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A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs

Derrick S. Haslem, S. Burke Van Norman, Gail Fulde, Andrew J. Knighton, Tom Belnap, Allison M. Butler, Sharanya Rhagunath, David Newman, Heather Gilbert, Brian P. Tudor, Karen Lin, Gary R. Stone, David L. Loughmiller, Pravin J. Mishra, Rajendu Srivastava, James M. Ford, and Lincoln D. Nadauld

QUESTION ASKED: What are the clinical outcomes and health care–associated costs in patients with advanced cancer who receive precision cancer medicine?

SUMMARY ANSWER: Patients who received precision cancer medicine experienced an improved progression-free survival (PFS; 22.9 weeks) compared with historical controls (12.0 weeks) who received standard treatments. The improved PFS was not associated with increased health care–associated costs.

WHAT WE DID: We conducted a matched cohort study of 72 patients with metastatic cancer of diverse subtypes. We analyzed the outcomes of 36 patients who received genomic testing and targeted therapy (precision cancer medicine) compared with 36 historical control patients who received standard chemotherapy (n = 29) or best supportive care (n = 7).

WHAT WE FOUND: The average PFS was 22.9 weeks for the precision medicine group and 12.0 weeks for the control group ($P = .002$) with a hazard ratio of 0.47 (95% CI, 0.29 to 0.75) when matching on age, sex, histologic diagnosis, and previous lines of treatment. In a subset analysis of patients who received all care within the Intermountain Healthcare system (n = 44), per patient charges were \$4,665 per week in the precision treatment group and \$5,000 per week in the control group ($P = .126$).

BIAS, CONFOUNDING FACTORS: The retrospective nature of the control cohort, in particular, raises the possibility of bias in the analysis. Controlling for the number of previous lines of treatment that a patient received before enrolling in the study serves to mitigate the risk of bias but does not completely eliminate the possibility. A statistical sensitivity analysis, included in the Appendix, affirms that a difference in performance status between the two cohorts was unlikely to account for the difference in PFS.

REAL-LIFE IMPLICATIONS: A major question surrounding the implementation of precision cancer medicine is its relevance in the community setting. Developing a model for the clinical implementation of precision medicine in a community setting is a necessary step in determining whether this approach warrants further consideration as a viable option for patients with advanced cancer. The survival and cost outcomes reported here were generated in an integrated health care delivery system with patients receiving treatment in a community cancer center and suggest that precision cancer medicine can be applied to the community setting with measurable patient benefit. **JOP**



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Abstract

Purpose

The advent of genomic diagnostic technologies such as next-generation sequencing has recently enabled the use of genomic information to guide targeted treatment in patients with cancer, an approach known as precision medicine. However, clinical outcomes, including survival and the cost of health care associated with precision cancer medicine, have been challenging to measure and remain largely unreported.

Patients and Methods

We conducted a matched cohort study of 72 patients with metastatic cancer of diverse subtypes in the setting of a large, integrated health care delivery system. We analyzed the outcomes of 36 patients who received genomic testing and targeted therapy (precision cancer medicine) between July 1, 2013, and January 31, 2015, compared with 36 historical control patients who received standard chemotherapy (n = 29) or best supportive care (n = 7).

Results

The average progression-free survival was 22.9 weeks for the precision medicine group and 12.0 weeks for the control group ($P = .002$) with a hazard ratio of 0.47 (95% CI, 0.29 to 0.75) when matching on age, sex, histologic diagnosis, and previous lines of treatment. In a subset analysis of patients who received all care within the Intermountain Healthcare system (n = 44), per patient charges per week were \$4,665 in the precision treatment group and \$5,000 in the control group ($P = .126$).

Conclusion

These findings suggest that precision cancer medicine may improve survival for patients with refractory cancer without increasing health care costs. Although the results of this study warrant further validation, this precision medicine approach may be a viable option for patients with advanced cancer.

ASSOCIATED CONTENT



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INTRODUCTION

Precision cancer medicine involves the detection of tumor-specific somatic mutations, including insertions/deletions (indels), single nucleotide variants, translocations, and copy number alterations, followed by treatment with therapeutics that specifically target identified actionable alterations.¹⁻⁷ This approach using precision medicine has largely been hampered by the high cost of testing and the extended turnaround times associated with in-depth genomic diagnostic analysis. However, advances in genomic technologies, including next-generation sequencing (NGS) and droplet digital polymerase chain reaction, have now rendered extended genomic analyses of human malignancies technologically and financially feasible for use in the clinic.⁸⁻¹⁰

Concomitant with these advances in genomic technologies, there have been significant advances in two overlapping areas of cancer research, each with major clinical ramifications; the first is a greater understanding of the underlying genomic alterations and molecular mechanisms of cancer, and the second is development of novel therapeutic agents and biomolecules that exploit specific genomic aberrations in tumors.¹¹⁻¹⁶ These advances are the underpinnings of the new precision cancer medicine clinical paradigm.¹⁷

In the precision medicine approach to cancer, the physician and patient use the identification of specific genetic aberrations that affect cancer-related genes to better inform treatment decisions. The underlying rationale is that this personalized diagnostic approach will lead to a clinical recommendation for targeted cancer therapies that will ultimately result in improved clinical outcomes. This approach has been successfully applied to single tumor types with predetermined genomic variants such as EGFR-positive non-small-cell lung cancer (NSCLC)¹⁸⁻²⁰ and BRAF-positive melanoma,^{14,21,22} whereas previous studies revealed that precision medicine can improve survival in a single cancer type.²³ Earlier studies indicated that targeted therapies given to patients whose tumors harbored specific alterations may improve outcomes as measured by tumor responsiveness.²⁴ However, the impact of precision medicine compared with standard therapies on survival and the effect of implementing sophisticated diagnostic technologies such as NGS on the costs of cancer care, remain unknown.

Our precision cancer medicine program was clinically established in a single region of the Intermountain Healthcare delivery system. Patients with advanced, refractory cancer were referred to the precision medicine clinic where they

received genomic testing, an in-depth interpretation of the genomic results from a multi-institutional molecular tumor board, and a list of treatment options for implementation at the discretion of the treating oncologist.

We report here the progression-free survival (PFS), total costs, and cost per week of survival associated with the initial cohort of patients who received targeted treatment in the precision cancer medicine program compared with control patients who received standard chemotherapy or best supportive care.

PATIENTS AND METHODS

The Intermountain Healthcare Institutional Review Board approved this study, and all living participants provided written informed consent before enrollment. The Board granted a waiver of consent for decedents.

Study Design

Research objectives

The objective of this retrospective observational study was to compare the outcomes of patients with cancer who were treated with precision cancer targeted therapies with a historical control cohort treated with a nontargeted approach.

Research subjects

Male and female adults with measurable recurrent/metastatic solid tumors for whom standard first-line treatments (proposed by the National Comprehensive Cancer Network [NCCN] guidelines) failed were included in this study. Other inclusion requirements were Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and adequate renal, hepatic, and bone marrow function. Patients who had only brain metastases or whose brain metastases had not been controlled for > 3 months and patients who were participating in a clinical trial with an experimental drug were excluded. Pregnant or breastfeeding women also were excluded.

All patients in the precision medicine group had tumor molecular abnormalities for which the Intermountain Healthcare Multi-Institutional Molecular Tumor Board (MTB) provided an interpretation. Actionable mutations were defined as variants that had been validated in the peer-reviewed literature and for which a targeted therapy was available. The MTB selected treatment options only for actionable mutations for which there was published clinical or preclinical evidence. Patients included in the control group received standard-of-care genomic testing only, without interpretation by the

MTB or molecularly targeted therapy beyond the relevant standard of care.

Sample size

A simulation power analysis was performed for a Cox proportional hazards model with 100,000 simulations. In determining the sample size that we used for study, we considered the methodology of Tsimberidou et al.²⁴

Selection of end points

The primary end point was PFS according to radiographic determination of tumor progression and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Tumor measurements by computed tomography imaging were obtained before treatment was initiated and every 8 weeks thereafter. Secondary end points included health care–associated cost of care.

Blinding

Clinician researchers were blinded to the identities of those in the control cohort. Cancer registrars selected the control cohort and provided data about the controls to the study statistician (A.M.B.).

Statistical Methods

A Cox proportional hazards model was fit for PFS. Treatment, sex, age, cancer type, and three or more lines of treatment were included in this model. A full likelihood ratio versus a reduced likelihood ratio test was performed comparing the full model to a reduced model containing only treatment. This test showed that the reduced model adequately fits the data, and only treatment is needed in the model ($P = .508$). Basic demographics as well as two-sample t tests and linear regression models were created to investigate the cost of therapy. Collecting demographic variables and using the Cox model controlled for confounding factors.

Cost Analysis

In calculating patient costs, a payer perspective was adopted. Patient costs were estimated by using standard Intermountain Healthcare payer charges. Only charges incurred between the treatment line start and end dates were included in the total charge estimates for each patient. Patient costs included all amounts for patient treatment, toxicity, patient sequencing, and targeted drug therapy. Treatment costs for both targeted and control patients included all facility-based and clinic-based charges associated with treatment, including

chemotherapy, drug, radiology, and laboratory costs. Palliative care costs were limited to daily reimbursement charge rates determined by the Centers for Medicare and Medicaid Services. Toxicity costs included all patient charges associated with treating the adverse effects resulting from treatment. Sequencing costs for target patients were obtained from the test provider and were based upon estimated payer reimbursement rates. Drug cost data were drawn from local specialty pharmacies and drug manufacturers and were based upon estimated payer reimbursement rates, including estimates of any out-of-pocket costs for the patient. A discount rate was not applied to costs to adjust for the time value of money. Given the limited availability of quality-of-life data for control patients, PFS weeks were not quality adjusted. The mean per patient cost per PFS week was calculated by adding the costs per PFS week for each patient and dividing by the total number of patients. Statistical comparisons of costs between precision medicine and control groups were performed by using a two-sided Wilcoxon rank sum test.

Molecular Diagnostic Testing

All samples analyzed were either formalin-fixed paraffin-embedded (FFPE) or fresh. Patient samples were analyzed in a Clinical Laboratory Improvement Amendments–certified laboratory. Genomic analysis included NGS-based oligoselective exon sequencing of 96 cancer-related genes: *ABL1*, *AKT1*, *ALK*, *APC*, *ATM*, *AURKA*, *AURKB*, *AXL*, *BCL2*, *BRAF*, *BRCA1*, *BRCA2*, *CCND1*, *CDH1*, *CDK2*, *CDK4*, *CDK5*, *CDK6*, *CDK8*, *CDK9*, *CDK12*, *CDKN2A*, *CEBPA*, *CSF1R*, *CTNNA1*, *CYP2D6*, *DDR2*, *DNMT3A*, *DPYD*, *EGFR*, *EPCAM*, *ERBB2*, *ERBB3*, *ERBB4*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC5*, *ERCC6*, *EZH2*, *ESR1*, *FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*, *FLT3*, *GNA11*, *GNAQ*, *GNAS*, *HNF1A*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *JAK3*, *KDR*, *KIT*, *KRAS*, *MAP2K1*, *MAP2K2*, *MAPK1*, *MET*, *MLH1*, *MPL*, *MRE11*, *MSH2*, *MTOR*, *MSH6*, *MYC*, *MUTYH*, *NOTCH1*, *NPM1*, *NRAS*, *PARP1*, *PARP2*, *PDGFRA*, *PIK3CA*, *PMS2*, *PTCH1*, *PTCH2*, *PTEN*, *PTPN11*, *RB1*, *RET*, *RUNX1*, *SMAD4*, *SMARCB1*, *SMO*, *SRC*, *STK11*, *TET2*, *TP53*, *UGT1A1*, *VEGFA*, *VHL*, and *WT1*. Sample tumor concentration of at least 40% was verified by board-certified anatomic pathologists. Samples were extracted by using the ReliaPrep FFPE gDNA miniprep kit (Promega, Madison, WI) for FFPE samples or the Puregene blood core Kit A (Qiagen, Santa Clarita, CA) for extracting fresh samples. DNA shearing to an average of 500 bp lengths was performed by using an M220 ultrasonicator (Covaris, Woburn, MA). Additional sample

preparation, library preparation, and NGS were performed by using the TOMAseq kit (adaptor, extension, and capture sets; TOMA Biosciences, Foster City, CA) according to the manufacturer's protocol and instructions. Library quantification was performed with a Bio-Rad q200 droplet digital polymerase chain reaction analyzer (Bio-Rad, Hercules, CA). Sequencing was performed on the MiSeq platform (Illumina, San Diego, CA). Data analysis, including curation, interpretation, alignment, and quality checks were implemented by using legacy algorithms, and the variant calling was done using FreeBayes. Patient samples were compared with a reference genome, and genetic variants, including copy number alterations, point mutations, frameshift mutations, translocations, and single nucleotide polymorphisms, were identified and reported. Some samples were initially tested by an external laboratory (Caris Biosciences, Foundation Medicine, or TOMA Biosciences), and those with sufficient quantity were subsequently reanalyzed by using the 96-gene panel described previously.

RESULTS

After obtaining informed consent, we evaluated 61 patients who had an actionable mutation and who subsequently received targeted therapy on the basis of the actionable mutation (precision cancer medicine), defined as known variants validated in peer-reviewed literature for which a targeted therapy was available. Given the heterogeneous nature of the treatment cohort in terms of tumor type, age, and sex, we sought to compare their outcomes with the outcomes of control patients

who were matched to treatment patients according to tumor type, age, sex, and number of previous lines of treatment. We searched our institutional enterprise data warehouse to identify historical control patients who had received standard therapy between July 2010 and January 2015 and who could be matched according to age, sex, diagnosis, and number of previous lines of treatment with patients who received precision medicine (Fig 1). Of the 61 patients with an actionable mutation who had received precision medicine, 36 had an institutional historical match (25 patients did not have a historical match). We gathered outcomes data from those 36 patients who received precision medicine and the 36 matched patients who received standard therapy, including standard molecular testing, for a total of 72 patients (Fig 1). Table 1 lists patients' demographic characteristics by treatment type. No significant differences were found between precision medicine and standard therapy groups except for race/ethnicity, which was 100% (n = 36) non-Hispanic white in the precision medicine arm and was 83.3% (n = 30) non-Hispanic white in the control arm, with 2.8% (n = 1) non-Hispanic black, 11.1% (n = 4) white and nonwhite Hispanic, and 2.8% (n = 1) other race/ethnicity. Mean age at time of treatment was 67.8 years for the precision medicine group and 67.0 years for the control group ($P = .748$). Both groups were 61% male (n = 44). Four precision medicine patients were matched at a later line than their controls resulting in average lines of treatment of 3.1 for the precision medicine group and 2.9 for the control group ($P = .168$). The cancer types were identically matched for both groups and were comprised of patients with diverse solid

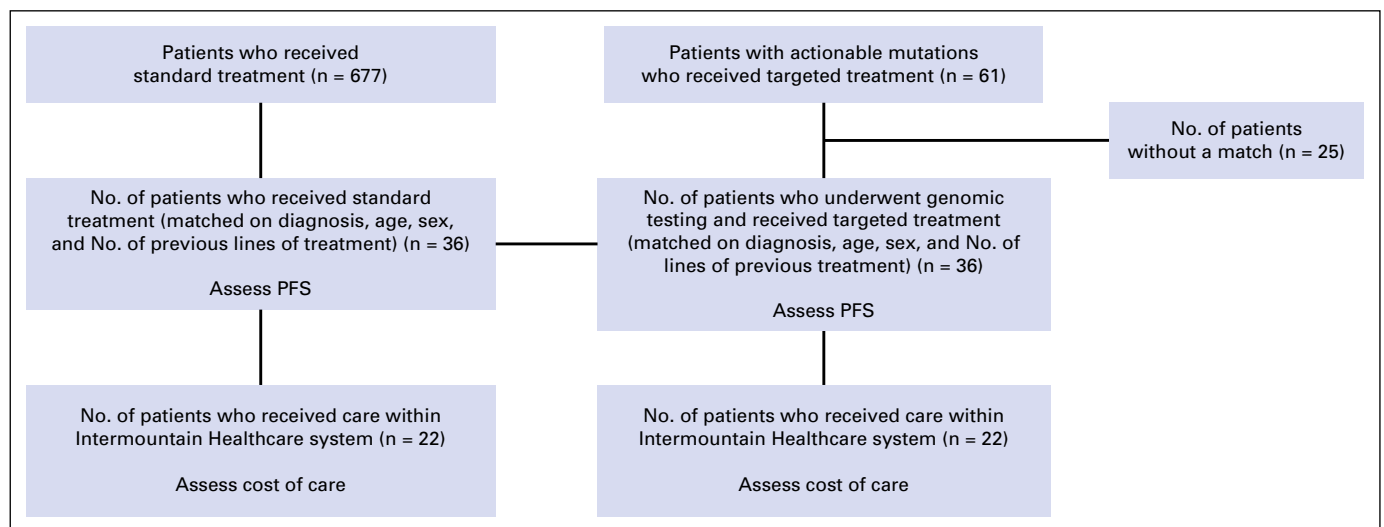


FIG 1. Schematic of the study design delineates the patient population from which the study was conducted. PFS, progression-free survival.

Table 1. Patient Characteristics

Characteristic	Patients Who Received Precision Medicine		Control Patients	
	No.	%	No.	%
Mean age, years	67.8		67	
Sex				
Male	22	61.1	22	61.1
Female	14	38.9	14	38.9
Race				
Non-Hispanic white	36	100	30	83.3
Non-Hispanic black	0	0	1	2.8
White and nonwhite Hispanic	0	0	4	11.1
Other	0	0	1	2.8
Line of treatment				
1st	0	0	1	2.8
2nd	19	52.8	19	52.8
3rd	9	25	8	22.2
4th	1	2.8	3	8.3
5th	2	5.6	1	2.8
6th	4	11.1	3	8.3
7th	1	2.8	1	2.8
Mean	3.1		2.9	
Type of cancer				
Bladder	2	5.6	2	5.6
Breast	5	13.9	5	13.9
Cholangiocarcinoma	1	2.8	1	2.8
Colon	8	22.2	8	22.2
Gastric	1	2.8	1	2.8
Head and neck	4	11.1	4	11.1
Lung	11	30.6	11	30.6
Melanoma	1	2.8	1	2.8
Ovary	1	2.8	1	2.8
Pancreas	2	5.6	2	5.6

tumor types encompassing 10 different histologically distinct cancers. NSCLC was the largest subtype ($n = 11$; 31%) in both cohorts (Table 1).

The actionable variant and targeted therapy for each patient in the precision medicine cohort is listed in Appendix Table A1 (online only). Patients in the historical control cohort had appropriate standard molecular testing according to NCCN guidelines at the time of their diagnosis. Three patients in the precision medicine cohort with NSCLC were found to harbor validated EGFR mutations, and they received erlotinib (Table A1); the EGFR mutations were not identified at the time of initial diagnosis. Five patients with breast cancer (with

hormone-negative [triple negative, $n = 2$] or hormone refractory [$n = 3$] disease) who received a targeted therapy after MTB interpretation, were included in the analysis.

The protocol-specified primary end point of PFS was significantly prolonged in the precision medicine group (Fig 2) compared with the control group (mean PFS, 22.9 v 12.0 weeks, respectively; $P = .002$). More specifically, precision medicine was associated with a 53% decreased risk of progression (adjusted hazard ratio, 0.47; 95% CI, 0.29 to 0.75; $P = .002$) when adjusted for age, sex, histologic diagnosis, and number of previous lines of treatment. At the time of study conclusion, four patients (11%) in the precision medicine arm had not yet progressed (Fig 2). A sensitivity analysis suggested that a difference in patient performance status between the two cohorts was unlikely to account for the difference in PFS (Appendix Fig A1, online only). The cohort of 25 patients who did not have a historical institutional match also demonstrated a prolonged PFS compared with the control cohort (19.3 weeks; $P = .026$).

To determine the costs associated with the two treatment approaches, we performed a health care–related cost analysis. We evaluated all of the patients from each cohort and identified 22 matched patient pairs who had received all of their care within the Intermountain Healthcare system and therefore had complete cost data available (Fig 1). An analysis of PFS in this subset of 22 matched patient pairs revealed the same statistically significant PFS improvement in the precision medicine cohort compared with the standard therapy cohort (21.4 v 11.0 weeks; $P = .004$; Table 2). As expected, total costs per patient during the study period were higher for the precision medicine treatment group than the control group (\$91,790 v \$40,782 per patient; $P = .002$; Table 2). Drug costs were the main factor contributing to the higher cost for precision medicine patients (\$59,259 v \$20,189 per patient; $P < .001$; Table 2). Patients in the precision medicine group had longer survival times resulting in lower patient costs per PFS week than the control group (\$4,665 v \$5,000 per week; $P = .126$) but did not reach a level of significance (Table 2).

DISCUSSION

The findings presented here examine survival and the health care–related costs associated with precision cancer medicine in a retrospective cohort of patients. The results suggest a survival benefit for patients who received precision cancer medicine treatment compared with patients who received standard therapy, although the potential contribution of the

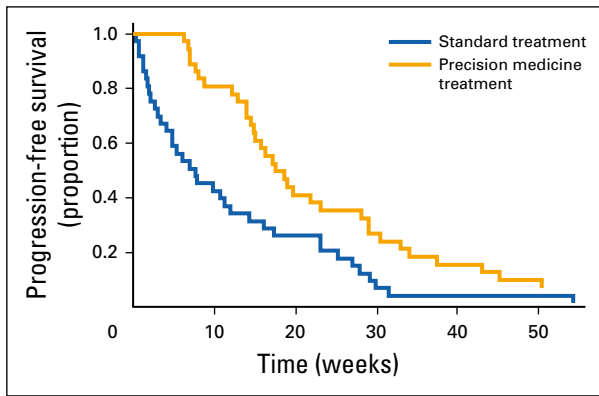


FIG 2. The progression-free survival of patients in the standard and precision medicine treatment cohorts were measured and compared over weeks. The fraction of patients surviving without disease progression is plotted against the number of progression-free weeks.

tumor's molecular composition to the resulting prolongation in PFS could not be assessed, given that the control cohort tumors did not undergo genomic analysis. A subset analysis of patients who received all care within the Intermountain Healthcare system determined that the costs associated with each cohort were not associated with a per week increase in health care costs. The simultaneous improvement in PFS, without increasing per week costs, suggests that a precision medicine approach may be a feasible option in patients with refractory cancer.

In a previous study, Tsimberidou et al²⁴ evaluated the outcomes associated with a phase I personalized medicine program and found that patients who received therapy on the basis of specific molecular alterations, independent of tumor type, experienced improved survival. Similarly, Kris et al²³ reported improved survival in patients with lung cancer when selecting therapies on the basis of oncogenic driver mutations. Although this study, along with those reported by Tsimberidou et al and Kris et al were not randomized trials, they

nevertheless suggest that molecularly guided therapies may improve survival in patients with advanced refractory cancer.

Although the improvement in PFS identified in this study partially results from identifying and treating previously known molecularly distinct cancer subtypes such as EGFR-positive lung cancer ($n = 3$ in the targeted treatment cohort), the majority ($n = 33$) of cases resulted from targeting distinct molecular alterations in diverse tumor types, regardless of histologic subtype. Many of the durable responses were the result of identifying well-known molecular alterations from a single cancer subtype, such as an activating c-KIT mutation commonly found in gastrointestinal stromal tumor, and targeting that alteration in a histologically different cancer such as melanoma. Similar responses were seen in FGFR1-amplified squamous cell lung cancer, FGFR2-mutant cholangiocarcinoma, and MEK1-activated NSCLC. Although similar responses in some tumor subtypes with these alterations have been reported previously as single case reports or case series,²⁵⁻²⁷ the findings presented here suggest that genomic profiling of diverse tumor subtypes followed by molecularly targeted treatment may improve outcomes.

The majority of patients in the control cohort were historical, having received their treatment within the same institution (Intermountain Healthcare) within the previous 5 years. The retrospective nature of the control cohort raises the possibility of bias in the analysis. Controlling for the number of previous lines of treatment that a patient received before enrollment in the study helps mitigate the risk of bias but does not completely eliminate the possibility. A statistical sensitivity analysis included in the Appendix (Fig A1, online only) affirms that a difference in performance status between the two cohorts was unlikely to account for the difference in PFS.

The cost associated with implementing novel medical treatment approaches has been historically difficult to measure because of limited availability of data and limitations on data

Table 2. Health Care–Associated Cost Outcomes

Cost Outcome	Patients Who Received Precision Medicine		Control Patients		P
	Mean (\$)	SD (\$)	Mean (\$)	SD (\$)	
Total costs per patient	91,790	85,070	40,782	42,267	.002
Total drug costs per patient	59,259	51,425	20,189	34,299	< .001
Cost per patient per progression-free survival week	4,665	3,041	5,000	6,509	.126

Abbreviation: SD, standard deviation.

sharing.¹⁷ The cost associated with precision cancer medicine remains a primary question for both payers and providers alike. We attempted to address that question by analyzing the costs associated with both study cohorts. The overall costs of treatment, including cost of testing and cost of drug, were higher in the precision medicine cohort, as might be expected in a cohort that experiences an increased survival time. Evaluating the two cohorts on a cost-per-week basis revealed that the two groups were not statistically different, and drug-related costs remained the primary driver of charges for both cohorts. In an era of increasing health care costs and static resources, measuring the value of treatment becomes critical to sustainability. Although the costs of large-scale genomic testing have historically precluded widespread adoption of precision medicine, the equivalence in cost per PFS week between the two cohorts suggests that widespread adoption of precision cancer medicine may no longer be constrained by economic metrics.

A major question surrounding the implementation of precision cancer medicine is its relevance in the community setting in which nearly 85% of patients with cancer treated in the United States receive their care. Developing a model for the clinical implementation of precision medicine in a community setting, therefore, is a necessary step in determining whether this approach warrants further consideration as a viable option for the vast majority of patients with advanced cancer. The survival and cost outcomes reported here were generated entirely in an integrated health care delivery system with patients receiving treatment in a community cancer center and suggest that precision cancer medicine can be applied to the community setting with measurable patient benefit. **JOP**

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Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs**

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Appendix

delta	PS has no effect on PFS		PS has about the same effect on PFS as treatment				PS has large effect on PFS
	gamma	0	0.6	1.2	1.8	2.4	3
-2.5		0.46521	2.08495	9.34408	41.87725	187.68082	841.1271
		(0.28733,0.75323)	(1.28772,3.37574)	(5.77114,15.12903)	(25.86447,67.8036)	(115.91651,303.87467)	(519.50177,1361.87177)
-2		0.46521	1.54457	5.12814	17.02602	56.52838	187.68082
		(0.28733,0.75323)	(0.95396,2.50081)	(3.16727,8.30299)	(10.51571,27.56689)	(34.91338,91.52529)	(115.91651,303.87467)
-1.5		0.46521	1.14424	2.81438	6.92226	17.02602	41.87725
		(0.28733,0.75323)	(0.70671,1.85265)	(1.73823,4.55678)	(4.27537,11.20786)	(10.51571,27.56689)	(25.86447,67.8036)
-1		0.46521	0.84768	1.54457	2.81438	5.12814	9.34408
		(0.28733,0.75323)	(0.52355,1.37247)	(0.95396,2.50081)	(1.73823,4.55678)	(3.16727,8.30299)	(5.77114,15.12903)
-0.5		0.46521	0.62797	0.84768	1.14424	1.54457	2.08495
		(0.28733,0.75323)	(0.38785,1.01675)	(0.52355,1.37247)	(0.70671,1.85265)	(0.95396,2.50081)	(1.28772,3.37574)
0		0.46521	0.46521	0.46521	0.46521	0.46521	0.46521
		(0.28733,0.75323)	(0.28733,0.75323)	(0.28733,0.75323)	(0.28733,0.75323)	(0.28733,0.75323)	(0.28733,0.75323)

FIG A1. Statistical sensitivity analysis of performance status (PS) on progression-free survival (PFS). Hazard ratios and 95% CIs were calculated for conditions in which the difference in performance status between precision medicine and control cohorts was large (delta = -2.5) or small (delta = 0). Gamma (0 to 3) represents the relative hazard of death for unmeasured performance status. Hazard ratios in green represent conditions in which targeted treatment causes an increase in PFS. Hazard ratios in black represent conditions in which targeted treatment neither increases nor decreases PFS significantly. Hazard ratios in red represent conditions in which targeted treatment causes a decrease in PFS.

Table A1. Summary of Actionable Alterations With Targeted Treatments

Cancer Type	No. of Lines of Treatment	Targeted Therapy	Actionable Alteration	Weeks
Bladder	2	Pazopanib	FGFR3 amplification	13
Bladder	2	Pazopanib	FGFR3 S249C	20
Breast	6	Everolimus	PIK3CA amplification	16
Breast	6	Everolimus	PIK3CA E545K	33
Breast	6	Everolimus	NF1 Q1798*	28
Breast	3	Everolimus	PIK3CA E418K	37
Breast	2	Everolimus	PTEN loss	14
Cholangiocarcinoma	2	Pazopanib	FGFR2 C382R	30
Colon	2	Everolimus	NF1 L581fs*	29
Colon	2	Trametinib	KRAS G12V	14
Colon	3	Pazopanib	FGFR1 amplification	8
Colon	6	Trametinib	NRAS Q61K	7
Colon	3	Trametinib	HRAS amplification	22
Colon	5	Trametinib	KRAS G12V	15
Colon	3	Everolimus	NF1 loss	7
Colon	6	Ado-trastuzumab	ERBB2 amplification	43
Gastric	3	Pazopanib	FGF4 amplifications	15
Head/neck	2	Erlotinib	EGFR S768_V769ins	9
Head/neck	2	Everolimus	MTOR A469T	18
Head/neck	2	Everolimus	PIK3CA amplification	23
Head/neck	2	Erlotinib	ERBB4 E452K	29
Lung	2	Erlotinib	EGFR E746_A750del	65
Lung	2	Trametinib	KRAS G12D	19
Lung	2	Everolimus	STK11 E57fs*	17
Lung	3	Everolimus	MTOR amplification	19
Lung	2	Erlotinib	EGFR E746_A750del	34
Lung	3	Trametinib	BRAF G469A	6
Lung	2	MEK inhibitor	BRAF N581S	11
Lung	2	Erlotinib	EGFR E746-A750 deletion	12
Lung	2	Trametinib	KRAS G12D	7
Lung	3	Pazopanib	PDGFRA amplification	14

(continued on following page)

Table A1. Summary of Actionable Alterations With Targeted Treatments (continued)

Cancer Type	No. of Lines of Treatment	Targeted Therapy	Actionable Alteration	Weeks
Lung	5	Pazopanib	FGFR1 amplification	74
Melanoma	3	Imatinib	KIT amplification	45
Ovary	2	Everolimus	PIK3R2 deletion	8
Pancreas	2	Trametinib	KRAS Q61H	19
Pancreas	4	Trametinib	KRAS G12D	20