DEVELOPING A COMPREHENSIVE FATTY LIVER DISEASE PROGRAM

Why should health systems develop a dedicated program focused on nonalcoholic fatty liver disease (NAFLD)?

Overview

Nonalcoholic fatty liver disease (pronounced "naphl-d") affects about 25% of the US population. Approximately 30% of those with NAFLD will develop a more severe form of liver disease called nonalcoholic steatohepatitis (NASH). Over the next 10 years, Sg2 forecasts increases in inpatient discharges and outpatient volumes for these conditions. If left untreated, 20% of NASH patients will develop severe liver scarring and degeneration (ie, cirrhosis). Liver transplants for end-stage fatty liver cirrhosis have increased by a staggering 280% in the past decade.

NAFLD arises concurrently with, and catalyzes progression to, numerous comorbidities. In response, leading health systems have developed multidisciplinary liver disease or hepatology programs to diagnose and treat NAFLD and NASH. Teams of providers, including dieticians, hepatologists, endocrinologists, genetic counselors, registered nurses, social workers, infectious disease specialists and transplant surgeons, collaborate to provide appropriate treatments at various stages of liver disease. Successful hepatology care collaborations remain with the patient from initial intake to diagnosis, treatment and all subsequent follow-up care, with each transition carefully linked to the next. Ultimately, the growing disease burden and opportunities for improved care signal that health systems can leverage these multidisciplinary programs to both strengthen NAFLD/NASH care linkage and grow their volumes.

Incidence, Acuity and Costs

The incidence of fatty liver disease is growing in the US, although patients fall on a wide continuum. Driven by decades of poor diet and sedentary lifestyles, nonalcoholic forms of fatty liver disease frequently coincide with obesity, addiction and mobility disorders. An increasing number of younger patients with obesity has collectively decreased the age of incident NAFLD. However, early-stage NAFLD is often asymptomatic, readily reversible and comparatively benign—similar to diabetes and chronic kidney disease. Other drivers of liver disease, including alcohol use, viral hepatitis and genetic factors, quicken the progression of the disease.

Untreated NAFLD leads to other chronic diseases and converts into an advanced, deadlier stage called NASH. This eventually occurs in about one-third of patients. NASH is characterized by inflammation and fat accumulation (steatosis) in the liver. Some consider NASH a manifestation of diabetes in the liver. Additional years of stress from early onset obesity has increased the prevalence of advanced liver diseases. Between 3% and 12% of the population is affected by NASH. By 2025, it is expected that more than 25 million Americans will have NASH-related liver disease.

Early diagnosis and intervention are key, as latent disease can quickly progress to irreversible stages. Progressive liver scarring (fibrosis) leads to cirrhosis and, ultimately, liver failure. This final stage, also referred to as decompensated cirrhosis, is ultimately experienced by 45% of patients with cirrhosis and requires a liver transplant to keep the patient alive.

As the population ages, admissions with previously undiagnosed decompensated cirrhosis will further burden health systems. A 2018 study showed that, between 2006 and 2013, inpatient fatty liver disease charges increased 207%. Accordingly, health systems will need a strategy to deal with this increasingly common comorbidity.

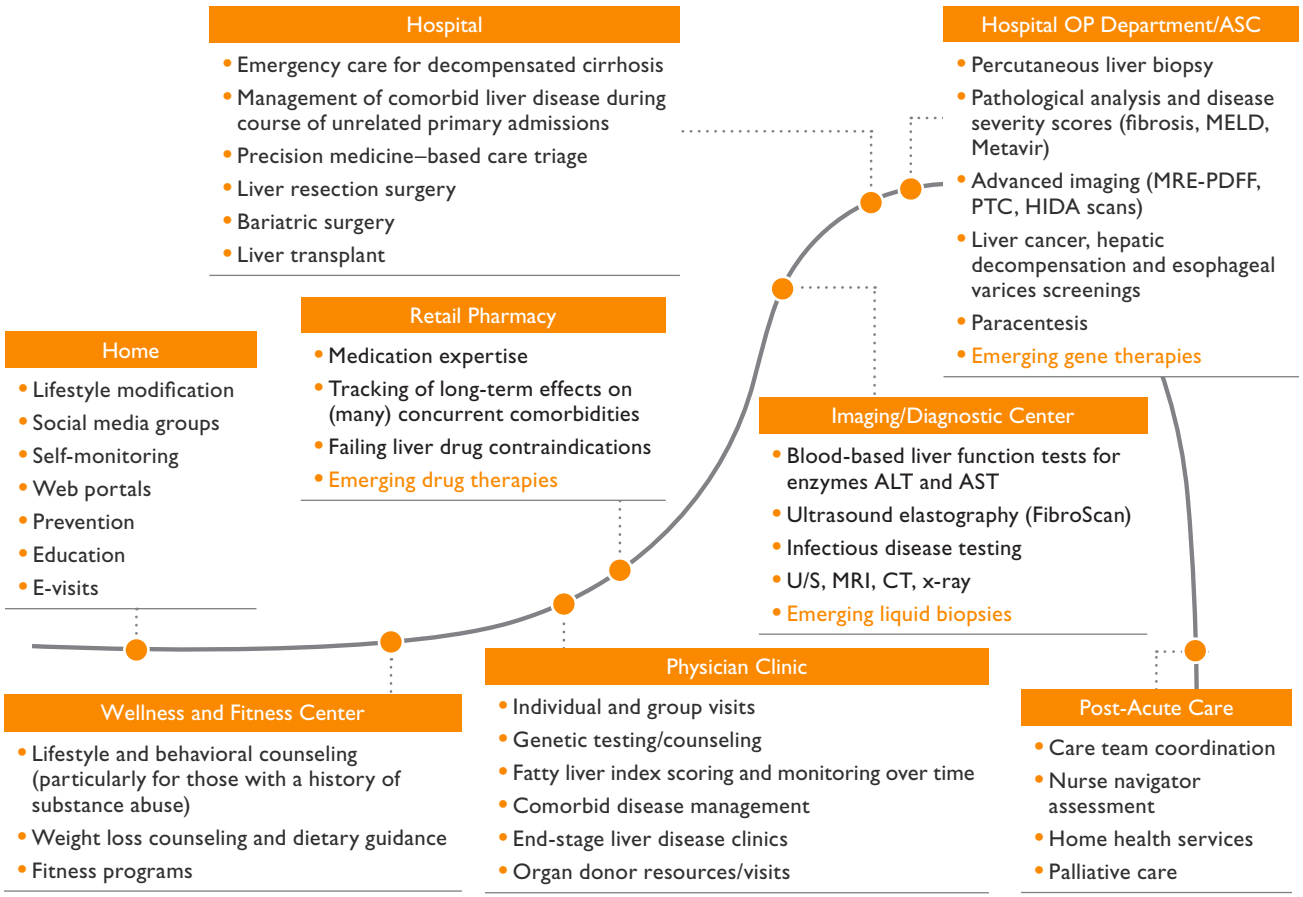
The Future of Clinical Management

Nonalcoholic fatty liver disease patients often initially present with general malaise during a primary care visit. They may be completely asymptomatic or have nonspecific symptoms, such as sleep disturbances and/or pain in the right upper quadrant. Increasingly, the initial finding is incidental during an imaging study for an unrelated concern.

Given these nonspecific symptoms, it is essential for all providers in the early stages of the care continuum to be aware of NAFLD and know where to refer the patient to obtain an official diagnosis. Early intervention and linkage to downstream care with coordination are key to reversing symptoms and halting disease progression.

Comprehensive fatty liver disease programs can be one way to address this issue, as such programs draw together a variety of disparate services. Patients enter through primary care, are generally managed in the outpatient setting, require ongoing imaging/diagnostic testing to monitor disease progression and ultimately may require referrals to receive a liver transplant or palliative care. Essential services are outlined throughout the System of CARE in Figure 1.

FIGURE 1. NAFLD/NASH SYSTEM OF CARE



ALT = serum alanine transaminase (aka alanine aminotransferase); ASC = ambulatory surgery center; AST = aspartate aminotransferase (aka SGOT); CARE = Clinical Alignment and Resource Effectiveness; HIDA = hepatobiliary iminodiacetic acid scan (aka hepatobiliary scintigraphy); MELD = model for end-stage liver disease; MRE = magnetic resonance elastography; PDFF = proton density fat fractionation; PTC = percutaneous transhepatic cholangiography; U/S = ultrasound. **Source:** Sg2 Analysis, 2018.

Diagnosis

Liver function can be determined via blood tests, ultrasound imaging and pathological analysis of liver biopsies. Although this may change within the next few years, at time of publication, liver biopsy remains the standard of care for diagnosing NASH.

Liver biopsies are typically performed subcutaneously by a gastroenterologist, hepatologist or radiologist. However, very obese patients may require more complicated approaches, including laparoscopic, transjugular or endoscopic procedures. The invasive procedure is quite painful, requires use of a long needle and introduces risk of severe complications, including death. Fear of the procedure itself motivates some to undergo extreme behavioral modifications to lose weight and exercise more frequently. Understandably, patients can be hesitant to undergo such procedures and are often lost to follow-up care. Therefore, care linkage is paramount.

At present, pathological analysis of liver biopsies by a pathologist is necessary to assign a fibrosis score between F0 (no fibrosis) and F4 (cirrhosis). This score determines treatment course. One-quarter of patients are F4 at initial diagnosis. Increased nonalcoholic fatty liver disease awareness in the primary care setting and the emergence of effective noninvasive screening modalities will lead to earlier diagnoses for many patients.

Blood-based tests performed by phlebotomists and lab technicians remain a staple for liver disease screening. However, these are notoriously unreliable, yielding results that vary by time of day, exercise history and time between meals. Diagnostic methods currently in development use advanced analytics that incorporate a combination of tissue pathology, clinical predictors and serum biomarkers. Watch for commercially available liquid biopsies to emerge on the market within a few years.

Imaging

Two imaging techniques can provide a noninvasive diagnosis of NASH and can be performed safely by a variety of providers (see Table 1). While they fall short of the gold standard of liver biopsy and fail to provide a fibrosis score, they can approximate disease stage.

TABLE 1. NONINVASIVE IMAGING TECHNIQUES TO DIAGNOSE NASH

VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY*	MAGNETIC RESONANCE ELASTOGRAPHY (MRE)
• It is a noninvasive technique for assessing the hardness of liver tissue. • Advantages of this technique include a lack of side effects; a global analysis of the liver as opposed to biopsy, which only samples a region; and the ability to frequently repeat the procedure. • It is useful for monitoring the progression of cirrhosis or advanced fibrosis. • It avoids the complications and risks associated with liver biopsy. • A disadvantage of this technique is the potential for underestimating or overestimating the extent of disease and disease types in some patients (particularly in obese patients). • Almost all NAFLD programs include this imaging modality as a first-line diagnostic option.	• It is a noninvasive technique for accurately detecting advanced fibrosis and cirrhosis. • It uses a specially designed sound wave–emitting probe to assess tissue hardness. • It is used in conjunction with MRI advanced visualization. • Many believe MRE provides better results than transient ultrasound elastography, especially for obese patients. • The disadvantages of this technique include high costs and restricted availability. • This device may be a differentiator for some advanced health systems.

*Often goes by "ultrasound elastography" or FibroScan®.
Sources: Brunt EM et al. *Nat Rev Dis Primers.* 2015;1:1–22; Sg2 Analysis, 2018.

Treatment

First-Line Therapies

First-line treatment for all patients should focus on dietary alterations and increased physical activity. These often reverse early stages of nonalcoholic fatty liver disease within weeks. In the majority of NASH patients, weight loss of about 5% to 10% can significantly improve liver health and comorbid metabolic disease.

In addition to lifestyle modifications, management of diabetes, hyperlipidemia, sleep disorders, mental health, underlying infections and hypertension improves care quality and outcomes for patients with NASH. Patients with more advanced steatohepatitis and fibrosis will require more aggressive lifestyle modifications and should be considered for pharmacotherapies that are also used to treat diabetes. Bariatric surgery is an emerging therapeutic intervention.

Patients whose NASH has led to irreversible fibrosis have few options. Paracentesis is a procedure to remove fluid that accumulates in the abdomen (called ascites) of cirrhotic patients.

For end-stage liver disease, liver transplantation is the last curative option. Patients require ongoing disease monitoring to assign/adjust their MELD score, which determines their position in the long waiting list for liver transplantation. Living-donor liver donations offer some patients the option to "step out of line" if patients are able to identify a qualifying donor. Living liver donors rely upon the diagnostic tests and imaging described above to ensure their liver is healthy enough to transplant.

Emerging Therapies

The disease progression of nonalcoholic fatty liver disease and steatohepatitis is unique to each patient. Accordingly, treatment should also be individualized. The emerging area of precision medicine holds much promise for subsegmenting NAFLD/NASH into distinct care pathways that will yield optimal effect. These approaches combine all known metrics about the patient. Within the next decade, advanced analytics that integrate genetic predisposition, inflammation state, liquid biopsy results and comorbidities may ultimately supplant liver biopsies and imaging to diagnose and stage the disease.

Pharmaceutical companies are in the final stages of developing new drugs and repurposing old drugs to treat NAFLD and NASH. These technological advancements have been catalyzed by the successful collaborations previously forged between big pharma and hepatologists to develop the direct-acting antiviral drugs that now serve as an outright cure for chronic hepatitis C infection. The development has been further accelerated by the ability to track efficacy through next-generation blood tests and noninvasive imaging techniques described above.

Expect a variety of new medical therapies to hit the market within the next 1 to 2 years. Some of the many targets of these medical therapies include the gut, fat storage, bacteria in the gut (microbiome), metabolic stress, inflammation and developmental processes that promote fibrosis. Many of these drugs are repurposed agents that work well and are well tolerated for other diseases but simply have not been tested until now for efficacy in NAFLD/NASH. The unmet pharmacological need coupled with minimally invasive monitoring of disease course have catalyzed the pharmaceutical industry's interest in this space.

Gene therapies are already available for some liver diseases. Co-option of the liver-targeted delivery of these therapies and the increased knowledge of genetics underlying (or protecting from) liver disease suggest we are likely to see NAFLD/NASH gene therapies on the market within 5 to 8 years.

Sg2 NAFLD Forecast

The incidence of nonalcoholic fatty liver disease and steatohepatitis will increase throughout the next decade, driven by an aging population and the rising prevalence of obesity. Sg2 forecasts a 10-year inpatient increase of 7% in the Liver Diseases, Noninfective CARE Family, which includes NAFLD and NASH.

Outpatient volumes of the Liver Diseases, Noninfective CARE Family will grow sharply. Sg2 projects a 20% growth in outpatient volumes over the next 10 years.

Liver diseases command strong procedural growth. Associated procedural volumes will rise over the next decade. More than 380,000 percutaneous biopsies were performed in 2018, and that number is expected to grow 17% by 2028. In 2018, over 92,000 paracenteses were conducted; by 2028, however, this procedure will grow by 19%. Liver transplants will grow by nearly 18% over the same time frame—constrained only by organ supply.

Dedicated Fatty Liver Disease Programs

Rising incidence rates of NAFLD and NASH create opportunities for health systems to grow volumes, but they also place increasing pressure on health systems to deliver well-coordinated care that effectively manages this complex patient population.

Dedicated programs can facilitate improved disease management by directing patients to the correct interventions and ensuring there are proper linkages between each phase of care. Focused programs can allow a health system to scale its services while also reducing some of the associated administrative costs, overhead costs, technology investments and service contract costs. Other methods of, and reasons for, developing a dedicated program are as follows.

Gather Disparate Services to Ensure Care Continuity

A fatty liver disease center is a convenient referral source for primary care providers. It also is a conduit for provider-provider education and best practices dissemination, as clinical care guidelines are poised to change in accordance with emerging pharmaceutical and gene therapies.

Furthermore, a 1-stop shop provides an intuitive entry point for patients who are aware of long-standing liver disease. These may or may not include NAFLD/NASH. Other common chronic liver conditions are portal hypertension, viral hepatitis and alcoholic liver disease. The most effective programs manage all these diseases and can juggle and triage their respective treatments.

Diagnostics remain the biggest barrier in starting treatment for nonalcoholic fatty liver disease. Many patients simply are not aware they have the condition until the disease has caused irreparable harm. The invasiveness of the liver biopsy procedure further lowers the diagnostic compliance rate. Programs should be mindful of these limitations and focus on a consumer/patient point of view to prevent patients from dropping out of care.

Early diagnosis is critical for optimal outcomes—but only if the patient is linked to subsequent care. As symptoms can be invisible for decades, many patients forget or do not understand their diagnosis, which leads to a missed opportunity to intervene when symptoms are reversible.

Manage Comorbid Admissions Efficiently to Capture Payer Volumes

Throughout the US, 90-day readmission rates are 21% for cirrhotic liver disease. Further, 1 in 4 of these readmissions is to a hospital different from the original point of discharge. High readmission rates occur because patients often continue to struggle with the same underlying issues—such as substance abuse, diabetes and obesity—that precipitated liver dysfunction and their initial hospitalization. Cirrhotic disease further complicates postdischarge plans for 2 reasons: first, it alters mental states, leading to confusion and difficulty remembering plans and following medical orders; second, cirrhotic disease slows the metabolism of drugs used to treat other coincident disease(s), which can make effective pharmaceutical management quite complicated. Daily follow-up with remote monitoring through virtual health care delivery is critical.

Hospitalization rates and lengths of stays are increasing, and readmissions are much higher than for other chronic conditions (heart or lung diseases). Despite this, postdischarge patients with chronic liver disease are surprisingly less likely to utilize post-acute care facilities like skilled nursing (8%) or home health (6%) than postdischarge patients with chronic obstructive pulmonary disease (12% and 11%, respectively). Given the opportunity to improve care management, health systems might consider participation in emerging value-based care initiatives. Programs such as the recently announced Bundled Payments for Care Improvement (BPCI) Advanced by CMS provide health systems with financial incentives to redesign care models for chronic liver diseases, including NAFLD/NASH.

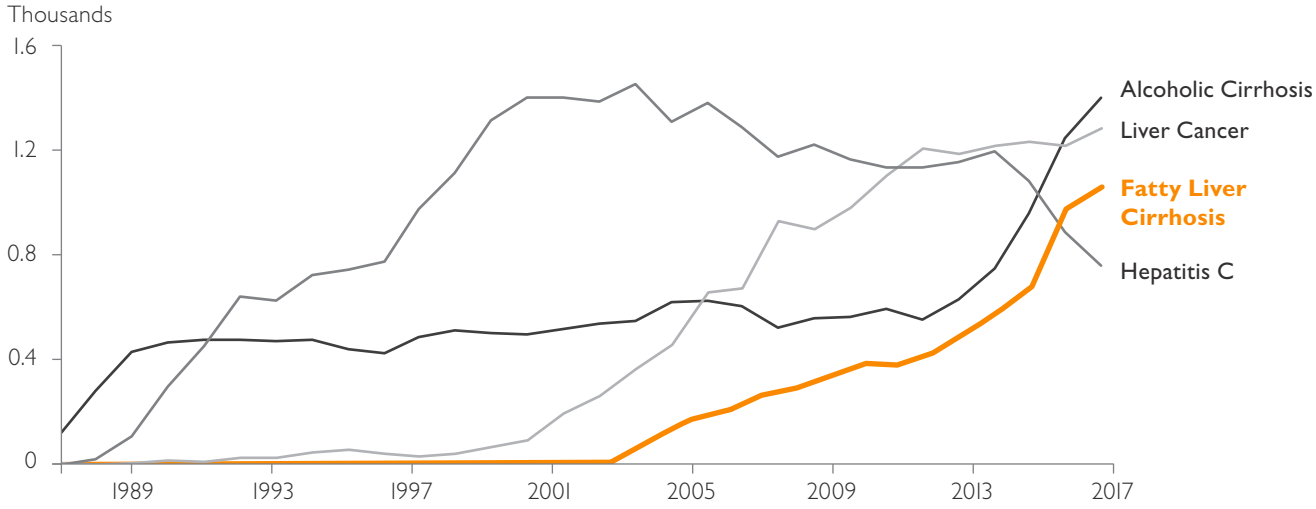
Commercial payers recognize that the ongoing obesity epidemic is leading to comorbid liver disease. As a result, health systems that provide post-acute care continuity for patients admitted to the hospital with NAFLD/NASH are well equipped to offer a bundled payment product through CMS. This experience can provide a means to negotiate with payers, including employers, to capture commercial volumes.

Channel Lucrative Referrals for Liver Transplant Procedures

Hepatology programs are essentially the lone referral source for liver transplant programs. All patients will be seen and managed at end-stage liver clinics prior to receiving a liver transplant. Although nonalcoholic steatohepatitis is currently the third-leading cause of liver transplantation, it is expected to surpass hepatitis C as the leading cause of liver transplants by 2022 (see Figure 2). Accordingly, systems hoping to grow or even sustain their liver transplant programs would do well to develop or align with a NAFLD/NASH program.

FIGURE 2. CHANGING LIVER TRANSPLANT INDICATIONS

Liver Transplant Volumes, by Recipient Diagnosis, OPTN Data, 1988–2017



Sources: US Department of Health and Human Services. Organ Procurement and Transplantation Network (OPTN). October 15, 2018; Sg2 Analysis, 2018.

Living liver donations currently make up the minority of liver transplants. While still a niche service that may not be practical for every organization, leading fatty liver disease centers are starting to aggressively market and grow these programs to circumvent the supply-limited growth of liver transplantation. A dedicated center can provide the means to identify and screen potential donors to maximize transplantation success. It can also provide a locus for outpatient engagement necessary for the frequent posttransplant follow-up visits.

Multidisciplinary Care for Fatty Liver Disease

Structurally, programs for nonalcoholic fatty live disease and steatohepatitis are often part of large, academic hepatology and gastroenterology divisions. These programs provide multidisciplinary care for NAFLD and NASH patients and coordinate related services and specialties (eg, diabetes management, transplantation, cancer care). Most programs also conduct clinical research around new diagnostic and treatment methods as well as optimal care plans for patients. Table 2 profiles several major fatty liver disease programs across the US.

TABLE 2. FATTY LIVER DISEASE PROGRAMS

University of Pittsburgh Medical Center for Liver Diseases (Pittsburgh, PA)	• Supplies a team of providers to treat patients living with fatty liver disease. This multidisciplinary care team includes physicians who are certified in internal medicine, gastroenterology, transplantation and endocrinology. Other providers include a genetic counselor and registered nurses. • Offers active clinical trials for patients living with liver diseases, given its location at an academic medical center • Provides FibroScan liver testing • Engages in community outreach through social media to increase early liver testing • Stresses the influence of NAFLD on diabetes, obesity, sleep apnea and polycystic ovarian disease through its outreach programs
Dignity Health St Joseph's Hospital and Medical Center, Center for Liver Disease and Transplantation (Phoenix, AZ)	• Provides a full-scale liver center, which is part of the community hospital • Tests patients with all forms of liver disease, including liver cancer (hepatocellular carcinoma), hepatitis C, hepatitis B, NAFLD, cirrhosis/NASH, and autoimmune and metabolic liver diseases • Includes a hepatitis C clinic • Provides satellite offices in California and Nevada in multiple communities • Offers a noninvasive test to stage liver disease • Delivers both IP and OP liver services and is run by hepatologists certified in liver transplantation, gastroenterology and internal medicine
Mount Sinai Hospital, Nonalcoholic Fatty Liver Disease Program (New York, NY)	• Works in conjunction with Mount Sinai Hospital diabetes programs, bariatric surgery programs and primary care physicians to quickly and accurately diagnose and preserve liver function • Offers clinical trials investigating new treatment options for NASH that reduce liver scarring • Focuses on dietary counseling (eg, abstaining from food high in sugar and fat), weight loss counseling and bariatric surgery. Offers comprehensive, integrated diagnostic services with pathology and radiology departments, including blood tests, ultrasound, CT scans, MRIs, FibroScan and liver biopsies. • Provides referrals to transplantation institute

Sources: University of Pittsburgh Medical Center. Center for Liver Diseases; Dignity Health St Joseph's Hospital and Medical Center. Center for Liver Disease and Transplantation; Mount Sinai. Nonalcoholic Fatty Liver Disease Program; Sg2 Analysis, 2018. All websites accessed August 2018.

Strategic Considerations

The number of patients diagnosed with nonalcoholic fatty liver disease is substantial and will continue to balloon, forcing health systems to reevaluate their existing practices and develop better, more coordinated efforts to manage care. As your health system equips itself for this future, consider the following action steps.

- **Gain market share** by creating a 1-stop shop for NAFLD/NASH. Build a multidisciplinary liver disease program that combines providers—including dieticians, hepatologists, endocrinologists, genetic counselors, registered nurses, social workers and transplant surgeons—who collaborate to provide care throughout the entire continuum of liver disease.
- **Ensure smooth linkage** between screening and diagnostics to prevent patients from forgoing care. Increase disease awareness at the primary care level through targeted outreach programs. Prevent patients from dropping out of care by offering less invasive diagnostic modalities such as transient ultrasound elastography and emerging liquid biopsies.
- **Consider enrollment** in CMS's BPCI Advanced program to develop programs that link inpatient care with post-acute care management for liver disease. Daily follow-up with virtual health consults will be critical to reduce readmission rates.
- **Grow liver transplants** by establishing a dedicated NAFLD/NASH end-stage disease clinic as a source for liver transplant candidate referrals—and for living-donor screens.
- **Track and offer emerging therapies** on the diagnostic and therapeutic fronts that will be available within the next few years. The sheer number of late-stage clinical trials and drug targets of focus suggests that new FDA approvals are imminent. Key to delivery and dissemination of these next-generation therapies will be a dedicated hepatology center. Building a program now is a sure bet to compete in this area of emerging epidemiological and technological interest.

Sg2 RESOURCES

- Resource Kit: Growing Your Medicine Service Line
- Technology Guide: Ultrasound

Sources: Nguyen AL et al. *Dig Dis Sci.* October 16, 2018. [Epub ahead of print]; Asrani SK et al. *Gastroenterology.* 2018;155(3):719–729; US Department of Health and Human Services. Organ Procurement and Transplantation Network. October 15, 2018; Diehl AM and Day C. *NEJM.* 2017;377(21):2063–2072; Drew L. *Nature.* 2017;551(7681):S86–S89; Eisenstein M. *Nature.* 2017;551(7681):S90–S91; DeWeerdt S. *Nature.* 2017;551(7681):S92–S93; Scott A. *Nature.* 2017;551(7681):S94–S95; Nogrady B. *Nature.* 2017;551(7681):S96; Tapper EB et al. *Clin Gastroenterol Hepatol.* 2016;14(8):1181–1188; Centers for Medicare & Medicaid Services (CMS). Bundled Payments for Care Improvement (BPCI) initiative: general information. Accessed March 2, 2018; CMS. BPCI Advanced. Accessed August 28, 2018; Centers for Disease Control and Prevention. Chronic liver disease and cirrhosis. Accessed August 28, 2018; Lee S et al. *Mol Syst Biol.* 2017;13(8):938; Weinstein G et al. *JAMA Neurol.* 2018;75(1):97–104; National Institute of Diabetes and Digestive and Kidney Diseases website. Accessed August 28, 2018; Benedict M and Zhang X. *World J Hepatol.* 2017;9(16)715–732; Sumida Y et al. *World J Gastroenterol.* 2015;20(20):475–485; Golabi P et al. *Expert Rev Gastroenterol Hepatol.* 2016;10(1):63–71; Shlamovitz GZ. Paracentesis. Medscape. July 5, 2018; Sg2 Analysis, 2018.