



## About LungSign™<sup>1</sup>

LungSign™ is a non-invasive, lung cancer detection test that indicates the likelihood of lung cancer in high risk individuals. It can detect early-stage, pre-symptomatic lung cancer before it is discernable by standard x-ray imaging.

LungSign™ is not meant to be used as a stand alone test for lung cancer. It should be interpreted in conjunction with recognized diagnostic procedures for the management of patients at risk of lung cancer or undergoing post-surgical follow-up. Patients with lung malignancies may have low scores. If a patient has relevant symptoms, further investigation is suggested.

### Indications for use

LungSign™ is indicated for the evaluation of patients suspicious for lung cancer due to their:

- Age – Over 50 years old
- Significant smoking history (over 20 pack-years) or exposure to industrial carcinogens
- Symptomology or clinical suspicion of lung cancer

The test has not been validated for patients who have received chemotherapy or radiotherapy and it has not been validated for patients who harbor cancers other than lung cancer.

### LungSign™ features:

- Sensitive
- Non-invasive
- Inexpensive
- Patient friendly
- Biologically relevant

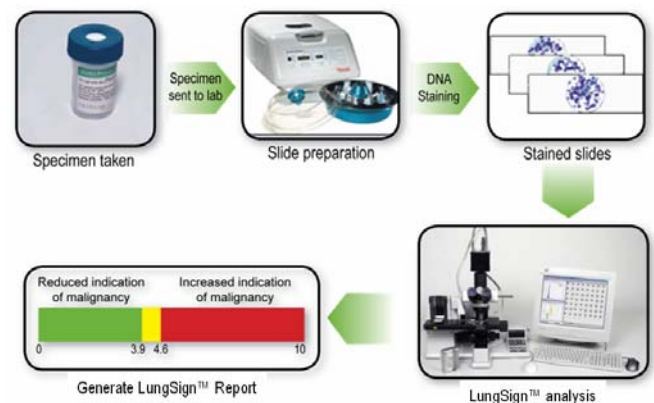
### How does LungSign™ work?

LungSign™ testing (Figure 1) begins with the collection of a good quality sputum specimen from a patient. Various devices are available to assist patients in the production of such specimens. The specimen is sent to the Perceptronix laboratory where it is analyzed by the LungSign™ automated image cytometer. The result is a single lung cancer likelihood related score derived from the measurements of thousands of cell nuclei.

The unique strength of the LungSign™ Test is that it does not rely upon frankly cancerous cells to indicate that a patient harbours lung cancer.

The LungSign™ Test primarily measures alterations to

normal cells that occur in the presence of a malignancy, a well-documented phenomenon known as Malignancy Associated Changes (“MAC”). This approach sidesteps the problem that cancer cells are seldom present in sputum. Consequently, LungSign™ can assess the likelihood of the presence of cancer from specimens which would not yield useful results via other assays such as conventional cytology or molecular marker based tests.



**Figure 1.** LungSign™ Test process.

### What LungSign™ measures

LungSign™ is based on the automated analysis of properties of epithelial cells present in a sputum specimen. The test measures properties of the cell nuclei such as DNA content, conformation and texture. It identifies possible malignant cells (reported independently) as well as changes in normal appearing cell nuclei that are associated with the presence of malignancy (MAC). Available nuclear information is combined into a single score for the specimen.

### Ordering LungSign™

LungSign™ should be requested and interpreted under the care of a physician. LungSign™ sample collection kits<sup>2</sup> are orderable by phone (1-888-629-8779) and over the Internet ([www.LungSign.com](http://www.LungSign.com)).

### LungSign™ Results

LungSign™ analysis results in a score which is reported to the physician in approximately two weeks.

LungSign™ provides a quantitative measure of cellular abnormality correlated with the presence of lung malignancy. Higher scores suggest an increased likelihood of the presence of lung cancer.



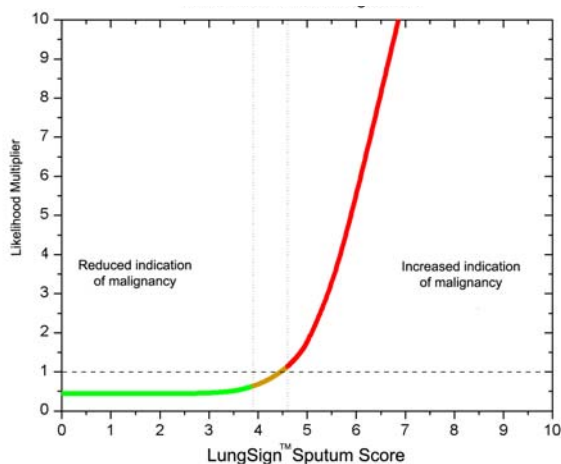
## Interpretation Guide

Scores fall into three categories as shown in Table 1.

**Table 1.** LungSign™ score ranges and corresponding interpretations with regard to likelihood of the presence of malignancy.

| LungSign™ Score | Interpretation   |
|-----------------|--|
| <3.9            | Decreased likelihood of malignancy                                       |
| 3.9—4.6         | Result indeterminate for increased or decreased likelihood of malignancy |
| >4.6            | Increased likelihood of malignancy                                       |

These categories are graphically illustrated in Figure 2, where the increase or decrease in the likelihood of the presence of malignancy is shown as a function of score.<sup>3</sup>



**Figure 2.** Approximate likelihood ratio multipliers for the odds of harboring lung cancer as a function of LungSign™ score. The red segment represents increased likelihood (scores > 4.6) and the green segment represents decreased likelihood (scores < 3.9), with scores in between (orange) considered indeterminate. For example, with a LungSign™ score of 6 the likelihood that the patient harbors a malignancy is increased by more than 5 times.

The likelihood multiplier updates the patient's post-test risk of lung cancer. It should be interpreted in the context of the relevant lung cancer risk factors and symptoms which specify the patient's pre-test likelihood of harboring the disease.

### Pre-test Risk for Screening Population (0.5-2%)

In a screening population consisting of asymptomatic individuals at risk of lung cancer due to age (over 50 years) plus heavy smoking (over 20 pack years) or carcinogen exposure, the disease prevalence may be between 0.5 – 2%.

### Pre-test Risk for Very High Risk Population (10%)

The additional presence of symptoms (such as persistent cough or shortness of breath) raise the likelihood of lung cancer and place the patient in a prevalence group that may be 10% or higher.

Table 2 shows estimates<sup>4</sup> of the LungSign™ predictive values (i.e. the probability of malignancy corresponding to a particular test score) for the 2% and 10% disease-prevalence groups.

**Table 2.** Interpretation Guide: Estimates<sup>4</sup> of the probability of malignancy for LungSign™ scores for different patient populations.

| LungSign™ score | Probability of malignancy            |  |
|-----------------|--------------------------------------|--|
|                 | Screening population (2% prevalence) | Very high risk population (10% prevalence) |
| 1               | 1                                    | 5  |
| 2               | 1                                    | 5  |
| 3               | 1                                    | 5  |
| 3.9             | 1                                    | 7  |
| 4               | 1                                    | 7  |
| 4.6             | 2                                    | 11   |
| 5               | 3                                    | 16   |
| 6               | 10                                   | 38   |
| ≥7              | ≥18                                  | ≥54  |

It may be difficult to categorize the patient's pre-test risk, and it is therefore suggested that patients with high scores and those with low scores but suspicious symptomology be referred for further evaluation.

#### Notes:

- LungSign™ is a test based on ClearSign™ technology. Data presented are quoted from the ClearSign™ clinical trial.
- The performance claims of ClearSign™ were established using induced sputum samples and have not been established for spontaneous product specimens.
- ClearSign™ performance was determined through a blinded clinical trial where the test was prospectively applied to participants who were suspicious for lung cancer. A total of 986 participants with analyzable specimens were included, of whom 330 were determined by conventional means to have lung cancer. The empirically observed performance was 91% specificity and 40% sensitivity for a ClearSign™ score threshold of 5.
- ClearSign™ was studied in a group of patients in the care of lung cancer specialists where the lung cancer prevalence was 33%. The predictive values shown in this table are estimates based on an extension of the test to lower disease-prevalence patient groups and should only be used for general guidance—they are not exact values for either prevalence group.