General Instructions

Follow-up visits are completed at weeks 12, 24, and 48 weeks following the initial baseline visit and at 24 week intervals thereafter. Regardless of whether the baseline evaluation is completed in one or more visits, the follow-up visits are calculated from the initial baseline visit.

The Follow-up Evaluation form is completed at all the protocol follow-up visits during the Cohort Study, with the exception of the week 12 visit (the Follow-Up Week 12 Evaluation form is completed at the week 12 visit).

Several sections of the Follow-up Evaluation form are only completed at the 48-week anniversary visits as noted on the data collection form.

There is a four (4) week window on either side of each follow-up evaluation date, beginning with the week 24 follow-up. However, information should be captured even when the evaluation is performed outside of this window.

This form captures information obtained from patient interview and medical record review. When information in the medical record conflicts with information provided by the patient, the medical record is normally considered to be the accurate source, although there may be instances when the information provided by the patient is more up to date or accurate. In this instance, the information from the patient may be used.

Information for the diagnostic, serology, virology, and laboratory sections of the form should be obtained from the patient's medical record.

The coordinator is responsible for obtaining the information recorded on this form. In non-English speaking patients, the interview may be performed through a certified interpreter. While a trained translator is preferred, a family member or friend of the patient (who speaks fluent English and the native language of the patient) may be acceptable for this role as determined on an individual basis.

Refer to the HBRN Cohort Codebook for items that require coded responses.

Specific Instructions

Patient ID**:**	Record the Patient ID in the top right hand corner of each page.
Date of Evaluation:	Record the date (month/day/year) that corresponds to the protocol visit.
Protocol visit:	Record the protocol timepoint that corresponds to the visit.
Last protocol visit:	Record the date (month/day/year) of the last routine protocol visit the patient completed. Do not count the date of a "special visit" as the last routine follow-up visit. For the most part, the last routine protocol follow-up visit should be about 24 weeks prior to the current protocol visit. This date should be provided to the patient as a reference when it is necessary to determine whether an event or procedure occurred during the follow-up interval.

Trial participant returning to Cohort: A participant, who participated in the Cohort Study, was enrolled in a HBRN trial, and then returns to the Cohort Study should resume participation in the Cohort Study with the next cohort follow-up visit being determined from the Cohort baseline visit date. At the first Cohort visit after the trial, for "Last protocol visit", record the date of the last protocol visit

completed in the trial. This date should be the reference for events, procedures, HBV medications, and laboratory results to be reported since the last protocol visit.

Section I: Medical History

Check "Yes", "No", or "Unknown" for each condition listed to indicate whether or not the patient has been diagnosed or told by a doctor that they have the condition, or is receiving treatment for the condition.

Diabetes: Juvenile (Type 1) or Type II onset diabetes, regardless of treatment (e.g. diet, exercise, oral medication, insulin). Gestational diabetes should not be captured here. If a pregnant woman is diagnosed with gestational diabetes check "No" but record any medications prescribed for the gestational diabetes in the medication section.

Hypertension: is normally diagnosed when a blood pressure of ≥ 140 systolic or ≥ 90 diastolic is noted on two separate occasions, or if the patient is currently on antihypertensive medication.

Hyperlipidemia: blood level elevation of lipids such as cholesterol, cholesterol esters, phospholipids and triglycerides, or on medication to lower these levels.

Infections:

HCV: documented positive anti-HCV test.

HIV: documented positive anti-HIV test.

HDV: documented positive anti-HDV test.

Other liver disease:

Alcoholic: liver damage due to alcohol use.

Non-alcoholic fatty liver disease: fat accumulation in the liver not associated with alcohol use.

Autoimmune: inflammation of the liver due to the immune system. Patient should have a documented diagnosis from a doctor and corresponding auto-antibody tests.

Genetic/metabolic: liver diseases that are inherited and/or related to the metabolism of proteins or metals in the liver.

Glomerulonephritis: inflammation of the glomeruli, may be acute or chronic or may occur on its own or in conjunction with another disease.

Vasculitis/Polyarteritis Nodosa: inflammation in the blood vessels. May be due to infection, medical conditions, or an immunological response.

Malignancy (other than HCC): Also referred to as cancer; a term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body. There are several main types of cancer. If the patient has been told by a physician that they have a malignancy or cancer, other than hepatocellular carcinoma (HCC) or liver cancer, check "Yes" and specify the type of malignancy/cancer in the space provided.

Section II: Medication History

Current Medications:

Check "Yes" or "No" to indicate if the patient is currently taking medication for one of the reasons listed. If yes, then check the appropriate category that corresponds to the reason the medication is being used. Note that investigator input may be required to determine the reason that a medication is taken since a given medication may fit into more than one of the categories listed, and it may be difficult to determine the reason a medication is taken.
Immunosuppressants: agents that suppress or prevent an immune response. Some common drugs in this class include but are not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, Cellcept, Prograf and Arava.

Lipid-lowering agents: agents that aide in blocking the absorption of cholesterol or reducing cholesterol levels. Common agents in this class include but are not limited to antihyperlipedmic combinations (Caduet, Simcor), bile acid sequestrants (cholestyramine, colestipol), cholesterol absorption inhibitors (Zetia), fibric acid derivatives (fenofibrate,fenofibiric acid, gemfibrozil), and statins (lovastatin, rosuvastatin, simvastatin).

Anticoagulants: agents used to prevent the formation of blood clots. Common agents in this class include but are not limited to warfarin, heparins, platelet aggregation inhibitor (aspirin, Plavix, Tirofiban)

Anti-hypertensive agents: agents that are used to treat high blood pressure. Common agents in this class include but are not limited to diuretics (Furosemide, Spironolactone), beta-blockers (atenolol, metoprolol), ACE inhibitors (Benazepril, Captopril, Lisinopril, Ramipril), Angiotensin II receptors (Candesartan, Losartin, Valsartan), Direct-acting vasodilators (hydralazine), centrally acting agents (methyldopa, clonidine)

Anti-diabetic agents: agents that aide in the control of high or uncontrollable blood sugar for Type 1 or Type 2 diabetes or gestational diabetes. Common agents in this class include but are not limited to insulin (injection or oral), metformin, antidiabetic combinations (containing metformin and another drug), sulfonylureas (glimepiride, glyburide, and tolazamide), and incretin mimetics (Byetta).

Estrogen/birth control pills (containing estrogen): estrogen agents are typically used to relieve symptoms of menopause and other conditions that cause low levels of estrogen. Forms of estrogen include oral, patches, or topical. Birth control agents are used for the prevention of pregnancy and other medical conditions which include but not limited to regulation of menstrual cycles, endometriosis, and acne. Record only if the birth control agent contains estrogen. A common agent includes but is not limited to ethinyl estradiol and can be administered as a patch, an injection, or orally.

Other antivirals: any antiviral agents that are not indicated for treatment of hepatitis B. Types of agents include but are not limited to treatment for:

- hepatitis C: ribavirin
- herpes infections (e.g. herpes zoster, HSV): famciclovir, valacyclovir (Valtrex), and acyclovir
- CMV retinitis: ganciclovir, valganciclovir, and cidofovir
- Influenza: ramantadine, oseltamivir (Tamiflu), and zanamivir (Relenza)

If it is unclear that a specific medication is being taken for one of these reasons, check with the investigator or a source such as www.drugs.com for a group classification.

Herbal/natural medications: Check "Yes" or "No" to indicate if the patient is currently taking any herbs, herbal or natural medicines. Check "Unknown" if it is not known whether the patient is taking any herbs, herbal or natural medications.

Vitamins and minerals: Check "Yes" or "No" to indicate if the patient is currently taking any vitamins or minerals. Items are to be taken as a separate supplement and may be in pill or liquid form. If yes, check the appropriate type. Check "Unknown" if it is not known whether the patient is taking any vitamins or minerals.

Multi-vitamin: a supplement containing three or more vitamins or minerals but no herbs, hormones, or drugs. Common brand names include but are not limited to Centrum or One-a-Day. There are also multi-vitamins available as generic and store brands or prenatal vitamins.

Vitamin D: supplement specific to vitamin D and may be in combination with calcium. Do not include if part of a multi-vitamin supplement. Common vitamin D and calcium combinations include but are not limited to Os-Cal, Viactive, and Caltrate+D. Record vitamin D and calcium combinations as both Vitamin D and Calcium supplements.

Vitamin E: supplement specific to vitamin E. Do not include if part of a multi-vitamin supplement.

Folate: supplement specific to folate. May also be referred to as folic acid or vitamin B_9. Do not include if part of a multi-vitamin supplement.

Iron: supplement specific to iron. Do not include if part of a multi-vitamin supplement.

Calcium: supplement specific to calcium and may be in combination with Vitamin D. May be noted as calcium citrate, calcium carbonate, or calcium lactate. Do not include if part of a multi-vitamin supplement. Common vitamin D and calcium combinations include but are not limited to Os-Cal, Viactive, and Caltrate+D. Record vitamin D and calcium combinations as both Vitamin D and Calcium supplements.

Other: a vitamin or mineral other than those listed, and not part of a multi-vitamin supplement.

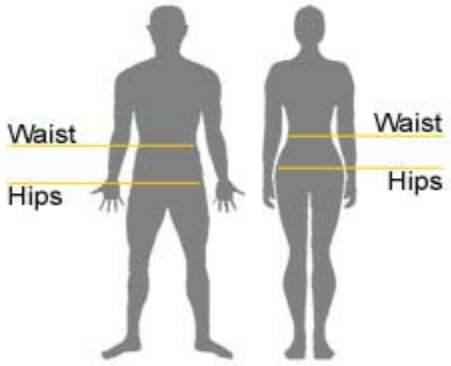
Section III: Physical Exam

Height: Record the patient's height at the time of the physical exam. Ask the patient to remove shoes prior to obtaining the measurement. Check "inches" or "cm" (centimeters) to indicate which unit of measure was used. If height was not measured then check "Not done". If for any reason (e.g. wheelchair-bound, equipment failure, etc.) a standing measurement is not obtained, record "Not done".

Weight: Record the patient's weight at the time of the physical exam. Check "lbs" (pounds) or "kg" (kilograms) to indicate which unit of measure was used. If weight was not measured then check "Not done".

Waist: Record the patient's waist circumference at the time of the physical exam. Do not complete a measurement in pregnant patients. Check "inches" or "cm" (centimeters) to indicate which unit of measure was used. If waist was not measured or the patient is pregnant then check "Not done".

To measure waist circumference, place a tape measure around the bare abdomen just above the hip bone (iliac crest). Be sure that the tape is snug (but does not compress skin) and that it is parallel to the floor. Ask the patient to relax, exhale, and then take the measurement.



Blood pressure: Record the patient's systolic and diastolic blood pressure in mmHg. Blood pressure should be obtained after the patient has been seated with both feet flat on the floor for at least 5 minutes. If blood pressure was not measured then check "Not done".

Current conditions: Check "Yes" or "No" for each item to indicate whether or not the patient currently has any of the following conditions, according to the study specific definitions provided below. If the assessment was not completed, check "Not Done".

Jaundice: Defined as the presence of bile pigment in the skin, mucous membrane, and sclera. There is a yellow discoloring of the skin, mucous membranes, and eyes.

Tender liver: Also known as tender hepatomegaly. The liver can be palpated and is tender.

Enlarged liver: Also known as hepatomegaly and is swelling of the liver beyond its normal size. An indication of enlarged liver is that the liver can be palpated below the costal margin (lower edge of ribs).

Enlarged spleen: Also known as splenomegaly and is swelling of the spleen beyond its normal size.

Peripheral edema: Defined as abnormal buildup of fluid in the ankles, feet, and legs.

Muscle wasting: Also known as muscle atrophy and is the loss and decrease in size of muscle tissue.

Spider angiomata: May also be recorded as spider angioma and is an abnormal collection of blood vessels near the surface of the skin. Appearance may have a red dot in the center, reddish extensions that reach out from the center, and lesion disappears with pressure and reappears when pressure is released.

Palmar erythema: Defined as an inflammatory redness of the palms of the hands.

Pregnancy: Check "Yes, pregnant now (or during follow-up interval)", "Yes, w/in 72 weeks", or "No" to indicate the pregnancy status for female patients. If the patient is male, check "N/A".

If yes, pregnant now (or during follow-up interval)

i. Record the month, day, and two digit year of the last menstrual period prior to the pregnancy. If any part of the date is not known, record "Unk".
ii. If patient was pregnant during the follow-up interval and an outcome was reached, e.g. miscarriage or termination, complete a pregnancy follow-up form.

If yes, w/in 72 weeks, check "Yes" or "No" to indicate if a pregnancy follow-up form was completed at the time of this protocol visit.

Section IV: Liver Decompensation or HCC

Check "Yes", "No", or "Unknown" for each item to indicate whether or not the patient currently has any of the liver conditions, according to the study specific definitions provided below.

Cirrhosis: Check "Yes" if there is a liver biopsy report indicating cirrhosis or clinical criteria that indicate the presence of:

Any one of the following:

- ascites or hepatic hydrothorax (see definition below)
- Variceal or portal hypertensive bleeding (see definition below)
- Hepatic encephalopathy (see definition below)
- Child-Turcotte-Pugh (CTP) score ≥ 7 (see calculation below)

OR

Any two of the following

- Splenomegaly (also known as enlarged spleen and is swelling of the spleen beyond its normal size)
- Nodular liver (documented by CT, MRI or liver ultrasound report)
- Platelet count below 120,000/mm^3 (result must be near to the time of diagnosis)

CTP score is calculated using the algorithm below.

		Number of points		
Items	**Units**	**1**	**2**	**3**
Serum albumin	g/dL	>3.5	2.8-3.5	<2.8
Serum total bilirubin No Gilbert's Syndrome	mg/dL	<2.0	2.0-3.0	>3.0

No hemolytic diseases Not receiving Ribavirin				
Serum total bilirubin Presence of Gilbert's Syndrome Hemolytic disorder such as patients receiving Ribavirin*	mg/dL	<4.0	4.0-7.0	>7.0
INR		<1.7	1.7-2.3	>2.3
Ascites		None	Mild^	Severe‡
Encephalopathy		None	Mild^	Severe‡

Note that if, in the opinion of the investigator, the patient has Gilbert's syndrome or a hemolytic disorder (e.g., patients receiving ribavirin) the level of the serum total bilirubin may be increased to as high as 3.99 mg/dL without considering the total bilirubin to be sufficiently elevated for the patient to receive a score of 2 in the CTP scoring system.

^ Mild means readily controlled by standard medical therapies.

‡ Severe means difficult to control or uncontrollable by optimal, maximally tolerated medical therapies.

The score is the sum of the scores for albumin, bilirubin, INR, ascites and encephalopathy (range 5-15)**.**

Class A = 5-6
Class B = 7-9
Class C = 10-15

If there is evidence of cirrhosis, complete the Follow-up Event form.

Hepatic encephalopathy: Characterized by recurrent disturbances of consciousness, impaired intellectual function, neuromuscular abnormalities, metabolic slowing on EEG and elevated serum ammonia levels. Symptoms include changes in mental state, consciousness, behavior and personality, decrease in performance of simple self-care tasks, and muscle spasms or rigidity. Also known as portal-systemic encephalopathy.

Medical record must indicate one of the following:

- Asterixis
- Clinical alteration in mental status with reversibility with therapy
- Two or more episodes of confusion consistent with encephalopathy

If yes to hepatic encephalopathy, check "None", "Mild", or "Moderate-severe" to indicate the stage of hepatic encephalopathy as determined by the investigator.

The West Haven classification is provided as a reference.

None	Grade 0	Lack of detectable changes in personality or behavior. Minimal changes in memory, concentration, intellectual function, and coordination. Asterixis is absent.
Mild	Grade 1	Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria, depression, or irritability. Mild confusion. Slowing of ability to perform mental tasks. Asterixis can be detected.
Moderate - Severe	Grade 2	Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis. Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
	Grade 3	Somnolent but can be aroused, unable to perform mental tasks, disorientation about time and place, marked confusion, amnesia, occasional fits of rage, present but incomprehensible speech
	Grade 4	Coma with or without response to painful stimuli

If the patient meets the definition of hepatic encephalopathy, the patient has met the definition of liver decompensation. Complete the Follow-up Event form.

Esophageal/gastric varices: Defined as dilated submucosal veins in the stomach or esophagus.

If yes, check “Yes”, “No”, or “Unknown” if the patient currently has variceal bleeding, defined as GI bleeding from varices present in the esophagus and/or stomach based on an endoscopy showing either:

- Direct evidence of variceal bleeding (bleeding varix, red wale sign)
- Moderate varices with no other site of bleeding identified and historical evidence for clinically significant upper GI bleeding.

Medical record must include an endoscopy report showing evidence of active or recurrent bleed within 48 hours of an episode.

If the patient meets the definition of variceal bleeding, the patient has met the definition of liver decompensation. Complete the Follow-up Event form.

Ascites: Defined as an excess of fluid in the peritoneal cavity that is either mild, moderate or marked on ultrasound, or is progressive on serial physical examinations, or requires diuretic therapy. Ultrasound report of minimal fluid around the liver does not meet the definition.

Medical record must indicate the presence of ascites or diuretic usage and one of the following:

- Paracentesis lab report
- Liver U/S report
- Liver CT report
- Liver MRI report

If ascites is present, check “Mild” or “Moderate to severe to indicate the grade.

Mild: managed without diuretics or controlled with diuretics without the need for paracentesis.

Moderate – severe: requires therapeutic paracentesis regularly.
If the patient meets the definition of ascites, the patient has met the definition of liver decompensation. Complete the Follow-up Event form.

HCC (hepatocellular carcinoma): Defined as cancer in the liver. The definition for the diagnosis of HCC follows the current AASLD guidelines:

- Nodules < 1 cm found on surveillance will be followed with ultrasound at intervals of 12-24 weeks until a diagnosis of HCC is made or no growth is seen over 2 years.
- Nodules equal to 1 cm or between 1 to ≤ 2 cm will be investigated further with dynamic studies, such as contrast ultrasound, triphasic CT or MRI with contrast. Two studies must agree with the appearance of HCC, such as hypervascularity with washout in the venous phase, before a diagnosis is determined.
- If the nodule is > 2 cm and has the typical features on a dynamic imaging technique or AFP > 200 ng/ml, a diagnosis of HCC may be made.
- If these conditions are not met, a biopsy may be performed. Biopsy slides will be collected at the time of diagnosis or surgery/transplant.

If the patient meets the definition of HCC, complete the Follow-up Event form and the HCC form. If a biopsy is performed, obtain slides for the HBRN.

Hepatic decompensation will be defined as the presence or diagnosis of any of the following:

- Ascites: as defined above.
- Hepatic hydrothorax: ascites associated pleural effusion.
- Variceal bleeding: as defined above.
- Portal hypertensive bleeding: gastrointestinal bleeding associated with portal hypertension.
- Hepatic encephalopathy: as defined above.
- Child-Turcotte-Pugh score ≥ 7: as defined above.

If the patient meets the definition of hepatic decompensation, complete the Follow-up Event form.

Section V: Diagnostic Tests

Imaging: Check "Yes" if the patient has had liver related imaging tests such as MRI, CT, ultrasound, PET, or PET/CT completed since the last protocol visit.

If yes, complete the following information.

Date of most recent test: Provide the month and two digit year of the most recent test performed since the last protocol visit, regardless of the type of imaging. If the month is unknown, record "Unk" and provide the two digit year. If both month and year are unknown, record "Unk" for each field.

Tests performed: Check all liver related imaging tests (CT, MRI, ultrasound, PET, or PET/CT) that were performed since the last protocol visit. If another type of imaging test was performed, check "Other" and specify the test in the space provided.
Report(s) available: Check "Yes" or "No" to indicate if one of more of the imaging reports from tests performed since the last protocol visit are available.

If yes, use the combined results from the imaging tests to record "Yes", "No" or "Unknown" for the following findings: nodular liver, abnormal liver texture, enlarged spleen, ascites, venous collaterals, or changes indicative of steatosis. If a finding that is not included in the list is indicated on a report, check "Yes" to Other and specify the result in the space provided.

Liver biopsy: Check "Yes" if the patient had a liver biopsy since the last protocol visit.

If yes, complete the Liver Biopsy form and complete the following information.

Date of most recent biopsy: Provide the month and two digit year of the most recent biopsy performed. If the month is unknown, record "Unk" and provide the two digit year. If both month and year are unknown, record "Unk" for each field.

Slides requested: Check "Yes" or "No" to indicate if slides (either unstained or stained) have been requested for the HBRN. Every effort should be made to obtain slides for the central reading. If possible, obtain slides that do not have to be returned to the local institution. If this is not possible, slides will be returned to the local institution after being read by the HBRN central pathologists.

Section VI: Treatment

HBV treatment: Check "Yes" or "No" to indicate if the patient has received treatment, either interferon or an oral antiviral agent for hepatitis B since the last protocol visit. *HBV/HIV co-infected participants*: check "N/A" and capture all HBV and HIV therapy on the AH Log.

If Yes, record the following information for each treatment the patient received:

Antiviral therapy: Record the appropriate code for the treatment. If you know that the patient received interferon or an oral antiviral but do not know the specific agent, record -3 (Unknown) for the antiviral therapy code.

Note: Tenofovir (TDF) = Tenofovir disoproxil fumarate
Tenofovir (TAF) = tenofovir alafenamide fumarate

Date started: Record the month, day, and two digit year that the treatment was started. If any piece of the date is not known, record "Unk".

Date stopped: Record the month, day, and two digit year that the treatment was stopped. If any piece of the date is not known, record "Unk". If the patient is currently on this treatment, do not complete the date stopped fields and check "Currently on Therapy".

Section VII: Serologies

Record the result and date of sample (month/day/year) for each serology test completed at the time of the evaluation or the most recent result obtained since the previous protocol evaluation. If a test was not completed as part of the evaluation or since the previous protocol evaluation, check "Not done".

Date of sample: Record the date of sample for the lab tests listed in this section. If a date of sample for a given lab is not the same, record the different date of sample next to the appropriate lab.

HBsAg:	Hepatitis B surface antigen
HBeAg:	Hepatitis B e antigen
Anti-HBs:	Antibody produced in response to HBV surface antigen
Anti-HBe:	Antibody produced in response to Hepatitis B e antigen
Anti-HDV:	Hepatitis delta antibody
Anti-HCV:	Hepatitis C antibody
Anti-HIV:	HIV antibody. A positive test must be confirmed by Western blot.
Anti-HBc IgM:	Hepatitis B core antibody

Section VIII: Virology Tests

HBV DNA level:

(1) Record the most recent DNA level completed at the time of the follow-up evaluation or the most recent result obtained since the previous protocol evaluation. If a result is not available, check "Unknown".
(2) Record the month and two digit year the sample was obtained. If the month is unknown, record "Unk" and provide the two digit year. If both month and year are unknown, record "Unk" for both month and year.
(3) Check "IU/mL" or "copies/mL" to indicate the unit of measure.
(4) Record the lower limit of detection for the test. If the lower limit of detection is not available or unknown, record "Unk".

Section IX: Labs

Record the most recent result for each lab test. Tests are to be completed at the time of the follow-up evaluation or within one month prior to the follow-up evaluation. If a test was performed more than once during the interval, record the result from the test performed closest to the time of the evaluation.

Fasting labs are to be completed at weeks 96, 144, 192, 240, and 288. The patient is to have had only water for the fasting period. A fasting period of 12 hours is optimal, with a minimum of 8 hours.

Fasting: Check "Yes" or "No" to indicate if the patient was fasting for this blood draw. If yes, record the length of the fasting period to the nearest hour.

Date of sample:	Record the date of sample (month/day/year) for the lab tests listed in this section.
Lab results:	(1) Record the result of the lab test. (2) If a date of sample for a specific lab is not the same as the date of sample recorded at the top of the section, record the date (month/ day/year) the sample was obtained. If any part of the date is unknown, record "Unk". (3) If the lab test was not completed or the result is not available, check "Not done".
ALT normal range:	If ALT is completed, record the lower and upper reference range of normal.
AST normal range:	If AST is completed, record the lower and upper reference range of normal.
Alkaline phosphatase normal range:	If alkaline phosphatase is completed, record the lower and upper reference range of normal.

Section X: Fibroscan and Breath Test

Fibroscan test:	Check "Yes" or "No" to indicate if a fibroscan was completed as part of the follow-up evaluation. If yes, i. Record the date (month/day/year) the fibroscan was performed. ii. Complete the Fibroscan Form.
Breath test:	Check "Yes" or "No" to indicate if a breath test was completed as part of the follow-up evaluation. If yes, i. Record the date (month/day/year) the breath test was performed. ii. Complete the Breath Test Form.

Section XI: Biospecimens

Samples obtained:	Check "Yes" or "No" to indicate if samples were obtained at this visit. If yes, check "NIDDK Repository", "Genetics", "Immunology study", or "Central lab" to indicate which samples were obtained.