*Early*CDT®–Liver

1. What is *Early*CDT®-Liver?

***Early*CDT®-Liver** is a simple blood test to aid detection and confirmation of HCC in association with imaging in high-risk patients with liver lesions of all sizes.

2. What are the key benefits of *Early*CDT-Liver?

- ***Early*CDT-Liver** is complementary to imaging for the diagnosis of HCC.
- The high specificity of the test makes it a clinically useful 'confirmation' test.
- It can detect HCC at all stages[1], with similar performance, for early and late stage disease. Importantly, it provides the benefit of significant lead time (earlier detection). Data shows that raised levels of autoantibodies can be used to detect cancer up to 4 years before it is detected by other methods[2,3].
- ***Early*CDT-Liver** has high accuracy, similar to CT, MRI, and ultrasound (85% to 95% depending on risk).
- Both Moderate and High Level results are clinically actionable, for example by accelerating follow-up or clinical intervention.

3. How does it work?

Oncimmune's proprietary ***Early*CDT®** cancer detection platform measures the presence in the blood of autoantibodies against specific tumor-associated antigens. These autoantibodies have the potential to signal the presence of cancer up to 4 years earlier than other methods, and can be applied to a wide range of solid tumor types. ***Early*CDT-Liver** measures a panel of seven autoantibodies, as well as alpha fetoprotein (AFP), to detect the presence of HCC.

4. Can you explain the possible test results?

***Early*CDT-Liver** test results are reported as No Significant Level of Biomarkers Detected, Moderate Level and High Level, depending on the level of biomarkers in the blood compared to appropriate cut-off values. The interpretation of these results is discussed below.

5. Are the performance claims for the *Early*CDT-Liver test supported?

- The ***Early*CDT®** cancer detection platform was exhaustively validated before launch with over 120,000 tests completed during development.
- The ***Early*CDT-Liver** test was developed and validated using samples from over 1,500 patients with benign and malignant liver disease as well as healthy controls.

6. How does *Early*CDT-Liver performance complement imaging modalities used in diagnosis of HCC?

- Ultrasound scanning is the first line screening test for patients at high risk of HCC according to AASLD[4] EASL[5] and APASL[6] guidelines.
- Patients identified with a lesion by ultrasound are often followed up by contrast enhanced CT or MRI to confirm the diagnosis of HCC. However, in a significant proportion of patients, the malignancy status of the patient's lesion cannot be determined from the results of the second imaging test.
- ***Early*CDT-Liver** also offers a complementary approach to contrast enhanced CT or MRI in patients whose diagnosis of HCC can be neither confirmed nor ruled out using these imaging techniques.
- In addition, ***Early*CDT-Liver** High result significantly enhances the chance of an ultrasound-identified liver nodule being malignant by three to six-fold.
- As a simple blood test, ***Early*CDT-Liver** can be used as a rule-in test to give the physician a high degree of certainty that a lesion is malignant.
- For instance, a positive ultrasound[7] followed by a negative CT gives little change in risk (4% goes to 8%) of the lesion being a cancer, but if this is followed by a High Level ***Early*CDT-Liver** result, the risk of the lesion being a malignancy increases to 53%, a greater than six-fold increase in risk.
- In patients with liver lesions less than 1cm, imaging modalities are less reliable, A Moderate or High Level ***Early*CDT-Liver** test result provides a higher level of certainty of cancer, which would indicate that accelerated follow-up is needed.
- If the ***Early*CDT-Liver** result is No Significant Level of Biomarkers Detected, then the patient's risk of malignancy does not change and they should be followed up according to your previously determined course of action.

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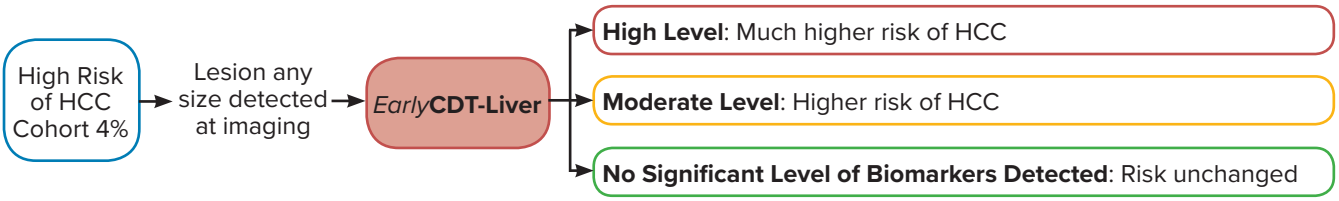
7. How does a patient's estimated risk of liver cancer change following an *Early*CDT-Liver test?

*Early***CDT-Liver** positive test results signal a significantly increased risk of HCC. The test can be used in combination with all imaging modalities to add confirmatory value to imaging.

***Early*CDT-Liver Test Result:**



The table shows the risk after imaging, and the risk change on a positive test result based on the initial cohort risk of 4%[i] as seen in in the USA:

***Early*CDT-Liver with Imaging**	**Positive Predictive Value (PPV) / Risk**				
			When imaging is followed by *Early*CDT-Liver		
Imaging Modality and Combination	**Initial High-Risk Cohort HCC Prevalence[i]**	**Risk with Positive Imaging**	**High Level[v]**	**High/Moderate[vi] Combined**	**No Significant Level of Biomarkers Detected**
Ultrasound[iv] only	4%	23%	80%	62%	No change from pre-test risk
Ultrasound + MRI	4%	81%	98%	96%	
Ultrasound + CT	4%	84%	99%	97%	
MRI[ii] only	4%	38%	89%	77%	
CT[iii] only	4%	43%	91%	81%	

PPV is the Positive Predictive Value – the percentage chance of a positive being a "true cancer"

i Initial Cohort Risk 4% taken from AASLD guidelines[4]

ii MRI: sensitivity 87%, specificity 94%[4]

iii CT: sensitivity 73%, specificity 96%[4]

iv Ultrasound: sensitivity 78%, specificity 89%[7]

v *Early***CDT-Liver** High Level result: sensitivity 41%, specificity 97%

vi Moderate & High Level result: sensitivity 54%, specificity 90% (Oncimmune data on file)

8. What if the patient's test result is High Level or Moderate Level?
   - A High Level test result is defined as one or more biomarkers in the *Early***CDT-Liver** panel being above the high cut-off value.
   - A Moderate Level test result is defined as one or more biomarkers in the *Early***CDT-Liver** panel being above the low cut-off value, but all are below the high cut-off value.
   - A High Level or Moderate Level test result indicates that the patient's risk of having HCC is greater than that predicted pre-test for the lesion and other relevant HCC risk factors.
   - This increased risk may warrant a recommendation for additional investigations. The recommendation should be consistent with the patient's history, overall risk profile, and guidelines.

   If HCC is not found, consider continued additional testing in the future. Other age- and gender-specific screenings for other cancers (for example, breast and colon), such as those recommended by the American Cancer Society (www.cancer.org) should also be considered[8].

9. What if the patient's test result is No Significant Level of Biomarkers Detected?
   - A No Significant Level of Biomarkers Detected test result is defined as all biomarkers in the *Early***CDT-Liver** panel being below the low cut-off value.
   - A No Significant Level of Biomarkers Detected test result indicates a lower likelihood of HCC than a Moderate or High Level result; however, it does not rule out the possibility of the patient having HCC now or in the future. The patient's risk of having HCC is unchanged. Patients should continue to be treated in the normal course, as if there had been no *Early***CDT-Liver** test performed.
   - You, their doctor, will determine continued monitoring and follow-up, consistent with the patient's history and overall risk profile.

10. How often do you recommend the patient have a repeat *Early***CDT-Liver** test given a No Significant Level of Biomarkers Detected test result?

    There is no recommended definitive repeat period as the patient's ongoing risk will vary according to the specific patient's risk factors.

11. Who should I test?

    High-risk patients with a liver lesion of indeterminate malignancy after ultrasound (often a liver lesion <1cm), contrast enhanced CT, or MRI scan. Patients should not be pregnant or have any personal history of any type of cancer.

12. How is *Early***CDT-Liver** different from other methods of liver cancer detection?
    - *Early***CDT-Liver** is a simple blood test.
    - The goal of this test is early cancer detection. Currently, most HCC cases are only detected once symptoms appear and usually in later stages of the disease.
    - Measuring autoantibodies has the potential to detect liver cancer in its early stages of development, giving the patient more treatment options with subsequent improved prognosis.
    - Some current methods of liver cancer detection, such as CT scanning, involve levels of radiation exposure.

13. Is *Early***CDT-Liver** different from genetic testing? How?

    *Early***CDT-Liver** is designed to indicate the presence of liver cancer cells in the body, i.e: liver cancer is present, not the likelihood of developing cancer in the future which is what genetic testing is often looking for. *Note: Currently there is no standardized genetic test for liver cancer.*

14. Where can patients take the test?

    In the U.S., you may request a kit for *Early***CDT-Liver** using our website order form, by calling Oncimmune Client Services at +1-888-583-9030, or by emailing ClientServices@oncimmune.com.

15. What is the sample provision process?

    A blood or serum sample is all that is required. A simple finger stick sample collection is offered Alternatively a blood draw into a red-top serum tube or serum separator tube (SST). Return pre-paid packaging is supplied. Samples of both blood and serum are shipped at ambient temperature.

16. How are the test results reported?

    Your patient's results are reported by fax only at present.

17. How long does it take to get results?

    You should receive the results within 5-7 days from the time the sample is received at our laboratory in De Soto, Kansas

18. How much does *Early***CDT-Liver** cost and is it covered by medical insurance?

- The cost of the *Early***CDT-Liver** test is low relative to many other tests, particularly as it is not a genetic test.
- Oncimmune works with all insurance carriers and files claims to both Medicare and commercial insurance plans.
- As a Medicare provider, Oncimmune will file a claim for Medicare beneficiaries being tested to aid in the assessment of malignancy risk of indeterminate liver lesions identified by imaging. Patients with private insurance need to confirm coverage with their insurance provider.
- Oncimmune offers a Patient Care Programme to enable patients to be tested even if they are denied insurance.
- For further information contact Oncimmune Client Services at +1-888-583-9030, or by emailing ClientServices@oncimmune.com.

19. Who is Oncimmune®?

- Oncimmune Plc is a leading global provider of early cancer detection tests. It is headquartered in Nottingham, UK, and provides a service from its CLIA[9] certified laboratory in De Soto, Kansas, USA.
- Oncimmune has pioneered the development of a proprietary autoantibody assay technology that has the potential to detect cancer up to 4 years earlier than other methods. Our technology platform *Early***CDT**® was launched in 2009 and has been extensively validated and can be applied to a wide range of solid tumor types.
- For more information please see http://oncimmune.com/about-oncimmune/

References

1. Macdonald I et al. Development and Validation of an ELISA test detecting a panel of Autoantibodies in combination with AFP for Early Detection of Hepatocellular Carcinoma. *Abstract submitted to ILCA 2018.*
2. Jett J, et al. Determination of the Detection Lead Time for Autoantibody Biomarkers in Early Stage Lung Cancer Using the UKCTOCS Cohort. *J Thorac Oncol. 2017; 12(11, Suppl 2):S2170.*
3. Zhong L, et al. Profiling tumor-associated antibodies for early detection of non-small cell lung cancer. *J Thorac Oncol. 2006; 1(6):513–519.*
4. Heimbach JK, et al. AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. *Hepatology 2018; 67(1):358-380.*
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol 2018*
6. Omata M, Cheng A-L, Kokudo N, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatology International. 2017;11(4):317-370.*
7. Chou R, et al. Imaging Techniques for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *Ann Intern Med. 2015; 162(10):697-711.*
8. Follow up of patients always remains the sole responsibility of the treating clinician.
9. CLIA (Clinical Laboratory Improvement Amendments) is a lab testing quality standard that was first established in 1988 in the US, and became part of the Federal Register in 1992. CLIA certification is required for any laboratory that performs tests on “materials derived from the human body” for diagnostic, treatment, health assessment or prevention purposes.