

# A Survey of Multidisciplinary Healthcare Providers Utilizing The Knowintegrativeoncology.Org Educational Platform

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## Research Article

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# Abstract

**Background:** Although the vast majority of cancer patients use natural health products (NHPs), 59% of oncology healthcare providers (HCP) report not receiving any education on NHPs.

KNOWintegrativeoncology.org (KNOW) is a web-based educational platform that provides up-to-date evidence on NHPs used in cancer care with a user-friendly interface. KNOW is a database of human studies systematically gathered from MEDLINE and EMBASE. We surveyed HCPs before and after accessing KNOW to identify their information needs regarding NHPs in cancer care, their preferred way to receive information, barriers they face accessing NHP information, and to obtain feedback on the website.

**Methods:** Recruitment was done through Beaumont Health Systems, the Society for Integrative Oncology, and the Andrew Weil Centre for Integrative Medicine, University of Arizona. HCPs who consented completed an initial survey and then a follow-up survey after being given access to KNOW for 4-6 weeks. Participants were required to access KNOW at least three times before completion of the follow-up survey.

**Results:** A total of 65 participants completed the initial survey, with 60% (n=39) from the conventional medical community, 33% (n=21) from the integrative medicine community, and 7% (n=5) from the research community. The majority of participants (82%; n=53) preferred educational websites to email updates, podcasts/webinars, in-house experts, PubMed searches and smartphone apps. The most common barriers identified to accessing information on NHPs were time, accessibility at point-of-care, and credibility of sources. A high number of participants were lost to follow up, with 18 participants demographically representative of the initial sample of 65 completing the follow-up survey. Half (n=9) of participants stated accessing the KNOW website changed their clinical practice. Close to 90% (n=16) reported they would recommend KNOW to a colleague.

**Conclusion:** The majority of oncology HCPs prefer to use, and already rely on, numerous web-based educational platforms to gather information on NHPs, with time, accessibility, and credibility being common barriers to obtaining information. Our study results indicate that KNOW helped reduce some of these barriers and HCPs were highly satisfied with the resource. KNOW is a comprehensive, easy-to-use web-based educational resource to access up-to-date research on NHPs in cancer care.

## Background

While the vast majority of cancer patients actively use natural health products (NHPs) during their systemic treatment for cancer,<sup>1-5</sup> knowledge about complementary and alternative medicine (CAM), also known as “integrative medicine”, amongst the conventional healthcare community is lacking. In a 2014 survey of American Society of Clinical Oncology members, two-thirds of oncologists indicated they did not have enough knowledge to answer questions from patients regarding herbs and supplements, and 59% had not received any education about the topic<sup>6</sup>. Oncology healthcare practitioners (HCPs) in

Canada were surveyed in 2015 and 69% reported receiving no formal training regarding NHPs, indicating an urgent need for improved CAM therapy education.<sup>7</sup> A third survey completed in Australia revealed that general practice doctors perceived a high level of need for CAM information resources due to a lack of knowledge coupled with a substantive level of interest to learn more.<sup>8</sup> Lastly, oncology HCPs in Germany were surveyed on their needs and preferences regarding CAM information and training.<sup>9</sup> Respondents highly preferred lectures, information platforms on the internet, workshops, and e-mail newsletters as methods of receiving information about CAM, and wanted summarized information that would support their understanding of how CAM therapies might aid in the management of side effects that arise from common conventional cancer treatments (e.g., chemotherapy and radiation).

In 2019, a study conducted in the United States audio-recorded patient-clinician interactions in medical oncology outpatient practices. Conversations that included discussions about CAM were found to have more psychosocial statements from both clinicians and patients, and were rated higher on patient-centeredness, positive patient and clinician affect, and patient engagement.<sup>10</sup> It is unrealistic, however, to expect oncology HCPs to have productive discussions about CAM when they largely feel unprepared to do so<sup>6</sup>. It is clear that oncology HCPs urgently need and want to have easy access to evidence-based CAM information. Increasing HCPs' knowledge about CAM therapies can help ensure patient information needs about these therapies are met, thus allowing for safer and more comprehensive cancer care.

In 2015, the Oncology Association of Naturopathic Physicians (OncANP) established KNOWintegrativeoncology (KNOW) an up-to-date, searchable database of human studies on NHPs in cancer care. KNOW's methodology involves systematically searching MEDLINE and EMBASE and then parallel screening these citations for inclusion criteria (English language, human oncology studies on secondary prevention: systematic reviews, meta-analyses, observational studies, clinical trials and case reports that include the use of herbs, supplements or diet). Included studies are then extracted for key information about population, intervention, comparator and outcome (PICO). For controlled trials, a Cochrane Assessment of Risk for Randomized Trials is conducted (11). The KNOW medical librarian, who had contributed to the building of the PubMed CAM filter, guided a multidisciplinary team of HCPs and researchers in creating a detailed custom search filter for KNOW that expanded on existing CAM filters. The custom search filter was built using naturopathic expertise to include synonymous terms and detailed keywords for herbs, supplements, nutrients and diet to capture more studies in MEDLINE and EMBASE.

In 2016, KNOW expanded to become a web-based educational platform to support integrative oncology education and clinical decision making. The KNOW team gathered user feedback from the Oncology Association of Naturopathic Physicians (OncANP) membership (450 HCP's) through an online survey as well as an hour-long interview of beta testers at various stages of their careers. The KNOW website was then extensively revised to make data searchable by tumor type, conventional treatment type, treatment side effect (e.g., peripheral neuropathy, nausea and vomiting, bone marrow suppression) and natural therapy type (e.g., green tea, Mediterranean diet, omega 3 fatty acids).

The choice to include EMBASE in KNOW's search strategy has proved to be important because international studies on NHPs identified in EMBASE can often be lacking in PubMed and MEDLINE search results. In order to demonstrate KNOW's reliability compared to PubMed, a quality analysis was undertaken in 2017 and again in 2019 by two independent reviewers. The results were presented at the Society for Integrative Oncology Conference and Oncology Association of Naturopathic Physicians conference in 2019. Both quality appraisals found significantly more title results in KNOW than in PubMed. For example, in a search for "Mucositis" + "cancer" + "glutamine", comparative analysis identified a total of 38 relevant studies identified through PubMed and KNOW. The search in KNOW identified 32/38 studies, with 18 of those not identified by PubMed. The PubMed search identified 20/38 studies, with 6 not identified by KNOW. This highlights the importance of searching EMBASE in addition to MEDLINE to yield more robust results.

Currently, KNOW is updated quarterly and contains studies published in EMBASE and MEDLINE from the year 2000 to present. In a KNOW search, results are listed according to level of evidence, with meta-analyses and systematic reviews listed first, then clinical trials, followed by observational studies and, finally, case reports. KNOW users can search for studies, see extracted details from the studies, copy and paste study references and also link to the article's abstract or full-text located online. The KNOW web-based educational platform is currently licensed by University of Arizona's Andrew Weil Center for Integrative Medicine and the Canadian College of Naturopathic Physicians. The number of providers currently using KNOW is estimated to be over 2500.

The aim of this research study was to describe oncology HCPs' information needs regarding NHPs in cancer care, their preferred way to receive information, barriers they face accessing NHP information, and to obtain feedback from multidisciplinary providers on the KNOW web-based educational platform. In addition, the impact of accessing and using KNOW on HCPs' clinical practice was examined.

## **Methods**

### **Study Design**

This was an observational, pre-post research study. Participants were required to answer two surveys: one at baseline and another at 4-6 weeks after accessing and using the KNOW website on at least three occasions.

### **Participants and Setting**

Participants were included in this study if they were oncology HCPs or integrative oncology researchers in the United States. Professions included were: medical oncologists, oncology nurses, oncology physician assistants, oncology pharmacists, radiation oncologists, oncology surgeons, oncology fellows, naturopathic physicians working in oncology and integrative oncology researchers. Enrollment began September 24th, 2020 and ended March 14th, 2021. Recruitment announcements were made via email through Beaumont Health Systems in Michigan, the Society for Integrative Oncology, and the Andrew Weil

Center for Integrative Medicine at the University of Arizona. There was no direct cost or compensation to participate in the survey; however, participants were offered access to the website for 12 months after completing the study.

## **Data collection**

The initial survey was comprised 18 items that assessed the HCPs' demographics (profession and age), information-seeking behavior related to NHPs (including resources used), preferred sources of NHP information, barriers to accessing NHP information, perceived credibility of NHP information resources, and continuing education needs related to NHPs. HCPs' knowledge about NHPs and preparedness to address clinical issues associated with NHPs were also assessed, but were not a focus of this study (Supplementary Material 1). The follow-up survey included the same questions as the initial survey (minus demographics) as well as the addition of eight items that assessed how accessing and using KNOW affected HCPs' clinical practice, what improvements were required to the KNOW platform, and whether HCPs would recommend KNOW to other clinicians (See Supplementary Material 2). The initial and follow-up surveys were created by a multidisciplinary research team composed of both conventional and integrative oncology HCPs and researchers. Surveys were distributed to consenting participants using the Research Electronic Data Capture (REDCap) website.

## **Statistical analysis**

Descriptive statistics (i.e., frequency, means) were used in this analysis to summarize key study variables.

## **Results**

### **Participants**

In total, 65 HCPs consented to participate and completed the initial survey. Table 1 shows the demographics of the sample. A total of 60% (n=39) of respondents were from the conventional healthcare community, 33% (n=21) were from the integrative or naturopathic community, and 7% (n=5) were integrative oncology researchers. Age distribution was diverse, with most respondents in the 40 to 49-years group. Only 18 respondents completed the follow-up survey after accessing KNOW, with profession and age distributions similar to that of the larger initial group surveyed at baseline.

Table 1  
Sample Demographics at Baseline and Follow-up

	Baseline (n=65)	Follow-up (n=18)
<i>Profession</i>		
Medical oncologist	22 (33.8)	6 (33.3)
Naturopathic physician	15 (23.1)	4 (22.2)
Nurse practitioner	6 (9.2)	1 (5.6)
Integrative medical doctor	5 (7.7)	2 (11.1)
Integrative oncology researcher	5 (7.7)	2 (11.1)
Radiation oncologist	3 (4.6)	-
Registered nurse	3 (4.6)	1 (5.6)
Pharmacist	2 (3.1)	1 (5.6)
Physician assistant	2 (3.1)	1 (5.6)
Oncology fellow	1 (1.5)	-
Other	1 (1.5)	-
<i>Age Group (Years)</i>		
20-29	3 (4.6)	1 (5.6)
30-39	10 (15.4)	3 (16.7)
40-49	26 (40.0)	5 (27.8)
50-59	17 (26.2)	6 (33.3)
60-69	7 (10.8)	3 (16.7)
70+	2 (3.1)	1 (5.6)

## Obtaining Information on Natural Health Products

The frequency of accessing information on NHPs varied between conventional and integrative HCPs (Table 2). Amongst conventional HCPs, 44.7% (n=17) reported gathering information daily or weekly, while the other 55.3% reported doing so monthly or less than monthly. Amongst integrative HCPs, 95.2% (n=20) reported seeking information daily or weekly, while only one person (4.8%) reported doing so monthly.

Table 2  
Frequency of Gathering Information about NHPs at Baseline

Baseline	Conventional HCPs (%) n=38*	Integrative/ CAM HCPs (%) n=21	Researchers (%) n=5
Daily	5 (13.1)	13 (61.9)	-
Weekly	12 (31.6)	7 (33.3)	-
Monthly	9 (23.7)	1 (4.8)	2 (40.0)
Less than monthly	12 (31.6)	-	3 (60.0)
*Conventional provider missing n=1			

Abbreviations: CAM, complementary and alternative medicine; HCPs, health care providers; NHPs, natural health products.

Table 3 shows the ways through which HCPs reported accessing information on NHPs. A total of 86.2% (n=56) of respondents stated they used a website to obtain information, with 78.5% (n=51) reporting they specifically used PubMed to search for information. Other top websites included Memorial Sloan Kettering Cancer Center, Up to Date, the National Cancer Institute, Natural Medicines Research Collaboration, and Beyond Conventional Cancer Therapies (see Supplementary Table 1). Amongst the integrative HCP community, PubMed (95.2% integrative vs. 66.7% conventional) and conferences (71.4% integrative vs. 43.6% conventional) were more frequently used compared to within the conventional HCP community. Websites not including PubMed, in general, saw more usage in the conventional HCP community compared to the integrative HCP community (94.9% conventional vs. 76.2% integrative). All other methods were used approximately the same between groups.

Table 4 shows the ways HCPs preferred to gather information on NHPs. Websites were the most preferred source (81.5%; n = 53). There were, however, large differences in actual versus preferred means of obtaining information with regards to: PubMed (78.5% actual vs. 47.7%

**Table 3: Frequency of Actual NHP Information Resources Used**

Resources Used	Conventional Providers (%) (n=39)	Integrative/CAM HCPs (%) (n=21)	Research Staff (%) (n=5)	TOTAL (%) (n=65)
Websites	37 (94.9)	16 (76.2)	3 (60.0)	56 (86.2)
PubMed Search	26 (66.7)	20 (95.2)	5 (100.0)	51 (78.5)
Conferences	17 (43.6)	15 (71.4)	2 (40.0)	34 (52.3)
Webinars or Podcasts	16 (41.0)	13 (61.9)	1 (20.0)	30 (46.2)
Google	15 (38.5)	9 (42.9)	3 (60.0)	27 (41.5)
In-House Expert	22 (56.4)	8 (38.1)	1 (20.0)	21 (32.3)
Email Updates	9 (23.1)	10 (47.6)	-	19 (29.2)
Smartphone Apps	6 (15.4)	3 (14.3)	1 (20.0)	10 (15.4)
E-Textbooks	3 (7.7)	6 (28.6)	-	9 (13.8)

Abbreviations: CAM, complementary and alternative medicine; NHP, natural health product preferred), conferences (52.3% actual vs. 16.9% preferred) and Google (41.5% actual vs. 7.7% preferred). These discrepant results may indicate a reliance on non-preferred sources of information (i.e., PubMed, conferences, Google), whereas HCPs would prefer websites for information about NHPs.

**Table 4: Frequency of Preferred NHP Information Resources**

Preferred Resources	Conventional Providers (%) (n = 39)	Integrative/CAM HCPs (%) (n = 21)	Research Staff (%) (n = 5)	TOTAL (%) (n = 65)
Websites	34 (87.2)	17 (81.0)	2 (40.0)	53 (81.5)
Email Updates	20 (51.3)	14 (66.7)	3 (60.0)	37 (56.9)
Webinars/Podcasts	14 (35.9)	16 (76.2)	5 (100.0)	35 (53.8)
In-House Expert	22 (56.4)	8 (38.1)	2 (40.0)	32 (49.2)
PubMed Search	23 (59.0)	8 (38.1)	-	31 (47.7)
Smartphone Apps	15 (38.5)	2 (9.5)	-	17 (26.2)
Conferences	5 (12.8)	5 (23.8)	1 (20.0)	11 (16.9)
E-Textbooks	5 (12.8)	3 (14.3)	-	8 (12.3)
Google	2 (5.1)	3 (14.3)	-	5 (7.7)

Abbreviation: CAM, complementary and alternative medicine; NHP, natural health product

#### *Barriers to Accessing Information on NHPs*

HCPs were asked to rate the barriers they experienced in obtaining information about NHPs on a scale of 0-5, where 0 is no barrier and 5 is a strong barrier. The strongest barriers according to mean intensity level were: time limitations (3.4/5), accessibility of data at point-of-care (3.1/5), credibility of sources (3.0/5), and lack of in-house experts to consult (2.2/5). Table 5 shows the full data on these four barriers. Other individual barriers identified included; lack of evidence, lack of detailed information on some products, cost and the organization and searchability of data.

**Table 5: Barriers to Accessing NHP Information**

Rating	Time (%)	Credibility of Sources (%)	Accessibility at POC	Lack of in-house expert
0 (No Barrier)	2 (3.1)	5 (7.7)	3 (4.6)	20 (30.8)
1	5 (7.7)	5 (7.7)	7 (10.8)	7 (10.8)
2	6 (9.2)	7 (10.8)	8 (12.3)	9 (13.8)
3	20 (30.8)	27 (41.5)	20 (30.8)	8 (12.3)
4	16 (24.6)	12 (18.5)	19 (29.2)	9 (13.8)
5 (Strong Barrier)	16 (24.6)	9 (13.8)	8 (12.3)	12 (18.5)
Mean	3.4/5	3.0/5	3.1/5	2.2/5

n = 65. Abbreviation: POC, point-of-care; NHP, natural health product

### *Impact of Accessing KNOW*

Of the 18 post-survey respondents, 50% (n=9) stated that accessing the KNOW platform changed their clinical practice. Of the nine HCPs who felt their practice had changed, 77.8% (n=7) said that accessing the website made their clinical decision more evidence based, 44% (n=4) felt more confident answering questions related to natural products, 44.4% (n=4) had a greater understanding about herb/supplement-drug interactions, and 44.4% (n=4) felt more comfortable recommending natural products they had not previously recommended.

### *Recommended Improvements to KNOW*

Recommendations for improvements to the KNOW platform fell into several categories, the most common being technical (i.e., search engine optimization, user interface and development of a smartphone app), integration into other resources (i.e., existing web-based health resources, linking to other internet-based resources), and expansion of scope (i.e., new topics, herb-drug interactions). Three-quarters of HCPs noted they would like to “add clinical tips” to the KNOW website and 38% suggested the KNOW developers “create an app”. Finally, 12.5% wanted additional information, such as NHP dosing and interaction with drugs (with links to supporting studies), and the mechanism of action of select NHPs.

With regards to the format in which studies are summarized, over 50% of respondents said they would be happy with a simple language summary of each research study with a hyperlink link to the study online. However, in the KNOW platform, features like full extractions of research studies that include details on population, intervention, comparator and outcome (PICO) as well as the Cochrane quality/risk assessment tool<sup>11</sup> were rated as important or very important by 75% of respondents.

### *Satisfaction with KNOW*

The majority of follow-up survey respondents (88.9%; n = 16) said they would recommend KNOW to a colleague or to their professional organization. Participants noted that the website was practical, helped save time, was comprehensive, and that it helped fill an unmet need as a resource for evidence-based integrative oncology recommendations. One respondent noted they did not think that it was more useful than PubMed. All qualitative feedback can be found in the Supplementary Material 3.

## **Discussion**

This survey is consistent with previous surveys that show variability in how often oncology HCPs gather information about NHPs<sup>7</sup> and that their preferred information source is web-based platforms.<sup>9</sup> In our study, integrative HCPs reported gathering information more frequently and consistently compared to conventional HCPs, with almost all integrative HCPs collecting data at least weekly. Conventional providers, in contrast, varied more in how often they accessed information, with over 50% reporting

monthly or less than monthly access. There was similarity in the ways that all HCPs access information, as well as the ways they prefer to access information, with websites being the top choice in each instance. It was interesting to note that there was great variability in the specific websites used, with five separate websites being used by more than 50% of respondents. This implies that HCPs use multiple websites in sourcing information about NHPs. This practice may be beneficial for minimizing the effects of bias that can occur from relying on any single website. It also suggests that one website alone was not sufficient to address questions about NHPs.

The most substantial barrier to accessing information was time, with 80% of respondents rating it 3 or greater out of 5. The second highest rated barrier to accessing NHP information was accessibility at point-of-care. Considering these barriers, it is reasonable that HCPs prefer web-based platforms to email updates (which may be more time efficient but not as searchable at point-of-care), podcasts/webinars (time consuming and not searchable at point-of-care), in-house experts (time efficient but not accessible in most cancer care settings), and PubMed searches (highly searchable at point-of-care but not time efficient). There was also a discrepancy of 30% or more between actual use versus preferred use of PubMed, conferences, and Google, perhaps indicating that there is a need to rely on these non-preferred information sources. In a previous survey, HCPs reported they were frequently unable to locate the CAM information they needed, had limited knowledge of existing CAM resources, and instead relied on MEDLINE.<sup>12</sup> Searchable educational websites, available at point-of-care, are likely the best way to assist HCPs in accessing information about NHPs.

Credibility of resources was rated, on average, 3 out of 5 as a barrier to accessing NHP information. In a previous study on web-based information about herbal medicines used in cancer care, it was found that most sites were low quality on a number of indicators, including accuracy of information, revealing sources of information, biased presentation of information or regularity of updates.<sup>13</sup> A number of features in KNOW help to avoid low quality indicators and augment its credibility. KNOW is based on quarterly, systematic searches of EMBASE and MEDLINE and all search results are displayed according to level of evidence with systematic reviews first, then clinical trials, then observational studies, and lastly, case reports. Full summaries provide an extraction of human research studies in chart format that includes: the title, a full reference, details about participants including tumor type and conventional treatments, the specific NHPs incorporated along with dosing and route of administration, side effects, adverse events and interactions, and a detailed outcomes report including the statistical analysis such as confidence intervals, p-values, and any descriptive analysis presented by the study authors. Randomized controlled trial summaries also include a Cochrane quality analysis report to assess for bias. A potential weakness of KNOW is that while side effects are noted, general cautions regarding NHPs are not included in the platform. This means that HCPs without background knowledge in NHPs may need to consult additional websites to learn more about safety considerations through monographs on specific NHPs. A possible improvement to KNOW would be to link to well referenced monographs, such as the National Cancer Institute's Physician Data Query Cancer Information Summaries for Integrative, Alternative, and Complementary Therapies.

Limited time, which was a significant barrier for HCPs seeking NHP information, may also account for why only 18 of the 65 initial respondents completed the follow-up survey. Oncology HCPs are increasingly burdened with growing caseloads, care complexity, and administrative burdens.<sup>14</sup> Other possible reasons for the low completion rate of the follow-up survey include its timing during the COVID-19 pandemic, lack of financial incentive, technical challenges accessing the KNOW website, and failure to use the KNOW website at least three times.

Despite the low final survey response rate, those who did respond came from diverse healthcare professions that reflected the demographics of the larger group of initial respondents. Final respondents were highly satisfied with the KNOW website. Most respondents identified search engine optimization and user interface as areas for improvement. There was contradictory feedback with regards to the summarizing format. Within KNOW, randomized controlled trials have a full summary that includes PICO, plus a Cochrane quality analysis. In contrast, most other study designs (systematic reviews, observational studies, case reports) contain just a summary with a link to the study and back end tagging of keywords to make it more searchable. Final respondents simultaneously indicated that a full PICO/Cochrane summary was important to them, but they would also appreciate a simple summary format. Future surveys will need to be conducted to confirm which style of study summary HCPs prefer and to gain input from a larger group of oncology HCPs.

The main limitation of this survey is the small group surveyed and low proportion of the group that provided feedback after utilization of the KNOWintegrativeoncology.org tool. There was a selection bias in favor of HCPs who have an affinity for such a tool because others who were less likely to use such an information source would likely have decided not to access KNOWintegrativeoncology.org in the first place and, thus, not completed the study. To address this limitation and expand on the generalizability of our findings, further survey work in another setting will be important to conduct.

## Conclusions

This study successfully gathered information about conventional and integrative HCPs information needs regarding NHPs in their daily oncology practices. The majority of HCPs prefer to use, and already rely upon, web-based educational platforms to gather information. The study also identified that there are significant barriers to accessing information about NHPs, including time, accessibility at point-of-care, and credibility of the information. An optimal solution seems to be a comprehensive website that contains up-to-date, reliable, information about a wide range of NHPs that is easy to navigate and can be used directly at the point-of-care. The goals of the KNOW platform are in line with these needs, indicating excellent potential for its applicability in cancer care settings. Most importantly, qualitative responses from participants indicated that the website changed their clinical practice and that most would recommend the website to a colleague or their profession. Many survey participants commented that there is a lack of resources available for information related to integrative cancer care, and that the KNOW web-based educational platform helped reduce some of the barriers reported. Future work will expand the survey to different locations including Canada and the United States to continue assessing HCPs' needs.

# Abbreviations

CAM: Complementary and Alternative Medicine

KNOW: Knowledge in Integrative Oncology Website

NHP: Natural Health Product

OncANP: Oncology Association of Naturopathic Physicians

PICO: Population, Intervention, Comparison, and Outcomes

RCT: Randomized Controlled Trial

REDCap: Research Electronic Data Capture

# Declarations

*Ethics Approval and Consent to Participate:* This study was approved by the Beaumont Institutional Review Board (Beaumont IRB #: 2020-119). All survey respondents signed an informed consent form prior to participating. All methods were performed in accordance with the relevant guidelines and regulations.

*Availability of Data and Materials:* Due to privacy concerns and the cost of archiving data, the data for this study has not been deposited in a public repository. However, a de-identified copy of the dataset is available, on request, by contacting Jen Green (jengreennd@gmail.com).

*Competing Interests:* CM, SS, and HW are paid contractors with KNOWoncology.org. There are no other conflicts of interest to declare.

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*Authors' Contributions:* JG and HW conceived of the study. LGB, DS, HS, JG and HW contributed to study design. HA and JG were responsible for the recruitment of participants. ML created the final dataset and conducted the analysis. All authors contributed to data interpretation and the writing of this manuscript.

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