

<https://doi.org/10.1038/s41698-025-01229-5>

Comparative cost analysis of a diagnostic multi-omics platform for decision support in advanced cancer – results from the Tumor Profiler Melanoma project

Check for updates

Tarun Mehra^{1,2}, Dominik Menges^{3,4}, Benedict Gosztonyi^{1,2}, Nicola Miglino^{1,2}, Alexander Ring^{1,2}, Laura Boos^{1,2}, Bettina Sobottka⁵, Tumor Profiler Consortium*, Viktor Hendrik Koelzer^{2,5,6}, Holger Moch^{2,5}, Nora C. Toussaint⁷, Mitchell Levesque^{2,8}, Egle Ramelyte^{2,8}, Johanna Mangana^{2,8}, Reinhard Dummer^{2,8,9} & Andreas Wicki^{1,2} ✉

While advances in the understanding of tumor biology through multi-omics profiling hold the promise of substantially improving patient outcomes, the cost implications of such strategies remain unclear. We therefore performed a comparative cost analysis of patients treated either within the Tumor Profiler (TuPro) melanoma project or from a control cohort who received treatment after standard next-generation sequencing testing. After adjustment of cohorts through inverse probability of treatment weighting, we found no evidence of statistically significant differences in total costs between the two cohorts (95% confidence interval –10% to +67%). Importantly, treatment costs (95% confidence interval –28% to +41%) were similar between the two cohorts. In conclusion, we found no evidence that treatment recommendations guided by advanced multi-omics profiling led to significantly higher treatment costs in a Swiss context.

Advancements in molecular diagnostics and development of targeted treatments including checkpoint-inhibitors have reshaped the landscape of oncology¹. Treatments are now moving from a one-size-fits-all approach towards individualized therapies. The aim is to tailor treatments based on the unique disease profile of each patient², improving efficacy whilst reducing toxicity. Indeed, especially later lines of palliative therapy often rely on conventional, generalized approaches. These beyond standard-of-care (SOC) treatments mostly offer moderate benefit. In these settings, response rates rarely exceed 20% and progression-free survival is often limited to a few months at best^{3–5}. These limitations highlight the potential value of more personalized strategies that can adapt to the unique characteristics of each patient's disease.

The Tumor Profiler project (TuPro) represents a significant effort to address these challenges by integrating multi-omics and functional data to personalize therapeutic decision-making in melanoma and other tumor entities⁶. The aim of TuPro was to assess the feasibility and efficacy of this approach in clinical decision-making⁷. The diagnostic assessments included single-cell RNA and DNA sequencing, proteomics, imaging mass cytometry (IMC), cytometry by time of flight (CyTOF) and drug screenings. Findings were synthesized into molecular summary reports, which were presented to a multidisciplinary tumor board that gave a therapy recommendation. Patients received either SOC treatments or highly individualized poly-biomarker-driven treatments (beyond SOC). The objective response rate in difficult-to-treat palliative patients beyond SOC ($n = 37$) was 38%, with a disease control rate of 54%. In a retrospective analysis, progression-free

¹University Hospital Zurich, Department of Medical Oncology and Hematology, Rämistrasse 100, 8091 Zurich, Switzerland. ²Faculty of Medicine, University of Zurich, Zurich, Switzerland. ³Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich (UZH), Zurich, Switzerland. ⁴Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet (KI), Stockholm, Sweden. ⁵Department of Pathology and Molecular Pathology, University Hospital of Zurich, Schmelzbergstrasse 12, 8091 Zurich, Switzerland. ⁶University Hospital Basel, Institute of Medical Genetics and Pathology, Schönbeinstrasse 40, 4031 Basel, Switzerland. ⁷ETH Zurich, Swiss Data Science Center, Wasserwerkstrasse 10, 8092 Zurich, Switzerland. ⁸University Hospital Zurich, Department of Dermatology, Gloriastrasse 31, 8091 Zurich, Switzerland. ⁹Department of Dermatology and Allergology, Kantonsspital Aarau, Aarau, Switzerland. *A list of authors and their affiliations appears at the end of the paper.

✉ e-mail: andreas.wicki@usz.ch

survival of patients with TuPro-informed therapy decisions in ≥ 3 rd line was significantly improved compared with a matched cohort of patients without TuPro-based decision support (exact and propensity-matched cohort: 8.34 vs 2.0 months, adjusted hazard ratio = 0.23, 95% CI 0.07–0.79)⁷.

However, while the feasibility of a comprehensive data-driven approach for the care of patients with cancer could be shown, the important question of its effect on costs, especially treatment costs, remained. Costs for health care are a pressing concern across OECD countries as health expenditures as a percentage of GDP have steadily increased, rising from approximately 5% in the 1970s to an average of about 9% by 2019 and exceeding 17% in the United States^{8,9}. Cancer care is a significant driver of healthcare expenditure, fueled by the high cost of diagnostics and advanced therapies¹⁰. The financial burden of cancer care in the United States was estimated at over 208 billion US Dollars in 2020¹¹. Indeed, in the TuPro study, the upfront cost of multi-omics diagnostics was higher than standard next-generation sequencing⁷. Furthermore, there may be a concern that personalized diagnostic approaches may lead to more combination therapies, which could increase costs by compounding drug costs for multiple therapeutic agents and via a shift toward newer and hence more costly targeted or immuno-therapies^{12,13}.

Here, we explore the question of whether the costs, including for treatment, diagnostics, and management of AEs, were different for patients with melanoma treated according to decisions informed by multi-omics tumor profiling in comparison to a control cohort consisting of patients treated according to current practice, within or beyond standard of care. To this end, we first performed a descriptive cost analysis, followed by a comparative cost analysis, using inverse probability of treatment weighting (IPTW) for adjustment between the two cohorts.

Results

Patient population

The analysed TuPro melanoma cohort comprised 89 patients with 176 treatment lines, the control cohort 124 patients with 182 treatment lines (Fig. 1).

Analyzing the patient characteristics of each cohort, the TuPro cohort contained younger patients (median 61 vs 66 years), more women (44% vs 34.0%) and more patients with stage IV disease (74% vs 43%). The median Charlson Comorbidity Index (CCI) was slightly lower in the TuPro cohort (7.0 vs 8.0). The results are depicted in Table 1.

Reverting to the perspective of treatment lines, the TuPro cohort comprised far more treatment lines whose intention of treatment was palliative beyond SOC (40% vs 11%), which was mirrored by a substantially higher number of treatments being the 4th line or later (44% vs 5%).

The TuPro cohort had fewer AEs (59.9% vs 78.4%) and fewer hospitalizations for AEs (72.5% vs 84.7%) in treatment lines compared to the control. The results can be found in Supplementary Table 6.

The composition of treatments varied substantially between the cohorts, with a substantially higher proportion of chemotherapy not combined with tyrosine kinase inhibitors (TKIs) or immunotherapy (IO) in the TuPro cohort (20.5% vs 8.2%), higher proportion of TKI monotherapy (8.0% vs 1.6%), lower proportion of mono-IO therapy (9.7% vs 44.0%), with a similar proportion of immunotherapy combinations (such as anti-PD-1/PD-L1 and anti-CTLA4 or anti-LAG3) (22.7% vs 23.1%) or TKI combination therapy (such as BRAF- and MEK inhibitors) (16.5% vs 15.4%). The results are summarized in Supplementary Table 7.

Descriptive analysis of cost differences

In unadjusted descriptive analyses, the median time on treatment was substantially lower for the TuPro cohort than in the control cohort (68.5 days, interquartile range (IQR) 33–206 vs 283.5 days, IQR 66–373). The cost of diagnostics was higher in the TuPro cohort (CHF 17,554 vs CHF 3058). The median cost incurred by treatment of AEs was CHF 0 in both cohorts. The median cost of treatment was lower in the TuPro cohort (CHF 29,149 vs CHF 94,264), as were the median total costs (CHF 50,255 vs CHF 98,087). However, the median treatment costs per day were higher in the TuPro cohort (CHF 361 vs CHF 302), as were the median total costs per day (CHF 713 vs CHF 389). The results are depicted in Fig. 2 and Supplementary Table 8.

The time on treatment and costs per treatment intention (adjuvant, palliative within SOC, and palliative beyond SOC) for the TuPro and control cohorts are depicted in Supplementary Table 9. In line with the overall results, for the palliative beyond SOC sub-group, median time on treatment, treatment costs, and total costs were lower for the TuPro cohort (88 vs 194 days, CHF 39,588 vs 94,112 and CHF 57,142 vs 1,09,158, respectively). Interestingly, median treatment cost per day in the beyond SOC setting was substantially lower in the TuPro cohort (CHF 427 vs 692); however, differences were not significant ($P = 0.21$).

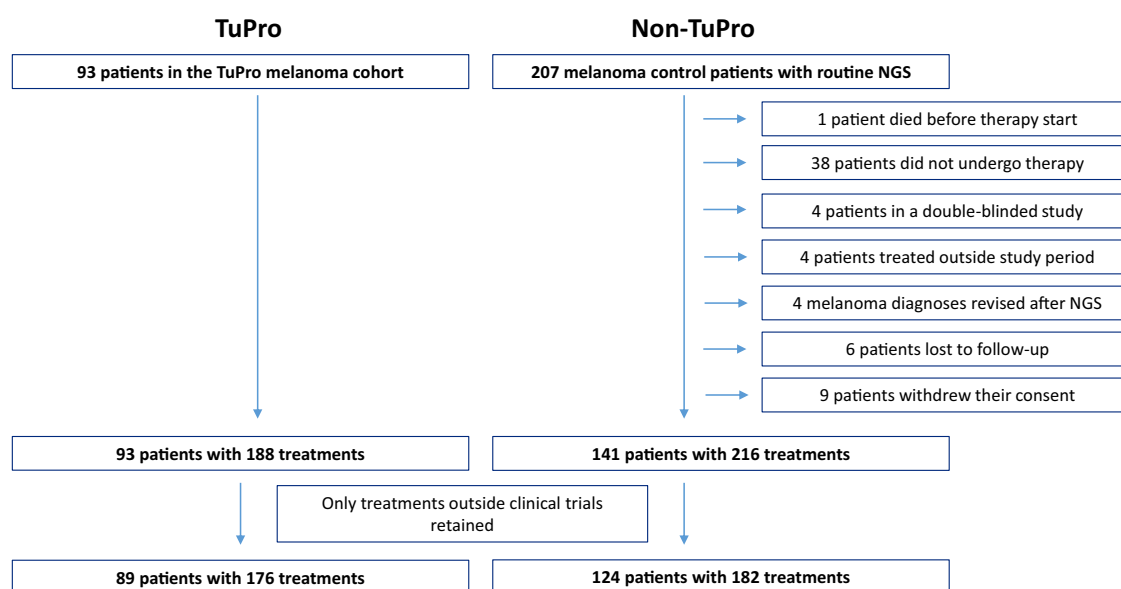


Fig. 1 | STROBE flow diagram showing patient selection for unmatched and matched TuPro (Tumor Profiler project) and synchronous Non-TuPro cohorts, including exclusions and losses to follow-up. NGS next-generation sequencing,

TuPro Tumor Profiler project melanoma patient cohort, Non-TuPro melanoma control cohort. Treatment lines included all lines, including subsequent treatments not guided by TuPro recommendations.

Table 1 | Patient characteristics of the unadjusted and IPTW-weighted TuPro and control cohorts

	Unadjusted			IPTW weighted		
	Non-TuPro (N = 124)	TuPro (N = 89)	SMD	Non-TuPro (N = 94.3)	TuPro (N = 83.3)	SMD
Age (y)	65.9 (53.7–73.5)	61.0 (52.0–73.0)	0.115	64.6 (53.7–73.4)	65.4 (53.0–75.0)	0.087
Age group			0.159			0.056
80+ years	14 (11.3%)	6 (6.7%)		11.1 (11.8%)	11.4 (13.7%)	
Gender			0.205			0.479
Female	42 (33.9%)	39 (43.8%)		29.6 (31.4%)	45.3 (54.4%)	
Stage			0.683			0.539
Stage I	1 (0.8%)	0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)	
Stage II	2 (1.6%)	0 (0.0%)		1.2 (1.3%)	0.0 (0.0%)	
Stage III	68 (54.8%)	23 (26.1%)		40.9 (43.4%)	17.3 (20.8%)	
Stage IV	53 (42.7%)	65 (73.9%)		52.1 (55.3%)	65.9 (79.2%)	
Missing	0 (0%)	1 (1.1%)				
ECOG			0.267			0.378
0	89 (76.7%)	71 (80.7%)		69.2 (73.4%)	67.8 (81.5%)	
1	22 (19.0%)	14 (15.9%)		21.1 (22.4%)	11.2 (13.5%)	
2	2 (1.7%)	3 (3.4%)		1.6 (1.7%)	4.2 (5.1%)	
3	3 (2.6%)	0 (0.0%)		2.4 (2.6%)	0.0 (0.0%)	
Missing	8 (6.5%)	1 (1.1%)				
Charlson Comorbidity Index	8.0 (7.0–9.0)	7.0 (6.0–9.0)	0.521	8.0 (7.0–9.0%)	8.0 (7.0–9.0%)	0.045
Missing	0 (0%)	1 (1.1%)		NA	NA	
Brain metastasis			0.006			0.182
Yes	24 (19.4%)	17 (19.1%)		23.1 (24.5%)	27.2 (32.7%)	
Location of primary			0.073			0.159
Skin	97 (78.2%)	69 (78.4%)		69.2 (73.4%)	66.0 (79.2%)	
Mucosal	6 (4.8%)	4 (4.5%)		3.3 (3.5%)	2.0 (2.4%)	
Uveal	8 (6.5%)	7 (8.0%)		8.0 (8.5%)	4.4 (5.3%)	
Unknown	13 (10.5%)	8 (9.1%)		13.7 (14.6%)	10.9 (13.0%)	
Missing	0 (0%)	1 (1.1%)				
Intention of treatment			1.123			0.557
Adjuvant	65 (52.4%)	13 (14.6%)		37.0 (39.2%)	16.0 (19.2%)	
Palliative - SOC	56 (45.2%)	47 (52.8%)		53.4 (56.7%)	54.0 (64.8%)	
Palliative - beyond SOC	3 (2.4%)	29 (32.6%)		3.9 (4.1%)	13.3 (15.9%)	
Treatment Line			1.471			0.583
0 (adjuvant)	65 (52.4%)	13 (14.6%)		37.0 (39.2%)	16.0 (19.2%)	
1	49 (39.5%)	20 (22.5%)		37.4 (39.7%)	39.0 (46.8%)	
2	8 (6.5%)	24 (27.0%)		14.9 (15.8%)	14.4 (17.3%)	
3	0 (0.0%)	13 (14.6%)		0.0 (0.0%)	%	
4+	2 (1.6%)	19 (21.3%)		5.0 (5.3%)	8.3 (9.9%)	
BRAF V600E Status			0.145			0.004
Non-Mutated	69 (56.1%)	43 (48.9%)		50.5 (54.0%)	44.8 (53.8%)	
Mutated	54 (43.9%)	45 (51.1%)		43.1 (46%)	38.5 (46.2%)	
Missing	1 (0.8%)	1 (1.1%)				

SMD standardized mean difference, SOC standard of care, y years, TuPro Tumor Profiler project melanoma cohort, synchronous Non-TuPro control cohort. N = refers to the number of treatment lines in the TuPro and Non-TuPro cohorts, respectively. All results are depicted as either median (interquartile range) or N (% of total). If multiple treatment lines were reported in a cohort, the patient characteristics at the first reported treatment line are rendered.

Cost comparison of matched cohorts

Results from primary analyses based on IPTW weighting and additional statistical adjustment for confounding are displayed in Fig. 3, with sensitivity analysis results presented in Supplementary Fig. 2.

Total costs were 23% higher (95% CI –10% to +67%, *p* = 0.19) and total costs per day were 21% higher (95% CI –15% to +71%, *p* = 0.29) in the TuPro cohort compared to the control group, but the difference was not statistically significant. Treatment costs (+1%, 95% CI –28% to +41%, *p* = 0.97) and

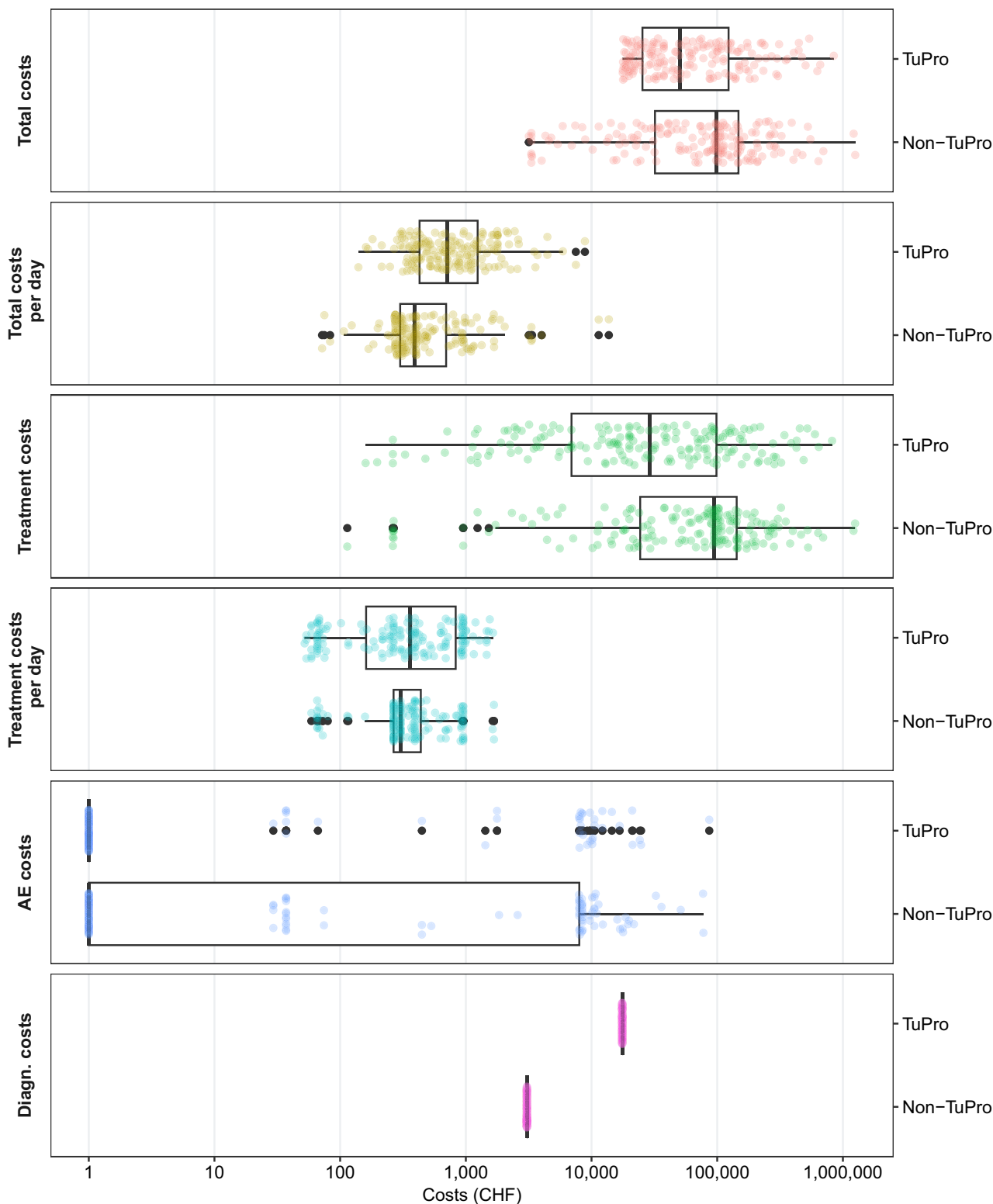


Fig. 2 | Box plots depicting the distribution of estimated costs for the unadjusted TuPro and Non-TuPro cohorts, treatment level perspective. TuPro Tumor Profiler project melanoma cohort, Non-TuPro control cohort, AE adverse events, AE costs costs incurred by the treatment of AEs, Diagn. Costs costs of initial diagnostic

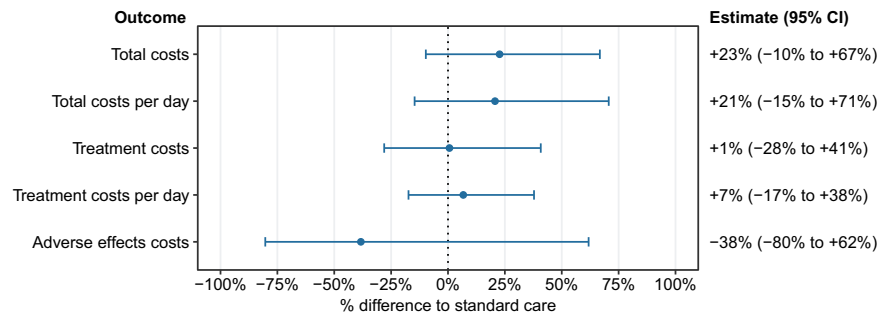
work-up, i.e., MelArray (standard next generation molecular sequencing panel) vs TuPro multi-omics testing, Total costs sum of treatment costs, AE costs and diagnostic costs. All costs in Swiss Francs (CHF).

treatment costs per day (+7%, 95% CI -17% to +38%, $p = 0.62$) were similar between the two groups. Meanwhile, costs incurred by treatment of AEs were estimated to be 38% lower (95% CI -80% to +62%) in the TuPro cohort, but with considerable uncertainty, not considered statistically significant.

Sensitivity analysis and subgroups

The results of sensitivity analyses using different statistical models are depicted in Supplementary Fig. 2. In summary, models yielded similar results with overlapping confidence intervals.

Fig. 3 | Forest plot of modeled cost comparisons between TuPro and control cohorts based on IPTW-weighted analyses and additional statistical adjustment for confounding. Adverse events costs costs incurred by the treatment of adverse events, CI confidence interval, IPTW inverse probability of treatment weighting, total costs sum of treatment costs, adverse events costs and costs for diagnostics (i.e., TuPro multi-omics profiling vs. standard next generation molecular panel), TuPro Tumor Profiler project melanoma cohort.



When analyzing subgroups by lines of treatment, consistent patterns were observed, and there was no evidence for a subgroup effect for total costs, total costs per day, treatment costs, and treatment costs per day. In analyses by intention of treatment, total costs were comparable in the TuPro cohort compared to the control in the palliative beyond SOC setting (-6%, 95% CI -33% to +32%), with treatment costs and treatment costs per day being 19% lower (95% CIs -47% to +26% and -41% to +11%, respectively). Subgroup analyses by treatment category were highly unstable with questionable interpretability and are thus not presented. Across BRAF status subgroups, we generally found higher total costs and treatment costs in TuPro vs the control among patients with positive BRAF status, but there was insufficient statistical evidence for such a subgroup effect.

To summarize, differences in total costs were non-significant, although diagnostic costs were substantially more expensive. Treatment costs were broadly comparable.

Discussion

In this comparative cost analysis of melanoma patients from the TuPro multi-omics guided treatment cohort and a synchronous control cohort receiving treatment based on standard NGS, we found a non-significant trend towards higher total costs (+23%, 95% CI -10% to +67%) and higher total costs per day (+21%, 95% CI -15% to +71%) with the TuPro cohort compared to the control group. However, we found broadly comparable treatment costs (+1%, 95% CI -28% to +41%) and treatment costs per day (+7%, 95% CI -17% to +38%). Differences in costs incurred by adverse events (-38%, 95% CI -80% to +62%) were non-significant. Meanwhile, diagnostic costs for the TuPro multi-omics diagnostics platform (CHF 17,554) exceeded conventional NGS (CHF 3058) substantially. Treatment costs accounted for the largest proportion of total costs in both cohorts, although the proportion was substantially higher in the control cohort, due to substantially longer time-on-treatment (Supplementary Fig. 3). We found no suggestion that the distribution of cost should differ for *BRAF* V600E mutated vs non-mutated subgroups (Supplementary Fig. 4) or by intention of treatment (Supplementary Fig. 5). Interestingly, there appeared to be a trend towards lower treatment costs in the TuPro in the palliative beyond SOC setting compared to the control group, although the finding is fraught with high uncertainty.

In unadjusted analyses, we found that the total costs and treatment costs from the TuPro cohort were lower than in the control cohort, owing to a substantially lower time on treatment. This is likely due to the fact that patients in the TuPro cohort were generally in later lines. Hence, controlling for confounding using multiple adjustments was necessary. Using a similar adjustment, ORR and PFS of the TuPro cohort compared favorably to the control cohort⁷, indicating that such an adjustment sufficiently corrected for potential differences in clinical outcomes between groups. Additionally, as previously described⁷, not all technologies planned according to the TuPro protocol were implemented prior to giving a treatment recommendation. Hence, on average, costs for diagnostics for multi-omics guided treatment recommendations could be substantially lower. However, even if the costs for multi-omics profiling were to increase by 25%, differences in total costs between cohorts remained non-significant. Increasing costs for the multi-

omics profiling by 50%, however, resulted in a significant difference in total costs (Supplementary Table 10). Results did not differ if a patient-level perspective instead of a treatment level perspective was adopted (Supplementary Table 11, Supplementary Figs. 6 and 7) and showed consistency in subgroup analyses.

Based on our study, the highest potential for multi-omics guided treatment decisions may lie in the palliative, beyond SOC setting, where high-quality evidence on the most suitable treatment option is scarce. Assuming a treatment duration of 1 year and extrapolating from our results from the beyond SOC subgroup, the hypothetical cost for 1 year of treatment, including diagnostic work-up and AE costs, would be CHF 1,73,314 for a patient treated in accordance with the TuPro protocol and CHF 2,55,664 for a patient with conventional NGS (difference of CHF -82,350). Extrapolating the data from the cost comparison of the total cohort, the cost for 1 year of treatment and a diagnostic work-up, as well as the costs for treatment of AEs, would be CHF 1,49,310 for TuPro and CHF 1,13,397 for the control cohort (a difference of CHF 35,913). In light of current prices for oncological care, the costs thus still seem to be contained for a multi-omics driven decision support program such as TuPro.

Indeed, immunotherapies such as checkpoint inhibitors can cost between \$100,000 and \$150,000 annually per patient, while cellular therapies like CAR-T often exceed \$350,000¹⁴. Within oncology, the efficacy of treatment options for later-line remains modest¹⁵ and hence, cost-effectiveness remains a challenge. Until recently, beyond-SOC options were limited to conventional chemotherapy such as dacarbazine or a rechallenge with immune checkpoint inhibitors¹⁶. Recently, treatment with tumor-infiltrating lymphocytes (TIL) has emerged as a further option in advanced melanoma having progressed under first-line therapy, achieving an objective response rate of 49%¹⁷. However, the price for a treatment with TILs for advanced melanoma in the United States exceeds USD 5,00,000¹⁸. Given the fact that TuPro melanoma achieved an objective response rate of 38% for a cohort of patients with far more advanced disease⁷, multi-omics tailored treatment recommendations appear to be an equally effective but potentially less costly treatment strategy for melanoma patients beyond SOC.

Our study has several limitations. First, the design was not randomized. Ideally, these findings would need to be corroborated in a prospective, randomized trial against a potentially new therapeutic gold-standard such as TILs, which, due to multiple constraints (ethical, financial and sample size), is unlikely to happen. However, due to the difficulty of recruitment for a prospective randomized trial to assess the efficacy of treatment options, we reason that such an observational study is a scientifically viable option, which allows, at a minimum, the generation of hypotheses and may, in addition to that, provide a foundation to estimate potential effect sizes for multi-omics programs. Second, we performed a comparative cost analysis and not a full cost-effectiveness assessment. However, due to the fact that there was no prospectively randomized control arm for the reasons mentioned above, quality of life was not assessed, and overall survival outcome is not the most robust outcome parameter in a later-stage, heavily pretreated palliative cohort, so this was not possible. Third, the analysis is heavily based on Swiss prices for drugs, patient visits and diagnostics. We are aware that cost structures vary considerably from country to country and that transferring

results in an international context warrants caution. However, recent publications do suggest that our findings may be true, at least for health care systems in the Western Hemisphere. Indeed, Owens et al. recently published very similar figures for advanced diagnostic profiling costs in pediatric cancer patients in Australia (Australian Dollars AUD 21,769 per molecular tumor board recommendation)¹⁹. Fourth, the cost analysis was performed from a third-party payer perspective and not from a full societal perspective, as quantification of differences in indirect costs and costs for implementing multi-omics profiling on a national scale could not be achieved with sufficient precision. Finally, there was substantial statistical imprecision in the results. We deem this to be primarily due to the sample size of the heterogeneous cohort in combination with the complex statistical methodology necessary to deal with confounding between the compared cohorts. Due to these limitations, our results should be interpreted with caution.

In conclusion, we did not find evidence of significant differences in treatment costs, albeit a non-significant trend toward higher total costs. We conclude that multi-omics-guided treatment decision support remains a suitable and cost-controlled option, especially in comparison to the costs of cellular therapies. We suggest that, in addition to a substantial clinical benefit, the multi-omics-guided treatment approach is possibly most economical for patients in a palliative, beyond SOC setting.

Methods

Design and dataset

The study was designed as a comparative cost analysis, with the investigated population being patients treated at the University Hospital of Zurich, Switzerland, either participating in the Tumor Profiler Melanoma (TuPro) study or not. The feasibility and effectiveness outcomes of the TuPro study have been published previously⁷.

The patient selection of the two cohorts is detailed in the STROBE Flowchart (Fig. 1).

The TuPro melanoma project cohort consisted of 93 patients with histologically confirmed malignant melanoma of any subtype who consented to participate in the TuPro project in the period January 2019 to November 2020. Four patients received experimental treatments within clinical trials and were excluded from this analysis due to unassessable treatment costs.

The control cohort consisted of 207 patients diagnosed with histologically confirmed malignant melanoma of any subtype, treated at the University Hospital of Zurich, who underwent standard next-generation sequencing (NGS) testing during the time span of February 2019 to July 2021, and provided a general research consent. Sixty-six patients were excluded: one patient died before therapy could be initiated, 38 did not undergo therapy, four had participated in a double-blinded clinical study, 17 from the control cohort received treatments within a trial setting, in 4 patients the treatment periods did not overlap with the defined inclusion period, four had their diagnosis of melanoma revised in due course, 6 were lost to follow-up, and nine withdrew consent.

Patient data were collected from the TuPro clinical database, the Swiss Melanoma Registry (SwiMelaReg) and extracted from electronic health records up until the end of follow-up on May 31, 2023.

The span of the inclusion period from the control cohort exceeded that of the TuPro cohort, to account for the time lag of therapy decisions based on TuPro results, which could have happened after accrual into the TuPro cohort had been stopped. We hence chose a longer accrual span for the control cohort to account for a similar time interval of treatment recommendations.

To account for possible shifts of costs into subsequent treatment lines, treatment lines included all lines, including subsequent treatments not guided by TuPro recommendations. In total, 89 patients with 176 corresponding treatment lines in the TuPro cohort and 124 patients with 182 treatment lines in the control cohort were retained for further analysis.

Costs

We defined the primary outcome as total costs, consisting of the individual components: treatment costs, costs for diagnostics and costs for AEs being

secondary outcomes. Treatment costs were estimated considering treatment schedule, time on treatment and official prices from the official Swiss medicines price list (*Spezialitätenliste*²⁰) as well as estimated costs for consultations by physicians, costs for laboratory analysis, disposables and nursing costs. Costs for treatment of AEs included estimated costs for an emergency consultation, as well as medication costs as per prices from the Swiss medicines price list (*Spezialitätenliste*²⁰). Costs for hospitalizations were calculated using Diagnosis-Related Groups (SwissDRG, catalog 2021²¹). Costs for diagnostics included costs for a MelArray panel in the control group (CHF 3058.40) or estimated costs for the Tumor Profiler diagnostics platform, as published previously (CHF 17,554.44)⁷. As previously described, the costs for multi-omics profiling were assessed as marginal costs of production, i.e., the cost of one additional analysis on an otherwise fully funded analysis platform running at full capacity⁷. The market price was used for the cost of the NGS genomic marker test. For experimental technologies, costs were assessed using Swiss research prices (Swiss Personalized Oncology program costs), accounting for personnel costs (analysis time & full-time-equivalent salary costs) as well as costs of reagents⁷. A list of the input parameters can be found in Supplementary Tables 1–4.

Conceptual approach of the comparative analysis

As the focus of this study was a cost analysis, we considered each treatment line as the basic element for our analysis. Due to relevant differences in patients and treatments between the TuPro cohort and the control group, we followed a conceptual approach and used several adjustment methods in the statistical analyses to ensure comparability between treatment lines. This approach differed from the comparative analysis in the initial publication from Miglino et al.⁷.

To determine potential confounders, we explored several covariates that were defined a priori based on clinical expert knowledge (Supplementary Table 5). From these, we identified potentially confounding covariates associated both with selection into TuPro and cost outcomes for a minimal adjustment set. An extended set of covariates used in sensitivity analyses was defined as all variables associated with either selection into TuPro or associated with the outcome. Interaction terms were assumed for treatment line and treatment duration since later-line treatments had shorter treatment durations until progression, as well as for age and Charlson Comorbidity Index (CCI) and ECOG status. This was done as we observed slight differences for these factors between cohorts, and since treatment selection may have also depended on these factors. Meanwhile, the latter interaction was not applied for AE costs, as higher age, CCI and ECOG were all expected to be associated with a higher risk of AEs. Directed acyclic graphs (DAGs) for the assumed relationships are shown in Supplementary Fig. 1.

Subgroup analyses

We conducted subgroup analyses by treatment line, intention of treatment (i.e., adjuvant, palliative SOC, and palliative beyond SOC), treatment category (i.e., chemotherapy only, TKI monotherapy, IO monotherapy, combination therapies, tumor vaccine, and bispecific T-cell engager therapy), *BRAF* V600E mutational status (i.e., negative vs. positive), and primary location of the tumor (i.e., skin, mucosal, uveal, and unknown). No subgroup analyses were conducted for AE costs due to data sparsity (low rate of AEs in study population: in total 78.4% of treatment lines without AEs in the TuPro cohort and 59.9% of treatment lines in the control cohort, Supplementary Table 6).

Statistical approach

Results were first analyzed descriptively and without adjustment. The non-parametric Mann–Whitney *U* test was used to analyze differences between unadjusted cohorts.

For adjustment of the cohorts, we applied inverse probability of treatment weighting (IPTW) to account for selection into the TuPro cohort. IPTW was implemented at the patient level based on patients' clinical status

at enrollment (i.e., at first treatment within the study). Propensity scores were estimated based on the minimal and the extended model using logistic regression. From this, IPTW weights for the average treatment effect (ATE) were estimated. Patient-level weights were then applied for all treatments provided to the respective patient. Two models were established, a main model with matching based on a limited covariable set and an additional IPTW model based on an extended covariable set for sensitivity analysis. As an alternative approach, propensity score matching (PSM) was implemented at the level of individual treatments for an additional sensitivity analysis. A genetic PSM algorithm was used with replacement and with exact matching by treatment line, in order to create two PSM datasets based on the minimal and the extended set of covariables for propensity score estimation.

Characteristics of the patients and treatments were compared descriptively based on the unweighted data, the IPTW weighted data, and the PSM datasets. A better covariable balance was achieved through IPTW and PSM. However, imbalances persisted and standardized mean differences after IPTW and after PSM were still greater than 0.1 for several covariates. Hence, additional adjustment for relevant confounders in statistical models was deemed necessary.

For the analysis of total costs and treatment costs, a generalized linear model (GLM) using IPTW and a gamma distribution with log-link was used. This model resulted in estimates that could be interpreted as a multiplicative effect (or percent difference) of TuPro-driven treatment compared to conventional treatment. In primary analysis, the minimal covariable set was used for IPTW estimation and additional adjustment. In sensitivity analyses, the same models were applied using IPTW and additional adjustment based on the extended covariable set, and using the PSM datasets with additional adjustment based on both the minimal and extended covariable set. In further sensitivity analyses, IPTW weighted linear models modeling the logarithm of the total and treatment costs were run, adjusting for the minimal and extended set of covariables. These results could also be interpreted as a multiplicative effect (or percent difference) of TuPro-driven compared to conventional treatment.

For the analysis of AE costs, a two-part hurdle model was used due to the zero-inflated nature of the data. In the first part, the probability of having zero AE costs was estimated. In the second part, the multiplicative effect was estimated among participants with non-zero costs using a gamma GLM. An adapted model for AEs was used (see conceptual approach), and the analysis was conducted using IPTW and additional adjustment based on the minimal covariable set. To calculate predicted AE costs, the first and second parts of the two-part model were then combined: the predicted probability of having non-zero costs was multiplied by the predicted AE costs occurring with each treatment line in a dataset, assuming all treatments were TuPro-driven or conventional. The effect of TuPro-driven compared to conventional treatment was then estimated by calculating the geometric mean of the ratio between the predicted AE costs assuming all treatments were TuPro driven and the predicted AE costs assuming all treatments were conventional. In a sensitivity analysis, the analysis was conducted using the PSM dataset with additional adjustment based on the minimal covariable set.

For subgroup analyses, models including an interaction term between treatment cohort (TuPro or Non-TuPro) and the corresponding variables were fit. Modeling for subgroup analyses was based on an IPTW weighted gamma GLM based on the minimal set of covariables. Stratum-specific effects for TuPro-driven treatment compared to conventional treatment were estimated from these interaction models. To test for subgroup effects, likelihood ratio tests comparing these interaction models and corresponding models without interaction but including the subgroup covariable were performed.

All results were estimated as multiplicative effects. Accounting for clustering at the patient-level using mixed-effects models was not possible since the sparsity of the data resulted in non-convergence of the corresponding statistical models.

Robust standard errors and resulting 95% confidence intervals (CIs) were estimated using the HC4m estimator proposed by Cribari-Neto et al.

for all main estimates²². For the subgroup analyses, regular standard errors were estimated since the robust standard errors were unstable due to the small sample size, resulting in partially narrower confidence intervals. For AE costs, 95% CIs were estimated using a bootstrap approach with 1000 repetitions, using the 2.5th and 97.5th percentiles of results (p -values were not estimable using this method).

Cases/treatment lines with missing data were excluded from the matched analysis. Missingness was limited: <5% in the IPCW model with a limited covariable set and for the PSM model, 30% in the IPCW model with an extended covariable set at the treatment level and 10.4% in the IPCW model with an extended covariable set at the patient level.

Results with a p -value < 0.05 were considered statistically significant. No p -value adjustment was conducted due to the exploratory nature of this study and for better interpretability. This article complies with the STROBE reporting guidelines²³.

Software

All analyses were conducted in R (v4.4.1). Data was collected in Microsoft Excel.

Ethics

This study followed the ethical principles outlined in the Declaration of Helsinki and subsequent amendments and was approved by the local ethics committee (BASEC: 2018-02050; 2021-01584). All participants provided their written consent prior to inclusion; patients in the TuPro cohort were required to provide project-specific written informed consent prior to enrollment, and patients in the control cohort had provided general consent as standard procedure in the University Hospital of Zurich. Data of patients for whom consent could not be obtained or for whom consent was unclear were not included in this study.

Data availability

Aggregated clinical data relevant to this publication have been made available as supporting information. To comply with applicable laws and regulations, including the Swiss Human Research Act, access to the patient-level clinical and biological data will be granted to registered users listed on the data access agreement with the TPC within 4 weeks of receipt of the Data Access Agreement, provided that the applicant submits all necessary ethics committee approval and supporting documents needed to meet the requirements of the agreement. Data access can be requested by contacting the TPC (nicola.migliano@usz.ch). The user institution agrees to destroy or discard the data once it is no longer used for the project, and in cases where data must be archived, it must be deleted within 10 years of the project's completion. If data has not been archived, it must be deleted no later than 2 years following the completion of the project. An extension to this period can be provided upon request to the TPC leadership. Data sharing is subject to honoring patient privacy and data integrity.

Received: 21 July 2025; Accepted: 27 November 2025;

Published online: 17 December 2025

References

1. Wahida, A. et al. The coming decade in precision oncology: six riddles. *Nat. Rev. Cancer* **23**, 43–54 (2023).
2. Tsimberidou, A. M. et al. Molecular tumour boards—current and future considerations for precision oncology. *Nat. Rev. Clin. Oncol.* **20**, 843–863 (2023).
3. Saint-Jean, M. et al. Chemotherapy efficacy after first-line immunotherapy in 18 advanced melanoma patients. *Medicine* **99**, e21329 (2020).
4. Yang, A. S. & Chapman, P. B. The history and future of chemotherapy for melanoma. *Hematol./Oncol. Clin.* **23**, 583–597 (2009).
5. Zimmer, L. et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. *Eur. J. Cancer* **75**, 47–55 (2017).

6. Irmisch, A. et al. The Tumor Profiler Study: integrated, multi-omic, functional tumor profiling for clinical decision support. *Cancer Cell* **39**, 288–293 (2021).
7. Miglino, N. et al. Feasibility of multiomics tumor profiling for guiding treatment of melanoma. *Nat Med.* <https://doi.org/10.1038/s41591-025-03715-6> (2025).
8. OECD. *Health at a Glance 2021: OECD Indicators* (2021).
9. Services, C. f. M. M. (2024).
10. Mariotto, A. B., Yabroff, K. R., Shao, Y., Feuer, E. J. & Brown, M. L. Projections of the cost of cancer care in the United States: 2010–2020. *J. Natl. Cancer Inst.* **103**, 117–128 (2011).
11. NIH, N. C. I. (DHHS, Bethesda, MD, 2024).
12. Devi, S. Rising costs of cancer medicines. *Lancet Oncol.* **25**, 1262 (2024).
13. Lu, C. Y., Terry, V. & Thomas, D. M. Precision medicine: affording the successes of science. *npj Precis. Oncol.* **7**, 3 (2023).
14. Hernandez, I., Prasad, V. & Gellad, W. F. Total costs of chimeric antigen receptor T-cell immunotherapy. *JAMA Oncol.* **4**, 994–996 (2018).
15. Boutros, A. et al. The treatment of advanced melanoma: current approaches and new challenges. *Crit. Rev. Oncol./Hematol.* **196**, 104276 (2024).
16. Zaremba, A. et al. The concepts of rechallenge and retreatment with immune checkpoint blockade in melanoma patients. *Eur. J. Cancer* **155**, 268–280 (2021).
17. Rohaan, M. W. et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N. Engl. J. Med.* **387**, 2113–2125 (2022).
18. Schubert-Zsilavec M, D. T. Lifileucel bei fortgeschrittenem Melanom zugelassen. *Pharmazeutische Zeitung* <https://www.pharmazeutische-zeitung.de/lifileucel-bei-fortgeschrittenem-melanom-zugelassen-145827/> (2024).
19. Owens, C. E. L. et al. The economic costs of precision medicine for clinical translational research among children with high-risk cancer. *npj Precis. Oncol.* **8**, 224 (2024).
20. Gesundheit, B. f. (Eidgenössisches Department des Innern EDI, Bern, Switzerland, 2023).
21. SwissDRG. (SwissDRG AG, Bern, 2021).
22. Cribari-Neto, F. & da Silva, W. B. A new heteroskedasticity-consistent covariance matrix estimator for the linear regression model. *AStA Adv. Stat. Anal.* **95**, 129–146 (2011).
23. von Elm, E. et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370**, 1453–1457 (2007).

Acknowledgements

We thank Mrs. Isabell Pieper Scholz for her contribution to the melanoma registry database. The melanoma registry database of the Department of Dermatology has been partially supported by an unrestricted grant to the University of Zurich from Novartis, BMS and Pierre Fabre. Additionally, a standard data report based on the melanoma registry database was purchased by Merck Sharp & Dohme. The Tumor Profiler Project is jointly funded by a public–private partnership involving F. Hoffmann–La Roche Ltd., ETH Zürich, University of Zürich, University Hospital Zürich and University Hospital Basel. This work was further supported by a grant from the Pro-medica Foundation and the endowment of the professorship for oncology (A.W.) of the University of Zurich. D.M. received project and salary funding for an unrelated project from the Swiss Cancer Foundation (SCF), the Dr. Arnold U. und Susanne Huggenberger–Bischoff Stiftung, and one further, private, not-for-profit research foundation from Switzerland requesting anonymity via the University of Zurich.

Author contributions

T.M., D.M., and A.W. conceptualized the project. N.M., A.R., L.B., B.S., V.H.K., H.M., N.C.T., M.L., E.R., J.M., and R.H., as well as the Tumor Profiler Consortium, generated the data. T.M. and B.G. retrieved the data. T.M.,

D.M., and B.G. led the analysis. A.W. was responsible for the overall leadership of the project and acquisition of funding. T.M. and D.M. drafted the first version of the paper. All authors contributed substantially to the generation, analysis and interpretation of the results. All authors were involved in the writing of the paper and approved the final version.

Competing interests

T.M., A.R., D.M., N.C.T., N.M., L.B., B.S., B.G., and A.W. declare no competing interests. V.H.K. reports being an invited speaker for Sharing Progress in Cancer Care (SPCC) and Indica Labs; advisory board of Takeda; and sponsored research agreements with Roche and IAG, all unrelated to the current study. V.H.K. is a participant in a patent application on the assessment of cancer immunotherapy biomarkers by digital pathology; a patent application on multimodal deep learning for the prediction of recurrence risk in cancer patients, and a patent application on predicting the efficacy of cancer treatment using deep learning. E.R. has intermittent project focused consultant/advisory relationships or has received speaker fees and/or travel support from Pierre Fabre, Regeneron, Sanofi, Bristol Myers Squibb, Merck Sharp & Dohme, Kyowa Kirin, and Eli-Lilly, outside of the submitted work. J.M. has intermittent project focused consultant/advisory relationships or has received speaker fees from Merck Sharp & Dohme, Novartis, Janssen, Bristol Myers Squibb and Pierre Fabre and has received travel support from Sunpharma, L' Oreal, Merck Sharp & Dohme, Bristol Myers and Squibb und Pierre Fabre outside of the submitted work. M.L. is a co-founder and board member of Oncobit and has received unrelated research funding from Roche, Novartis, Bacoba, Oncobit, Scailyte, Molecular Partners, and Leica. R.D. has intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, T3 Pharma, MaxiVAX SA, Pfizer and Simcere outside the submitted work. R.D. is a Senior medical advisor of the company Oncobit. H.M. declares obtaining research funding for his institution by Roche AG.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41698-025-01229-5>.

Correspondence and requests for materials should be addressed to Andreas Wicki.

Reprints and permissions information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025

Tumor Profiler Consortium

Rudolf Aebersold¹⁰, Melike Ak⁸, Faisal S. Al-Quaddoomi^{11,12}, Silvana I. Albert¹³, Jonas Albinus¹³, Ilaria Alborelli⁶, Sonali Andani^{12,14,15,16}, Per-Olof Attinger¹⁷, Marina Bacac¹⁸, Monica-Andreea Baciu-Drăgan¹⁹, Daniel Baumhoer⁶, Beatrice Beck-Schimmer²⁰, Niko Beerenwinkel^{12,19}, Christian Beisel¹⁹, Lara Bernasconi²¹, Anne Bertolini^{11,12}, Bernd Bodenmiller^{22,23}, Ximena Bonilla¹⁴, Lars Bosshard^{11,12}, Byron Calgua⁶, Ruben Casanova²³, Stéphane Chevrier²³, Natalia Chicherova^{11,12}, Ricardo Coelho²⁴, Maya D'Costa¹⁷, Esther Danenberg²⁵, Natalie R. Davidson¹⁴, Reinhard Dummer, Stefanie Engler²³, Martin Erkens²⁶, Katja Eschbach¹⁹, Cinzia Esposito²⁵, André Fedier²⁴, Pedro F. Ferreira¹⁹, Joanna Ficek-Pascual^{12,14,15,27,28}, Anja L. Frei¹⁶, Bruno Frey²⁹, Sandra Goetze¹³, Linda Grob^{11,12}, Gabriele Gut²⁵, Detlef Günther³⁰, Pirmin Haeuptle³¹, Viola Heinzelmann-Schwarz^{24,32}, Sylvia Herter¹⁸, Rene Holtackers²⁵, Tamara Huesser¹⁸, Alexander Immer^{14,33}, Anja Irmisch⁸, Francis Jacob²⁴, Andrea Jacobs²³, Tim M. Jaeger¹⁷, Alva R. James^{12,14,15}, Philip M. Jermann⁶, André Kahles^{12,14,15}, Abdullah Kahraman^{12,16,34}, Viktor H. Koelzer^{6,16,35}, Werner Kuebler³⁶, Jack Kuipers^{12,19}, Christian P. Kunze³⁷, Christian Kurzeder³⁸, Kjong-Van Lehmann^{14,39,40,41}, Mitchell Levesque⁸, Ulrike Lischetti²⁴, Flavio C. Lombardo²⁴, Sebastian Lugert¹⁷, Gerd Maass²⁹, Markus G. Manz¹, Philipp Markolin¹⁴, Martin Mehnert¹³, Julien Mena¹⁰, Julian M. Metzler⁴², Nicola Miglino^{1,35}, Emanuela S. Milani¹³, Holger Moch¹⁶, Simone Muenst⁶, Riccardo Murri⁴³, Charlotte KY Ng^{6,44}, Stefan Nicolet⁶, Marta Nowak¹⁶, Monica Nunez Lopéz²⁴, Patrick GA Pedrioli⁴⁵, Lucas Pelkmans²⁵, Salvatore Piscuoglio^{6,24}, Michael Prummer^{11,12}, Laurie Prélôt^{12,14,15}, Natalie Rimmer²⁴, Mathilde Ritter²⁴, Christian Rommel²⁶, María L. Rosano-González^{11,12}, Gunnar Rättsch^{12,14,15,27,45}, Natascha Santacroce¹⁹, Jacobo Sarabia del Castillo²⁵, Ramona Schlenker⁴⁶, Petra C. Schwalie²⁶, Severin Schwan¹⁷, Tobias Schär¹⁹, Gabriela Senti²¹, Wenguang Shao¹³, Franziska Singer^{11,12}, Sujana Sivapatham²³, Berend Snijder^{10,12}, Bettina Sobottka¹⁶, Vipin T. Sreedharan^{11,12}, Stefan Stark^{12,14,15}, Daniel J. Stekhoven^{11,12}, Tanmay Tanna^{14,19}, Alexandre PA Theocharides¹, Tinu M. Thomas^{12,14,15}, Markus Tolnay⁶, Vinko Tosevski¹⁸, Nora C. Toussaint⁷, Mustafa A. Tuncel^{12,19}, Marina Tusup⁸, Audrey Van Droogen¹³, Marcus Vetter⁴⁷, Tatjana Vljajnic⁶, Sandra Weber²¹, Walter P. Weber⁴⁸, Rebekka Wegmann¹⁰, Michael Weller⁴⁹, Fabian Wendt¹³, Norbert Wey¹⁶, Andreas Wick^{1,35}, Mattheus HE Wildschut^{1,10}, Bernd Wollscheid¹³, Shuqing Yu^{11,12}, Johanna Ziegler⁸, Marc Zimmermann¹⁴, Martin Zoche¹⁶ & Gregor Zuend⁵⁰

¹⁰ETH Zurich, Department of Biology, Institute of Molecular Systems Biology, Otto-Stern-Weg 3, 8093 Zurich, Switzerland. ¹¹ETH Zurich, NEXUS Personalized Health Technologies, Wagistrasse 18, 8952 Zurich, Switzerland. ¹²SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland. ¹³ETH Zurich, Department of Health Sciences and Technology, Otto-Stern-Weg 3, 8093 Zurich, Switzerland. ¹⁴ETH Zurich, Department of Computer Science, Institute of Machine Learning, Universitätsstrasse 6, 8092 Zurich, Switzerland. ¹⁵University Hospital Zurich, Biomedical Informatics, Schmelzbergstrasse 26, 8006 Zurich, Switzerland. ¹⁶University Hospital Zurich, Department of Pathology and Molecular Pathology, Schmelzbergstrasse 12, 8091 Zurich, Switzerland. ¹⁷F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4070 Basel, Switzerland. ¹⁸Roche Pharmaceutical Research and Early Development, Roche Innovation Center Zurich, Wagistrasse 10, 8952 Schlieren, Switzerland. ¹⁹ETH Zurich, Department of Biosystems Science and Engineering, Mattenstrasse 26, 4058 Basel, Switzerland. ²⁰University of Zurich, VP Medicine, Künstlergasse 15, 8001 Zurich, Switzerland. ²¹University Hospital Zurich, Clinical Trials Center, Rämistrasse 100, 8091 Zurich, Switzerland. ²²ETH Zurich, Institute of Molecular Health Sciences, Otto-Stern-Weg 7, 8093 Zurich, Switzerland. ²³University of Zurich, Department of Quantitative Biomedicine, Winterthurerstrasse 190, 8057 Zurich, Switzerland. ²⁴University Hospital Basel and University of Basel, Department of Biomedicine, Hebelstrasse 20, 4031 Basel, Switzerland. ²⁵University of Zurich, Institute of Molecular Life Sciences, Winterthurerstrasse 190, 8057 Zurich, Switzerland. ²⁶Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Grenzacherstrasse 124, 4070 Basel, Switzerland. ²⁷AI Center at ETH Zurich, Andreasstrasse 5, 8092 Zurich, Switzerland. ²⁸Life Science Zurich Graduate School, Biomedicine PhD Program, Winterthurerstrasse 190, 8057 Zurich, Switzerland. ²⁹Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany. ³⁰ETH Zurich, Department of Chemistry and Applied Biosciences, Vladimir-Prelog-Weg 1-5/10, 8093 Zurich, Switzerland. ³¹Cantonal Hospital Baselland, Medical University Clinic, Rheinstrasse 26, 4410 Liestal, Switzerland. ³²University Hospital Basel, Gynecological Cancer Center, Spitalstrasse 21, 4031 Basel, Switzerland. ³³Max Planck ETH Center for Learning Systems, Tübingen, Germany. ³⁴FHNW, School of Life Sciences, Institute of Chemistry and Bioanalytics, Muttenz, Switzerland. ³⁵University of Zurich, Faculty of Medicine, Zurich, Switzerland. ³⁶University Hospital Basel, Spitalstrasse 21/Petersgraben 4, 4031 Basel, Switzerland. ³⁷University Hospital Basel, Department of Information- and Communication Technology, Spitalstrasse 26, 4031 Basel, Switzerland. ³⁸University Hospital Basel, Brustzentrum, Spitalstrasse 21, 4031 Basel, Switzerland. ³⁹Cancer Research Center Cologne-Essen, University Hospital Cologne, Cologne, Germany. ⁴⁰Center for Integrated Oncology Aachen (CIO-A), Aachen, Germany. ⁴¹Joint Research Center Computational Biomedicine, University Hospital RWTH Aachen, Aachen, Germany. ⁴²University Hospital Zurich, Department of Gynecology, Frauenklinikstrasse 10, 8091 Zurich, Switzerland. ⁴³University of Zurich, Services and Support for Science IT, Winterthurerstrasse 190, 8057 Zurich, Switzerland. ⁴⁴University of Bern, Department of BioMedical Research, Murtenstrasse 35, 3008 Bern, Switzerland. ⁴⁵ETH Zurich, Department of Biology, Wolfgang-Pauli-Strasse 27, 8093 Zurich, Switzerland. ⁴⁶Roche Pharmaceutical Research and Early Development, Roche Innovation Center Munich, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany. ⁴⁷University Hospital Basel, Brustzentrum & Tumorzentrum, Petersgraben 4, 4031 Basel, Switzerland. ⁴⁸University Hospital Basel and University of Basel, Department of Surgery, Brustzentrum, Spitalstrasse 21, 4031 Basel, Switzerland. ⁴⁹University Hospital and University of Zurich, Department of Neurology, Frauenklinikstrasse 26, 8091 Zurich, Switzerland. ⁵⁰University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland.