

ASSOCIATION OF COMMUNITY  
CANCER CENTERS

MULTIDISCIPLINARY HEPATOCELLULAR  
CARCINOMA CARE  
ENVIRONMENTAL SCAN



Association of Community Cancer Centers



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# ENVIRONMENTAL SCAN SUMMARY

## INTRODUCTION

The Association of Community Cancer Centers (ACCC) is conducting a Multidisciplinary Hepatocellular Carcinoma (HCC) Care education program in partnership with the Cancer Support Community (CSC), the American Cancer Society (ACS), and the Global Liver Institute (GLI). The main goals of the program are to

- Understand the current communication landscape between healthcare providers and HCC patients
- Identify effective HCC healthcare practices and potential gaps in provider-patient communications
- Raise awareness and increase education about HCC management in the community setting
- Establish a central hub of HCC resources and tools to support multidisciplinary cancer care teams.

A collection of HCC resources is available on the ACCC website at [acc-cancer.org/projects/hcc/resources](https://acc-cancer.org/projects/hcc/resources).

This environmental scan outlines:

- Effective practices and community cancer program challenges in managing HCC
- Highlights from an ACCC provider survey on delivery of HCC care
- Top findings from recent publications, articles, and clinical updates about HCC management
- Opportunities for further exploration in ACCC's Multidisciplinary HCC Care education program

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**HCC incidence has been rising rapidly in the United States over the last 20 years, and in the last few decades, HCC-related deaths have increased faster than deaths associated with any other cancer type.**

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## EFFECTIVE PRACTICES FOR MANAGING HCC IN COMMUNITY CANCER PROGRAMS

Potential effective practices for managing HCC care and considerations for community cancer programs were identified based on discussions with the project's expert Advisory Committee, project partner organizations, and a literature review. (Table 1)

Table 1. Potential Effective Practices for Managing HCC in Community Cancer Programs	
ATTRIBUTE	COMMENTS
Has a multidisciplinary team (MDT) or access to an external expert tumor board	A dedicated hepatobiliary MDT may be beyond the scope of most community cancer programs because HCC is a less common diagnosis. An alternative is having a gastrointestinal (GI) MDT that includes a medical oncologist, gastroenterologist, pathologist, surgeon, radiologist, a nurse navigator and other allied healthcare providers, AND access to an external multidisciplinary liver tumor board for timely case reviews. A close working relationship with a liver transplant program is also key. An expert liver tumor board should include a medical oncologist, a pathologist, a hepatologist, a hepatobiliary surgeon, an interventional radiologist, and a nurse navigator. Patient navigation is essential for HCC patients who often need to see several specialists in the course of their care. A nurse navigator who specializes in liver or GI diseases is especially helpful.
Conducts regularly scheduled multidisciplinary team evaluations of HCC patient cases	The relatively small population of HCC patients in most community cancer programs should make routine (vs. "as needed") MDT reviews feasible for all HCC cases.
Promotes and supports HCC screening through operational pathways that foster collaboration with other community healthcare providers	Has established regular operational pathways to communicate with clinicians in the community (primary care providers, gastroenterologists, hepatologists) who screen populations at risk in accordance with national guidelines (increasing the likelihood of diagnosis at earlier stages); when possible, participates in education for community PCPs, GIs, infectious disease providers (IDs), and other specialists.
Follows national HCC guidelines	Has operational pathways that outline guidelines for diagnostic testing, staging, and treatment (including consideration of clinical trials).
Has formal internal operational pathways to unify, streamline, and document care	Has operational pathways in place that include local program care options that fall within guidelines and to document adherence to guidelines and quality-of-care metrics.
Provides patient-centered care	Enables shared treatment decision-making by educating and discussing all aspects of care in accordance with patient preferences, encourages two-way communication, considers and supports non-clinical (i.e., practical aspects of care) as well as clinical aspects of care, provides psychosocial support, and evaluates effectiveness of patient-provider communications.

## ACCC PROVIDER SURVEY KEY FINDINGS

For its Multidisciplinary HCC Care Education Project, ACCC along with the project Advisory Committee and project partners, American Cancer Society, Cancer Support Community, and the Global Liver Institute, developed and launched a survey to understand the perspectives and experiences of the multidisciplinary cancer team in caring for patients with HCC and to:

- Learn how providers in community cancer programs around the United States are managing care for HCC patients
- Better understand effective practices, tools and resources, challenges, and education needs for the multidisciplinary team members who care for HCC patients in community settings

Highlights from the provider survey are available on pages 31 and 32 of this report. Table 2 summarizes key findings from the ACCC survey, which was conducted in July 2018.

Table 2. Key Findings from ACCC Provider Survey on HCC Care in the Community Setting	
Nearly <b>4 in 10</b> programs have a <b>specialized GI multidisciplinary team</b> (MDT) and a medical oncologist is the first specialist seen by HCC patients at 6 in 10 programs.	
<b>Two-thirds</b> of the programs with a specialized MDT conduct HCC institutional grand rounds/tumor boards for other programs.	<b>85%</b> of cancer programs without a specialized MDT consult with a tumor board.
About <b>half</b> report having a formal program or protocol that outlines adherence to the <b>NCCN guidelines</b> for HCC management.	
About <b>1/3 lack support for screening</b> in their medical community and <b>lack psychosocial services</b> for HCC patients. Almost <b>4 in 10</b> say more than 50% of HCC patients receive active treatment at their center.	
Nearly two-thirds of survey respondents report they <b>always discuss prognosis/risks/benefits</b> of various treatments in accordance with patient preferences. <b>One-half</b> say they always encourage patients to <b>share in treatment decisions</b> .	<b>85%</b> say <b>pharmaceutical patient assistance programs</b> are helpful in supporting HCC patients and <b>54%</b> say <b>non-pharmaceutical patient assistance programs</b> are helpful.
Only <b>25%</b> of MDTs caring for HCC patients include a <b>financial advocate</b> , and just 24% report having a <b>nurse navigator</b> .	
About <b>half</b> say their cancer program team initiates discussions with all HCC patients about participation in <b>clinical trials</b> .	About <b>1/3</b> have limited to no access to <b>clinical trials</b> .
<b>Top provider education needs</b> include HCC guideline updates, criteria for screening, and the role of liver transplant for select patients.	

## HEPATOCELLULAR CARCINOMA OVERVIEW

Hepatocellular Carcinoma (HCC), the most common primary liver malignancy (80 to 90% of cases in the United States) [ACS 2018; SEER 2018], is one of the most challenging cancers to diagnose and treat. [Mazzanti 2016] The estimated numbers for U.S. 2018 new cases and deaths are 42,220 and 30,200, respectively, with less than 18% of patients surviving 5 years, based on data for HCC and intrahepatic bile duct cancer combined. [SEER 2018] While HCC incidence is expected to rise dramatically in coming years, little information has been gathered about managing care for patients with HCC in community cancer programs. [Harlan 2015] With the U.S. incidence of HCC increasing, quantifying its associated medical costs is important for development of healthcare policies related to surveillance and treatment of chronic liver disease and HCC. [Kaplan 2018] HCC is now among the more frequent causes of cancer-related deaths. [Personeni 2017] One U.S. study estimates that HCC is expected to become the third largest cause of cancer death in the United States by 2030, behind lung and pancreatic cancer but ahead of colorectal cancer. [Rahib 2014]

### Disparities

From 2000 through 2016, HCC death rates increased significantly for both men and women—with the death rate for men between two and two-and-a-half times greater than that for women. U.S. HCC death rates increased for non-Hispanic white, non-Hispanic black, and Hispanic adults, but declined for adult non-Hispanic Asian/Pacific Islanders. [Xu 2018] According to the Centers for Disease Control and Prevention, death rates vary by U.S. locations; the lowest death rates for HCC in 2016 were in Vermont and the highest were in Washington, D.C. [Xu 2018] Various other studies have found disparities in diagnosis and treatment of HCC, for example:

- A review of National Cancer Database (NCDB) patients with curable HCC from 1998 to 2011 found 43,859 patients with characteristics predictive of having surgery and of long-term survival. The study found that patients were more likely to receive surgery if they were Asian or white race, had private insurance, higher income, better education, or treatment at an academic center (private insurance and treatment at an academic center were the only variables associated with improved survival). [Hoehn 2015]
- An analysis of data from the Pennsylvania Cancer Registry for all patients diagnosed with HCC from 2006–2011 found that surgical referral was less likely among older, male patients with Medicaid insurance and advanced tumor stage at diagnosis. [Chidi 2016]
- The first population-based study to evaluate HCC therapy provided in the community analyzed data for 946 HCC patients in the 2007 National Cancer Institute's Patterns of Care study and noted the following: liver transplants, embolization, or radiofrequency ablation for Barcelona Clinic Liver Cancer (BCLC) stage A patients were performed significantly less often for non-Hispanic blacks, Hispanics, patients in the highest income quartile and patients with Medicaid; patients with stage D disease were less likely to receive HCC therapy if they had Medicaid compared to private insurance; higher all-cause mortality was associated with treatment in a hospital without a residency training program, more advanced stage, and lack of appropriate treatment. [Harlan 2015]



## Screening

Much of the future burden of HCC is associated with hepatitis C virus (HCV) infection and may be avoidable through increased HCV detection and effective antiviral therapies. [Siegel 2018] However, the increasing incidence of HCC has also been linked to non-alcoholic fatty liver disease (NAFLD). [Kasmari 2017; Younossi 2016] NAFLD is often considered to be the hepatic sign of metabolic syndrome. [Younossi 2016] Therefore, targeted screening and treatment of HCV, treatment of diabetes, and primary prevention of obesity are key in reducing future HCC incidence in the U.S. [Petrick 2016]

State-level statistics are important in cancer-control planning, early detection, and prevention efforts. [Islami 2017] Much of the observed variation in liver cancer rates is attributed to differences in risk among subpopulations. Existing disparities could be dramatically reduced—and a substantial proportion of liver cancer deaths could be averted—through prevention, early detection, and treatment, including improvements in vaccination against hepatitis B virus, screening and treatment for chronic HCV infections, maintaining a healthy body weight, access to high-quality diabetes care, prevention of excessive alcohol consumption, and tobacco control. [Islami 2017]

For individuals at risk for HCC, U.S. guidelines recommend implementation of screening with ultrasound (US) every six months for individuals, and some U.S. retrospective studies have shown a better prognosis in HCC patients diagnosed in screening programs. [Pascual 2016] The American Association for the Study of Liver Diseases (AASLD) recommends screening adults with cirrhosis because it improves overall survival and suggests surveillance with US, with or without alpha-fetoprotein (AFP), every six months. [Medscape 2017; Heimbach 2018] NCCN guidelines also recommend screening for individuals at risk for HCC with US alone or the combination of US plus AFP. [NCCN 2018] However, about 20% to 50% of patients presenting with HCC have previously undiagnosed cirrhosis; thus, these patients would not be identified for screening (if the presence of cirrhosis alone defines the population to be screened). [NCI 2018] Consequently, many patients with cirrhosis have an advanced-stage HCC at initial diagnosis making treatment more complex due to the various clinical and radiological considerations for patients with dual disease (i.e., cirrhosis and HCC). [Colagrande 2016]

Currently there is no data to determine which type of surveillance—US alone or the combination of US plus AFP—leads to a greater improvement in survival; given the projected growing burden of HCC the AASLD also recommends further study on screening tests. [Heimbach 2018]

McGowan et al. surveyed primary care physicians (PCPs) and found that only a minority screen their cirrhotic patients for HCC, concluding that efforts to enlist PCPs in HCC surveillance may be best served by increasing their knowledge of effective HCC therapies. [McGowan 2015] Adding prompts and “dashboards” in the electronic medical record within a hospital system used by local PCPs can be helpful as well. [Benner 2017]

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Note: ACCC HCC Project Advisory Committee members and project partners mentioned that although screening for HCC is easy, the ability to coordinate HCC screening guidelines across the continuum of care is challenging. Insurance and patient compliance can be barriers to screening as well. More education on HCC screening for primary care providers, gastroenterologists, and infectious disease specialists is needed along with operational pathways that help coordinate care for patients.

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## HCC Stage at Diagnosis and Implications for Treatment

Clinicians face several challenges in developing and implementing public health measures and treatment strategies for HCC because of its multifaceted nature. [Personeni 2017] In patients with sufficient liver function the disease may progress silently and escape early detection due to vague complaints and non-specific symptoms. [Dimitroulis 2017] Despite screening efforts, most HCC patients are diagnosed at an advanced stage. [Boyvat 2017; Crissen 2014] In smaller-size tumors, low sensitivity of ultrasound and poor-quality CT scans, difficulties in getting samples for histopathological evaluation, and significant comorbidities preclude timely diagnosis and delay treatment; indeed, the ambiguity of some diagnostic imaging findings, delays in hospital admission and imaging reports deprive many patients of the opportunity for early, effective treatment. [Pazgan-Simon 2015] Delays in diagnostic follow-up can allow for significant tumor growth and lead to lower chances for effective treatment options. [Patel 2015] In addition, many patients have multiple comorbidities; more than 90% of patients have serious underlying liver disease making selection of cancer treatment modalities which will not further damage liver reserve extremely important. [Mazzanti 2016] Further, although liver transplant may be the best option for patients with early-stage HCC, the shortage of available organs is an issue. [Balogh 2016] All liver transplant candidates in the U.S. must be listed with the United Network for Organ Sharing (UNOS) before a donor liver can be allocated. Based on Organ Procurement and Transplantation Network (OPTN) data as of August 8, 2018, the waiting list of candidates for a liver was 13,726. [UNOS 2018] Living with HCC places a high burden on patients' daily lives, including their mood, energy levels, ability to exercise and work, and relationships with family and friends. [Gill 2018]

Although many challenges remain, in the last decade HCC treatment has improved significantly and treatment options include: curative approaches—surgical resection, orthotopic liver transplant, and ablative techniques such as thermal ablation—as well as noncurative approaches to prolong survival by slowing tumor progression—transarterial chemoembolization, transarterial radioembolization, stereotactic body radiation therapy, and systemic therapy. [Finn 2018]

Systemic therapy is the mainstay of treatment for the many patients who are diagnosed at an advanced stage or have poor liver reserve. [Eatrdes 2017] Sorafenib, a tyrosine kinase inhibitor, first approved for renal cell carcinoma in 2005, and later approved for unresectable HCC in 2007, was the only U.S. Food and Drug Administration (FDA) approved drug for HCC systemic care until recently. Four additional medications, regorafenib, nivolumab, lenvatinib, and pembrolizumab, were approved by the FDA in April 2017, September 2017, August 2018, and November 2018, respectively. [Stivarga® 2017; Opdivo 2017; Lenvima 2018; Keytruda 2018] However, whether and how to treat patients with advanced HCC is complex and should be considered by members of an expert multidisciplinary team on an individual, case-by-case basis. [Finn 2018; Johnson 2018]

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Note: Project Advisory Committee members and project partners mentioned that individual cancer programs may have preferences among different treatment options, and with recent therapeutic developments, including systemic drug approvals, HCC treatment has become more complicated.

In addition to following treatment guidelines, given the increasing complexity in treating patients with advanced HCC, community cancer programs may need to develop their own operational pathways to become more uniform and streamlined in care delivery.

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## **Multidisciplinary Team Approach, Access to Expert Tumor Boards, and Adherence to Guidelines**

In caring for patients with HCC, community cancer programs benefit from effective collaboration among primary care physicians, gastroenterologists and hepatologists, surgeons, diagnostic and interventional radiologists, medical oncologists, and transplant programs through the continuum of care. [Benner 2017] Since HCC patients often have at least two conditions with competing mortality risks (liver cancer and cirrhosis of the liver), no single provider can adequately meet all of the HCC patient's care needs. [Naugler 2015] Providers and cancer programs that manage patients with HCC are increasingly aware of the need to build their own expert team or consult with an established one, as indicated by respondents to the ACCC survey. The availability of new communication technologies, such as teleconferencing or teleconsultation, offers the possibility of multidisciplinary expansion into underserved or rural areas and correctional facilities. [Naugler 2015]

Optimal HCC management is achieved through in-depth knowledge of liver diseases (such as cirrhosis) as well as liver cancer. An interdisciplinary approach, involving medical and radiation oncologists, interventional radiologists, hepatologists, and hepatic surgeons, improves communication and delivery of optimal treatment. [Finn 2018; Rich 2017; Pinter 2016; Grandhi 2016] Based on evidence that a multidisciplinary clinic with a dedicated tumor board review for HCC can increase survival for HCC patients [Yopp 2014], practice guidance from AASLD states that HCC patients be seen in these settings if feasible and if not, referral to a center with a multidisciplinary clinic should be considered. [Marrero 2018] HCC patients managed through a multidisciplinary tumor board were more likely to have presented at an earlier tumor stage with a higher chance of receiving HCC treatment, independent of the model used for end-stage liver disease score, serum AFP, and tumor stage, and there was significantly greater patient survival. [Agarwal 2017] MDTs have been shown to lead to higher utilization of guideline-recommended curative therapies, which was associated with improved overall survival for patients with early-stage HCC. [Serper 2017]

Nurses are a critical member of the multidisciplinary team necessary for HCC care. [Fioravanti 2018] Nurse navigators, in particular, guide patients through hospital and social services processes, provide psychosocial support, assist with making insurance and social service referrals, address healthcare transportation needs, coordinate and/or document tumor board discussions, help with efficient care delivery, discern the need for and arrange culturally competent care, and stay in close communication with the patient across the care continuum. [Shockney 2016]

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**More financial resources are needed for patients with Medicare and Medicaid.**

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Virtual tumor boards that connect providers across geographic locations and institutions have been studied to see if they positively affect care for patients with HCC in community settings that lack expert tumor boards; however, more studies are needed. [Salami 2015] Shea et al. identified specific challenges, including timing and reimbursement issues that if addressed, might make virtual tumor board participation by community-based cancer programs more feasible. [Shea 2014]

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Note: Project Advisory Committee members and project partners mentioned that the vast majority of HCC patients are seen in the community; having an expert MDT, whether located in the community cancer program or from an external expert tumor board, is one of the most critical aspects of HCC care. The MDT is essential because of the many factors in addition to stage that are involved in appropriate treatment selection (for example, who is transplantable, who is surgically resectable, and/or which systemic therapy may be best).

According to the Advisory Committee and project partners, access to an expert, evidence-based and highly experienced tumor board is an unmet need for many community cancer programs. Solutions may come in the form of regional centers of excellence that can serve as resources for smaller community cancer programs and/or virtual tumor boards. Specialists that are essential to an expert tumor board include an engaged and interested medical oncologist, an interventional radiologist, a hepatic surgeon, and a hepatologist. An alternative is having a gastrointestinal (GI) MDT that includes a medical oncologist, gastroenterologist, pathologist, surgeon, radiologist, a nurse navigator, and other allied healthcare providers. It is not essential to have a transplant surgeon—community cancer programs can coordinate with a transplant center.

The Advisory Committee and project partners also raised the question: Who is the “quarterback” for the patient’s care? The group expressed interest in learning whether a specialist from a specific discipline works best in this role or if the type of specialist is irrelevant as long as one provider is recognized as the lead clinical coordinator.

Because HCC patients may also be challenged by comorbidities and need access to comprehensive supportive care, the Advisory Committee and project partners cited the many benefits nurse navigators who are knowledgeable about GI and/or liver diseases bring as part of the MDT and in care coordination for the patient.

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## Access to Clinical Trials

HCC treatment is often effective for early-stage disease, but despite progress in diagnosis and treatment of advanced-stage HCC, it is still the second most common cause of cancer-related death worldwide. [Golabi 2017] Although standard approaches effectively address local lesions, they fail to eliminate residual cancer cells, which leads to tumor recurrence and metastasis. [Xie 2018] Future studies on HCC management are needed to prolong survival with better quality of life for HCC patients, especially for those who have refractory, relapsed, or symptomatic metastatic HCC. Fortunately, several new promising treatments are under development in either pre-clinical or clinical stages of testing. [Daher 2018; Gill 2018; Heimlich 2018, Personeni 2017; Xie 2018]

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Note: Project Advisory Committee members and project partners mentioned the importance of patient access to new treatments and clinical trials.

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## Patient-Centered Care

Patient-centered care includes providing access to screening in accordance with recommended guidelines, educating patients on the diagnosis and treatment options, involving the patient in the decision-making process, determining treatment based on the latest evidence and in alignment with the patient's preferences, and supporting patients and families. [Street 2016] In general, patient-centered care is an indicator of quality healthcare and also contributes directly or indirectly to improved clinical outcomes and health-related quality of life. [Street 2016] In HCC specifically, a focus on patient-centered care is positively associated with screening in chronic liver disease patients. [Farvardin 2017; Li 2017] In addition, the findings of Gill et al. from a 13-country survey to better understand the HCC patient journey underscore the value of and need for patient-centered care. The study authors asked HCC patients for three words that best described their feelings at diagnosis and the five most common words were fear, worry, scared, anxiety and shock. The authors also reported that 68% of patients felt they did not receive enough information about HCC at time of diagnosis. [Gill 2018]

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Note: Project Advisory Committee members and project partners shared the view that patient-centered care is key and specifically mentioned that the practical aspects of patients' lives, such as cost, transportation issues, and/or unmet psychosocial needs—often identified as barriers to care—are as critical to patient-centered care as clinical aspects of care.

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## OPPORTUNITIES AND CONSIDERATIONS FOR CLOSING GAPS IN HCC CARE

### Screening

Of the small percentage of ACCC survey respondents who report taking part in a surveillance effort, a subset say it has helped them to diagnose patients earlier. Project Advisory Committee members agree that while screening for HCC is outside the scope of most community programs, the reality is that a fair amount of screening may be taking place in the community. Establishing communication and operational pathways among cancer programs and community PCPs, GIs, and IDs could help to facilitate diagnosis and result in more treatment options and better treatment outcomes. There may be an opportunity to survey providers around this topic, and share knowledge and resources related to screening among community cancer programs.

### Multidisciplinary Team Approach

Most respondents to the ACCC provider survey (61%) report that their cancer programs do not have a specialized hepatobiliary multidisciplinary team. In 6 of 10 programs a medical oncologist or hematologist/oncologist is the first specialist the patient diagnosed with HCC sees, and 13% of respondents report that the first specialist seen is a hepatologist. Other respondents say patients may see both of these specialists,

depending on who diagnoses the patient, or the patient first sees a hepatic surgeon or surgical oncologist, an interventional radiologist, or a gastroenterologist who then refers the patient to a medical oncologist or interventional oncologist, depending on the patient's HCC stage. To increase understanding of HCC management in the community, answers are needed to the following questions:

- Does which provider the patient sees first make a difference in treatment selection, patient experience, and/or patient outcome?
- Which provider is serving as the "quarterback," the one physician coordinating care for the patient and the communication "hub" for the patient's clinical management? The Advisory Committee expressed interest in learning which provider type (if any) is most effective in this role.
- Only 24% of respondents to the ACCC survey report having nurse navigation services for HCC patients. What is the difference in the patient experience and provider satisfaction among programs that have a liver-specialist nurse navigator, a general nurse navigator, or no nurse navigator?

### **Virtual Tumor Boards**

The ACCC survey asked: "Would access to a virtual expert tumor board be helpful to your HCC patients?" More than half of respondents (57%) were not sure, 24% said yes, and 20% answered no. Both the literature and advisors suggest that the timing issues and knowledge about virtual tumor boards might be challenges that provider education could address.

### **Treatment Guidelines**

About half (52%) of respondents' cancer programs have a formal program or protocol that outlines adherence to the National Comprehensive Cancer Network (NCCN) guidelines for HCC management, another 5% are currently developing one, and 43% are not developing one at the time of the survey. None of the respondents indicate using American Association for the Study of Liver Diseases (AASLD) or American College of Gastroenterology (ACG) guidelines. As the ACCC survey reveals, provider education on HCC guidelines is needed, and was a top request from survey participants.

Respondents to the ACCC provider survey report that less than 50% of patients seen in community cancer programs are receiving active treatment. Further exploration could provide insight into this statistic.

- Why are less than half of HCC patients at respondents' programs receiving active treatment? Are financial barriers, such as lack of healthcare coverage or payer challenges, impeding access?
- Are these patients being referred to academic centers for care?
- Are patients diagnosed with late-stage HCC choosing to receive supportive care only?
- Are patients waiting for a liver transplant?

A clearer picture of these and other programmatic and patients' issues could help improve care for patients with HCC.

## Follow-up Care

About one-third of survey respondents indicate having HCC survivorship programs and another 13% report that they are developing one. Survivorship planning is a critical component of care coordination for patients with cancer. For those with HCC, a survivorship care plan is imperative given the complexity of a dual-diagnosis in those patients with both cancer and liver disease, the rate of recurrence for a significant proportion of patients, and (as for many cancer survivors) the importance of understanding which healthcare provider to see if problems arise once they have completed treatment for HCC.

## Clinical Trials

Respondent to the ACCC survey answered a series of questions about HCC clinical trials. Slightly more than half (52%) say their cancer program initiates discussions with all HCC patients about participation in clinical trials, and another 24% report that they help patients who ask about clinical trials get more information. Others say they either only discuss trials with patients who have advanced disease with no curative standard treatment options or if they have an appropriate study for the patient.

## Patient-Centered Care

Responses to the provider survey reflect strong communication between clinicians and patients, with between 86% and 93% of respondents reporting that clinicians communicate with patients on 14 out of 17 key communication aspects “most of the time,” “almost always,” or “always.” Gathering details on how these programs are accomplishing this and making education and resources to all community cancer programs would be helpful.

# HEPATOCELLULAR CARCINOMA CARE LITERATURE REVIEW

## INCIDENCE AND MORTALITY

Hepatocellular carcinoma (HCC) is one of the most challenging cancers to diagnose and treat. [Mazzanti 2016] It is the most common primary liver malignancy (80% to 90% of cases in the United States) and is on the rise. [ACS 2018; SEER 2018] The incidence rate has doubled around the world since the 1970s and has been rising rapidly in the United States over the last 20 years. [Fioravanti 2018; Petrick 2016] The estimated numbers for U.S. new cases and deaths for 2018 are 42,220 and 30,200, respectively, with less than 18% of patients surviving 5 years (based on data for HCC and intrahepatic bile duct cancer combined). [SEER 2018] HCC is now among the more frequent causes of cancer-related deaths. [Personeni 2017] From 2000 through 2016, death rates increased significantly for both men and women, with the death rate for men more than twice the rate for women. In the U.S., HCC death rates increased for non-Hispanic white, non-Hispanic black, and Hispanic adults, but declined for adult non-Hispanic Asian/Pacific Islanders. [Xu 2018] Due to patients, generally, being diagnosed at late stage HCC, median survival is approximately 6 to 20 months. [Golabi 2017; Haberal 2017] In the last few decades, HCC-related deaths have increased faster than deaths associated with any other cancer type. [Golabi 2017] A U.S. study estimates that HCC is expected to become the third largest cause of cancer death in the U.S. by 2030, behind lung and pancreatic cancer but ahead of colorectal cancer. [Rahib 2014]

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**HCC incidence has been rising rapidly in the United States over the last 20 years, and in the last few decades, HCC-related deaths have increased faster than deaths associated with any other cancer type.**

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Using U.S. mortality data from 1990 through 2014 from the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) provided through the National Cancer Institute's Surveillance, Epidemiology, and End Results program, Islami et al. examined HCC trends for incidence, survival, and mortality and provided state-level death rates for non-Hispanic white, black, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native populations. Disparities in liver cancer death rates by race/ethnicity range from 5.5 per 100,000 in non-Hispanic whites to 11.9 per 100,000 in American Indians/Alaska Natives) as well as by state (from 3.8 per 100,000 in North Dakota to 9.6 per 100,000 in the District of Columbia) and by race/ethnicity within states. [Islami 2017] According to the CDC the lowest death rates for HCC in 2016 were in Vermont and the highest were in Washington, D.C. [Xu 2018]

## RISK AND PROTECTIVE FACTORS

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**Diabetes, obesity, and related NAFLD are risk factors for HCC with clinical features distinct from those of virus-induced HCC.**

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Hepatitis-C virus (HCV)-related cirrhosis has accounted for most cases of HCC (50%–70%), along with the other main risk factors including Hepatitis B virus (HBV)-infection (especially among immigrants from HBV-endemic areas); alcoholic cirrhosis; diabetes; and nonalcoholic fatty liver disease (NAFLD). [Singal 2015] In Western countries, diabetes, obesity, and NAFLD (the hallmarks of the spectrum of metabolic syndrome) are more frequently recognized as HCC risk factors [Younossi 2015] and are associated with clinical features that are distinct from those of virus-induced HCC. [Degasperis 2016]

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**Wong et al. showed that independent of HCV therapy, clinical cure, and other background risks, Hispanic ethnicity with  $\geq 2$  metabolic risk factors significantly increased risk for HCC and liver function decline.**

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Much of the future burden of HCC associated with HCV infection has the potential to be averted through increased HCV detection and well-tolerated antiviral therapies. [Siegel 2018] Of note, the increasing incidence of HCC has been linked to NAFLD, which is often considered to be the hepatic sign of metabolic syndrome. [Kasmari 2017; Younossi 2016] The National Health and Nutrition Examination Survey (NHANES) data from 1999–2006, estimated that 68 million U.S. adults had metabolic syndrome. [Mozumdar 2011] Wong et al. studied whether metabolic syndrome increased the risk of HCC and other liver-related complications in cirrhotic Hispanic patients with chronic HCC. In a retrospective cohort study (N=3,503) at Stanford University between 1997 and 2015, 238 patients developed HCC and 448 patients suffered liver deterioration. The incidence of HCC and liver deterioration increased with Hispanic ethnicity, diabetes, and number of metabolic risk factors. The analysis showed that, independent of HCV therapy and cure and other background risks, Hispanic ethnicity with  $\geq 2$  metabolic risk factors significantly increased the risk of HCC and liver function decline. [Wong 2018] A U.S. study found that individuals with a first-degree family history of liver cancer were up to four times more likely to develop liver cancer than the general population, suggesting that certain shared genetic and environmental factors influence the risk of developing the disease. [Turati 2012]

Some possible protective factors have been described in various studies published in the last decade, including dietary (fish, vegetables, omega-3 fatty acids, vitamin E, coffee drinking) and medication (statins and beta-blockers) factors. [Pascual 2016]

## NEEDS FOR SCREENING, EARLIER DIAGNOSIS, AND PROMPT TREATMENT INITIATION

Much of the observed variation in liver cancer rates is attributed to differences in risk among subpopulations and existing disparities could be dramatically reduced—and a substantial proportion of liver cancer deaths could be averted—through prevention, early detection, and treatment, including: improvements in vaccination against hepatitis



B virus; screening and treatment for chronic hepatitis C virus infections; maintaining a healthy body weight; access to high-quality diabetes care; preventing excessive alcohol drinking; and tobacco control—at both the state and national levels. [Islami 2017] State-level statistics can inform state cancer-control planning, early detection, and prevention efforts. [Islami 2017]

In some community programs, GI and hepatology specialists screen for HCC and may try to engage primary care providers as well. [Benner] Screening helps to detect early-stage disease and facilitates treatment options. Targeted screening and treatment of HCV, treatment of diabetes, and primary prevention of obesity are key in reducing future HCC incidence in the U.S. [Petrick 2016] As the prevalence of metabolic syndrome increases globally, targeted health interventions are needed to help curb the effects of metabolic syndrome. [Wong 2018] U.S. and European guidelines recommend implementation of screening programs with ultrasound (US) every six months for individuals at risk for HCC, and some European and U.S. retrospective studies have shown a better prognosis in HCC patients diagnosed in screening programs. [Pascual 2016] The current guidelines from both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver recommend the Barcelona Clinic Liver Cancer (BCLC) classification as the staging system for prognosis and treatment allocation. [Pascual 2016] AASLD considers HCC screening cost-effective for patients with HBV whose expected HCC risk exceeds 0.2% per year, as well as for those with HCV whose expected HCC risk exceeds 1.5% per year. [Medscape 2017] AASLD further recommends screening of adults with cirrhosis because it improves overall survival and suggests screening using U/S, with or without alpha-fetoprotein (AFP), every six months. Currently there is no data to determine which type of screening—US alone or the combination of US plus AFP—leads to a greater improvement in survival and given the projected growing burden of HCC, the AASLD also recommends further study on screening tests. NCCN guidelines also recommend screening for individuals at risk for HCC with US alone or the combination of US plus AFP. [Heimbach 2018; NCCN 2018]

Most HCC patients are diagnosed at an advanced stage. [Boyvatt 2017; Crissien 2014] The disease may progress silently in patients with sufficient liver function and escape early detection due to vague complaints and non-specific symptoms. [Dimitroulis 2017] McGowan et al. surveyed primary care physicians (N=391) and found that only a minority screen their cirrhotic patients for HCC, and their knowledge of effective HCC therapy options is suboptimal. The study authors concluded that efforts to enlist PCPs in HCC screening may be best served by increasing their knowledge of effective therapies. [McGowan 2015] Adding prompts and “dashboards” in the electronic medical record within the hospital system can be helpful as well. [Benner 2017] Although cirrhotic patients are followed routinely with imaging, clinical and biochemical parameters, 20% to 50% of patients presenting with HCC have previously undiagnosed cirrhosis and are not screened (if the presence of cirrhosis alone defines the population to be screened). [NCI 2018] Consequently, many patients with cirrhosis have an advanced-stage HCC at initial diagnosis making treatment more complex due to various other clinical and radiological considerations. [Colagrande 2016]

Several diagnostic challenges were summarized by Pazgan-Simon et al. from three case reports: particularly in smaller-size tumors, low sensitivity of ultrasound imaging and poor-quality CT scans may preclude early diagnosis and intervention; difficulties in getting samples for histopathological evaluation, e.g., specimens of insufficient size obtained during the targeted fine needle biopsy; subdiaphragmatic or periportal lesions; significant comorbidities that preclude timely histopathological diagnosis and delay treatment in many cases; the ambiguity of some diagnostic imaging findings;

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**U.S. and European guidelines recommend screening with ultrasound every six months for at-risk individuals and some retrospective studies show better prognosis in patients diagnosed in screening programs.**

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**AASLD considers HCC screening cost-effective for patients with HBV whose expected HCC risk exceeds 0.2% per year, as well as in those with HCV whose expected HCC risk exceeds 1.5% per year.**

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**Patel et al. in a study of 457 HCC patients found that nearly 20% of HCC patients wait more than three months from presentation to diagnosis, which can contribute to interval tumor growth.**

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and delay in hospital admission and imaging reports deprive many patients of the opportunity for early, effective treatment. [Pazgan-Simon 2015] With HCC, delays in diagnostic follow-up of as little as three months can allow for significant tumor growth and lead to lower chances for effective treatment options. Patel et al. in a study of 457 HCC patients found that nearly 20% of HCC patients wait more than three months from presentation to diagnosis, which can contribute to interval tumor growth. In this study, delays in diagnosis related to providers failing to recognize positive screening tests, patients missing radiology appointments, and insensitive diagnostic tests (especially common—present in more than one-third of cases—among patients who presented as outpatients). [Patel 2015] Akce et al. investigated predictors of treatment delays and their impact on survival in a retrospective study of a national cohort Department of Veterans Affairs patients with HCC from October 1, 2004, to September 30, 2011. Treatment delay was defined as greater than 60 days between HCC diagnosis and first treatment. Treatment was categorized as curative (surgery or ablation), liver-directed therapy, or chemotherapy. Among 742 HCC patients, 223 (30%) had a treatment delay; most patients were BCLC stage C (43%), and 131 patients (17.7%) had metastatic disease. Treatment delay was not associated with increased risk of death for earlier stage HCC; however, treatment delay was associated with decreased risk of death for patients with BCLC stage C, a finding that may be due to delays related to coordination of curative and liver-directed therapy that may result in improved survival. [Akce 2017]

Radiofrequency ablation, liver transplantation, and tumor resection are potentially curative treatment options. [Waghray 2015] Liver transplantation addresses patients with underlying liver disease (cirrhosis) as well as HCC; surgical resection removes HCC tumors but is of limited value for HCC patients with advanced cirrhosis. [Golabi 2017] Using expanded patient selection criteria for liver transplant (beyond tumor size and number alone), such as alpha-fetoprotein and other biologic markers, has improved risk assessment for tumor recurrence. [Gunsar 2017]

Golabi et al. examined HCC patient data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database between 2001 and 2009. Patients were treated with liver transplant, surgical resection, or nonsurgical treatment (N=11,187). Mortality within two years of HCC diagnosis was significantly higher in patients treated with surgical resection than liver transplant, although patients who had liver transplant were younger and sicker (defined as decompensated cirrhosis: 80% vs. 23%). In multivariate analysis, older age, stage of HCC other than local, and being treated with surgical resection were independent predictors of death within two years. [Golabi 2017]

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**In a NCDB multi-year review, Asian or white patients with private insurance, higher income, better education, or treatment at an academic center were more likely to receive surgery for curable HCC.**

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A review of the National Cancer Database (NCDB) for all patients with curable HCC (stage I/II) from 1998 to 2011 (N=43,859) found that only 39.7% of patients received surgery (resection [34.6%], transplant [28.7%], radiofrequency ablation [27.1%], and other therapies) for curable HCC, possibly as a result of multiple socioeconomic variables (patients were more likely to receive surgery if they were Asian or white race, had private insurance, higher income, better education, or treatment at an academic center (P<0.05). However, private insurance and treatment at an academic center were the only variables associated with improved survival (P<0.05). [Hoehn 2015]

Sociodemographic and geographic barriers for surgery referral were investigated by Chidi et al. Their study looked at data from the Pennsylvania Cancer Registry for all patients diagnosed with HCC from 2006–2011 to analyze the sociodemographic and geographic factors associated with surgery referral and receipt of the recommended surgical intervention. The study authors reported that surgical referral was less likely among older, male patients with Medicaid insurance and advanced tumor stage at diagnosis. Having a surgical center nearby was not associated with receipt of surgical intervention ( $p=0.27$ ); about 41% of patients ( $N=3,576$ ) were referred for surgery and of those referred, 87.0% ( $N=1,276$ ) underwent a surgical intervention. [Chidi 2016]

## STAGING, PROGNOSIS, AND TREATMENT SELECTION

HCC management has focused on: prevention, early diagnosis and hepatic resection, or transplantation; combination therapies to downstage more advanced HCC and make it operable; and improve underlying liver status to prolong the survival period. [Mazzanti 2016; Dimitroulis 2017]

The multifaceted nature of HCC challenges clinicians in developing and implementing public health measures and treatment strategies. [Personeni 2017] Disease-free survival, as well as cancer recurrence and mortality rates, vary according to selected treatment modalities. [Golabi 2017] HCC prognosis is often poor, and treatment is challenging in part because many patients with HCC have multiple comorbidities that have bearing on their underlying liver disease and need to be considered together. More than 90% of HCC patients have serious underlying liver disease and require HCC treatment that does not cause further liver damage. [Mazzanti 2016]

Accurate staging [Pascual 2016] and a detailed clinical and radiologic workup are essential for appropriate treatment selection. Treatment is based on liver function, size and number of tumors, biomarkers, macrovascular invasion, extrahepatic spread of disease [Boyvat 2017; Pascual 2016], and other patient characteristics. Imaging plays an increasingly important role in HCC staging. Cassinotto et al. discussed key achievements in HCC imaging over recent years, noting that current techniques with various imaging modalities enable radiologists to differentiate between the numerous histological patterns seen in liver nodules and allow for the detection of ever smaller tumors. While the number and variety of radiological features have increased, they are also more complex and require updates be made to decision algorithms and consensus guidelines. [Cassinotto 2017]

In the last decade HCC treatment has improved significantly and treatment options include the curative approaches—surgical resection, orthotopic liver transplant, and ablative techniques such as thermal ablation—and noncurative approaches that attempt to prolong survival by slowing tumor progression—transarterial chemoembolization, transarterial radioembolization, stereotactic body radiation therapy, and systemic chemotherapy. [Finn 2018]

Haberal et al. analyzed the results of 552 liver transplants on HCC patients between December 1988 and January 2017, applying expanded criteria for liver transplant (regardless of tumor size and number, including patients without major vascular invasion and without distant metastasis, and those with negative cytology); in adults, 5-year survival was 58.7% and 10-year survival was 49.7%. The study data suggests that liver transplant is safe and effective in patients with HCC in combination with interventional radiology procedures, regardless of tumor size and number, without major vascular invasion and distant metastasis. [Haberal 2017] While liver transplant may be the best option for patients with early-stage HCC, the shortage of available

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**More than 90% of HCC patients have serious underlying liver disease and need HCC treatment that does not cause further liver damage.**

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**Current imaging techniques enable radiologists to differentiate between the numerous histological patterns seen in liver nodules and allow the detection of ever smaller tumors; however, radiological features are more complex and require updates to guidelines to account for new epidemiological data.**

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organs is an issue. (Balogh 2016] All liver transplant candidates in the U.S. must be listed with the United Network for Organ Sharing (UNOS) before a donor liver can be allocated. Based on Organ Procurement and Transplantation Network (OPTN) data as of August 8, 2018, the waiting list of candidates for a liver was 13,726. [UNOS 2018]

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**Whether and how to treat patients with advanced HCC is complex and should be considered by members of an expert multidisciplinary team on a case-by-case basis.**

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Although early-stage disease is generally treated with surgical resection, transplant, or locoregional therapies, systemic therapy is the mainstay of treatment for the many patients diagnosed at an advanced stage or with poor liver reserve. [Eatrdes 2017] Regardless of the disease stage, different interventional radiological treatments are available that offer curative or palliative options in the management of this disease. [Boyvart 2017] However, whether and how to treat patients with advanced HCC is complex and should be considered by members of an expert multidisciplinary team on a case-by-case basis. [Finn 2018; Johnson 2018]

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**Until recently, sorafenib (originally approved for RCC in 2005) was the only FDA-approved drug for HCC systemic care. However, regorafenib, nivolumab, lenvatinib, and pembrolizumab received FDA approval in April 2017, September 2017, August 2018, and November 2018, respectively.**

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Chemoembolization is the most widely used treatment for unresectable HCC or progression after curative treatment. [Pascual 2016] Until recently, sorafenib (approved for HCC in 2007) was the only FDA-approved drug for HCC systemic care. Sorafenib, a tyrosine kinase inhibitor, is indicated for unresectable HCC. [Nexavar 2010] Four other multi-targeted medications, regorafenib, nivolumab, lenvatinib, and pembrolizumab, received FDA approval in April 2017, September 2017, August 2018, and November 2018, respectively. [Stivarga® 2017; Opdivo 2017; Lenvima 2018; Keytruda 2018] Regorafenib is a multi-tyrosine kinase inhibitor indicated for use in patients with HCC previously treated with sorafenib, nivolumab is a PD-1-blocking antibody (checkpoint inhibitor) indicated in HCC patients previously treated with sorafenib. [Stivarga® 2017; Opdivo 2017] Nivolumab received accelerated approval for HCC patients previously treated with sorafenib based on the results of CHECKMATE-040, a multicenter, open-label trial; continued approval may be contingent on verification and clinical benefit in clinical trials. [Opdivo 2017] Lenvatinib has emerged as a systemic therapy for first-line treatment of patients with unresectable HCC. The approval was based on REFLECT, an international, multicenter, randomized, open-label, noninferiority trial, conducted in 954 patients with previously untreated, metastatic, or unresectable HCC. Patients were randomized to lenvatinib or sorafenib therapy that was continued until radiological disease progression or unacceptable toxicity. Data from the REFLECT trial (published in February 2018) showed: The median overall survival (OS) by investigator review with lenvatinib was 13.6 months compared with 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79-1.06); lenvatinib was statistically superior to sorafenib for progression-free survival (PFS)—median PFS was 7.4 versus 3.7 months for lenvatinib and sorafenib, respectively; and time-to-progression (TTP)—was 8.9 months for lenvatinib compared with 3.7 months for sorafenib.

In November 2018 the Food and Drug Administration announced accelerated approval of pembrolizumab (Keytruda) for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Approval was based on KEYNOTE 224, a single-arm, multicenter trial enrolling 104 patients with hepatocellular carcinoma. Patients were required to have disease progression on or after sorafenib or were intolerant to sorafenib, have measurable disease, and Child-Pugh Class A liver impairment. The major efficacy outcome measure was confirmed overall response rate, as assessed by independent central review (ICR) according to RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). The confirmed ICR-assessed overall response rate was 17% (95% CI: 11, 26), with one complete response and 17 partial responses. Response durations ranged from 3.1 to 16.7 months; 89% of responders had response durations of 6 months or longer and 56% had response durations of 12 months or longer.

## RESEARCH AND CLINICAL TRIALS

HCC treatment is often effective for early-stage disease, but despite progress in diagnostics and advanced-stage HCC treatment, HCC is still the second most common cancer-related death worldwide. [Golabi 2017] Although standard approaches effectively address local lesions, they often fail to eliminate residual cancer cells, which can lead to tumor recurrence and metastasis. [Abou-Alfa 2015; Agarwal 2017; Balogh 2016; Daher 2018; Grandhi 2016; Mazzanti 2016; Rich 2017; Singal 2015; Waghray 2015; Xie 2018] Future studies on HCC management are needed to prolong survival with better quality of life for HCC patients, especially for those with refractory, relapsed, or metastatic HCC. Research into several new treatments are underway either in pre-clinical or clinical studies [Daher 2018; Gill 2018; Heimlich 2018, Personeni 2017; Xie 2018]. During the past two decades, researchers and clinicians have achieved a significant increase in knowledge about the clinical and molecular heterogeneity of HCC, including increased clinical trial activity in patients with poor prognostic factors, e.g., macrovascular invasion and extrahepatic spread. [Finn 2018] For earlier diagnosis of HCC or precancerous forms of HCC, the contributions of hepato-specific contrast agents are promising, but these need to be validated in large-scale studies. [Cassinotto 2017]

In addition to the study comparing nivolumab or lenvatinib with sorafenib [Bristol-Myers Squibb 2018; Eisai Limited 2018; Kudo 2018], Heimbach et al. described other combined therapy approaches being investigated in ongoing phase 3 clinical trials to improve survival in patients who have advanced HCC with metastatic disease. [Heimbach 2018] These include:

- Comparing the survival benefits of sorafenib versus radioembolization in advanced HCC with macrovascular invasion [Singapore General Hospital 2018]
- The added benefits of hepatic arterial chemoinfusion for advanced HCC with portal vein tumor thrombus with sorafenib versus sorafenib alone [Sun Yat-sen University 2018]
- Comparing sorafenib with or without stereotactic body radiation in patients with advanced HCC to assess the added benefits of stereotactic body radiation to sorafenib [Radiation Therapy Oncology Group 2018]

In recent years, tumor immunotherapy has emerged as a promising method for inhibiting tumor progression, relapse, and metastasis. Xie et al. reviewed the mechanism, rationale for research, and current advances for immunotherapy approaches in HCC. [Xie 2017] Continuing investigation of immune checkpoint inhibitors and other immunotherapeutic approaches (adoptive cell therapy, cancer vaccination, oncolytic viruses) is a promising area of research for HCC. Studies have looked at potential biomarkers to determine which patients will derive benefit from specific systemic therapies. Notably, the phase 3 METIV-HCC trial, the first biomarker-driven trial, may have paved the way for HCC clinical trials with biomarker-based strategies. [Daiichi Sankyo 2018; Personeni 2017] However, more studies are needed to continue investigation into biomarkers as they relate to the management of HCC. [Balogh 2016; Eatrdes 2017]

Active research in supportive care for HCC patients will hopefully lead to better quality of life (QoL) for HCC patients. [Colagrande 2016] There is a need for new late-stage treatment options that afford better QoL for HCC patients. [Gill 2018] Of note, in a phase 3, multicenter, randomized, open-label study, QoL was evaluated descriptively



for patients with unresectable HCC who received first-line systemic treatment with lenvatinib or sorafenib. In the study, 954 patients were randomized to lenvatinib (N=478) or sorafenib (N=476) and key QoL outcomes for patients progressing 3 months or less versus more than 3 months were modeled longitudinally and summarized. More patients experienced disease progression earlier on therapy with sorafenib compared to therapy with lenvatinib. Baseline QoL was more severely impacted for HCC patients who progressed earlier while on therapy, raising the possibility that better QoL is an added benefit for patients treated with lenvatinib. While functional and symptom differences in QoL measures were not statistically significant, these differences also favored patients treated with lenvatinib. [Hudgens 2018]

## MULTIDISCIPLINARY TEAM APPROACH AND ACCESS TO EXPERT TUMOR BOARDS

In community-based HCC programs, developing an effective collaboration among primary care physicians, gastroenterologists, hepatologists, surgeons, diagnostic and interventional radiologists, oncologists, and transplant programs through the continuum of cancer care is key. [Benner 2017] Optimal HCC management is achieved through in-depth knowledge of liver diseases such as cirrhosis and liver cancer—an interdisciplinary approach involving surgeons, interventional radiologists, oncologists, and hepatologists is necessary. [Finn 2018; Pinter 2016] Based on evidence that a multidisciplinary clinic with a dedicated tumor board review for HCC can increase survival for HCC patients, practice guidance from AASLD states that HCC patients be seen in these settings if feasible or referral to a center with a multidisciplinary clinic should be considered. [Marrero 2018]

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**Practice guidance from AASLD states that HCC patients be seen in an MDT with dedicated tumor board review for HCC if feasible, or referral to a center with a multidisciplinary clinic should be considered.**

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The results of a study by Agarwal et al. showed that HCC patients managed through a multidisciplinary tumor board were more likely to have presented at an earlier tumor stage with a higher chance of receiving HCC treatment, independent of model for end-stage liver disease score, serum AFP, and tumor stage—and that there was significantly greater patient survival. [Agarwal 2017] Since combination therapy (i.e., systemic, surgical, and/or radiological therapies) is often necessary, HCC calls for a multidisciplinary approach to determine the most appropriate treatment and sequencing of treatments for optimal patient outcomes. [Grandhi 2016] A multidisciplinary approach that involves hepatologists, surgeons, interventional radiologists, radiation oncologists, and medical oncologists can improve communication and delivery of optimal treatment. [Rich 2017]

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**No single provider can adequately deal with all of the HCC patient's needs. Multidisciplinary teams have evolved for care coordination, reassessments, and timely changes in treatment plans for treating patients with this complex disease.**

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Since HCC patients often have at least two conditions with competing mortality risks (cancer and underlying liver disease), no single provider can adequately deal with all of the HCC patient's needs. [Naugler 2015] Multidisciplinary teams have evolved for care coordination, reassessments, and timely changes in treatment plans for treating patients with this complex disease. Providers or sites that manage patients with HCC are increasingly aware of the need to build their own expert team or consult with an established MDT. The availability of new communication technologies, such as teleconferencing or teleconsultation, offers the possibility of expanding the MDT approach to HCC care into underserved or rural areas, and correctional facilities. [Naugler 2015]

Although the availability of resources for HCC patient care varies among cancer programs, development access to a virtual MDT extends the reach of experts to a wide spectrum of clinical practices. Virtual tumor boards that connect providers across geographic locations and institutions have been studied to see if they positively

affect care for patients with HCC receiving care in community settings that lack expert tumor boards, but more studies are needed. [Salami 2015] Shea et al. identified specific challenges that, if addressed, might make virtual tumor board participation by community-based cancer programs more feasible, including timing and reimbursement issues. [Shea 2014]

Naugler et al. suggest a strategy for collaboration that includes the following: Allocating appropriate resources by having representatives from multidisciplinary specialties (e.g., medical director of the proposed group, liver treatment directors, a chief medical officer, board members, and transplant administrators) meet with hospital or clinic administration. MDT providers may include a transplant hepatologist (ideal) or gastroenterologist, a transplant surgeon, a hepatobiliary surgeon, an interventional radiologist, a diagnostic body radiologist, a radiation oncologist, a medical oncologist, a pathologist, a palliative care specialist, and a nurse navigator who is also an HCC specialist, with additional support services from psychologists, social workers, and nutritionists. Cancer programs without an orthotopic liver transplantation facility must have a relationship with such a facility. Establish a director or co-directors of the MDT for triage, prioritization; review to ensure that case presentations are receiving adequate consideration; guidance for the team on quality control; research and clinical trials; and community outreach. [Naugler 2015]

Nurses are a critical member of the MDT necessary for HCC care. As such, nurses need to be aware of the issues in managing HCC patients so that more HCC patients can have extended life with good quality. [Fioravanti 2018] Nurse navigators guide patients through hospital and social services processes, provide psychosocial support, assist with making insurance and social service referrals, address healthcare transportation needs, coordinate and/or document tumor board discussions, help with efficient care delivery, discern the need for and arrange culturally competent care, and stay in close communication with the patient across the care continuum. [Shockney 2016]

Serper et al. conducted a national, retrospective cohort study of patients diagnosed with HCC from January 1, 2008, through December 31, 2010 (N=3,988), and followed through December 31, 2014, who received care through the Veterans Administration (128 centers). Outcomes were receipt of active HCC therapy (liver transplantation, resection, local ablation, transarterial therapy, or sorafenib) and overall survival. In liver resection, ablative therapy and transarterial therapy were associated with reduced mortality; subspecialist care by hepatologists, medical oncologists, or surgeons within 30 days of HCC diagnosis and review by a multidisciplinary tumor board were associated with reduced mortality. The study authors identified important demographic, clinical, and care delivery characteristics that affect receipt of active HCC therapy and overall survival and found that multidisciplinary tumor boards led to higher utilization of guideline-recommended curative therapies, which was associated with improved overall survival for patients with early-stage HCC. [Serper 2017]

## SUPPORTIVE CARE

Living with HCC places a high burden on patients' daily lives, including their mood, energy levels, ability to exercise and work, and relationships with family and friends. [Gill 2018] Supportive care is important in the care of HCC patients, although there is limited data about best supportive (palliative) care in advanced HCC. The goal of supportive care (to improve the patient's quality of life) and its definition (supportive care for cancer patients is the multi-professional attention to the individual's overall physical, psychological, spiritual, and cultural needs and should be available at all stages of the illness, for patients of all ages, and regardless of the current intention of

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**Supportive care is important for HCC patients at every stage of the disease to avoid complications and to address symptoms and treatment side effects.**

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**Depression and anxiety are reported by more than 60% of HCC patients.**

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any anti-cancer treatment) implies its importance during every stage of the disease. Yet, supportive care is marginally discussed at best in all HCC guidelines. Supportive care should be part of HCC management to avoid complications and to address symptoms and treatment side effects. [Kumar 2014] The most common symptoms reported by HCC patients are sleep disturbances, depression, fatigue, malnutrition, anorexia, pain and psychological issues; sleep problems are reported by 50–65% of patients with cirrhosis and physicians should perform a routine assessment of sleep quality and time and evaluate daytime sleepiness; depression and anxiety are reported by more than 60% of HCC patients; fatigue is very frequent in HCC; other HCC-related issues include pain, malnutrition, anorexia and cachexia, muscle cramps. [Colagrande 2016]

## HCC GUIDELINES

The AASLD published a 2018 guideline for the surveillance, diagnosis, and treatment of HCC occurring in the setting of adults with cirrhosis. The guideline focuses on clinical practice areas including screening of patients with cirrhosis for HCC, establishing the diagnosis of HCC and therapeutic treatment options, as well as 2018 updates to earlier guidelines on HCC epidemiology, staging, diagnosis, and treatment.

- AASLD Guidelines for the Treatment of HCC identified key questions that healthcare providers face: Should adults with cirrhosis undergo surveillance for HCC and if so, which surveillance test is best? Should adults with cirrhosis and suspected HCC undergo diagnostic evaluation with multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging (MRI)?
- Should adults with cirrhosis and an indeterminate hepatic nodule undergo a biopsy, repeated imaging, or alternative imaging for the diagnostic evaluation?
- Should adults with Child-Pugh Class A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or locoregional (LRT) therapy?
- Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy? Should adults with cirrhosis and HCC (T1) awaiting liver transplantation be treated or undergo observation?
- Should adults with cirrhosis and HCC (Organ Procurement and Transplantation Network [OPTN] T2) awaiting liver transplantation undergo transplantation alone or transplantation with bridging therapy while waiting?
- Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) undergo transplantation after being downstaged to within Milan criteria?
- Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?
- Should adults with Child-Pugh Class A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease be treated with systemic or locoregional therapies or no therapy?

AASLD guidelines on treatment include the following:

- Resection is the treatment of choice for solitary tumors in non-cirrhotic patients or cirrhotic patients with well-preserved liver function; pre- or post-resection adjuvant therapy is not recommended.



- Liver transplantation is the best available curative option for patients with early-stage non-resectable HCC who meet the Milan criteria (single tumors  $\leq 5$  cm in diameter or no more than three nodules  $\leq 3$  cm in diameter in patients with multiple tumors).
- Use of resection rather than radiofrequency ablation for adults with Child-Pugh A cirrhosis and resectable T1 or T2 HCC. However, ablation should be considered as definitive treatment for patients with stage 0-A tumors who are not candidates for resection or transplantation.
- Use of bridging therapy to maintain tumor burden within Organ Procurement and Transplant Network (OPTN) T2 (Milan) criteria, but the AASLD does not recommend any one form of liver-directed bridging therapy over another.
- Use of downstaging therapy to bring selected patients within the Milan criteria.
- Recommends transarterial chemoembolization as first-line non-curative therapy for advanced disease.
- Sorafenib is recommended for patients who have preserved liver function and cannot benefit from surgery, transplantation, ablation, or transarterial chemoembolization.
- Yttrium-90 radioembolization is not recommended outside of clinical trials.
- Systemic or selective intra-arterial chemotherapy is not recommended. [Heimbach 2018]

## FINANCIAL COST OF CARE

With the U.S. incidence of HCC increasing, quantifying its associated medical costs is important for development of healthcare policies related to screening and treatment of chronic liver disease and HCC. [Kaplan 2018] In the first population-based study to evaluate therapy provided for HCC in the community, Harlan et al. sought to characterize HCC diagnosis, treatment, and survival patterns for patients treated in community settings by analyzing data for 946 HCC patients in the 2007 National Cancer Institute's Patterns of Care study to examine patient and provider factors associated with treatment and survival by stage at diagnosis. Overall, the study identified those least likely to receive specific therapies in a variety of healthcare settings, with these specific findings: Liver transplants, embolization, or radiofrequency ablation for Barcelona Clinic Liver Cancer (BCLC) stage A patients were performed significantly less often for non-Hispanic blacks, Hispanics, patients in the highest income quartile, and patients with Medicaid. Patients with stage D disease were less likely to receive HCC treatment therapy if they had Medicaid insurance compared to private insurance ( $p < 0.001$  for all). In multivariable analyses, higher all-cause mortality was associated with treatment in a hospital without a residency training program, more advanced stage, and lack of appropriate treatment. [Harlan 2015]

## PATIENT-CENTERED CARE

As is the case with many cancers, patients with HCC need more accessible information about their diagnosis and treatment. In general, patient-centered care—which includes helping navigate patients to the care they need; respecting their preferences; providing timely, relevant, and understandable information; supporting the patient and family; involving the patient in decision-making; and aligning evidence-based decision-making with patient preferences—is an indicator of quality healthcare and contributes directly or indirectly to improved clinical outcomes and health-related quality of life. [Street 2016] A focus on patient-clinician communication is positively associated with HCC screening in patients with chronic liver disease. [Farvardin 2017; Li 2017]

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**The first population-based study to evaluate HCC therapy provided in the community found that liver transplants, embolization, or radiofrequency ablation for BCLC stage A patients were performed significantly less often for non-Hispanic blacks, Hispanics, patients in the highest income quartile, and patients with Medicaid; patients with stage D disease were less likely to receive HCC treatment therapy if they had Medicaid insurance compared to private insurance.**

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Gill et al. conducted a 13-country patient survey to better understand the HCC patient journey by collecting demographic, diagnostic, and treatment information from 256 patients found that 68% felt they did not receive enough information about HCC at diagnosis. Respondents were asked for three words that best described their feelings upon diagnosis of HCC; the five most common words were fear, worry, scared, anxiety, and shock. Of survey respondents, 81% receiving sorafenib, 45% receiving selective internal radiation therapy (SIRT), and 32% receiving transarterial chemoembolization (TACE) reported impaired quality of life. While 42% and 19% of patients treated with sorafenib rated their current QoL as poor or good, none rated it as excellent, respectively—compared with SIRT (22%, 33%, and 6%) or TACE (11%, 37%, and 13%). [Gill 2018] A focus on patient-clinician communication is also positively associated with HCC screening in chronic liver disease patients. [Farvardin 2017; Li 2017]

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## APPENDIX

### HIGHLIGHTS FROM THE 2018 ACCC PROVIDER SURVEY ON MULTIDISCIPLINARY HEPATOCELLULAR CARCINOMA CARE

In July 2018, ACCC launched a survey to gain perspectives from members of the multidisciplinary care teams at community cancer programs. ACCC developed the survey in consultation with the HCC Advisory Committee and project partners to:

- Learn how community cancer program providers around the United States are managing care for HCC patients
- Better understand best practices, effective tools, resources, challenges, and education needs for the multidisciplinary team members who provide care for HCC patients in a community setting

As a result of discussions with the project Advisory Committee members and a HCC literature review to identify best practices, the survey focused on exploring the degree to which community cancer programs are engaged in the following:

- Employing a multidisciplinary team approach to treat patients, including those with dual diagnoses of liver disease and cancer (local expert team or multidisciplinary expertise through access to expert tumor boards, regional knowledge sharing and use of virtual tumor boards)
- Coordinating treatment planning among oncology, hepatology, interventional radiology and surgery, using national guidelines and local cancer program pathways for consistency and quality assurance
- Having the benefit of HCC screening in their medical community to improve patient outcomes through collaboration among community oncologists, primary care physicians, gastroenterologists, endocrinologists, infectious disease specialists, and hepatologists for:
  - Timely referrals for diagnosis and treatment planning
  - Appropriate selection of therapeutic approach in an era of expanding treatment options
- Referring patient to clinical trials and participate in conducting trials
- Practicing patient-centered care, including attention to coverage/insurance issues (such as pre-approvals/prior authorizations for consultations and medications), coordination of appointments and shared-decision making to align clinical goals with patient preferences and psychosocial needs
- Using and tracking the application of national guidelines

The online survey also included a series of questions about helpful tools and resources, challenges and education needs. An online questionnaire was sent to ACCC members in July 2018, and the survey remained open for one month. The project partners and advisors were invited to let colleagues at their institutions and at referring cancer programs know that their participation in the survey was welcome and appreciated. The key findings and survey highlights are presented below.



## WHO RESPONDED TO THE SURVEY?

Survey respondents were asked to provide their primary clinical role in caring for HCC patients. 58% of the respondents are nurses, including 29%, nurse navigators and 10%, each in nurse coordinator or nurse manager roles. Another 10% of respondents are social workers/case managers and 6% define their role as cancer program administrator/practice manager or practice administrator advanced practice provider. Other respondents include a medical director, an interventional oncologist, an oncology chaplain, a multidisciplinary team manager, a lay navigator, marketing staff, and a public health officer. The years of experience among respondents ranges from less than 5 years (21%) to 21 years or more (35%), with 18% having between 5 and 10 years and 25% having between 11 to 20 years of experience. (N=28)

## CANCER PROGRAM CHARACTERISTICS

Respondents describe their facility as a non-teaching community hospital (42%), an academic medical center or teaching hospital (16%, each), private practice (10%), a freestanding cancer center (6%). An additional 10% describe their facility as a research facility, hospital-based outpatient clinic or community teaching hospital. All U.S. regions are represented by the respondents, with most being from the Northeast region (26%), 16% each from the Southeast, Midwest, Southwest, or Northwest regions and 10% from the Mid-Atlantic region. (N=31)

Respondents (N=31) estimate the number of HCC patients treated by their cancer program annually as <10 (32%), between 21 and 50 (26%), between 11 and 20 (19%), >100 (16%) and 51-80 (6%). Almost half (47%) of respondents say that <20% of patients treated received active treatment for HCC (versus observation, referral or supportive care only), while a third say >50% of patients receive active care at their center. (N=30)

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Note: The Advisory group pointed out that “active treatment” was not defined in the survey question, leaving it open to interpretation by respondents. Case reviews by multidisciplinary tumor boards are associated with a higher likelihood of receiving active HCC therapy—and as such may point the way for improvements in care. Little is known about other factors that may affect receipt of active therapy and subsequent outcomes of HCC patients in the community setting. This is an important question for further research.

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About 16% of respondents report that their cancer program is in a medical community that has a surveillance program for populations at risk for HCC, 37% of respondents say their cancer center is not part of such a community and the plurality (41%) don't know. (Fig. 7)

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Note: The Advisory group noted that many providers in various communities may be screening populations at risk for HCC within their own practices, but a unified, pathway-driven program across specialties may be lacking. Shared resources for developing unified programs could contribute to more evidence-based HCC care. (N=31)

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A medical oncologist or hematologist/oncologist is the first specialist seen by HCC patients among 61% of respondents and among 13% of respondents, HCC patients are seen first by a hepatologist. Other respondents say the patient sees both of these specialists, it depends on who diagnoses the patient or, a hepatic surgeon or surgical oncologist, an interventional radiologist, a gastroenterologist who then will refer to a medical oncologist or interventional oncologist, depending on the patient's HCC stage. (N=31)

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Note: The Advisory group expressed the view that what matters most is that patients are cooperatively managed by hepatologists, transplant and hepatobiliary surgeons, medical oncologists, interventional radiologists, and supportive care specialists. The group discussed whether or who does a patient with an HCC diagnosis see first correlates with the degree of HCC expertise among the multidisciplinary team or other factors (such as who is available to meet with the patient). Again, this is an area that might benefit from additional exploration considering its relevance to treatment selection.

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## MULTIDISCIPLINARY TEAMS

Most respondents (61%) are from cancer programs that don't have a specialized hepatobiliary multidisciplinary team, but nearly 4 in 10 programs do (38%) and 66% of these programs conduct HCC institutional grand rounds/tumor boards for other cancer care providers. (N=31) Among centers with teams, the composition and degree of specialization vary: 83% of teams include a radiation oncologist; 75% include a medical oncologist or hematologist/oncologist; 67% include a hepatobiliary surgeon, interventional radiologist or social worker/case manager; 50% include an advanced practice provider, GI specialist nurse navigator, pathologist, or surgical oncologist; 42% include a hepatologist; 33% include a transplant surgeon, radiologist, pharmacist or palliative care specialist; 25% include a financial advocate, nurse manager or nurse navigator. Other team reported by respondents include a liver specialist nurse navigator, pharmacy technician, research nurse and oncology chaplain. (N=12)

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Note: The advisory group discussed how realistic it is for many community cancer programs to have a specialized multidisciplinary team because of the volume of HCC patients in their care. A more attainable goal for some community cancer programs may be to have these cases folded under a GI multidisciplinary team that deals with liver surgery and other related care. However, most community hospitals do not have a GI team either. More study is also needed to understand how best to share specialized HCC expertise for the benefits of patients among community cancer programs and between academic centers and community cancer programs.

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Respondents from cancer programs without a specialized hepatobiliary multidisciplinary team manage HCC patients as follows: in consultation with tumor boards/expert tumor boards (85%); in consultation with or by referring to an HCC oncology specialist (21%, consult, 37% refer) or an expert hepatologist for liver disease (21%, consult, 26% refer); by referring to an expert diagnostic radiologist (21%); by referring to an expert interventional radiologist (21%), and by referring to clinical trials (32%). One respondent's program refers to a virtual tumor board. In response to the

question, “Would access to a virtual expert tumor board be helpful to your cancer program for the management of HCC patients?” 24% of respondents say yes and 57% are not sure, while 20% say no.

Among survey respondents, multidisciplinary team reviews of all HCC patient cases are conducted regularly (36%) or as needed (22%) at their cancer programs. (N=22)  
 Note: The advisory group noted that every HCC case should be reviewed by a tumor board and given the relatively low volume of HCC patients this should be an achievable goal. Patient advocacy partners mentioned the opportunity to educate patients on self-advocacy in making sure their cases are reviewed by expert multidisciplinary teams.

## CLINICAL TRIALS

About half of respondents (52%) say their cancer program initiates discussions with all HCC patients about participation in clinical trials and another 24% help patients get more information if they ask about clinical trials. Others say they either only discuss trials with patients who have advanced disease with no curative standard treatment options or if they have an appropriate study for the patient. (Table 3)

Table 3. Cancer Programs and HCC Clinical Trials	
<i>% that discuss trials with all HCC patients (N=21)</i>	<i>% that conduct HCC trials (N=11)</i>
52	55

## GUIDELINES

About half (52%) of respondents’ cancer programs have a formal program or protocol that outlines adherence to the National Comprehensive Cancer Network (NCCN) guidelines for HCC management, another 5% are currently developing one and 43% are not developing one at the time of the survey. None of the respondents indicate using American Association for the Study of Liver Diseases (AASLD) or American College of Gastroenterology (ACG) guidelines.

## PATIENT-CENTERED CARE

The survey explored coordination of patient appointments and communications among providers and patients. Relatively few responded to this question, but those who did (N=9) indicated that someone at their cancer center scheduled:

- Diagnostic evaluations by multiple physician specialists at a single appointment on the same day whenever possible
- Tests or consultations with multiple providers at one visit as needed for subsequent visits whenever possible

Respondents were asked how often they explain how their cancer program staff communicates about specific aspects of HCC care to patients, ranging from never or rarely to always. (Table 4)

**Table 4. Percentage of Cancer Programs Communicating with HCC Patients about Specific Aspects of Care\*  
(N ranged from 13 to 14)**

We ask patients' preferences for receiving information about their diagnosis/treatment, including language, including/excluding family members, participation in treatment decisions, disease severity, and expected treatment outcomes	79%
We explain the team members' roles	85%
According to patient preferences, we explain the diagnosis/next steps and answer questions	93%
According to patient preferences, we explain the patient's HCC stage	86%
According to patient preferences, we discuss prognosis/risks/benefits of various treatments	93%
We ask patients about QoL preferences and then make treatment recommendations	86%
We encourage patients to share in treatment decisions	93%
We explain the benefits of symptom management and encourage an open dialogue	93%
We offer supportive (palliative) care at the start of treatment	57%
We are proactive about asking patients about symptoms at every visit	93%
We are proactive about telling patients how to recognize when they might need emergency care and what to do	93%
We encourage patients to ask questions and make it easy for them to reach a team member	93%
We are proactive about asking patients about distress (depression and anxiety) at every visit	92%
We refer patients for treatment for depression/anxiety based on psychosocial screening	87%
We connect patients with financial counseling and treatment assistance programs	86%
We take out-of-pocket costs into consideration when making treatment recommendations	72%
When needed, we facilitate a transition to hospice care	93%
<i>*Combined % responding most of the time, almost always or always</i>	

## BARRIERS, CHALLENGES, AND WAYS TO IMPROVE HCC PATIENT CARE

Respondents say the barriers or challenges that their cancer program or practice faces in managing patients with HCC include: (N=13)

- Lack of psychosocial services, lack of surveillance (screening) for early diagnosis in their medical community, or no access/limited access to clinical trials, 31% each
- Delayed appropriate treatment (e.g., patients referred to our cancer program were under care of a general oncologist or general gastroenterologists who were not well-versed in which patients may be candidates for curative therapy), diagnostic or monitoring tests reimbursement/healthcare coverage issues, or drug or other treatment reimbursement/healthcare coverage issues, 23% each
- Delayed diagnosis (e.g., patients referred to your program are diagnosed in late stages even when they have sought earlier evaluation for symptoms) or insurance/healthcare coverage issues for referral for evaluation at our cancer program, 15% each
- Diagnostic or monitoring tests reimbursement/healthcare coverage issues, 7%.

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Note: Patient advocacy partners underscored the importance of for psychosocial services for HCC patients.

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A few respondents offer these answers to the question: *What are some ways your cancer program could improve HCC patient management?* (N=4)

- Expert clinicians
- Increased financial support
- Use of nurse navigator
- Community-based screening programs
- Psychosocial management
- Having a financial counselor on site
- Developing a codified standard protocol

## HELPFUL RESOURCES

Respondents find pharmaceutical (85%) and non-pharmaceutical patient assistance programs (54%) to be helpful in their cancer programs and about a third use ACCC's Patient Assistance Guide (31%) and ACCC Financial Advocacy Network (38%). (N=13) Respondents also say that more financial resources for patients insured by Medicare and Medicaid would be helpful, along with better patient education materials. The materials used for patient education now include education materials developed by their cancer programs (29%), HCC education materials developed by advocacy organizations (64%), as well as chemo, nutrition, and radiation guides. (N=14)

## PROVIDER EDUCATION NEEDS

Respondents (N=14) say they would be most likely to seek more education and information about:

- Updates on HCC guidelines (57%)
- Screening and surveillance and transplant criteria for patients with early stage HCC (50% each)
- Updates on treatment options for early, intermediate, and late stage HCC and research and clinical trials updates (43% each)
- Long-term follow-up (36%) and diagnostic testing and staging (29% each)
- Palliative care (14%) (N=14)

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### MULTIDISCIPLINARY HEPATOCELLULAR CANCER CARE ADVISORY COMMITTEE

**Tiffany Brosius, RN, BSN, OCN**

Nurse Navigator  
*Winship Cancer Institute of Emory University  
Atlanta, GA*

**Danielle D'Aguanno, MSW, LSW**

Lead Transplant Social Worker  
*Einstein Medical Center  
Philadelphia, PA*

**Matthew Dugan, DO**

Medical Oncologist  
*New England Cancer Specialists  
Scarborough, ME*

**Anurag Maheshwari, MD**

Gastroenterology/hepatology specialist  
*The Institute for Digestive Health and Liver Diseases  
Mercy Medical Center  
Baltimore, MD*

### PROJECT PARTNERS

**Donna Cryer, JD**

President & CEO  
*Global Liver Institute*

**Hildy Dillon, MPH**

Vice President  
Education & Support Programs  
*Cancer Support Community*

**Katherine Sharpe, MTS**

Senior Vice President  
Patient and Caregiver Support  
*American Cancer Society, Inc.*

**Philip A. Philip, MD, PhD, FRCP**

Professor of Oncology and Pharmacology  
Director, GI and Neuroendocrine Oncology  
*Karmanos Cancer Institute  
Wayne State University  
Detroit, MI*

**Melanie Byrne Thomas, MD**

Vice Department Chair, Hematology-Oncology  
Associate Center Director for Experimental  
Therapeutics  
*Gibbs Cancer Center and Research Institute  
Spartanburg Healthcare System  
Spartanburg, SC*

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Director, Development

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Director, Provider Education

**Leigh M. Boehmer, PharmD, BCOP**

Medical Director, Education

**Amanda Patton, MA**

Senior Manager, Editorial

**Clare Karten, MS**

Consultant  
*CTK Consults*



Association of Community Cancer Centers

1801 Research Boulevard, Suite 400  
Rockville, MD 20850  
301.984.9496  
[acc-cancer.org](http://acc-cancer.org)

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