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Scientific organizations are all aligned on the message that we need to implement NGS, but we need national guidelines.

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Dr Nicola Normanno, the Director of the Translational Research Department of one of Italyâ??s national cancer institutes, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, and president of the Italian Cancer Society explains Italyâ??s progress with next-generation sequencing (NGS) and the creation of molecular tumour boards. He also discusses the need for partnerships between institutions and pharma companies and predicts the positive impact of precision medicine on the Italian system.

Can you give us a brief overview of your research background in oncology and explain what the Istituto Nazionale Tumori IRCCS Fondazione G. Pascale does?

I was trained as a medical oncologist but I have always run translational research programmes. My career began at the National Institutes of Health (NIH, Bethesda. USA) in the early nineties and then in 1994, I moved to the National Cancer Institute of Naples here in Italy. Apart from my position at IRCCS, I am president of the Italian Cancer Society and of the International Quality Network for Pathology (IQN Path), an association whose members are mainly from other scientific organizations involved in biomarker testing including the Italian Association of Medical Oncology (AIOM).

The Istituto Nazionale Tumori IRCCS â??Fondazione G. Pascaleâ?• is a national cancer institute. In Italy, we have a peculiar organization where we have a number of national cancer institutes that

operate at a regional/national level. I am the head of the research department.

My research has always been focused on translational oncology starting with the EGFR system. However, over time my research work become â??agnosticâ?•, which means that we are now applying our knowledge to molecular biology in different tumor types. In particular, we use next-generation sequencing (NGS) in research and clinical practice and have introduced NGS for clinical trials in Italy, and also liquid biopsy. We are involved in a number of clinical trials in which we are handling the translational research part for the discovery of new biomarkers.

I am in a peculiar position because I have expertise in molecular biology and yet I have been trained as a medical oncologist. Therefore, I am an atypical figure who brings together the clinical part with lab experience.

Many in Italy have spoken about health equity in Italy and the difference between the regions. Is that something visible at the research level?

Actually, I launched an initiative that set out to map the status of biomarker testing in Europe. With respect to Italy, we found a huge difference in capabilities for biomarker testing, in particular for NGS capability, between the north and the south of the country. I am referring to clinical practice, but also to something at the border between clinical practice and clinical research. Most labs that do clinical research learn how to use NGS, testing for tissue and now also for liquid biopsy. Labs that are not involved in clinical research often have little expertise in NGS, and this is leading to a slow uptake of NGS testing in our country. We estimated that less than 2 percent of biopsies in Italy are tested withNGS overall. Specifically, if we look at lung cancer, the tumour type for which all national and international guidelines recommend the use of NGS, we estimate that no more than 35 to 40 percent of Italian patients are tested with NGS. One of the reasons for this is varying reimbursement. In Italy we have a system that is organized on a regional basis, which leads to differences between regions with respect to reimbursement policy. In addition, there is a problem of capability. Academic institutions have more capacity to run NGS tests and there is a clear gradient, if you go from north to south, with a reduction in the number of labs that have this capability. There is also a low level of attention of the health system for biomarker testing, the system is mainly focused on the drugs.

What I am trying to do through my teaching, and also when I talk to patients and to people in the regulatory agency is to get them to understand that the whole story of precision medicine is not all about drugs. You need the drug as well as the biomarker and if you do not work on both of these aspects, you will never be able to provide precision medicine to patients.

What needs to happen in order to bridge the gaps you mentioned?

For the first time, last year, we saw the introduction of an NGS and molecular tumour board in an Italian law, as well as a plan for the creation of referral centers for NGS testing. Now, as always, it will take time for all of this to be implemented. Guidelines have to come from the department of health; we are still missing this part. What we are doing is to work with patientsâ?? organization to push the system because patients are important drivers of change. Patient organizations must be involved and must be part of the process. On the other hand, scientific organizations are all aligned on the message that we need to implement NGS, but we need national guidelines of how to use NGS, on which patients should be tested, and on a common minimum reimbursement fee for NGS that every region can adopt.

Now, however, there is this level of uncertainty because the government is going to be replaced in the next few months, which means there will be a transition period. All of this has already been released and approved, but it will take one or two years before it is applied.

Once these policies are fully introduced, will the survival rates of cancer patients in Italy increase?

If we are talking about lung cancer, which is the main example I can give, we have several biomarkers and matched active drugs that have been already approved, and we know that for these patients, at least in certain subgroups of these patients, we can expect a survival rate that is much higher than with chemotherapy or immunotherapy. Thus, there is no doubt that this has been demonstrated. If you do not use NGS for genomic profiling, we know that these patients are not receiving the most active treatments. On the other hand, they might receive a therapy that is very costly and not as effective, such as immunotherapy. So, testing helps to find appropriate treatment and improve survival.

In addition to the standard testing for known biomarkers, comprehensive genomic profiling can discover alterations that might give opportunity for experimental treatments, through clinical trials or expanded access programmes. However, for some patients with actionable mutations there are no clinical trials available which is a clear limit for the development of precision medicine. This clearly indicates that we need a different organization. The cases for comprehensive genomic profiling should be chosen by the molecular tumour board, with rules that need to be shared at a national level. The access to drugs has been solved in other countries where there are national programmes for patient screening, and then there are agreements with pharma companies to access drugs that are not approved yet for specific tumor tyepes and/or alterations. I think we need a national program in which we can conjugate the clinical research with the need to collect data from these patients. This should be under the control of the Italian drug agency so that we can collect data from patients who are treated with experimental drugs â??at this point they are still experimental drugsâ??and then we can learn whether or not they are active in defined subgroups of patients.

What I propose is a collaboration between the public health system and the pharmas. The national health system makes the infrastructure available (labs, hospitals) and will follow the patients, while the pharma companies will provide the drugs for free. And if there is any demonstration of activity of a drug for a new indication, the data collected by the Italian drug agency could also be used to change or extend the field of application of the drug. Therefore, this could be a good way for academia and pharma to collaborate with the control from the government. We would give patients the opportunity to potentially access new drugs while collecting new data. Because in many cases, we are talking about rare mutations and rare types of cancer, we need to have a national programme where we can put together all of the experience from academic centres. I think we could take advantage of what has been done in other countries to establish a national programme for precision medicine that would be centrally organized.

Are you suggesting adopting a genomic bank like in the UK that would map Italian cancer patients?

What we can do once we have fully established the molecular tumour boards, is select patients to undergo comprehensive genomic profiling that would be covered by public funds. There are some funds that have already been identified to cover this. Once we identify patients that are eligible for specific treatments, they should be entered into a national programme with the data being collected

at the national level. In this way, we will have increased knowledge of the genomic profiling of cancer patients in Italy.

Actually, I am the principal investigator of a national study, the RATIONAL study, promoted by the Federation of the Italian Cooperative Oncology Groups (FICOG), which is collecting data from patients that are tested with NGS. We have two pathways of enrolment. On one hand there are patients that have received an NGS test in clinical practice or any kind of clinical program, local or regional. We simly collect the sequencing data ans well as information on patientsâ?? treatment and outcome. But we also offer the possibility to patients who do not have access to NGS to get an NGS test as part of the programme. We have about ten pharma companies as sponsors. So far, we have enrolled over 1,300 patients and over 1,000 cancer patients in Italy have gained access to NGS thanks to this study. This is a good example of collaboration between academia and pharma to give the possibility to patients to access to NGS testing.

You mentioned taking advantage of the data already being generated. What about real-world data?

We always have new drugs targeting rare mutations, rare cancers, and it is very unlikely that we will have any randomized phase three trials to approve these drugs. Thus, we have approved drugs based on phase one, maybe phase two clinical trials, with a small number of patients and we do not know with any certainty if these drugs work or not, and if the biomarker is adequate. I see the importance of real-world data in a kind of post-market evaluation of the activity and toxicity of drugs. For a new drug or a new target that is approved based on phase one or phase two trials, there should be a post-market evaluation with real-world data. With this data, we can discover that the drug is working well, or we may discover that the drug is working on a certain subgroup of patients, which would mean we need additional experimentation. Or, we may discover that the drug is not working at all.

Could the data piece also play a role in drug pricing?

Some of the pharma companies that are sponsoring the study I mentioned asked if they could use the data to negotiate with the Italian Medicines Agency (AIFA) because there is no national data of this kind in Italy. This is very important because when a company goes to negotiate with AIFA, the first thing AIFA will ask is how many patients you expect to treat. If you do not know the exact patient population it very difficult to address this. Now we are clearly generating some evidence, but we need to do more.

How would you evaluate the level of translational science in Italy, particularly in oncology?

One of the major limitations in Italy is that we have very little research and development support from pharma companies. Translational research is useful, but in the end, if you do not have any possibility of interacting with pharma, that is a limitation. There are exceptions, but in public health institutions it would be difficult to generate a spin off, for example, to develop a new idea. The system is not very flexible. There is little investment in R&D from pharma companies. When I was working at the NIH in the US, there were maybe 20 to 30 biotech company nearby and if you had an idea, you could go and discuss with them how to develop it from a commercial standpoint. Now with the funds from the recovery fund, maybe some of the companies will invest into translational research.

You were at the NIH in the US. Many of the researchers doing translational research there leave to create companies. Would you say that in Europe part of the problem is that researchers do not want to leave their institutions?

They do not want to leave because the system is not as flexible here as it is in the States. It is not easy to find a job in Europe, so if you leave your permanent position to open your own company, it is a bigger risk. To find funds for that kind of company is not easy either. What I find funny is that sometimes the department of health wants to apply the same rules that work in the United States, but the context is completely different.

Almost 15 years ago, there was a company that asked the technicians in one of my labs if they wanted to come to work at the company and no one accepted. People think that if they work for the public system, they will continue to work for the public system for ever, whereas if they move to the private sector, the possibilities will be limited. That is a market reality. The oncology field is very limited in Italy.

In your view, what is the future of biomarkers?

They will be able impact early phases of the disease, so biomarkers will be employed for the detection of minimal residual disease and early diagnosis of cancer. In this respect, I think that the the integration of different types of biomarkers will improve the diagnostic accuracy of the test. I do not see that any kind of omics by themselves will be able to provide an answer, but I think that integration with artificial intelligence may be the key to moving to real precision medicine.

Precision medicine has opened up tremendous possibilities yet there is still a difference between the concept and applying it to clinical practise. What is the reason for this, particularly within the context of European healthcare systems?

We have a national system that allows us to give every drug to every patient, and patients push to receive these drugs. However, with the increased cost of drugs and the increased demand, we will not be able to sustain the system. Precision medicine is an answer to this problem because if we find clear indicatorsâ??using biomarkers, genomics or other methodsâ??that will tell us which patients are going to benefit from drugs and which patients are not going to benefit, then I can justify why we are treating only a fraction of the patients. Otherwise, we will continue to add costs for the new drugs with limited effects.

Precision medicine is the answer to containing costs in the system. Otherwise, we will continue to give immunotherapy to all patients when we know it works in 15 or 20 percent, which costs thousands of euros.

Thus the protocols and the sequencing for each treatment would have to change based on an individualized approach?

If we find the right biomarkers and study the characteristics of the disease and of the patients then we can use this information to define a strategy of treatment rather than simply use the first line, etc.

There are patients, for example, that might benefit from both immunotherapy or target therapy. If you have clear biomarkers, you will be able to identify the patient that will never respond to target therapy. If we have more insights into the characteristics of the tumour and of the patient, we can base our decision on specific factors. This does not mean that doctors will not make decisions but that they will be able to base decisions on factors that have been scientifically proven. This can be used to improve the appropriateness of the treatment and overall improve the therapeutic strategy.

My generation was raised in the era of the large randomized clinical trial in which there were 1,000 patients versus 1,000 patients and the best treatment was decided by comparing one arm against the other. We have to move away from this idea to the idea that each patient might be a different case, which is precision medicine.

Is there anything else you would like to share with our global audience?

The only thing I would like to say is that it is very important at this stage to increase the collaboration between pharma and academia. Clearly, we are in a phase in which we need to implement precision medicine in Italy and we need this close collaboration between academia and pharma in order to do that.

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