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CONFERENCE REPORT

Fontan-Associated Liver Disease

Proceedings from the American College of Cardiology Stakeholders Meeting, October 1 to 2, 2015, Washington DC

Writing Committee

Curt J. Daniels, MD, FACC, *Co-Chair*
Elisa A. Bradley, MD, FACC, *Co-Chair*
Mike J. Landzberg, MD, *Co-Chair*

Jamil Aboulhosn, MD, FACC, FSCAI
Robert H. Beekman III, MD, FACC
Wendy Book, MD, FACC
Michelle Gurvitz, MD, FACC
Anitha John, MD, PhD, FACC
Binu John, MD, MPH
Ariane Marelli, MD, MPH, FACC, FAHA, FRCPC
Bradley S. Marino, MD, MPP, MSCE, FACC
L. LuAnn Minich, MD, FACC, FAAP, FAHA
John J. Poterucha, MD
Elizabeth B. Rand, MD
Gruschen R. Veldtman, MBChB, FRCP

Conference Participants

Curt J. Daniels, MD, FACC, *Chair*
Michael J. Landzberg, MD, FACC, *Co-Chair*

Leadership Committee

Jamil Aboulhosn, MD, FACC, FSCAI
Robert H. Beekman III, MD, FACC, FAAP
Wendy Book, MD, FACC
Gruschen R. Veldtman, MBChB, FRCP

Elisa A. Bradley, MD, FACC
Dori Carson
Stephen Cook, MD, FACC
Jason Deutch, MBA
MaryJane Farr, MD, MSc, FACC
Michelle Gurvitz, MD, FACC
David Hickam, MD, MPH
Robert Jaquiss, MD, FACC
Kathy Jenkins, MD, MPH, FACC
Anitha John, MD, PhD, FACC
Binu John, MD, MPH
Scott Leezer, BA
Jodi Lemacks, JD
Ariane Marelli, MD, MPH, FACC, FAHA, FRCPC
Bradley S. Marino, MD, MPP, MSCE, FACC
L. LuAnn Minich, MD, FACC, FAAP, FAHA
Gail Pearson, MD, ScD, FACC, FAHA
John J. Poterucha, MD
Elizabeth B. Rand, MD
Averell H. Sherker, MD, FRCPC
Rachel Steury, ACNP
Glenn R. Tringali
Robert Venick, MD, FACG

Address for correspondence: Dr. Elisa Bradley, 473 West 12th Avenue, DHLRI Suite 200, Columbus, Ohio 43220. E-mail: elisa.bradley@osumc.edu.

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ABSTRACT

Over the past decade, as the majority of patients with single ventricle anatomy who have undergone the Fontan operation reach adulthood, a newly recognized disease process, Fontan-associated liver disease (FALD), has emerged. FALD is an extracardiac complication that may lead to substantial comorbid disease and premature mortality. The risk factors, pathophysiology, longitudinal consequences, and therapeutic options related to FALD remain poorly defined. Although we recognize that Fontan circulatory properties are associated with extracardiac organ dysfunction, numerous gaps in our understanding of the nature of this relationship exist. Such extracardiac manifestations, in addition to other late complications of the circulation, can significantly affect quality of life and healthcare use. Therefore, to initiate a formal evaluation of FALD, the American College of Cardiology (ACC) sponsored a stakeholders meeting on October 1 to 2, 2015, in Washington, DC. The goal of the meeting was to bring together subspecialty experts in the fields of adult and pediatric hepatology, congenital cardiology (adult congenital and pediatric cardiology), heart failure/transplant, epidemiology, and cardiothoracic surgery, as well as patient advocates, patients, parents of children and young adults who have had the Fontan procedure, and research organizations and societies to discuss the current state of FALD. Topics included gaps in knowledge, optimal care, research opportunities and barriers, and sound practices to guide providers, patients, and families. This report summarizes findings from the stakeholders meeting and seeks to establish a platform for understanding and addressing FALD.

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In the United States, mortality rates for congenital heart disease (CHD) patients have substantially decreased, as much as 40%, over the last 4 decades (1). Mortality in children has decreased by 31%, and the age at death generally has moved steadily toward older age; now, 76.1% of deaths occur in adulthood (2,3).

Overall, decreasing mortality rates for persons with CHD have been matched by increasing prevalence of CHD in adults, albeit with long-term survival and healthcare resource needs varying substantially with CHD anatomic classification and physiological severity. The median age of patients with severe CHD increased from 11 years in 1985 to 17 years in 2000, and to 25 years in 2010 (**Figure 1**). Likewise, the prevalence of CHD increased by 18% in children compared to 85% in adults from 1985 to 2000, leading to equal numbers of adults and children with CHD in the studied population in 2000 (4-6). By 2010, the number of adults with CHD exceeded the number of children, with adults accounting for two-thirds of all CHD and severe CHD patients (**Figures 2A and 2B**) (5). Severe CHD, a group to which single-ventricle Fontan patients belong, had a prevalence of 1.76 per 1,000 children and 0.62 per 1,000 adults (5). These findings are consistent with those of a systematic review in which the prevalence of severe CHD was estimated at 0.93 per 1,000 adults (7). An analysis conducted in conjunction with the CDC used empirical data from the Quebec CHD database for 2010 to generate age- and race-adjusted numbers for people living with CHD in the United States. It was estimated that in 2010, 2.4 million people were living with CHD in the United States—1.4 million adults and 1 million children—of whom 300,000 had severe CHD (8). Despite current aggregate CHD survival rates to adulthood nearing 90%, persons with severe CHD (inclusive of patients with single-ventricle anatomy status post [s/p] Fontan operation) had survival to a similar age of only 56%, underscoring an important emerging medical crisis (9,10).

Recognizing outcomes disparities for those with Fontan-associated liver disease (FALD), a stakeholder's conference was convened at the American College of Cardiology (ACC) Heart House in Washington, DC. The purpose of the conference and of these proceedings is to review current gaps in knowledge, clinical care, and research, and to develop sound practices to guide providers, patients, and families.

1. OUTCOMES IN ADULT SINGLE-VENTRICLE S/P FONTAN OPERATION

The live birth prevalence of single-ventricle anatomy is estimated to be 35 per 100,000 (9,11). Prior to the 1970s, most children born with single-ventricle anatomy failed to survive into adulthood. With the advent of the Fontan operation, children not only survived, but did so without cyanosis (12). Over the decades since the introduction of the Fontan operation, many modifications have been made to the surgical procedure in attempts to improve flow dynamics and diminish late sequelae (13). Preoperative and postoperative management have also improved, such that the large majority of single-ventricle patients (5,14) are now expected to survive well into adulthood. Indeed, in the modern era, 10-year survival is estimated to be 95% to 98%, compared with 79% in those operated on before 1990 (15). However, late cardiovascular and noncardiovascular complications due to underlying congenital heart anatomy, surgical interventions, and ultimately, the Fontan physiology (16) negatively impact quality of life and may lead to premature death.

Common cardiovascular complications after the Fontan operation include arrhythmias, heart failure, and thromboembolic events (16). Long-term follow-up suggests 59% freedom from adverse cardiovascular events 5 years after the Fontan operation and only 29% freedom at 15 years (14). Adverse events included supraventricular tachycardia, need for pacemaker, stroke, pulmonary embolus, Fontan-associated heart failure defined as New York Heart Association functional class III/IV, protein-losing enteropathy, plastic bronchitis, need for Fontan

FIGURE 1 Median Age of Patients With Severe Congenital Heart Disease Over Time in 1985, 2000, and 2010

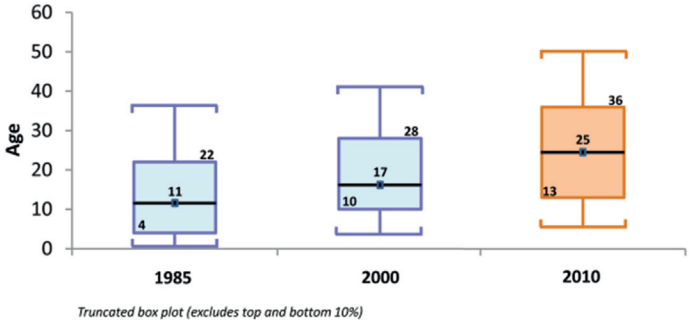
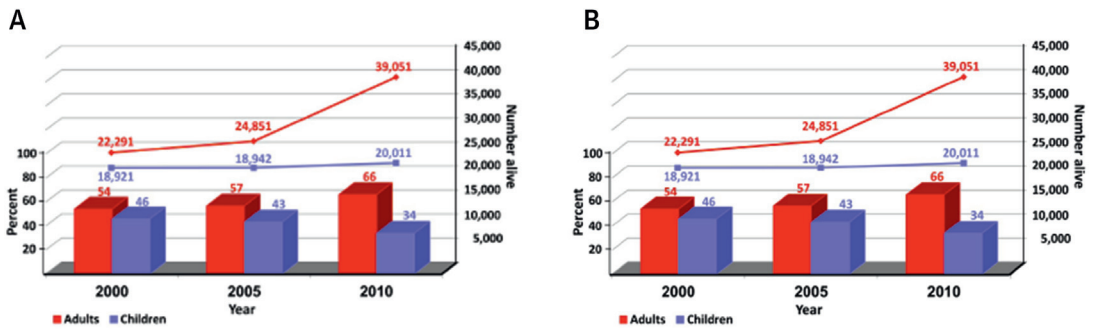


FIGURE 2 The Number and Proportions of Adults and Children in Quebec, Canada, With All Congenital Heart Disease and Severe Congenital Heart Disease Over Time



The number and proportions of adults and children in Quebec, Canada, with **(A)** all congenital heart disease over time in 2000, 2005, and 2010 and **(B)** congenital heart disease over time in 2000, 2005, and 2010.

conversion or takedown, transplant, or death. Other reported cardiovascular effects include exercise intolerance, diastolic dysfunction, and venous stasis (17,18).

Late complications in Fontan patients also arise from noncardiovascular organ systems. The etiology of these findings is likely multifactorial and may be related to the underlying condition, the surgeries required to complete the Fontan circulation, the abnormal physiology of chronically elevated central venous pressures, and underlying genetic predisposition. In the pulmonary circulation, decreased forced vital capacity and restrictive lung disease (19,20) exacerbate the low cardiac output state, further limiting exercise tolerance and increasing vulnerability to lower respiratory infections. Although renal glomerular filtration rate is typically preserved in early adult years, there is often evidence of microalbuminuria (21). From a hematological perspective, patients are prone to thrombosis, hemorrhage, and complications of erythrocytosis if they have low oxygen saturation from residual right to left shunts (22–24). Finally, evidence suggests that patients with a Fontan operation have increased anxiety and depression, more neuropsychological deficits, and lower employment status than the general population (25). FALD is an extracardiac complication that has now recognized with increasing frequency in adolescent and adult patients with a Fontan physiology.

2. FONTAN-ASSOCIATED LIVER DISEASE

2.1. Background: Liver Anatomy, Physiology, and FALD

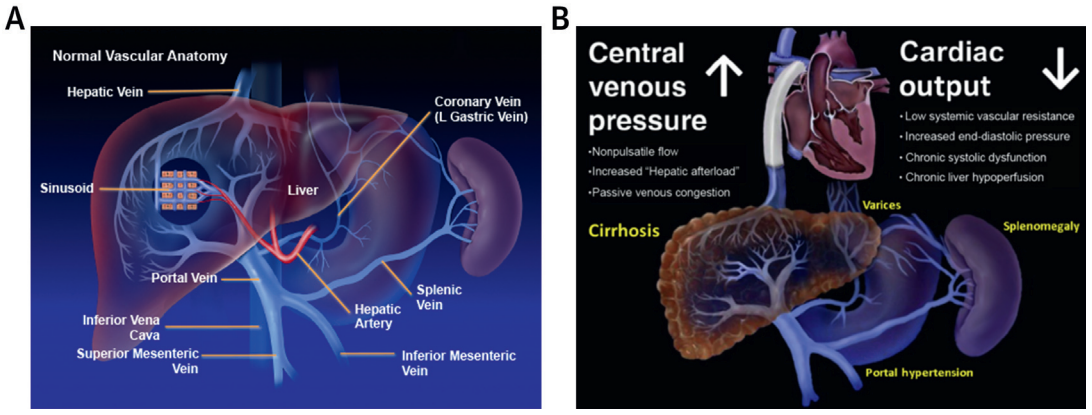
In the normal state, the liver receives about 25% of cardiac output (26). The liver has a dual blood supply, receiving blood from the portal vein and hepatic artery. The portal vein delivers 70% to 80% of the hepatic blood supply and about 50% of the oxygen. Blood from both the portal vein and hepatic artery circulates through the liver via sinusoids lined by fenestrated endothelial cells. Normal hepatic sinusoidal pressure is approximately 5 mm Hg. Blood exits the liver via hepatic veins that drain into the inferior vena cava.

In cases where portal vein flow is attenuated, such as from impaired hepatic venous outflow, overall hepatic blood flow is preserved through augmentation of hepatic arterial flow (autoregulation) up to 30% to 60% above baseline (27). Consequently, hepatic injury due to impairment of portal vein flow is exacerbated by conditions that also lead to impairment of hepatic arterial flow (27). Conversely, decreases in hepatic arterial blood flow are not compensated by increases in portal flow (**Figures 3A and 3B**) (28).

Physiological derangements, medical complications, and surgical interventions over a lifetime with single-ventricle circulation may all contribute to liver pathology. In utero, structural and functional cardiac perturbations that limit systemic perfusion and elevate central venous pressures (such as in hypoplastic left heart syndrome [29,30] with tricuspid regurgitation and atrial septal restriction) are likely to contribute to early liver injury. Postnatally, patients with hemodynamic collapse or severe congestive heart failure may develop ischemic liver injury associated with marked acute increase in transaminases. The liver may be similarly affected by perioperative ischemia, such as in the early post-operative phases following arterial or superior caval shunts. Single-ventricle patients may also experience other hepatic insults, such as chronic hepatitis C infection acquired from blood transfusions received prior to the institution of effective screening of the blood supply in 1992.

When the Fontan connection is established, venous pressures rise abruptly, frequently to 2 to 6 times baseline values, and cardiac output often diminishes.

FIGURE 3 Normal Vascular Anatomy of the Liver



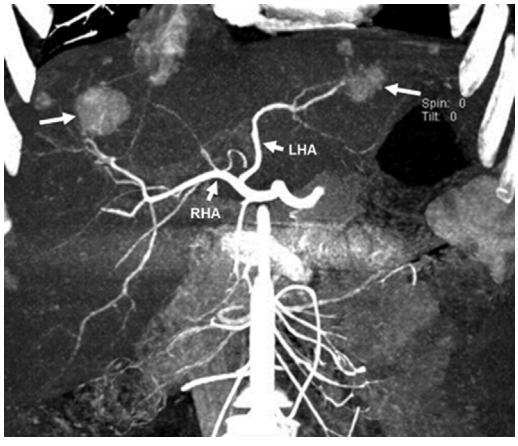
(A) The liver has a dual blood supply: portal vein and hepatic artery. The portal vein is formed by the union of the superior mesenteric vein (which collects blood from the bowel) with the splenic vein (which collects blood from the spleen). Normally, blood from the coronary vein drains into the portal system. After progressive ramifications, blood from the portal vein and hepatic artery join at the hepatic sinusoids, a specialized capillary system that is extensively interconnected. Hepatic sinusoidal blood drains into hepatic venules and then into collecting veins that unite to form the hepatic veins through which blood leaves the liver, draining into the vena cava and the right heart. Reprinted with permission from the American Gastroenterological Association Institute, Bethesda, Maryland. **(B)** In the Fontan anatomy, increased central venous pressure and nonpulsatile flow leads to a state of passive venous congestion secondary to increased hepatic afterload. Decreased cardiac output and increased central venous pressure ultimately lead to cirrhosis along with secondary effects of varices, splenomegaly, and portal hypertension.

During exertional stress, these adverse hemodynamics may be exacerbated. Exercise provokes rises in central venous pressures to levels that may reach 20 to 30 mm Hg (18,31-33). This is accompanied by compromised cardiac output relative to the demands of the exercising muscle (33), contributing to local and systemic tissue hypoxia and ischemia (34).

The Fontan hemodynamic milieu provides a predisposed environment for chronic hepatic injury (35-37). It is speculated that the continuous increase in central venous pressure associated with Fontan physiology may cause more liver injury than intermittent or pulsatile increases in systemic venous pressure, as might occur in a patient with long-standing tricuspid regurgitation. High central venous pressures are transmitted to the hepatic veins (so-called "hepatic afterload") and in turn to hepatic sinusoids. Because hepatic sinusoids lack valves, portal vein pressures are proportionately increased, leading to a decrease in portal venous inflow. The hepatic arterial buffer response results in greater arterialization (i.e. a larger portion of hepatic blood flow being derived from the hepatic artery) of liver blood flow under these circumstances. However, when the venous pressures exceed 20 to 25 mm Hg, hepatic arterial buffer responses cannot adequately compensate, leading to reduced liver perfusion and ensuing injury—especially in the context of impaired cardiac output (37). There is indirect evidence for arterialization of hepatic blood flow in patients after Fontan surgery. Arterialized nodules are often observed in Fontan patients (**Figure 4**), analogous to Budd-Chiari syndrome, where there is venous outlet obstruction and arterialization of liver inflow (38).

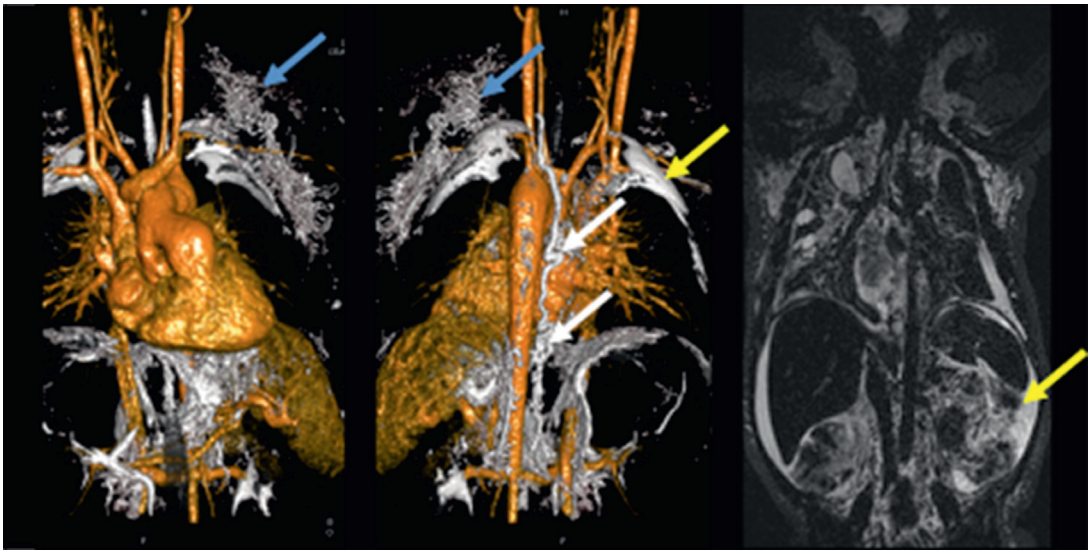
Inherent in this hypertensive venous physiology is a greater dependence on the lymphatic circulation through microcirculatory adaptation that keeps edema thresholds

FIGURE 4 Arterial Phase CT Scan



There are 3 larger nodules present and at least 2 smaller nodules. LHA = left hepatic artery; RHA = right hepatic artery.

FIGURE 5 T2-Weighted MRI Images Demonstrating Lymphatic Pooling and Lymphatic Overflow Representing Lymphangiectasia, and Abnormal Lymphatic Drainage With Associated Tissue Edema



White areas: Blue arrows indicate abnormal lymphatic collaterals; white arrows indicate abnormal thoracic duct tortuosity; yellow arrows indicate tissue edema and "pools" of fluid accumulation presumably related to lymphatic overload and drainage abnormality. MRI = magnetic resonance imaging. Images courtesy of Yoav Dori, MD, PhD.

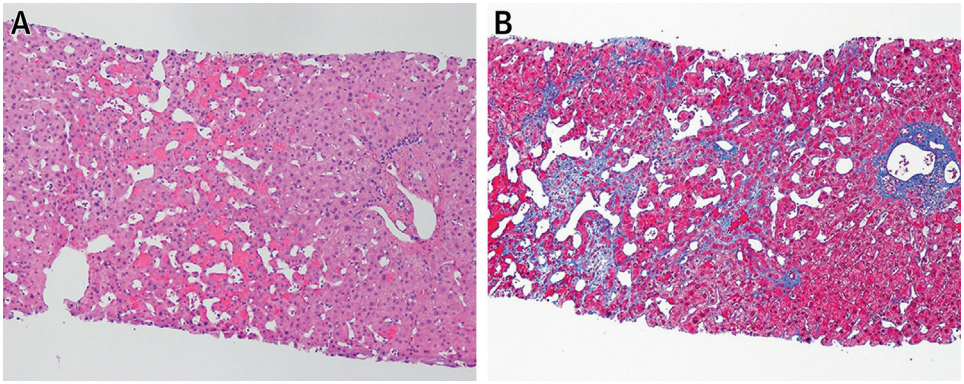
low (39,40). Because central venous pressures in the downstream superior caval vein are also elevated, lymphatic decompression via the lymphatic duct is compromised, and lymphatic overload is commonplace in Fontan circulations. Hepatic congestion is also associated with greater activation and dependence on the lymphatic circulation (41). Therefore, when lymphatic drainage is in any way impeded, as is often the case in the Fontan physiology (40,42), lymphatic-mediated congestion further contributes to sinusoidal dilation (**Figure 5**) (43).

Not surprisingly, after Fontan surgery, nearly all patients will have abnormal liver histology (35,44). High central venous pressure and impaired hepatic venous drainage result in sinusoidal dilatation around the central veins (hepatic acinar zone 3 or centrilobular area). Extravasation of red blood cells into the space of Disse is felt by some pathologists to confirm resistance to hepatic venous outflow. Hemorrhagic necrosis can ensue, although inflammatory cells are absent (44). Persistence of this insult may contribute to the development of pericentral and perisinusoidal fibrosis. When fibrosis progresses, central-to-central vein or central-to-portal vein bridging occurs. Staging of fibrosis is done using a semiquantitative scale ranging from 0 (no fibrosis) to 4 (cirrhosis) (**Figures 6A and 6B**). Cirrhosis is defined as fibrosis encircling nodules with regeneration of hepatocytes. Compensated cirrhosis may be asymptomatic with preserved hepatic synthetic function, but decompensation typically ensues as liver disease progresses. There is a degree of interobserver/intraobserver variability with liver biopsy specimens and their interpretation, and therefore, the results should also be analyzed in reference to the clinical findings.

Even with early stages of fibrosis, ascites may result from increased sinusoidal pressure and impaired lymphatic drainage (45). In afflicted patients with Fontan physiology, ascites is characterized as fluid protein of >3 mg/dL and a SAAG (serum albumin-albumin level ascitic fluid) >1.1 g/dL (46). Importantly, the absence of ascites does not exclude advanced liver disease or Fontan failure. Mild increases in spleen size may be seen even in patients without cirrhosis. The risk of cirrhosis is correlated with increased systemic venous pressure and time after Fontan (47). In one case series, 43% of patients had advanced fibrosis 30 years after Fontan operation (48). Patients with cirrhosis and very high portal pressures may form portosystemic collaterals, including esophageal varices. The presence of portosystemic collaterals generally indicates marked increases in portal pressures and a poor prognosis (49). It is important to distinguish these from the systemic-pulmonary venovenous collateralization seen after Fontan surgery, typically in patients with higher systemic venous pressures.

The following sections provide the current state regarding FALD and the gaps and disparities in our

FIGURE 6 Sinusoidal Dilatation and Congestion: H & E Stain and Masson Trichrome Stain



(A) H & E stain. **(B)** Masson trichrome stain: moderate (stage 2 to 3) hepatic fibrosis. Both panels courtesy of J. Poterucha.

knowledge to better understand, evaluate, and treat this disease process and patient population.

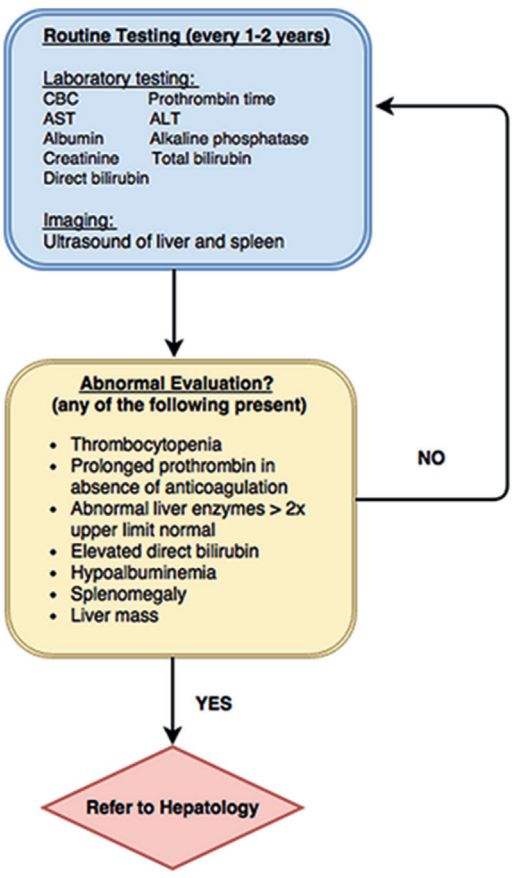
2.2. Evaluation of FALD

In most cases of FALD, liver disease is found incidentally, rarely causing subjective complaints from patients or objective physical examination findings until late in the course of disease. FALD, like other forms of liver disease, currently requires a multidimensional evaluation consisting of: clinical examination, laboratory data, and imaging, with or without histological evaluation. The difficulty lies with interpretation of this data in the unique single-ventricle/Fontan population, where characteristics of FALD differ from the expected changes found in other causes of liver disease. Current evaluation of the liver in FALD varies among institutions. In general, this evaluation relies on local CHD and hepatology expertise, and would, at least in part, be comprised of the assessment outlined in Figure 7. Typically, the evaluation starts with clinical history and physical examination. On examination, the liver size can be normal, enlarged if there is chronically elevated central venous pressure or small when there is advanced disease and cirrhosis. Jaundice, spider angiomata, splenomegaly, and varices are not common until advanced disease is present. Fontan patients may experience dependent edema, which can be related to the Fontan circulation itself or to underlying liver disease. Ascites is present in a minority of patients, but is not specific for FALD, as it may also be present in protein-losing enteropathy and various subtypes of Fontan failure (see phenotype of the failing Fontan circulation).

2.2.1. Laboratory Data

Liver enzymes and bilirubin are typically normal or mildly elevated. The degree of liver enzyme elevation does not

FIGURE 7 Typical Current Evaluation of FALD



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; FALD = Fontan-associated liver disease.

correlate with the degree of histological fibrosis (50). The serum protein and albumin levels are generally normal, except in patients with failing Fontan physiology, advanced liver disease, or protein-losing enteropathy, where the levels are reduced. Coagulopathy, as indicated by a raised serum international normalized ratio (INR), may be present, but may be difficult to assess in individuals on warfarin therapy. In the Fontan circulation, there may be mild thrombocytopenia, and serial decline in platelet counts may correlate with advancing hepatic fibrosis (51). Even modestly reduced platelet counts may be meaningful as a marker of hepatic fibrosis, but may also reflect splenomegaly secondary to elevated central venous pressure. In patients with functional or anatomic asplenia, the platelet count is not helpful in interpreting the degree of liver disease.

Calculated scores such as the MELD (Model for End-stage Liver Disease) and PELD (Pediatric End-stage Liver Disease) were developed for the assessment of patients with other forms of liver disease and are less useful for the assessment of the degree of liver compromise in congestive hepatopathy. These risk scores rely heavily upon derangements in serum INR and cannot be used in Fontan patients who are frequently on warfarin therapy. The MELD XI score, which use serum bilirubin and serum creatinine while excluding INR, may predict outcomes in Fontan patients, although this marker is heavily influenced by renal function (15). Proprietary tests such as FibroSURE, which includes an assessment of multiple serum markers (gamma-glutamyl transpeptidase, alpha 2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, alanine transaminase), have only been validated in patients with hepatitis C and rely on inflammatory markers that are not expected to be relevant in FALD. The VAST (Varices, Ascites, Splenomegaly, Thrombocytopenia) score, which gives a point each for varices, ascites, splenomegaly (>13 cm on any imaging), or thrombocytopenia (<150,000 platelets/μL), is a strong marker for portal hypertension. It is a simple scoring system that has been utilized in the Fontan population to predict risk for adverse events such as death, transplant, or hepatocellular carcinoma (HCC) (49). In non-FALD liver cirrhosis, alpha fetoprotein is followed to screen for HCC, and may therefore be useful in FALD patients with cirrhosis.

2.2.2. Imaging

The majority of Fontan patients demonstrate abnormal liver imaging characteristics ranging from mild changes of congestive hepatopathy (hepatomegaly and dilated hepatic veins) to more severe changes that suggest advanced fibrosis (nodular liver texture and characteristics of portal hypertension). Individuals with cirrhosis are frequently compensated, meaning that there is preserved hepatocellular function with normal bilirubin, albumin, and INR (51). Commonly used noninvasive imaging modalities such as ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) may not accurately predict the degree of hepatic fibrosis when compared with histopathological liver biopsy specimens (52). These modalities are, however, capable of identifying nodules and masses within the liver. Nodules may reflect cirrhosis, focal nodular hyperplasia, or HCC. Dual-phase CT and MRI imaging with gadoxetate disodium (Eovist, Bayer, Whippany, New Jersey) are especially useful in differentiating these commonly found hypervascular liver nodules from hepatic tumors. The additional use of elastography (using magnetic resonance or ultrasound-based techniques) provides an assessment of liver stiffness, which is generally increased in this population and may help identify patients with more advanced liver disease. Patients with longer duration of Fontan circulation generally demonstrate increased liver stiffness suggestive of increased fibrosis (53–55). The utility of elastography is limited by the inability of liver stiffness to distinguish between the contributions of congestion and fibrosis. Following trends over time may have more clinical utility than a single evaluation.

2.2.3. Invasive Evaluation

Invasive hemodynamic evaluation is used to place imaging findings into anatomic and physiological context, with the potential to alter modifiable derangements. Of note, the measurement of hepatic vein wedge (as a surrogate of portal vein) pressure may have limited value in patients after Fontan operation, due to the presence of venous collaterals. However, a hepatic vein wedge pressure to free hepatic vein pressure gradient of >5 mmHg is strongly suggestive of sinusoidal portal hypertension due to cirrhosis. In contrast, normal values do not exclude the presence of advanced liver disease and fibrosis.

2.2.4. Histopathology

Histopathological evaluation of the liver parenchyma via percutaneous or transvenous biopsy is the gold standard for assessing the degree of fibrosis and establishing the diagnosis of cirrhosis. The biopsy route may affect the sample characteristics with percutaneous samples sometimes of better quality and more reflective of parenchymal changes than transvenous specimens that may include portions of the hepatic venous wall, particularly in small children. Coagulopathy due to liver disease or anticoagulants may preclude percutaneous biopsy. In addition, Fontan anatomy may make it difficult to access the liver via the internal jugular vein. The degree of liver fibrosis or cirrhosis does not always correlate well with imaging or laboratory findings, and therefore, the role and timing of initial liver biopsy and follow-up biopsies in this population remains uncertain. Fibrosis is typically patchy in

FALD therefore additional research is necessary to ascertain the value of targeted biopsy versus multimodality assessment of fibrosis. With FALD, liver biopsy is most likely unnecessary when there is no imaging or laboratory evidence of advanced liver disease. Also, biopsy may not be necessary if there is clear evidence of *clinical* cirrhosis and significant portal hypertension (splenomegaly, esophageal varices, and thrombocytopenia). Liver biopsy is most helpful when there is evidence of liver disease *(of any kind)* from imaging studies, when there is no clear evidence of clinical cirrhosis, and when staging the degree of liver disease will aid in decision-making and/or frequency of surveillance. Biopsy should be interpreted by an experienced hepatopathologist who understands the clinical context for which the biopsy was performed.

2.3. Gap Analysis: Evaluation

2.3.1. Risk Factors

Risk factors for FALD include both cardiac and extracardiac mechanisms, reflecting the systemic effects of the Fontan anatomy/physiology. Although there is no prospective study of specific risk factors that contribute to FALD, several important clinical factors have been identified in cross-sectional studies that are associated with higher risk for FALD. These include: higher Fontan pressures (53,54), increasing age (49,55–57), longer duration of Fontan (55,57–59), underlying hepatitis B or C, alcohol abuse, and hepatotoxic drug use. In addition, timing of diagnosis, postoperative hospitalization, degree of cyanosis, presence of fenestration, type of Fontan, presence of arrhythmia, elevated pulmonary vascular resistance, diastolic dysfunction, comorbid systemic disease, obesity, and nonalcoholic fatty liver disease may complicate the clinical picture in ways that are poorly understood and require further study. It is likely that FALD results from multiple insults sustained from various mechanisms over years to decades. Better characterization of risk factors is needed and would allow for earlier screening of high-risk patients and possibly the institution of prevention measures.

2.3.2. Noninvasive and Invasive Evaluation

Blood tests, ultrasound, advanced imaging (CT/MRI), elastography, and liver biopsy have all been studied in non-Fontan liver disease (60–68). Studies evaluating these measures in FALD have been performed; however, small numbers of patients limit the ability to determine clinical utility (36,49,54,57–59,69–72). A general review of noninvasive and invasive testing in non-Fontan liver disease and FALD, along with disparities between evaluations in these different populations, is outlined in **Table 1**. These data highlight that in FALD, liver function testing is not as useful until end-stage disease is present, and ultrasound/advanced imaging are poorly validated. Invasive evaluation of liver disease with biopsy is not well studied in FALD, and there are potentially higher risks due to underlying coagulopathy and systemic disease resulting from Fontan anatomy and physiology. A better understanding of how to evaluate FALD with diagnostic testing is necessary.

2.4. Therapy

FALD is a recently described, poorly understood disease process, and as such, medical therapies specific for this disorder have not been identified (73–77). Nevertheless, preventive, medical, surgical, and transplant strategies beneficial in similar disease processes may be applicable in FALD. Prior to initiating a treatment strategy, all efforts should be made to exclude reversible anatomic issues that may lower cardiac output and/or raise Fontan pressures, such as obstruction within the Fontan circuit. The Fontan operation for complex single ventricle anatomy creates a unique circulation with great anatomic variance and a broad spectrum of late outcomes. Therefore, a systematic evaluation by an experienced multidisciplinary CHD provider team is recommended prior to initiating treatment in patients with the Fontan operation presenting with liver disease. Evaluation often requires imaging and hemodynamic assessment. Discussion of therapy here assumes that anatomy and physiology have been optimized and that arrhythmic issues have been appropriately addressed.

2.5. Medical Therapies for FALD

The hemodynamic consequences of FALD vary based on the extent and stage of the liver involvement, but also on concomitant function of other organ systems such as the heart, pulmonary vasculature, venous vasculature, lungs, and kidneys. Thus, FALD may be the result of many different pathophysiological perturbations, so it is unlikely that a single medical strategy will be identified. One approach is to consider medical therapy for FALD in the context of the hemodynamic phenotype of the failing Fontan circulation (**Table 2**). The relationship between proposed hemodynamic classification systems for “failing Fontan” circulation and FALD require further study so as to best understand the potential for therapy.

Therapies for acquired systolic heart failure have been well studied over the past 4 decades, and are effective in preventing the onset of clinical heart failure in adults with acquired heart disease (without CHD) with asymptomatic ventricular dysfunction (78,79), reducing mortality due to both sudden death and progressive heart failure (80–83), reducing hospitalizations (84), and effectively palliating patients with symptoms of decompensated systolic heart failure and congestion (85). Although their use in patients with Fontan physiology to

TABLE 1 Noninvasive and Invasive Testing in Non-Fontan Liver Disease and FALD

Diagnostic Study	Non-Fontan Liver Disease	FALD
Liver function tests	■ Positive correlation between synthetic liver function and standard serologic liver testing ■ MELD score validated to quantify severity of liver disease and predict short-term transplant mortality (60)	■ Standard serologic liver tests poorly correlate with degree of liver disease (37,48) ■ Higher percentage of patient on vitamin K antagonists, and overall lack of correlation between MELD and severity of liver disease limit use of MELD (73) ■ MELD-IX may be associated with increased risk for mortality (16)
Ultrasound	■ Specific, reliable, cost-effective first-line imaging study to assess for cirrhosis (61–63) ■ Positive predictive value in detecting chronic liver disease is 98% (64)	■ Not studied in Fontan population specifically; lack of normative data in FALD
CT/MRI	■ Radiation exposure with CT ■ Most sensitive diagnostic tool for evaluating morphological liver changes (63) ■ Both CT and MRI are poor at detecting morphological changes with *early* cirrhosis, although show nodularity and atrophic/hypertrophic changes with advanced liver disease	■ Radiation exposure with CT ■ Both CT and MRI are poor at detecting morphological changes with early cirrhosis, although show nodularity and atrophic/hypertrophic changes with advanced liver disease ■ Mixed results on usefulness in FALD (37,48,55,58,72)
Elastography	■ Ultrasound TE can be unreliable in up to 20% of measurements, particularly if the patient is obese or has ascites (66) ■ ARFI, which allows selection of a region of interest, has similar results to TE ■ SSI utilizes multiple pulse wave beams and allows evaluation of several fronts over time, which is expected to overcome limitations (obese, ascites) of TE ■ All types of elastography have low reproducibility and are operator-dependent, limiting usefulness ■ MRE has shown reasonably good sensitivity and specificity in detecting a difference between early- and late-stage fibrosis (66)	■ Liver stiffness has correlated with more severe fibrosis in a small number of studies with a low number of patients. However, neither fibrosis nor stiffness has reliably correlated with serologic liver tests (37,57,58,69) ■ Direct comparison of types of elastography in the Fontan population is lacking
Biopsy	■ Gold standard for diagnosis, assessment of prognosis, and assist in therapeutic decisions (67) ■ Relatively well tolerated with mild-moderate complications in up to 5% and death in <1/10,000 biopsies (67)	■ May carry higher risk due to underlying coagulopathy and increased use of vitamin K antagonist therapy in Fontan patients ■ Lack of operator experience in Fontan patients with multisystem disease may lead to a higher complication rate; this is not well studied

ARFI = acoustic radiation force impulse imaging; CT = computed tomography; FALD = Fontan-associated liver disease; MELD = Model for End-stage Liver Disease; MRE = magnetic resonance elastography; MRI = magnetic resonance imaging; SSI = supersonic shear wave imaging; TE = transient elastography.

alter or mitigate FALD may seem attractive due to the successes in acquired heart disease, such use for all heart failure therapies, including aldosterone antagonists, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, is speculative and requires further study.

Nonselective beta-blocker therapy (e.g., propranolol or nadolol) in the setting of cirrhosis has been shown to improve portal pressure and decrease variceal bleeding in patients with portal hypertension and varices (86,87), although its benefit is neutral in those without variceal bleeding (88). The major mechanism of action is through splanchnic vasodilatation. Given the high rate of sinus node dysfunction in the Fontan population, caution is advised when using beta-blockers.

Pulmonary arterial hypertension-specific therapy in those with Fontan physiology and FALD requires meticulous hemodynamic assessment prior to initiation with an understanding that there are no placebo-controlled randomized trials that uniformly support their use and

TABLE 2 Phenotypes of the "Failing Fontan" Patient

	Phenotype I FFrEF	Phenotype II "FFpEF"	Phenotype III "FFnH"	Phenotype IV "FFLA"
Description	Fontan failure with reduced ejection fraction (FFrEF); "systolic heart failure"	Fontan failure with preserved ejection fraction (FFpEF); "diastolic heart failure"	Fontan failure with normal heart (FFnH); "noncardiac failure" Perhaps most relevant to discussion of FALD	Fontan failure with lymphatic abnormalities (FFLA); "plastic bronchitis and PLE," which may occur in the absence or presence of significant FALD
Systolic function	Reduced	Normal	Normal	Normal
Ventricular EDP	Elevated	Elevated	Normal	Low or normal
Cardiac output	Low or normal	Low or normal	Normal	Normal
SVR	Elevated	Elevated	Low or normal	Low or normal

EDP = end-diastolic pressure; FALD = Fontan-associated liver disease; FFLA = Fontan failure with lymphatic abnormalities; FFnH = Fontan failure with normal heart; FFpEF = Fontan failure with preserved ejection fraction; FFrEF = Fontan failure with reduced ejection fraction; SVR = Systemic vascular resistance.

benefit. The patient with Fontan physiology may demonstrate pulmonary vascular remodeling as one of the primary etiologies for heart failure, and thus may benefit from these therapies (89,90). Measurement of pulmonary vascular resistance is technically complicated and inaccurate in a nonpulsatile passive pulmonary blood flow circulation. In addition, elevated systemic venous pressures may lead to venovenous collaterals, creating a "normal" transpulmonary gradient when significant pulmonary vascular disease may be present. Based on a single hemodynamic study of transpulmonary gradient (TPG) in patients with s/p Fontan operation before and after heart transplant—TPG measured before and after the placement of pulsatile flow to the pulmonary bed in the form of a functioning transplanted heart—a mean increase of 6.8 mm Hg TPG was found after transplant (90). Given a normal TPG of ≤10 mm Hg in a normal circulation, with an upper cut off of 15 mm Hg signifying potential reversibility due to pulmonary venous congestion, one can infer that a normal TPG in a patient with s/p Fontan operation is 3 to 6 mm Hg, and anything in excess of that may represent resistance in the pulmonary vascular bed. Although there is very limited evidence to back up these assumptions, pulmonary vasodilators should be reserved for those patients who have progressive clinical deterioration in the setting of elevated TPG, despite maximal medical therapy. Only in theory, initiation of pulmonary vasodilators in this setting may potentially reduce the hepatic congestion and palliate FALD, although studies beyond safety and exercise tolerance are lacking (91,92). In the setting of cirrhosis, pulmonary vasodilator therapy may play a role in treating portal-pulmonary hypertension, a secondary pulmonary vascular disease (WHO Group 1) specifically related to portal hypertension from cirrhosis and renal hypoperfusion from decompensated portal hypertension (93).

For patients with decompensation related to hepatorenal syndrome (HRS), careful hemodynamic assessment to confirm low systemic vascular resistance is advised. In the setting of hepatorenal syndrome, therapies to increase circulating volume, such as albumin, and therapies to increase mean arterial pressure, including midodrine and terlipressin, have been demonstrated to be helpful in the patient with cirrhosis (94). Studies of such therapies are lacking in the Fontan population.

2.6. Isolated Heart or Combined Heart-Liver Transplantation for FALD

Heart transplantation in the patient with FALD is fraught with risk and uncertainty. To date, there is no validated scoring system or other mechanism to predict hepatic recovery and perioperative survival after isolated heart transplantation in patients with a failed Fontan circulation and significant hepatic fibrosis and portal venous outflow obstruction. Patients with FALD and synthetic liver dysfunction and clinical cirrhosis or localized HCC will generally require a combined heart-liver transplant (CHLT) because the underlying Fontan physiology precludes liver transplantation alone.

Indications for liver transplantation include: HCC within Milan criteria (95), requirement for heart transplantation in the presence of decompensated liver disease or intrahepatic portal hypertension, and liver dysfunction as defined by a MELD score >15 (in the absence of warfarin anticoagulation) (96,97).

There is now increasing recognition that primary HCC can occur in patients with FALD (98). Therapies include local-regional (radiofrequency ablation, ethanol injection), surgical resection, transplantation, and medical therapy. Orthotopic liver transplantation is the curative treatment of choice in patients with early HCC who are not candidates for ablation, as may occur in FALD.

Reported single-center and larger dataset analyses of isolated heart transplant have shown that although early mortality is higher in CHD patients, late survival is equal, if not superior, to noncongenital cohorts undergoing transplant (71,99–105).

CHLT is complex and remains a relatively uncommon procedure in the United States with a limited number of centers that offer the procedure (97,106–115). According to United Network for Organ Sharing (UNOS) data, although there were over 96,000 liver and 67,000 heart transplants between the years of 1987 and 2010, the number of CHLTs was only 97 (113). Of these, over half were performed between 2005 and 2010, indicating an increasing willingness of centers to offer the procedure. Although the most common indication for combined transplantation was cardiac amyloidosis, 17 patients underwent transplantation for congenital heart disease including FALD. The median age of subjects was 43 years. The median 1- and 5-year survival rates of the CHLT cohort were 84% and 72%, respectively, comparable to outcomes after either organ alone. The numbers of patients with amyloid, who typically have normal liver function and are technically easier to perform procedures on, probably favorably skew these results. A more recent publication identified 27 adult congenital heart patients, presumably all with FALD, who underwent CHLT in the United States through 2014, accounting for 20% of the total CHLT performed. Midterm survival in this group was no different than the noncongenital population (107).

When patients are listed in UNOS for CHLT, the primary organ that is dysfunctional determines the priority on the waiting list. In the setting of FALD, heart disease is usually the primary reason for CHLT, and as such, waitlist status is driven by the heart transplant allocation criteria. This is based on the medical need and geographic

distribution of donor organs. Highest priority status (status 1A) is based on treatment, including a requirement of high doses of intravenous inotropes with continuous pulmonary artery pressure monitoring, ventricular assist device with complications, and dependency on a ventilator or other imminent life-threatening complications. As patients with s/p Fontan operation often are not candidates for these therapies, most subjects with FALD who are listed for heart transplantation are listed as status 1B based on exception criteria. If the heart is the primary organ, the liver is usually drawn from the local donor pool. In cases where the liver disease is the primary indication for CHLT, patients are listed on liver transplantation criteria.

Patients with FALD listed for CHLT face unique challenges. Many subjects have donor-specific antibodies because of prior transfusions. Although high titers of donor-specific antibody are associated with poorer outcomes in cardiac transplantation, antibody-mediated rejection is uncommon in liver transplantation (115). Although placement of a liver allograft, before the heart, has a theoretical benefit of reducing donor-specific antibody titers, the heart allograft is usually performed first because of potential hemodynamic instability during liver transplantation. Surgical technique during (isolated) orthotopic heart transplant in Fontan patients can be challenging because of prior sternotomies and a requirement to reconstruct the great vessels during cardiac transplantation.

Key Points:

1. Liver risk score that combines liver biopsy findings with MELD-XI (MELD without INR) may help identify patients who can safely undergo (isolated) orthotopic heart transplant without orthotopic liver transplant.
2. Unique challenges for CHLT in the Fontan population include: 1) high titers of donor-specific antibodies that may have adverse outcomes on the cardiac but not hepatic allograft; 2) need for reconstruction of the right pulmonary artery and/or other large vessels during cardiac transplantation; and 3) longer wait-list times and higher wait-list mortality.
3. Combined heart and liver transplantation has been performed in select quaternary transplant centers with 1- and 5-year survival rates matching the results of heart or liver transplantation alone. Concomitant transplantation of the liver may decrease the risk of cardiac allograft rejection and vasculopathy.

2.7. Gap Analysis: Therapy and Transplant

There are currently no studies that have evaluated medical therapies for liver disease in the FALD population, representing a huge gap in our knowledge regarding treatment for this disease. As with many populations, when end-stage disease is present in a patient with s/p Fontan operation, candidacy and opportunities for transplant may be examined. Isolated heart transplant is most commonly considered. Unfortunately, the format of data gathered from UNOS does not allow for tracking of patients with s/p Fontan operation, and linked data between the Thoracic and Liver Registries of UNOS is limited. As such, it does not allow for comprehensive understanding about the state of the liver with FALD. Data examining transplant outcomes, heart and liver graft function, major adverse events, and survival in both waitlisted and transplant groups is crucial to understanding the point at which FALD is significant to warrant CHLT consideration. This type of insight would allow a more comprehensive understanding of FALD and help guide future assessment when considering isolated heart versus CHLT. As well, more comprehensive data collection by UNOS would provide the basis to develop a risk score so that heart transplant can be performed in isolation before the need for liver transplant. Currently, this important data is not being collected.

3. FONTAN-ASSOCIATED LIVER DISEASE: RESEARCH AND BARRIERS TO UNDERSTANDING

3.1. Research Directions

The gaps in knowledge about FALD outlined in this document far outnumber the current knowledge. Definition and characterization of critical aspects of disease histology and physiology remain central to improve understanding of FALD causation and modulating factors, natural course, modifiable contributors, treatment, and prevention. In laying out a research agenda, we focus on this core knowledge gap, and have adhered to a few key principles that are also aligned with the National Heart, Lung, and Blood Institute; ACC; and other national and regional funding agency priorities (which are to take advantage of existing resources when available, form partnerships, link clinic and research, and maximally involve patients).

3.2. Definition

At present, multiple structural and several functional liver abnormalities have been identified in patients after Fontan surgery, but it is often unclear whether they are incidental or pathological. A generalized characterization of FALD, sufficiently broad as to allow study of fundamental aspects and the relationship, if any, to congestion or fibrosis, appears foundational to other aspects of FALD research efforts. Structured assessment of biological specimens and relationship to clinical outcomes is suggested in the following text, so as to best define disease and promote ability for further focused studies.

3.3. Epidemiology

The absence of comprehensive data on all patients who undergo Fontan surgery limits our ability to understand epidemiology and modulating factors surrounding meaningful outcomes for patients in whom a Fontan procedure is considered or performed. A registry of patients with severe CHD enrolled either at the time of recognition of physiology that will lead ultimately to Fontan procedure or at the time of Fontan surgery, provides a necessary substrate for such foundational research. This could occur through an existing registry, (e.g., Society of Thoracic Surgeons Congenital Heart Surgeons database), a data-sharing collaboration among several existing registries (e.g., Fontan registries from the Pediatric Heart Network, Pediatric Heart Network, and the Alliance for Adult Research in Congenital Cardiology [AARCC]), or a new effort, such as leveraging the ACC's National Cardiovascular Data Registry methodology and platform technology (e.g., PINNACLE [Practice INNovation And Clinical Excellence] and IMPACT [Improving Pediatric and Adult Congenital Treatment]), to establish a longitudinal CHD registry. Attracting patients to registries can be facilitated by leveraging social media (116), as well as via partnerships with patient advocacy organizations (i.e., the Adult Congenital Heart Association, Mended Little Hearts, Pediatric Congenital Heart Association, or the Congenital Heart Foundation).

The registry goal would be to standardize patient characterization and follow-up, so as to determine the prevalence; demographics; contributing causes; and the timing, onset, and progression of critical outcomes, such as FALD. The registry could also be a resource for obtaining and banking biospecimens, conducting translational studies of biomarkers, studying genotype-phenotype correlations, carrying out "-omics" studies, and serving as infrastructure for registry-based clinical trials.

3.4. Pathophysiology

The absence of: 1) viable animal and computational models of Fontan circulation and vascular dynamics; and 2) an understanding of mechanisms related to liver fibrosis in general hamper the study of FALD pathology and physiology. This gap particularly includes mechanisms of, and susceptibility to, hepatic injury (including hypoxia, flow, pressure, cyanosis, inflammation, and thrombosis). In both animal models and in humans, there needs to be longitudinal characterization of histology, inflammatory state, genetics, and proteomics. At present, insights into the pathophysiology of FALD may most readily spring from characterizing existing liver biopsy samples (currently stored at several academic sites) from patients who have had the Fontan operation. Partnerships between academic centers, the National Institutes of Health, and industry are anticipated so as to allow for optimal tissue characterization and correlation between samples and clinical patient outcomes.

3.5. Diagnosis/Surveillance

Research on diagnosis and surveillance requires understanding of pathophysiology, currently absent in FALD. Until this is known, the optimal content, timing, and frequency of diagnostic tests (including liver biopsy) will be difficult to determine. Research is needed to identify biomarkers that may signal early determinant or predictive hepatic changes, or that can be used for definitive diagnosis and monitoring of hepatic disease. It would also be helpful to develop and investigate the diagnostic and predictive roles of both single-point and longitudinal rest and exercise hemodynamics.

3.6. Prevention

Research that will lead to prevention of FALD will rely on an accurate and widespread acceptance of disease definition, together with improvements in our understanding of its epidemiology, causation, modulation, penetrance, expression, and pathophysiology. It may be possible, for example, to mine registry data to identify factors that could be modified to prevent the initial injury (primary prevention), or the progression of identified injury (secondary prevention). Research is also needed on fundamental ways to improve the aspects of Fontan physiology found to be instrumental in disease modulation or causation, potentially including identifying the optimal timing for the Fontan procedure and developing right ventricular pumps that could augment the Fontan circulation with pulsatile subpulmonary flow.

3.7. Treatment

Research on treatment of FALD might occur through new partnerships between federal (such as the National Institutes of Health), regional, and local funding sources, together with academia, and industry. For example, the hundreds of liver biopsy samples mentioned earlier could be harnessed as a resource for testing of novel compounds. A Fontan registry could be used to evaluate current therapies, using retrospective case-control or prospective designs. When therapeutic agents are ready for clinical trials, the infrastructure of existing research networks such as the Pediatric Heart Network together with AARCC can be employed to conduct Phase I to III trials.

3.8. Research Resources

FALD is within the missions of the NIDDK, National Heart, Lung, and Blood Institute, ACC National Cardiovascular Data Registry, and AARCC platforms and existing registries; funded efforts to harmonize and further explore these datasets as well as to create a new, longitudinal registry with standardized measures and follow-up would

be valuable for research efforts. Patient advocacy groups, as well as social media, should be harnessed to bring as many patients together as possible to help understand FALD and other aspects of Fontan physiology.

4. ADVOCACY AND PATIENT-CENTERED CARE

FALD is a relatively new entity among CHD specialists and hepatologists. Not surprisingly, awareness of this condition has lagged further among patients with a Fontan operation and their family members. Rarely is long-term liver function a part of the discussion at the time of a Fontan procedure and even later during sequential follow-up visits in pediatric cardiology. Clinicians often find discussion of this ill-defined entity to be uncomfortable, and feel unprepared and reluctant to discuss the uncertainty about future prognosis and disease progression with families.

On a community level, primary care providers and other specialists have even less or no familiarity with FALD. Lack of appropriate care and referral for adult CHD, as well as absence of recognition of this disease, are likely to compound the effects of this and other extracardiac manifestations late after Fontan surgery. Arguably, of the extracardiac manifestations related to prior Fontan surgery, FALD is one of the most important reasons to include highly skilled and trained CHD cardiologists (pediatric and adult CHD) as a part of the care team in this patient group.

Limited advocacy efforts in CHD, and more specifically in patients with s/p Fontan operation, are concerning as this population continues to grow and show improved long-term survival. Programs aimed at education and awareness about this topic currently do not exist, and are needed at the patient and healthcare provider level. As with any evolving disease, there is also evolution of knowledge about the disease, recognition, screening, and treatment options. Great care must be taken to accurately disseminate what is currently known, but equally as important, what is unknown and where future research should be undertaken.

5. SUMMARY, STAKEHOLDERS, SOUND PRACTICE, AND NEXT STEPS

5.1. Summary and Stakeholders

The goal of this stakeholders meeting was to outline the current state of knowledge about FALD and to develop a multidisciplinary approach to prevention, screening, and treatment in this unique group of patients. Meeting participants had a breadth of experience with pediatric and adult patients with s/p Fontan operation and unique knowledge and perspective relative to their skillset.

5.1.1. Pediatric Cardiologists, Adult Cardiologists, Adult Congenital Heart Disease Specialists, Heart Failure/Transplant Specialists, Pediatric and Adult Hepatologists, and Liver Transplant Specialists

These specialties work closely with patients longitudinally and are often responsible for coordination of care between specialty and general medical care providers. They are often the first people notified when complex congenital heart patients are feeling poorly or need to be seen for acute care, many times bypassing general medicine specialists. It is this group that provides expert cardiac care and is also responsible for discussion of natural history of single ventricle and Fontan anatomy, including multisystem involvement such as liver disease. These providers belong or work closely with the American College of Cardiology (ACC), Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Association for the Study of Liver Diseases (AASLD), and American Academy of Pediatrics.

5.1.2. Primary Care and Other Healthcare Providers

Family practitioners, pediatricians, internists, and obstetricians/gynecologists provide frequent care to complex congenital heart patients for problems such as the common cold, contraception, and pregnancy. These providers work closely with cardiologists and assist in immediate and long-term decisions regarding health and safety. Some of these providers are directly involved in coordinating subspecialty care for extracardiac manifestations of disease, such as nephrology, hematology, and hepatology. These providers work closely with the American Academy of Family Physicians, American Academy of Pediatrics, American College of Physicians, and several internal medicine subspecialty boards governed under the American Board of Internal Medicine.

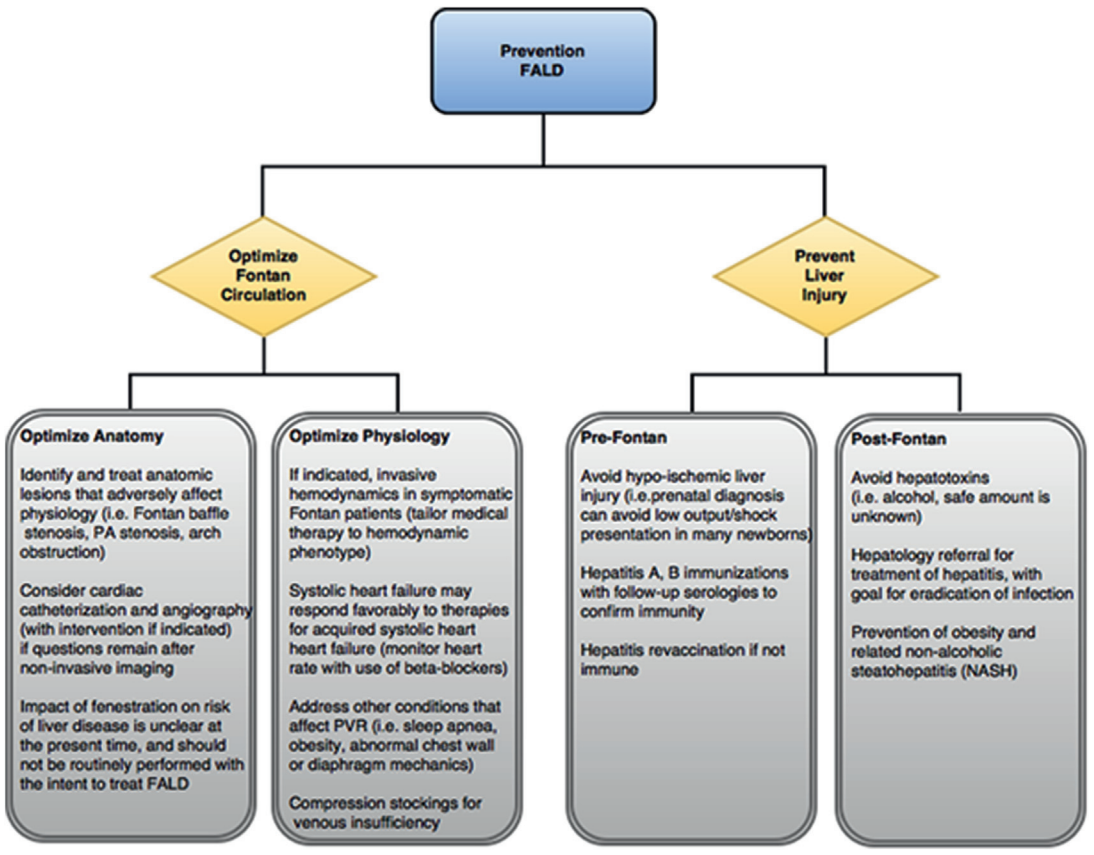
5.1.3. Research Scientists, Funding Agencies

Researchers, epidemiologists, academic physicians, and clinicians are involved in basic, clinical, and translational research about single-ventricle anatomy and Fontan physiology. They are key personnel to help better understand and change outcomes and care in this complex population. These people are supported by funding agencies, legislators, and policy makers that are members of or work with publicly funded agencies, the National Institutes of Health, American Heart Association, Center for Disease Control and Prevention, and other organizations and funding sources.

5.1.4. Patients, Parents, Legislators, and Advocacy Organizations

Patients and patient families are unique members of this stakeholders group, recounting a lifetime of

FIGURE 8 Recommended Steps to Prevent and Slow the Progression of FALD



FALD = Fontan-associated liver disease; NASH = nonalcoholic steatohepatitis; PA = pulmonary artery; PVR = pulmonary vascular resistance.

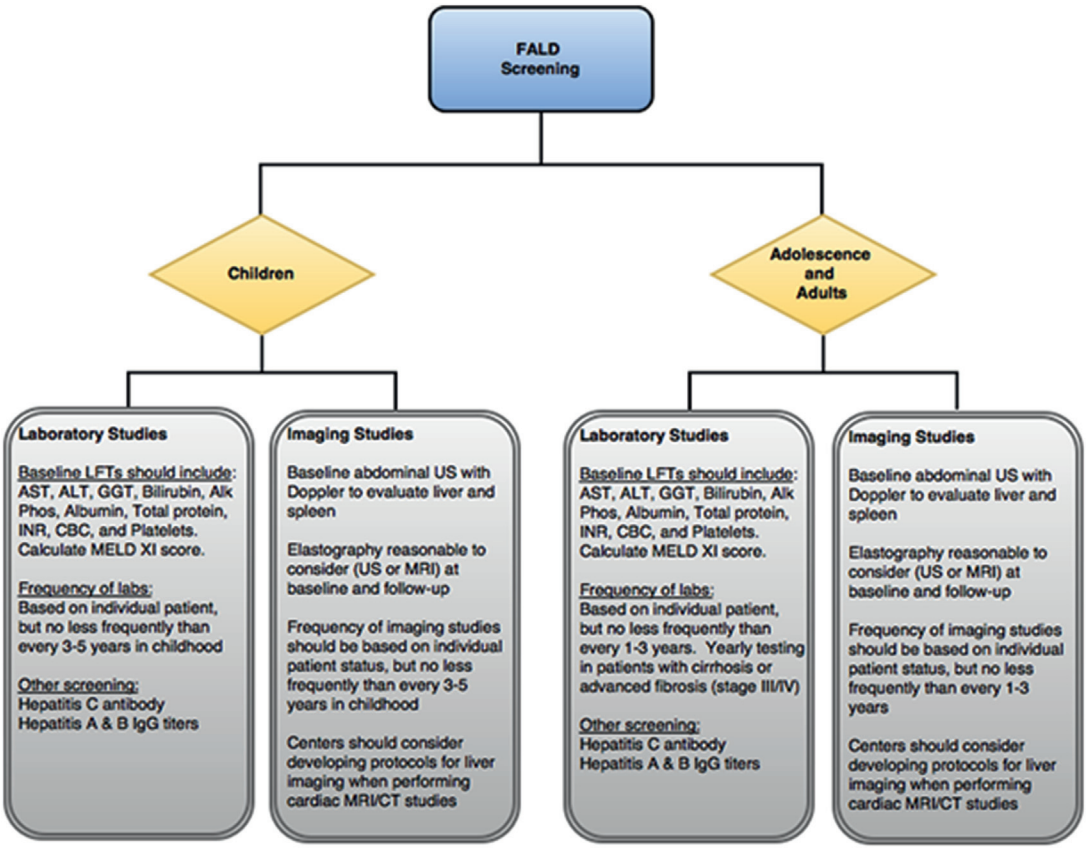
subspecialty cardiac and specialized surgical care. They have lived through the changing landscape of CHD, often recounting stories told of poor survival, high risk, and unknown outcomes associated with their underlying heart defects. Their experience provides crucial insight to the patient-centered approach of multidisciplinary care and provides important information to build more coordinated and communicative care, particularly as extracardiac disease, such as FALD, is approached.

5.2. Sound Practice (Figures 8, 9, and 10)

After careful review of the literature, the committee presents recommendations for sound practice in the prevention, screening, and care of FALD. Recommended prevention strategies are based on optimization of underlying cardiac anatomy and Fontan physiology, as well as prevention of pre- and post-Fontan liver injury (Figure 8). Optimization of anatomy and physiology is important, as residual anatomic lesions and adverse hemodynamics can lead to negative consequences for the liver in this group of patients. Importantly, many of these lesions and abnormal hemodynamics can be relieved to improve the physiological milieu of the patient with s/p Fontan operation. Recognition and treatment of other comorbid diseases, such as obesity and pulmonary disease, can have a positive impact on pulmonary vascular resistance and overall hemodynamics. This results in increased energy, improved exercise tolerance, and regression of noncardiac end-organ damage.

Screening for FALD is variable between patients, and to some extent, should be individualized. However, at minimum, children should receive baseline measures of liver function 5 years after the Fontan operation, or sooner if there is a clinical suspicion of liver injury or Fontan failure. Adolescence and adults should have evaluation of liver function every 1 to 3 years, due to more rapid progression of liver disease in some patients. In addition to routine (at minimum yearly) history taking and physical examination, screening should consist of a

FIGURE 9 FALD Screening Recommendations for Children (<12 Years of Age) and Adolescence/Adults (≥12 Years of Age) With Fontan Anatomy



Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CT = computerized tomography; FALD = Fontan-associated liver disease; GGT = gamma-glutamyltransferase; IgG = immunoglobulin G; INR = international normalized ratio; LFT = liver function tests; MELD XI = Model for End Stage Liver Disease excluding INR; MRI = magnetic resonance imaging; US = ultrasound.

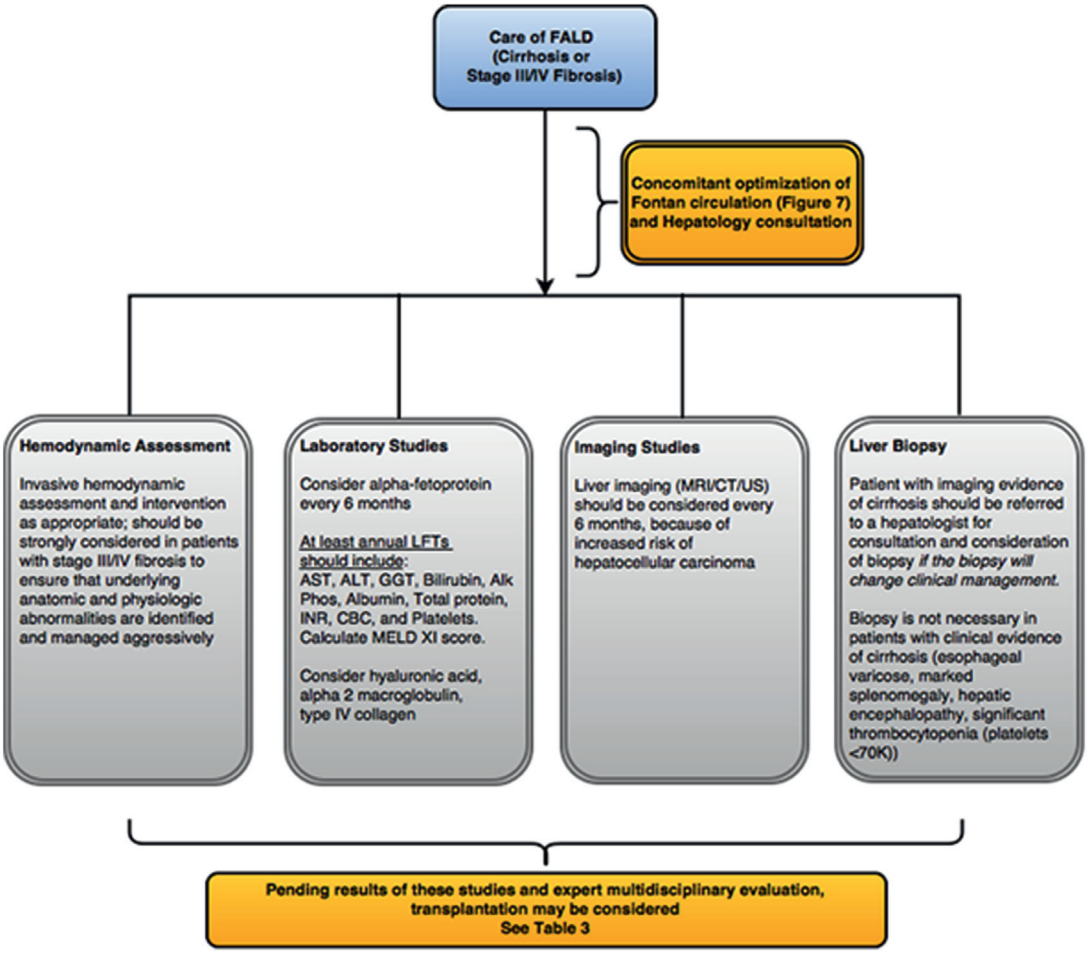
combination of laboratory studies; evaluation of other hepatic exposures, such as Hepatitis A, B, and C; and liver imaging (Figure 9). Although not of proven benefit in FALD, vaccination with HAV and HAB should be considered.

Once advanced FALD is identified, revisiting protocols to optimize Fontan anatomy and physiology and hepatology referral should be completed. Additional laboratory studies are indicated at this time, and the frequency of liver imaging is increased to every 6 months. Liver biopsy may be helpful at this stage if it will change clinical management, but requires careful consideration of risk and benefit. Ultimately, isolated heart or combined heart-liver transplant may be considered, but requires coordination of care with a multidisciplinary team inclusive of hepatology, congenital heart disease, and surgical specialists (Figure 10, Table 3).

5.3. Action Strategies, Next Steps

Over the past decade, we have learned through case series studies and single institution reports that FALD is ubiquitous. Every patient with Fontan physiology where the hepatic veins are incorporated into the Fontan circulation will develop some degree of liver disease. For many, FALD will advance and contribute to the long-term morbidity and mortality. The impact to patients, families, and health care systems within and outside of congenital heart disease has raised widespread concern, and as such, has prompted the need for a stakeholders meeting to recognize the gaps in knowledge, care, and research and to develop a strategy to move forward. We

FIGURE 10 Noninvasive and Invasive Monitoring, Evaluation, and Care of the Fontan Patient With FALD



Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CT = computerized tomography; FALD = Fontan-associated liver disease; GGT = gamma-glutamyltransferase; INR = international normalized ratio; MELD XI = Model for End Stage Liver Disease excluding INR; MRI = magnetic resonance imaging; US = ultrasound.

are now learning that we need an investment toward research and technologies post-Fontan operation that matches our past and current commitment to pre-Fontan patients. The most basic epidemiologic questions on estimates of the incidence and prevalence of U.S. adult Fontan patients are not known. We do not know how many patients are surviving, their health care status, or their risk factors for morbidity and mortality. We need a

TABLE 3 Considerations in the Fontan Patient With FALD Undergoing Evaluation for Transplantation

Transplantation Considerations
■ Patients requiring a heart transplant DO NOT REQUIRE concomitant liver transplant if they do not have cirrhosis based on strong clinical evidence (esophageal varices, marked splenomegaly, hepatic encephalopathy) or biopsy-proven.
■ Patient with clinical, imaging, or biopsy evidence of cirrhosis, or have a diagnosis of HCC, should be assessed by an experienced multidisciplinary team with combined expertise in congenital heart disease, hepatology, heart transplant, and liver transplant. Some, but not all, of these patients may need combined heart-liver transplant.
■ Every patient being considered for heart transplant needs evaluation by a transplant hepatologist. Post-heart transplant management should continue in conjunction with hepatologist.
■ Patients who undergo heart transplant in the setting of cirrhosis may be at risk for future HCC. These patients need ongoing follow-up with a hepatologist and HCC screening if evidence of cirrhosis persists after heart transplant.

FALD = Fontan-associated liver disease; HCC = hepatocellular carcinoma.

TABLE 4 Fontan-Associated Liver Disease Action Items

FALD Action Items
■ Partner with the CDC to determine the incidence and prevalence of CHD in the U.S. and, in particular, Fontan patients.
■ Develop a longitudinal registry for FALD and Fontan patients through partnerships with the ACC, AHA, AAP, NHLBI, NDDK, and ACHA.
■ Develop multi-institutional studies in pathophysiology, detection of disease, and preventive therapies of FALD through partnership with AARCC, NHLBI, NIDDK, PCORI, PHN, and industry.
■ Develop a strategy and approach to heart failure therapies (medical and mechanical) through partnerships with CT surgery, industry, heart failure cardiologists, hepatologists, AARCC, NHLBI.
■ Develop a strategy to address the discrepancies in transplant data collection and listing for Fontan patients through partnership with UNOS.
■ Engage patient organizations, patients, and families affected by FALD to voice their opinion and advocate for publicly funded national organizations (NHLBI, NDDK, PCORI, CDC, and UNOS) to dedicate specific funding and resources toward Fontan patients and FALD.

AAP = American Academy of Pediatrics; AARCC = Adult Alliance for Research in Congenital Cardiology; ACC = American College of Cardiology; ACHA = Adult Congenital Heart Association; AHA = American Heart Association; CDC = Centers for Disease Control; CHD = Congenital Heart Disease; FALD = Fontan-associated liver disease; NHLBI = National Heart, Lung, and Blood Institute; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; PCORI = Patient-Centered Outcomes Research Institute; PHN = Pediatric Heart Network; UNOS = United Network for Organ Sharing.

strategy to answer these questions and solve these issues. Collaborations between major health care societies and organizations; researchers and research institutions; and subspecialists in congenital cardiology, hepatology, CT surgery, and heart failure/transplant is required to facilitate the necessary resources to positively affect the Fontan population.

Throughout the stakeholders meeting, the participants focused on identifying gaps, the strategies to better understand the path forward, and those responsible to facilitate this process. The gaps are well developed throughout the document and support a very specific call to action (Table 4). Through these action items with focused, dedicated partnership and patient advocacy, we will better understand and change the course for patients with single-ventricle/Fontan and FALD.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—FONTAN-ASSOCIATED LIVER DISEASE CONFERENCE PROCEEDINGS

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Curt J. Daniels	The Ohio State University College of Medicine—Associate Professor of Clinical Internal Medicine & Pediatrics, Division of Cardiovascular Medicine	None	None	None	None	■ American Board of Internal Medicine	None
Elisa A. Bradley	The Ohio State University College of Medicine—Assistant Professor of Internal Medicine, Division of Cardiovascular Medicine	None	None	None	None	None	None
Jamil Aboulhosn	David Geffen School of Medicine—Health Sciences Assistant Clinical Professor, Medicine	■ Actelion ■ Edwards Lifesciences*	None	None	■ Actelion	None	None
Robert H. Beekman III	University of Michigan—Professor of Pediatric Cardiology	None	None	None	None	■ National Pediatric Cardiology Quality Improvement Collaborative†	None
Wendy Book	Emory University, Professor of Internal Medicine, Division of Cardiovascular Medicine; Director, Adult Congenital Heart Center	None	None	None	■ Centers for Disease Control*	■ American Partnership for Eosinophilic Disorders†	None
Michelle Gurvitz	Harvard Medical School—Assistant Professor of Pediatrics; Attending Physician, Department of Cardiology	None	None	None	None	■ Adult Congenital Heart Association† ■ Pediatric Congenital Heart Association†	None
Anitha John	George Washington School of Medicine- Associate Professor of Pediatrics; Director, Washington Adult Congenital Heart Program	None	None	None	None	None	None
Binu John	McGuire VA Medical Center—Medical Director of Liver Transplantation; Virginia Commonwealth University—Assistant Professor of Medicine	None	None	None	■ Gilead*	None	None
Ariane Marelli	McGill University—Professor of Medicine, Division of Cardiology, Faculty of Medicine	None	None	None	None	None	None
Bradley S. Marino	Ann and Robert J. Lurie Children's Hospital of Chicago—Attending Pediatric Cardiologist; Northwestern University Feinberg School of Medicine—Professor of Pediatric Cardiology	None	None	None	None	None	None
L. LuAnn Minich	University of Utah School of Medicine and Primary Children's Medical Center—Director of Pediatric Cardiovascular Research; Associate Director, Division of Pediatric Cardiology	None	None	None	None	None	None
John J. Poterucha	Mayo Clinic—Consultant, Division of Gastroenterology and Hepatology, Department of Internal Medicine; Mayo Clinic College of Medicine-Professor, Department of Internal Medicine	None	None	None	None	None	None
Elizabeth B. Rand	Children's Hospital of Philadelphia—Pediatric Gastroenterologist, Division of Gastroenterology, Hepatology and Nutrition; Medical Director, Liver Transplant Program	None	None	None	None	None	None

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Gruschen R. Veldtman	Cincinnati Children's Hospital—Director of Adult Congenital Heart Disease; UC Department of Pediatrics—Professor	None	None	None	■ United Therapeutic*	■ UpToDate†	None
Mike J. Landzberg	Boston Children's Hospital— Associate in Cardiology; Associate Director, Adult Pulmonary Hypertension Program; Boston Adult Congenital Heart—Director; Harvard Medical School—Assistant Professor of Medicine	None	None	None	■ Actelion (DSMB) ■ Actelion ■ CORVIA Harvard Clinical Research Institute (DSMB)	None	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

DSMB = Data Safety Monitoring Board.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—FONTAN-ASSOCIATED LIVER DISEASE CONFERENCE PROCEEDINGS

Reviewer	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Devyani Chowdhury	Cardiology Care for Children—Pediatric Cardiologist	None	None	None	None	None	None
Stephen C. Cook	Helen Devos Children's Hospital—Director, Adult Congenital Heart Disease Center	None	None	None	None	None	None
Swee Chek Quey	National University of Singapore—Associate Professor	None	None	None	None	None	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC Disclosure Policy for Writing Committees.

APPENDIX 3. ABBREVIATIONS

AARCC = Adult Alliance for Research Congenital Cardiology
ACC = American College of Cardiology
CHD = congenital heart disease
CHLT = combined heart-liver transplant
CT = computed tomography
FALD = Fontan-associated liver disease
HCC = hepatocellular carcinoma
INR = international normalized ratio
MELD = model for end-stage liver disease
MRI = magnetic resonance imaging
TPG = transpulmonary gradient
UNOS = United Network of Organ Sharing