European Alliance for Personalised Medicine

White Paper on Lung Cancer in Europe

Lung cancer patients need action at EU level

Unnecessary deaths of lung cancer sufferers could be avoided if there was greater access to innovative treatment and more efficient organisation of research.

Improvements depend primarily on greater collaboration between Member States and across the healthcare sector. The collaboration should include patients, caregivers and patient organisations, who have an indispensable contribution to make.

This document aims to increase awareness of the needs. It is a direct appeal to policymakers, legislators and regulators to encourage innovation and to broaden access to treatment, and to all stakeholders to work more closely together to reduce the burden of lung cancer on patients and on society.

What is lung cancer?

Lung cancer is the biggest global killer of all cancers. Fewer than half of newly diagnosed lung cancer patients live beyond a year, with only 16 percent surviving for five years.

Most lung cancer begins in the cells that line the bronchial tubes and there are two main types: non-small cell lung cancer (the most common) and small cell lung cancer, which makes up roughly one-fifth of all cases.

Sometimes the lung cancer is made up of both types. This is called mixed small cell/large cell cancer. And, if the cancer started somewhere else in the body but spread to the lungs, that is metastatic cancer to the lung.

Lung cancer is such a huge killer partly because it is harder to detect in its early stages. By the time a person begins to notice symptoms, it has often spread to other parts of the body and is, therefore, harder to treat.

In Europe specifically, the overall five-year survival for men with lung cancer is only 11.2% and for women it is 13.9%.

Because it is so difficult to diagnose, 80% percent of patients with lung cancer die within one year of diagnosis.

Another terrifying statistic is that today's patient diagnosed with lung cancer has the same likelihood of dying from the disease as he or she did 40 years ago.

It is clear that physicians need more effective ways to detect and target these cancers.

Lung cancer in women is on the rise

Lung cancer in women has increased by a staggering 600% over the past 30 years. Today, more women are killed each year by lung cancer than they are by breast, ovarian and uterine cancer combined.

Mortality rates have been rising throughout the last two decades in the EU, reaching the predicted breast cancer rates (which have been falling steadily).

The majority of lung cancers in both sexes are caused by smoking, but about 15 percent are not, and the majority of those non-smokers are women, mostly young women. Various theories have been posited for this (estrogen as a tumour promoter, is one example) but scientists are not sure.

Many lung cancer tumours have estrogen receptors on them. The two different types are alpha and beta. Alpha is associated with breast cancer and lung cancers, in both sexes, can have estrogen receptor beta. One theory raised is that because females have more estrogen circulating, they are more likely to have a reaction with the estrogen receptor beta.

Stefania Vallone, from Women Against Lung Cancer, said: "Many citizens are asking: 'Why does Europe matter? How does Europe help us?' In the era of personalised medicine, the EU can help in many ways.

"Personalised medicine starts with you and me. It's all about empowering the patient and giving the right

treatment to the right one at the right time - in our case for the lung cancer patients. Sound simple? Well, it isn't, for a variety of reasons, but the concept is already starting to revolutionise medicine and the way treatment is delivered."

More research is desperately needed, and the EU should promote this.

The fight against lung cancer is lagging behind

European Respiratory Society lung cancer expert Prof. Jean-Paul Sculier, said: "The battle against lung cancer is lagging behind, for example, the fight against breast cancer. One reason is a general lack of funding for research. Another reason is a relative lack of patient advocacy because so many patients die."

But at least a lot of Europe is doing better than the UK. Britain's survival rate was at 10% by 2000, but this behind a 14% survival rate achieved in Austria in the 1990s. By the 2000s 18% of patients diagnosed with lung cancer in Austria survived – almost twice the rate in the UK.

Five other European countries (Finland, Germany, Italy, the Netherlands and Norway) also recorded better survival rates for lung cancer in the 1990s than Britain managed in the 2000s. But every Member State could do better.

Prevention can achieve a lot

More effort is needed in prevention. Public awareness of the disease and the risk factors should be developed, particularly among younger people, women and even doctors.

For example, usually it does not occur to primary-care physicians to suggest a chest X-ray or a scan for a young woman who has never smoked, because it is not commonly known that these women can develop lung cancer.

As mentioned above, lung cancer kills so many people in part because it is hard to detect at more curable stages, unlike lumps in breasts, for instance.

Nothing in a person's lungs betrays the presence of a nodule or mass.

Pulmonologists have tried for decades to find ways to detect lung cancer earlier. Europe needs to find ways to detect this disease before it is too late to effectively treat the patient, and this will only be achieved through more research.

What is changing in medicine?

With the increased knowledge of the human genome, physicians can analyse a patient's genetic make-up - with careful consideration to the tumour cells, which can be unique - and target therapy to treat the individual patient and the individual tumour.

As with many patients and treatments, some may respond effectively to various chemotherapy and other options but others will not.

Personalised medicine allows scientists to investigate a tumour and try to identify genes to predict for drug sensitivity, or genes that may possibly predict patients who will do better and need no further treatment, or those who might benefit from further treatment.

In the future, more and more treatment decisions will be based upon the molecular characteristics of an individual tumour. More research could lead to identifying lung cancer earlier, which would increase the cure rates immesnsely.

'Personalised medicine' for patients with non-small-cell lung cancer is already here. For example, pathologists can perform the most complete and accurate subtyping of tumours possible.

Next-generation sequencing could allow extensive genetic analysis of single samples, although various technical, logistical and ethical (Big Data and data protection, for example) problems need to be solved.

Legislators have a role to play here, without doubt.

The benefits of R&D

In the US, the first immune-based treatment for lung cancer recently won approval from the Food and Drug Administration.

The drug, Nivolumab, is one of a class of medicines that free the body's own immune system to allow it to attack tumours.

It was approved last year to treat advanced cases of the skin cancer melanoma but, while melanoma was known to be vulnerable to attack from the immune system, there were doubts that this would be true for lung cancer.

In one trial, lung cancer patients receiving the drug lived a median of 9.2 months compared with 6.0 months for those who received the standard chemotherapy for such patients. By another measure, the so-called hazard ratio, the risk of death was 41% lower for those who received Nivolumab.

Modern medicine is seeing much more multidisciplinary care. More and more patients are being treated with combinations, such as surgery and chemotherapy, chemotherapy and radiation therapy, surgery and radiation therapy etc.

Research into the biochemical pathways and genetics of the disease is beginning to translate into effective new treatments and a better understanding of the behavior of individual tumours.

Targeted therapies can now zero-in on particular cells and cell processes closely tied to the growth or spread of tumours. For some, such treatments produce less side effects than traditional chemotherapy, which also attacks healthy cells, and have a bigger impact.

But driving down the lung cancer death toll will require not only more research and an array of new treatments but integrated efforts to improve lung cancer prevention.

More health literacy is required

Understanding a new diagnosis is frightening and, because treatments are moving so fast due to developments in science, often confusing. Patients need to realise that treatment strategies will depend on the type of lung cancer, what stage it has reached, their general health and more.

Add to this the treatment options of surgery, radiation therapy, chemotherapy and established or experimental targeted drugs, plus the various possible side-effects and it becomes a minefield. Healthcare workers must play a vital role empowering the patient to allow him or her to fully understand the circumstances and make choices (where they are available).

Effective action for lung cancer patients depends on a coherent European strategy, and a common approach to mobilising and integrating scarce and scattered resources.

The true value of potential treatments is too often ignored

The differing ideas about what constitutes 'value' in modern medicine are currently being debated in Europe and beyond.

The concept as a stand-alone is vague, so how do we define it? How do we measure a human life – or indeed improved quality of life - against the cost of a treatment? Do we judge the individual's contribution, fiscally and otherwise, to society and weigh it against a price? What about the moral issues involved in such judgments? And who should make the judgments?

Patients, when they understand their options, will have their own views on what constitutes value, depending on their circumstances - "Will I get better? Will I live longer? Will my quality of life improve? What are the side effects?"

Payers, when they weigh societal and individual benefits against cost and other considerations, may take a different approach.

Meanwhile, manufacturers and innovators must operate within limits of 'value' that are as yet unclear.
The waters are extremely muddy and there is an urgent need for clarity.

As it stands, generally speaking, the value of a new therapeutic strategy or treatment is determined by the amount of clinical benefit it can achieve balanced against its cost. The necessary evidence of this clinical benefit is derived from clinical research, usually randomised trials.

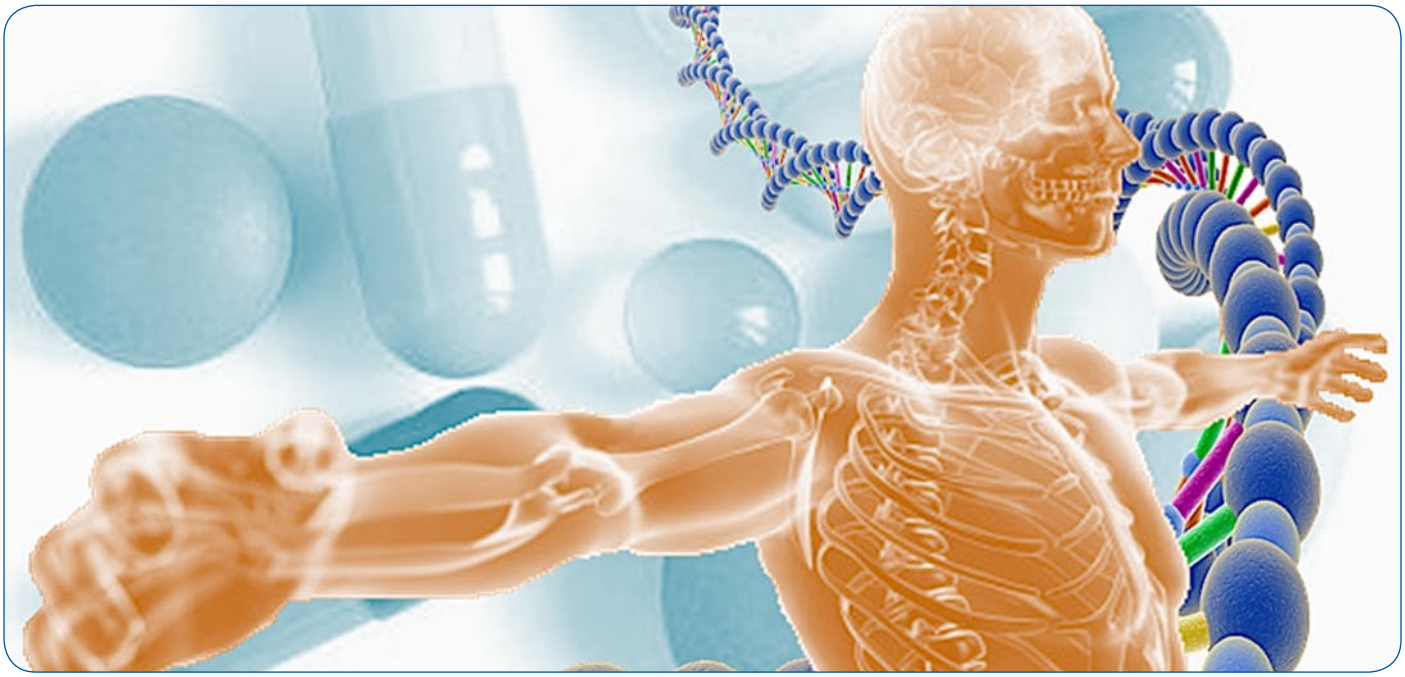
The latter produce data in respect of efficacy, safety and overall benefit. At the moment, there is a lack of a standard to establish the degree of clinical benefit of, for example, cancer therapies, which means that conclusions and recommendations derived from studies are often disputed.

Potential benefits of any new treatment can be described as bringing longer life or an improved quality of life. With guidelines for what constitutes one definition of 'value' now suggested in cancer there is a hope that they will be endorsed by health authorities across the European Union.

But let us not forget that there is a solid argument that value should always be defined in respect of the 'customer', Value in healthcare depends on results and outcomes – vital to the patient - regardless of the volume of services delivered, yet elsewhere ofyen the value is always going to be seen as relative to cost.

For this and other reasons, patients should always be involved at all levels in discussions about what constitutes value, which requires on their part a high level of health literacy and up-to-the minute expert advice surrounding available treatments, side effects and impact on lifestyle.

For patients, doctors, payers and industry the basic tenet is



that, in order to understand value, one must first understand a treatment, plus any other treatment options, and consider what it (or they) can provide.

Quality of life for one means added-value for all.

Involve the patient

Patients are too frequently excluded from critical aspects of the discussions on lung cancer treatment – and even when they are invited, they are often marginalised, as the agenda is already fixed by others.

Patients have little voice in clinical trial design, while their perspectives on ethics and risk-benefit are largely neglected in the assessment process of clinical trial authorisation applications.

Meanwhile, they have little or no say in long-term budget planning or in discussions of pricing and reimbursement of treatments.

Personalised medicines and lung cancer

Methods that enhance personalised medicine:

- Next generation genomics
- Advanced high throughput screening
- High-speed proteomics
- Non-invasive imaging
- Integrated computational platforms
- Nanotechnology for oral medicines
- Management patient-centred, and IT monitored

Innovations to tackle lung cancer:

- Prevention could include electronic cigarettes
- Detection – an example is low-dose CT scans
- Surgery - these will include robotics
- Radiotherapy - IMRT, Cyberknife, Protons
- Medicines - targets; alk, EGFR, met
- Immunotherapy – anti-rogue Tcell antibodies, CARs

An agenda for change

This White Paper calls for an acknowledgement that lung cancer is one of Europe's biggest killers and that the European Union can play an important role in helping to tackle this disease

The EU should put guidelines in place that will allow Member States to set-up quality assured early detection programmes for lung cancer, as has already been the case with EU guidelines on colorectal cancer screening and diagnosis (2011), on breast cancer (2006) and cervical cancer (2008) screening and diagnosis (2006).

There is a need for increased public-private partnerships, such as IMI II, as evidenced by the outcomes from the U-Biopred: Towards personalised therapy in asthma.

And Europe would benefit from increased collaboration between pharmaceutical researchers to find the best treatments for patients, which will reduce the cost burden for individual companies in developing treatment.

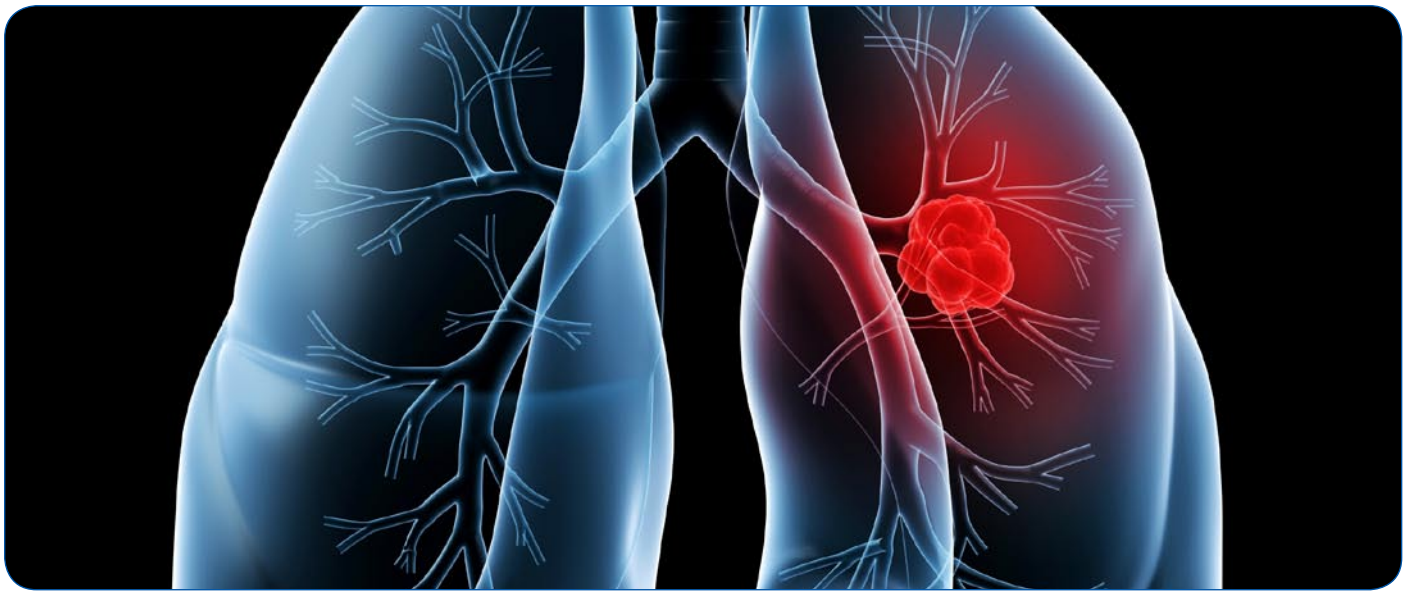
As an example of the latter, on 4 November, Merck and Pfizer announced the initiation of an international Phase III study of an investigational cancer immunotherapy treatment.

Other requirements are:

Easing access to innovative treatments

National cancer plans need to prioritise funding for lung cancer research and treatment, based on dialogue between opinion leaders in the medical professions, commercial and academic research, and paying agencies, so that as new treatments become available, patients are not deprived for reasons of finance.

Greater coordination of product assessment is essential to eliminate anomalies in reimbursement and to achieve greater alignment in access to new lung cancer treatments EU-wide.



Greater transparency and flexibility is needed in pricing and reimbursement of treatments, with the involvement of all stakeholders – not just researchers, industry, payers and policymakers, but also patients.

The evaluation of the cost and benefit of new treatments should include a discussion of their value for society. The patient view of value should be given greater weight in assessments, and quality of life measures need to be adapted to reflect real value added by new treatments as experienced by patients. Better data derived from new mechanisms are needed on long-term population-based results, so as to better understand the true impact and value of therapies, with outcomes linked to health economy research.

The gaps created by differing national reimbursement systems need to be filled. Exploration is needed of imaginative possibilities, such as a medicines equity fund for life-threatening diseases within the framework for EU structural funds, to allow patients from countries where treatment standards are coparatively low to have equal access to treatment.

Patient story

Susan, from Yorkshire, England, was diagnosed with lung cancer in the summer of 2004. She was a 40-year-old non-smoker, generally fit and healthy.

She received chemotherapy and was in hospital for a week at a time. Initially she was told that having the tumour removed was 'impossible', yet one surgeon agreed to perform the operation. This gave Susan a chance to live and she survived.

She has many thoughts, these days, surrounding lung cancer and the big one which keeps coming back is: "We absolutely need to find a way of successfully identifying this disease at a much earlier stage in order to stop the deaths, the carnage. Despite the side-effects of the treatment, I was pretty lucky. But so very many others are not."

Including patients in lung cancer policy formation

Empowerment and involvement of patients and patients' organisations means they should be allowed to contribute to shaping an adequate comprehensive European response to lung cancer, and be given access to the information they need to perform this role.

Patients should be represented formally on regulatory and payer bodies such as the EMA and HTA agencies, committees and organisations drafting treatment guidelines, and patient surveys collecting data on quality of service or similar information from patients.

Patients should be entitled as individuals to a voice in the choice of treatment and care that they are offered.

Patients' representatives should be allowed input to discussions of long-term budget planning.

Patients should be included in clinical trial design and in ethics committees.

Promoting research into lung cancer

Research into early detection of lung cancer needs boosting, with platforms for effective collaboration between academia, industry and healthcare systems, better access to limited numbers of trial subjects, and adaptations to clinical trial design and regulations.

The EU should allocate long-term funds for research into early detection and innovative treatments for lung cancer, with increased investment in European research centres, and with advanced databases of biological and clinical data and clinical databases for outcomes research.

Regulations need to be adapted to allow more sharing of patient data and biological materials, and this should be taken account of in the discussion over Data Protection.

Improved coordination of clinical trials - and of recruitment – is needed, with better access to information for researchers, doctors and patients. New methodologies for clinical research should be accepted.

Academia and industry should be encouraged to cooperate in discovery and validation of pre-treatment predictive biomarkers for the stratification of patients for treatment.

A clear focus on late translational research, particularly into clinical effectiveness, can identify tangible benefits for the health economy in the short- to medium-term.

A new collaborative infrastructure for molecular pathology/ bioinformatics is needed to develop the predictive assays for targeted personalised medicine.

Member States and the EU institutions should act together to overcome the barriers to innovation, including recognising the real value of new treatments and making access to them easier, boosting research across Europe, and including all stakeholders – and particularly patients – in policy formation.

Regine Deniel Ihlen, from Lung Cancer Europe summed it up, saying: "This is crunch time for Europe. The clock is ticking for patients. But there is time. Time that allows us to put the patients at the centre of their own care but it also means prioritisation is the order of the day.

"Better health for citizens and patients is essential to Europe's prosperity. We cannot grow without healthier citizens that can contribute to the Member Sate and the EU project."

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EAPM's 'STEPs' campaign

The STEPs initiative calls on Europe's decision-makers to commit to the following STEPs for 2014-2019:

STEP 1: Ensuring a regulatory environment which allows early patient access to novel and efficacious personalised medicine (PM)

STEP 2: Increasing R&D for PM, while also recognising its value

STEP 3: Improving the education and training of healthcare professionals

STEP 4: Supporting new approaches to reimbursement and HTA, required for patient access to PM

STEP 5: Increasing awareness and understanding of PM

EAPM believes that achieving these goals will improve the quality of life for patients in every country in Europe.

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