Impact on costs and outcomes of multi-gene panel testing for advanced solid malignancies: a cost-consequence analysis using linked administrative data

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Summary

Background To date, economic analyses of tissue-based next generation sequencing genomic profiling (NGS) for advanced solid tumors have typically required models with assumptions, with little real-world evidence on overall survival (OS), clinical trial enrollment or end-of-life quality of care.

Methods Cost consequence analysis of NGS testing (555 or 161-gene panels) for advanced solid tumors through the OCTANE clinical trial (NCT02906943). This is a longitudinal, propensity score-matched retrospective cohort study in Ontario, Canada using linked administrative data. Patients enrolled in OCTANE at Princess Margaret Cancer Centre from August 2016 until March 2019 were matched with contemporary patients without large gene panel testing from across Ontario not enrolled in OCTANE. Patients were matched according to 19 patient, disease and treatment variables. Full 2-year follow-up data was available. Sensitivity analyses considered alternative matched cohorts. Main Outcomes were mean per capita costs (2019 Canadian dollars) from a public payer's perspective, OS, clinical trial enrollment and end-of-life quality metrics.

Findings There were 782 OCTANE patients with 782 matched controls. Variables were balanced after matching (standardized difference <0.10). There were higher mean health-care costs with OCTANE ($79,702 vs. $59,550), mainly due to outpatient and specialist visits. Publicly funded drug costs were less with OCTANE ($20,015 vs. $24,465). OCTANE enrollment was not associated with improved OS (restricted mean survival time [standard error]: 1.50 (±0.03) vs. 1.44 (±0.03) years, log-rank p = 0.153), varying by tumor type. In five tumor types with ≥35 OCTANE patients, OS was similar in three (breast, colon, uterus, all p > 0.40), and greater in two (ovary, biliary, both p < 0.05). OCTANE was associated with greater clinical trial enrollment (25.4% vs. 9.5%, p < 0.001) and better end-of-life quality due to less death in hospital (10.2% vs. 16.4%, p = 0.003). Results were robust in sensitivity analysis.

Interpretation We found an increase in healthcare costs associated with multi-gene panel testing for advanced cancer treatment. The impact on OS was not significant, but varied across tumor types. OCTANE was associated with greater trial enrollment, lower publicly funded drug costs and fewer in-hospital deaths suggesting important considerations in determining the value of NGS panel testing for advanced cancers.

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Keywords: Precision oncology; Cost-consequence analysis; NGS; Molecular profiling; Matched therapies

Research in context

Evidence before this study

Next generation sequencing (NGS) to identify clinically actionable genomic alterations is increasingly used to support clinical decision making in oncology. However, a deeper understanding of the costs and consequences of NGS testing are needed to inform its wide implementation in managed health care systems. A PubMed search was conducted on Dec 17 2023 using the terms cost consequence analysis AND cancer AND ((next generation sequencing) OR (molecular profiling)) and we reviewed all the publications excluding reviews. To the best of our knowledge, no prior publications have conducted cost-consequence studies for NGS profiling in a pan-cancer cohort of patients including end-of-life quality metrics. Moreover, other forms of economic analyses on the topic are limited, and most often use models that require assumptions. These may include assumptions on access to matched therapies, treatment-alteration match rates or assumptions on real-world effectiveness of selected treatments.

Added value of this study

A retrospective matched cohort study using health administrative data on observed costs and outcomes was conducted with patients diagnosed with advanced or metastatic solid tumors enrolled in the OCTANE clinical trial. Despite increased associated costs in patients undergoing NGS within the OCTANE trial there was no significant impact on overall survival, though this varied across tumor types. At the same time, there was higher clinical trial enrollment, fewer publicly funded drug costs and fewer in-hospital deaths associated with NGS testing in OCTANE.

Implications of all the available evidence

The costs and consequences associated with NGS observed in this study could be of utility for managed health care systems as well as practicing physicians that order NGS tests for patients with advanced solid tumors.

Introduction

Genomic profiling by next generation sequencing (NGS) is increasingly important to identify clinically actionable mutations to inform choice of targeted drug therapies and/or immunotherapies in oncology.[1] Rapid advances in technology now enable comprehensive testing of large panels (approximately 300–500 genes) of clinically relevant genes from tumor derived nucleic acids in clinical testing laboratories rather than the standard of single gene testing.[2] However, lack of tumor tissue available for molecular profiling and turnaround times for test results constrain the broad implementation of comprehensive genomic profiling across tumor types. For those patients with access to NGS, the low frequency of specific actionable alterations as well as treatment access also limit the impact of precision oncology. Moreover, there are significant costs and resource allocation considerations required for testing all patients with advanced solid tumors.[3] In managed health care systems where universal panel testing is often not reimbursed, additional questions remain to be addressed including whether all cancer types benefit from testing and how testing impacts downstream health care utilization, such as clinical trials where precision matched drug treatments are provided by the sponsor, the burden of visits for outpatient management, hospital admissions or end-of-life care.

To evaluate the clinical utility of tissue-based NGS panel testing, several academic institutions have instituted prospective programs with longitudinal follow up.[4,5] The Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) (NCT02906943) was a prospective study in the province of Ontario, Canada from 2016 to 2019 that included 7 academic hospitals to advance NGS panel testing, and data sharing and to create a province-wide repository of biospecimens for future research.[6] Ontario is a publicly funded, single-payer health care system where broad panel testing for all solid tumors is not reimbursed by the publicly-funded health care system and private-pay testing is not routinely performed. The main inclusion criteria for OCTANE included patients ≥18 years old diagnosed with advanced or metastatic solid tumors, with an ECOG performance status of 0–1, with sufficient formalin-fixed archived tumor tissue available for molecular profiling and adequate organ function with a life expectancy of more than 6 months assessed by the investigator. Patients were required to have archival

formalin-fixed paraffin embedded samples for NGS testing as well as blood samples. Patients could not have received more than 2 lines of prior cytotoxic therapy for their recurrent/metastatic disease, with the exception of patients being considered for phase 1 clinical trials who could be more heavily pretreated.

Here we evaluate the real-world impact on healthcare costs and consequences in terms of overall survival (OS), trial enrollment and end-of-life quality of care associated with the use of tissue-based NGS testing compared with no use of NGS testing in a public universal health system. We selected this approach, knowing a priori that similar to international experiences, match rates based on alterations in OCTANE was relatively low (17% of patients with actionable mutations), and thus may have limited impact on survival, while still influencing costs and other outcomes.[6,7]

Methods

Study population and design

We performed a cost-consequence analysis to investigate the economic impact of panel testing in a publicly-funded health care system. This is a form of economic analysis undertaken to provide information on disaggregated costs and a range of outcomes, allowing the reader to judge the relevance and importance of the information to their own context.[8] Cost-consequence analyses are recommended for complex interventions that have multiple possible effects that may not be limited to changes in quality-adjusted life years.

A retrospective cohort study was performed with patients diagnosed with advanced or metastatic solid tumors in Ontario (Canada) enrolled in the OCTANE clinical trial at Princess Margaret Cancer Centre (PMCC) from August 1, 2016 until March 31, 2019, when trial accrual was primarily at PMCC. This period was chosen to ensure complete follow-up of all patients to death or 2.5 years from index date. The primary exposure was trial enrollment in OCTANE with performance of NGS. Canada has a provincial government-run single-payer system. During the time-period considered, two different in-house targeted panels were used as technology evolved to cover a higher number of genes within the OCTANE protocol, largely (82%) a 555 gene panel (Supplementary Text 1). This study received ethics approval through the Ontario Cancer Research Ethics Board (Clinical Trials Ontario Project 1217). Fourteen tumor groups (e.g., breast, ovary, uterus, colon and rectum) were classified based on the International Classification of Disease in Oncology, third edition (ICD-O-3), morphology and topography codes from the Ontario Cancer Registry (OCR).

A contemporaneous, matched comparison cohort was identified based on patients diagnosed with advanced or metastatic solid tumors treated in Ontario during the study period. Comparison patients were eligible for matching if they received palliative systemic therapy, radiotherapy or metastasis surgery, and had similar tumor information as with the OCTANE patients (Fig. 1). Patients were matched according to 19 variables including but not limited to age, sex, place of residence, tumor site, symptom burden, income quintile, comorbidities and prior lines of systemic therapy (all variables listed in Table 1 except maximum ESAS scores of treatable, untreatable and mood symptoms). Information on covariates is provided in Supplementary Text 2.

The Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022), and Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepidemiology (RECORD-PE) reporting guidelines were followed.

Data sources and linkage

Information on accrued OCTANE patients included their health insurance number, demographic information, gene panel utilized, date of enrollment, date of results reporting and identified alterations. Using the health insurance number, those patients were deterministically linked to Ontario administrative data sources housed at ICES (formerly the Institute for Clinical Evaluative Sciences), where all analyses occurred. Details of the multiple linked administrative health databases are provided in Supplementary Text 3.

Derived variables

Index date was defined as the date in which NGS results were reported in the OCTANE cohort. In the comparison cohort that did not undergo NGS, eligible patients were first grouped with OCTANE patients based on similar disease information and period of first palliative treatment for advanced or metastatic disease diagnosis. The index date in the comparison cohort was created using the date of first palliative treatment and respective average time intervals from the corresponding OCTANE patients.

Outcomes

The primary outcomes were mean per capita costs from a payer's perspective (2019 Canadian dollars [CAD]), OS, clinical trial enrollment and end-of-life quality metrics. Costs were analyzed on a 2-year time horizon from index date due to completeness of the cost data. Given the short time horizon, no discount rate was used. OS was measured from the index date to date of last follow-up or death.

Patient-level administrative data sources were used to measure healthcare utilizations. These included physician reimbursement data on all outpatient primary care and specialist visits, hospital admission data from all Ontario hospitals, provincial emergency department

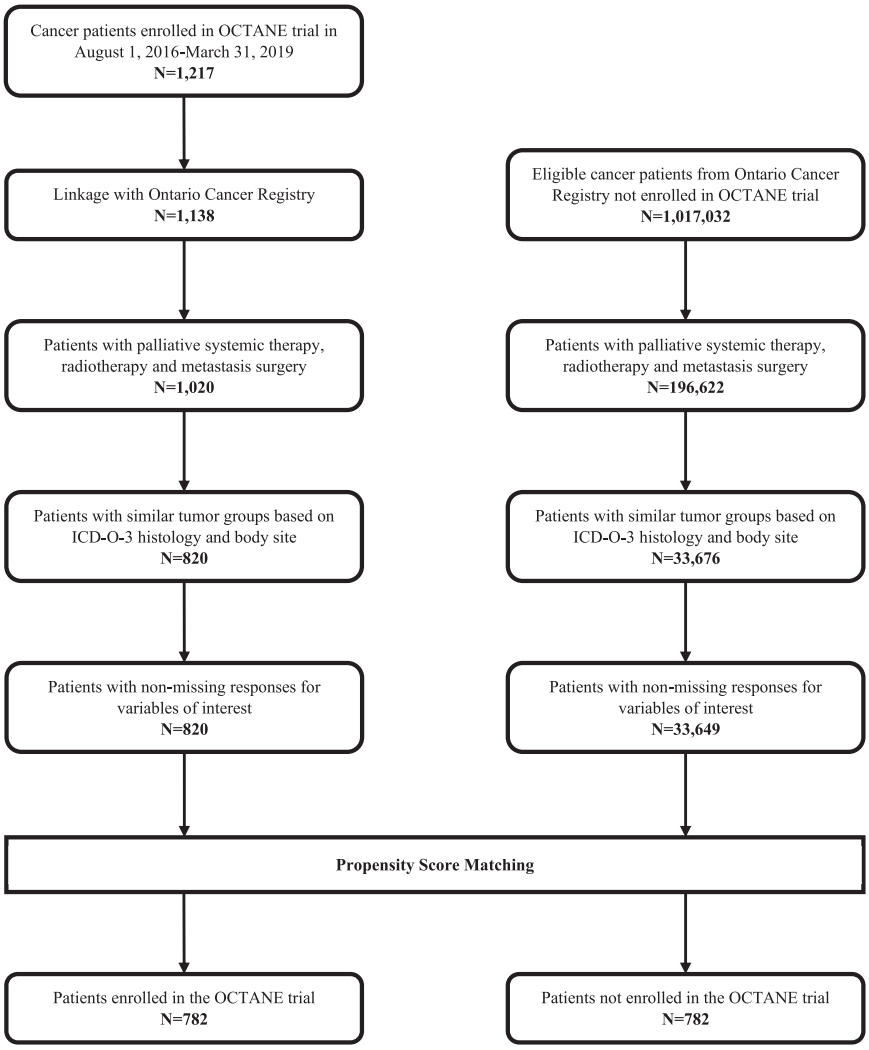

***Fig. 1:* Study flow diagram**. ICD-O-3: International classification of diseases for oncology, third edition.

data, provincial home care and long-term care data, publicly funded prescription medications and systemic treatment data. Costs were estimated with the ICES costing algorithm based on a case mix costing approach as previously reported.[9–12] A second ICES algorithm included person-level direct costs for publicly funded systemic therapies and specific privately funded systemic therapies (e.g., named investigational agents used in clinical trials with known costs).

End-of-life quality indicators were previously-described measures of aggressive care (e.g., death in hospital, use of chemotherapy in last two weeks of life,[13,14] intensive care unit (ICU) admission at end-of-life) and supportive care at the end-of-life (home care, physician home visits),[15] measured via administrative data. Enrollment in clinical trials other than OCTANE post index date was captured via provincial systemic therapy data. Alteration-treatment match rates were described based on OncoKB level 1-4 alterations.[7,16] Costs and other outcomes were also described for tumor groups with 35 or more OCTANE patients, given limited power of smaller samples.

Statistical analysis

Patients enrolled in the OCTANE protocol at PMCC were propensity score matched 1:1 to contemporaneous comparison patients in each tumor group using a greedy algorithm with calipers of 0.2 of the standard deviation of the logit of propensity scores for all variables described in Table 1.[17] We considered a standardized difference (std. diff.) of ≤ 0.1 to represent balance between groups. Differences in mean costs, clinical trial enrollment and end-of-life quality metrics were assessed with standardized differences using a more conservative threshold of >0.2 for detecting effect sizes, and paired t-tests and McNemar's tests for

Patient characteristics	Unmatched			Matched		
	OCTANE enrollment		Std. diff.	OCTANE enrollment		Std. diff.
	Yes (N = 820)	No (N = 33,649)		Yes (N = 782)	No (N = 782)	
Age						
Mean ± SD	58.4 ± 12.6	66.4 ± 12.8	0.63	58.6 ± 12.3	59.5 ± 12.8	0.02
Sex						
Female	606 (73.9%)	18,960 (56.4%)	0.37	585 (74.8%)	585 (74.8%)	0.00
Male	214 (26.1%)	14,689 (43.6%)	0.37	197 (25.2%)	197 (25.2%)	0.00
Income quintile						
1 (Lowest)-2	281 (34.3%)	13,850 (41.16%)	0.14	270 (34.5%)	277 (35.4%)	0.02
3–5 (Highest)	539 (65.7%)	19,799 (58.84%)	0.14	512 (65.5%)	505 (64.6%)	0.02
Place of residence						
West Ontario	87 (10.6%)	10,325 (30.7%)	0.51	85 (10.9%)	70 (8.9%)	0.06
Toronto/Central Ontario	586 (71.5%)	12,243 (36.4%)	0.75	553 (70.7%)	555 (71.0%)	0.01
East/North Ontario	147 (17.9%)	11,081 (32.9%)	0.35	144 (18.4%)	157 (20.1%)	0.04
Urban/rural residence						
Urban/suburban	796 (97.1%)	30,456 (90.5%)	0.27	758 (96.9%)	755 (96.6%)	0.02
Rural	24 (2.9%)	3193 (9.5%)	0.27	24 (3.1%)	27 (3.4%)	0.02
Comorbidity index[a]						
Mean ± SD	0.82 ± 1.20	0.92 ± 1.43	0.08	0.82 ± 1.22	0.93 ± 1.30	0.09
Number of years from most recent diagnosis to index date						
Mean ± SD	2.82 ± 2.96	2.62 ± 3.20	0.07	2.70 ± 2.78	2.63 ± 3.05	0.02
Tumor group						
Breast	96 (11.7%)	7414 (22.0%)	0.28	96 (12.3%)	96 (12.3%)	0.00
Ovary	240 (29.3%)	3626 (10.8%)	0.47	238 (30.4%)	238 (30.4%)	0.00
Uterus	118 (14.4%)	1986 (5.9%)	0.28	117 (15.0%)	117 (15.0%)	0.00
Other female genital organs	35 (4.3%)	310 (0.9%)	0.21	32 (4.1%)	32 (4.1%)	0.00
Male genital organs	34 (4.2%)	4768 (14.2%)	0.35	34 (4.4%)	34 (4.4%)	0.00
Colon and rectum	70 (8.5%)	4210 (12.5%)	0.13	67 (8.6%)	67 (8.6%)	0.00
Urinary tract	31 (3.8%)	998 (3.0%)	0.05	27 (3.5%)	27 (3.5%)	0.00
Pancreas	23 (2.8%)	997 (3.0%)	0.01	19 (2.4%)	19 (2.4%)	0.00
Stomach and esophagus	24 (2.9%)	1317 (3.9%)	0.05	23 (2.9%)	23 (2.9%)	0.00
Biliary tract	43 (5.2%)	1177 (3.5%)	0.09	37 (4.7%)	37 (4.7%)	0.00
Respiratory and intrathoracic organs	33 (4.0%)	4384 (13.0%)	0.33	31 (4.0%)	31 (4.0%)	0.00
Brain and oral cavity	22 (2.7%)	1067 (3.2%)	0.03	20 (2.6%)	20 (2.6%)	0.00
Melanoma and skin	23 (2.8%)	1171 (3.5%)	0.04	20 (2.6%)	20 (2.6%)	0.00
Thyroid, soft tissue and unspecified sites	28 (3.4%)	224 (0.7%)	0.20	21 (2.7%)	21 (2.7%)	0.00
Number of years from first diagnosis to first palliative treatment						
Mean ± SD	1.61 ± 2.86	1.61 ± 2.81	0.00	1.50 ± 2.69	1.49 ± 2.89	0.01
Palliative treatment[b]						
Systemic therapy	766 (93.4%)	28,309 (84.13%)	0.30	732 (93.6%)	724 (92.6%)	0.04
Number of lines of systemic therapy						
Mean ± SD	1.82 ± 1.34	1.17 ± 0.90	0.58	1.80 ± 1.27	1.83 ± 1.54	0.02
Radiotherapy	261 (31.8%)	13,314 (39.6%)	0.16	245 (31.3%)	249 (31.8%)	0.01
Metastasis surgery	124 (15.1%)	2807 (8.3%)	0.21	113 (14.5%)	103 (13.2%)	0.04
Health system[c]						
Specialist visits	810 (98.8%)	26,382 (78.4%)	0.68	773 (98.9%)	773 (98.9%)	0.00
Symptom assessments	724 (88.3%)	23,379 (69.5%)	0.47	686 (87.7%)	706 (90.3%)	0.08
Maximum score of any treatable symptoms[d]						
Mean ± SD	4.05 ± 3.02	3.07 ± 3.29	0.31	4.08 ± 3.03	4.10 ± 3.24	0.01

(Table 1 continues on next page)

Patient characteristics	Unmatched			Matched		
	OCTANE enrollment		Std. diff.	OCTANE enrollment		Std. diff.
	Yes (N = 820)	No (N = 33,649)		Yes (N = 782)	No (N = 782)	
(Continued from previous page)						
Maximum score of any untreatable symptoms[d]						
Mean ± SD	4.95 ± 3.06	3.88 ± 3.58	0.32	4.94 ± 3.08	5.12 ± 3.22	0.06
Maximum score of any mood symptoms[d]						
Mean ± SD	3.59 ± 2.93	2.50 ± 3.00	0.37	3.58 ± 2.95	3.51 ± 3.11	0.02
Palliative care services	472 (57.6%)	19,124 (56.8%)	0.01	452 (57.8%)	492 (62.9%)	0.10

Std. Diff., standardized difference; SD, standard deviation; ED, emergency department. Number of hospitalizations, number of ED visits, and number of cancer diagnoses are not shown in the table; all of them were well balanced between cohorts at standard difference ≤0.10. [a]Elixhauser comorbidity index was measured within a 5-year lookback period from index date; total comorbidity score excluded indices for lymphoma, metastatic cancer and solid tumor without metastases. [b]Treatment was measured prior to index date. [c]Health system consultations and services were measured within a 16-week lookback and lookforward period from index date; specialist visits were abstracted in OHIP based on consultations and assessments from medical oncologists, gynecologic oncologists, hematologists or internal medicine specialists; symptom assessments were abstracted in ESAS; palliative care services were abstracted in OHIP, DAD, NACRS, CCRS and HCD based on specific inpatient, outpatient, long-term care and home care services. [d]Scores for each symptom reported in ESAS range from 0 to 10; the 9 symptoms were categorized into 3 broader groups: Treatable symptoms (pain, nausea and shortness of breath), untreatable symptoms (tiredness, drowsiness, lack of appetite and wellbeing) and mood symptoms (anxiety and depression).

Table 1: **Baseline characteristics of the OCTANE and matched cohorts.**

detecting statistical significance. Kaplan–Meier and Cox regression methods were used. Estimations for mean survival time and its standard error from the Kaplan–Meier analysis were restricted to the largest event time. For tumor groups of adequate size, subgroup analyses for differences in costs, clinical trial enrollment, end-of-life quality and OS were done with the Benjamini-Hochberg (BH) method, which controls the false discovery rate for multiple hypothesis testing.[18] The threshold for statistical significance was $p < 0.05$. The SAS software version 9.4 was used for data analyses (SAS Institute, Cary, NC).

Sensitivity analysis

We performed sensitivity analyses with different propensity-matched cohort definitions: (1) inclusion of only those receiving palliative systemic therapy (2) matching to only those treated at PMCC not enrolled on OCTANE (3) matching to only those treated outside of PMCC. We also explored (4) the impact of additional matching variables: receipt of early palliative care (palliative care consultation prior to the index date or within 8 weeks following the index date) and clinical trial enrollment prior to the index date.

Ethics statement

The OCTANE protocol was approved by the Ontario Cancer Research Ethics Board (NCT02906943). Study participants grant access to medical health records and their OHIP (Ontario Health Insurance Plan) number to link to provincial health administrative databases for future research. Participants agree to de-identified clinical and genomic data-sharing for research.

Role of the funding source

The funders of the study played no role in study design, data collection, analysis, interpretation of data, in writing of the manuscript or the decision to submit the manuscript for publication. PN and TPH had full access to all the datasets. All the authors included in this publication reviewed the manuscript and agreed to submit for publication.

Results

Propensity score matching

From August 1, 2016 until March 31, 2019, there were 1217 patients enrolled in the OCTANE clinical trial in PMCC. The most common reasons for exclusion were due to those patients where no appropriate potential match could be found for tumor histology and body site (n = 200) or no palliative treatments before the index date (n = 118). After these exclusions, there were 782 OCTANE patients and 33,649 non-OCTANE patients (Fig. 1). The baseline characteristics of OCTANE and comparison cohorts prior to and following matching are summarized in Table 1. After matching, the std. diff. for matching variables were all ≤0.10.

Total and mean per capita costs

After propensity-matching, there were more general health-associated costs in the case of OCTANE patients (mean cost: $79,702 vs. $59,550, std. diff. = 0.39, $p < 0.001$). The greatest contributors to this difference were increased costs related to hospital outpatient clinic visits (total cost: $6,687,146 vs. $3,728,204, mean cost: $8,696 vs. $5,114, std. diff. = 0.65) and costs associated with outpatient oncology visits (total cost: $22,419,770 vs. $15,337,892, mean cost: $33,165 vs. $26,197, std. diff. = 0.24) (all $p < 0.05$) (Table 2). With respect of costs of systemic therapies publicly reimbursed, reduced costs were observed for the OCTANE cohort (total cost: $11,949,174 vs. $12,892,906, mean cost: $20,015 vs. $24,465, std. diff. = 0.09). However, when including costs of privately funded medications, total costs were

Type of service	Cost description	OCTANE enrollment				Std. diff.
		Yes (N = 782)		No (N = 782)		
		Total	Mean	Total	Mean	
Short episodes (<60 days)	Inpatient hospitalization and rehabilitation cost	$14,273,617	$25,534	$11,721,076	$23,969	0.06
	Hospital outpatient clinic visit cost	**$6,687,146**	**$8696**	**$3,728,204**	**$5114**	**0.65**
	Same day surgery cost	$398,880	$1621	$358,425	$1732	0.06
	ED visit cost	**$1,047,871**	**$1723**	**$801,756**	**$1373**	**0.26**
	Dialysis clinic visit cost	$99,446	$9041	$413,049	$45,894	0.69
	Oncology clinic visit cost	**$22,419,770**	**$33,165**	**$15,377,892**	**$26,197**	**0.24**
Long-term episodes	**CCC, LTC and inpatient mental health cost**	**$829,482**	**$12,761**	**$867,384**	**$11,565**	**0.10**
Visits/Claims	FFS GP/FP visit cost	$1,501,900	$2021	$1,452,915	$1974	0.02
	FFS specialist visit cost	**$5,575,655**	**$7167**	**$4,118,526**	**$5370**	**0.34**
	Non-FFS GP/FP visit cost	$16,013	$41	$13,332	$40	0.02
	Other non-FFS visit cost	**$2,288,496**	**$2976**	**$1,784,063**	**$2357**	**0.26**
	Lab and non-physician cost	**$137,926**	**$245**	**$104,155**	**$195**	**0.19**
	FHO/FHN capitation cost	$160,339	$243	$145,785	$222	0.10
	Home care services cost	$3,410,934	$5610	$3,515,876	$6168	0.08
	Non-anticancer related drug cost	$2,297,449	$3706	$2,165,908	$3411	0.04
NGS	Panel test cost	$1,182,400	$1512	N/A	N/A	N/A
Systemic therapy	Publicly reimbursed anticancer related drug cost	$11,949,174	$20,015	$12,892,906	$24,465	0.09
	Publicly and privately reimbursed anticancer related drug cost	$16,280,297	$25,359	$14,356,394	$26,342	0.02
Total	**Total without anticancer related drug cost**	**$62,327,308**	**$79,702**	**$46,568,394**	**$59,550**	**0.39**
	Total with publicly reimbursed anticancer related drug cost	**$74,276,482**	**$94,983**	**$59,461,300**	**$76,037**	**0.25**
	Total with publicly and privately reimbursed anticancer related drug cost	**$78,607,605**	**$100,521**	**$60,924,788**	**$77,909**	**0.29**

Std. Diff., standardized difference; ED, emergency department; CCC, complex continuing care; LTC, long-term care; FFS, fee for service; GP, general practitioner; FP, family practitioner; FHO, family health organization; FHN, family health network; NGS, next generation sequencing test. Costs in **bold** indicate statistical significance based on the paired t-test.

Table 2: **Healthcare costs of the OCTANE and matched cohorts.**

higher in the OCTANE cohort (total cost: $16,280,297 vs. $14,356,394, mean cost: $25,359 vs. $26,342, std. diff. = 0.02). For illustration purposes, Supplementary Table S1 describes the regimens of privately funded medications after the index date for the OCTANE and matched patients.

Overall survival impact

Enrollment in OCTANE was not associated with significant longer OS (restricted mean survival time (RMST) [standard error]: 1.50 (±0.03) vs. 1.44 (±0.03) years, hazard ratio (HR) [95% confidence interval (CI)]: 0.91 (0.80–1.03), log-rank p = 0.153) (Fig. 2).

Treatment and end-of-life quality metrics

Enrollment in OCTANE was associated with greater palliative systemic therapy (84.4% vs. 71.0%, std. diff. = 0.33), lines of therapy (mean [standard deviation]: 2.1 (±1.1) vs. 1.8 (±1.1), std. diff. = 0.28) and clinical trial enrollment (first-line: 15.1% vs. 5.9%, std. diff. = 0.30; any-line: 25.4% vs. 9.5%, std. diff. = 0.43) after the index date (all p < 0.05). Specifically, in the OCTANE cohort 54.5% of the population had actionable mutations detected based on OncoKB. These rates varied across cancer types (Supplementary Table S2). Among them 8.2% of those with alterations received molecularly guided therapies. For those patients receiving matched treatments, at least 25.7% received them in the context of clinical trials. For those treatments not on trials, drugs were received through various access programs, or out of pocket payment. The distribution for the classes of systemic therapies delivered before and after the index date for the OCTANE and matched cohorts is included in Supplementary Table S3.

End-of-life quality metrics were measured for 511 OCTANE and 487 matched patients who died after the index date. Enrollment in OCTANE was associated with significantly less death in acute inpatient care facilities (10.2% vs. 16.4%, std. diff. = 0.18, p = 0.003). Other metrics showed little difference though favored OCTANE: aggressive care (27.4% vs. 33.1%, std. diff. = 0.12, p = 0.141), inpatient hospital admission within 30 days of death (8.2% vs. 10.1%, std. diff. = 0.06, p = 0.080), and systemic therapy at the end-of-life (4.1% vs. 6.6%, std. diff. = 0.11, p = 1.000) (Table 3).

Costs and outcomes by tumor groups

Healthcare costs were investigated for subgroups with breast, ovarian, uterine, colorectal and biliary tract cancers where there were 35 or more OCTANE patients (Supplementary Tables S4–S8). The general health-associated costs were higher for OCTANE patients

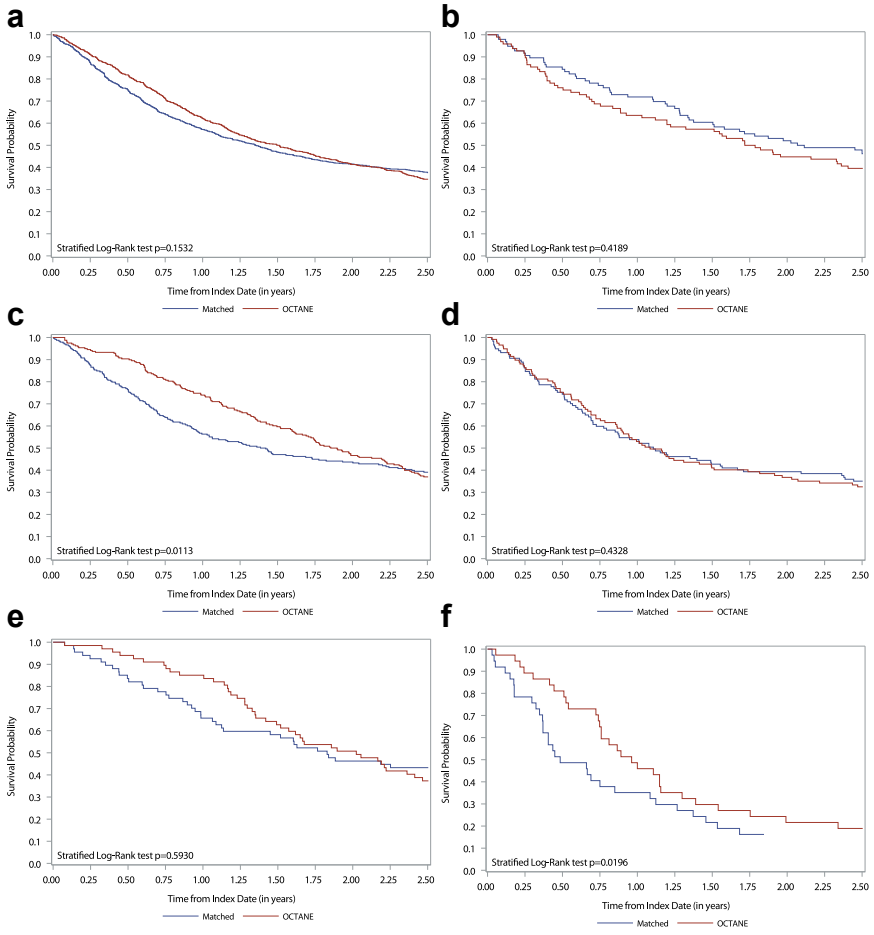

Fig. 2: **Overall survival of the OCTANE and matched cohorts.** Number at risk cannot be shown due to administrative data regulations on small cell reporting. (a) All patients. (b) Patients with breast cancer. (c) Patients with ovarian cancer. (d) Patients with uterine cancer. (e) Patients with colorectal cancer. (f) Patients with biliary tract cancer.

EOL type	EOL description	OCTANE enrollment			Std. diff.
		Total (N = 998)	Yes (N = 511)	No (N = 487)	
Summary indicators[a]	Aggressive care	301 (30.2%)	140 (27.4%)	161 (33.1%)	0.12
	Supportive care	713 (71.4%)	371 (72.6%)	342 (70.2%)	0.05
Aggressive care indicators	>1 ED visit[b]	40 (4.0%)	20 (3.9%)	20 (4.1%)	0.01
	>1 inpatient hospital admission[b]	91 (9.1%)	42 (8.2%)	49 (10.1%)	0.06
	Death in acute inpatient care	**132 (13.2%)**	**52 (10.2%)**	**80 (16.4%)**	**0.18**
	ICU admission[b]	82 (8.2%)	42 (8.2%)	40 (8.2%)	0.00
	Palliative systemic therapy[c]	53 (5.3%)	21 (4.1%)	32 (6.6%)	0.11
Supportive care indicators	Palliative nursing and PSW visit[d]	668 (66.9%)	350 (68.5%)	318 (65.3%)	0.07
	Physician house visit[c]	427 (42.8%)	214 (41.9%)	213 (43.7%)	0.04

Std. Diff., standardized difference; ED, emergency department; ICU, intensive care unit; PSW, personal support worker. Indicators in **bold** indicate statistical significance based on McNemar's test. [a]Composite score for occurrence of at least one of the respective EOL individual indicators. [b]EOL indicator measured within 30 days of death. [c]EOL indicator measured within 2 weeks of death. [d]EOL indicator measured within 6 months of death.

Table 3: **End-of-life quality (EOL) metrics of the OCTANE and matched cohorts for dying patients.**

with ovarian cancer (total cost: $21,697,945 vs. $12,819,247, mean cost: $91,168 vs. $53,862, std. diff. = 0.70), uterus cancer (total cost: $7,675,444 vs. $5,607,858, mean cost: $65,602 vs. $47,930, std. diff. = 0.39) and colorectal cancer (total cost: $6,661,307 vs. $4,966,525, mean cost: $99,422 vs. $74,127, std. diff. = 0.43) (all $p < 0.05$). The main contributor was hospital outpatient clinic visits (all $p < 0.05$). Reduced costs of publicly reimbursed systemic therapy were observed for the OCTANE cohort of breast cancer patients (total cost: $1,461,725 vs. $4,139,829, mean cost: $18,272 vs. $47,584, std. diff. = 0.49, $p = 0.005$, BH adjusted $p = 0.010$). Higher publicly reimbursed systemic therapy costs were associated with OCTANE enrollment for patients with ovarian cancer (total cost: $4,105,059 vs. $1,644,744, mean cost: $20,733 vs. $10,611, std. diff. = 0.43) and colorectal cancer (total cost: $1,747,033 vs. $812,934, mean cost: $30,121 vs. $16,591, std. diff. = 0.58) (all $p < 0.05$).

Amongst the tumor subgroups, OCTANE enrollment was associated with statistically significant longer OS in ovarian cancer (RMST: 1.69 (±0.05) vs. 1.45 (±0.06) years, HR: 0.64 (0.50–0.83), log-rank $p = 0.011$, BH adjusted $p = 0.049$) and biliary tract tumors (RMST: 1.16 (±0.13) vs. 0.80 (±0.11) years, HR: 0.65 (0.40–1.06), log-rank $p = 0.020$, BH adjusted $p = 0.049$).

Enrollment in OCTANE was associated with greater clinical trial enrollment for patients with breast cancer (19.8% vs. ≤5.2%, std. diff. = 0.45–0.64), ovarian cancer (26.9% vs. 14.3%, std. diff. = 0.32) and uterine cancer (42.7% vs. 8.6%, std. diff. = 0.85) (all $p < 0.05$). OCTANE patients with colorectal cancer were more exposed to supportive care (73.8% vs. 60.5%, std. diff. = 0.29, $p = 0.008$, BH adjusted $p = 0.040$).

Sensitivity analysis

There were similar findings with restriction to those receiving palliative systemic therapy, and when matching only to those treated at PMCC, except that the latter control group had slightly lower mean drug costs compared to matched OCTANE patients (e.g., mean publicly funded cost: $21,023 vs. $17,617, std. diff = 0.09, $p = 0.030$). Findings were similar to the primary analysis when matching was restricted to patients treated outside PMCC, but with greater differences in trial enrollment (29.9% vs. 4.1%, std. diff. = 0.73, $p < 0.001$). Additional matching for early palliative care and prior clinical trials showed greater differences in end-of-life quality: Less aggressive care at end-of-life (26.8% vs. 35.1%, std. diff. = 0.18, $p = 0.054$) and less death in hospital for OCTANE patients (10.3% vs. 17.9%, std. diff. = 0.22, $p = 0.005$).

Discussion

Routine genomic testing for treatment decision making is considered a standard practice for a variety of cancers.[19,20] Despite broad implementation of NGS panel testing, a paucity of data exists defining costs and consequences of NGS panel testing using real-world population-based data. In this study, we explored health-associated costs of NGS panel testing, and outcomes including OS within OCTANE. Overall, in the context of a low alteration-treatment match rate, the use of NGS panel testing was associated with increased costs and no detectable survival benefit, similar to short-term findings from British Columbia's Personalized OncoGenomics (POG) program[7,21] Added outpatient clinic visits (e.g. for trials, treatments and follow-up) were a major driver of cost differences. Interestingly, when stratified by tumor cohorts, we observed variation in survival by subgroup that remained significant for biliary cancer and ovarian cancer after adjustment for multiple comparisons. These observations are important for hypothesis generation. Moreover, patients enrolled in OCTANE had more clinical trial enrollment and less death in hospital which have practical implications for patient care.

Prior studies have evaluated the cost of NGS panel testing by the use of budget impact models including multiple assumptions that may limit the external applicability of the results to real-world contexts.[22] For example, some prior studies have included the assumption that patients have wide access to all the potential matched therapies available or lack real-world efficacy outcomes and instead use survival times obtained on clinical trial reported data.[22] The use of estimates based on clinical trial data may overestimate the benefit provided by NGS panel testing.

All of these limitations can be addressed by the use of administrative data. The main advantage of this study is the use of only real-world data related to treatment access and patient care trajectories in a universal healthcare system. Hence, the estimation of the real-world impact of NGS panel testing may be more accurate. The comprehensive evaluation of end-of-life quality assessments across administrative databases enabled us to study the impact of NGS panel testing on these variables. To the best of our knowledge, this is the first study incorporating these endpoints. Importantly, there was less death in hospital observed in patients included in the OCTANE cohort.

In this population-based analysis, OCTANE patients also had lower publicly-funded systemic therapy costs, though increased clinical trial access and greater overall health care costs. Importantly, these trial drug costs will eventually be borne by the public for reimbursed agents. These findings provide important perspectives to private and public payers alike. The fact that OCTANE enrollment was also associated with more clinical trial access as first line of treatment after the index date supports the use of NGS to increase the breadth of treatment options available including targeted and experimental therapeutics.

With respect to the end-of-life observations, better end-of-life quality metrics was observed in patients included in the OCTANE cohort. Significantly fewer inpatient care deaths and numerically fewer systemic therapy treatments within the last 14 days of life were observed in the OCTANE group. A better planning of systemic therapy options and end-of-life planning using the NGS panel prognostic information may have impacted therapy avoidance and the less aggressive care observed in the OCTANE group near the end-of-life. In this regard, a broader number of patients receiving end-of-life care at home was observed in the OCTANE cohort. Other potential explanations include the likely association of NGS panel testing with early palliative care referral and more intense multidisciplinary team involvement in the care of cancer patients which have been shown to improve disease outcomes.[23] Despite the comprehensive number of palliative care quality metrics analyzed, we acknowledge that additional end-of-life quality metrics such as preferred place of death were not captured in our work.[24] Despite these limitations, our results unveil several downstream effects of NGS beyond clinical trial or targeted therapies access.

To our knowledge, this is the first study assessing the impact of NGS panel testing in clinical practice across these multiple outcomes by linking the results of genomic profiling with administrative data. However, despite our efforts to propensity match our cohorts, it is noteworthy that both the OCTANE and non-OCTANE matched cohorts were enriched to include patients who were younger, predominantly female and from higher income backgrounds that may limit the generalizability of our findings. An additional limitation of our model is the lack of consideration of the intrinsic prognostic implications of every single genomic alteration. The impact of therapy avoidance due to the genomic assay was not assessed. Further limitations include a predominance of gynecological malignancies or other tumor histologies with fewer known actionable alterations, and underrepresentation of melanoma or lung cancer with well-described effective targeted therapies available. This could have impacted on the lack of OS benefit observed in the OCTANE cohort. Despite this limitation, in the subgroup analysis, OS differences were observed for ovarian cancer and biliary tract cancers where current evidence supports molecular profiling and matching patients to targeted therapies with proven benefit (e.g. PARP inhibitors and ovarian cancer subtypes).[25,26]

Also, we acknowledge that despite the vast array of variables available for matching, there may be residual unobserved confounding, including confounding by indication or disease severity, potentially introducing selection bias. For instance, residual imbalance could have led to more fit and proactive patients in the OCTANE group, whose phenotype led to trial enrollment. Provider or institutional characteristics might also be imbalanced. To mitigate this risk, sensitivity analysis considered geography-based and pre-OCTANE trial enrollment criteria. There is also a small risk of misclassification of OCTANE enrollment in potential matching patients. Our sensitivity analysis rules this out as an explanation for study findings. Despite a significant association with OS observed in ovarian cancer and biliary tract tumors, no statistically significant OS benefit was associated with NGS panel testing in the overall group of patients enrolled in OCTANE. This may be related to the low alteration-treatment match rate observed in the OCTANE cohort across cancer types (Supplementary Table S2). Similar to other public healthcare systems in Europe, Canadian access to publicly-funded targeted therapies matching genomic alterations is limited which could have influenced our ability to detect a meaningful OS benefit in the OCTANE group.[27,28] During the course of the study, additional types of actionable genomic variants (copy number alterations and fusion genes) were reported with the introduction of the Oncomine version 3 panel that were not reported during the study period. Moreover, our understanding of the clinical actionability of alterations is rapidly evolving and different tumor-agnostic matched therapies or predictive biomarkers such as homologous recombination deficiency (HRD) have been approved or recommended by the U.S Food and Drug Administration (FDA) or treatment guidelines since the time of data cut off,[29–31] however, to efficiently evaluate the OS impact of NGS tumor testing sufficient follow up time was required since the study intervention.

In conclusion, we found an increase in healthcare costs associated with multi-gene panel testing for advanced cancer treatment. The impact on OS was not significant, but varied across tumor types. OCTANE was associated with greater trial enrollment, lower publicly funded drug costs and fewer in-hospital deaths suggesting important considerations in determining the value of NGS panel testing for advanced cancers that deserve further investigation.

Contributors

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Data sharing statement

The full dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and therefore may require modification.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102443.

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