

ESMO Patients Guide Series

ESMO Personalised Medicine

“What is
**personalised
medicine?**”

“Let us help you
understand”



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE



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Personalised
Cancer Medicine:
An ESMO Guide
for Patients

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“ This guide for patients has been initiated by the European Society for Medical Oncology (ESMO) Personalised Medicine Task Force as part of the ESMO strategic activities to assist patients, their family members and friends to understand better the factors that may influence the personalised approach to the prevention, diagnosis and treatment of cancer.

Personalised cancer management – which means giving patients the optimum treatment according to their individual circumstances (including their genetics) and the molecular characteristics of their tumours – is a key theme of ESMO in 2013. Indeed, it is a key theme for oncologists in general, and in all aspects of medicine. Integrating research and innovation directed towards personalised care is also an objective of the European Union’s “Horizon 2020” science funding programme. Therefore, this book is produced in a timely fashion to provide unbiased information on the current understanding of personalised cancer medicine, and the achievements and strengths of medical professionals in the fight against cancer. We are sincerely grateful to representatives of different European cancer patient advocacy groups and to members of the ESMO Cancer Patient Working Group, who provided their views and comments on different issues in personalised cancer medicine that are presented in this book.

Our goal was not to present the personalised medicine achievements in every tumour type or to elaborate on situations where it is not yet a part of standard practice. Instead, in this material we provide a state of the art on governing principles, illustrating them through examples of personalised medicine approaches in several tumour types. Personalised medicine is the future of cancer medicine. To make it a reality in the near future and to offer improved treatments, the patient’s active role is crucial. ESMO is committed to educate patients in this evolving approach, so they can better understand the main principles and how they can contribute to the great advances. Well-informed patients and educated choices matter.

This book does not seek to replace a medical consultation. The statements from the book cannot be taken as medical advice and so, for any question about your disease or treatment, please consult your doctor.

The ESMO Personalised Medicine Task Force



Martine Piccart

ESMO President



Fortunato Ciardiello

Chair of the ESMO
Personalised Medicine
Task Force

Preface Comment

ESMO Supported 2013 World Cancer Day by Cautioning That the Era of Personalised Cancer Medicine Is Not Here Yet

“The European Society for Medical Oncology (ESMO) supported the 2013 World Cancer Day by trying to dispel the myth that personalised medicine is already a reality for all cancer types and all cancer patients, highlighting the need for more in-depth education and wider collaborations between researchers, oncologists and patients.

Basically, personalised medicine in cancer refers to the possibility to deliver the right treatment based on the characteristics of the individual's tumour and genetics, using targeted therapies directed at efficiently killing tumour cells.

“Personalised medicine is the dream of every oncologist and the legitimate expectation of every cancer patient,” says Professor Martine Piccart, ESMO President. “However, currently we are not yet in the era of personalised oncology but in the era of stratified oncology, which means we are able to classify cancers according to critical targets against which we hope to develop effective drugs. Modern technologies such as deep DNA sequencing will be powerful tools in the future allowing us to identify drugable mutations*.”

Underscoring these developments is the need to educate oncologists by untangling the literature and clarifying new research advances. “Providing targeted education and fostering research is the surest route to fully realising the goal of personalised medicine in the near future,” says Professor Piccart. “ESMO is fully committed to take all necessary steps to encourage this progress.”

One essential issue is the vast amount of information that has been and continues to be generated. “Oncology practitioners need help to be able to put this information into the perspective of their

*Please see the Glossary for definitions of words that are asterisked.

patients and to translate science into what will actually provide clinical benefit for them,” Professor Piccart cautions.

To this end, personalised medicine has become a linchpin of ESMO’s educational strategies. Professor Fortunato Ciardiello, Chair of the ESMO Personalised Medicine Task Force, emphasises that the personalisation of cancer care is now a common theme throughout all ESMO activities, offering a rich source of references through which oncologists can obtain as much valuable information as possible.

An example of this is the ESMO Symposia on Signalling Pathways in Cancer, a series of personalised medicine events dealing with the evaluation of tumours at the molecular and cellular pathway levels. The goal is to shed light on the complexity of molecular pathways and give practical guidance to clinicians on applying this knowledge towards personalised treatment for their patients.

Professor Piccart recalls that the predecessor of personalised medicine as we understand it now was first applied in the field of breast cancer, following the recognition of hormone-dependent cancers and the consequent development of agents that targeted their receptors.

A highly effective monoclonal antibody against the HER2 receptor in breast cancer was introduced back in the nineties and revolutionised the way some breast cancers are treated. Indeed, it works only in women whose tumours over-express the HER2 protein (a key growth factor receptor at the surface of the cancer cell), in approximately 25% of breast cancer patients. Furthermore, resistance to this drug was recognised early, making research and development of new therapies crucial even for this highly targetable cancer.

“There is a huge need to improve molecular screening in breast cancer, as one way to identify driver mutations that may serve as targets for novel treatment strategies of the cluster of breast cancer diseases.”

In the meantime, research in other areas has moved at a rapid pace, most evidently in lung and colorectal cancer.

“Oncologists have a double duty: to raise awareness of the current achievements of targeted therapies, of their high potential and the necessary requirements, and to guide their patients in seeking out clinical trials where their tumours can be better profiled, so that they can gain access to novel treatments.”

Patients themselves can play an important role in the acceleration of the process towards truly personalised medicine. ESMO has plans to help patients understand how they can contribute to achieve this goal. “Clinicians should ensure that what they offer to their patients is not sub-optimal! For example, where treatment relies heavily on the evaluation of critical receptors in the tumour, these delicate tests must be done in laboratories using high-quality control procedures,” stresses Professor Piccart.

“We must provide good education to oncologists and to patients, and we have an obligation to support research,” notes Professor Piccart in summarising the role of ESMO, which represents a natural reference for medical oncologists in the progress towards personalisation of cancer treatment.

“We are progressively moving towards personalised oncology, and this will be a huge achievement for oncologists and cancer patients alike; we will be able to select the right treatment, avoiding both under- and over-treatment. But there is clearly a long way to go towards achieving this goal. We need to collaborate very intensively with partners in and outside of Europe and make sure we don’t sit back in the myth that personalised cancer medicine is already here.”

Personalised Cancer Medicine: Fact Sheet

Cancer as a Worldwide Problem

Despite advances made in diagnosis and treatment over the last 20 years, cancer is still the second leading cause of death.

Personalised Medicine: General Definition

Personalised management is considered as the future of cancer care: medicine aiming at giving patients the best treatment according to their personal medical history, their physiological status, and the molecular characteristics of their tumours.

Recent Approach to Cancer

Until recently researchers and clinicians thought that all cancers deriving from the same site were biologically similar and they classified the disease based on cell type (as determined by microscope assessment), size and presence/absence of regional nodes or distant metastases, as well as other features that may be observed on the tumour sample.

Surgery has been, and still is, the cornerstone of treatment for the majority of cancer patients, together with chemotherapy and radiation therapy. These treatments may have drawbacks and side effects, particularly chemotherapy and radiotherapy, which, by killing cells that divide rapidly, kill cancer cells but also heavily affect healthy cells, resulting in partial efficacy and unwanted side effects.

New Evidence in Cancer Biology

It is now clear that tumours derived from the same organ can differ in extremely important ways, although the “old” diagnostic parameters are still essential elements for treatment decisions.

In recent years, our understanding of tumour biology has improved significantly. One step forward is represented by the possibility to classify cancers based on critical molecular targets identified by the high-quality translational research of the last decades.

What is Targeted Therapy?

Drugs specifically acting against molecular targets in cancer cells – called targeted therapies – have been developed and are used to counteract some types of cancer in selected patients, but many targets still need to be discovered and many drugs must yet be developed or improved.

An example of targeted therapy

One example of targeted therapy is the identification in women with breast cancer of the HER2 target, whose presence or absence gives the physician the indication to prescribe a particular therapy. Despite this great development it has been observed that unfortunately only one half of women with HER2-positive breast cancers respond to anti-HER2 therapies, calling for the need to further understand the biology of tumours to better target the tumour.

What Needs to be Done From Now On

It is so essential to pursue efforts in cancer research and gather comprehensive information on each tumour in order to be able to identify all involved targets and hence determine the most appropriate treatment for each tumour and patient – be it used to cure, to slow down the growth of cancer cells, or to relieve symptoms.

What Patients Should be Aware of

Important information about the patient's disease can be identified by tissue and blood sampling. This means obtaining one or more samples from the patient's tissues and tumour.

These samples can undergo various examinations. Despite possibly delaying treatment, these examinations are extremely valuable to characterise the tumour and thus determine the most appropriate treatment.

The time at which samples are taken depends on the cancer type and stage of the disease. Biological samples can indeed be very useful in the initial phases of disease; however, it is also very important for patients to know that they can be just as useful in case cancer comes back, but it may also happen that if cancer returns a new sample is needed. Patients have to make sure that their donated biological samples will be kept at a biobank that can be accessed any time.

In addition, patients help future patients when they give permission to use their blood and tissue samples in experimental research. However, the need for patients to re-consent every time their data is used is a hurdle that is currently limiting researchers' efforts.

Patients should be aware that personalised medicine is based on testing in molecular diagnostic laboratories and therefore it might not be available in all medical centres.

What Patients Should Look For While Receiving Treatment

The optimal management of personalised care is based on a trusting relationship between the patient, the physician, and – importantly – the multidisciplinary team taking care of him/her. A holistic approach should take into consideration not only the biological characteristics of the tumour but also the patient's physiological and psychological status over their lifetime.

Some Challenges that Need to be Solved

The challenges of personalised treatments include other aspects, such as the right of every patient to gain access to highly effective and affordable targeted therapies and the need to raise awareness among the medical community as well as among patients and their care providers.

A Need for Education and Research

It is only through targeted education and continuous advancement in research that the goal of personalised medicine to provide the “right treatment to the right patient at the right time” will be achieved.

Personalised Medicine and Patient Education



Lorenz Jost

Chair of the ESMO
Cancer Patient
Working Group

“When we talk about personalised medicine, we are talking about the selection of a treatment based on the results of biological or molecular tests of the tumour that may offer an additional treatment option, on top of the standard treatment available.

There are false hopes and fears and there are exaggerated expectations among patients regarding the response, the survival or the cure that these kinds of treatments may offer; there is even the likelihood, unfortunately, that only a small fraction of patients actually have a tumour that can be used as a target in personalised medicine.

I also encounter some generalised fears among patients, especially in Europe; patients fear that they are being exposed to some kind of genetically modified substance and they have reservations about that. One patient told me, “I don’t eat gene food, why should I get those shots?”

Then there are other problems, as well. There are difficulties in obtaining material for testing for personalised medicine. This may be stressful for patients because they have to undergo repeated biopsies to provide enough material to do the testing.

And then there are difficulties in access to personalised medicine, because in personalised medicine the specific drugs are not easily available everywhere and they also cost a lot. Coverage of the costs may be a problem even in high income countries, so it is sometimes very hard to overcome the difficulties in funding for personalised medicine.

All these issues have to be addressed by the ESMO Cancer Patient Working Group and other organisations, which need to explain the situation to patients and to offer a realistic picture of what personalised medicine can really offer.

What Is Personalised Medicine?

Personalised medicine can be described as: “The right medicine for the right patient at the right time”.

In 2012 there were 2.6 million people in the European Union (EU) with newly diagnosed cancer.

Although early detection and improved treatments are saving many lives, cancer is still the second most frequent cause of mortality and is responsible in the EU for an annual 1.3 million deaths. With an ageing population, the cancer burden in the EU is projected to continue rising to 3.2 million new diagnoses and 1.7 million cancer deaths in 2030. Cancer was newly diagnosed in 12.7 million people and accounted for 7.6 million deaths worldwide in 2008; and 1.4 million new cases and 0.6 million deaths were reported for the USA.

In recent years we have witnessed many advances in the treatment of the majority of tumours, allowing an increase in survival rates and improved quality of life. We have made many advances in lung cancer, breast cancer and colon cancer, which are the tumours with the highest incidence, but advances have also been made in rarer tumours.

In particular, the last decade has seen the introduction and provided support for the concept of personalised therapy, where “personalised” means ideally giving the best treatment for each individual patient. Personalised medicine is commonly considered as a shift away from the “one-size-fits-all” approach, towards one in which healthcare is based on the individual’s biological characteristics within a specific sociocultural and environmental context. The longer-term promise of personalised medicine is not only to more effectively treat patients, but also to prevent disease based not only upon genetic prediction but also upon physiological status over the patient’s lifetime.



Fortunato Ciardiello
Chair of the ESMO
Personalised Medicine
Task Force

What Is Personalised Medicine?

Let me try to explain what we, as medical oncologists, think is meant by personalised medicine. First of all, personalised medicine does not mean doing whatever we wish with an individual patient – treatment remains founded on the same evidence-based medical approach that has made effective treatments the standard or the state of art.

Personalised medicine comes from the results of research efforts over the past 20 to 30 years to understand the complexity of cancer. Not only between different tumour types and organs, but also within any tumour,

there is enormous heterogeneity. As a result, an approach of providing the same kind of therapy to the same patients just because their tumours arise in the same organ – breast, lung, prostate or whatever – will be effective in general, but does not work for everyone, unfortunately.

What we have learned in the past five to ten years is that we can stratify, within a given tumour type, different groups of patients and disease settings in which some molecular aspects, some biomarkers, or some genetic alterations differ. For example, we have identified a subgroup of patients with breast cancer who have HER2 gene amplification and over-expression, and for these patients there are therapies that are effective. However, this is just the first step in the search for personalised medicine.

We are now in the area of research into mutation and expression analysis and, with the technologies that are available today, we can go even deeper in describing, for example, why unfortunately only one-third to one-half of women with HER2-positive breast cancers respond to anti-HER2 therapies, or why mechanisms of resistance to therapy develop.

So, the aim of personalisation of medicine is to better understand the biology and the pathology of the tumour of each individual patient. The key issue is that going from an organ disease (breast cancer) to a stratified disease (HER2-positive or HER2-negative tumour), to an HER-positive tumour in a patient with all these gene activation characteristics can help us understand which is the most effective treatment strategy and whether we have effective drugs available for doing this.

What Is the Aim of Personalised Medicine?



Sabine Tejpar
ESMO Faculty

The aim of personalised medicine is clearly to make therapy more efficient for patients. A very, very small step in the process is to try to identify for every patient the main molecular driver of their tumour. We have to understand that patients differ between each other, although they may have the same cancer type; for example, every patient with breast cancer or bowel cancer will have a unique tumour. This is entirely new knowledge, so what we are trying to do now in the medical community is to identify for each patient his/her type of disease and then to give the drug that will work best.



Solange Peters
ESMO Faculty

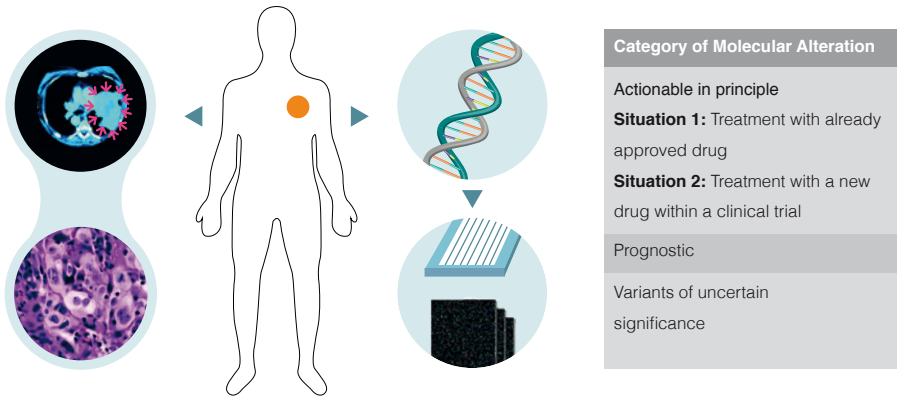
We are moving forward with an incredible amount of new data and innovative knowledge on genetic characteristics and subsequent proteomic changes* in the tumour. The challenge is now about how to exploit this information in order to offer targeted treatment and generally improve patient care. I do not think there is any field of oncology which is not concerned with this development. We now know that development of cancer is a multi-step process; so if you learn to know better the serial modifications at the cell level, there will be ways to target these steps in every tumour. Two major questions for the moment are political:

1. Where should research invest more priority and money?
2. How do we ensure equity in terms of accessibility to these new technologies, expensive strategies and treatments?

These questions will probably direct the order of discovery, but they will not change the fact that personalised medicine will eventually concern every type of tumour in the future.

Figure 1. A Concept of Personalised Cancer Medicine.

On the left side, we can see a computed tomography (CT) scan showing a tumour in the lung. On the image below, a histological section is shown, basically representing how the pathologist sees the tumour tissue under the microscope. This panel is considered to be “classical” medicine in terms of the approach to treatment. On the right panel, we can see a schematic of molecular analysis of the tumour with possible findings: an actionable mutation and consequently treatment with an already approved drug or with a new drug within the context of a clinical trial. The findings could also indicate a prognosis or could be of non-significant relevance.



Adapted from Garraway L *et al.* J Clin Oncol 2013; 31(15): 1803-1805, with permission.

Personalisation of Oncological Treatments: The Story

For a number of years we have classified tumours according to their site of origin and using a classification system called “TNM”. Researchers and clinicians once thought that all cancers that derived from the same site were biologically similar and they differed perhaps only in their pathohistological* grading. This grading is a score which classifies tumours from

1 to 3, where 1 is the least aggressive tumour and 3 is the most undifferentiated tumour. Other clinical differences were distinguished based on the presence of regional node metastases or distant metastases. Most of the tumours were therefore classified within the “TNM” system, where T corresponds to the diameter of the primary tumour, N to the presence of regional nodes, and M to distant metastases.

For at least three decades, personalisation of oncology was based only on these parameters and on the patient’s physical condition, and even now these represent the fundamental elements for treatment decisions. Chemotherapy, surgery and radiation therapy were once the only treatment options for cancer. Although these treatments are still used, oncologists know that some patients respond better to certain drugs than to others and that a surgical approach is not always indicated.

In recent years, researchers have studied thousands upon thousands of samples from all types of tumours. They have discovered that tumours derived from the same body site can differ in very important ways.

Firstly, there is histology*. The pathologist is able to distinguish different subtypes of cancer with the microscope. When a patient is diagnosed with a cancer, he/she will undergo a biopsy or a fine-needle aspiration. In some tumour types, debulking or removal of the primary tumour also allows sampling for tissue examination. Some cells of the tumour which have been removed will be taken and analysed. This examination allows the pathologist to confirm a cancer diagnosis, but, through particular colorations of the tissue sample, the pathologist is also able to provide clinicians with a lot of additional information, such as the tumour’s histological characterisation, its hormone sensitivity, and its grade of differentiation*.

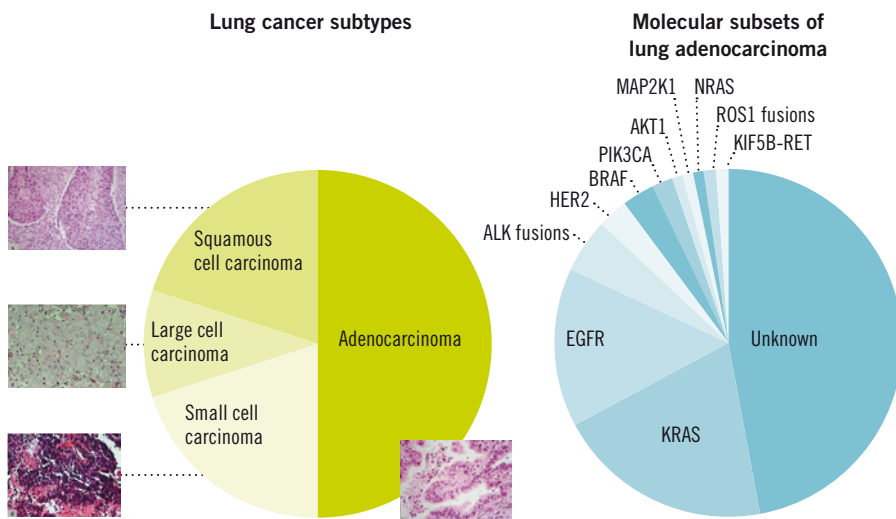
For example, in the treatment of lung cancer the histology provides very useful tools to decide the best drug for the treatment of the patient. Clinical studies have shown that for a patient with lung adenocarcinoma* there might be more chance of a response if the drugs pemetrexed or bevacizumab are added to the chemotherapy, while for a patient with lung cancer of squamous* histology, it would be more beneficial to add gemcitabine or vinorelbine. A similar example may be observed

for other cancers. For the treatment of oesophageal cancer it is mandatory to know if the tumour is squamous or not, because although deriving from the same organ, the treatment approach is completely different.

This information is a useful tool in the first step of the personalisation process. For example, lung cancer can be divided as a first step into non-small cell lung cancer and small cell lung cancer, which are two completely different neoplasms*. Within the non-small cell lung cancer category, there are again several different tumour types. Breast cancer can also be divided into two major categories: the hormone-sensitive neoplasms and the HER2-positive diseases. Lung and breast cancers are only two examples, because it is possible to recognise several entities within the same tumour type for many other cancers.

Figure 2. Lung Cancer – Not One Disease: Histological (Tissue) and Molecular Subtypes of Lung Cancer.

On the left side, four histological subtypes of lung cancer. On the right side, a pie chart showing the percentage distribution of molecular subsets of lung adenocarcinoma.



Adapted from Petersen I. Dtsch Arztebl Int 2011; 108(31-32):525-531 (left) and Pao W & Hutchinson KE. Nature Med 2012; 18(3): 349-351, with permission.



Fortunato Ciardiello

Chair of the ESMO Personalised
Medicine Task Force

Personalisation Requires Humanisation of Medicine

We don't have the definitive solution for all cancers yet, but it is very important for patients and patient organisations to understand a few issues. First of all, personalisation requires the humanisation of medicine. We know that these technologies have led to less effective face-to-face interaction between patient and doctor. It will be very hard, for example, to start talking to patients about the evaluation of 255 genes that may be altered in a tumour that metastasises to the brain; we need to begin seeing through the eyes of

our patients. So personalisation starts with an individual relationship on the part of the physician and the medical team who are taking care of the patient.

Personalisation also depends on a multidisciplinary approach; we need a range of experts, because we need the medical oncologist, the surgeon and the expertise of the molecular pathologist, who should be part of the team in a more effective, integrated way than before. We don't need the pathology report alone; we need to interact with all professionals, including nurses, who are dealing with the patient. This, to me, will create a lot of problems in terms of organisation of care and in terms of cost, but it is the only way to bring together knowledge on the biology and pathology of tumours for effective treatment in every single patient. Our effort at ESMO is to bring this broad knowledge to the general public, to medical oncologists and to the community of doctors involved in cancer.

The New Era: Discovery of DNA

The instructions for biological patterns are written into our chromosomes. Everything about our bodies is written in our DNA (“deoxyribonucleic acid”) that forms the genes within our chromosomes. We now understand that some genes contribute significantly to making us resistant to

illness, while other genes may make us more susceptible to specific diseases. In our chromosomes there are also instructions to make drugs work, or fail, or to produce side effects. The human genetic code is often the key to health and to disease.

Cancer is a result of damage to our genes. Cancer occurs when the switches inside our genes that control cell growth do not work. For example, if a growth gene is supposed to be turned off, in cancer it is turned on. If a genetic switch is designed to prevent cancer growth, in this case it fails. Cells that should be at rest begin to divide, and tumours develop. These damaged growth genes are called “oncogenes”.

The damage can occur for three reasons.

- First, we may be born with a defective gene, such as the BRCA breast cancer gene.
- Second, exposure to toxins in our environment, such as cigarette smoke, can damage our genes.
- Finally, the genes can simply wear out, which partially accounts for the increase in cancer incidence as we age.

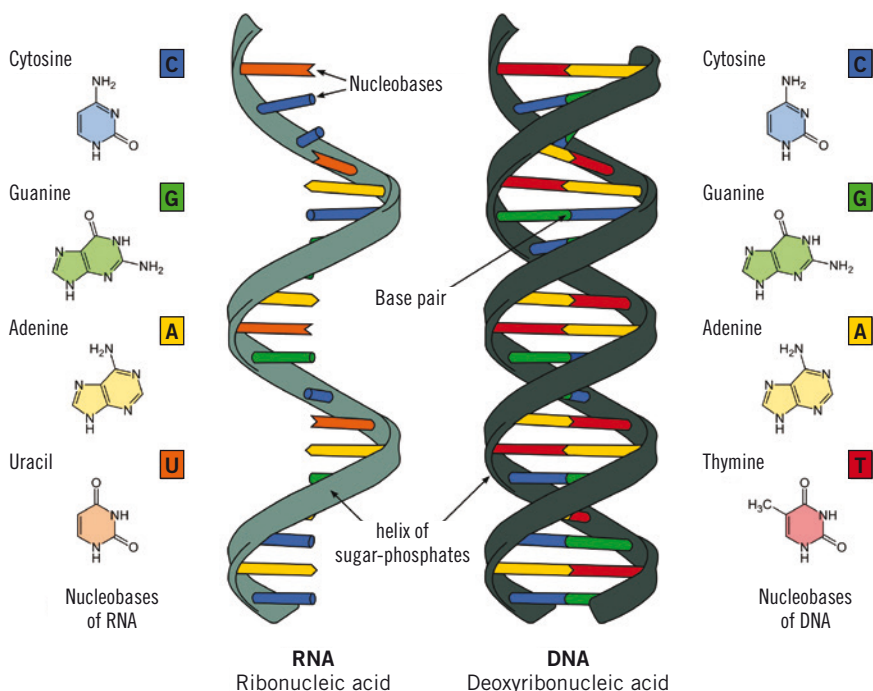
Knowing that oncogenes are the key, there can be no doubt that gene-based prevention and therapy will be crucial in winning the war on cancer.

Now, things are changing and advances in technology and the results of the Human Genome Project* have enabled researchers to identify the molecular features of each single tumour. Researchers have found that there is a wide heterogeneity among apparently similar tumours.

Genes play a fundamental role in cancer. Each person has about 25 000 genes, which are stored in the nucleus, the vital centre of every cell. In the nucleus there is the DNA. DNA is a double-stranded molecule shaped into a double helix. DNA is formed by pairs of bases denoted by four letters: A, T, C and G. The sequence of the letters enclosed in the gene sends a specific message through the RNA (“ribonucleic acid”) with the instructions on how to build a specific protein. If the message is clear and correct, the protein will be correct. If an alteration occurs in the gene, the instructions on how to build the protein will be wrong and therefore the message will not be delivered correctly.

Figure 3. The Structures of RNA and DNA.

Ribonucleic acid (RNA) is a single-stranded molecule, formed from nucleobases denoted by four letters: C, G, A and U. Deoxyribonucleic acid (DNA) is a double-stranded molecule shaped into a double helix and formed by pairs of nucleobases denoted by four letters: C, G, A and T. The sequence of the letters enclosed in DNA sends a specific message through the RNA with the instructions on how to build a specific protein. In other words, the genes in DNA encode protein molecules, and sending messages through the RNA is a process of decoding the instructions for making proteins, which carry out all the functions necessary for life.



Based on content in Wikipedia (http://en.wikipedia.org/wiki/Main_Page)

One of the major discoveries of the last decade has been the identification of some specific alterations that are able to change the signal in the tumour cell and create a phenomenon called “addiction”. This phenomenon means that the tumour can survive and reproduce itself mainly because this alteration is present. These alterations may be of different types. The majority of them are gene mutations, translocations and amplifications.

It is therefore intuitive that giving a drug that targets these specific alterations is fundamental in fighting the war against cancer. This is the biological basis of personalised medicine.

To explain briefly, it means that we have to deeply analyse each tumour of every patient in order to identify those genetic characteristics that make the tumour able to survive. As a result, we can choose the appropriate drugs to target the specific alterations. The clearest examples of this process are in melanoma, lung cancer and breast cancer.

For instance, in lung cancer, the presence of mutations in the epidermal growth factor receptor (EGFR) renders the tumour highly sensitive to EGFR tyrosine kinase inhibitors. When oncologists identify these mutations in a patient's tumour, they may observe that the lesion disappears a few weeks after treatment. A similar response may be observed after treatment with BRAF inhibitors in patients with melanoma or with gastrointestinal stromal tumours (GIST) that express the c-kit gene.

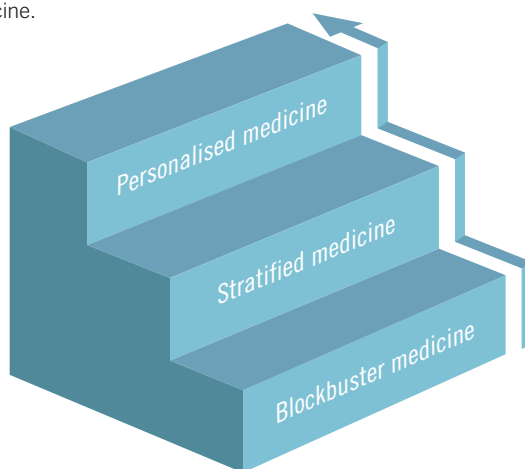
Unfortunately, oncogene addiction is not the only process underlying carcinogenesis* and tumour growth. The tumour environment and so-called “epigenetic” alterations* play an important role in rendering the fight against cancer more and more challenging. Despite the enormous recent advances, a specific alteration has not been identified in all cancers. The hope is that the possibility of sequencing the full genome – which means every gene – will give us new insights and therefore new drugs for our patients.

It is also important to explain something more about familial cancer. In the DNA of some individuals a “germline” mutation* may be present. This means that a particular mutation is conferring susceptibility to that person to develop a particular type of cancer during his/her life. For instance, BRCA is an alteration for which there is a particular predisposition to have a breast cancer or ovarian cancer in one's life. A woman with a BRCA gene mutation can transmit this alteration to her female descendants, so her daughters and following generations of female family members can therefore inherit this predisposition. Germline mutations are present in all the cells of our body.

Mutations that are not germline are called somatic mutations*, which are acquired mutations and are found generally only in the tumour. Distinct from germline mutations, somatic mutations are not inherited.

Figure 4. Personalised Medicine: A Stepwise Process.

The move from blockbuster or empirical medicine* towards personalised medicine is a stepwise process. We are currently on the second step of stratified medicine and moving up the stairs towards personalised medicine.



Jørgensen JT. Expert Rev Mol Diagn 2008; 8: 689-695, with permission.

Personalised Medicine and Pathology



Angelo Paolo Dei Tos
Pathologist, ESMO Faculty

Will molecular pathology evolve from pathology?

You need to give a name to a tumour, and a pathologist is the professional who gives a name to tumours. The variety of cancers is broad; when we say “sarcoma”, “carcinoma”, or “lymphoma”, we actually say nothing, because we have hundreds and hundreds of diseases within these categories that need to be recognised. And the reason for recognising them is exactly related to personalisation.

The biology of cancer is very complex, and admittedly we have been very naive in the past. We always thought that the problem was how genes become altered in the cancer cell, but actually it is even more complex than that and also involves the way genes direct how they are read; it is the flow of information that comes from genes to the making of their proteins which is as important as the aberration of the genome.

Question from Selma Schimmel: “What do European patients really need to know, and learn and understand, regarding their own role in advancing molecular pathology, considering the importance that tissue analysis potentially plays in tailoring therapy?”

Dr Dei Tos: One of the best questions would be: “Who is the owner of the tissue?” You, the patient, are the owner of the tissue. So what can we as physicians do? We need tissue because all of the information that we need is sitting in the tissue, in the biopsy samples. I know it is sometimes difficult

to get samples, but we desperately need them. If we do not analyse them, there is no way to provide any new information.

We are facing obstacles currently because the whole issue of tissue sampling has been regulated under the umbrella of privacy, which is of course important. Defending your rights as a human being is a key issue, but we should also try to focus a little bit on the necessity to use that tissue. Of course, we need to have rules, but the approach we are currently facing is basically preventing clinical research and translational research under the excuse of protecting our privacy as human beings, and this is an increasing obstacle. We as researchers, as molecular geneticists, as pathologists, are really looking into a future in which it is becoming increasingly difficult to try to answer the basic question of cancer genomics. Why? Because it is becoming increasingly difficult to use tissue for these purposes.



Stefania Vallone

Women Against Lung Cancer
Europe

ESMO Cancer Patient Working
Group member

With the new therapeutic approach and the use of targeted therapy, molecular testing is gaining a very relevant role. It is very important for us, as advocates, to educate patients in these issues. So patients have to receive very clear and transparent information.

It should be the doctor who explains to the patient the reason why molecular testing is performed; the doctor has to explain that molecular testing will find whether there is some tumour characteristic which can be targeted with one of these therapies, in order to determine if maybe the patient is the right candidate to receive targeted therapy and perhaps to benefit from it.

I really believe that the communication between the doctor and patient must be very accurate and must educate, meaning that the patient has to understand the precise situation. This can be important also to empower the patient in treatment decisions, but it is important that he/she knows that not every patient may be a candidate for receiving targeted therapy and to understand why this is the case.

Figure 5. Progressing Towards Personalised Medicine.

- ▶ Different tumour types are increasingly divided into very small subgroups carrying a rare molecular alteration.
- ▶ Most new drugs are targeting these infrequent events.
- ▶ Clinical trials are testing the use of high throughput molecular technologies* in the context of personalised cancer medicine.
- ▶ There are a growing number of newer techniques to optimise genomic testing, including the virtual cell programme, which foresees testing of a piece of patient's tumour tissue in the laboratory in order to mimic what would happen in the human body (e.g. drug sensitivity).
- ▶ Clinical research is today focusing on target identification at the patient level.

Understanding How To Personalise Each Individual Treatment

Chemotherapy

In the past, the most important part of the treatment of many cancers was chemotherapy, due to the systemic nature of most of the disease and the potential of malignant cells to spread to other parts of the body early in the course of the disease. Today, in the era

of targeted therapy, chemotherapy still remains the cornerstone of treatment for the majority of malignant diseases.

The mechanism that underlies chemotherapy is based on killing cells that divide rapidly. Rapid cell division is one of the main properties of most cancer cells. Unfortunately, chemotherapy also harms healthy cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles. This effect on healthy cells results in the most common side effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract) and alopecia (hair loss).

In the past, one of the major problems with chemotherapy was acute nausea and vomiting. However, nowadays several powerful anti-nausea agents are available and this problem has become more manageable.

Chemotherapy works throughout the whole body, while surgery and radiation therapy (acting as local treatments) have an effect on cancer cells in specific areas of the body. Chemotherapy is also active on cancer cells that have metastasised or spread to other parts of the body, away from the primary site of the original tumour. The effect of chemotherapy on the whole body is also very important after surgery.

Many chemotherapeutic agents are employed in the treatment of cancers and generally they are used either as a single agent or in certain combinations. A combination of drugs with different actions can work together to kill more cancer cells. It can also reduce the chance that the cancer may become resistant to any single chemotherapeutic drug.

To understand if a drug or a combination of drugs is working, your oncologist will evaluate how well your treatments are performing by periodically repeating radiological examinations such as computed tomography (CT) scans or magnetic resonance imaging (MRI), blood tests or other investigations. The appearance or the lack of side effects does not tell us whether or not a treatment is working.

If chemotherapy has an unselective effect, it is possible to tailor the treatment in many cases by using specific biomarkers. Biomarkers help doctors know more about an individual person's tumour, allowing them to take better decisions. This is the first step in personalised medicine. Biomarkers may also be useful tools for monitoring the response to treatment and for detecting recurrences or progression.

In order to personalise chemotherapy, doctors may use genetic biomarkers, which are either specific genetic alterations expressed in tumour cells or protein alterations that are present in tumour tissue or revealed when blood tests are analysed. The presence of a biomarker can predict the outcome of the treatment strategy. New biomarkers and genetic profiles are constantly being discovered. Some examples of biomarkers that may predict the outcomes of chemotherapy are ERCC1 for cisplatin, thymidylate synthase for pemetrexed, HER2 for anthracyclines, etc. For instance, a low level of ERCC1 in a tumour predicts a good outcome from the use of cisplatin.

It is also worth mentioning that every tumour is different. No two tumours are the same, just like every individual is different. Therefore it is also possible that genetic somatic alterations may render people susceptible to treatments, in terms of toxicity and efficacy, in different ways. These alterations, which are also present in normal tissue, are generally called polymorphisms.

Radiation therapy

Radiation and radioactivity were discovered more than 100 years ago. Since then, advances in technology and a better understanding of its effects on the body have made radiation therapy an important part of cancer treatment. In fact, more than half of all people with cancer will receive radiation as at least one part of their cancer treatment.

Radiation is energy that is carried by waves or a stream of particles. Radiation therapy works by damaging the genes (DNA) in cells. Genes control how cells grow and divide. When radiation damages the genes of a cancer cell, the tumour cannot grow and divide any more. Over time, the cell dies. This means that radiation can be used to kill cancer cells and shrink tumours. Cancer cells tend to divide quickly and to grow out of control. Radiation therapy kills cancer cells that are dividing, but it also affects the dividing cells of normal, healthy tissues.

The damage to normal cells causes unwanted side effects. Each time radiation therapy is given, there needs to be a balance between destroying the cancer cells and minimising the damage to normal cells. Radiation does not always kill cancer cells or normal cells right away. It might take days or even weeks of treatment for cells to start dying, and the cells may continue dying for months after treatment

ends. Tissues that grow quickly, such as skin, bone marrow and the lining of the intestines, are often affected right away. In contrast, nerve, breast, brain and bone tissue shows later effects. For this reason, radiation treatment can have side effects that might not be seen until long after the treatment has ended.

Radiation is considered a local treatment because only cells in and around the cancer are affected. Radiation cannot cure cancer that has already spread to distant parts of the body, because most forms of radiation therapy do not reach all parts of the body. Radiation is used to treat cancer in several ways. Some cancers are very sensitive to radiation. Radiation may be used by itself in these cases to make the cancer shrink or disappear completely. For other cancers, radiation may be used before surgery (as pre-operative therapy) to shrink the tumour, or after surgery to prevent the cancer from coming back (this is called adjuvant therapy). Radiation may also be used at the same time as chemotherapy in some cases. When radiation is used in combination with other forms of therapy, the treatment is planned by the surgeon, medical oncologist and radiation oncologist, all working together with the patient.

Personalised treatment is fundamental for patients who need to be treated with radiation therapy.

First of all, not all radiation techniques are the same. It is important that the radiation oncologist chooses the most appropriate technique for each patient. Then, the radiation oncologist must select the field of radiation, which must be large enough to cure the cancer but avoiding acute and long-term toxicity to the healthy parts of the patient. For instance, a radiation oncologist irradiating the lung will preserve as much as possible of the heart, spinal cord and other parts of the lung, and if irradiating the rectum an oncologist will preserve the surrounding areas, the bladder and the remaining bowel.

Defining the radiation dose is the final step in personalisation of the radiation treatment. Clinical studies have identified the correct dose to be delivered in each individual situation.

Targeted therapies

Targeted therapy drugs work differently to standard chemotherapeutic drugs. They attack cancer cells and, in particular, the targets which are strategic points for cell survival, cell replication and metastases. They generally create little damage to normal cells. In fact, these drugs tend to have different side effects to traditional chemotherapeutic drugs. Targeted therapies are used to treat many kinds of tumours: certain types of lung, pancreatic, head and neck, liver, colorectal, breast, melanoma and kidney cancers. Targeted therapies are a major focus of cancer research today.

Many future advances in cancer treatment will probably come from this area. There are many different targeted therapies in use and new forms are appearing all the time. Depending on the type of cancer and the way it spreads, targeted therapy can be used to cure the cancer, to slow the cancer's growth, to kill cancer cells that may have spread to other parts of the body or to relieve symptoms caused by the cancer.

Your doctor will talk to you about the goals of your therapy before you start the treatment. The most common way to give these drugs is as a pill (by mouth) or infused into a vein (intravenous or IV). Although targeted therapy drugs do not affect the body in the same way as standard chemotherapy, they still cause side effects. Side effects from these drugs depend largely on what the drug is targeting. Some drugs target substances that are more common in cancer cells, but are also found in healthy cells. So these drugs may affect healthy cells too, causing some side effects.

When drugs attack more than one target, side effects are more likely. Patients often become discouraged about how long their treatment lasts or the side effects that they have. Within the concept of personalisation of treatment, it is possible to change the drug or treatment schedule if side effects are not controlled. However, in recent years, the treatment of more frequent side effects has also been improved. More patients are aware of the side events and are more informed about their disease than in the past.

Personalisation of Treatment

We can divide targeted therapies into two main categories: antibody drugs and small molecules. Antibody drugs are man-made versions of immune system proteins that have been designed to attack the

external part of cells at certain targets, generally called receptors. Receptors can be considered the antennas of the cells. They transmit signals from the surrounding environment to the nucleus of the cell. Some receptors are fundamental to the vital processes of the cell. Targeting certain receptors means preventing the transmission of some survival signals to the tumour cells. Trastuzumab (Herceptin®) is, after tamoxifen, the second targeted therapy drug ever used to treat cancer and it is a monoclonal antibody directed at a receptor called HER2. This targeted therapy greatly improves the survival rate of women with breast cancer expressing the HER2 receptor.

Therefore, the determination on tissue blocks of the presence of expression of HER2 is one of the best examples of personalisation of treatment. A knowledge of the cancer characteristics and a determination of the tissue characteristics of each patient allows the doctor to select patients for the best treatment.

Other examples of monoclonal antibodies are cetuximab and panitumumab, which have been developed to treat colon cancer. At first it seemed as if these drugs were a failure, because they did not work in many patients. Then it was discovered that if a cancer cell has a specific genetic mutation, known as KRAS, these drugs will not work. This is another excellent example of using individual tumour genetics to predict whether or not a treatment will work. In the past, the oncologist would have had to try each therapy on every patient and then change the therapy if the cancer continued to grow.

The other type of targeted therapy drugs are not antibodies. Since antibodies are large molecules, this other type is called “small-molecule” targeted therapy drugs. The small molecules attack cancer cells from the inner vital processes. Also, in this case, the small molecules prevent the broadcast of vital signals that regulate the survival of the tumour.

There are several examples of targeted drugs that changed the natural history of some cancers. One example is imatinib mesylate (Gleevec®), which is used in GIST, a rare cancer of the gastrointestinal tract, and in certain kinds of leukaemia. Imatinib targets abnormal proteins, or enzymes, that form on and inside cancer cells and promote uncontrolled tumour growth. Blocking these enzymes inhibits cancer cell growth. Gefitinib (Iressa®) is used to treat advanced non-small cell lung cancer. This drug hits the internal part of the EGFR. These receptors are found on the surface of many normal cells, but certain cancer cells have many more of them. EGFR take in the signal that tells the cell to grow and divide. When gefitinib blocks this signal, it can slow or stop cell growth.

However, gefitinib does not work in all patients when trying to treat lung cancer, but only

in a particular subtype. About 10% of patients show genetic alterations called “EGFR mutations” in their tumours at diagnosis. These particular mutations mean that the EGFR is always turned on and therefore there is a continuous signal to the cell to grow and divide. Gefitinib is able to switch off this signal and to stop cell growth in this subtype of patients. After a few weeks, the tumour disappears. Unfortunately, these mutations are rare and they are mainly present in never-smokers, who are the minority of patients.

Another, similar example in lung cancer is provided by crizotinib (Xalkori®). Patients with ALK translocations, which is another rare type of alteration present mainly in never-smokers, experience a rapid shrinkage in their tumours when treated with this drug.

Another example of small molecules is represented by sunitinib (Sutent®). This drug is used to treat advanced kidney cancer and some GIST. Sunitinib is considered a multitarget agent because it blocks the vascular endothelial growth factor (VEGF) receptor and other enzymes. By doing all of this, sunitinib slows cancer growth and stops tumours from creating their own blood vessels to help them grow and metastasise. In this case, no biomarkers have been identified to help select patients who are responders from patients who are nonresponders.

The Challenges of Genetic Marker Testing Requirements



Kathy Oliver

International Brain
Tumour Alliance
ESMO Cancer Patient Working
Group member

One of the worries I have as a patient advocate is that personalised medicine could become exclusive medicine when targeted therapies could create “haves” and “have nots” based on whether a patient’s genetic profile is favourable to a particular therapy being developed. So we need to ensure that academic institutions and industry are incentivised to develop innovative medicines to treat the “have nots” as well as the “haves” who, through no fault of their own, may find themselves with no treatment options at all, based on their genetic characteristics. There is, of course, also the worry about cost and how we can ensure equitable access to personalised medicine for all patients.

We also need to ensure that diagnostics are consistently accurate from lab to lab and centre to centre, so that no patient is denied a therapy on the basis of an inadequately validated assay.



Angelo Paolo Dei Tos

Pathologist, ESMO Faculty

The issue of accuracy in molecular testing is critical.



Fortunato Ciardiello

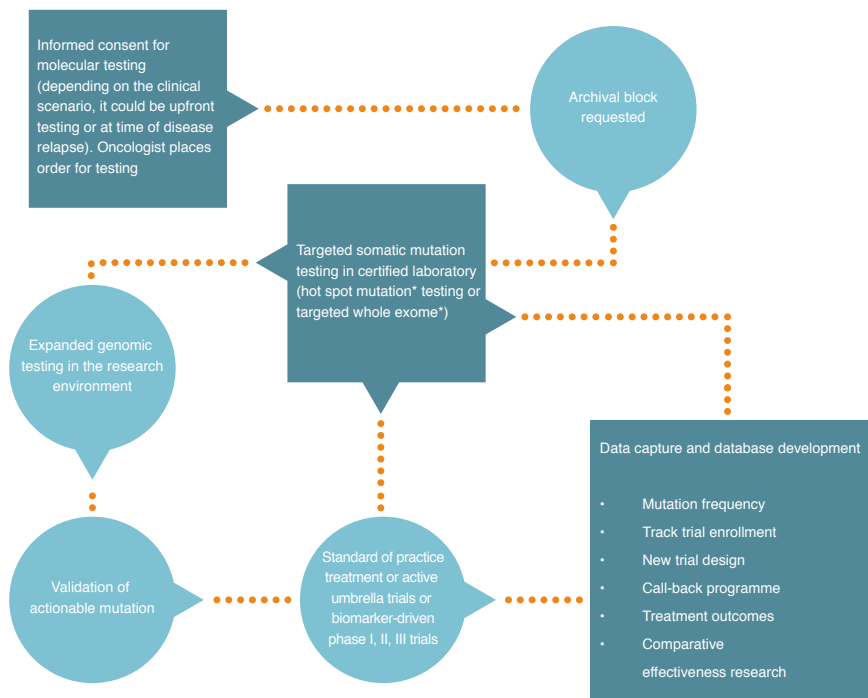
Chair of the ESMO Personalised
Medicine Task Force

Adequate testing is very important, especially for drugs that are already on the market – even more important than for an experimental drug in the clinical trial setting.

Figure 6. Flow of Tumour Specimen and Related Data in a Typical Personalised Medicine Project.

Exploring the clinical utility of comprehensive genomic testing.

After the patient's informed consent, tumour and normal DNA is extracted in a certified laboratory. After targeted somatic mutation testing, more extended testing is performed in a research environment. Test results are shared with the treating oncologists, and validation of research findings is pursued if any clinically relevant research findings are found. Therapeutic decisions are based only on validated test results.



Adapted from Meric-Bernstam F *et al.* J Clin Oncol 2013; 31(15): 1849-1857, with permission.

Understanding How To Personalise Your Disease: Three Examples

Lung cancer

Lung cancers can be divided into two main entities: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The majority of lung cancers can be attributed to smoking habits. NSCLC and SCLC are different diseases with different prognoses and different treatments. Among NSCLC tumours there are other subgroups: the

adenocarcinomas, the squamous cell carcinomas and some other, rare types. These are characterised by different sensitivities to particular agents. For example, adenocarcinomas are more sensitive to pemetrexed. In the last decade, many genetic alterations have been discovered. Specifically, EGFR mutations confer on these tumours a strong sensitivity to EGFR tyrosine kinase inhibitors. EGFR mutations are mainly present in never-smokers and Asians. Another important alteration, recently discovered, is the EML4-ALK translocation. Again, this is represented more commonly in never-smokers. A family of drugs, called ALK inhibitors, are very effective against this translocation. In the last few years, many new alterations have been identified and specific targeted agents to each of them are under investigation, with promising results.

The hope for the Human Genome Project is to personalise treatment through identifying the best targeted drug for each single alteration.

How Will Personalised Medicine Affect Lung Cancer Patients?



Fortunato Ciardiello

Chair of the ESMO Personalised Medicine Task Force and an expert in lung cancer

What we are doing in lung cancer is, unfortunately, not the same for squamous cell carcinoma as in lung adenocarcinoma. In lung adenocarcinoma we are starting to stratify tumours and therefore patients because, fortunately, some of these alterations are mutually exclusive and just one of these alterations is the major driver. So if this alteration is, as we say, "drugable", it is possible to obtain a specific therapeutic effect. In squamous cell carcinoma, we do not have very selective molecular drivers that allow us to use selective therapies.

It is very important that patients become aware of molecular testing. It is also very important in the diagnosis of metastatic disease that we make all efforts to obtain the best quality biopsy material, because the pathology report is very important, not only in terms of histology but also in terms of molecular alterations. This is becoming more and more important in lung cancer.

Breast cancer

Breast cancers can be divided into two main categories: the hormone-sensitive and the non-hormone-sensitive tumours, and they can be divided again into HER2-positive and HER2-negative tumours. These characteristics can render certain tumours particularly sensitive to hormonal treatments and to anti-HER2 agents, such as trastuzumab, lapatinib, pertuzumab and TDM-1.

Another example of personalised medicine, which is relevant for women diagnosed with breast cancer, is that genetic testing on the cancer itself (Oncotype DX) can help determine the need for chemotherapy and whether the chemotherapy will work.

Personalised Medicine in Breast Cancer



Martine Piccart

ESMO President and an expert
in breast cancer

My two messages for patients:

Patients should know that, today, their treatment relies heavily on the evaluation of a few critical targets in the tumour, such as the hormone receptors and HER2 receptors, using some delicate tests that are not always performed to the highest standards. So patients have to make sure that these tests are done in a laboratory that satisfies quality control criteria.

The second message is that science is moving very rapidly and it is always recommended that patients see if there are interesting clinical trial opportunities where their tumour will be profiled in a more aggressive way than is done routinely, so that they may possibly have access to some of the very smart targeted drugs in development.

Colon cancer

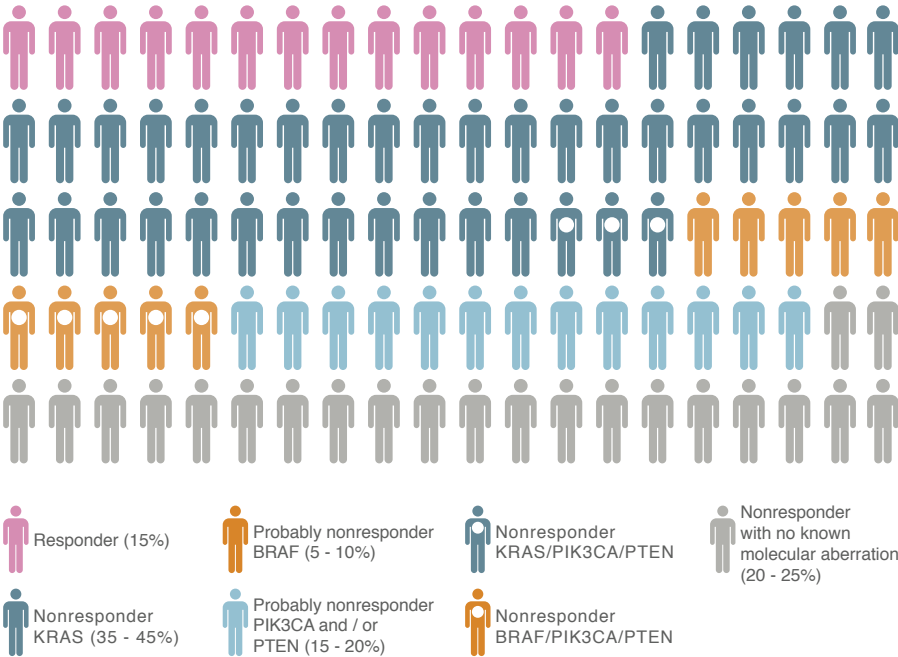
The last decade has seen the introduction of antibodies against EGFR, which is one of the most activated genes in colon cancer. These two antibodies are called cetuximab and panitumumab.

Research has identified that the expression of a particular type of KRAS mutation in some patients renders the tumour insensitive to these drugs, while the remaining 80% of patients may achieve a benefit if treated with these agents.

Figure 7. Graphic Representation of a Cohort of 100 Patients With Colorectal Cancer Treated With Targeted Drugs Cetuximab or Panitumumab.

Patients who respond or do not respond to the treatment, based on their molecular profile, are indicated with different colours.

The genetic milieu of individual tumours and their impact on clinical response are listed. KRAS, BRAF, and PIK3CA somatic mutations, as well as loss of PTEN protein expression, are indicated according to different colour codes. Molecular alterations mutually exclusive or co-existing in individual tumours are indicated using different colour variants. The relative frequencies at which the molecular alterations occur in colorectal cancers are described, and those patients who respond to the treatment and who do not are indicated with different colours.



Adapted from Bardelli A *et al.* J Clin Oncol 2010; 28(7): 1254-1261, with permission.



Eric Van Cutsem

Member of the ESMO
Personalised Medicine Task
Force, ESMO Faculty and an
expert in colorectal cancer

Personalised Medicine in Colorectal Cancer

Recent work through collaboration in European consortia has contributed enormously to the unravelling of predictive factors of resistance to the anti-EGFR antibodies, cetuximab and panitumumab. This work helps to better understand which patients will not benefit from these drugs. More recent work is now expanding from KRAS as a predictive factor of resistance to the other, more rare RAS genes, such as H-Ras and N-Ras. We will therefore talk of testing for the RAS mutations instead of the KRAS mutations.



Josep Tabernero

ESMO Faculty and an expert in
colorectal cancer

It is important for patients to know that their disease is complex. We are getting there; we are learning a lot about the science of this disease. We are trying to differentiate as much as possible the disease of one specific patient from the disease of another patient.

We also have to take into consideration the clinical situation of the disease. It is not the same to have local disease as it is to have metastatic disease; and even if the patient has metastases, the location of the metastases and the location of the potential site for surgery are important factors.

More and more, patients will need to understand that in order to best define their disease, we need access to tissue specimens, we need access to the tumours. We need to collect blood samples sometimes in order to characterise at any point in time how the disease is progressing. This is crucial for patients to get the best treatment options, but also to design new clinical trials that eventually will lead to more successful treatments.



Jean-Yves Blay

ESMO Faculty and an expert
in sarcoma

How Will a Personalised Approach in Medical Oncology Affect Sarcoma Patients?

The first point is to ensure that the tumour is being managed by an experienced centre; reference centres are identified within networks in all countries and they should be contacted to ensure optimal multidisciplinary management.

The second important message is to ensure that the tumour has the correct histological diagnosis and now, often, molecular diagnosis. This is also ensured by a reference centre, within a network of collaborating pathologists and pathology laboratories.

And the third point is that patient participation in clinical research is essential, and is a criterion of the quality of patient management. It has long been known that patients who participate in clinical trials do better overall for many reasons, including selection, but also because of the early availability of innovative treatments.

There are different ways to gain information on the existence and location of an expert centre. The internet plays a central role for this purpose. We have to improve our tools to simplify the task of patients in finding the most appropriate centre nearby for all countries of the EU. That is an important task and I think multinational organisations such as ESMO have a key role to play in that.



Fortunato Ciardiello

Chair of the ESMO Personalised
Medicine Task Force

Is Personalisation of Medicine in Cancer Possible in Any Tumour Type?

The answer is certainly yes, because every tumour is heterogeneous and for any tumour type in a patient we can find the possibility of exploiting this, but the path and the pace are different tumour by tumour. The best examples are in breast cancer and some leukaemias.

Patients should understand that it is very important to be involved more actively in clinical trials. Also, clinical trials should be done to try to obtain more knowledge on the mechanisms of the disease. The era of very

large clinical trials – of 5000 patients in a randomised clinical trial in which we investigate standard chemotherapy plus or minus a new agent – has ended. These are too expensive and the results are very minimal. So we have to retune. The interaction with patients is also very important. Every time that a patient signs a consent form to enter a clinical trial, the patient is hoping to receive a better treatment. But whatever comes from that individual experience, the trial should also be useful in gathering knowledge that can be used for other patients. So donating tumour tissues, blood samples, and other parts of the body is a very important issue. This is a very long process that will involve us for many years. Maybe when I retire as a physician we will still be working on that, because fighting cancer is not so easy.

Some 30 or 40 years ago we were talking about cancer as not being a curable disease. We are working to cut out the 'not' from the definition of cancer, but personalisation of medicine requires not only a lot of awareness by the patient and a lot of awareness by patient focus groups, but also requires putting pressure on the governing bodies. In the beginning, personalisation of medicine is going to be expensive. There are some concerns that personalisation of medicine is going to be too expensive. On the other hand, personalisation of medicine represents trying to get the best possible results for the individual patient, and the issue of cost is something that comes after.

Why Is the Process of Personalised Medicine Frustratingly Slow?



Sabine Tejpar

ESMO Faculty

We have to understand the biology behind personalised medicine. The main reason for the slow progress is the lack of mature scientific insights through which we have something to offer.



Solange Peters
ESMO Faculty

The only way to move forward, to prove the concepts, to find new drugs, is to have very good collaborative groups and to make the efforts together. In order to test a treatment in 100 patients we sometimes need dozens of centres, with one or two patients per centre. We really have to strengthen and reinforce in the future all the collaborative ways to work, without any – or minimal, at least – competitive ways of thinking. We have to work together to make the science evolve and forget about the national or regional representation of research that we have had in the past. I think the priority now is to have really good networks of institutions in order to make new treatments rapidly reach our patients.



Sabine Tejpar
ESMO Faculty

The real advantages of personalised medicine are, of course, that we will be able to provide a given patient with a much higher level of care, a much higher level of therapeutic efficacy than we can attain now.

There will also probably be other ways of monitoring patients, of maybe having repeat samples taken for doing molecular diagnosis; otherwise we cannot personalise the treatment. These are the two aspects that we will have to work on in the next few years to implement personalised medicine in clinical practice.

Table 1. Challenges in Personalised Cancer Medicine.

Scientific

- The molecular mechanisms of diseases
- The molecular mechanisms of the drug

Development of Companion Diagnostics

- Biomarker selection

Drug-Diagnostic Co-Development

- Clinical research

Commercial

Regulatory

Reimbursement

Logistics

Education

Data Protection

Why Is It Important For Cancer Patients To Understand Personalised Medicine?

Although the cancer field is moving towards personalised medicine, with drugs being targeted to specific tumours, a recent survey has shown that many patients are unaware that this revolution is taking place.

“Clearly, there remains a need for patients to be better informed about personalised medicine, which is a shared responsibility among the multidisciplinary healthcare team, patient support groups, and the

media,” says Sabine Tejpar, MD, University Hospital of Leuven, Belgium. Dr Tejpar presented the results of the survey at the 2012 ESMO Congress. For patients to benefit from these targeted therapies, a tumour sample must be sent for analysis, and this biomarker analysis can take one week or longer.

The survey concluded that the majority of patients (74%) would be ready to delay treatment for this period to undergo additional tumour testing, in the hope that they may benefit from personalised therapy. The same survey found that the majority of patients would allow hospitals to retain their tumour samples for future research.

This is a major topic, because patients must be aware that nowadays several new examinations can be performed on their tissues and tumour samples, but that these examinations can delay their treatment. Patients must be aware that the examinations are performed mainly on their biospecimens. Biospecimens are materials taken from the human body, such as tissue, blood, urine or saliva, which can be used in directing patient care or be processed and stored for future medical research. In the majority of cases these tissues are the same as used for the diagnosis of cancer. Therefore patients do not undergo any additional steps, other than to consent to the use of their biospecimens for the examination. In recent years an awareness has grown that the characteristics of tumours may change and patients may be asked to submit to a new biopsy to re-personalise their therapy.

From biospecimens, we can extract DNA with an opportunity to find millions and millions of pieces of information. Therefore there is a clear value in collecting biological material for doing research. In fact, several institutions are creating biobanks or biorepositories. The term “biobanks” can be defined in many ways, but the definition adopted here will be “an organised collection of human biological material and associated information stored for one or more research purposes”. In these libraries of stored biospecimens, personal information is highly protected and all the data are anonymised or “blinded”. These libraries are crucial to ongoing

research for identifying new targets and new prognostic factors. Each specimen may contain DNA, RNA, proteins or other molecules that will help researchers to better understand why and how the cancer developed and, perhaps, provide insight towards the development of new therapies.

In some institutions, patients are asked, for this reason, to donate their biospecimens for research. The biobanks need a high-quality standard of tissue samples for the development of personalised medicine. Unfortunately, nowadays research in this field is hampered by the low quality of tissue samples and the poor level of their storage. The possibility of having large numbers of samples allows scientists to identify specific alterations in DNA, RNA and proteins. This helps at several levels. Firstly, it helps to identify new targets for new drugs. Secondly, it is fundamental to identifying new prognostic factors, which means that patients, through their genetic characteristics, can receive the most appropriate and effective, or least toxic, drug.

A prognostic marker is a tool which is able to predict prognosis, the length of life, and the possibility to be cured or to relapse. A predictive marker is linked to the treatment, because it is able to predict the treatment outcomes: if the treatment works, if the treatment harms or if the treatment is not likely to work.

For these reasons, it is important that patients and families are aware of these developments and help physicians and researchers to spread the message of the importance to use and to donate their tissues for research purposes, because they can help other patients in the future.

Advocate Perspectives in Tissue Collection and Research

Question from Selma Schimmel: “One of the patient advocate and research perspectives is really the daunting task of trying to explain the importance of tissue and biospecimen collection to the very patients that you work with every day.”



Kathy Oliver

International Brain
Tumour Alliance
ESMO Cancer Patient Working
Group member

We, as patient organisations, are ideally placed to help educate patients about the rewards and challenges of personalised medicine. We can ensure that patients comprehend the terminology involved by speaking a language that they understand and by connecting them to reliable resources that will help them fathom this brave new world of genetic profiling, personalised medicine and diagnostics.

We are seeing the development, too, of personalised vaccines and immunotherapies for which patients will need a piece of their tissue so that a vaccine can be made specifically for that individual. It would therefore be helpful if, when a patient's tissue is donated for research, some of that tissue is banked for a patient's own possible use in the future for a bespoke cancer vaccine.



Francesco De Lorenzo

European Cancer Patient
Coalition
ESMO Cancer Patient Working
Group member

We feel that information is the first medicine for a cancer patient, and that even more information is required for personalised medicine.

What I really think we should try to do is to let cancer patients know that personalised medicine is an additional treatment; it is not the only treatment. We should let the cancer patient know that chemotherapy is still a very good treatment and there are several hormonal treatments, surgery and so on available, because otherwise we are giving very bad information and giving a hope that cannot be satisfied.

Cancer professionals should put more effort into the organisation of biobanks. We have been working with the Organisation of European Cancer Institutes (OEI) and we ask that, at the moment when the patient gives a specimen, he/she also has the right of future use of this specimen. We have been working with Dr Paolo Casali to publish a document on this. A patient should, first of all, be able to learn the results of tissue analysis by himself/herself or from the general practitioner, and secondly, the patient should have the right to give the specimen under the condition that a piece of the specimen has to be kept for future need. This is something that has to be accepted also by the scientific community.



Jola Gore-Booth

EuropaColon
ESMO Cancer Patient Working
Group member

Dr Sabine Tejpar's recent survey on 811 patients from Argentina, China, France, Germany, Italy, Spain and the UK posed certain questions. I was surprised by the survey results because, working with patients, I had envisaged different answers to the questions. One of the questions was: Would patients be prepared to give tissue to hospitals? Almost all the patients, 91%, would allow a hospital to retain a tumour sample for future research. So I think we have something really significant here, and I would like to add that Dr Tejpar said something very important: "I as a doctor, as a clinician, wouldn't feel comfortable to ask for tissue if I didn't know that I had something to deliver; if I know that I have something to deliver and give something back, then I have no hesitation to ask a patient for tissue. They can always say 'No' but I have to ask the question."



Fortunato Ciardiello

Chair of the ESMO Personalised
Medicine Task Force

What the European Organisation for Research and Treatment of Cancer has tried to do is to start a new concept of collaboration at the medical oncologist level to offer patients throughout Europe easier access to new treatments within clinical trials using the personalised approach.

This seems simple, but it is actually very complex. So, in several countries we have groups that will work together collecting samples from metastatic colorectal cancer patients, hopefully at the time of diagnosis of metastatic disease; patients will start their own specific treatments for the metastatic disease, but the samples will be centralised to check if there is more complex gene expression present. This gene mutation analysis will hopefully be able to select specific patients who later, after failure of second- or third-line therapy, are candidates for treatment with a newly available treatment.

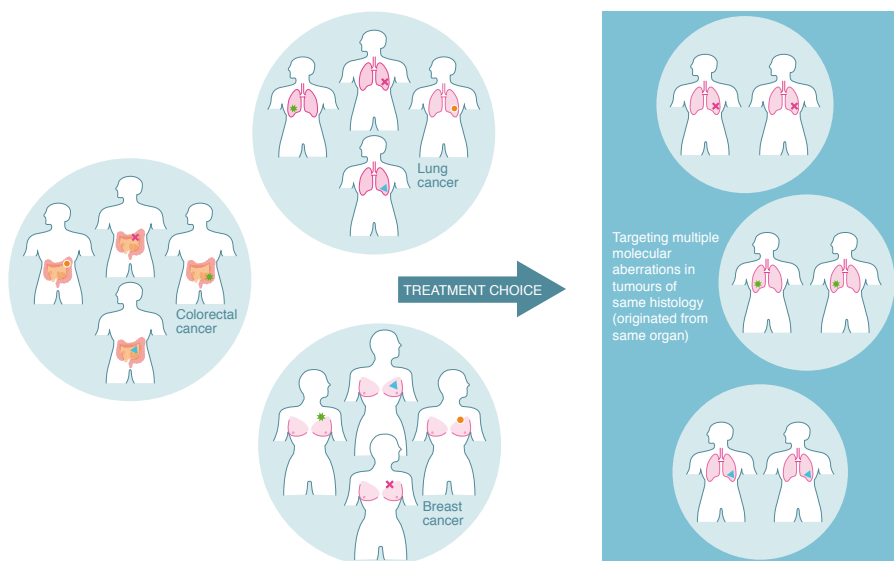
What Should Patients Know About Personalised Medicine and Clinical Trials?

Patients should be aware that participating in specific clinical trials is very important both for the individual patient and for society. They should be aware that a biopsy or a blood sample will make a difference; it will allow them to have more information that can, if used in the right way, be important in defining now, and increasingly in the future, which is the best treatment approach for them.

Figure 8. Histology-Based Clinical Trial Design to Evaluate Multiple Molecular Aberrations.

The treatment is selected to target different molecular alterations that appear in tumours located in the same organ (lung).

In the left panel, we can see three groups of patients with lung, colorectal and breast cancers. Symbols (blue triangle, green star, red cross, and orange circle) denote different genomic aberrations detected in their tumour samples. Clinical trials are conducted on specific tumour types, with patients undergoing molecular profiling and then being matched to specific drugs on the basis of molecular aberrations identified in their tumour samples. In the right panel, we can see patients, all with primary tumour located in same organ (lung), in whom the treatment is selected to target specific molecular aberrations.

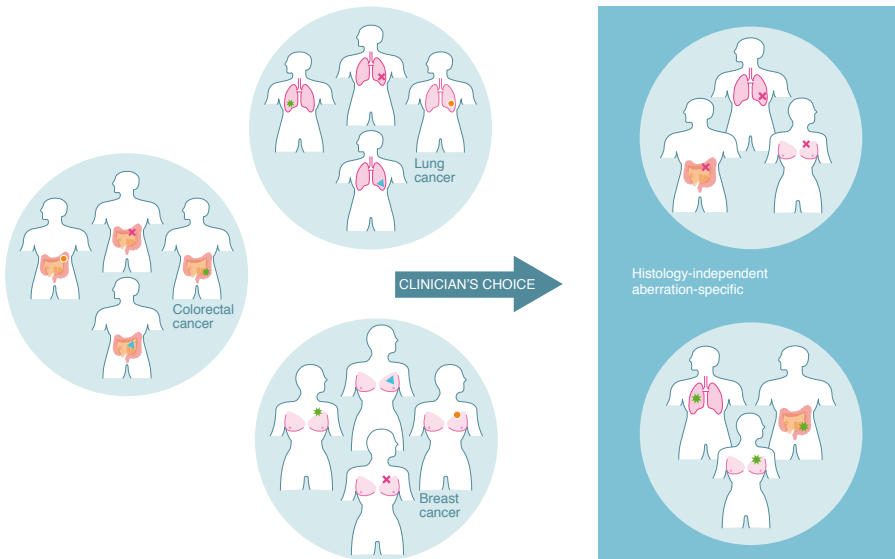


Adapted from Sleijfer S *et al.* J Clin Oncol 2013; 31(15): 1834-1841, with permission.

Figure 9. Histology-Independent, Aberration-Specific Clinical Trial Design.

The treatment is selected to target the same molecular alteration which appears in tumours in different organs.

In the left panel, we can see three groups of patients with lung, colorectal and breast cancers. Symbols (blue triangle, green star, red cross, and orange circle) denote different genomic aberrations detected in their tumour samples. Clinical trials are conducted to evaluate matching of drugs to specific molecular aberrations across different tumour types, with patients undergoing molecular profiling and then being matched to specific drugs on the basis of genomic aberrations identified in their tumour samples. In the right panel, we can see patients with tumours, but now located in different organs, and in whom the treatment is selected to target specific molecular aberrations, regardless of the primary site of the tumour.



Adapted from Sleijfer S *et al.* J Clin Oncol 2013; 31(15): 1834-1841, with permission.

Personalisation of Healthy Living

Our growing body of knowledge is increasing the awareness that we must live taking care of our lives. In particular, it has been demonstrated in the general population that smoking habits, alcohol

and obesity cause damage to DNA or exploit genetic weaknesses.

Our increased understanding of the genetic basis of disease has helped us to realise how important it is that we take good care of our bodies. Several lines of research are now ongoing to identify the genetic weaknesses and the predispositions of each individual to develop cancers. This means that, through advances in genetic techniques, it will become possible to identify those people who are more likely to develop cancers and therefore also to personalise their lifestyle according to their genetic features.

However, it may be that some cancers will not be affected by lifestyle changes and healthy living and will not be capable of being prevented, and these will present even further challenges to the scientific community.

Personalised Cancer Care

Question from Selma Schimmel: “How do we unify patient advocate efforts? We need to promote awareness and public understanding of this paradigm shift that cancer research is global in nature. So how do we take the global message forward, knowing that the internet allows patients all over the world to read common information, that research doesn’t happen in a vacuum and the tissue that’s collected in Hamburg may have an impact on a cancer centre in Rochester?”



Kathy Redmond
Editor, *Cancer World* magazine

I think it is interesting that we use the term “personalised medicine” as if it’s a new concept, when actually high-quality cancer care has always been personalised. For many years we have said that care should be patient-centric and clinical decisions should be tailored not only to patients’ genetic makeup but also their preferences, physical well-being and social circumstances. This is better described as personalised cancer care. Personalised medicine – the development of drugs that are targeted to a specific mutation – represents an important scientific development but unfortunately there has been much hype surrounding this advance which in reality has only had a limited impact on cancer patients. This hype is creating unrealistic expectations about what

personalised medicine can deliver for the vast majority of patients today, and strong advocacy efforts are required to convey clear messages about which cancers are currently benefiting from personalised medicine but also the potential of targeted therapies for cancer patients. A key part of this message is that mutation testing should be performed by laboratories with certified competence to carry out the test, since accuracy and consistency of results are important. Unfortunately, mutation testing, when there is a drug to target the mutation, is still not widely available to European citizens today. In some countries patients face important barriers in accessing targeted drugs even when there is a clear indication based on mutation testing. This is also an important advocacy issue.

Another message that needs to be communicated is that targeted drug therapy complements and enhances treatment with surgery and radiotherapy and that cancer treatment has to be planned by a multidisciplinary team working within the context of properly organised cancer services.

The final message to communicate is that improvements in cancer outcomes will come only when patients receive the right treatment (be it surgery, drugs or radiotherapy) from the right people at the right time. The right people are competent health professionals who have both experience and specialist training in cancer.



Francesco De Lorenzo

European Cancer Patient
Coalition
ESMO Cancer Patient Working
Group member

What Is the Future of Personalised Cancer Medicine in Europe?

From the patient side, personalised medicine will bring better treatments, while at the same time creating a major shift in healthcare systems. The meaning of personalised medicine is totally obscure for the lay public, patients and often for politicians and policy makers. Access to personalised medicine will depend on a shift in thinking in the entire area of healthcare and will need a new social health contract which will necessitate re-negotiation with society. Central to this negotiation will be the patients and patient organisations. It is important to acknowledge that not in every place

where cancer patients receive treatment is the best treatment available. In a European context, this is not only particular to Eastern Europe but it also occurs within Western Europe, where access to treatment is very different if we take two Member States such as the UK and Italy, and look at northern and southern regions of these Member States. Therefore, a collective EU action is needed through a harmonised approach that tackles health inequalities.

So what does the concept of personalised medicine promise? It provides the “right treatment to the right patient at the right time”. This is the critical point for the patient so as to ensure that the patient is not over-treated or under-treated. From an economic perspective, with increased targeted treatments there will be a reduced risk of expensive treatments being used on patients who will not be responsive, so offering more value for healthcare and offering benefits to patients, society and healthcare systems in the long run.

How can the promise be realised?

Changes will be necessary in the way medicines are developed, regulated and rewarded. Greater collaboration will be needed across a wide range of actors in healthcare, in particular with the patients. And systems will need to catch up with science. This was a key message that the cancer patient community has conveyed within the European Alliance for Personalised Medicine stakeholder initiative. In particular, in the area of research, we have called for:

- More multidisciplinary research, with closer collaboration between drug and diagnostic developers, clinicians, biologists, biostatisticians and information and communications technologists.
- Infrastructures that can support large screening platforms to identify target populations, and that provide relevant IT tools such as simulation or computer-assisted decision-making.
- Increased basic and collaborative pre-competitive research into biomarkers.
- Additional funding for international academic clinical trials in all disease areas.

All in all, the regulatory environment must allow every patient access to personalised medicine. This is very important. Research must be increased and findings that will facilitate personalised medicine co-ordinated. In this context, new approaches to reimbursement are needed to ensure that new treatments can become accessible for patients.

In terms of infrastructure, a European Institute should be created for translating the laboratory information into medicine. This, I feel, is the major and urgent point that the EU should support Member States to develop. If there is not such a translation, there will be no personalised medicine. Additionally, continuous training of healthcare professionals is needed and this has to be done through the development of guidelines which must become a living document so as to respond to technological and scientific changes that occur regularly. Only in this way can the patient receive the right treatment at the right time. Of course, patients should be a central part of this dialogue for the development of these guidelines. Therefore, we call on the EU Health Commissioner to work on the development of guidelines for personalised medicine that can be used at the national level by a range of stakeholders and to create the infrastructures so that these can be developed.

Finally, awareness of personalised medicine among patients and the general public is essential. The translation of the promise of science into reality – from personalised medicine to better quality of life – will not be effective if there is not a proper understanding among patients.

Adenocarcinoma is a cancer type that originates from epithelial tissue. Epithelial tissue includes, but is not limited to, the surface layer of skin, glands and a variety of other tissues that line the cavities and organs of the body. To be classified as adenocarcinoma, the cells do not necessarily need to be part of a gland, as long as they have secretory properties. Well-differentiated adenocarcinomas tend to resemble the glandular tissue from which they are derived, while poorly differentiated adenocarcinomas may not. By staining the cells from a biopsy, a pathologist can determine whether the tumour is an adenocarcinoma or some other type of cancer. Adenocarcinomas can arise in many tissues of the body due to the ubiquitous nature of glands within the body. While each gland may not be secreting the same substance, as long as there is a secretory function to the cell, it is considered glandular and its malignant form is therefore named adenocarcinoma. Please note that tumours of endocrine glands (e.g. pancreas, adrenal gland, etc.) are typically not referred to as adenocarcinomas, but rather are often called neuroendocrine tumours. If the glandular tissue is abnormal but benign, it is called adenoma. Benign adenomas typically do not invade other tissue and rarely metastasise. Malignant adenocarcinomas invade other tissues and often metastasise.

Carcinogenesis is a process by which normal cells are transformed into cancer cells. It is characterised by a progression of changes at the cellular, genetic and epigenetic level that ultimately reprogram a cell to undergo uncontrolled cell division, thus forming a malignant mass.

Empirical medicine is medicine guided by practical experience or observations and not derived from the “scientific method”. The term empirical treatment is also used when a treatment is started before a diagnosis is confirmed. The most common reason for this is that confirming a diagnosis may take time, and a delay in treatment can harm the patient. An example is treatment with antibiotics, when there may be no time to wait for the results of isolation of the causal factor of infection. However, once the causal factor is identified and its sensitivity or resistance to treatment with different antibiotics is tested, a doctor can adjust the treatment. In the cancer field, oncologists in the past treated most patients diagnosed with a certain tumour type with the same drug or drug combination, but not all patients responded to such therapy. More recently, more scientific data from research has become available, making it possible to move from such empirical treatment to treatment adjusted for particular patient subgroups, based on an analysis of tumour and patient characteristics.

Epigenetics is the study of changes in gene expression, caused by mechanisms other than changes in the underlying DNA sequence. It basically refers to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Examples of epigenetic alterations are DNA methylation and histone modification.

The **exome** is a part of the genome formed by nucleotide sequences, called exons, that are encoded by genes. Although the exome represents a very small portion of the genome, mutations in the exome are thought to harbour 85% of disease-causing mutations. Therefore, exome sequencing may determine the genetic basis of some diseases.

A **germline mutation** is any detectable and heritable variation in the lineage of germ cells. Mutations in these cells are transmitted to offspring, while those in somatic cells are not. A germline mutation gives rise to a constitutional mutation in the offspring, that is, a mutation that is present in virtually every cell.

Grade of differentiation reflects how much tumour cells differ from the cells of the normal tissue from which they have originated. The grade score (G1 up to G4) increases with the lack of cellular differentiation. Tumours may be graded on four-tier, three-tier or two-tier scales, depending on the institution and the tumour type. Grading of tumours is different from staging, which is a measure of the extent to which the cancer has spread to other parts of the body.

High throughput technologies are important because demands for faster, more efficient, and cheaper methods of drug discovery have taken the forefront. High throughput screening is a method used particularly in drug discovery. Using robotics, data processing and quality control software, liquid handling devices, and sensitive detectors, high throughput screening allows researchers to quickly conduct millions of chemical, genetic or pharmacological tests. Through this process, they can rapidly identify active compounds, antibodies or genes which modulate a particular biomolecular pathway. The results of these experiments provide starting points for drug design and for understanding the interaction or role of a particular biochemical process in biology. High throughput cell biology is the use of new types of equipment with classical cell biology techniques to address biological questions that are otherwise unattainable using conventional methods. It may incorporate different techniques to permit rapid, highly parallel research into how cells function and interact with each other and how pathogens exploit these processes in disease. High throughput biology serves as one facet of what has also been called “omics research” – the interface between large scale biology (genome, proteome, transcriptome), technology and researchers.

Histology is a study of cell and tissue structures, performed by examination under a microscope. Histology is the study of healthy tissue and pathology includes the study of unhealthy tissue. The term “**pathohistological**” refers to studying characteristics of tumourous tissue under the microscope.

A **hot spot mutation** is any locus in the deoxyribonucleic acid sequence or on a chromosome where mutations or aberrations occur preferentially.

The **Human Genome Project** is an international scientific research project with a primary goal of determining the genetic makeup of the human species. The first official funding for the Project originated from the USA governmental agencies. A working draft of the genome was announced in 2000 and a complete one in 2003, with further, more detailed analysis still being published. Most of the government-sponsored sequencing was performed in universities and research centres from the United States, the United Kingdom, Japan, France, Germany and Spain. Researchers continue to identify protein-coding genes and their functions; the objective is to find disease-causing genes and possibly use the information to develop more specific treatments. The genome of any given individual (except for identical twins and cloned organisms) is unique; mapping the human genome involves sequencing multiple variations of each gene. The Project did not study the entire DNA found in human cells; about 8% of the total genome remains unsequenced.

In genetics, a **mutation** is a change of the nucleotide sequence of the genome. Mutations result from unrepaired damage to DNA or to RNA genomes (typically caused by radiation or chemical mutagens), from errors in the process of replication, or from the insertion or deletion of segments of DNA by mobile genetic elements. Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes, including evolution, cancer and the development of the immune system. Mutation can result in several different types of change in sequences. Mutations in genes can either have no effect, alter the product of a gene, or prevent the gene from functioning properly or completely. Mutations can also occur in non-genic regions.

Neoplasm is an abnormal mass of tissue as a result of the abnormal growth or division of cells. Prior to neoplasia, cells often undergo an abnormal pattern of growth, such as metaplasia or dysplasia. However, metaplasia or dysplasia does not always progress to neoplasia. The growth of neoplastic cells exceeds, and is not co-ordinated with, that of the normal tissues around it. The growth persists in the same excessive manner even after cessation of the stimuli. It usually causes a lump or tumour. Neoplasms may be benign, pre-malignant (carcinoma *in situ*) or malignant (cancer).

Proteomic changes represent changes in the expression, localisation, function, and interactions of proteins expressed by genetic material.

Mutations that are not germline are **somatic mutations**, which are also called acquired mutations.

Squamous tumour originates from a type of epithelial cell called the squamous cell. These cells form the main component of the superficial part of the skin, and squamous cell carcinoma is one of the major forms of skin cancer. However, squamous cells also occur in the lining of the digestive tract, lungs and other areas of the body, and therefore squamous cell carcinoma occurs as a form of cancer in diverse tissues, including the lips, mouth, oesophagus, urinary bladder, prostate, lung, vagina and cervix among others. Despite sharing the name squamous cell carcinoma, the cancers of different body sites can show tremendous differences in their presenting symptoms, natural history, prognosis and response to treatment.

This Glossary includes content based on entries in Wikipedia (http://en.wikipedia.org/wiki/Main_Page).

Acknowledgements

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Conflict of interest disclosure:

Dr Marina Garassino – No conflicts of interest to declare.

Notes

[illegible]

This image shows a single sheet of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

This image shows a single sheet of white paper with horizontal blue or grey ruling lines. The lines are evenly spaced and run across the width of the page. There are approximately 20 lines visible. The paper has a slight shadow on the right side, suggesting it's resting on a surface.

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Patients are the driving force and inspiration behind our oncology-related events, educational programmes, and the reason why oncologists are constantly pushing the edge of science to revise existing therapies and find new treatment options. Patient activities fulfil one of ESMO's most important objectives – to disseminate knowledge to cancer patients, their caregivers, advocacy groups and the public.

For more information please visit esmo.org/Patients