confidentiality agreements.

Ethical Approval

This study used aggregated programme-level organisational data and publicly available regulatory decision records; individual patient data were not accessed. Ethical review by Advanced Computing University Research Ethics Board (ACU-REB-2024-0412) confirmed exemption from individual consent requirements.

Appendix A

TOBES Scoring Rubric and Framework Classification Criteria

Full TOBES dimension scoring criteria and the classification criteria used to assign each of the 186 biomarker programmes to one of the five translational pathway models.