Clinics in Oncology

Research Article
Published: 25 Nov, 2021

Assessing Barriers to Cancer Clinical Trial Enrollment: A Potential Application of a Clinical Decision-Support Tool

Shawn Hsu[1], Ana Paula Cupertino[2], Fergal Fleming[1], David C Linehan[1], Arpan Patel[3], Patrick Reagan[3], Katherine J Rosen[1], Eric Snyder[2], Myla Strawderman[4], Larissa Temple[1] and Paul Barr[3]*

[1]Department of Surgery, University of Rochester Medical Center, USA

[2]James P Wilmot Cancer Institute, Community Outreach & Engagement, University of Rochester Medical Center, USA

[3]Division of Hematology/Oncology, University of Rochester School of Medicine and Dentistry, USA

[4]Department of Biostatistics and Computational Biology, University of Rochester, USA

Abstract

Introduction: Despite the importance of clinical trials for improving cancer therapies, enrollment in clinical trials remains limited and many trials are interrupted due to barriers to enrollment. Identifying clinical trial recruitment barriers is necessary to guide future interventions to improve this process.

Methods: This is a retrospective study from April 2019 to October 2020 at a multi-site academic medical system. New cancer patients receiving systemic chemotherapy navigated using a decision-support tool were identified and categorized based on a hierarchical framework for clinical trial recruitment, which includes structural, clinical, physician, and patient domains. Multivariable logistic regression was performed to determine predictors of progression through each barrier domain.

Results: A total of 1,725 patients with breast, gastrointestinal, genitourinary, lung, or hematopoietic cancers were navigated using the decision-support tool and 15.5% were referred for clinical trial screening. Overall, 72.3% (1,248/1,725) of patients did not have a trial available and 27.0% (129/477) of patients with a trial available were ineligible. There were significant differences in trial availability ($p<0.0001$) and eligibility ($p<0.0001$) between different tumor groups. Among those eligible for an available trial, breast cancer patients and those ≥ 75 years old were less likely to be referred for clinical trial screening. Participation rates were similar for Black patients (89%, 95% CI = 71% to 98%) and white patients (91%, 95% CI = 88% to 95%).

Conclusion: Trial availability was the most significant barrier to clinical trial enrollment. Decision-support platforms are promising tools for understanding enrollment barriers and facilitating recruitment. Future studies will explore specific reasons for differences in trial availability across tumor groups.

OPEN ACCESS

Correspondence:
Shawn Hsu, Department of Surgery, University of Rochester Medical Center, 601 Elmwood Ave, BOX SURG, Rochester, NY 14642, USA, Tel: (585) 275-6578;
E-mail: shawn_hsu@urmc.rochester.edu

Received Date: *16 Oct 2021*
Accepted Date: *13 Nov 2021*
Published Date: *25 Nov 2021*

Citation:
Hsu S, Cupertino AP, Fleming F, Linehan DC, Patel A, Reagan P, et al. Assessing Barriers to Cancer Clinical Trial Enrollment: A Potential Application of a Clinical Decision-Support Tool. Clin Oncol. 2021; 6: 1880.

ISSN: 2474-1663

Introduction

In 2020, there were approximately 1,806,590 new cancer cases and 606,520 cancer deaths [1]. Fortunately, the mortality rate from cancer has been decreasing since 1991 with an overall decline of 26% to 29% by 2017 [1,2]. This is likely in part due to the efficacy of early cancer detection and the development of new treatments as a result of therapeutic clinical trials [1,3]. Furthermore, some data suggests improved overall survival for patients enrolled in clinical trials [4,5]. However, only 2% to 6% of all cancer patients enroll in a clinical trial [6-8] and up to 22% of clinical trials are never completed due to low enrollment [9]. This not only results in lost resources put into planning, initiating, and implementing these trials, but also represents missed opportunities for advancing cancer therapies. Increasing clinical trial enrollment is a public health priority since improving current therapies and understanding the safety and efficacy of novel therapies will ultimately translate into improved survival and better quality of life for cancer patients.

Despite the National Institute of Health Revitalization Act of 1993 which called for increased representation of women and minorities in clinical research [10], minorities continue to be underrepresented in cancer clinical trials [6,7]. Low minority accrual in clinical trials is in part due

to distrust, historical mistreatment of minorities, lack of education, religious or cultural beliefs, and attitudes about clinical trials [11-14]. Despite these barriers minorities are more likely to participate in clinical trials when cultural, language, and community values are incorporated. However, recent literature suggests that there is no difference in the willingness of minorities to participate in clinical trials compared to non-Hispanic whites [15], and multiple studies have shown that underrepresented minorities tend to have positive attitudes towards clinical trials and are willing to enroll when trials involve community-based approaches [15-18].

Systems-level barriers such as screening for clinical trials during complex routine cancer care directly impact recruitment in clinical trials, but many previous studies focus on patient-level barriers such as attitudes regarding randomization or fear of clinical side-effects [19-27]. This focus on patient-level barriers is understandable given that patients ultimately decide whether or not to participate in a clinical trial. However, a recent systematic review and meta-analysis using a theoretical enrollment barriers framework, which conceptualizes barriers to recruitment into structural, clinical, physician, and patient barrier domains, demonstrated that the lack of trial availability and eligibility accounted for over three-fourths of why cancer patients did not enroll in a clinical trial [28]. This underscores the importance of evaluating the trial enrollment process in its entirety by using a comprehensive framework.

Since many cancer centers are using decision-support tools to decrease treatment variation and costs [29,30], the ability to use the data collected by these tools to identify enrollment barriers would help cancer centers improve their process. The recently embedded decision-support tool at our institution that includes open clinical trials enables the ability to evaluate barriers to clinical trial recruitment. The use of a decision-support tool improves our ability to investigate enrollment barriers by allowing us to trace barriers from the patient to the structural level since it tracks the total number of presenting patients. Results will inform training and interventions designed to overcome barriers to clinical trial enrollment and ultimately improve trial recruitment.

Methods

This is a retrospective study using data collected at the University of Rochester Medical Center Wilmot Cancer Institute from April 2019 to October 2020. New patients navigated using the clinical decision-support platform with breast; Gastrointestinal (GI), Genitourinary (GU), lung, or hematopoietic cancers were included. This study was determined to meet criteria for exemption by the University of Rochester institutional review board (IRB#00006115).

Oncology pathways and workflow

ClinicalPath™ by Elsevier is a clinical decision-support tool which recommends either therapeutic pathways or clinical trial referral utilizing patients' cancer information (Figure 1). The tool was customized to include interventional treatment trials available at our institution. Trials are added to the decision-tree after discussion with the principal investigator immediately after IRB approval. Trial availability is determined by cancer type and stage plus or minus other variables such as tumor markers and whether the patient is a candidate for radiotherapy, chemotherapy, or surgery. When patients are navigated in the decision-support tool, trials available to the patient are recommended as the preferred treatment. During the study, there were 20 interventional treatment trials open for breast, 14 for GI, 21 for GU, 22 for lung, and 67 for hematopoietic cancer patients. Furthermore, 11 trials remained open for the entire duration of the study, 130 trials opened after the study began and remained open throughout, two trials opened and closed during the study, and one trial was open before but closed during the study (Table 1).

When the decision-support tool is used to navigate a patient, the provider is prompted with questions based on branching logic that must be answered to proceed. The input to each question impacts the subsequent questions that are asked. This data is then used to determine trial availability or treatment pathways for a given patient. If a trial is available, the provider is prompted to refer the patient to the appropriate trial management group to initiate or continue the screening process. If the provider does not wish to refer the patient to be screened for an available trial, a reason must be entered and therapy recommendations are provided. Decision-support tool utilization rates, defined as the number of patients navigated divided by the total number of new cancer patients receiving chemotherapy, were tracked during the study period.

Barrier domains

A theoretical framework for understanding clinical trial enrollment barriers, which has been used in previous studies [23,24,28,31], includes four barrier domains (structural, clinical, physician, and patient) that can be used to conceptualize where patients are lost during the enrollment process. Essential to this framework is the idea that the enrollment process is hierarchical; meaning addressing each barrier after the first one is conditional upon passing the previous barrier. For example, a patient must have a trial available before they can be evaluated for eligibility, and they must be eligible before the trial can be discussed and offered. Patients were categorized into these domains based on the aforementioned decision-support tool's workflow (Figure 1).

Potential predictors of enrollment

Factors considered to potentially affect progression through each barrier domain included age (<60, 60-64, 65-74, and ≥ 75 years old), self-reported race (white, Black, or other), tumor group, and Area Deprivation Index (ADI). Patients were categorized by tumor groups to see if enrollment barriers varied across groups. ADI is a census tract-based socioeconomic ranking index that is divided into percentiles with higher percentiles indicating greater deprivation or lower SES. Each patient was assigned an ADI based on their census block group. For the purposes of analysis, the ADI was further divided into tertiles with the 1st tertile indicating the highest SES and the 3rd tertile indicating the lowest SES.

Data analysis

Descriptive statistics were generated for barrier domains across tumor group, age, race, and ADI tertiles. The proportion of patients passing each barrier is compared by these characteristics, unadjusted for other factors, using the Chi-square test. The odds of passing each barrier, independent of the other factors in the model, were estimated using multivariable logistic regression. Analysis followed a hierarchical model to mirror that of the trial enrollment framework. Each barrier domain has a separate model, conditional upon passing the previous domains. The proportion of subjects with a missing ADI was small and a complete case analysis is reported. Data analysis was performed using SAS® software, Version 9.4 of the SAS System for Windows.

Results

A total of 1,725 patients with breast, GI, GU, lung, or hematopoietic cancers were navigated using the decision-support tool from April 2019 to October 2020. Of these patients, 13.4% had breast, 29.3% had GI (colorectal, gastroesophageal, or pancreatic), 15.5% had GU (bladder, prostate, or renal), 22.7% had lung, and 19.1% had hematopoietic (leukemia, lymphoma, or multiple myeloma) cancer. Most navigated patients were white (86.3%), ≥ 60 years old (72.2%), and in the 2nd tertile ADI (65.7%). Similarly, most patients who presented to the cancer center during the study period were white (87.3%) and ≥ 60 years old (72.7%). Decision-support tool utilization rates varied across tumor groups but overall improved during the study period (Figure 2). The average utilization rate was 46.9% in breast, 52.2% in GU, 54.6% in hematopoietic, 74.0% in GI and 79.2% in lung cancers. The most recent utilization rates were over 70% for the majority of tumor groups.

Structural domain

Overall, 15.5% of patients in this sample were sent to screening for an interventional, treatment trial. The largest barrier to screening was trial availability as 72.3% did not have a trial available based on the characteristics of the patient's cancer (Table 2). However, the extent of this structural barrier differed significantly by tumor group (p<0.0001). No trial was available for 86.5% of lung, 82.4% of GI, 68.4% of breast, 56.6% of GU, and 55.6% of hematopoietic cancer patients (Table 2). Trial availability did not differ significantly based on race or ADI but did differ significantly based upon age with those ≥ 60 having fewer trials available.

The multivariable model for each domain is shown in Table 3. Compared to GU patients, GI patients were 73% less likely (OR=0.27, p<0.0001), breast patients were 46% less likely (OR=0.54, p=0.002), and lung patients were 80% less likely (OR=0.20, p<0.0001) to have a trial available after adjusting for age, race, and ADI. Those 60 to 64 (OR=0.62, p=0.01) and 65 to 74 (OR=0.69, p=0.01) years old were significantly less likely to have a trial available compared to those <60 years old on multivariable analysis as well.

Clinical domain

Ineligibility is the second most important barrier limiting participation in clinical trials. Overall, 27.0% of patients with a trial available were ineligible (Table 2). Ineligibility varied significantly by tumor group (p<0.0001). GU cancer patients had the highest ineligibility rate (47.4%), followed by breast (35.6%), lung (26.4%), GI (18.0%), and hematopoietic (12.3%) cancer patients. Among those patients with a trial available, patients with GI (OR=4.51, p<0.0001), lung (OR=2.48, p=0.01), and hematopoietic (OR=6.64, p<0.0001) cancers were more likely to meet eligibility criteria compared to GU patients on multivariable analysis (Table 3). Eligibility did not vary by age, race, or ADI.

Physician domain

Of the 348 patients eligible for an available trial, 298 (85.6%) were offered a trial. Among those eligible for an available trial, patients with breast cancer had significantly lower odds of recruitment by the provider than those with GU cancer (OR=0.28, p=0.02) after controlling for age, race, and ADI (Table 3). Patients ≥ 75 years old had lower odds of recruitment compared to patients <60 years old (OR=0.25, p=0.002) on multivariable analysis. Race and SES were not found to be significant predictors of recruitment by the physician.

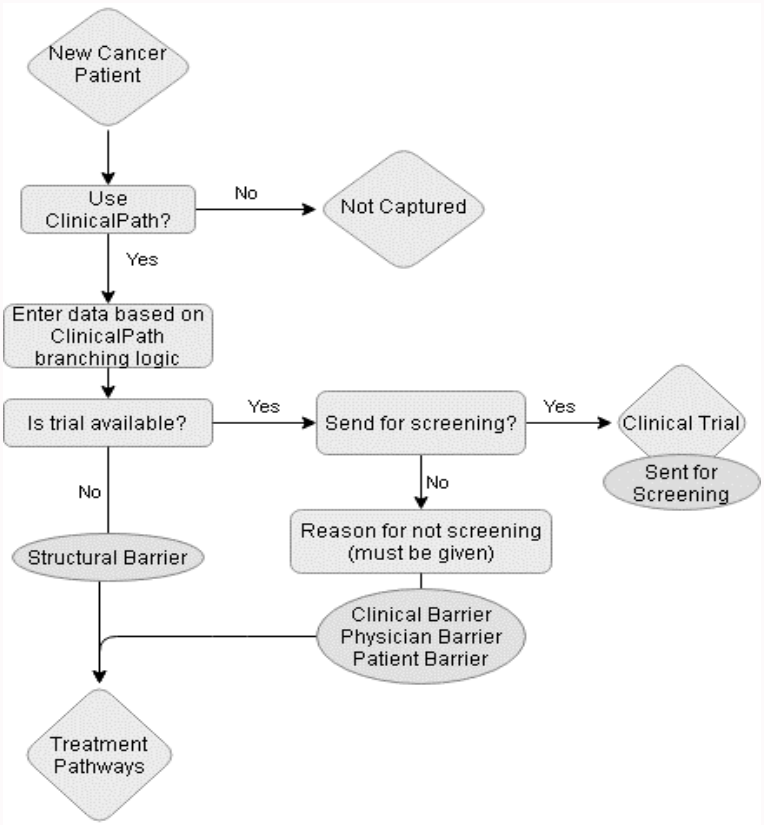

Figure 1: ClinicalPath™ workflow.

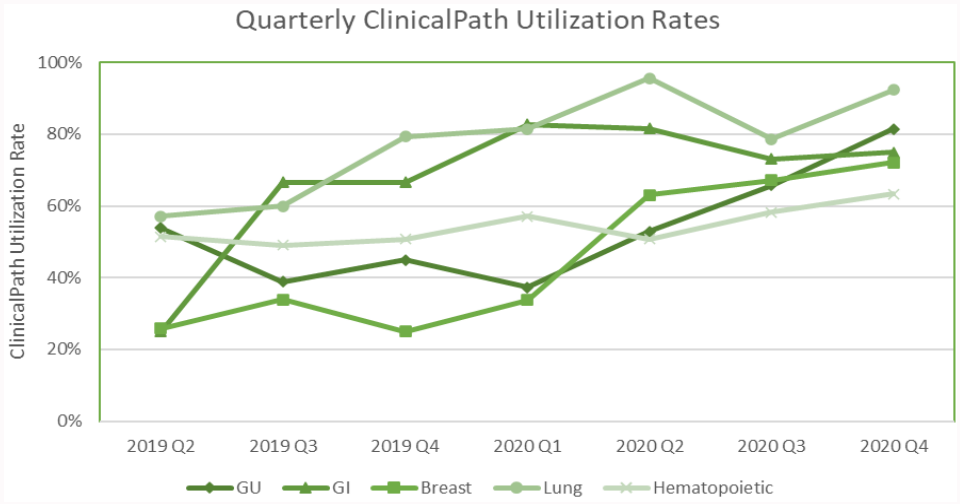

Figure 2: Quarterly ClinicalPath™ utilization rates.

Table 1: Number of interventional, treatment trials open from April 2019 to Oct 2020.

Tumor Group	Open Throughout Study Period	Open and Closed During Study Period	Open During Study Period	Closed During Study Period	Total
Breast	0	0	20	0	20
Gastrointestinal	0	0	14	0	14
Genitourinary	1	1	19	0	21
Lung	2	0	20	0	22
Hematopoietic	8	1	57	1	67
Total	11	2	130	1	144

Patient domain

Of the 298 patients offered a trial, 268 (89.9%) agreed to proceed to screening. Among those recruited by their provider, patients in the 1st ADI tertile were less likely to agree to screening (OR=0.32, p=0.05) compared to patients in the 2nd tertile. There was no difference in willingness to proceed to screening between Black and white patients (OR=0.63, p=0.54). Neither tumor group nor age was found to be statistically significant predictors of agreeing to screening.

Discussion

Recruitment to cancer clinical trials involves overcoming multiple barriers that limit equal participation in trials across cancer types and patient characteristics. When ClinicalPath™ is integrated into routine care; it is a promising tool for improving clinical trial recruitment as it collects data regarding potential barriers to enrollment. This data can help identify subgroups of patients for which trials are not available and may help address physician-level barriers as providers are prompted to consider clinical trials by the tool. In this study, 72.3% of patients did not have a trial available and 27% of those with a trial available were ineligible. Barriers to enrollment did not vary significantly across white and Black race, although the small sample of Black patients resulted in imprecise estimates for this comparison.

Congruent with published literature, we found that trial availability was the most significant barrier to enrollment [28]. These points to further examination of trial availability first and foremost since addressing downstream barriers will not be as effective if structural barriers continue to play a significant role. Furthermore, by understanding which patients do not have a trial available, we can detect and fill gaps in our trial portfolio. We also found that trial availability varies across tumor groups. This variation helps direct attention to comparative analysis of high performing and underperforming groups as these differences across tumor groups represent opportunities to learn from those with lower structural barriers and implement targeted interventions for those with higher structural barriers.

No significant difference was detected across barrier domains between white and black patients, though the sample size for Black patients was small. In fact, minorities accounted for a small portion of patients presenting to the cancer center as 86.3% of the navigated sample were white patients. A previous study similarly showed that black and Hispanic patients were less likely to present to an NCI-designated cancer center after controlling for travel distance and other demographic variables [32]. In addition, a literature review found no difference between white and minority patients in terms of willingness to enroll in clinical trials [15]. Taken together, this suggests that ensuring equal access to clinical trials may be more impactful than interventions aimed at changing attitudes or beliefs since minorities appear to be just as willing to participate if given the chance. Ensuring equal access is particularly pertinent to cancer centers with rural sites as trials are likely available at the cancer center itself rather than the more distant locations, which may unintentionally exclude those of lower SES or minorities. To optimize recruitment, more studies must be performed to determine the specific barriers to minority access and enrollment.

An important feature of a useful clinical decision-support tool is its ability to provide the denominator of patients presenting with cancer, which allows us to trace barrier domains from the structural to the patient level. The decision-support tool utilization rate is the

Table 2: Sequential barriers to clinical trial enrollment by demographic characteristics.

Barrier Domain		Structural		Clinical		Physician		Patient	
	Total n	No Trial Available n (%)	Trial Avail n	Ineligible n (%)	Eligible n	Not Offered n (%)	Offered Trial n	Not Screened n (%)	Sent for Screening n (%)
All Patients	1,725	1,248 (72.3)	477	129 (27.0)	348	50 (14.4)	298	30 (10.1)	268 (89.9)
Tumor Group		**p<0.0001**		**p<0.0001**		p=0.06		p=0.12	
Genitourinary	267	151 (56.6)	116	55 (47.4)	61	7 (11.5)	54	7 (13.0)	47 (87.0)
Breast	231	158 (68.4)	73	26 (35.6)	47	13 (27.7)	34	5 (14.7)	29 (85.3)
Gastrointestinal	506	417 (82.4)	89	16 (18.0)	73	11 (15.1)	62	10 (16.1)	52 (83.9)
Lung	392	339 (86.5)	53	14 (26.4)	39	6 (15.4)	33	2 (6.1)	31 (93.9)
Hematopoietic	329	183 (55.6)	146	18 (12.3)	128	13 (10.2)	115	6 (5.2)	109 (94.8)
Age		**p=0.02**		p=0.30		**p=0.02**		p=0.58	
<60	480	324 (67.5)	156	37 (23.7)	119	15 (12.6)	104	7 (6.7)	97 (93.3)
60 - 64	269	207 (77.0)	62	15 (24.2)	47	3 (6.4)	44	5 (11.4)	39 (88.6)
65 - 74	562	419 (74.6)	143	38 (26.6)	105	13 (12.4)	92	11 (12.0)	81 (88.0)
≥ 75	414	298 (72.0)	116	39 (33.6)	77	19 (24.7)	58	7 (12.1)	51 (87.9)
Race		p=0.56		p=0.65		p=0.68		p=0.09	
White	1,489	1,083 (72.7)	406	108 (26.6)	298	42 (14.1)	256	23 (9.0)	233 (91.0)
Black	133	91 (68.4)	42	11 (26.2)	31	4 (12.9)	27	3 (11.1)	24 (88.9)
Other/Unkn	103	74 (71.8)	29	10 (34.5)	19	4 (21.1)	15	15 (26.7)	11 (73.3)
National ADI		p=0.18		p=0.23		p=0.33		p=0.09	
1st Tertile	156	106 (68.0)	50	18 (36.0)	32	3 (9.4)	29	6 (20.7)	23 (79.3)
2nd Tertile	1,133	834 (73.6)	299	80 (26.8)	219	28 (12.8)	191	15 (7.9)	176 (92.2)
3rd Tertile	377	264 (70.0)	113	26 (23.0)	87	16 (18.4)	71	7 (9.9)	64 (90.1)
Missing	59		15		10		7		

*p-values are from Chi-squared tests

primary determinant of this denominator's accuracy. The utilization rate presented in this study only includes new patients and would not include established patients who have switched between therapeutic trials. However, the impact of patients switching between trials was mitigated by the fact that the study was over 18 months rather than a longer timeframe. The present study found that decision-support tool usage varies by tumor groups, but utilization is increasing overall, likely due to a combination of education, benchmarking, physician championing, and increased informatics support. This improvement in decision-support tool utilization will help better delineate barriers over time.

The usefulness of a clinical decision-support tool in the context of clinical trial enrollment depends on the appropriate placement of trials into the decision-tree and the automated algorithms developed to determine eligibility. If appropriately maintained, a decision-support tool can be particularly helpful for providers who are not familiar with the trials available at an institution as its use only requires knowledge about the patient. Therefore, implementation of a decision-support tool may be helpful for increasing enrollment from our regional sites. However, if the decision-tool functions outside the formal trial screening procedures of the cancer center, the provider's degree of local clinical trial knowledge impacts the categorization of the clinical barrier for a given patient. For example, a physician who is not familiar with a trial may send an ineligible patient for screening when prompted, whereas a physician who is more familiar with the trial may recognize that the patient is ineligible and not send the patient for screening. The presence of both types of providers in this analysis results in an underestimation of the ineligibility rate, and the degree of underestimation corresponds to the proportion of each in a given tumor group.

There are some limitations to this study. First, generalizing these results to the institution is tied to the utilization of the clinical decision-support tool. Although ongoing efforts have improved decision-support tool utilization, barriers to clinical trial enrollment could not be assessed in patients who were not navigated. As our utilization increases, we will be able to further evaluate barriers. Second, the interpretation of the results for clinical, physician, and patient-level barriers are limited given the large structural barrier resulting in a small sample size at the barrier domains downstream. In addition, the reasons for non-referral at the clinical, provider, and patient-level were given by providers prior to the formal screening procedure and reflect to some degree their knowledge of trials at the institution rather than the formal result of screening. Often providers will pre-screen patients prior to utilizing the decision-support tool, which further complicates the interpretation of these downstream domains.

Conclusion

Barriers to clinical trial enrollment exist at all levels, although it is evident that trial availability remains one of the most significant barriers. Our data also dispels the often-circulated misperception that Black patients are less willing to participate in clinical trials, as we saw no racial differences in participation in the subset of eligible patients who were offered trial participation.

Clinical decision-support platforms may be promising tools for clinical trial enrollment but are not without limitations and pitfalls.

Table 3: Multivariable logistic model predicting progression through each barrier domain.

Barrier Domain	Structural		Clinical		Physician		Patient	
	Trial Available (n=1666)		Eligible for Trial (n=462)		Patient Recruitment (n=338)		Sent for Screening (n=291)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Tumor Group								
Genitourinary	1		1		1		1	
Breast	0.54 (0.37, 0.79)	**0.002**	1.70 (0.89, 3.25)	0.11	0.28 (0.09, 0.85)	**0.02**	0.44 (0.10, 1.85)	0.26
Gastrointestinal	0.27 (0.19, 0.38)	**<0.0001**	4.51 (2.27, 8.94)	**<0.0001**	0.63 (0.22, 1.83)	0.4	0.40 (0.12, 1.37)	0.14
Lung	0.20 (0.14, 0.30)	**<0.0001**	2.48 (1.19, 5.14)	**0.01**	0.87 (0.26, 2.93)	0.82	1.48 (0.26, 8.53)	0.66
Hematopoietic	0.99 (0.70, 1.39)	0.94	6.64 (3.49, 12.65)	**<0.0001**	1.01 (0.36, 2.84)	0.99	1.62 (0.44, 5.96)	0.46
Age								
<60	1		1		1		1	
60 - 64	0.62 (0.43, 0.89)	**0.01**	1.16 (0.55, 2.47)	0.7	1.56 (0.41, 5.97)	0.51	0.43 (0.12, 1.54)	0.2
65 - 74	0.69 (0.51, 0.92)	**0.01**	1.10 (0.62, 1.97)	0.75	0.71 (0.29, 1.70)	0.44	0.61 (0.20, 1.83)	0.38
≥ 75	0.77 (0.56, 1.05)	0.1	0.85 (0.47, 1.55)	0.59	0.25 (0.11, 0.61)	**0.002**	0.39 (0.11, 1.36)	0.14
Race								
White	1		1		1		1	
Black	1.20 (0.79, 1.81)	0.4	0.99 (0.44, 2.23)	0.98	1.43 (0.42, 4.80)	0.57	0.63 (0.15, 2.70)	0.54
Other/Unkn	1.07 (0.66, 1.73)	0.79	0.60 (0.25, 1.43)	0.25	0.89 (0.23, 3.41)	0.87	0.22 (0.06, 0.80)	**0.02**
National ADI								
1st Tertile	1.24 (0.85, 1.81)	0.27	0.62 (0.31, 1.22)	0.17	1.78 (0.49, 6.40)	0.38	0.32 (0.11, 0.95)	**0.05**
2nd Tertile	1		1				1	
3rd Tertile	1.19 (0.90, 1.57)	0.22	1.37 (0.77, 2.42)	0.28	0.60 (0.29, 1.26)	0.18	0.89 (0.32, 2.51)	0.83

The use of decision-support tools in the context of clinical trial enrollment is more helpful for providers without detailed knowledge of the trials available at the institution. The data that is collected through these tools has the potential for improving trial enrollment if its use is properly implemented and monitored. Decision-support tools may be most effective for increasing trial enrollment when incorporated into regional sites.

Our study suggests that trial availability is a significant barrier to enrollment at our institution and that it varies across tumor groups. The specific reasons for the differences in trial availability are being explored further within specific tumor groups. We have tasked disease working groups, which each manage clinical trials for a specific group of cancers, with identifying the populations most in need of trial opportunities and prioritizing appropriate studies. Such efforts will increase trial availability for a larger proportion of the patients treated at our center.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
2. An Update on Cancer Deaths in the United States | CDC. Accessed March 3, 2021.
3. Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer. 2020;126(10):2225-49.
4. Unger JM, Barlow WE, Martin DP, Ramsey SD, Leblanc M, Etzioni R, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. J Natl Cancer Inst. 2014;106(3):dju002.
5. Chow CJ, Habermann EB, Abraham A, Zhu Y, Vickers SM, Rothenberger DA, et al. Does enrollment in cancer trials improve survival? J Am Coll Surg. 2013;216(4):774-81.
6. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. JAMA. 2004;291(22):2720-6.
7. Stewart JH, Bertoni AG, Staten JL, Levine EA, Gross CP. Participation in surgical oncology clinical trials: Gender-, race/ethnicity-, and age-based disparities. Ann Surg Oncol. 2007;14(12):3328-34.
8. Scoggins JF, Ramsey SD. A National cancer clinical trials system for the 21st century: Reinvigorating the NCI cooperative group program. J Natl Cancer Inst. 2010;102(17):1371.
9. Korn EL, Freidlin B, Mooney M, Abrams JS. Accrual experience of national cancer institute cooperative group phase III trials activated from 2000 to 2007. J Clin Oncol. 2010;28(35):5197-201.
10. Freedman LS, Simon R, Foulkes MA, Friedman L, Geller NL, Gordon DJ, et al. Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993 - The perspective of NIH clinical trialists. Control Clin Trials. 1995;16(5):277-85.
11. Branson RD, Davis K, Butler KL. African Americans' participation in clinical research: Importance, barriers, and solutions. Am J Surg. 2007;193(1):32-9.
12. Seto B. History of medical ethics and perspectives on disparities in minority recruitment and involvement in health research. Am J Med Sci. 2001;322(5):248-50.
13. Freeman HP, Payne R. Racial Injustice in Health Care. N Engl J Med. 2000;342(14):1045-7.
14. Advani AS, Atkeson B, Brown CL, Peterson BL, Fish L, Johnson JL, et al. Barriers to the participation of African-American patients with cancer in clinical trials: A pilot study. Cancer. 2003;97(6):1499-506.
15. Wendler D, Kington R, Madans J, Wye GV, Christ-Schmidt H, Pratt LA, et al. Are racial and ethnic minorities less willing to participate in health research? PLoS Med. 2006;3(2):e19.

16. Greiner KA, Friedman DB, Adams SA, Gwede CK, Cupertino P, Engelman KK, et al. Effective recruitment strategies and community-based participatory research: Community networks program centers' recruitment in cancer prevention studies. Cancer Epidemiol Biomarkers Prev. 2014;23(3):416-23.

17. Cupertino AP, Saint-Elin M, De Los Rios JB, Engelman KK, Greiner KA, Ellerbeck EF, et al. Empowering Promotores de Salud as partners in cancer education and research in rural southwest Kansas. Oncol Nurs Forum. 2015;42(1):15-22.

18. Cupertino AP, Molina CSP, de los Rios JB. Knowledge, Awareness, and Interest in Cancer Clinical Trials among Rural Latinos Following Brief Education by Promotores de Salud. J Community Med Health Educ. 2015;05(04):1-9.

19. Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. Cancer. 2008;112(2):228-42.

20. Meropol NJ, Buzaglo JS, Millard J, Damjanov N, Miller SM, Ridgway C, et al. Barriers to clinical trial participation as perceived by oncologists and patients. J Natl Compr Cancer Netw. 2007;5(8):655-64.

21. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer: A meta-analysis and systematic review of patient-reported factors. Lancet Oncol. 2006;7(2):141-8.

22. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: A systematic review. J Clin Epidemiol. 1999;52(12):1143-56.

23. Klabunde CN, Springer BC, Butler B, White MS, Atkins J. Factors influencing enrollment in clinical trials for cancer treatment. South Med J. 1999;92(12):1189-93.

24. Unger JM, Hershman DL, Albain KS, Moinpour CM, Petersen JA, Burg K, et al. Patient income level and cancer clinical trial participation. J Clin Oncol. 2013;31(5):536-42.

25. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine E, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003;21(12):2268-75.

26. Jenkins V, Fallowfield L. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. Br J Cancer. 2000;82(11):1783-8.

27. Ellis PM, Butow PN, Tattersall MHN, Dunn SM, Houssami N. Randomized clinical trials in oncology: Understanding and attitudes predict willingness to participate. J Clin Oncol. 2001;19(15):3554-61.

28. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst. 2019;111(3):245-55.

29. Jackman DM, Zhang Y, Dalby C, Nguyen T, Nagle J, Lydon CA, et al. Cost and survival analysis before and after implementation of dana-farber clinical pathways for patients with stage IV non-small-Cell lung cancer. J Oncol Practic. 2017;13(4):e346-52.

30. Ellis PG, O'Neil BH, Earle MF, McCutcheon S, Benson H, Krebs M, et al. Clinical pathways: Management of quality and cost in oncology networks in the metastatic colorectal cancer setting. J Oncol Pract. 2017;13(5):e522-8.

31. Javid SH, Unger JM, Gralow JR, Moinpour CM, Wozniak AJ, Goodwin JW, et al. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials (SWOG S0316). Oncologist. 2012;17(9):1180-90.

32. Huang LC, Ma Y, Ngo JV, Rhoads KF. What factors influence minority use of National Cancer Institute-designated cancer centers? Cancer. 2014;120(3):399-407.