SPONSORED GENETIC TESTING PROGRAM FOR LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAOD)

Sponsored by:

ultragenyx pharmaceutical

SPONSORED GENETIC TESTING PROGRAM FOR LC-FAOD

WHAT ARE LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAOD)?

LC-FAOD are a group of rare autosomal recessive disorders caused by defects in enzymes necessary for the metabolism of long-chain fatty acids to support the ongoing energy needs of major organ systems, including the heart, skeletal muscle and liver. LC-FAOD include the following types[1-3]:

- Carnitine palmitoyltransferase (CPT) I deficiency
- Carnitine-acylcarnitine translocase (CACT) deficiency
- Carnitine palmitoyltransferase (CPT) II deficiency
- Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Mitochondrial trifunctional protein (TFP) deficiency
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency

Clinical manifestations of LC-FAOD are heterogeneous, may be acute or chronic and often phenotypically present as fatigue (physical and/or mental) and/or with episodic exacerbations of rhabdomyolysis, cardiomyopathy and hypoketotic hypoglycemia, which often require hospitalization and can lead to death.[2,4]

WHY CONDUCT GENETIC TESTING FOR LC-FAOD?

- Verification of diagnosis may be required before determining patient eligibility for reimbursement.
- Accurate diagnosis of LC-FAOD may have an impact on clinical management of the condition, including customizing care to a patient's specific needs, providing patients with the appropriate genetic counselling support and connecting patients and their families to patient advocacy organizations and other resources.

This program provides testing for variants in up to 24 genes. The genes in the panel are known to be associated with the ß-oxidation of fatty acids, carnitine shuttle, carnitine transport, ketogenesis and conditions that may cause similar abnormal profiles on plasma acylcarnitine analysis. Below is a list of the disorders (and *genes*) associated with LC-FAOD that are tested:

- Carnitine palmitoyltransferase type I (CPT I) deficiency (*CPT1A*)
- Carnitine-acylcarnitine translocase (CACT) deficiency (*SLC25A20*)
- Carnitine palmitoyltransferase type II (CPT II) deficiency (*CPT2*)
- Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (*ACADVL*)
- Mitochondrial trifunctional protein (TFP) deficiency (*HADHA*, *HADHB*)
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (*HADHA*)

ENROL YOUR PATIENTS IN SPONSORED GENETIC TESTING

ELIGIBILITY CRITERIA

In order to take part in sponsored genetic testing for LC-FAOD, patients must meet at least 1 of the following criteria:

- Patient has a completed UltraCare Start Form for LC-FAOD

OR

- Patient is suspected of having, or has a known diagnosis of, a long-chain fatty acid oxidation disorder AND a plasma acylcarnitine test that either has been performed (regardless of result—abnormal or normal) or has been ordered
  - Carnitine palmitoyltransferase (CPT) I deficiency
  - Carnitine-acylcarnitine translocase (CACT) deficiency/carnitine palmitoyltransferase (CPT) II deficiency
  - Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency/mitochondrial trifunctional protein (TFP) deficiency
  - Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency

Providing a copy of plasma acylcarnitines results, or any other confirmatory tests, when available, is strongly encouraged. These results are helpful for variant interpretation and in some cases can make a difference in the final interpretation of the variant.

HOW TO SUBMIT A PATIENT TEST

Complete the enclosed Invitae Test Requisition Form (TRF).	Collect a blood or buccal swab sample from your patient using the sample kit provided.	Ship the completed TRF and patient sample using the prepared packaging and prepaid label.

For detailed instructions, see the **"Submitting a Patient Test"** section.

Test results are usually available within 10 to 21 calendar days from when sample processing begins. You will be notified via email (or fax) to access results through Invitae's secure site.

QUESTIONS ABOUT GENETIC TESTING FOR LC-FAOD?

Contact UltraCare by phone at **1-833-388-5872 (U-LTRA)**, by fax at **1-833-592-2273 (CARE)** or online at **ultracaresupport.ca**

SUBMITTING A PATIENT TEST

ENSURE YOU HAVE A TEST KIT AND A TEST REQUISITION FORM (TRF) FROM YOUR ULTRAGENYX FIELD PERSONNEL.

STEP 1: OBTAIN KIT

Your Ultragenyx field personnel is the best resource to provide you with kits and to help answer any questions you might have regarding this program.

You may also obtain kits via Invitae at **invitae.com/request-a-kit** or by contacting Global Support via telephone at **1-888-332-6039** or email at **globalsupport@invitae.com**.

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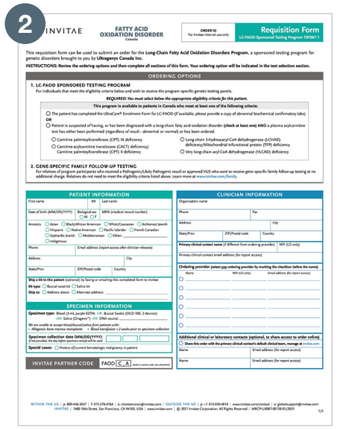
Note: You have the option to order the following sample collection kits: Blood (3-mL purple EDTA) -OR- Buccal Swab -OR- Saliva (Oragene™) -OR- Assisted Saliva. However, blood and buccal swab sample collection kits are recommended. Please reach out to your Ultragenyx field personnel for details.

STEP 2: COMPLETE THE TRF

Complete the enclosed LC-FAOD Test Requisition Form (TRF887). Copies of the form are available in the back-page pocket of this brochure. You may also contact your Ultragenyx field personnel for additional copies or with any queries regarding this form.

2


INVITAE
FATTY ACID OXIDATION DISORDER
Requisition Form
LC-FAOD Sponsored Testing Program TRF887 I
ORDERING OPTIONS
PATIENT INFORMATION
CLINICIAN INFORMATION
SPECIMEN INFORMATION
INVITAE PARTNER CODE
FAOD C A

Important notes:

- Ensure all fields of the TRF are completed. In order to get a confirmation that the test samples have been received and access test result reports, an email address must be provided. If an email address is not provided, Invitae will fax the test result reports.
- Patients who cannot provide an in-person sample may provide a buccal swab sample from home. To have a Buccal Swab Specimen Collection Kit shipped directly to your patient's home, please mark this in the "Patient Information" section of the TRF.
- It is strongly encouraged to include clinical history information, including a copy of plasma acylcarnitine results or any other confirmatory tests, with the form, when available. This information is useful for variant interpretation.

STEP 3: LABEL THE SAMPLE TUBE

Before the sample is collected, ensure the sample tube is properly labelled with:

- Patient's first and last name
- Patient's date of birth (MM/DD/YYYY)
- Sample collection date (MM/DD/YYYY)

The patient's name, the patient's date of birth and the sample collection date written on the sample tube must match exactly what is written on the TRF.

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STEP 4: COLLECT THE PATIENT SAMPLE

Collect a patient sample according to the type of collection kit you are using: blood or buccal swab.

For blood collections:

Collect a blood sample using the Invitae Blood Collection Kit. Blood samples can be collected at your institution. If this is not available, contact Invitae Global Support via telephone at **1-888-332-6039** or email at **globalsupport@invitae.com** to locate a blood draw location.

If using a blood draw location, note that patients need to arrive with 3 items:

- Signed TRF
- Invitae Blood Collection Kit
- Blood draw form from your blood draw location

Note: Labs do not have Invitae kits in stock.

4a

For buccal swab collections:

Collect a buccal sample using the Invitae Buccal Swab Specimen Collection Kit.

- Patients should be instructed not to eat, drink, smoke or chew gum for 30 minutes before providing a sample.
- Follow instructions included inside the collection kit.

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FIND MORE INFORMATION ABOUT SPECIMEN REQUIREMENTS AT
invitae.com/en/specimen-requirements

SUBMITTING A PATIENT TEST

STEP 5: PACKAGE THE KIT

- Place the tube with the collected sample in the small plastic bag and seal it.
- Place this bag, along with the completed TRF, in the cardboard box.
- Place the box inside the shipping bag and seal the bag.

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STEP 6: PREPARE THE SHIPPING DOCUMENTS

- Locate the **customs declaration letter** (included with your collection kit).
  – There is no need to write anything on this letter.
- Locate the **air waybill** (AWB, included with your collection kit).
  – Fill out section 1 with your information.
  – In section 8, sign on the “Sender’s Signature” line.
- Locate the **pro forma invoice** (included with your collection kit) and complete it as follows:
  1. Fill out the “Ship from” section with your information.
  2. Enter today’s date in the upper right corner.
  3. Leave the “Invoice #” line blank.
  4. Leave the “Tax ID” line blank.
  5. Under “Est. ship date,” enter the date you will mail the package.
  6. Under “Carrier,” enter *FedEx*.
  7. Under “Port of loading,” enter the city and country you will ship from. You can leave “Port of discharge” blank.
  8. Under “AWB number,” enter your FedEx tracking number, which can be found on the air waybill.
  9. Sign and date the form.

  Leave all other lines blank.
- Apply the document holder to the outside of the shipping bag.
- Insert the pro forma invoice(s), customs declaration letter and AWB inside the document holder. **Do not** seal the document holder.

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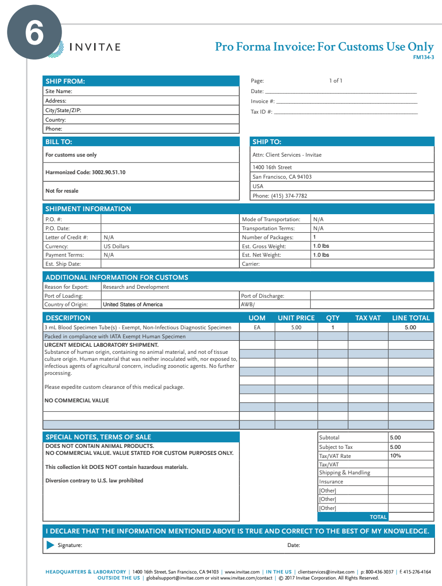
INVITAE Pro Forma Invoice: For Customs Use Only

STEP 7: DROP OFF OR SCHEDULE A PICKUP

- Schedule a pickup by visiting **fedex.com** or bringing the package to your local FedEx office.

Once the patient sample and completed TRF have been couriered and you have received the email confirmation, proceed to step 8 to activate your account and access results through Invitae’s secure portal. Test results are usually available within 10 to 21 calendar days from when sample processing begins.

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STEP 8: ACTIVATE YOUR INVITAE PORTAL ACCOUNT

You will receive an email from Invitae when your order has been received. Please follow the instructions in the email to activate your Invitae portal account. You will be able to track the status of your test and view all test result reports through the portal. If you choose not to create an Invitae account, test results will be faxed if a fax number was provided on the TRF.

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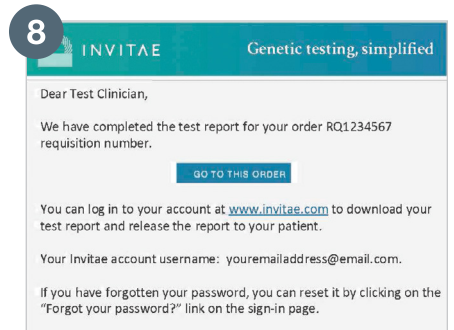
INVITAE Genetic testing, simplified

Dear Test Clinician,

We have completed the test report for your order RQ1234567 requisition number.

GO TO THIS ORDER

You can log in to your account at www.invitae.com to download your test report and release the report to your patient.

Your Invitae account username: youremailaddress@email.com.

If you have forgotten your password, you can reset it by clicking on the “Forgot your password?” link on the sign-in page.

STEP 9: CHECK FOR COMMUNICATIONS FROM INVITAE

Invitae’s Client Services team will reach out to you directly to confirm discrepancies and resolve any issues. To avoid any delays, please respond to these communications as quickly as possible.

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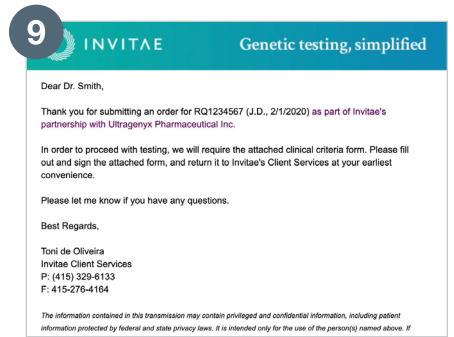
INVITAE Genetic testing, simplified

Dear Dr. Smith,

Thank you for submitting an order for RQ1234567 (J.D., 2/1/2020) as part of Invitae’s partnership with Ultragenyx Pharmaceutical Inc.

In order to proceed with testing, we will require the attached clinical criteria form. Please fill out and sign the attached form, and return it to Invitae’s Client Services at your earliest convenience.

Please let me know if you have any questions.

Best Regards,

Toni de Oliveira
Invitae Client Services
P: (415) 329-6133
F: 415-276-4164

STEP 10: VIEW TEST RESULTS

You will receive an email from Invitae when the test result report is available. Click the link in the email to view the test results in the secure Invitae portal.

For questions regarding privacy, please email Invitae at globalsupport@invitae.com.

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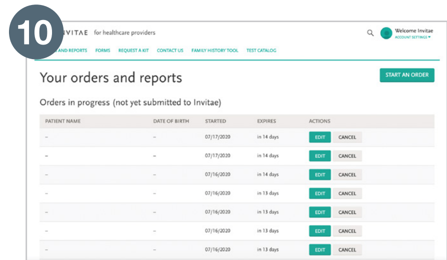

IS IT AN LC-FAOD? CONFIRM THE DIAGNOSIS WITH SPONSORED TESTING.

An accurate diagnosis of an LC-FAOD may impact management of the condition. It can help customize care to the specific needs of a patient and may be required for reimbursement of treatment.

HOW TO SUBMIT A PATIENT TEST

Complete the enclosed Invitae Test Requisition Form (TRF).

Collect a blood or buccal swab sample from your patient using the sample kit provided.

Ship the completed TRF and patient sample using the prepared packaging and prepaid label.

For detailed instructions, see the “Submitting a Patient Test” section.

For patients meeting the eligibility criteria, this program is provided at no charge.

QUESTIONS ABOUT THE LC-FAOD TESTING PROGRAM?

To learn more about the LC-FAOD testing program, contact Ultragenyx field personnel or visit Invitae online at **invitae.com/en/lc-faod.**

References:

1. Roe CR, Brunengraber H. Mol Genet Metab. 2015;116(4):260-268.
2. Knottnerus SJG, Bleeker JC, Wüst RCI, et al. Rev Endocr Metab Disord. 2018;19(1):93-106.
3. Wanders RJ, Ruiter JP, IJLst L, Waterham HR, Houten SM. J Inherit Metab Dis. 2010;33(5):479-494.
4. Vavlukis M, Eftimov A, Zafirovska P, et al. Case Rep Genet. 2014;2014:496410.

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