Predictive Biomarkers in Lung Cancer

GLOBAL LUNG CANCER COALITION

A *predictive biomarker* is a microscopic characteristic of cancer cells that can be used to help cancer doctors choose the most effective treatments for some cancers.

Though you may not think it, we use something similar in our daily lives. We use visible similarities and differences (markers) in our biological make-up to make some choices. For example, a person with fair skin and red hair will be more at risk of sunburn than someone who has dark skin when exposed to the sun for the same period. Fair skin could be called a predictive marker for the risk of sunburn, and something that we can see. Using this information (observable fair skin), people can avoid sunburn.

People have many differences like this. Lung cancer cells have differences too. Some of those differences can be seen under a microscope. For decades, these observable differences were all that we had to separate one sort of tumour (or type of lung cancer) from another. While they did help us improve treatments, the approach was not very precise and did not allow for treatments to be personalised – that is, our goal of matching every patient with the best possible treatment for them. The good news is we can now do this better because we can detect even smaller differences.

Our knowledge has expanded greatly, particularly over the past 15 years, in four important ways:

• Firstly, under an ordinary microscope, tumour cells may look the same. However, we have been able to detect even smaller molecules on some tumour cells that we now know can cause these cells to grow and multiply.

These molecules are proteins. Proteins that play an important role in the body, doing most of the work in cells, and are required for the structure, function and regulation of the body's tissues and organs.

• The next major advance was understanding that these cancer-driving proteins were only present in cells that also showed changes in their DNA, the building blocks of all our cells. DNA joins together in unique, repeatable sequences, or codes, that tell the body how to make all its proteins. It's a bit like a recipe book. We need these codes for our bodies to make or replace worn out tissue and machinery inside our cells.

If a DNA code is altered, the reasons for which remain uncertain, the building blocks can link together in a different order and cells may start to create abnormal proteins. Copying the DNA codes to build and replicate cells day after day, year after year is itself a complex process and sometimes an error occurs, particularly following such exposures or other triggers.

• Tests, called biomarkers, were developed that could identify some of these important changes in cancer cell DNA and these can now be used routinely in clinical care.

• The final and important step was a range of new drug treatments that focus on the abnormal proteins created by these DNA changes. Once we know the code, the very best treatment can be offered.

• The changes in tumour cell DNA are called mutations. These mutations are biomarkers because they help us to tell one sort of lung cancer tumour cell from another.

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• The DNA code of tumours is much less stable than in normal body tissues. During the course of treatment, further changes in tumour DNA can sometimes happen. This may mean your cancer team may consider obtaining another sample of tumour tissue (biopsy) to retest the DNA to make sure you are still receiving the best treatment or if another treatment would now be better.

There are many types of lung cancer. The two main types are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The most common type is NSCLC.

Non-small cell lung cancer

NSCLC can be split into 3 types:

• ***Adenocarcinoma*** is a little more common in women and is also the most common type of lung cancer amongst people under 45 and is seen in approximately 50% of all cases of NSCLC. It is more frequently seen in the outer parts of the lung and develops from a particular type of cell that produces mucus and can lead to a chronic cough.

• ***Large cell carcinoma*** this type of lung cancer tends to grow quite quickly and often arises in the larger air passages. It tends to spread outside the lung at an earlier stage.

• ***Squamous cell carcinoma*** is the most common type of primary lung cancer in the UK and often forms in the larger, more central airways.

Biomarkers	Estimated frequency in NSCLC adenocarcinoma
EGFR-sensitizing	**15%**
EGFR other	2%
KRAS	**25%**
ALK	7%
HER2	**2%**
BRAF V600E	2%
BRAF other	**1%**
ROS1	2%
RET	**2%**
NTRK1	0-5%
MET	**3%**
MAP2K1	0-5%
PIK3CA	**1%**
NRAS	0-5%
>1 mutation	**3%**
Unknown	31%

Reference from *Hirsch F, et al. New and emerging targeted treatments in advanced non-small-cell lung cancer. Lancet. Vol 388. September 3, 2016*

New NSCLC biomarkers continue to emerge, but the most common biomarkers at this time are:

EGFR

The EGFR gene produces a protein found on the surface of cells that helps them grow and divide. Some NSCLC cells have too much of this protein which makes them grow faster than usual. This form of mutation is more common in people of Asian origin, women and never-smokers.

ALK fusions

This mutation occurs when two genes (such as EML4 and ALK) become fused and the activity of the ALK oncogene is increased. It is mostly found in younger people (usually 55 and under) and never-smokers.

MET

There are several different types of MET gene, which occur in people who are current or past smokers, rather than never-smokers.

RET

RET fusions occur by joining parts of two different genes together to form a fusion gene. Fusion genes and the fusion protein that come from them may lead to the development of some types of cancer. This gene mutation is passed from parent to child. Close relatives of those with this gene can be tested to see if they have it.

ROS1

ROS1 fusions, like ALK fusions are formed when the ROS1 gene and a second gene break apart and become joined.

KRAS

The KRAS gene mutation is more often found in people who smoke.

NTRK

NTRK fusions are formed when a piece of the NTRK gene and a piece of another gene fuse or join and cause cell growth and cancer. There is no one type of patient who is most likely to have an NTRK gene fusion.

BRAF

This mutation provides instructions for making a protein that helps chemical signals enter cells. In a cancer tumour, this signal can cause cells to divide and cancer to grow. It is more common in women than men and tends to affect current or former smokers.

PD-L1

One of the jobs of the body's immune system is to destroy damaged cells, such as cancer cells. However, cancer cells can sometimes find ways to trick the immune system into thinking they are normal cells and should not be attacked. This allows them to grow and spread. One way this happens is through proteins called checkpoint proteins.

PD-L1 is found on normal tissue surface and healthy cells and some cancers disguise themselves by making their own PD-L1. These cells are then not spotted by the checkpoints which means the immune system does not destroy them. Undetected the cancer cells can continue to grow without being slowed down or stopped.

Immunotherapy, sometimes also called immune-oncology (IO), is a type of treatment for NSCLC which reactivates the immune system, helping it to recognise and attack the abnormal cancer cells.

PD-L1 expression	Estimated frequency in NSCLC adenocarcinoma
	33% : >50% tumour proportion score (TPS) 30% : 1-49% TPS **37% : <1% TPS**

Reference from *The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. Author Keith M Kerr et al https://doi.org/10.1016/j.lungcan.2021.02.026*

Small cell lung cancer

This type of lung cancer is made up of small round cells that form fleshy lumps and usually start in the larger airways. The cell reproduces and grows very quickly and may spread to lymph nodes and/or other organs in the body.

There are no biomarkers to guide therapy planning in SCLC yet, however this may change as further research in this area progresses.

Why is it helpful to find out which lung cancer biomarker you have?

More drug therapies are being developed all the time and we can expect new clinical trials and treatment options for lung cancer patients in the future. Each drug will only be effective against the gene mutation for which it was developed. Your healthcare professional will advise you on what treatment is the best one for you.

Testing to detect biomarkers varies greatly, and guidelines for testing will vary from one country to another and perhaps even from one hospital to another.

In some countries it is routine for patients who have NSCLC to have their tumours tested for gene mutations so doctors know if a specific drug or even a clinical trial for new drugs might work for them. We strongly recommend asking your healthcare professional to test for any of the known mutations to see if you are eligible for a targeted therapy drug or a clinical trial.

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This information leaflet has been produced by the Global Lung Cancer Coalition (GLCC) secretariat and reviewed by lung cancer experts. For more information on the support and information services available in your country, visit: www.lungcancercoalition.org Version 1.0 – March 2022.