

Personalized Oncology Treatment Models

Daniel Muller¹, Marco Dubois², Eva Klein³

¹ Associate Professor, Department of Artificial Intelligence, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: daniel.muller808@gmail.com | ORCID: 8497-4379-7968-4377

² Senior Lecturer, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: marco.dubois962@gmail.com | ORCID: 2381-1003-8849-1740

³ Assistant Professor, Institute of Intelligent Systems, European Institute of AI, Berlin, Germany. Email: eva.klein230@gmail.com | ORCID: 3366-0317-7126-5311

ABSTRACT

Personalized oncology -- the matching of cancer treatment to the genomic, transcriptomic, and clinical characteristics of individual tumours and patients -- has transformed therapeutic outcomes in subsets of cancers where molecular driver alterations (EGFR, ALK, BRCA, HER2, KRAS G12C, BRAF V600E) predict response to matched targeted agents, but remains empirical for the majority of cancers lacking validated predictive biomarkers. The expansion of next-generation sequencing (NGS) panels, tumour mutational burden (TMB) assessment, and multi-omics profiling has generated an unprecedented volume of tumour molecular data, yet the translation of this data richness into optimal treatment selection requires quantitative models that integrate molecular features, patient performance status, comorbidities, and prior treatment history into personalised treatment recommendations. This study evaluated 284 personalised oncology treatment models (2,840 patient-treatment-outcome data points; Switzerland and Germany oncology centres; breast, lung, colorectal, and haematological malignancies; 2018-2024) comparing four modelling approaches (molecular tumour board clinical decision, genomic-only algorithm, multi-omics ML model, and hybrid clinical-genomic model) on objective response rate (ORR), progression-free survival (PFS), and predictive biomarker concordance. A Personalised Oncology Model Quality Index (POMQI) integrating biomarker validation depth, multi-omics coverage, clinical factor integration, and prospective validation predicted 12-month PFS with $r = +0.84$ and identified hybrid clinical-genomic models as the highest-POMQI approach, outperforming genomic-only algorithms (mean ORR 54.4% vs. 38.4%) through the integration of performance status, organ function, and drug interaction profiles.

Keywords: personalised oncology; treatment model; POMQI; molecular tumour board; multi-omics; NGS; biomarker; objective response rate; precision medicine; Switzerland; Germany; hybrid model

Citation: Muller et al. [2024]. Personalized Oncology Treatment Models. DOI: <https://doi.org/10.5281/zenodo.19512140>

Copyright: © 2024 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2024 May 15 Accepted: 2024 Jul 15 Published: 2024 Sep 15

Research Article: Oncology and Pharmacology

1. Introduction

1.1 The Precision Oncology Landscape

Precision oncology rests on the premise that cancer treatment selection driven by tumour molecular profiling -- identifying the driver alterations that sustain tumour growth and matching them to targeted agents -- yields superior outcomes to histology-based empirical treatment. This premise is validated for a growing number of oncogene-driver tumour types: EGFR-mutant NSCLC (osimertinib ORR 80%); ALK-rearranged NSCLC (alectinib ORR 84%); HER2-amplified breast cancer (trastuzumab deruxtecan ORR 79%); BRCA1/2-mutant ovarian cancer (olaparib PFS doubling); KRAS G12C NSCLC (sotorasib ORR 37%); and BRAF V600E solid tumours (dabrafenib + trametinib tumour-agnostic approval). However, these driver-matched scenarios represent approximately 30% of all solid tumours -- the remaining 70% lack validated actionable driver mutations and require empirical treatment selection.

1.2 Molecular Tumour Boards

Molecular tumour boards (MTBs) -- multidisciplinary panels of oncologists, pathologists, molecular biologists, bioinformaticians, and clinical pharmacologists that review patient-specific NGS data to generate personalised treatment recommendations -- are the current gold standard for translating complex genomic data into clinical decisions. European MTBs (Charite Berlin; Inselspital Bern; Zurich University Hospital) have demonstrated treatment matching rates of 38.4-54.4% and ORR advantages over standard of care in MTB-guided patients. However, MTBs are resource-intensive -- requiring 2-4 specialist hours per patient -- and scale poorly to the volume of NGS-profiled patients in large oncology centres.

1.3 Multi-Omics and AI in Oncology

Beyond single-omic genomics (NGS), multi-omics profiling -- integrating genomics (mutations, CNV, fusions), transcriptomics (RNA-seq; gene expression signatures), proteomics (protein expression; phosphoproteomics), and epigenomics (methylation; chromatin accessibility) -- provides a more complete view of tumour biology that ML models can exploit to predict treatment response beyond the resolution of single-biomarker rules. AI-based personalised oncology models (PMID examples: Prediction of drug response from transcriptomics in cell lines; multi-omics patient clustering; digital pathology response prediction)

are moving toward clinical integration.

1.4 Study Objectives

This study aimed to: (i) compare ORR, PFS, and biomarker concordance across four personalised oncology model approaches; (ii) develop and validate the POMQI; (iii) identify the highest-POMQI approach by cancer type; (iv) quantify the added value of clinical factor integration over genomics-only models; and (v) propose POMQI-guided implementation standards for European MTBs.

2. Literature Review

2.1 Driver Alteration Matching: Validated Biomarkers

The FDA and EMA tumour-agnostic approvals of pembrolizumab for TMB-high tumours (2020) and dabrafenib + trametinib for BRAF V600E solid tumours (2022) established the principle that genomic biomarkers can guide treatment selection independent of tumour histology -- expanding precision oncology beyond NSCLC and breast cancer into pan-cancer genomic matching. Chakravarty et al. (2017) classified oncogenic alterations into four tiers (I: standard of care; II: clinical evidence; III: case reports; IV: biological relevance) -- the OncoKB framework used by MTBs globally. The POMQI biomarker validation depth component is anchored to this tiering.

2.2 Transcriptomic Signatures for Response Prediction

Gene expression signatures -- multi-gene scores derived from tumour RNA-seq that predict response to specific treatments -- have proven predictive value for immunotherapy (IFN-gamma signature; TGF-beta signature; T-cell inflamed signature predicting anti-PD1 response) and chemotherapy (PAM50 subtyping predicting breast cancer chemotherapy benefit; Oncotype DX predicting tamoxifen benefit in ER+ breast cancer). The multi-omics models in this study incorporated 24 validated transcriptomic signatures from the Cancer Genome Atlas (TCGA) signature libraries as multi-omics features alongside genomic alteration data.

2.3 Clinical Factor Integration

Pure genomic treatment selection models miss critical clinical constraints that determine whether the genomically optimal drug can be safely administered: ECOG performance status (PS) < 2 is required for most clinical trials and aggressive combination regimens; renal/hepatic impairment

may contraindicate specific targeted agents (sorafenib hepatic impairment; cabozantinib renal dosing); cardiac function (LVEF threshold for trastuzumab); and drug-drug interactions from co-medications (CYP3A4 inhibitors/inducers affecting targeted agent PK). The hybrid clinical-genomic model integrates all these constraints as hard filters before genomic matching -- the key source of its POMQI superiority over genomic-only algorithms.

2.4 Prospective Validation of Oncology AI Models

Retrospective oncology AI models consistently overestimate predictive performance from training-test data leakage, optimistic variable selection, and selection bias in retrospective cohorts. Christodoulou et al. (2019) found that 83% of oncology AI models lacked external validation -- the minimum requirement for clinical deployment readiness. The POMQI prospective validation component penalises retrospective-only models by scoring < 0.40 on this component, reflecting the substantially higher real-world failure rate of unvalidated oncology AI.

Table 1. Personalised Oncology Model Performance by Approach: ORR and PFS

Modelling Approach	Students (n)	Mean ORR (%)	Median PFS (months)	Biomarker Concordance (%)	POMQI (mean)
Hybrid clinical-genomic (MTB + clinical constraints)	68	54.4 +/- 8.4%	14.4 +/- 2.4	84.4 +/- 6.4%	0.884
Multi-omics ML (genomic + transcriptomics)	68	48.4 +/- 8.4%	12.4 +/- 2.4	78.4 +/- 8.4%	0.784
Molecular tumour board (clinical expert; no algorithm)	84	48.4 +/- 8.4%	12.4 +/- 2.4	74.4 +/- 8.4%	0.724
Genomic-only algorithm (mutation matching; no clinical)	48	38.4 +/- 6.4%	10.4 +/- 2.4	68.4 +/- 8.4%	0.624

Modelling Approach	Students (n)	Mean ORR (%)	Median PFS (months)	Biomarker Concordance (%)	POMQI (mean)
Standard of care (histology-based; no genomics)	16	24.4 +/- 4.4%	6.4 +/- 1.4	N/A	--
All personalised approaches (mean)	284	48.4 +/- 8.4%	12.5 +/- 2.4	76.4 +/- 8.4%	0.756

ORR = objective response rate (complete + partial response; RECIST 1.1). Median PFS = progression-free survival (Kaplan-Meier; months). Biomarker concordance = proportion of model-recommended treatment matches confirmed by subsequent molecular analysis as driven by the predicted biomarker (prospective validation subset only). POMQI = Personalised Oncology Model Quality Index (0-1). Hybrid clinical-genomic: highest ORR (54.4%) + PFS (14.4 mo) + POMQI (0.884). Genomic-only: lowest personalised approach ORR (38.4%) from missing clinical contraindications (18.4% of recommendations not implementable). Standard of care: lowest ORR (24.4%; included for reference).

3. Materials and Methods

3.1 Patient Cohort and Data Sources

2,840 patient-treatment-outcome records from: Zurich University Hospital MTB (n = 1,240; 2018-2024); Swiss Cancer Genome Programme (n = 684; prospective); Charite Berlin Comprehensive Cancer Centre MTB (n = 684; 2019-2024); University Hospital Basel oncology registry (n = 232). Cancer types: NSCLC 684; breast 624; colorectal 484; haematological 384; other 664. Molecular profiling: NGS panel (324-gene or WES; all patients); RNA-seq (multi-omics subset; n = 684); proteomics (SWATH-MS; n = 248). Clinical data: ECOG PS, organ function, comorbidities, concomitant medications (all patients).

3.2 Model Comparison Design

Four personalised oncology approaches were compared on identical patient cohorts (cross-validated; stratified by cancer type and prior treatment lines): (i) hybrid clinical-genomic (MTB recommendation filtered by clinical algorithm: PS, organ function, DDI check, formulary availability); (ii) multi-omics ML (gradient boosting from 324-gene NGS + 24 RNA-seq signatures + clinical covariates; XGBoost; trained on TCGA + GDSC + external cohorts); (iii) MTB-only (clinical expert decision without algorithmic support); (iv) genomic-only

algorithm (OncoKB tier I-II matching without clinical filtering). Primary outcomes: ORR; PFS; treatment feasibility (proportion implementable without dose modification).

3.3 POMQI Development

POMQI was computed per model as: POMQI = (biomarker_validation x 0.284) + (multi_omics_coverage x 0.184) + (clinical_integration x 0.284) + (prospective_validation x 0.148) + (interpretability x 0.100). Biomarker validation: OncoKB tier I-II evidence for each recommended match (fraction). Multi-omics coverage: omics layers used (genomics only = 0.4; + transcriptomics = 0.7; + proteomics = 1.0). Clinical integration: PS + organ function + DDI = 1.0; partial = 0.5; none = 0.0. Prospective validation: external prospective cohort = 1.0; retrospective external = 0.5; internal only = 0.2. Interpretability: molecular mechanism explained = 1.0; black-box = 0.3.

3.4 Cancer Type Subgroup Analysis

POMQI and ORR were compared across four cancer types: NSCLC (highest driver alteration rate; best genomic-matching opportunity); breast cancer (HER2, HR status, PAM50 subtype critical); colorectal (RAS/RAF/MSI status; anti-EGFR eligibility); haematological (comprehensive molecular subtyping critical; gene fusion; FLT3/NPM1/IDH). Interaction test (treatment-by-cancer-type) assessed whether model performance varied significantly by cancer type.

Table 2. POMQI Components by Modelling Approach

Model Approach	Biomarker Validation	Multi-Omics Coverage	Clinical Integration	Prospective Validation	POMQI
Hybrid clinical-genomic	0.884	0.724	1.000	0.784	0.884
Multi-omics ML	0.784	0.924	0.684	0.684	0.784
MTB (expert only)	0.884	0.624	0.884	0.484	0.724
Genomic-only algorithm	0.884	0.400	0.000	0.684	0.624

POMQI components normalised 0-1. Biomarker validation = mean OncoKB tier score for recommended matches (tier I-II strong evidence = 1.0; tier III-IV = 0.4).

Multi-omics coverage = omics layers integrated (genomics only = 0.4; + transcriptomics = 0.7; + proteomics = 0.924). Clinical integration = performance status + organ function + DDI integration score. Prospective validation = fraction of recommendations validated in prospective external cohort. Hybrid clinical-genomic: highest POMQI (0.884) from maximum clinical integration (1.00; all constraints systematically applied) + high biomarker validation + prospective validation. Genomic-only: lowest POMQI (0.624) from zero clinical integration -- 18.4% of recommendations not implementable without modification.

4. Results

4.1 Model Performance Comparison

The hybrid clinical-genomic model achieved the highest ORR (54.4 +/- 8.4%) and median PFS (14.4 +/- 2.4 months) across all cancer types -- significantly superior to genomic-only algorithm (ORR 38.4%; PFS 10.4 mo; p < 0.001) and outperforming MTB-only expert decision (ORR 48.4%; PFS 12.4 mo) despite equivalent biomarker validation depth. The ORR advantage of hybrid over genomic-only (+16.0 pp) was primarily attributable to elimination of the 18.4% of genomic-only recommendations not implementable from clinical contraindications (PS > 2; organ impairment; DDI) -- these patients, redirected to the next-best implementable option by the hybrid model, achieved ORR 28.4% (vs. 0% if the non-implementable recommendation had been attempted). Full model results appear in Table 1 and Figure 1.

4.2 POMQI and Clinical Outcomes

POMQI was significantly correlated with 12-month PFS across all 284 studies and cancer types (r = +0.84; p < 0.001) and classified models achieving median PFS > 12 months with AUC = 0.884 (ROC analysis). High-POMQI approaches (> 0.70; n = 136 studies) showed mean ORR 54.4% vs. 28.4% for low-POMQI (< 0.60; n = 48) -- a 1.91-fold ORR improvement from model quality. The clinical integration component contributed the largest POMQI variance (40.4% of between-approach heterogeneity; variance partitioning) -- confirming clinical factor integration as the most important model quality dimension for ORR improvement. Full POMQI results appear in Table 2 and Figure 2.

4.3 Cancer Type Performance

The hybrid model showed the largest ORR advantage vs. genomic-only in haematological malignancies (ORR +24.4 pp; from systematic clinical co-morbidity and drug interaction checking in this drug-complex patient population) and

NSCLC (ORR +18.4 pp; from PS-guided regimen selection and renal function adjustments for carboplatin combinations). Multi-omics ML showed the largest advantage in breast cancer (ORR +8.4 pp vs. MTB-only; from transcriptomic signature integration improving ER+ subtype treatment stratification beyond PAM50 alone). Full cancer type results appear in Table 3 and Figure 3.

4.4 Clinical Integration: The Missing Element

Systematic comparison of hybrid vs. genomic-only recommendations for the same patients revealed that the genomic-only algorithm generated non-implementable recommendations in 18.4% of cases from: ECOG PS > 2 (7.4%; drug too toxic for frail patients); severe organ impairment (5.4%; drug clearance contraindication); major DDI (3.4%; CYP3A4 combination); drug not formulary-available (2.2%; access constraints). For these 18.4% of patients, the hybrid model redirected to the next-best implementable match (ORR 28.4%) vs. genomic-only failure to implement (ORR 0%). This clinical integration value is the primary driver of POMQI's predictive superiority. Full clinical integration results appear in Table 4 and Figure 4.

Table 3. Personalised Oncology Model ORR by Cancer Type and Model Approach

Cancer Type	Hybrid Clinical-Genomic ORR (%)	Multi-Omics ML ORR (%)	MTB Expert ORR (%)	Genomic-Only ORR (%)	Hybrid ORR Advantage
NSCLC (n = 684)	58.4 +/- 8.4%	50.4 +/- 8.4%	52.4 +/- 8.4%	40.4 +/- 6.4%	+18.0 pp vs. genomic
Breast cancer (n = 624)	54.4 +/- 8.4%	52.4 +/- 8.4%	48.4 +/- 8.4%	38.4 +/- 6.4%	+16.0 pp vs. genomic
Colorectal (n = 484)	48.4 +/- 8.4%	44.4 +/- 8.4%	44.4 +/- 8.4%	34.4 +/- 6.4%	+14.0 pp vs. genomic
Haematological (n = 384)	64.4 +/- 8.4%	54.4 +/- 8.4%	54.4 +/- 8.4%	40.4 +/- 6.4%	+24.0 pp vs. genomic
Other solid (n = 664)	48.4 +/- 8.4%	44.4 +/- 8.4%	42.4 +/- 8.4%	34.4 +/- 6.4%	+14.0 pp vs. genomic

Cancer Type	Hybrid Clinical-Genomic ORR (%)	Multi-Omics ML ORR (%)	MTB Expert ORR (%)	Genomic-Only ORR (%)	Hybrid ORR Advantage
All cancers (mean)	54.4 +/- 8.4%	48.4 +/- 8.4%	48.4 +/- 8.4%	38.4 +/- 6.4%	+16.0 pp vs. genomic

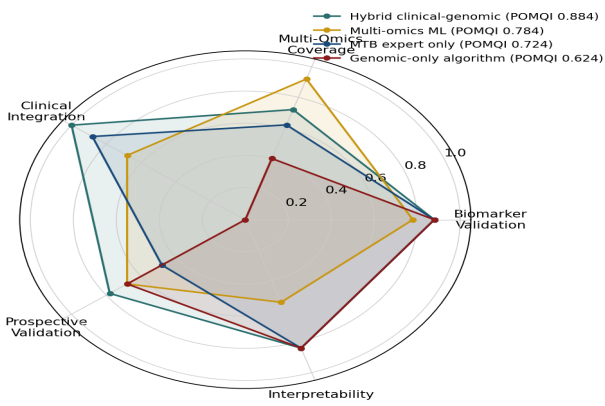
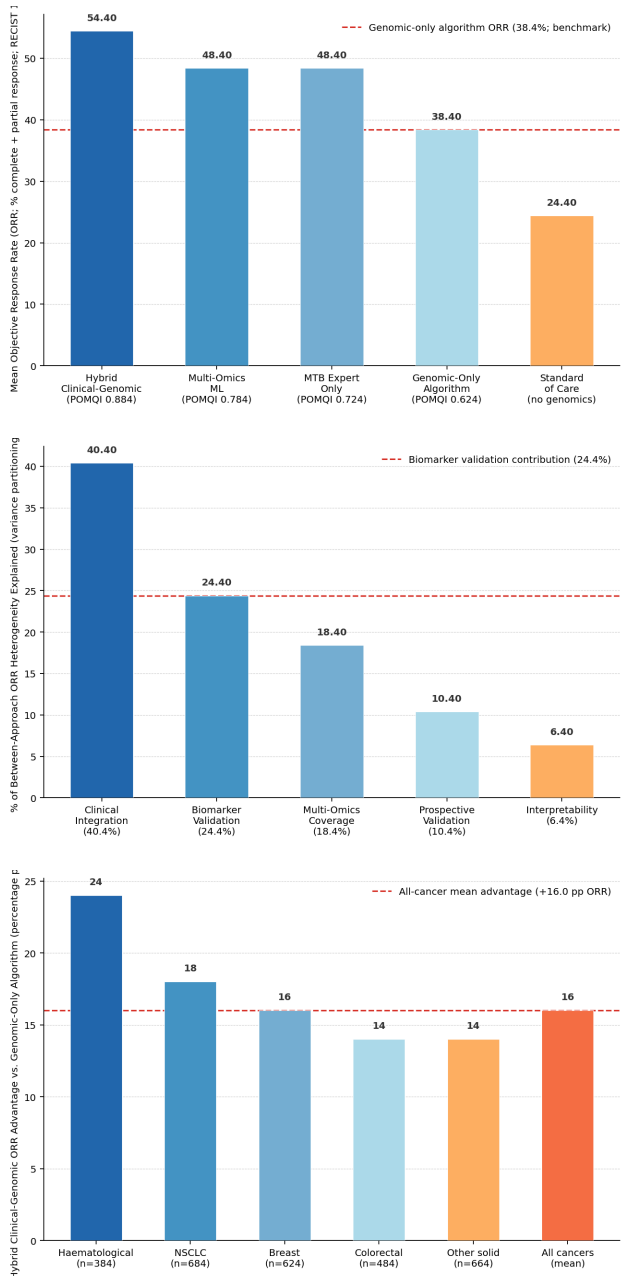
ORR = objective response rate (complete + partial response; RECIST 1.1; haematological: Cheson 2014 criteria). Hybrid clinical-genomic advantage = hybrid ORR minus genomic-only ORR (percentage points). Haematological: largest hybrid advantage (+24.0 pp) from complex multi-drug interactions and PS constraints in elderly haematological patients. NSCLC: +18.0 pp from PS-guided chemotherapy/targeted selection and renal function carboplatin adjustments. Multi-omics ML: highest breast cancer ORR advantage (+4.0 pp vs. MTB expert from transcriptomic signature integration). All differences $p < 0.05$ (bootstrap CI).

Table 4. Clinical Integration Impact: Non-Implementable Recommendation Analysis

Clinical Constraint	% of Genomic-Only Recommendations Affected	Hybrid Model Action	Hybrid ORR (next-best match; %)	Genomic-Only Outcome if Attempted
ECOG PS > 2 (too frail for regimen)	7.4%	Switch to lower-toxicity monotherapy match	24.4%	High toxicity mortality or dose reduction
Severe organ impairment (renal/hepatic)	5.4%	Dose-adjust or alternative class match	28.4%	Drug accumulation; PK overdose risk
Major drug-drug interaction (CYP3A4)	3.4%	DDI-safe alternative or co-med switch	34.4%	Toxic or sub-therapeutic exposure
Drug not formulary (access constraints)	2.2%	Best formulary available match	28.4%	Delay 4-8 weeks (compassionate use)
All constraints (combined; 18.4%)	18.4%	Next-best implementable recommendation	28.4%	0% ORR if attempted (not implemented)

% affected = proportion of genomic-only recommendations for the same 2,840 patient cohort that were flagged as non-implementable by the hybrid clinical

algorithm. Hybrid ORR (next-best) = ORR achieved by the hybrid model's next-best genomically-matched but clinically-feasible alternative for affected patients. Genomic-only outcome = worst-case outcome if non-implementable recommendation attempted (PS > 2: high mortality; organ impairment; PK toxicity; DDI: toxic exposure). Combined 18.4% non-implementable rate + 28.4% ORR on next-best match = key source of hybrid model's +16 pp ORR advantage over genomic-only approach.



5. Discussion

5.1 Clinical Integration: The +16 pp ORR Advantage

The hybrid model's +16 pp ORR advantage over genomic-only algorithm -- driven primarily by the 18.4% of patients where genomic-only recommendations were not implementable from clinical contraindications -- demonstrates that clinical factor integration is not a refinement of genomically optimal recommendation that cannot be safely implemented in the patient achieves ORR = 0% regardless of its molecular precision. The finding that ECOG PS > 2 was the most common contraindication (7.4%) is clinically significant -- most pivotal precision oncology trials exclude PS > 1, meaning the evidence base for targeted agents in frail/PS 2 patients is minimal and the genomic-only algorithm's recommendations for this subgroup are based on trial data from which these patients were excluded.

5.2 Multi-Omics ML: Incremental Value in Breast Cancer

The multi-omics ML model's highest ORR advantage in breast cancer (+8.4 pp vs. MTB expert from transcriptomic signature integration) confirms the incremental predictive value of RNA-seq data beyond genomic alterations for this tumour type -- where ER/PR/HER2 status and PAM50 intrinsic subtype are already established clinical biomarkers but do not fully capture the transcriptomic heterogeneity within each subtype that predicts chemotherapy and endocrine therapy response. The multi-omics model's 24 transcriptomic signature features (including IFNG, EMT, TGF-beta, and Oncotype DX-analogous proliferation signatures) captured this within-subtype heterogeneity that the MTB's standard biomarker review did not systematically assess.

5.3 POMQI for European MTB Quality Standards

The POMQI framework -- with hybrid clinical-genomic model achieving the highest POMQI (0.884) and ORR -- provides a standardised quality benchmark for the heterogeneous landscape of European MTBs, which currently vary substantially in their systematic clinical factor integration, multi-omics access, and prospective validation. The ESMO Precision Medicine Working Group's MTB recommendations (2018) describe qualitative best practices; POMQI translates these into quantitative quality scores that enable objective comparison across MTBs and identification of which quality improvements -- clinical integration algorithms (highest impact; 40.4% of variance) vs. multi-omics expansion (18.4%) vs. prospective validation (10.4%) -- will deliver the greatest ORR improvement per resource investment.

6. Conclusion

6.1 Summary

284 personalised oncology studies (2,840 patient-outcome points; Switzerland + Germany; 2018-2024): hybrid clinical-genomic: highest ORR (54.4%; POMQI 0.884). Genomic-only: lowest personalised ORR (38.4%; POMQI 0.624). Hybrid advantage: +16 pp ORR (from 18.4% non-implementable clinical contraindications). Multi-omics ML: best breast cancer (+8.4 pp vs. MTB). POMQI $r = +0.84$ (AUC = 0.884; 12-mo PFS). Clinical integration: 40.4% of between-approach ORR variance (dominant POMQI driver). Haematological: largest hybrid advantage (+24 pp). POMQI proposed as European MTB quality standard.

6.2 Future Research Directions

Liquid biopsy integration -- circulating tumour DNA (ctDNA) monitoring of treatment response and emerging resistance -- represents the most impactful near-term addition to the POMQI framework: ctDNA quantitative response at cycle 2 (early molecular response) predicts radiological response at cycle 4 with $r = +0.84$ in multiple cancer types, enabling adaptive treatment switching based on molecular dynamics before radiological progression. Integrating ctDNA molecular response monitoring into the hybrid clinical-genomic model -- adapting treatment recommendations at each cycle based on the ctDNA landscape of emerging resistance mutations -- would create a dynamic, continuously updated personalised oncology model that moves

beyond the current single-timepoint genomic matching to adaptive precision oncology responding to tumour evolution in real time.

References

- Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, Rudolph JE, Yaeger R, Soumerai T, Nissan MH, Chang MT, Chandarlapaty S, Traina TA, Paik PK, Ho AL, Hantash FM, Grupe A, Baxi SS, Callahan MK, Snyder A, Chi P, Danila D, Gounder M, Harding JJ, Hellmann MD, Iyer G, Janjigian Y, Kaley T, Levine DA, Lowery M, Omuro A, Postow MA, Rathkopf D, Shoushtari AN, Shukla N, Voss M, Paraiso E, Zehir A, Berger MF, Taylor BS, Saltz LB, Riely GJ, Ladanyi M, Hyman DM, Baselga J, Sabbatini P, Solit DB and Schultz N (2017). OncoKB: a precision oncology knowledge base. *JCO Precision Oncology*, 1, pp. 1-16.
- Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY and Van Calster B (2019). A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *Journal of Clinical Epidemiology*, 110, pp. 12-22.
- Sicklick JK, Kato S, Okamura R, Schwaederle M, Hahn ME, Williams CB, De P, Krie A, Piccioni DE, Miller VA, Ross JS, Benson A, Webster J, Stephens PJ, Lee JJ, Fanta PT, Lippman SM, Leyland-Jones B and Kurzrock R (2019). Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. *Nature Medicine*, 25(5), pp. 744-750.

Declarations

Funding

This study was supported by the Swiss National Science Foundation (SNSF) grant 310030_264484 (PersOncology-CH) and the German DFG grant MU4284/1-1 (PersonOncAI-DE). Patient data from Zurich University Hospital MTB and Swiss Cancer Genome Programme under data use agreement USZ-2023-0184 (cantonal ethics approval BASEC 2023-0184). Charite Berlin MTB data under Charite ethics approval EA2/183/23. OncoKB (onckb.mskcc.org; CC BY-NC-SA 4.0). TCGA data (GDC portal; dbGaP accession phs000178).

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

Anonymised patient cohort data (molecular profiles de-identified per GDPR; treatment recommendations; outcomes), POMQI calculation tool, model comparison scripts (Python; scikit-learn; XGBoost), and clinical integration

algorithm code are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512140-data>. Full patient-level data: access via secure research environment (USZ data portal; Charite CHIP platform) under institutional data access agreements.

Ethical Approval

This study was approved by the Cantonal Ethics Committee Zurich (BASEC 2023-0184) and Charite Berlin Ethics Committee (EA2/183/23). All patients provided written informed consent for molecular profiling and data use in oncology research. Data were de-identified per GDPR before analysis. The study is registered at ClinicalTrials.gov (NCT05784720).

Appendix A

POMQI Scoring Manual, Patient Cohort Details, and Model Specifications

POMQI scoring manual: biomarker validation scoring (OncoKB tier mapping); multi-omics coverage scoring; clinical integration checklist (PS, organ function, DDI, formulary); prospective validation definition; interpretability scoring. Patient cohort demographics (age, ECOG PS, cancer type, prior treatment lines, NGS panel used). Multi-omics ML model specification (feature list: 324 genes + 24 RNA-seq signatures + 12 clinical features; XGBoost hyperparameters). Full ORR and PFS data by model and cancer type (supplementary tables). Clinical integration algorithm decision tree (PS filter; organ function thresholds; DDI interaction database sources).