Title

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Authors

Natesan, Divya
Eisenstein, Eric L
Thomas, Samantha M
et al.

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Authors:

Divya Natesan, MD[1,2]

Eric L. Eisenstein, DBA[3]

Samantha M. Thomas, MS[4,5]

Neville C. W. Eclov, PhD[2]

Nicole H. Dalal, MD[2]

Sarah J. Stephens, MD[2]

Mary Malicki, MSN, ACNP[2]

Stacey Shields, ANP-BC[2]

Alyssa Cobb, RN, BSN[2]

Yvonne M. Mowery, MD, PhD[2,5]

Donna Niedzwiecki, PhD[4, 5]

Jessica D. Tenenbaum, PhD[4]

Manisha Palta, MD[2,5]

Julian C. Hong, MD, MS[6,7,8]

1. Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC
2. Department of Radiation Oncology, Duke University, Durham, NC
3. Duke Clinical Research Institute, Duke University, Durham, NC
4. Department of Biostatistics and Bioinformatics, Duke University, Durham, NC
5. Duke Cancer Institute, Duke University, Durham, NC
6. Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA
7. Bakar Computational Health Sciences Institute, University of California, San Francisco, San Francisco, CA

8. UCSF-UC Berkeley Joint Program in Computational Precision Health, San Francisco, San Francisco, CA

Corresponding Author:
Julian C. Hong, MD, MS
Department of Radiation Oncology and Bakar Computational Health Sciences Institute
University of California, San Francisco
UC Berkeley-UCSF Joint Program in Computational Precision Health
1825 Fourth Street, Suite L1101
San Francisco, CA 94158

Phone: (415) 502-1645
E-mail: julian.hong@ucsf.edu

Teaser: A single-institution randomized controlled study in which electronic health record-based machine learning accurately identified patients at high risk for acute care (emergency visit or hospitalization) during radiotherapy (RT) and targeted them for supplemental clinical evaluations.

Conflict of Interest Notification:
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Abstract

Background: Machine learning (ML) can cost-effectively direct healthcare by identifying patients most likely to benefit from preventative interventions, and thus avoid negative and expensive outcomes. The System for High-Intensity Evaluation During Radiation Therapy (SHIELD-RT; NCT04277650) study was a single-institution randomized controlled trial in which electronic health record-based ML accurately identified patients at high risk for acute care (emergency visit or hospitalization) during radiotherapy (RT) and targeted them for supplemental clinical evaluations. This ML-directed intervention resulted in decreased acute care utilization. However, given limited prospective data demonstrating ML's ability to direct interventions *cost-efficiently*, an economic analysis was performed.

Methods: We conducted a post hoc economic analysis of SHIELD-RT, which included RT courses from January 7, 2019 to June 30, 2019. ML-identified high-risk courses (≥10% risk of acute care during RT) were randomized to standard-of-care weekly clinical evaluations versus the intervention of mandatory, twice-weekly evaluations. Both arms allowed ad hoc supplemental evaluations per clinician discretion. The primary outcome was the between-group difference in mean total medical costs during RT and in the 15 days following RT. Acute care costs were obtained via institutional cost accounting. Physician and intervention costs were estimated via Medicare and Medicaid data. Negative binomial regression was used to estimate cost outcomes after adjustment for patient and disease factors.

Results: A total of 311 high-risk courses were randomized 1:1 to the standard-of-care group or the intervention group. Unadjusted mean intervention group supplemental visit costs were $155 per course (95% confidence interval [CI], $142 to $168). The intervention group had fewer acute care visits per course than the standard-of-care group (0.31 vs. 0.47; P=0.04). The total mean adjusted cost per course was lower for the intervention group than for the standard-of-care group ($1494 vs. $3110; 95% CI, $1450 to $1783; P=0.03).

Conclusion: In this economic analysis of a randomized, controlled, healthcare ML study, mandatory supplemental evaluations for ML-identified high-risk patients were associated with both improved clinical outcomes and reduced total medical costs. Further study is needed to determine whether the economic results are generalizable.

Introduction

Cancer patients undergoing therapy often have acute symptoms related to their disease, treatments, or comorbidities that result in unplanned emergency room (ER) visits or hospitalizations. Unplanned acute care for oncology patients not only impacts quality of life, but also contributes to rising medical costs for patients, health systems, and payers.[1-3] In 2015, the United States spent an estimated $80.2 billion on oncology care. Of that, 38% was related to hospitalizations,[4] which are the largest contributor to cost for most cancer types during the initial year of diagnosis and in the final year of life.[5] Consequently, appropriate use of acute care for cancer patients has been an emerging priority for the Centers for Medicare and Medicaid Service (CMS), which recently implemented quality measures assessing acute care visits during chemotherapy treatments.[6]

Several strategies have been described in the literature to reduce unplanned acute care for cancer patients,[7] such as identifying high-risk patients using predictive modeling[8-11] and increasing supportive care within existing oncology workflows.[12,13] We previously reported the prospective, randomized, System for High Intensity Evaluation During Radiation Therapy (SHIELD-RT) study, which used a machine-learning (ML) algorithm to identify patients undergoing radiotherapy (RT) who were at high risk (≥10%) of an ER visit or hospitalization.[11,14] In SHIELD-RT, high-risk patients who were randomized to receive mandatory, twice-weekly on-treatment evaluations were less likely, compared with those who received standard-of-care once-weekly clinical evaluations, to require acute care visits during RT (12.3% vs. 22.3%) and during the acute toxicity window, defined as the start of RT until 15 days after RT was completed (22.1% vs. 32.5%). Ad hoc supplemental evaluations, if deemed necessary by the treating radiation oncologist, were allowed in both arms and were often reactive and occurring late in treatment. SHIELD-RT also demonstrated good calibration and strong performance for the ML model (area under the receiver operating characteristic curve 0.851), and patients identified as low risk had a low rate of acute care visits both during RT (2.7%) and in the 15 days after RT (6.3%).

In addition to improving clinical outcomes and quality of life, preventative ML-guided interventions have the potential to reduce medical costs for health systems, payers, and patients by directing interventions in a cost-efficient manner. Broadly applied interventional strategies, like more frequent clinical evaluations, can be more costly and resource-intensive than is feasible in many clinics. ML offers the potential to more accurately identify

high-risk patients and direct an intervention in a cost-efficient fashion. Because there are limited studies analyzing the economic implications of ML-guided interventions, particularly in the prospective setting,[15] such assessments will be key to evaluating the impact, feasibility, and value of ML applications in the oncology workflow.[16]

Considering the benefit of reducing acute care requirements demonstrated by SHIELD-RT, we sought to evaluate the potential economic benefit of ML-directed, mandatory, twice-weekly visits versus standard-of-care, once-weekly visits during and following RT. We hypothesized that in this ML-identified population, escalated preventative intervention would reduce total medical costs, even after accounting for the cost of the intervention.

Methods

SHIELD-RT Overview

SHIELD-RT was a prospective, randomized, controlled, quality-improvement study approved by the Duke Health Institutional Review Board (Pro00100647) and registered on ClinicalTrials.gov (NCT04277650). We previously reported the development and internal validation of multiple ML-based modeling approaches, which were applied to electronic health record and cancer treatment data to predict incidence of an acute care visit (ER visit or hospitalization) during 8134 outpatient RT courses from the Duke Cancer Center from January 2013 to December 2016.[11] At that time, multiple modeling approaches (least absolute shrinkage and selection operator [LASSO]-based logistic regression, random forest, support vector machine, and gradient boosted trees) were compared, with the gradient boosted tree approach (XGBoost) demonstrating the best performance and carried forward. For the SHIELD-RT study, the model was retrained on the entire original cohort and locked for the duration of the study. The final model included a broad range of predictive factors, including treatment parameters, encounter history, vitals, age, and laboratory results.[14]

As previously described, all adult outpatient RT courses for all disease sites with or without concurrent systemic therapy (chemotherapy or immunotherapy) from January 7, 2019 to June 30, 2019 at the Duke Cancer Center were included, with the exception of total body irradiation, as these patients were planned for admission for hematopoietic stem-cell transplantation.[11,14] Data for 963 treatment courses were evaluated by an ML

algorithm to identify high-risk courses (with ≥10% risk of acute care visit during RT). This threshold was selected based on clinical significance, the Youden cut point during retrospective development,[11] and the ability of personnel to carry out the intervention. A total of 311 RT courses among 305 patients considered high risk were subsequently randomized either to standard-of-care weekly clinical evaluations (controls) with ad hoc supplemental evaluations per clinician discretion, or to the intervention of mandatory, twice-weekly evaluations (Fig. 1), also with ad hoc supplemental evaluations per clinician discretion.

Randomization was performed per RT course, and patients undergoing multiple eligible courses were randomly assigned separately for each one. A permuted block randomization schema with a block size of six was generated using SAS 9.4 (SAS Institute; Cary, NC) by the trial statistician. No stratification variables were used. Random treatment assignment was conducted for eligible patients using REDCap.[17] Interventional mandatory supplemental visits were initiated in the second week of treatment and conducted by attending physicians, resident physicians, advanced practice providers, or nurse clinicians. When possible, a primary radiation team member was responsible for interventional evaluations. Assignment to the intervention was unblinded to the study team and patients.

The primary endpoint of the randomized component of the study was the rate of acute care visits during RT, defined as unplanned ER visits or hospitalizations; planned admissions for procedures or chemotherapy were not included. The sample size was calculated to require 314 treatment courses, with 80% power to detect a difference between 20% and 10% of patients requiring acute care visits in the control and intervention arms, respectively, with a one-sided significance level of 0.05. The primary findings and further details of this study were previously published.[14]

Economic Study Overview

We conducted a cost-minimization analysis to compare medical costs associated with the randomized component (standard vs. intervention strategies) in the SHIELD-RT clinical trial.[18] The objective was to identify short-term financial benefits that may accrue through the interventional visits during the acute toxicity window (defined as during RT until 15 days after RT is completed). Non-financial benefits, such as improvements in patient health

and quality of life, were not considered. The analysis was conducted from a health system perspective in the study period to encompass all acute care visits likely related to acute toxicity from therapy. The primary analysis evaluated total medical costs. Secondary analyses evaluated total variable costs and preventable acute care visit costs. Variable costs vary in direct proportion to patient volume and represent the immediate financial benefits of switching from standard to interventional strategies during RT.[19] The SHIELD-RT clinical study reported that the intervention preferentially reduced acute care visits defined as preventable by the Centers for Medicare and Medicaid Service (CMS). We also evaluated whether there were treatment-related differences in the costs of these visits. Most patients underwent a single treatment course. However, a small number (6, in the randomized component of the study) underwent more than one course. Therefore, all analyses were performed on a course, not patient, level.

Healthcare Resource Use

SHIELD-RT included information on two healthcare resources: acute care visits and supplemental, second-weekly treatment visits in the intervention arm. Acute care visits included hospital admissions and ER visits during RT or within 15 days of RT completion. This extended period was selected to more accurately capture acute care visits related to treatment-related toxicity, which can often persist or have delayed onset after radiation. Diagnoses were defined based on ICD-10 codes associated with each course. Resource utilization (e.g., room, ancillary patient services) was obtained for each acute care encounter and was ascribed to those with outside hospital acute care using diagnosis-related group (DRG) codes. Data regarding the intervention of mandatory supplemental evaluation visits also were collected, including adherence, length of visit, and treatments that occurred during the visit.

Acute Care Cost Data

Cost data for all acute care visits at our institution and affiliated hospitals during SHIELD-RT were extracted from the Duke Health System cost accounting system. In that system, costs are derived via a bottom-up costing method; the accounting system adds component costs to obtain total cost. Total cost, by revenue center, was

extracted for each acute visit encounter. Inpatient physician costs were dependent on length of stay and estimated from the Medicare Physician Fee Schedule using associated Healthcare Common Procedure Coding System (HCPCS) codes and Specific Medicare Administrative Contractor (MAC) locality of North Carolina. Emergency, surgery, and anesthesia physician costs were also estimated from the Medicare Physician Fee schedule using associated HCPCS codes and MAC locality of North Carolina. Actual cost data for hospitals outside of our institutional network were not available, and, therefore, cost data for these 19 visits were extrapolated using cost data for similar DRG codes at our institution.

Supplemental Visit Cost Data

The cost of the intervention included costs for the supplemental, second-weekly provider visits and any pharmaceutical interventions that were provided during supplemental visits. Any supplemental provider visits or evaluations (either ad hoc or planned within this intervention) were not charged additionally, as all treatment management visits were bundled within the radiotherapy fee schedule. However, for the purposes of estimating overall costs of the intervention, supplemental provider visit costs were estimated from the Medicare Physician Fee Schedule using associated HCPCS codes. Pharmaceutical intervention costs were estimated from Medicaid National Average Drug Acquisition Cost data.

Statistical Analysis

Patient and course characteristics were summarized using N (%) and median (interquartile range, IQR) for categorical and continuous variables, respectively. Differences between groups were tested using the chi-square or Fisher's exact tests for categorical variables and Wilcoxon Rank Sum tests for continuous variables. Rates of admissions and ER visits during RT + 15 days were estimated as the mean number of visits out of all randomized courses and compared between arms with Wilcoxon Rank Sum Tests.

Cost data were summarized as mean (standard deviation, SD) by study arm and compared on a per course basis between arms with parametric t-tests. An analysis of CMS-designated acute care visits was also carried out on a per event basis to characterize whether overall cost differences were attributable to a reduction in acute care

events and/or a difference in the cost of events when they did occur (i.e., a reduction in severity translating to reduced costs during a hospital admission). The difference in means was also estimated and reported with 95% confidence interval (CI). Parametric methods for comparison of cost data were used based on common practice, as actual cost should be considered when estimating differences, as opposed to ranking cost data, which diminishes the impact of large and small cost observations. Data were examined for extreme outliers, and sensitivity analyses were conducted where seven extreme outliers were removed and one very extreme outlier was removed. The results of these sensitivity analyses did not differ from the analysis of the full cohort, so they are not reported.

Linear, Poisson, and negative binomial regression modeling were examined, and the type of model with the lowest Akaike information criteria for the outcome of total medical costs with intervention (the negative binomial model) was selected for adjusted modeling of all cost outcomes. All models were adjusted for pre-determined variables: patient age, sex (male or female), race (White/Caucasian, Black or African American, or other/unknown), planned number of RT fractions, disease extent (no metastatic, limited metastatic, or widely metastatic), treatment with concurrent systemic therapy (yes or no), and marital status (married/life partner or unmarried/no life partner). Tolerance and variance inflation factors were examined for each covariate to ensure that there was no risk of collinearity among these covariates. Adjusted mean costs and rate ratios, along with associated 95% CIs were estimated from each model and reported. All statistical analyses were conducted using SAS version 9.4. No adjustments were made for multiple comparisons.

Results

Demographics

Patient demographic, disease, and treatment characteristics of randomized courses in SHIELD-RT have been previously described.[14] There were no significant between-arm differences in demographic, disease, or treatment characteristics (age, sex, race, ethnicity, marital status, disease site, concurrent systemic therapy, or number of radiation treatments). Most patients were non-metastatic and treated with curative intent, and this was not significantly different between arms (no metastatic disease: 67.5% vs. 66.9%; P=0.82; curative intent: 70.7% vs. 74.7%; P=0.44).

Interventions During Supplemental Visits

Patients randomized to intervention underwent a median of three supplemental visits (IQR, 1–5) during treatment. A total of 79.9% (445 of 557) of planned supplemental visits were completed, with a median of 0 missed visits per course (IQR 0–1). Providers spent a median 6 minutes (IQR 5–9) during each supplemental visit. Nineteen courses (12.3%) in the interventional arm received a pharmaceutical intervention during a supplemental visit. Overall, 14 (9.1% of intervention courses) received intravenous fluids, 4 (2.6%) received pain medications, 3 (1.9%) received electrolyte replacement, 2 (1.3%) received steroids, 2 (1.3%) received anti-emetics, 1 (0.6%) received antibiotics, and 1 (0.6%) received an anxiolytic.

Acute Care Visits

Patients randomized to the intervention group had fewer acute care visits per course compared with those in the standard-of-care group (0.31 vs. 0.47; P=0.04; Table 1). Hospital admissions were the primary type of acute care visits per course in the intervention and standard-of-care groups (0.19 and 0.26, respectively; P=0.09). Fewer patients in the intervention group had one or more acute care visits (22.1% vs. 32.5%). The median number of acute care visits was slightly lower in the intervention group (0 visits [IQR, 0–0] vs. 0 visits [IQR, 0–1]; P=0.05).

Total Medical Costs

Total mean unadjusted medical costs per course trended lower for the intervention group compared with the standard-of-care group ($2294 and $4432; 95% CI -$55 to $4331; P=0.06; Table 2). Intervention group supplemental visits costs averaged $155 per course (95% CI, $142 to $168). Acute care visit costs per course were lower for the intervention group ($2139 vs. $4322; 95% CI, $100 to $4486; P=0.04). Inpatient room costs, the greatest contributor to treatment-related total medical cost between groups, were also lower for the intervention group ($989 vs. $2286; difference in means, $1297 per course; 95% CI, $29 to $2565; P=0.05).

Total adjusted medical costs per course were lower for the intervention group compared with the standard-of-care group (1494 vs. $3110; 95% CI, $1450 to $1783; P=0.03; Table 3). Adjusted acute care visit

costs per course were slightly lower for the intervention group and the standard-of-care group ($1298 and $3161, respectively; 95% CI, $1533 to $2193; P=0.19), as were adjusted inpatient room costs per course, which accounted for most of the total adjusted medical cost difference between groups ($542 and $1612; difference in means, $1071; 95% CI, $865 to $1276; P=0.20).

Variable Medical Costs

Variable medical cost results largely paralleled total medical cost results. Unadjusted variable medical costs per course trended lower for the intervention group compared with the standard-of-care group ($1334 and $2449, respectively; difference in means, $1115; 95% CI, -$99 to $2330; P=0.07; Table 4). Interventional twice-weekly on-treatment evaluation costs averaged $155 per course (95% CI, $142 to $168). Variable acute care visit costs were lower for the intervention group ($1179 vs. $2449; 95% CI, $56 to $2485; P=0.04), as were inpatient room costs per course, which also primarily drove treatment-related medical cost differences between groups ($481 vs. $1177; difference in means, $696; 95% CI, $56 to $1337; P=0.03).

Total adjusted variable medical costs per course were lower for the intervention group compared with the standard-of-care group ($879 vs. $1746; 95% CI, $776 to $957; P=0.04; Table 5). Interventional supplemental visit adjusted variable costs averaged $122 per course (95% CI, $109 to $137). Total acute care visit variable costs per course trended lower for the intervention group compared with the standard-of-care group ($686 and $1814, respectively; 95% CI, $943 to $1312; P=0.15), as did adjusted variable inpatient room costs per course ($241 and $857; 95% CI, $508 to $724; P=0.14).

CMS-Defined Preventable Hospitalization Costs

Total costs per preventable acute care visit were similar for the intervention and standard-of-care groups ($7564 and $9326, respectively; difference in means, $1761;95% CI, -$4706 to $8229; P=0.58), as were total inpatient costs ($6850 and $7891; difference in means, $1041;95% CI, -$5243 to $7325; P=0.74). Variable costs per preventable acute care visit were also similar for the intervention and standard-of-care groups ($4204 and $5365,

respectively; difference in means, $1162; 95% CI, -$2651 to $4974; P=0.54), as were variable inpatient costs per preventable acute care visit ($3905 and $4725; difference in means, $820; 95% CI, -$2957 to $4596; P=0.66).

Discussion

In this healthcare economic analysis of the randomized SHIELD-RT study, we demonstrate that ML-guided, interventional, twice-weekly visits resulted in decreased acute care costs, as well as improved clinical outcomes, for high-risk patients undergoing RT. Such analyses are critical to demonstrate the economic impact of prospective ML applications in clinical settings.[20] Accurate identification of patients at risk for high-cost acute care allows ML to direct care cost-efficiently and sustainably.

The rising costs of oncology care have increasingly burdened patients and health systems, fueling an interest in value-based care.[4] Costs related to acute care are the primary driver of regional cost variations for cancer patients.[1] Therefore, reducing preventable acute care visits may not only improve patient quality of life, but also decrease costs for patients, health systems, and payers. This study suggests that it would be advantageous for payors to reimburse additional visits to prevent costly future acute care visits.

Identifying high-risk patients, enhancing outpatient services, and improving symptom management pathways have all been identified as strategies to reduce acute care for cancer patients[7]. SHIELD-RT targeted high-risk cancer patients undergoing RT with enhanced preventative outpatient evaluations and, consequently, reduced hospital admissions and emergency visits from 33% to 22%.[14] Efficient cost and resource utilization are important, as many centers (including our academic center) are unable to support universal twice-weekly clinical visits. The 10% threshold in the SHIELD-RT study was determined both from a statistical and pragmatic perspective, given the personnel available to implement the intervention. In comparison to these high-risk patients, low-risk patients experienced a 2.7% event rate during RT and a 6.3% event rate during the 15 days after RT. A similar risk reduction in this population would have a much lower absolute reduction in events and costs, reducing efficiency. Nevertheless, given the strong calibration for our model, different risk thresholds could be selected considering the unique resources available at a given clinical site.[14]

Furthermore, data describing the cost-effectiveness of ML applications in an oncology population are scarce, limiting adoption into clinical practice. In non-oncology fields, retrospective economic evaluations comparing ML applications to standard care found ML approaches to be cost saving.[21]

In this analysis, interventional costs (inclusive of supplemental visits and acute care costs) were significantly lower compared with the standard of care (adjusted mean estimate, $1494 vs. $3110). This lower cost reflects the reduction in acute care utilization previously reported by our group.[14] Differences in inpatient costs were primarily related to rooming costs, followed by costs for ancillary services such as diagnostic studies and costs for inpatient physician. We also identified that when CMS-defined preventable events occurred, their costs were not significantly different between randomized arms, suggesting that the overall cost benefit in high-risk patients was likely driven more by a reduction in events than by differences in costs per event.

Importantly, costs of the supplemental provider visits were low (unadjusted mean, $155; adjusted mean, $122), particularly compared with the high-cost savings associated with reduced acute care visits. The number of courses requiring pharmaceutical administrations during the supplemental visits was small (12.3%), contributing to the low cost of this intervention. We suspect that the primary benefits of the intervention, which influenced reduced acute care utilization in those with supplemental visits, were increased patient education, enhanced patient monitoring, anticipatory guidance regarding side effects, and preventative toxicity management. As provider time during the supplemental visit was low, this represents a feasible strategy that minimally disrupts the clinical workflow.

Taken together, the SHIELD-RT clinical and economic results suggest that the preventative intervention of supplemental evaluation during RT for high-risk cancer patients is a dominant treatment strategy. Our study is strengthened by the use of prospective cost data obtained directly from the institution. Given the randomized nature of the study, the costs associated with standard-of-care weekly visits served as an accurate comparator to the intervention arm.

There are several important limitations to this analysis. Whereas acute care and supplemental radiation oncology visit costs are outlined in this study, there may be other outpatient medical visits (e.g., medical oncology or palliative care visits) and non-medical costs (e.g., patient wait time, family caregiver time) that are not captured

in this analysis. Although we do not anticipate that these costs would alter our study results, these omissions should be acknowledged. The randomized study was also designed pragmatically to compare ML-based supplemental visits against the standard of care (ad hoc supplemental visits per clinician discretion only), and, therefore, it is not known whether other approaches, such as pre-treatment physician risk designation, or simpler approaches, such as logistic regression, may have had similar clinical or cost impacts. In addition, we previously reported that clinicians tended to have looser calibration in their early treatment risk assessments of patients randomized to intervention.[14] Furthermore, generalizability of this economic analysis is unknown, given geographic and institutional variability in operational costs. A study is ongoing to evaluate the generalizability of the model across a network of academic and community-based hospitals with geographic, demographic, and technical diversity. Our analysis is also limited to the timeframe specified a priori during study design, including prospective data collection 15 days post-treatment. Evaluation of greater timeframes may also be informative to determine if there are longer-term impacts from this strategy, particularly for cancer survivors who experience chronic toxicities from therapy. Finally, it is necessary to determine the costs of the operations of ML infrastructure and services to determine value and feasibility of the ML application, particularly including the resources necessary for routine continued implementation and surveillance. These upfront costs are challenging to quantify in the present state. However, they should be an area of future investigation as minimal data exist on this topic.[15]

In the era of increasing value-based healthcare, ML-directed clinical workflows have the potential to improve care delivery, individualize patient treatments, and reduce healthcare costs. As demonstrated in other domains of medicine, patient education interventions may be a cost-effective strategy for high-risk cancer patients. Further robust health economic evaluations of ML applications, inclusive of operational ML costs, are necessary to understand the feasibility of ML adoption into clinical practice.

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	Standard (N=157)	**Intervention (N=154)**	**P-Value**
Patients/Courses with Acute Care Visit(s)	51 (32.5%)	34 (22.1%)	0.04
Acute Care Visits Per Randomized Course – Mean (SD)			
Any Visit	0.47 (0.80)	0.31 (0.66)	0.04
Admissions	0.26 (0.51)	0.19 (0.50)	0.09
ER Visits	0.21 (0.54)	0.12 (0.38)	0.10
Total Visits (ER and Admissions)			
0	106 (67.5%)	120 (77.9%)	
1	34 (21.6%)	24 (15.6%)	
2	12 (7.6%)	8 (5.2%)	
3	4 (2.6%)	1 (0.7%)	
4	1 (0.6%)	1 (0.7%)	
Median (IQR)	0 (0 - 1)	0 (0 - 0)	0.05
Total Admissions			
0	121 (77.1%)	131 (85.1%)	
1	31 (19.8%)	18 (11.7%)	
2	5 (3.2%)	4 (2.6%)	
3	0 (0%)	1 (0.7%)	
Median (IQR)	0 (0 - 0)	0 (0 - 0)	0.20

	Standard (N=157)	Intervention (N=154)	P-Value
Total ER Visits			
0	132 (84.1%)	139 (90.3%)	
1	19 (12.1%)	12 (7.8%)	
2	4 (2.6%)	3 (2%)	
3	2 (1.3%)	0 (0%)	
Median (IQR)	0 (0 - 0)	0 (0 - 0)	0.08

Table 1. Acute Care Utilization

Data are presented as N (%) unless otherwise specified. Percentages may not add up to 100 due to rounding or missing values. Abbreviations: SD=standard deviation, IQR=interquartile range.

	Standard (N=157)	Intervention (N=154)	Difference in Means (95% CI)	P-Value
Total Medical Costs ($)	4432 (12,300)	2294 (6382)	2138 (-55, 4331)	0.06
Acute Care Visit Costs ($)	4432 (12,300)	2139 (6380)	2293 (100, 4486)	0.04
Inpatient ($)	3927 (11,662)	1892 (5998)	2035 (-40, 4111)	0.06
Room ($)	2286 (7269)	989 (3367)	1297 (29, 2565)	0.05
ICU Room ($)	769 (4199)	147 (1627)	622 (-91, 1335)	0.09
Non-ICU Room ($)	1517 (3839)	842 (2921)	675 (-87, 1437)	0.08
Inpatient Physician Cost ($)	197 (601)	149 (590)	48 (-85, 181)	0.48
Rounding ($)	126 (311)	77 (225)	49 (-11, 110)	0.11
Surgery ($)	14 (125)	28 (240)	-14 (-57, 28)	0.51
Anesthesia ($)	57 (328)	44 (276)	13 (-55, 80)	0.71
Ancillary/Patient Services ($)	1444 (4304)	754 (2279)	691 (-80, 1461)	0.08
Labs/Radiology/Diagnostics ($)	569 (1500)	322 (863)	247 (-27, 521)	0.08
Pharmacy ($)	461 (1773)	246 (1102)	215 (-115, 545)	0.20
Surgical, Anesthesia, Cardiology, Respiratory, Rehabilitation, Speech ($)	415 (1932)	186 (891)	229 (-108, 566)	0.18
Emergency Cost ($)	505 (1680)	247 (608)	258 (-25, 541)	0.07
Emergency Services ($)	477 (1653)	229 (568)	248 (-29, 525)	0.08
Emergency Physician ($)	28 (54)	18 (42)	10 (-1, 21)	0.08
Supplemental Visit Costs ($)	0 (0)	155 (82)	-155 (-168, -142)	<0.001
Provider ($)	0 (0)	152 (81)	-152 (-165, -140)	<0.001

	Standard (N=157)	Intervention (N=154)	Difference in Means (95% CI)	P-Value
Medications/Treatments ($)	0 (0)	3 (8)	-3 (-4, -1)	<0.001

Table 2: Unadjusted Medical Costs During Radiotherapy + 15 Days

Data are presented as mean SC (standard deviation) unless otherwise specified. Abbreviations: CI=confidence interval, ICU=intensive care unit.

	Standard (95% CI) (N=157)	Intervention (95% CI) (N=154)	Difference in Predicted Means (95% CI)	Intervention vs. Control Rate Ratio (95% CI)	P-Value
Total Medical Costs ($)	3110 (1505, 6429)	1494 (775, 2881)	1616 (1450, 1783)	0.48 (0.25, 0.94)	0.03
Acute Care Visit Costs ($)	3161 (746, 13,400)	1298 (354, 4755)	1863 (1533, 2193)	0.41 (0.11, 1.56)	0.19
Inpatient ($)	2749 (596, 12,667)	1082 (295, 3966)	1667 (1367, 1967)	0.39 (0.1, 1.59)	0.19
Room ($)	1612 (265, 9825)	542 (117, 2501)	1071 (865, 1276)	0.34 (0.06, 1.8)	0.20
ICU Room ($)	0 (0-NE)	0 (0-NE)	0 (0, 0)	0.03 (0, 0.76)	0.03
Non-ICU Room ($)	1236 (204, 7497)	517 (112, 2382)	719 (559, 879)	0.42 (0.07, 2.35)	0.32
Inpatient Physician Cost ($)	126 (26, 600)	58 (15, 222)	68 (53, 82)	0.46 (0.1, 2.12)	0.32
Rounding ($)	113 (24, 537)	51 (14, 186)	62 (49, 74)	0.45 (0.11, 1.9)	0.28
Surgery ($)	0 (0, NE)	0 (0, NE)	0 (0, 0)	3.06 (0.01,724.12)	0.69
Anesthesia ($)	0 (0,511)	0 (0, 389)	0 (0, 0)	2.97 (0.02, 566.11)	0.68
Ancillary/Patient Services ($)	943 (214, 4151)	442 (123, 1583)	501 (399, 603)	0.47 (0.13-1.76)	0.26
Labs/Radiology/Diagnostics ($)	388 (99, 1519)	205 (60, 698)	183 (144, 223)	0.53 (0.15, 1.81)	0.31
Pharmacy ($)	416 (70, 2476)	140 (34, 588)	275 (223, 327)	0.34 (0.07, 1.73)	0.19
Surgical, Anesthesia, Cardiology, Respiratory, Rehabilitation, Speech ($)	213 (49, 928)	33 (8, 133)	180 (158, 201)	0.16 (0.03, 0.85)	0.03
Emergency Cost ($)	383 (91, 1607)	230 (56, 951)	153 (110, 196)	0.6 (0.15, 2.43)	0.47
Emergency Services ($)	361 (86, 1510)	216 (52, 891)	145 (104, 186)	0.6 (0.15, 2.41)	0.47
Emergency Physician ($)	19 (6, 60)	13 (4, 38)	6 (4, 8)	0.68 (0.22, 2.04)	0.49
Supplemental Visit Costs ($)	0 (0, 0)	122 (109, 137)	-122 (-123, -122)	-	-
Medications/Treatments ($)	0 (0, 0)	0.3 (0.1, 2)	-0.4 (-0.4, -0.3)	-	-
Provider ($)	0 (0, 0)	120 (107, 134)	-120 (-121, -119)	-	-

Table 3: Adjusted Medical Costs During Radiotherapy + 15 Days

Data are presented as predicted mean (95% CI) unless otherwise specified. All estimates are adjusted for patient age, sex (male or female), race (White/Caucasian, Black or African American, or other/unknown), marital status (married or life partner or unmarried and no life partner), planned number of radiotherapy fractions, treatment with concurrent systemic therapy, and disease extent (no metastatic, limited metastatic, or widely metastatic).

Abbreviations: CI=confidence interval, ICU=intensive care unit, NE=non-estimable due to small number of patients with these costs.

	Standard (N=157)	Intervention (N=154)	Difference in Means (95% CI)	P-Value
Total Medical Costs ($)	2449 (6741)	1334 (3673)	1115 (-99, 2330)	0.07
Acute Care Visit Costs ($)	2449 (6741)	1179 (3671)	1270 (56, 2485)	0.04
Inpatient ($)	2234 (6511)	1075 (3497)	1159 (-10, 2328)	0.05
Room ($)	1177 (3688)	481 (1662)	696 (56, 1337)	0.03
Inpatient Physician Cost ($)	197 (601)	148 (590)	49 (-84, 182)	0.47
Ancillary/Patient Services ($)	860 (2630)	446 (1445)	414 (-61, 889)	0.09
Emergency Cost ($)	215 (765)	104 (267)	111 (-17, 240)	0.09
Supplemental Visit Costs ($)	0 (0)	155 (82)	-155 (-168, -142)	<0.001
Provider ($)	0 (0)	152 (81)	-152 (-165, -140)	<0.001
Medications/Treatments ($)	0 (0)	2.7 (8.2)	-2.7 (-3.9, -1.4)	<0.001

Table 4: Unadjusted Variable Medical Costs During Radiotherapy + 15 Days

Data are presented as mean SD unless otherwise specified. Abbreviations: SD=standard deviation, CI=confidence interval, ICU=intensive care unit.

	Standard (N=157)	Intervention (N=154)	Difference in Predicted Means (95% CI)	Intervention vs. Control Rate Ratio (95% CI)	P-Value
Total Medical Costs ($)	1746 (871-3499)	879 (470-1644)	866 (776, 957)	0.5 (0.26-0.96)	0.04
Acute Care Visit Costs ($)	1814 (436-7535)	686 (194-2418)	1128 (943, 1312)	0.38 (0.1-1.4)	0.15
Inpatient ($)	1649 (365-7447)	596 (168-2114)	1053 (877, 1229)	0.36 (0.09-1.43)	0.15
Room ($)	857 (140-5247)	241 (51-1125)	616 (508, 724)	0.28 (0.05-1.53)	0.14
Inpatient Physician Cost ($)	126 (27-601)	58 (15-219)	69 (54, 83)	0.46 (0.1-2.08)	0.31
Ancillary/Patient Services ($)	590 (134-2595)	253 (73-876)	336 (273, 399)	0.43 (0.12-1.6)	0.21
Emergency Cost ($)	161 (43-599)	91 (24-343)	70 (53, 86)	0.57 (0.15-2.1)	0.39
Supplemental Visit Costs ($)	0 (0-0)	122 (109-137)	-122 (-123, -122)	-	-
Medications/Treatments ($)	0 (0-0)	0.4 (0.1-2.2)	-0.4 (-0.4, -0.3)	-	-
Provider ($)	0 (0-0)	120 (107-134)	-120 (-121, -119)	-	-

Table 5: Adjusted Variable Medical Costs During Radiotherapy + 15 Days

Data are presented as predicted mean (95% CI) unless otherwise specified. All estimates are adjusted for patient age, sex (male or female), race (White/Caucasian, Black or African American, or other/unknown), marital status (married or life partner or unmarried and no life partner), planned number of RT fractions, treatment with concurrent systemic therapy, and disease extent (no metastatic, limited metastatic, or widely metastatic).

Abbreviations: CI=confidence interval, NE=non-estimable due to small number of patients with these costs.

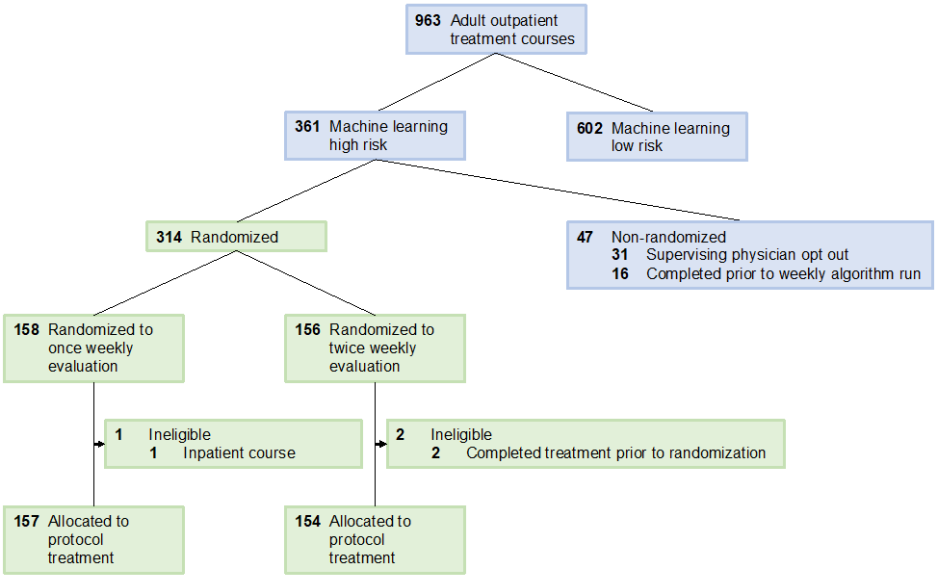

Figure 1: SHIELD-RT CONSORT.

The diagram depicts the study design. Patients who were identified as high risk by the machine learning algorithm were randomized to receive either standard-of-care weekly clinical evaluations or the intervention of mandatory, twice-weekly evaluations.