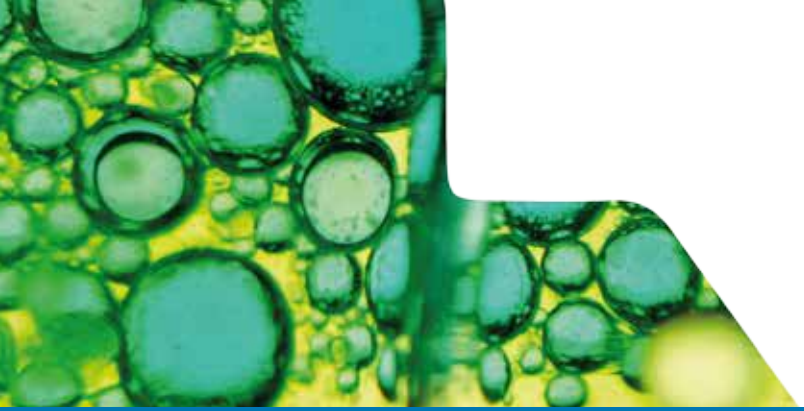


*Early*CDT®–Lung

Frequently Asked Questions (FAQs) for Physicians

oncimmune®

Leading early cancer detection

1. What is *Early*CDT®-Lung?

- A **simple blood test** to aid in the risk assessment and early detection of lung cancer in **high-risk patients** and to stratify indeterminate pulmonary nodules for the risk of malignancy.

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

- The overall accuracy is **92%**[1].
- Can detect lung cancer up to **4 years earlier**[2] than other methods.
- Shows a **3x** to **16x risk increase** with a Moderate or High Level test result.
- *Early*CDT-Lung offers a **complementary approach to annual CT** screening.
- Can be billed to **Medicare Part B and most major private health insurances** in the US by the test provider.

3. How does it work?

- When a tumor is present it produces abnormal proteins (known as antigens).
- Cancer antigens are different to 'normal' antigens so the body reacts to these antigens by producing autoantibodies. These autoantibodies, which can arise in the earliest stages of cancer and have been shown to be present at all stages, are produced in sufficient quantities to be measured in an individual's blood using a simple blood test.
- Oncimmune's proprietary *Early*CDT® cancer detection platform was developed to measure 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 four years earlier than other methods and can be applied to a wide range of solid tumor types.
- *Early*CDT-Lung measures a panel of seven autoantibodies to detect the presence of lung cancer.

4. Can you explain the possible test results?

- *Early*CDT-Lung test results are reported as Low Level, Moderate Level and High Level, depending on the level of autoantibodies in the blood compared to low and high cutoff values for each autoantibody. The interpretation of these results is discussed below (questions 9 to 11).

5. How accurate is *Early*CDT-Lung and what are the performance statistics?

- The overall accuracy is 92%.
- Table 1 shows that *Early*CDT-Lung performs favorably when compared with other established cancer detection tests.

1 Chapman CJ, Healey GF, Murray A, et al. *Early*CDT®-Lung test: improved clinical utility through additional autoantibody assays. Tumor Biol. 2012;33(5):1319-1326.

2 Zhong L, Coe SP, Stromberg AJ, et al. Profiling Tumor-Associated Antibodies for Early Detection of Non-small Cell Lung Cancer. J Thor Oncol 2006;1:513-519.

Table 1[3]:

	Accuracy	Performance (PPV)[a]
*Early***CDT-Lung (High)**[b]	**97%**	**1 in 5**
*Early***CDT-Lung (Moderate & High)**[b]	**92%**	**1 in 10**
CT Screening (Annual)[c]	73%	1 in 25
Mammography[d]	92%	1 in 26
Cologuard®[e]	84%	1 in 27

Assumed cancer rates[f]: *Early***CDT-Lung** & CT Screening = 1.2%, Mammography = 0.8%, Cologuard® = 0.6%
True Positive = cancer False Positive = no cancer

NB: Approximately ⅔ of High and Moderate Level results are High Level. More detailed performance analysis is available at www.oncimmune.com/earlycdt-test/further-information

6. Are the performance claims for the *Early***CDT-Lung** test supported?

- The test was exhaustively validated before launch with over 120,000 patient samples being used.
- The test has also been independently audited[4] since commercial launch in clinical practice on a large sample set of 1,600 patients and the results published. The conclusion on all occasions has been that the test performs as expected.
- The initial results of the largest randomized trial ever conducted for the early detection of lung cancer using biomarkers; the National Health Service (NHS) Scotland ECLS study of 12,000 high-risk smokers, were presented by the NHS in Sept 2015 at the World Conference on Lung Cancer, Denver, USA[5]. These results showed performance was as expected and importantly that there was a shift to Stage 1 & 2 cancers of 50% (80% were early stage in the trial as opposed to 30% early stage using current clinical practice) thus demonstrating the early detection performance of the test, which is key to mortality benefit.

3 a) Positive Predictive Value - the number of positive test results required to detect a cancer.
b) Boyle P, Chapman CJ, Holdenrieder S, et al. Clinical validation of an autoantibody test for lung cancer. Ann Oncol 2011;22(2):383-389.
Chapman CJ, Healey GF, Murray A, et al. *Early***CDT®-Lung** test: improved clinical utility through additional autoantibody assays. Tumor Biol 2012;33(5):1319-26.
Healey GF, Lam S, Boyle P, et al. Signal stratification of autoantibody levels in serum samples and its application to the early detection of lung cancer. J Thorac Dis 2013;5(5): 618-625.
c) The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
Aberle, DR, DeMello S, Berg CD, et al. Results of the Two Incidence Screenings in the National Lung Screening Trial. N Engl J Med 2013;369:920-931.
d) National Cancer Institute. Breast Cancer Surveillance Consortium: Evaluating Screening Performance in Practice. NIH Publication No. 04-5490. Bethesda, MD: National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, April 2004.
e) Imperiale TF, Ransohoff DF, Itzkowitz SH et al., N Engl J Med 2014; 370(14):1287-1297.
f) Assumed cancer rate (NB: *Early***CDT-Lung** has an additional 50% for look-forward (equivalent to 1.8%))

4 Jett JR, Peek LJ, Fredericks L, et al. Audit of the autoantibody test, *Early***CDT-Lung**, in 1600 patients: An evaluation of its performance in routine clinical practice. Lung Cancer 2014;83:51-55.

5 Sullivan F & Schembri S. Progress with an RCT of the Detection of Autoantibodies to Tumour Antigens in Lung Cancer Using the *Early***CDT-Lung** Test in Scotland (ECLS). J Thor Oncol 2015;10:S306.

7. How does *Early***CDT-Lung** performance compare to Annual CT Screening?

- While the performance metrics compare favorably with annual CT screening (see Table 1) it is the combination of both tests that yields the most benefit.
- *Early***CDT-Lung** offers a complementary approach to annual CT screening which is the gold standard in the USA for early lung cancer detection if the patient meets the high-risk criteria set by USPSTF[6].
- Annual CT screening has been shown to reduce mortality from lung cancer provided that:
  - The patient is high risk (as defined by the National Lung Screening Trial (NLST)[7] in the USA), that is, 55-74 years old with 30+ pack years smoking history or have quit within the last 15 years.
  - Testing is on an annual basis as the reported performance metrics from the NLST rely on annual screening and cannot be applied to the performance of a single CT scan. A single CT scan is less sensitive and has more false positives.
- As a simple blood test, *Early***CDT-Lung** can be used when an individual is at increased risk but does not meet the criteria for annual CT screening. It can also be used when individuals are unwilling or unable to undergo lifelong annual CT screening.
- In either case, a Moderate or High Level *Early***CDT-Lung** result can be followed by suitable CT scans to confirm the presence of lung cancer early with the patient, physician and insurers better aware of the risk of cancer developing. See Appendix 1 for more details.
- The *Early***CDT-Lung** test can also be used in conjunction with a CT scan and other diagnostic imaging techniques to further assess the risk of lung cancer being present where indeterminate lung nodules have been detected but have not been diagnosed as malignant.[8] See Appendix 2.

8. How does a patient's estimated 1-year risk of lung cancer change following an *Early***CDT-Lung** test?

- Using the example of a 65 year old male with a 45 pack year smoking history, as the table below illustrates:

Test Result	1-Yr Risk	Increase in 1-Yr Risk
Low Level	1.2%	Unchanged at 1.2%
Moderate Level	3.5%	3x
High Level	19.3%	16x

- If the patient has a Moderate Level test result, the estimated 1-year risk of having lung cancer nearly triples to **3.5%**.

6 Final Update Summary: Lung Cancer: Screening. U.S. Preventive Services Task Force. July 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening

7 The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
Aberle DR, DeMello S, Berg CD, et al. Results of the Two Incidence Screenings in the National Lung Screening Trial. N Engl J Med 2013;369:920-931.

8 Massion P, Healey GF, Peek LJ, et al. Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-Based Risk Models for Detection of Lung Cancer. J Thor Oncol 2017; 12(3):578-584

- If the patient has a High Level test result, the estimated 1-year risk of having lung cancer is **19.3%**, an increased risk of over 16 times.
- If the patient has a Low Level test result, the estimated 1-year risk of lung cancer is essentially unchanged from their pre-test high-risk status of **1.2%**.
- A personalized report reflecting the estimated risk of your specific patient as calculated based upon age, gender, smoking history and their *Early***CDT-Lung** test result is available online at: http://www.oncimmune.com/earlycdt-test/risk-calculator

9. What if the patient's test result is High Level or Moderate Level?

- A **High Level** test result is defined as one or more autoantibodies in the *Early***CDT-Lung** panel being above the high cutoff value.
- A **Moderate Level** test result is defined as one or more autoantibodies in the *Early***CDT-Lung** panel being above the low cutoff value but all are below the high cutoff value.
- A High Level or Moderate Level test result indicates that the patient's risk of having lung cancer is greater than that predicted by their gender, age, smoking history and other risk factors.
- This increased risk may warrant a recommendation for additional testing, which may include CT imaging. The recommendation will be consistent with the patient's history and overall risk profile, which could include prior radiological findings.
- "Potential Monitoring Guidelines" which you may wish to consider are provided in Appendix 3.
- If lung cancer is not found, a physician may recommend continued additional testing in the future. Other age- and gender-specific screenings for other cancers (for example, breast and colon), as recommended by the American Cancer Society (www.cancer.org), should also be considered.

10. What if the patient's test result is Low Level?

- A **Low Level** test result is defined as all autoantibodies in the *Early***CDT-Lung** panel being below the low cutoff value.
- A Low Level test result indicates a lower likelihood of lung cancer than a Moderate or High Level result**, however it does not mean that the patient does not have, or will not develop lung cancer** because in order to be eligible for the test your patient was already at an elevated risk of lung cancer as predicted by age, gender, smoking history and other risk factors. This has not changed appreciably.
- You, their physician, will determine continued monitoring and follow-up, consistent with the patient's history and overall risk profile.

11. How often do you recommend the patient have a repeat *Early***CDT-Lung** test given a Low Level test result?

- We do not recommend a definitive repeat period as you will have to take into account your patient's on-going risk. The *Early***CDT-Lung** test can detect cancers up to four years earlier than other methods. Our general advice for repeat testing is between 1 and 2 years to test for new lung cancers that may have developed since the previous test was undertaken.

12. Who should I test[9]?

- High-risk patients – those who are at risk of lung cancer due to a combination of age, gender, smoking history and other risk factors such as environmental exposures (radon, dust, asbestos, radioactive substances), those with a history of emphysema/COPD, or first degree relative family history.
- It is intended to be used in conjunction with standard clinical practice for the assessment of lung cancer in patients who:
  - Are diagnosed with indeterminate pulmonary nodule(s)[10]
  - Are ≥50 years of age with at least a 20 pack year smoking history (equivalent to smoking one pack of cigarettes per day for 20 years)
  - Are 40-49 years of age with a ≥20 pack year history plus at least one additional risk factor
- Patients should not have any personal history of any type of cancer (exception: basal cell carcinoma)
- Full list of lung cancer risk factors: www.oncimmune.com/earlycdt-test/risk-lung-cancer

*Note: The risk groups defined for Early***CDT-Lung** *are lower than those recommended for CT screening in the US. Only 30%[11] of lung cancers fall into the population recommended for CT screening. A High or Moderate Level Early***CDT-Lung** *result indicates an increased risk, that is greater than the entry level risk criteria for CT screening in the US. This enables more high-risk patients to be triaged for CT work up.*

13. Why is *Early***CDT-Lung** not recommended for those with a previous history of cancer and why is basal cell carcinoma an exception?

- Test performance may vary for patients with a previous history of cancer or cancer treatment. The panel of autoantibodies measured has been optimized to detect lung cancer, not other types of cancer, and the control population used to validate the test did not include any patients with a history of cancer. The exception to this recommendation is for patients with a history of basal cell carcinoma (BCC). A study was conducted, and the data suggested that BCC does not impact the *Early***CDT-Lung** result.

14. How is *Early***CDT-Lung** different from other methods of lung cancer detection?

- *Early***CDT-Lung** is a simple blood test.
- The goal of this test is early cancer detection. Currently most lung cancer cases are only detected once symptoms appear and usually in later stages of the disease.
- Measuring a panel of autoantibodies has the potential to detect lung cancer in its early stages of development, giving the patient more treatment options with subsequent improved prognosis.

9 *Early***CDT-Lung** is not recommended for use in patients <40 yrs of age

10 Massion P, Healey GF, Peek LJ, et al. Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-Based Risk Models for Detection of Lung Cancer. J Thor Oncol 2017; 12(3):578-584

11 Pinsky PF and Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen 2012;19(3):154-156.

- Current methods of lung cancer detection, including x-ray and CT scanning, involve levels of radiation exposure.

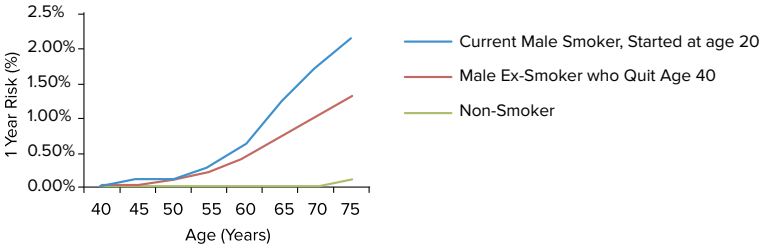
15. Is *Early***CDT-Lung** different from genetic testing? How?

- *Early***CDT-Lung** is designed to indicate the presence of lung cancer cells in the body at any stage, 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 lung cancer.

16. How does smoking cessation affect risk?

- As the following graph illustrates, stopping smoking reduces lung cancer risk, however it is important to note that early cessation is key as the effects of smoking accrue over time. The graph compares the 1 year risk[12] of developing lung cancer in a current smoker, an ex-smoker who quit at the age of 40 and a non-smoker. The graph assumes that at age 40, both had a 20 pack year smoking history and that the current smoker continues to smoke at the same level.

Comparison of 1 Year Risk on Male Current, Ex-Smoker and Non-Smoker



17. What is a pack year?

- It is a way to quantify the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack year is equal to smoking 20 cigarettes (1 pack) per day for 1 year.

18. Where can patients take the test?

- Contact client services at 1-888-583-9030 for a local test provider in the US. Current test providers in the UK and in other regions of the world are listed on our website: http://www.oncimmune.com/earlycdt-test/test_providers

19. What is the sample reporting process?

- The blood sample is drawn by, or sent to, the test provider, and the serum is separated.
- The sample is then sent to Oncimmune's CLIA-certified[13] laboratory in De Soto, Kansas, USA for testing, analysis and reporting.

12 Spitz MR, Hong WK, Amos CI, et al. A Risk Model for Prediction of Lung Cancer. J Nat Cancer Inst 2007;99:715-26

13 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.

- The test providers have full sample collection and sending instructions.

20. How are the test results reported?

- Your results are sent directly to the test provider who will then pass on the results to you to discuss with your patient.

21. How long does it take to get results?

- This may vary according to test provider but the test provider should receive your patient's results 5-7 days from the time the sample is received at the laboratory.

22. How much does the test cost and is it covered by medical insurance in the US or by the NHS or medical insurance in the UK?

- In the US, *Early***CDT-Lung** may be billed to Medicare Part B and most major private insurances by the test provider using CPT code 83520 x 7 units. Patients should contact their chosen test provider for insurance billing questions.
- In the US, if the patient chooses to pay out-of-pocket, the self-pay price is comparable to many US insurance plans' co-pays or deductibles for other cancer detection tests. Oncimmune's Client Services Department at 1-888-583-9030 can advise on self-pay options.
- The cost of *Early***CDT-Lung** is not currently covered by the NHS or medical insurance in the UK. Patients will pay for the cost of the test themselves. The cost varies according to the test provider.

23. Which autoantibodies are measured by the test?

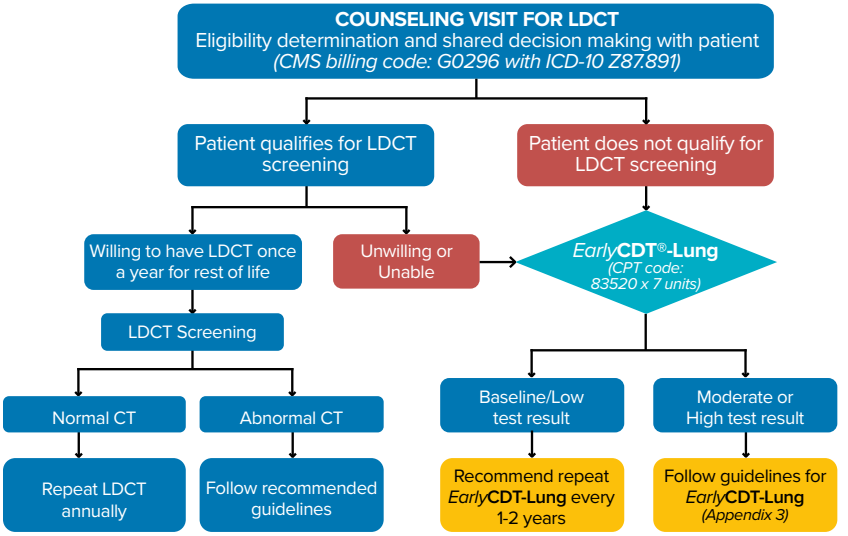
CAGE	NY-ESO-1
GBU4-5	p53
HuD	SOX-2
MAGE A4	

24. Who is Oncimmune®?

- Oncimmune is a leading early cancer detection company. It has pioneered the development of autoantibody assay technologies that have the potential to allow cancer detection up to four years earlier than other methods and be applied to a wide range of solid tumor types.
- Oncimmune Ltd is headquartered in Nottingham, UK, and testing is conducted in our CLIA-certified laboratory, based in De Soto, Kansas, USA.
- In 2009, the company launched its proprietary platform technology for early cancer detection, called *Early***CDT**®.
- For additional information please call Client Services 1-888-583-9030 or email clientservices@oncimmune.com in the US, and elsewhere please call +44 (0) 115 8231869 or email contact@oncimmune.co.uk.

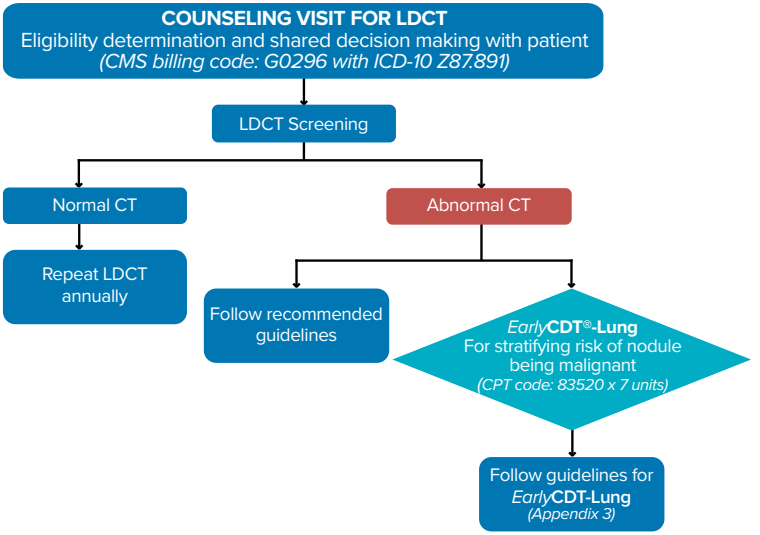
Appendix 1

Integration of *Early***CDT-Lung** into Low-Dose CT (LDCT) Screening Program in USA



Appendix 2

Risk Stratification of Patients with Indeterminate Pulmonary Nodules



Appendix 3

Potential Monitoring Guidelines[14] you may consider if the patient has a Moderate or High Level test result are as follows:

<u>If no nodule is seen on the initial CT scan:</u>

Nodule size	Moderate Level *Early*CDT-Lung	High Level *Early*CDT-Lung
No Nodule	Repeat LDCT scan at 12 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung	Repeat LDCT scan 6 months. If unchanged, repeat LDCT scan at 12 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung

If a new nodule(s) is detected on any follow-up CT scan, physicians will need to consider actual size, nature of nodule and theoretical doubling time to determine further treatment.

<u>If a nodule is seen on the initial CT scan:</u>

Nodule size	Moderate Level *Early*CDT-Lung	High Level *Early*CDT-Lung
Less than 8 mm	Repeat LDCT scan at 6 months. If unchanged, repeat LDCT scan at 12 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung	Repeat LDCT scan 3 months. If unchanged, repeat LDCT scan at 9 months. If unchanged, repeat LDCT scan at 15 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung
≥8 mm to <20 mm	Repeat LDCT scan at 3 months or consider diagnostic evaluation as indicated. If unchanged, repeat LDCT scan at 9 months. If unchanged, repeat LDCT scan at 15 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung	Repeat LDCT scan at 3 months or consider diagnostic evaluation as indicated. If unchanged, repeat LDCT scan at 9 months. If unchanged, repeat LDCT scan at 15 months. If unchanged, repeat LDCT scan at 24 months. If unchanged at 24 months, repeat *Early*CDT-Lung
20 mm or greater	Patient is at high risk of lung cancer. Physician judgment required to guide further investigation.	Patient is at very high risk of lung cancer. Physician judgment required to guide further investigation.

If on a follow-up CT scan there is an increase in nodule size compared to any previous CT scan or a new nodule(s) is detected, physicians will need to consider actual size, nature of nodule and theoretical doubling time to determine further treatment.

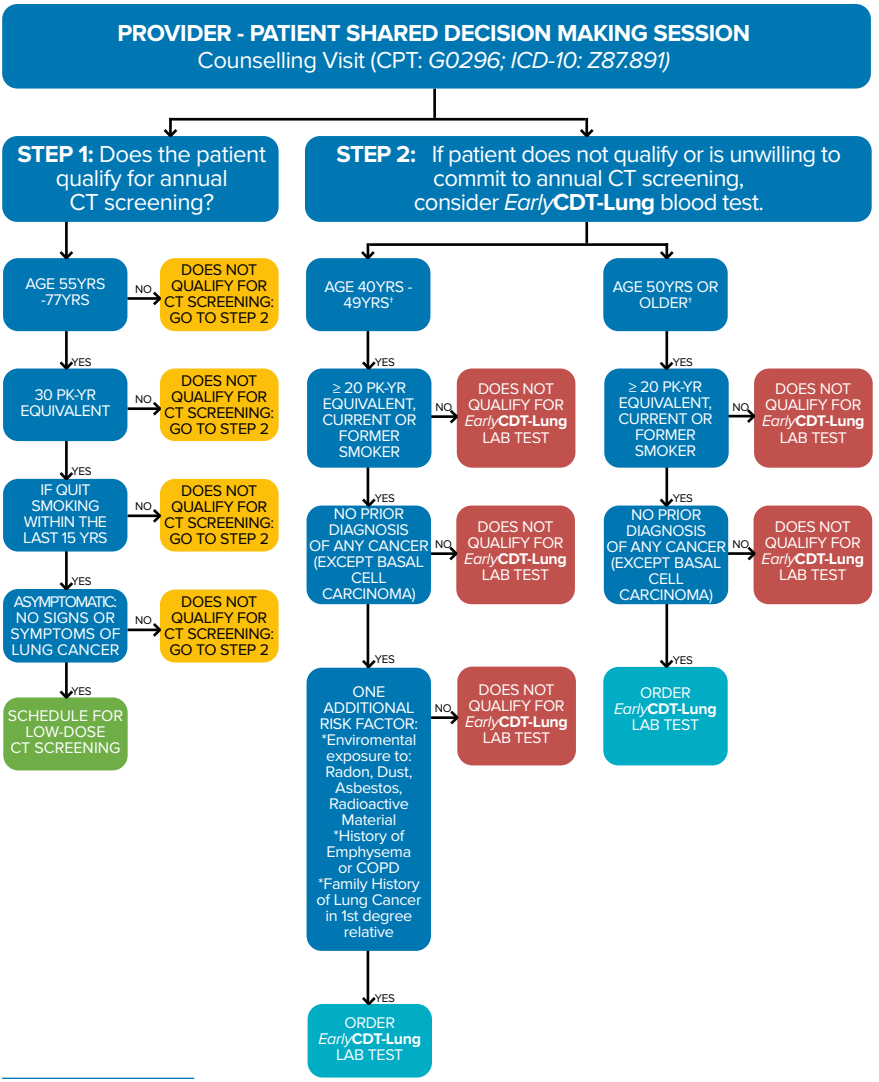
14 Follow-up of patients always remains the sole responsibility of the treating clinician.

Appendix 4
How do I determine whether my patient qualifies for CT screening or *Early***CDT-Lung**?

US Preventive Services Task Force (USPSTF) Guidelines recommend annual screening for lung cancer with low-dose computed tomography (LDCT) for patients who meet the eligibility criteria.

The Problem

More than 70% of all patients diagnosed with lung cancer fall outside the defined high risk group who are eligible for low-dose CT screening.[§]



§ Pinsky PF and Berg CD. J Med Screen. 2012;19(3):154-156

† *Early***CDT-Lung** is not recommended for patients <40 years of age

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