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Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline

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DOI https://doi.org/10.1200/JCO.23.02596

ABSTRACT

PURPOSE To guide clinicians, adults with cancer, caregivers, researchers, and oncology institutions on the medical use of cannabis and cannabinoids, including synthetic cannabinoids and herbal cannabis derivatives; single, purified cannabinoids; combinations of cannabis ingredients; and full-spectrum cannabis.

METHODS A systematic literature review identified systematic reviews, randomized controlled trials (RCTs), and cohort studies on the efficacy and safety of cannabis and cannabinoids when used by adults with cancer. Outcomes of interest included antineoplastic effects, cancer treatment toxicity, symptoms, and quality of life. PubMed and the Cochrane Library were searched from database inception to January 27, 2023. ASCO convened an Expert Panel to review the evidence and formulate recommendations.

RESULTS The evidence base consisted of 13 systematic reviews and five additional primary studies (four RCTs and one cohort study). The certainty of evidence for most outcomes was low or very low.

RECOMMENDATIONS Cannabis and/or cannabinoid access and use by adults with cancer has outpaced the science supporting their clinical use. This guideline provides strategies for open, nonjudgmental communication between clinicians and adults with cancer about the use of cannabis and/or cannabinoids. Clinicians should recommend against using cannabis or cannabinoids as a cancer-directed treatment unless within the context of a clinical trial. Cannabis and/or cannabinoids may improve refractory, chemotherapy-induced nausea and vomiting when added to guideline-concordant antiemetic regimens. Whether cannabis and/or cannabinoids can improve other supportive care outcomes remains uncertain. This guideline also highlights the critical need for more cannabis and/or cannabinoid research. Additional information is available at www.asco.org/supportive-care-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted December 20, 2023
Published March 13, 2024

Evidence Based Medicine Committee approval: November 14, 2023

J Clin Oncol 42:1575-1593
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INTRODUCTION

Cannabis is a genus of flowering plants that humans have used as fiber (hemp), medicinally, and for its mind-altering effects (eg, euphoria, relaxation, amplified sensory experience, altered perception of time). The two most studied cannabinoids include delta-9-tetrahydrocannabinol (THC), well-recognized for its mind-altering effects, and cannabidiol (CBD). Cannabis, however, contains hundreds of bioactive ingredients—many not fully characterized—including dozens of phytocannabinoids, as well as phenols and terpenes. Such compounds may work together through complicated synergistic and inhibitory interactions, coined the entourage effect.[1] Therefore, cannabis and cannabinoids are not a single product or drug, and scientific evidence for THC's biological impacts may not fully capture the effects of whole-plant cannabis. A brief history of the evolution in the legal status of these agents in the United States is provided in Box 1.

Medical cannabis may be defined as an array of nonpharmaceutical, herbal cannabinoid products used with therapeutic intent, sometimes following clinician recommendation. Cannabinoids are compounds that interact with endocannabinoid receptors throughout the central and peripheral nervous system, on immune cells and organs, and elsewhere in the body. They may be endogenous (endocannabinoids), plant-based (phytocannabinoids), or

THE BOTTOM LINE

Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline

Guideline Questions

(1) How should clinicians and adults with cancer communicate about cannabis and/or cannabinoids?
(2) Does use of cannabis and/or cannabinoids by adults improve cancer-directed treatment?
(3) Does use of cannabis and/or cannabinoids by adults with cancer reduce treatment-related toxicities, palliate cancer symptoms, or improve quality of life (QOL)?

This guideline defines cannabis and/or cannabinoids as encompassing full-spectrum cannabis, herbal cannabis derivatives, and synthetic cannabinoids; single cannabinoids, as well as combinations of cannabis ingredients.

Target Clinical Population

Adults with cancer who use or are interested in using cannabis and/or cannabinoid products for medical purposes.

Target Audience

Clinicians providing care to adults with cancer; the health systems in which they work; adults with cancer and their caregivers; and researchers.

Methods

An Expert Panel convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature and expert opinion.

Note. In the United States, the Controlled Substance Act renders cannabis with >0.3% delta-9-tetrahydrocannabinol (THC) schedule I. This status signifies that cannabis has no accepted medical use and a high potential for abuse.[20] The schedule I designation creates frequent conflicts between federal and state laws, as 38 states now allow medical cannabis use by adults with qualifying conditions. In addition, the schedule I designation creates challenges for cannabis and/or cannabinoid researchers who face sparse funding opportunities, scarce sources for trial products, regulatory barriers, and procedural obstacles. The designation also generates challenges for clinicians wishing to guide adults with cancer using or considering the use of cannabis and/or cannabinoids: insufficient evidence base, limited federal oversight of nonpharmaceutical cannabinoid product manufacturing, and theoretical legal liability.

RECOMMENDATIONS

Clinical Communication and Education

Recommendation 1.1

Health systems and clinicians, in partnership, should provide adults with cancer unbiased, evidence-based cannabis and/or cannabinoid educational resources to facilitate clinical communication, informed decision making, and systematized approaches to care (Good practice statement).

Recommendation 1.2

Given the high prevalence of cannabis and/or cannabinoid use among adults with cancer, clinicians should routinely and nonjudgmentally inquire about cannabis use (or consideration of use) and either guide care or direct adults with cancer to appropriate resources (Good practice statement).

Note. Clinicians should remain sensitive to cannabis regulations' disproportionate impacts on marginalized communities and work to omit cannabis-related and other biases (eg, racial, ethnic, and socioeconomic) from clinical discussions about cannabis and/or cannabinoids. Table 1 offers suggestions for cannabinoid history taking.

Recommendation 1.3

When adults with cancer use cannabis and/or cannabinoids outside of evidence-based indications or clinician recommendations, clinicians should explore goals, educate, and seek to minimize harm (Good practice statement).

Cancer Treatment

Recommendation 2.1

Clinicians should recommend against use of cannabis and/or cannabinoids to augment cancer-directed treatment unless in the context of a clinical trial (Type: Evidence based; Evidence quality: Very low; Strength of recommendation: Weak).

Recommendation 2.2

Clinicians should recommend against use of cannabis and/or cannabinoids in place of cancer-directed treatment (Type: Informal consensus; Evidence quality: Very low; Strength of recommendation: Strong).

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THE BOTTOM LINE (CONTINUED)

Note. Cannabis and/or cannabinoids used as cancer-directed treatment may cause significant clinical (eg, fatigue, confusion, feeling high) and financial toxicities without good-quality evidence of clinical benefit.

Cancer Treatment-Related Toxicity, Symptoms, and QOL

Recommendation 3.1

Adults with cancer who receive moderately or highly emetogenic antineoplastic agents with guideline-concordant antiemetic prophylaxis and experience refractory nausea or vomiting may augment their antiemetic regimen with dronabinol, nabilone, or a quality-controlled oral 1:1 THC:CBD extract (Type: Evidence based; Evidence quality: Moderate for dronabinol and nabilone, Low for 1:1 THC:CBD extract; Strength of recommendation: Weak).

Note. Cannabis and/or cannabinoids are one of several pharmacologic options for adults with cancer experiencing refractory nausea and vomiting despite optimal prophylaxis. For such individuals, the 2020 ASCO antiemetics guideline[22] recommends the addition of olanzapine (if not already prophylactically administered), otherwise the addition of an antiemetic from a different class (eg, a neurokinin–1 receptor antagonist, dopamine receptor antagonist, benzodiazepine, or synthetic THC).

Recommendation 3.2

Outside of a clinical trial, clinicians should not recommend that adults with cancer use 300 mg or more per day of oral CBD to manage symptom burden due to lack of proven efficacy and risk for reversible liver enzyme abnormalities (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

Note. In adult and pediatric populations without cancer, reversible liver enzyme abnormalities primarily occurred in study participants taking 300 mg or more per day of oral CBD.[23]

Recommendation 3.3

Evidence remains insufficient to recommend for or against cannabis and/or cannabinoids in managing cancer treatment-related toxicities or symptoms (including cancer pain), aside from clinical settings addressed in recommendations 3.1 and 3.2 or within the context of a clinical trial (Table 2).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A1 (online only). A handout for patients is available in Appendix 1. More information, including a supplement with evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides information about the methods used to develop this guideline. Patient information is also available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all people with cancer should have the opportunity to participate.

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synthetic (eg, dronabinol, nabilone) and are involved in widespread homeostatic processes throughout the body. Although the endocannabinoid system remains only partially elucidated, researchers have identified two endocannabinoids (anandamide and 2-arachidonoylglycerol), two catabolic enzymes (ie, fatty acid amide hydrolase and monoacylglycerol lipase), and two main endocannabinoid g-protein–coupled receptors (cannabinoid receptor type 1 [CB1] and type 2 [CB2]). While CB2 receptors are prevalent on immune cells, CB1 receptors are found at high concentrations in the brain and peripheral nervous system. There, they operate in a retrograde fashion to modulate activity of several other noncannabinoid neurotransmitters (Fig 1).[6]

Data suggest that from 20% to more than 40% of adults with cancer report cannabis use.[7-12] A recent observational study of adults undergoing cancer treatment at a National Cancer Institute–designated cancer center (N = 267) showed that those who used cannabis, as compared with those who did not, experienced more severe cancer-related symptoms and perceived cannabis as less harmful.[7] Regarding modes of cannabis use, participants tended to rely on edibles (65%) or combusted cannabis (51%). The most common medical reasons for cannabis use were antineoplastic effects, pain, insomnia, anxiety, nausea, vomiting, and poor appetite. Indeed, both qualitative and quantitative research suggest that adults with cancer use cannabis and/or cannabinoids for multisymptom management (eg, pain, nausea, vomiting, anorexia, cachexia, anxiety, depression, insomnia), cancer-directed therapy, and for its euphoric effects.[7-16]

Sociobehavioral research indicates that many oncologists discuss medical cannabis and/or cannabinoids with patients, typically because adults with cancer and their caregivers raise the topic; however, less than a third of oncology clinicians feel confident to make clinical recommendations.[17] Moreover, adults with cancer using medical cannabis report

BOX 1. History of Cannabis and Cannabinoids in the United States

- For millennia, humans have used cannabis medicinally. Inspection of a 500 BCE Siberian mummy revealed her to be riddled with breast cancer and buried alongside a satchel of cannabis.[2]
- In the early 20th century, the US federal and state cannabis laws agreed in their permissive stance toward medical cannabis.
- In the 1930s, a media campaign linked cannabis use to criminality and insanity. It was seemingly spurred by timber interests (hemp competed with wood in paper manufacture) and xenophobia.[3]
- In 1937, the Marihuana Tax Act was passed over the American Medical Association's opposition.
- In 1968, in response to global interest in cannabis research, the United States appointed the University of Mississippi as the federal grower of cannabis for research purposes.[4]
- In 1970, the Controlled Substance Act assigned cannabis a schedule I status, labeling it not acceptable for medical use.[4]
- In the mid-1980s, dronabinol (synthetic tetrahydrocannabinol) was FDA-approved for cancer-related nausea and vomiting.[4]
- In 1996, California comprehensively legalized medical cannabis statewide. To date, 38 states, the District of Columbia, and several territories have since legalized medical cannabis. Cancer is one of the few health conditions that qualifies for medical cannabis in almost every such state law.[5]
- In 2012, Colorado and Washington legalized cannabis for adult nonmedical use, followed by another 21 states to date.
- Between 2017 and 2019, the first herbal cannabinoid (CBD) was FDA-approved and assigned a DEA schedule V status. A federal bill legalized the cultivation and sale of cannabis containing high levels of CBD and low amounts of THC (<0.3%), although regulatory ambiguities persist.

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receiving little clinical specification or guidance from their oncology team regarding safety and optimal use. Instead, they turn to nonmedical sources, including cannabis dispensary personnel, for advice. These professionals consider themselves unevenly trained in cannabis therapeutics.[8,18]

This ASCO guideline builds on important efforts to collate scientific information about clinical use of cannabis and cannabinoids and provide guidance for clinicians, adults with cancer, caregivers, researchers, and oncology institutions. An example of a resource that was consulted in generation of these guidelines is the National Academies of Sciences, Engineering and Medicine's monograph, The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.[19]

GUIDELINE QUESTIONS

This clinical practice guideline addresses three clinical questions in adults with cancer: (1) How should clinicians and adults with cancer communicate about cannabis and/or cannabinoids? (2) Does use of cannabis and/or cannabinoids by adults improve cancer-directed treatment? (3) Does use of cannabis and/or cannabinoids by adults with cancer reduce treatment-related toxicities, palliate cancer symptoms, or improve quality of life (QOL)?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A2). Four full panel meetings were held, and members were asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, and draft content and to review and approve drafts during the entire guideline development. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the panel via email to coordinate the process to completion. The guideline recommendations were sent for an open-comment period of 2 weeks allowing the public to review and comment on the recommendations after

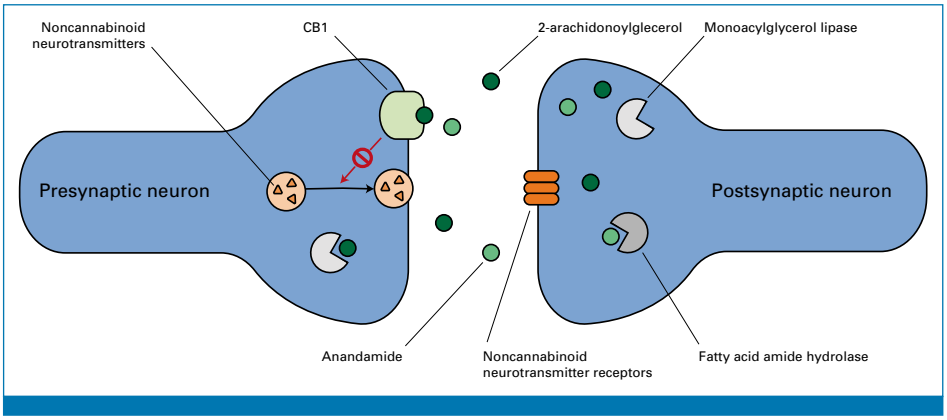

FIG 1. Endocannabinoid System. The endocannabinoid system exerts a widespread neuromodulatory effect. Research has identified two endocannabinoids (anandamide and 2-arachidonoylglycerol), two catabolic enzymes (ie, fatty acid amide hydrolase and monoacylglycerol lipase), and two main endocannabinoid g-protein–coupled receptors (CB1 and CB2). CB1 receptors are found at high concentrations in the brain and peripheral nervous system, operating in a retrograde fashion (ie, endocannabinoids bind to CB1 receptors on presynaptic terminals) to modulate activity of several other noncannabinoid neurotransmitters. CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2.

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submitting a confidentiality agreement. Public comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. All funding for the administration of the project was provided by ASCO.

A systematic review of the literature provided the evidence base for the guideline. PubMed and the Cochrane Library were searched for systematic reviews, randomized controlled trials (RCTs), and cohort studies published from the database's inception to January 27, 2023. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: Adults (18 years or older) with solid tumors or hematologic malignancies, including long-term survivors and those at the end of life;
- Interventions: Cannabis and/or cannabinoids, including pharmaceuticals;
- Comparisons: Placebo, an active comparator, or usual care;
- Outcomes: Antineoplastic effects (response rate, progression-free survival, disease-free survival, overall survival), cancer symptoms, toxicity of cancer treatment, or QOL.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (3) published in a language other than English.

A guideline implementability review was conducted. On the basis of the review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of the recommendation and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[34,35] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. When little or no direct evidence was available, the Expert Panel considered the appropriateness of providing good practice statements on the basis of discussion and criteria provided by the GRADE Working Group.[36] Good practice statements are recommendations that are important and actionable but not appropriate for formal ratings of the quality of the evidence.[36]

The ASCO Expert Panel and guidelines staff will work with co-chairs and Expert Panel to update these guidelines with any substantive changes as evidence emerges. On the basis of a formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This manual is the most recent information as of the publication date.

TABLE 1. Taking an In-Depth History of Cannabis and/or Cannabinoid Use

Topic of Inquiry	Sample Response
Goals of use	Treat cancer Manage side effects or symptoms Improve quality of life Achieve euphoria or a high feeling
Product supply	Medical cannabis dispensary Adult-use cannabis dispensary Homegrown Pharmacy Informal source
Formulations	Ratios of active ingredients (eg, THC and CBD) Inactive ingredients (eg, coconut oil) Herbal (eg, whole leaf, concentrates, distillates) *v* synthetic
Route(s) of administration	Smoked Vaporized Vaped Oral Topical Rectal/vaginal
Dosing schedule	As needed Nightly Twice daily
Perceived benefits	Antineoplastic effects Nausea/vomiting Appetite Sleep Pain Anxiety Mood Quality of life Other
Adjunct *v* replacement antineoplastic strategies	Use as an adjunct to standard treatments Use as a replacement for standard treatments
Use history	Age of first use Presence of cannabis-use disorder
Concomitant medications	Other psychoactive drugs Drug-drug interactions (eg, warfarin, buprenorphine, tacrolimus)
Contraindications	History of psychosis Current elevated liver enzyme for those considering CBD ≥ 300 mg per day[21]
Information source(s)	Clinicians Scientific press Cannabis dispensaries Lay press or internet Friends and/or family

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 366 publications were identified in the literature search. After applying the eligibility criteria, 16 remained: 11 systematic reviews[24,25,27-30,32,37-40] and five RCTs or cohort studies not captured by the included systematic

TABLE 2. Summary of Recommendations Pertaining to Use of Cannabis and/or Cannabinoids for Cancer Symptoms, Toxicity of Cancer Treatment, or QOL

Outcome	Certainty of the Evidence	Direction of Effect	Recommendation
Chemotherapy-induced nausea and vomiting[22,24-26]	Moderate for dronabinol and nabilone; low for THC:CBD extract	Benefit	Weakly in favor (see recommendation 3.1)
Total symptom burden in adults with advanced cancer[21]	Low for high-dose oral CBD	—[a]	Weakly against (see recommendation 3.2)
Cancer pain[27,28]	Moderate for nabiximols	—[a]	None
Sleep, in patients with chronic cancer pain[29]	Moderate for oral cannabinoids (nabiximols or nabilone)	—[a]	None
Low weight or poor appetite[30,31]	Low for dronabinol, nabilone, THC/CBD extract, THC	—[a]	None
Quality of life[21,30,32]	Low for THC, THC/CBD, dronabinol, nabilone, and CBD	None or small detrimental effect	None
Anxiety and depression[33]	Very low for THC, THC:CBD, dronabinol, nabilone, nabiximols	—[a]	None

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.
[a]No clear evidence of benefit or harm in relation to specified outcome.

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reviews.[21,26,41-43] After the completion of the literature search, the Multinational Association for Supportive Care in Cancer (MASCC) published two additional cannabis systematic reviews, one on psychological symptoms[33] and one on cancer pain.[44] These publications were added to the current review.

In RCTs of cannabis and/or cannabinoids concerning treatment toxicity or symptom management in oncology, the primary outcomes of interest have been chemotherapy-induced nausea and vomiting (CINV); cachexia, poor appetite, and weight loss; and pain. Studies have also reported on sleep, QOL, and mood outcomes. Limitations of this body of evidence include varying interventions, lack of standardized universal good manufacturing practices, small sample sizes, short follow-up, and limited information regarding effectiveness in the setting of current supportive care practices. Few studies have addressed antineoplastic effects in adults with cancer, including potential interactions with various systemic cancer therapies. Nevertheless, one emerging question is whether cannabis negatively affects outcomes in adults with cancer receiving immunotherapy. Characteristics and results of included studies are provided in the Data Supplement (online only).

Evidence Quality Assessment

The quality of evidence was assessed for each outcome of interest. This rating includes factors such as study design, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect, assessed by one reviewer. Evidence quality ratings for cannabis and/or cannabinoids in relation to cancer symptoms, treatment toxicity, and QOL are provided in Table 2, with additional tables and details provided in the Data Supplement. Refer to Appendix Table A1 for definitions of the quality of the evidence and the Methodology Manual (available at www.asco.org/guideline-methodology) for more information. For cannabinoids other than the US Food and Drug Administration (FDA)–approved products, evidence was very low or low for all outcomes.

RECOMMENDATIONS

Clinical Question 1

How should clinicians and adults with cancer communicate about cannabis and/or cannabinoids?

Recommendation 1.1

Health systems and clinicians, in partnership, should provide adults with cancer unbiased, evidence-based cannabis and/or cannabinoid educational resources to facilitate clinical communication, informed decision making, and systematized approaches to care (Good practice statement).

Recommendation 1.2

Given the high prevalence of cannabis and/or cannabinoid use among adults with cancer, clinicians should routinely and nonjudgmentally inquire about cannabis use (or consideration of use) and either guide care or direct adults with cancer to appropriate resources (Good practice statement).

Note. Clinicians should remain sensitive to cannabis regulations' disproportionate impacts on marginalized communities and work to omit cannabis-related and other biases (eg, racial, ethnic, and socioeconomic) from clinical discussions about cannabis and/or cannabinoids. Table 1 offers suggestions for cannabinoid history taking.

Recommendation 1.3

When adults with cancer use cannabis and/or cannabinoids outside of evidence-based indications or clinician

recommendations, clinicians should explore goals, educate, and seek to minimize harm (Good practice statement).

Literature review and analysis. The literature review did not identify any publications that met the inclusion criteria.

Clinical interpretation. Translating these guidelines into clinical practice calls for the recognition of key points. To mitigate both undue task burden on ground-level clinicians and variability in clinical practice, recommendation 1.1 calls on health systems to participate in the provision of unbiased, evidence-based cannabis and/or cannabinoid educational resources and to systematically disseminate them to all in patient-facing roles. Such system-level action empowers members of multidisciplinary oncology clinical teams broadly to guide adults with cancer to cannabis and/or cannabinoid educational resources deemed appropriate by their organization.

Recommendations 1.2 and 1.3 also encourage clinicians to explore the role of cannabis and/or cannabinoids for symptom management, proactively or in response to patient or caregiver requests. When faced with a dearth of effective options with higher levels of evidence, consideration of cannabis and/or cannabinoids for symptom relief—specifically for refractory CINV when standard-of-care antiemetic regimens are ineffective—now falls within accepted standards of oncologic practice.

Clinical Question 2

Does use of cannabis and/or cannabinoids by adults improve cancer-directed treatment?

Recommendation 2.1

Clinicians should recommend against use of cannabis and/or cannabinoids to augment cancer-directed treatment unless in the context of a clinical trial (Type: Evidence based; Evidence quality: Very low; Strength of recommendation: Weak).

Recommendation 2.2

Clinicians should recommend against use of cannabis and/or cannabinoids in place of cancer-directed treatment (Type: Informal consensus; Evidence quality: Very low; Strength of recommendation: Strong).

Note. Cannabis and/or cannabinoids used as cancer-directed treatment may cause significant clinical (eg, fatigue, confusion, high feeling) and financial toxicities without good-quality evidence of clinical benefit.

Literature review and analysis. Evidence regarding antineoplastic effects of cannabis and/or cannabinoids is limited.[37,38] A phase Ib RCT of 21 individuals with recurrent glioblastoma after radiotherapy and first-line chemotherapy with temozolomide reported that the addition of nabiximols (a pharmaceutical 1:1 THC:CBD sublingual metered-dose spray) to dose-intense temozolomide had acceptable safety and tolerability. The study did not identify any drug-drug interactions.[45] Owing to the high interpatient variability in pharmacokinetics and pharmacodynamics of nabiximols, dosing was individualized to 3-12 sprays/day, on the basis of a dose-ranging trial in adults with chronic pain.[46] Investigators also explored an efficacy end point of 6-month progression-free survival (PFS) and 1-year overall survival (OS). Although PFS at 6 months was the same, 1-year survival was higher in the nabiximols arm than in the placebo arm. Of note, the small study was not powered for survival as an end point. The investigators recommended further exploration in an adequately powered RCT.[45]

The possibility that cannabis and/or cannabinoids may worsen outcomes among adults with cancer treated with immunotherapy has been reported by two cohort studies.[47,48] In a prospective observational study of 102 consecutive adults with advanced cancer treated with immunotherapy (n = 68 immunotherapy alone, n = 34 immunotherapy plus cannabis), use of cannabis was associated with a shorter median time to progression (3.4 months *v* 13.1 months, $P = .003$) and shorter median OS (6.4 months *v* 28.5 months, $P = .0009$).[47] Additionally, in a retrospective study of 140 adults with advanced cancer treated with nivolumab, cannabis use was not significantly associated with PFS or OS but was associated with a lower treatment response rate (15.9% *v* 37.5%, $P = .02$).[48] Given the study design limitations, these data are hypothesis-generating, requiring further validation. A 2023 MASCC guideline nonetheless recommended against cannabinoids for any indication among adults with cancer receiving a checkpoint inhibitor.[44]

Clinical interpretation. Discordance between the Expert Panel's recommendation against cannabis and/or cannabinoids as an anticancer treatment and the plethora of anecdotes supporting their use warrants discussion. Online information about cannabis and/or cannabinoids as cancer cures is widespread, if often misaligned with scientific evidence. Such misinformation can spur unrealistic expectations for cancer treatment that is natural and free from side effects.[49] Indeed, online searches for cannabis and cancer have increased 10 times the rate of searches for standard therapies, with cannabis as a cancer cure representing the largest category of searches on alternative cancer treatments.[50] In a recent review, the top false news story claiming cannabis and/or cannabinoids as a cancer cure generated over 100-fold more social media engagements than the top evidence-based accurate news article debunking the story.[50] This trend is not limited to the online space. In a review of 77 unique case reports describing adults with various cancers using cannabis and/or cannabinoids as a cancer-directed treatment, the supporting evidence was judged to be weak in more than 80% of cases.[51] Unfortunately, a published series of adults with cancer receiving cannabis and/or cannabinoids excluded those receiving <6 months of treatment while disregarding the concomitant conventional anticancer treatment in nearly all patients.[52] This perhaps well-intentioned but uncritical approach to reporting data

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was perpetuated in a recent review,[53] which used a social media report as evidence of continuing cannabis and/or cannabinoid benefit. These problems reinforce the need for high-quality evidence to support clinical interventions before incorporating cannabis and/or cannabis as anticancer agents.

With immunotherapy. A specific issue pertains to combining cannabis and cannabinoids with anticancer immunotherapies. Immunotherapies are established treatment strategies to activate the immune system to recognize and attack cancer cells. Immunotherapies changed the outcome of many cancers and even provided potential cures in metastatic disease. Nevertheless, efficacy is often limited because of local tumor-induced immune suppression. While broadly, cannabis and/or cannabinoids have anti-inflammatory properties, which may be beneficial in reducing cancer-associated inflammation, such properties are likely strongly undesirable during targeted activation of T-cell–specific anticancer immunotherapy. Cannabinoids modulate various aspects of the immune system: the proliferation, activation, and cytotoxic activity of T cells; the production of cytokines and chemokines by granulocytes; the function of dendritic and natural killer cells; the chemotactic capacity of neutrophils; and/or the rapid expansion and recruitment of immunosuppressive immature myeloid cells and myeloid-derived suppressor cells.[54-56] Prolonged cannabis consumption could possibly interfere with immunotherapy and hinder humoral immunity.

Although the interaction between cannabinoids and anticancer immunotherapy is likely complex and incompletely understood, recent studies provide clinically relevant observations. For example, cannabis consumption was associated with reduced response rates to nivolumab.[48] In a prospective follow-up study of adults with various metastatic cancers initiating immunotherapy, cannabis consumption correlated with a significant decrease in time to tumor progression and decreased OS.[47] A similar study assessing cannabis' influence on immune checkpoint inhibitors' efficacy in adults with non–small cell lung cancer reported numerically lower OS in cannabis users, not reaching statistical significance.[57] Preclinical and clinical data describe the mechanistic potential for adverse effects of cannabis use during immunotherapy treatment through suppression of T-cell antitumor immunity by inhibiting Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling through cannabinoid receptor type 2.[58] This study showed that THC directly reduced the therapeutic effect of PD-1 blockade. Similarly, the endogenous cannabinoid anandamide also impeded antitumor immunity, indicating an immunosuppressive role of the endogenous cannabinoid system. Continued collection of real-world data in patients who are concomitantly using immunotherapy and cannabis and/or cannabinoids is important.

With radiotherapy. The literature search did not identify any relevant publications investigating the anticancer use of cannabis and/or cannabinoids in combination with radiotherapy. However, a more recent phase I study of CBD in patients with recurrent prostate cancer after definitive localized therapy with either prostatectomy or primary radiotherapy to the prostate reported on safety and tolerability in this setting.[59]

Clinicians and adults with cancer should be aware of (1) the lack of evidence-based data supporting use of cannabinoids and/or cannabis as anticancer treatments and (2) preliminary observational data reporting poor clinical outcomes in adults receiving immunotherapy while using cannabis and/or cannabinoids. On the basis of available data, clinicians should advise caution for adults receiving immunotherapy using or considering use of cannabinoids and/or cannabis.

Clinical Question 3

Does use of cannabis and/or cannabinoids by adults with cancer reduce treatment-related toxicities, palliate cancer symptoms, or improve QOL?

Recommendation 3.1

Adults with cancer who receive moderately or highly emetogenic antineoplastic agents with guideline-concordant antiemetic prophylaxis and experience refractory nausea or vomiting may augment their antiemetic regimen with dronabinol, nabilone, or a quality-controlled oral 1:1 THC:CBD extract (Type: Evidence based; Evidence quality: Moderate for dronabinol and nabilone, Low for 1:1 THC:CBD extract; Strength of recommendation: Weak).

Note. Cannabis and/or cannabinoids are only one of several pharmacologic options for adults with cancer experiencing refractory nausea and vomiting despite optimal prophylaxis. For such individuals, the 2020 ASCO antiemetics guideline[22] recommends the addition of olanzapine (if not already prophylactically administered), otherwise the addition of an antiemetic from a different class (eg, a neurokinin–1 [NK1] receptor antagonist, dopamine receptor antagonist, benzodiazepine, or synthetic THC).

Recommendation 3.2

Outside of a clinical trial, clinicians should not recommend that adults with cancer use 300 mg or more per day of, oral CBD to manage symptom burden due to lack of proven efficacy and risk for reversible liver enzyme abnormalities (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

Note. In adult and pediatric populations without cancer, reversible liver enzyme abnormalities primarily occurred in study participants taking 300 mg or more per day of oral CBD.[23]

Recommendation 3.3

Evidence remains insufficient to recommend for or against cannabis and/or cannabinoids in managing cancer treatment-related toxicities or symptoms (including cancer pain), aside from clinical settings addressed in

recommendations 3.1 and 3.2 or within the context of a clinical trial (Table 2).

Literature review and analysis.

CINV. The effects of adding cannabis and/or cannabinoids to current antiemetic regimens remain uncertain, as most CINV studies were conducted before the availability of evidence-based guidelines and modern antiemetic prophylactic regimens,[22,60] including triple prophylaxis (combination of an NK1 receptor antagonist, 5HT3 receptor antagonist, and corticosteroid) and quadruple prophylaxis (triple prophylaxis plus olanzapine).[61] A 2015 Cochrane review of nabilone and dronabinol in relation to CINV reported benefits in some measures of nausea and/or vomiting,[25] as did a 2020 systematic review of oral cannabinoids.[24] Oral cannabinoids were accompanied by increased dysphoria, euphoria, and sedation.[24] A majority of the studies included in these analyses were published in the 1970s and 1980s.[24,25]

Suggestive evidence of the benefit of adding cannabis and/or cannabinoids to current antiemetic regimens is provided by a 2020 randomized phase II trial,[26] with a phase II/III update recently presented at the ASCO 2023 Annual Meeting.[62] This Australian trial enrolled adults with cancer who experienced CINV during moderately or highly emetogenic chemotherapy despite guideline-consistent antiemetic regimens. In a blinded crossover design, adults with cancer received one cycle of 1-4 self-titrated capsules of oral THC 2.5 mg:CBD 2.5 mg three times daily from the day before chemotherapy to 5 days after, as well as one such cycle of placebo. During the third chemotherapy cycle, adults with cancer received their preferred intervention, still blinded. The primary outcome was complete response (no vomiting and no rescue medication during hours 0-120). The phase II published complete response rates were 25% with oral THC:CBD and 14% with placebo (relative risk, 1.77 [90% CI, 1.12 to 2.79]). Eighty-three percent of adults with cancer preferred the oral THC:CBD regimen over placebo. These data support the use of oral THC:CBD cannabis extract in adults who experience CINV during moderate and highly emetogenic intravenous chemotherapy regimens despite guideline-consistent antiemetic prophylaxis.

The 2022 MASCC guideline on cannabinoids for GI symptoms in adults with cancer suggests against use of cannabinoids in the following circumstances: treatment of nausea and vomiting unrelated to chemotherapy; first-line treatment in the prevention of CINV; and prevention of radiotherapy-induced nausea and vomiting.[40] The MASCC guideline suggests that cannabinoids may be considered for refractory CINV in adults with cancer who are not on checkpoint inhibitors.[40]

Radiation-induced nausea and vomiting. Fewer studies have addressed cannabis and/or cannabinoids in relation to nausea and vomiting in patients receiving radiotherapy. Most RCTs were conducted in the 1980s and did not provide clear evidence of benefit.[63] A 2016 trial compared nabilone with placebo in patients receiving radiotherapy for head and neck cancer. Nausea and use of antiemetic medications were secondary outcomes and did not vary significantly by study arm.[41]

Weight and appetite. A 2022 systematic review and meta-analysis evaluated cannabis and/or cannabinoids with cachexia outcomes.[30] The four included RCTs assessed THC 2.5 mg[64]; a cannabis extract with THC 2.5 mg and CBD 1 mg[64]; dronabinol[65,66]; and nabilone.[67] Cannabinoids did not have a statistically significant effect on appetite on the basis of a meta-analysis of three RCTs and very low quality of evidence. Two RCTs reported on weight, without any benefit in either trial. Compared with an active comparator (megestrol acetate) or placebo, cannabinoids were associated with a small detriment in QOL. The lack of benefit reported for cachexia outcomes is consistent with the 2020 ASCO cachexia guideline, which provided a weak recommendation against cannabinoids for treating cachexia in adults with advanced cancer.[31]

Pain. A 2021 systematic review evaluated noninhaled medical cannabis or cannabinoids in adults with chronic cancer or noncancer pain.[28] Four RCTs focusing on cancer pain[68-70] (one publication addressed two trials[70]) compared nabiximols with a placebo. In a meta-analysis, the relationship between nabiximols and pain (as assessed by 10-cm visual analog scale [VAS]) was not statistically significant (mean difference [MD], −0.10 [95% CI, −0.28 to 0.09]). In studies of noncancer pain, a meta-analysis of 23 RCTs indicated a small but statistically significant improvement in patient-reported pain with the intervention (MD, −0.63 [95% CI, −0.96 to −0.29]). A nonsignificant effect of cannabinoids on cancer pain was also reported in a 2020 meta-analysis of five RCTs.[27] The 2023 MASCC guideline on cancer-related pain does not recommend cannabinoids for cancer pain outside of an RCT.[44]

Sleep. A 2022 meta-analysis evaluated cannabinoids and sleep among adults with cancer pain, noncancer pain, or other conditions.[29] On the basis of five RCTs, cannabinoids were associated with a very small improvement in sleep in adults with cancer pain (weighted mean difference [WMD] on a 10-cm VAS, −0.19 [95% CI, −0.36 to −0.03], moderate certainty of evidence). A larger benefit was observed in 11 RCTs of patients with noncancer pain (WMD, −0.99 [95% CI, −1.41 to −0.57], high certainty of evidence, $P = .001$ for interaction).

Anxiety and depression. A 2023 MASCC systematic review assessed cannabis in relation to anxiety, depression, and insomnia.[33] The review noted that none of the included studies addressed psychological symptoms as primary outcomes in adults with cancer. The authors concluded that no recommendation was possible regarding use of cannabis for anxiety or depression.[33] An additional RCT published after the search window of the MASCC review addressed CBD oil versus placebo in patients with advanced cancer. Anxiety was a secondary outcome and did not differ significantly between study arms.[21]

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Total symptom burden. A phase IIb RCT compared CBD oil with placebo in 144 adults receiving palliative care for advanced cancer.[21] The intervention consisted of CBD oil 100 mg/mL, with a dose titrated every third day from 0.5 mL once daily to a maximum of 2 mL three times daily. The median patient-selected dose of CBD was a total of 400 mg per day. The primary outcome—change in Total Symptom Distress Score as measured by the Edmonton Symptom Assessment Scale (ESAS)[71]—did not differ significantly between study arms. Of note, however, the ESAS queries in-the-moment symptom burden, which, in a palliative care population, is likely to be volatile in a given day, let alone across the 2 weeks separating comparison time points in this study.

Quality of life. A 2022 systematic review evaluated cannabis in relation to QOL and symptoms among patients with advanced cancer who were receiving palliative care. Six RCTs reported on QOL, with no clear evidence of benefit. QOL, however, tended to be a secondary outcome.[32] QOL was also reported in a 2022 systematic review of THC, THC plus CBD, dronabinol, and nabilone in relation to appetite and weight.[30] The intervention did not improve appetite or weight and had a small, detrimental effect on QOL (standardized mean difference, −0.25 [95% CI, −0.43 to −0.07]). In patients undergoing radiotherapy for head and neck cancer, a 15-point improvement in the global QOL scale of the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) was the primary outcome of a 2016 RCT.[41] Fifty-six patients were randomly assigned to 7 weeks of nabilone or placebo. Twenty-four patients dropped out before the end of the study. No statistically significant differences existed between study arms in QOL or specific symptoms. QOL was a secondary outcome in a trial of CBD oil versus placebo in relation to total symptom burden among patients with advanced cancer. QOL did not vary significantly by study arm.[21]

Clinical interpretation. Limited high-quality clinical evidence exists on using cannabis and/or cannabinoids for management of cancer treatment-related toxicities, palliation of cancer symptoms, or improvement of QOL with cancer. Yet, the current evidence, as summarized, provides opportunities for clinical interpretation and future directions. Most extant research focuses on THC, with only one study evaluating CBD (on symptom burden).[21] The THC studies show varying and conflicting effects ranging from pain relief, improved appetite, and improved sleep to dysphoria and slight worsening of QOL. There are several possible explanations for these conflicting results.

Biphasic effects. In preclinical models, cannabinoids exhibit biphasic effects including excitatory versus depressant, anxiolytic versus anxiogenic, and hypoalgesia versus hyperalgesia.[72] This biphasic phenomenon has also been reported in human studies: lower doses of THC reduce pain, whereas higher doses increase pain and anxiety.[73,74] In a previously cited study,[68] three doses of nabiximols (low, medium, and high) were compared with placebo. Overall, there was no difference between nabiximols and placebo, but in a secondary analysis, the low and medium doses met the primary end point, whereas the high dose did not. These potentially opposing effects of THC at low and high doses highlight the need for more studies focusing on specific formulations, dosing, and target plasma levels. Furthermore, dosing of THC is challenging because of the heterogeneity of available products, individual differences in pharmacokinetics and metabolism, and mode of consumption (eg, inhaled versus ingested).[75] Although THC appears to have a dose-dependent reduction in nausea and improvement in sleep, this may come at the expense of adverse effects, possibly explaining the poor results on QOL.

Synthetic cannabinoids. In addition to the possible biphasic effects of the cannabinoids, there are differences in potency between natural and synthetic THC. Synthetic cannabinoids, particularly agonists of cannabinoid receptors, are more potent than natural cannabinoids and may lead to more severe adverse effects.[76] Furthermore, synthetic THC may lead to overstimulation of the endocannabinoid system, resulting in negative effects on treatment-related toxicities, cancer symptom palliation, or effects on QOL.

Refractory CINV. The integration of cannabis and/or cannabinoids in refractory CINV requires particular attention, given the early, promising data to support their use. Results of a recent phase II/III trial support using oral THC and CBD in a 1:1 ratio for adults with cancer who experienced CINV during moderately or highly emetogenic chemotherapy despite guideline-consistent antiemetic regimens.[26,62] Data indicated improved complete response (no vomiting and no use of rescue medications) and no significant nausea. Clinicians, adults with cancer, and caregivers should all note that these study participants received quality-assured capsules; each capsule contained THC 2.5mg: CBD 2.5mg. Participants could self-titrate from 1 up to 4 total capsules per day (THC 10mg: CBD 10mg), as tolerated. The availability of similar regulated products across all clinical settings is highly variable. Moreover, despite most participants receiving then-guideline-concordant antiemetic triple prophylaxis, only 10% received quadruple prophylaxis with olanzapine. Quadruple prophylaxis that includes olanzapine is recommended for patients who receive high-emetic risk antineoplastic therapies.[22]

It is also important to place recent study results[26] within the context of limited data supporting other cannabinoid interventions for refractory CINV. In cases of refractory CINV due to moderate to highly emetogenic intravenous chemotherapy, synthetic cannabinoids such as dronabinol and nabilone may be used as salvage antiemetics.[22,77] Oral dronabinol may be started at a 2.5 mg dose three times a day and can be up-titrated to 10 mg three to four times daily. Oral nabilone may be initiated at 1 mg twice daily and up-

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titrated to a maximum of 2 mg four times daily.[78] No dose modifications are required for renal or hepatic impairment. However, the adverse effects and risk for drug interactions can be a significant dose-limiting barrier, especially for adults with cancer and advanced age who frequently experience polypharmacy.[79]

Common challenges when using cannabis and/or cannabinoids include a sense of euphoria, drowsiness, dizziness, vertigo, and hallucinations.[80] For example, in the phase II study of cannabis extract for refractory nausea and vomiting, participants reported sedation (19%), dizziness (10%), and disorientation (3%).[26] Therefore, in addition to appropriate patient selection, clinicians must address key clinical considerations, including counseling, formulation choice, administration route, side effects assessment, and optimal dose titration using a start low, go slow approach while balancing potential risks and benefits.

DISCUSSION

Access to cannabis and cannabinoids has outpaced the science supporting evidence-based indications for their use. Simultaneously, anecdotal experience among adults with cancer using cannabis and/or cannabinoids continues to promote strong incentives for use despite an absence of objective evidence, creating ongoing clinical challenges and opportunities in the care of adults with cancer. Consequently, the Expert Panel believes addressing the lack of high-quality clinical evidence is critical.

PHARMACOKINETICS AND PHARMACODYNAMICS

The specification and concentration of the hundreds of bioactive ingredients in the cannabis plant vary by strain.[81] Nearly universal to all species is the presence of THC and CBD. The pharmacokinetics of THC and CBD, including their bioavailability, vary according to formulation and route of administration. For example, the body will only absorb about 4%-12%[82] of orally ingested THC versus 10%-35%[83] of inhaled THC. Once absorbed, cannabinoids are rapidly distributed systemically. The psychoactive effects of inhaled or smoked cannabis generally occur in seconds to minutes and last 2-3 hours. By contrast, oral THC onset is 30 minutes to 2 hours, lasting 5-8 hours.[84,85] Importantly, adults with cancer who are unfamiliar with using oral cannabis products must be cautioned that the onset may be ≥1 hour after ingestion; they should also be careful about stacking doses to avoid side effects (eg, euphoria, drowsiness, dizziness, vertigo, hallucinations, mood changes).[86,87] Furthermore, administration with a high-fat meal significantly increases oral cannabinoid absorption and may exacerbate these effects. Dosing should start at the lowest possible dose and be increased gingerly with sufficient time between doses to gauge effects. Most cannabinoids, including THC, are highly lipid soluble, resulting in adipose tissue accumulation.[88] This phenomenon can lead to a gradual release of stored THC after periods of adipose breakdown, frequently occurring in adults with cancer.

Cannabis and/or cannabinoids have a range of biological actions, including inhibition of the cytochrome P450 family of enzymes (specifically CYP3A4, UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19).[89] Consequently, there is a potential for drug-drug interactions mediated through altered drug metabolism pharmacokinetics. A review reported a generally low probability of clinically relevant drug interactions with cannabis and/or cannabinoids. [90] However, drug interactions with warfarin were classified as very high risk and buprenorphine and tacrolimus as high risk.[90] Cytochrome P450 family enzymes are also responsible for the metabolism of many established chemotherapeutics, potentially increasing the toxicity or decreasing the potency of proven therapies.[91,92] There is a considerable body of preclinical work investigating the potential interactions between cannabis and/or cannabinoids with systemic anticancer agents, but very few include in vivo pharmacokinetic studies.[93] Similarly, there are only scant clinical data on such interactions. A study in adults taking cannabis (as an herbal tea) showed no significant impact on clearance of, or exposure to, either irinotecan or docetaxel.[94] There were no apparent effects of nabiximols on the pharmacokinetics of temozolomide in another small clinical study.[45] A clear limitation of both studies is that, by the nature of cannabis and cannabinoids, it is not possible to extrapolate these clinical findings to other cannabis and/or cannabinoid preparations, never mind other cytotoxic agents. The paucity of available data on drug-drug interactions is a concern as, in most cases, clinicians will be unable to provide informed, scientifically supported answers as to the potential for cannabis and/or cannabinoids interactions with approved anticancer therapeutics.

POTENTIAL SHORT- AND LONG-TERM RISKS

While, with appropriate dosing and titration, cannabis and/or cannabinoids are well tolerated, adults with cancer considering their use should be aware of both common side effects (eg, dizziness, confusion, dry mouth, and fatigue) and more serious side effects (eg, as tachycardia, orthostatic hypotension, severe confusion, and paranoia). To minimize adverse effects, particularly in older adults and in those naïve to cannabis and/or cannabinoids, products should be started at a low dose and slowly increased until the desired effect (eg, antiemesis) is achieved.[80] Notably, adults with cancer who ingest excessive cannabis and/or cannabinoids are not at risk for respiratory depression as they might be with inappropriately dosed opioids. Nevertheless, cannabis and/or cannabinoid overdoses can be distressing and multiple poorly controlled acute symptoms may place an individual at high risk for falls and health care utilization.

Although free of many of THC's neuropsychiatric liabilities, CBD presents risks for hepatotoxicity. A meta-analysis

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outside of oncology, primarily in adults and children with seizures and neurogenerative disorders, reported a nearly 6-fold increase in liver enzyme elevation and drug-induced liver injury. Particularly, the pooled proportion of elevated liver enzymes was 0.07 (95% CI, 0.05 to 0.12), whereas the pooled proportion of those with drug-induced liver injury was 0.03 (95% CI, 0.10 to 0.06). No cases were reported in adults using a total CBD dose of <300 mg/day.[23] The package insert for CBD, FDA-approved for pediatric epilepsy and administered twice daily at 5-25 mg/kg/day, describes dose-related, reversible transaminase elevations, typically occurring in the first 2 months after CBD initiation and with 13% reaching three times the upper limit of normal. One-third resolved spontaneously, and the remaining cases improved after dose reduction or treatment discontinuation.[95] In studies of CBD-predominant products employed in adult oncologic populations, effects on hepatic enzymes have not been reported.[21,96-98] Both the monitoring of liver enzymes with CBD use, as well as the consideration of possible CBD effect in the setting of new or worsening hepatotoxicity, may nonetheless be important in the cancer setting.

Clinicians, adults with cancer, and caregivers should understand the degree of risk for the emergence of long-term side effects with cannabis and/or cannabinoid use.

- GI: *Cannabinoid hyperemesis syndrome* after long-standing cannabis use (ie, >4 times per week for over a year) is an increasingly recognized clinical scenario characterized by cyclical emetic episodes, mimicking cyclic vomiting syndrome, and relieved by hot showers.[99,100] High-dose cannabis use precedes the development of cannabis hyperemesis in most cases. Treatment focuses on cannabis cessation.[101]
- Cardiovascular: Cardiovascular side effects may include arrhythmias and orthostatic hypotension, but there is no evidence that cumulative lifetime use is associated with a higher incidence of cardiovascular disease or associated mortality.[102]
- Respiratory: Conflicting data exist regarding cannabis use and respiratory disease, often confounded by concomitant nicotine use. It remains unclear if cannabis use is associated with impaired lung function, asthma, chronic obstructive pulmonary disease, and pneumonia risks.[103-105]
- Oncologic: No clear evidence demonstrates that cannabis inhalation increases risk of lung cancer.[106,107] The association between cannabis use and cancer development remains unclear, except for a possible link with testicular cancer.[107]
- Psychiatric: In addition to risk for long-term physical side effects, chronic cannabis use carries long-term psychiatric risks, which may be correlated with cumulative exposure including age of first use. Cannabis and/or cannabinoid use may be associated with an increased risk for developing depressive disorders[108] and may exacerbate psychiatric disorders in vulnerable individuals.[109] Ten percent of adults with chronic cannabis use may also develop *cannabis use disorders*,[110] associated with clinically significant impairment or distress, including using more cannabis than expected and difficulty in cutting back on use.[111,112] Data specific to cannabis use disorder in adults with cancer are lacking. Outside of oncology, a randomized trial found that participants who received a medical cannabis card had an almost two times greater incidence (17% versus 9%) of developing cannabis use disorder within 12 weeks than controls without a medical cannabis card.[113] The early onset of cannabis use, especially weekly or daily use, strongly predicts future dependence.[114] Clinicians should also recognize that long-term daily cannabis users may experience non–life-threatening withdrawal symptoms after cessation of cannabis, including irritability, restlessness, anxiety, sleep disturbances, appetite changes, and abdominal pain. Symptoms usually occur within 3 days after cessation and may last up to 14 days.[115]
- Driving Safety: Cannabis users are also at higher risk of motor vehicle accidents. A meta-analysis of nine epidemiologic studies found that cannabis use by drivers was associated with a significantly increased risk of crash involvement. Specifically, drivers who test positive for cannabis or self-report using cannabis are more than twice as likely as other drivers to be involved in motor vehicle crashes.[116] For example, with the increasing access to cannabis across the United States from 2000 to 2018, the percentage of fatal motor vehicle accidents involving cannabis alone and cannabis with alcohol has increased, specifically from 9.0% in 2000 to 21.5% in 2018 for cannabis alone and 4.8% in 2000 to 10.3% in 2018 for cannabis with alcohol. Furthermore, higher blood levels of cannabis are associated with an increased risk of fatal motor vehicle accidents coinvolving alcohol.[117] Therefore, cannabis use while driving remains a serious topic to discuss with adults with cancer using cannabis and/or cannabinoids.

PATIENT AND CLINICIAN COMMUNICATION ABOUT MEDICAL CANNABIS

Cannabis and/or cannabinoid use continues to be addressed in stigmatizing ways within health care settings. Adults with cancer may be reticent to discuss their interest or use with clinicians because of fears about being censured.[118] To promote the safe, appropriate, and effective use of cannabis and/or cannabinoids, clinicians, adults with cancer, and their caregivers should engage in open, nonjudgmental conversations about the potential risks and benefits of their use in cancer care. These conversations should omit pejorative terms commonly associated with substance use (eg, user, addict) and reflect the language used by the adult with cancer and their caregiver. For example, while marijuana is perceived by some communities to be a racialized term associated with cannabis prohibition,[119] it may be the preferred term for some with cancer and their caregivers.

Clinicians should invite adults with cancer to express their knowledge, attitudes, and goals of care related to cannabis

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and/or cannabinoids, as well as prior and current history of use (Table 1). The latter may include an assessment of the amount and types of cannabis products taken, including the THC:CBD ratio, and mode(s) of administration (eg, inhaled, ingested, transdermal). The perceived effectiveness and side effects of cannabis and/or cannabinoids should also be explored. Clinicians may favor formally sourced cannabis products (eg, from a medical dispensary) over those informally sourced. In many jurisdictions, the former will have undergone testing of key cannabinoid concentrations, as well as for the presence of heavy metals and contaminants.

Clinicians should also provide recommendations to adults with cancer regarding driving or engaging in safety-sensitive work (eg, working with vulnerable populations, operating heavy equipment) after the consumption of cannabis and/or cannabinoids when cognitive and physical impairment is likely (up to 12 hours, depending on the type of cannabis product). Table 3 provides some general safety points. Given the varying legal status of medical and nonmedical cannabis in different jurisdictions, it is prudent to discuss with adults with cancer and their caregivers how medical cannabis and/or cannabinoids are regulated in their region and how to access legal, quality-controlled sources to avoid interactions with law enforcement. For clinicians who lack knowledge and training related to medical cannabis or feel uncomfortable discussing the topic, a referral to a regional medical cannabis specialist or clinic may optimize comprehensive and informed care. Oncology clinicians should maintain ongoing communication with these clinical partners to ensure safe cannabis and/or cannabinoid use.

TABLE 3. General Safety Awareness

Potential for Risk	Management Strategies
Storage	Although best practices for safekeeping are not defined, accidental exposures to cannabinoid products, particularly for children and pets, should be prevented. Baked goods and candies containing cannabis are particularly risky. Encourage cannabis storage separate from other foods and drinks, in a locked location, out of sight and reach of children and pets. Commercially available products should be clearly labeled and in child-resistant packaging.
Driving	Driving should be avoided while under the influence of cannabis, which can more than double one's risk of a motor vehicle accident.[116] Jurisdictions vary regarding the legality of driving while using cannabis: from zero tolerance for any THC or cannabis metabolites to set THC limits or permissible inference.
Patient factors	Substance use disorder history may predispose one to problem cannabis use in the cancer setting. Concurrent opioid use can increase risk for pharmacodynamic drug-drug interactions. Cannabis use may exacerbate psychotic disorders. Some drugs commonly used in oncology (eg, warfarin, buprenorphine, tacrolimus[90]) may lead to pharmacokinetic drug-drug interactions with cannabis and/or cannabinoids. Administration of oral cannabinoids with high-fat meals significantly increases their absorption. Reversible liver enzyme elevation may occur in the setting of use of CBD ≥300 mg per day.[23]

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

HEALTH DISPARITIES

When establishing the role of medical cannabis and/or cannabinoids in cancer care, certain societal disparities call for awareness by all members of multidisciplinary clinical oncology teams. First is the disproportionate impact of state and federal cannabis laws on minorities. Although decriminalization and legalization of cannabis in many states resulted in fewer arrests for nonviolent possession, African American patients are still 3.6 times more likely to be arrested for cannabis possession than their White counterparts (despite the prevalence of cannabis use being approximately equal between the groups).[120,121] Even as the Biden administration has vowed to pardon those with simple cannabis possession offenses (October 2022), a recent 5-year analysis of federal arrests for cannabis possession found that 71% of federal offenders sentenced identified as Hispanic, with 70% being sentenced to prison.[122] This disparate enforcement of cannabis policies causes downstream consequences of a criminal record on employment and access to housing, as well as a generational effect on the families.[123] As such, awareness within the health care team of past cannabis use and its long-term social impacts reflects a dimension of delivering culturally competent cancer care.[124]

Second, the wide variability in cannabis laws across states has created many differences in which medical conditions qualify for medical cannabis, the types of cannabis products sold, permissible cannabis quantities, and the availability of dispensaries. Collectively, these differences reflect the structural barriers to medical cannabis accessibility facing adults with cancer.[125] Moreover, the ability to overcome these barriers varies across racial and ethnic groups, as evidenced by the current proportion of medical cannabis users being predominantly White.[126] Clinical teams must be aware of societal biases, stigma, and circumstances surrounding cannabis that may lead adults with cancer to underreport their cannabis use on the basis of lived experience and observations within their communities.[127]

COST IMPLICATIONS

Most private and government payers do not cover medical cannabis and/or nonpharmaceutical cannabinoids, leaving adults with cancer to bear associated costs. Common sources for purchase include state-regulated medical cannabis or adult-use dispensaries and other community sources. Out-of-pocket costs may include state cannabis program

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enrollment, usually as a one-time fee of $50-$200 US dollars (USD); costs of the cannabis product itself; and accessories for use, such as a vaporizer pen. National trends confirm a steady rise in the spot price over the past 3 years for wholesale cannabis.[128] In fact, the median monthly costs for adults with cancer averages $60-$80 USD, but with wide ranges and subsets of adults with cancer spending up to several hundreds of dollars a month, especially when considering high-dose tinctures with misinformed goals of treating the underlying cancer.[129,130]

Cannabis spot indices and benchmarks that track wholesale price longitudinally, including costs by region, demonstrate the variability of cost both by the quality of products and by geography.[131] Perceived costs to adults with cancer can be a barrier to oncology clinicians who may otherwise want to recommend a time-limited trial of cannabis.[132] Cost may lead adults with cancer to stop using or use cannabis less frequently or in lesser amounts than desired.[129] High regulated product costs can also push patients toward informal and unregulated sources.[133] Adults with cancer should be aware of any financial counseling services available to address this complex and heterogeneous landscape when discussing financial issues and concerns.

BARRIERS TO RESEARCH

The Expert Panel acknowledges many barriers to the conduct of medical cannabis and/or cannabinoid research. The status of cannabis (containing >0.3% THC) as an illegal drug in most countries limits research funding and study drug access. In the United States, the National Institute on Drug Abuse has funded the bulk of cannabis research and is understandably focused on the potential risks more than the potential benefits.[134] The University of Mississippi has served as the sole supplier of cannabis for research purposes since 1968, even following a 2016 announcement from the US Drug Enforcement Administration (DEA) that licenses would be granted to other producers.[135] The University's product offerings are not nearly broad enough regarding potencies and formulations to reflect the cannabis products sourced formally or informally to adults with cancer.

PRIORITIES FOR FUTURE RESEARCH

Numerous gaps in our understanding of cannabis and/or cannabinoids and adults with cancer warrant further investigation. Here, the Expert Panel proposes some priorities for future research to guide the safe and effective use of cannabis and/or cannabinoids in cancer care.

Clinician Communication About Cannabis and/or Cannabinoids

- What is the nature of health care disparities pertaining to medical cannabis and/or cannabinoids and adults with cancer, and what are effective means to address these disparities?
- What are optimal strategies to maximize communication in the oncology clinic regarding medical cannabis and/or cannabinoids?

Cannabis and/or Cannabinoids and Cancer Treatment

- Do cannabis and/or cannabinoids possess clinically meaningful anticancer activity?
- What are optimal clinical trial designs and end points to assess efficacy of cannabis and/or cannabinoids in treating cancer?
- What is the effect of cannabis and/or cannabinoids use on clinical outcomes in adults with cancer receiving systemic cytotoxic chemotherapy (including antibody-drug conjugates), targeted therapy, immunotherapy and cellular or vaccine therapies as cancer-directed treatment?
- What is the impact of cannabis and/or cannabinoid use on clinical outcomes in adults with cancer receiving radiation with or without systemic therapies?
- Are there clinically significant pharmacokinetic and pharmacodynamic interactions between highly concentrated extracts (oils) of cannabis and/or cannabinoids (including CBD) and systemic anticancer therapies?

Cannabis and/or Cannabinoids to Mitigate Cancer Treatment-Related Toxicities, Palliate Symptoms, and Improve QOL

- What is the effectiveness of botanical cannabis as a first-line antiemetic in adults with cancer receiving cytotoxic chemotherapy agents?
- Can cannabis and/or cannabinoid use minimize polypharmacy in CINV prevention?
- What is the optimal mode of cannabis administration when targeting refractory CINV?
- With cancer-related pain, does cannabis and/or cannabinoids use reduce opioid requirements?
- Are cannabis and/or cannabinoids effective for the prevention or treatment of chemotherapy-induced peripheral neuropathy?[96]
- How does cannabis and/or cannabinoid use in adults with cancer affect sleep, fatigue, and sleep architecture?
- What are the acute and chronic neuropsychiatric impacts of cannabis and/or cannabinoid use in adults with cancer receiving cancer-directed therapy?
- How do cannabis and/or cannabinoids affect symptom management and care of children, adolescents, and young adults with cancer?

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from May 17, 2023, through May 31, 2023. Response categories of Agree as written, Agree with suggested modifications, and Disagree, see comments were

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captured for every proposed recommendation, with 59 written comments received. For each recommendation, the proportion of respondents who agreed or agreed with slight modifications ranged from 75% to 97%. Expert Panel members reviewed the comments and determined whether to maintain the original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before EBMC review and approval.

The full draft manuscript was reviewed by four external reviewers with content expertise. Reviewer comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the EBMC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting and identify any other barrier to implementation of which a reader should be aware. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate the implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all people with cancer should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. A patient handout is provided in Appendix 1.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[136] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[137] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Antiemetics[22] (https://ascopubs.org/doi/10.1200/JCO.20.01296)
- Cancer Cachexia[138] (https://ascopubs.org/doi/10.1200/JCO.23.01280)
- Management of Anxiety and Depression in Adult Survivors of Cancer[139] (https://ascopubs.org/doi/10.1200/JCO.23.00293)
- Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers[140] (https://ascopubs.org/doi/10.1200/JCO.20.01399)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[141] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between sex and anatomy.[142-145] With the acknowledgment that ASCO guidelines may affect the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws on data on the basis of gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with a comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

I.M.B. and E.J.R. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.02596.

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ACKNOWLEDGMENT

The Expert Panel wishes to thank Drs Sarah Rutherford, Lillian Siu, Deborah Allen, Dylan Zylla, Ramy Sedhom, Vinnidhy Dave, NP Katherine Bukolt, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

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APPENDIX 1. CANNABIS DURING CANCER: ASCO INFORMATION FOR ADULTS WITH CANCER

What is Cannabis?

For thousands of years, humans have used the cannabis (marijuana) plant as medicine. The plant has hundreds of parts. The two parts researchers have studied most are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC can cause a high feeling while CBD does not. Different cannabis products have different amounts of THC and CBD.

Should I Talk to My Cancer Team About Cannabis?

If you decide to medicate with cannabis, please tell your cancer team. Your team may ask you several questions about the cannabis products: your goals in use, how much THC and CBD are in them, how often you use them, how you take them, how they make you feel, where you get them, and how much they cost. These questions help with your cancer care plan. If you are thinking of cannabis but have not yet started, please also share this with your cancer team. They can help you weigh the benefits and risks of cannabis or send you to someone who can.

What Can Cannabis Help With During Cancer?

Data suggest that cannabis may improve nausea and vomiting from chemotherapy when standard drugs do not work well enough. Research also suggests that cannabis may help with pain that is not caused by cancer. There is no evidence that supports using cannabis to treat cancer itself.

How Can Cannabis Be Taken During Cancer?

If a person with cancer medicates with cannabis, most cancer doctors prefer that they take it by mouth (edible). Cannabis by mouth can take up to 2 hours to have its full effect, so be careful not to take too much. Other common ways to take cannabis include breathing in smoke or vapor. When breathed in, cannabis works almost right away.

Can Cannabis Interact With the Medications I Take?

Data suggest that some cancer treatments do not work as well as they should with cannabis. These cancer treatments are called immunotherapies. If you are on immunotherapy, you may prefer to avoid cannabis. Cannabis can also make the unwanted side effects of some pain and anxiety medications stronger. You may choose to avoid taking cannabis at the same times as these other medications.

What Are the Side Effects of Cannabis?

Common risks of cannabis include feeling sleepy, dizzy, confused, and having a dry mouth. More serious risks include a racing heartbeat, feeling extremely dizzy or confused, and having breaks with reality (paranoia or psychosis). You may wish to avoid cannabis if you have a history of having breaks with reality. Older adults may be at higher risk of confusion and falls when using cannabis than younger people. Cannabis can also make driving dangerous, so avoid driving when you are feeling the effects of cannabis. For most people, this means waiting 5-8 hours after cannabis; for others, it may take longer.

Are There Other Risks of Taking Cannabis?

Cannabis can pose a danger to children and pets, so be sure to store cannabis in a safe place. Cannabis is federally illegal in the United States. Local laws around cannabis vary. It is important to understand both federal and local laws if you are considering cannabis.

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TABLE A1. Recommendation Rating Definitions[146]

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

TABLE A2. Cannabis and Cannabinoids in Adults With Cancer Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Ilana M. Braun, MD, co-chair	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Consultation-liaison psychiatry, psycho-oncology
Eric J. Roeland, MD, co-chair	Oregon Health and Science University, Knight Cancer Institute, Portland, OR	Medical oncology, palliative care, symptom science
Donald I. Abrams, MD	University of California San Francisco Osher Center for Integrative Health, San Francisco, CA	Integrative oncology
Holly Anderson, RN	Breast Cancer Coalition of Rochester, Rochester, NY	Patient representative
Lynda G. Balneaves, RN, PhD	University of Manitoba, Winnipeg, MB, Canada	Nursing, psychosocial oncology, integrative oncology
Gil Bar-Sela, MD	Emek Medical Center, Afula, Israel	Clinical oncology
Daniel W. Bowles, MD	University of Colorado Cancer Center, Aurora, CO	Medical oncology
Peter R. Chai, MD	Brigham and Women's Hospital, Boston, MA	Emergency medicine, Toxicology
Anuja Damani, MD	Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India	Palliative care
Arjun Gupta, MD	University of Minnesota, Minneapolis, MN	Medical oncology
Sigrun Hallmeyer, MD	Advocate Lutheran General Hospital, Park Ridge, IL	Medical oncology, PGIN representative
Ishwaria M. Subbiah, MD	Sarah Cannon Research Institute, Nashville, TN	Medical oncology, palliative care, integrative medicine
Chris Twelves, MD	University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom	Cancer pharmacology
Mark S. Wallace, MD	University of California San Diego, La Jolla, CA	Pain management
Kari Bohlke, ScD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guidelines Staff (Health Research Methods)

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